Cost-effectiveness of human alpha-1 proteinase inhibitor (Respreeza®) *for maintenance treatment, to slow the progression of emphysema in adults with documented severe A1PI 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 A1PI deficiency.*

The NCPE has issued a recommendation regarding the cost-effectiveness of human alpha-1 proteinase inhibitor (Respreeza®). Following NCPE assessment of the applicant's submission, human alpha-1 proteinase inhibitor (Respreeza®) is not considered cost-effective *for maintenance treatment, to slow the progression of emphysema in adults with documented severe A1PI deficiency (e.g. genotypes PiZZ, PiZ,(null), Pi(null,null), PiSZ).* Therefore reimbursement is not recommended.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant's (CSL Behring's) economic dossier on the cost effectiveness of human alpha-1 proteinase inhibitor (Respreeza®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We

also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

National Centre for Pharmacoeconomics **December 2016**

Summary

In June 2016, CSL Behring submitted a dossier examining the cost effectiveness of human alpha-1 proteinase inhibitor (Respreeza®) for maintenance treatment, to slow the progression of emphysema in adults with documented severe A1PI 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 A1PI deficiency**.**

The recommended dose of human A1PI (Respreeza ®) is 60 mg / kg administered weekly over 15 minute infusions. The expected duration of use is long-term chronic therapy. In line with the SPC for Respreeza ®, first infusions should be administered under the supervision of a healthcare professional experienced in the treatment of A1PI deficiency but subsequent infusions can be administered by a caregiver or by the patient, however human A1PI (Respreeza ®) is expected to be administered in an outpatient hospital setting only.

In the submission, the economic evaluation evaluates human A1PI (Respreeza ®) and best supportive care compared with best supportive care alone. Best supportive care is defined as standard COPD therapies.

1. **Comparative effectiveness of human A1PI (Respreeza ®)**

The efficacy and safety of human A1PI (Respreeza ®) supporting marketing authorisation was primarily based on the pivotal phase III randomized, placebo-controlled, double-blind, multicentre study (RAPID) and an interim analysis of the open label, uncontrolled phase IV extension study (RAPID extension). The primary endpoint of the RAPID trial was to investigate the effect of human A1PI (Respreeza ®) on the progression of emphysema, assessed by the annual rate of change in lung density, measured as the 15th percentile of the frequency histogram of the lung pixels (PD15) measured by a centralised, standardised computed tomography (CT) lung densitometry. CT scans were acquired at 2 inspiration states: total lung capacity (TLC); volume of gas in the lungs after full inspiration and

functional residual capacity (FRC); