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

CSL Behring UK Limited  

08 July 2016  

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

**ADVICE**: following a full submission assessed under the orphan equivalent process  
**human alpha₁-proteinase inhibitor (Respreeza®)** is not recommended for use within NHS Scotland.  

**Indication under review**: For maintenance treatment, to slow the progression of emphysema in adults with documented severe alpha₁-proteinase inhibitor (A1-PI) deficiency.

Treatment with human A1-PI for two years reduced the rate of lung density loss compared with placebo; however, there is a lack of robust evidence concerning the clinical relevance of this outcome. No improvement in pulmonary exacerbations, lung function or quality of life was demonstrated.

The submitting company did not present a sufficiently robust clinical or economic analysis and in addition their justification of the treatment’s cost in relation to its benefits was not sufficient to gain acceptance by SMC.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Overleaf is the detailed advice on this product.

**Chairman,  
Scottish Medicines Consortium**
**Indication**
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 [FEV1] predicted, impaired walking capacity or increased number of exacerbations) as evaluated by a healthcare professional experienced in the treatment of alpha₁-proteinase inhibitor deficiency.

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.

**Dosing Information**
60mg/kg body weight administered once weekly as an intravenous (IV) infusion over approximately 15 minutes.

**Product availability date**
March 2016
Human alpha₁-proteinase inhibitor meets SMC orphan equivalent criteria.

**Summary of evidence on comparative efficacy**
Deficiency of alpha₁-proteinase inhibitor (A1-PI) is a rare, autosomal recessive genetic disorder. In response to inflammation or infection, A1-PI plasma concentrations increase rapidly in order to protect lung tissue from lysis. A1-PI deficiency causes uncontrolled destruction of lung parenchyma resulting in progressive emphysema which is potentially fatal (mean life expectancy of patients with PiZZ variant is 48 to 52 years for smokers and 60 to 68 years for non-smokers). Human A1-PI is the first UK licensed disease-modifying treatment for patients with emphysema due to deficiency of A1-PI. Replacement maintenance treatment with human A1-PI increases serum and lung concentrations in patients with A1-PI deficiency. It is intended that human A1-PI would be added to conventional treatments for emphysema.

The submitting company has requested that SMC considers human A1-PI when positioned for use in patients with severe A1-PI deficiency or progressive lung disease that meet all of the following criteria:

- Diagnosis of severe A1-PI deficiency (A1-PI level <11µM)
- Ratio of FEV1/FVC <0.7 (indicating moderate airways obstruction) or emphysema demonstrated by computed tomography (CT) scan via multi-disciplinary team consensus
- FEV1 30% to 70% predicted
- Rapidly declining lung function (as measured by FEV1 or diffusing capacity of the lung for carbon monoxide [DLco]) or lung density decline

The evidence supporting the marketing authorisation is from a phase III, double-blind, randomised, placebo-controlled study (RAPID) and an open-label, uncontrolled, phase IV extension study (Study 3001).

RAPID recruited 180 patients aged 18 to 65 years with emphysema secondary to A1-PI deficiency (serum A1-PI concentration ≤11µM) and FEV1 35% to 70% predicted. After a screening period of one
to four weeks, patients were randomised equally (stratified by centre) to receive two years treatment with weekly intravenous (IV) infusion of human A1-PI 60mg/kg or placebo. The primary endpoint assessed annual rate of change in lung density measured as the 15th percentile of the frequency histogram of the lung pixels (PD15) measured by CT. Data were collected at two states of inspiration: total lung capacity (TLC=volume of gas in the lungs after maximal inspiration) and functional residual capacity (FRC=volume of gas in the lungs at end expiration during tidal breathing). There were three primary outcomes: assessments of PD15 density at TLC alone, at FRC alone and a combined assessment summing density values calculated at both TLC and FRC. The primary analyses were in the modified intention-to-treat (ITT) population excluding patients for whom no lung density measurements were available, and in the per protocol population excluding patients with a major protocol violation. There was a significant improvement (reduction in loss) in mean annual rate of lung density change between the human A1-PI and placebo groups when measured at TLC; relative reduction of 34% (2.2 to 84.5) in favour of human A1-PI. The primary outcome was not met when measured at FRC alone or when the TLC and FRC results were combined.

Table 1: Treatment comparison for annual rate of change in physiologically adjusted PD15 (g/L) at TLC and FRC states combined and separately based on a random regression model (modified ITT population)

<table>
<thead>
<tr>
<th>Inspiration state</th>
<th>Annual rate of change in physiologically adjusted PD15 (g/L) (SE)</th>
<th>Difference: human A1-PI minus placebo</th>
</tr>
</thead>
</table>
| TLC + FRC combined | Human A1-PI (N=92)  
-1.50 (0.22)  
Placebo (N=85)  
-2.12 (0.24) | 0.62  
95% CI  
-0.02 to 1.26  
p-value  
0.06 |
| TLC only          | Human A1-PI (N=92)  
-1.45 (0.23)  
Placebo (N=85)  
-2.19 (0.25) | 0.74  
95% CI  
0.06 to 1.42  
p-value  
0.03 |
| FRC only          | Human A1-PI (N=92)  
-1.55 (0.24)  
Placebo (N=85)  
-2.02 (0.26) | 0.48  
95% CI  
-0.22 to 1.18  
p-value  
0.18 |

Adjusted PD15=Lung volume-adjusted 15th percentile of the lung density; CI=confidence interval; FRC=functional residual capacity; TLC=total lung capacity; N=number of patients who had at least one CT scan available; SE=standard error.

Secondary efficacy outcomes were: number of exacerbations, exacerbation duration and severity, FEV1, single-breath diffusion capacity, baseline and achieved A1-PI concentrations, incremental shuttle walk test results and body-mass index. There were no significant differences between treatment groups for any secondary outcomes except A1-PI concentration, which was significantly increased in the human A1-PI group compared with the placebo group: treatment difference 10.05µM (p=0.02). The mean duration of exacerbations (0.26 years versus 0.18 years) and the percent mean duration of exacerbations (relative to patient’s total treatment duration) (14% versus 11%) were slightly higher with human A1-PI compared with placebo. The mean duration of hospitalisations (0.04 years versus 0.02 years) and the percent mean relative duration of hospitalisations due to exacerbations (6.2% versus 2.2%) were also slightly higher for the human A1-PI group compared with the placebo group. Health related quality of life (HRQoL) was measured using the St George’s Respiratory Questionnaire (SGRQ), for which high scores represent increased disability. After 24 months there was no significant difference between treatment groups in SGRQ total score or in the sub-scores for symptoms, activity or impact.

Study 3001 is an ongoing, open-label, uncontrolled extension to the RAPID study. All patients from outside the US who completed RAPID were offered open-label treatment with human A1-PI.
60mg/kg/week for a further two years. Of the 140 patients that enrolled in the extension study, 76 patients had previously been treated with human A1-PI in RAPID (early start patients) and 64 patients had previously been treated with placebo (delayed start patients). Results are available from a second interim analysis that included 97 patients who had completed the 48 month (parent and extension) study. In the delayed start group, the annual rate of decline in lung density reduced from 2.06g/L/year while on placebo to 1.31g/L/year on human A1-PI. The annual rate of decline was 1.08 g/L/year in the early start group.

Summary of evidence on comparative safety

In the RAPID study almost all patients reported adverse events: 99% (92/93) patients in the human A1-PI group reported a total of 1,298 treatment-emergent adverse events, and 99% (86/87) patients in the placebo group reported 1,068 events. Severe events were reported in 27% (25/93) and 31% (27/87) patients in the respective groups. The most commonly reported treatment-emergent adverse event was headache which was reported in 40% (37/93) and 38% (33/87) of patients in the human A1-PI and placebo groups respectively. Treatment-emergent adverse events led to withdrawal from the study in one patient (1.1%) in the human A1-PI group and in four patients (4.5%) in the placebo group.

The summary of product characteristics (SPC) notes that hypersensitivity reactions may occur, including in patients who have tolerated previous treatment with human A1-PI. This is a potential concern as patients and caregivers are permitted to administer human A1-PI IV infusions after appropriate training.

Summary of clinical effectiveness issues

Clinical manifestations of A1-PI deficiency include low levels of A1-PI in the serum and lungs, progressive pulmonary emphysema, liver cirrhosis and (rarely) panniculitis (inflammation of subcutaneous fatty tissue). The pathogenesis of the liver disease component of A1-PI deficiency is caused by accumulation of abnormal A1-PI in the liver cells and exogenous A1-PI therapy does not improve it. Emphysema due to A1-PI deficiency is difficult to differentiate from asthma or COPD. The condition is often not diagnosed until patients are in their thirties or forties, and it is estimated that up to 90% of patients with A1-PI deficiency remain undiagnosed. Although licensed human A1-PI replacement therapies have been available in other countries for many years, the product under review is the first to be licensed in the UK. The relevant comparator is therefore best supportive care (BSC), which comprises the standard treatment options for COPD including long-acting inhaled bronchodilators, inhaled corticosteroids, antibiotics, systemic corticosteroids, and supplemental oxygen for specific cases. Human A1-PI meets SMC orphan-equivalent criteria.

The submitting company has requested that SMC considers human A1-PI when positioned for use in patients with severe A1-PI deficiency or progressive lung disease that meet all of the following criteria:

- Diagnosis of severe A1-PI deficiency (A1-PI level <11µM)
- Ratio of FEV1/FVC <0.7 or emphysema demonstrated by CT scan via multi-disciplinary team consensus
- FEV1 30% to 70% predicted
- Rapidly declining lung function (as measured by FEV1 or DLco) or lung density decline

Clinical experts consulted by SMC considered that there is unmet need in this therapeutic area, namely the lack of a disease-modifying treatment for emphysema due to A1-PI deficiency.
The RAPID study demonstrated that treatment with human A1-PI reduced the rate of lung density loss compared with placebo.\(^6\)

Limitations of the evidence include the primary outcome being a surrogate measure of progressive destruction of the lung parenchyma in emphysema.\(^1\) There is a lack of robust evidence that slowing the loss of lung density translates into a clinically relevant effect.\(^1\) The relationship between loss of lung density and mortality has been investigated in an observational study that included 77 patients from the UK A1-PI deficiency registry who had never received human A1-PI therapy and had two quantitative CT scans. Compared with no decline in lung density, slow (\(\leq 2\text{g/L/year}\)) decline showed a numerical trend towards increased mortality (\(p=0.0650\)), and rapid decline (\(>2\text{g/L/year}\)) showed a significant association with increased mortality (\(p=0.026\)).\(^{10}\) The primary outcome in the RAPID study was met when measured at the TLC inspiration state, but not at FRC or at the combination of the two inspiration states.\(^6\) The European Public Assessment Report states that lung loss measured at TLC via whole lung CT densitometry is considered a relevant endpoint to use as it measures the physiological change in the organ which is affected by the disease. A panel of experts consulted by the European Medicines Agency confirmed that CT density measurements performed at TLC ensure much lower variability than the scans taken at FRC.\(^1\)

In the RAPID study, treatment with human A1-PI for two years did not demonstrate significant improvement over placebo in: the rate of pulmonary exacerbations (numerically higher in active group) or in their duration (numerically longer in active group) or severity; FEV1 (numerically worse in active group); single-breath diffusion capacity (numerically worse in active group); exercise capacity (numerically worse in active group) or quality of life.\(^6\) However, the progression of emphysema in A1-PI deficient patients is slow, and RAPID was not powered to detect an effect on lung function or on rate and severity of exacerbations.\(^1\) A1-PI deficiency is a life-long condition and it is not known if the treatment effect of human A1-PI continues beyond four years.\(^6\) The safety and efficacy of human A1-PI in patients \(\geq 65\) years of age have not been established in specific clinical studies.\(^5\)

Clinical experts consulted by SMC considered that human A1-PI is a therapeutic advancement as it may slow the progression of emphysema and considered that its place in therapy is in patients with severe A1-PI deficiency and progressive lung disease. The introduction of this medicine may impact on the patient and service as lifelong weekly IV infusions are required.

### Patient and Clinician Engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of human alpha-1 proteinase inhibitor as an orphan equivalent medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- Severe alpha-1-proteinase inhibitor (A1-PI) deficiency is a rare, life-limiting, genetic disorder characterised by progressive emphysema with frequent exacerbations, which can be debilitating and causes considerable morbidity. Patients are predominantly diagnosed in their 30s or 40s.
- Human A1-PI offers a therapeutic advance which may slow the progression of emphysema, with a reduction in the associated disability and early mortality. There are no other disease modifying treatments available.
- This medicine is already available to patients in other countries.
- Patient reported outcomes suggest that human A1-PI provides an opportunity to stabilise the condition, to reduce the frequency and severity of exacerbations and associated hospital admissions and to increase quality of life.
• Stabilisation of the condition would also have a strong positive impact on patients’ and carers’ ability to work and to lead a fulfilled family and social life.

**Additional Patient and Carer Involvement**

We received patient group submissions from Alpha 1 Awareness UK and the Alpha-1 UK Support Group. Alpha 1 Awareness UK has not received any pharmaceutical company funding in the last two years. The Alpha-1 UK Support Group has received 75% pharmaceutical company funding, including from the submitting company. Representatives from the Alpha-1 UK Support Group also participated in the PACE meeting. Alpha 1 Awareness UK did not participate in the PACE meeting, although highlighted many of the points captured through PACE.

**Summary of comparative health economic evidence**

The company submitted a cost-utility analysis consisting of a semi-Markov model comparing human A1-PI with BSC in the treatment of patients with severe A1-PI deficiency. The positioning considered is in patients with FEV1 predicted of 30-70% and rapidly declining lung function as a marker of disease progression (as measured by lung density by CT scan). The comparator is appropriate as there are no other licensed treatments for severe A1-PI deficiency in the UK. The model consisted of 8 health states consisting of FEV1 predicted ≥50%, or FEV1 <50% and a lung density decline state (no, slow or rapid decline); in addition, eligible patients (ie those in the FEV <50% and slow or rapid lung density decline states) could transition to a lung transplant state. The model contained a death state, although mortality probability was modelled separately based on a survival analysis. The time horizon for the economic analysis was lifetime with one year cycles, consisting of 40 years with the patient starting age in the model assumed to be 51 years in line with mean age in the RAPID clinical study.

The clinical data used in the economic model were from a post-hoc analysis of the RAPID study. This provided data on the change in lung density decline and mortality over a 4 year period for human A1-PI (two year randomised controlled trial data and two year open label extension), and for 2 years for placebo/BSC. Observational data from the UK registry of A1-PI deficiency patients with eight year follow-up was then used to estimate decline in FEV1 over time across both treatment groups, and the association between speed of lung density decline and mortality. The probability of death was then extrapolated for 30 years to the full model time horizon by fitting a parametric function to the observed data for the following sub-groups: FEV1 ≥50% (all lung density decline groups), FEV1 <50% plus no decline, plus slow decline, or plus rapid decline. In the base case, the Weibull represented the best fitting function in each case. Patients eligible for lung transplant were assumed to be those in the FEV1 <50% and slow or rapid decline states, with an assumption that only patients up to the age of 65 would be eligible. Transition probability estimates for lung transplant were based on published data in severe A1-PI deficiency patients in England (6.8% probability per year), and resulted in a predicted 30% of patients in the human A1-PI group and 22% of patients in the BSC group receiving lung transplantation over the lifetime duration of the model. An annual mortality associated with transplantation was included based on published estimates. It was assumed that the lung density decline benefits of continuous treatment with human A1-PI would be maintained over the lifetime horizon.

Utility estimates for FEV1 ≥50% and <50% states were based on EQ 5D data from the UK Registry for A1-PI deficiency. Utilities post-transplantation were estimated as 0.82 in the first year and 0.91 in subsequent years, based on a published study in patients from the Netherlands with end stage pulmonary disease. No additional disutilities were applied in the base case for lung density decline states. No disutilities were applied for additional adverse events associated with human A1-PI treatment on the grounds that the impact of these on HRQoL would be minimal.
Medicine acquisition and administration costs were included for human A1-PI, based on a patient weight of 75.9kg (from the RAPID study) meaning weekly administration of 5 vials assuming medicine wastage. Duration of treatment was assumed to be lifetime with no discontinuations, and 100% adherence was assumed based on findings from the RAPID study. Costs for disease management in FEV1 $\geq$50% and FEV1 <50% states were based on a published UK study in COPD patients, and the cost of lung transplantation was based on a published economic evaluation.

The base case incremental cost-effectiveness ratio (ICER) for human A1-PI versus BSC was estimated at £274,390 per quality adjusted life year (QALY) gained. This was based on incremental QALYs of 1.586 (incremental life years of 2.2 years) and incremental costs of £435,277. The main driver of cost is the additional medicines’ cost for human A1-PI, with some additional costs also associated with disease management and additional lung transplants performed in the human A1-PI group. Sub-group analysis was performed for FEV1 $\geq$50%, FEV1 <50%, and FEV1 <50% and rapid lung density decline sub-groups, with ICERs of £300k/QALY, £223k/QALY and £219k/QALY respectively.

A scenario analysis in which a 20% utility increase and disease management cost decrease for no lung density decline states combined with a 20% utility decrease and cost increase for the rapid decline states resulted in an ICER estimate of £245k/QALY. The results were sensitive to variations in most outcomes parameters: varying human A1-PI and BSC mortality rates in years 1-4 of the model resulted in an ICER range of £198k–£354k/QALY; excluding lung transplantation from the model increased the ICER to £389k/QALY; varying FEV1 <50% utility by the 95% CIs of the gamma distribution (0.21–0.92) resulted in an ICER range of £222k–£381k/QALY. There was also sensitivity to variation in the annual probability of requiring a lung transplant, and annual probability of death post-transplant, lower utility in post first year transplant state, and to varying the discount rate for costs or QALYs. Regarding costs, the greatest sensitivity was to varying patient weight (66kg–84.5kg) so that either 4 vials or 6 vials are required per administration with an ICER range of £223k–£326k/QALY.

The main strengths of the analysis are the availability of observational data to at least enable an attempt to develop an association between lung density decline and clinically relevant outcomes, which is lacking from the clinical study data, and the availability from this source of EQ 5D based utilities for FEV1 health states that seem to have face validity.

However, there are a number of key weaknesses with the economic evaluation:

- The model structure is based on a definition of lung density decline groups with no decline, slow decline and rapid decline (<0g/l/year, 0-2g/l/year and >2g/l/year respectively) stated to be based on definitions from experts at the UK Registry. Varying this definition could change the cost-effectiveness results but the company did not provide sensitivity analysis to test this aspect of the model, citing feedback from the UK Registry that a greater selection of cut-offs had been assessed but were no more informative, and that there were low numbers of patients to robustly assess outcomes associated with >3g/l/year definition of rapid decline. In addition, SMC clinical expert responses indicate that lung density decline is not commonly used in clinical practice; other measures, such as FEV1, are used to monitor disease progression.
- The survival benefit estimated for human A1-PI is a key driver of the cost-effectiveness results. There is inherent uncertainty associated with the extrapolation of mortality based on the surrogate outcome of speed of lung density decline (given the RAPID study found no difference in FEV1 predicted outcomes). There is also uncertainty associated with the analysis of the observational UK Registry data in that a significant relationship between speed of lung density decline and mortality could not be robustly established, and the extrapolation of these data for a further 30 years is associated with high uncertainty. The extrapolation of mortality is also conditional on the assumption that the treatment effect of human A1-PI is maintained over the duration of the time horizon in order to see the long term mortality benefits. Sensitivity
analysis was provided which reduced the time horizon to 30 and 20 years, and this increased the ICER to £283k and £307k respectively. A scenario analysis was also provided which used only the RAPID study data plus the registry data up to 10 years with no further benefit applied beyond this period. This increased the ICER to £387k.

- There is uncertainty over the predicted estimates of lung transplantation in the model. Higher rates of lung transplantation in the human A1-PI group are associated with improved ICERS, largely due to better HRQoL outcomes assumed post-transplant. The probability of transplant is based on data from England on rates of lung transplant in severe A1-PI deficiency patients, and the company stated that, as no lung transplantations are performed in Scotland, eligible patients receive these in England. However, given the lack of transplants performed in Scotland, the estimates based on English data may be too high. In addition, there is uncertainty over the eligibility criteria used (ie patients with FEV1 <50% and at least slow decline in lung density will receive a lung transplant up to age 65), and there are concerns that these criteria are too broad. Scenario analysis has indicated increased ICERS associated with excluding, or assuming fewer, transplants in the model (£310k/QALY using a lower annual probability of 3.68%, and £389k/QALY assuming a lung transplantation rate of zero). Using narrower eligibility criteria for lung transplantation (ie FEV <50% and rapid lung density decline) increased the ICER to £637k. SMC clinical expert responses indicated there is some uncertainty associated with the assumption that human A1-PI will impact on the rate of lung transplantation.

The Committee also considered the benefits of human A1-PI in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that the criterion for the absence of other treatments of proven benefit was satisfied. In addition, as human A1-PI is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee was unable to accept human A1-PI for use in NHS Scotland.

**Additional information: guidelines and protocols**

The Global Initiative for Chronic Obstructive Lung Disease (COPD) updated its global strategy for the diagnosis, management and prevention of COPD in 2016. The document states that although young patients with severe hereditary alpha-1 antitrypsin deficiency and established emphysema may be candidates for alpha-1 antitrypsin augmentation therapy, the therapy is very expensive, is not available in most countries, and is not recommended for patients with COPD that is unrelated to alpha-1 antitrypsin deficiency.

The National Institute for Health and Care Excellence (NICE) published clinical guideline 101 (COPD in over 16s: diagnosis and management) in 2010. This document recommends that in those with an onset of COPD symptoms under 40 years or a family history of alpha-1 antitrypsin deficiency, patients should be referred to a specialist service to identify alpha-1 antitrypsin deficiency, consider therapy and screen family. The guideline states that alpha-1 antitrypsin replacement therapy is not recommended for patients with alpha-1 antitrypsin deficiency.

The NICE guideline predates the licensing of human A1-PI.
**Additional information: comparators**

The relevant comparator is best supportive care. Human A1-PI is intended to be added to conventional treatment for emphysema.

**Cost of relevant comparators**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Regimen</th>
<th>Cost per year (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human alpha₁-proteinase inhibitor</td>
<td>60mg/kg once weekly, by intravenous infusion</td>
<td>57,200</td>
</tr>
</tbody>
</table>

Cost from company submission.

**Additional information: budget impact**

The submitting company estimated there would be 56 patients eligible for treatment with human A1-PI in year 1 and 61 patients in year 5. The estimated uptake rate was 50% in year 1 (28 patients) and 90% in year 5 (55 patients), with a discontinuation rate of 6.8% applied to each year.

The gross impact on the medicines budget was estimated to be £1.5m in year 1 rising to £2.9m in year 5. As no medicines were assumed to be displaced, the net medicines budget impact is the same as the gross.
References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.


15. Chronic obstructive pulmonary disease in over 16s: diagnosis and management NICE guidelines [CG101] Published date: June 2010

This assessment is based on data submitted by the applicant company up to and including 13 May 2016.

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.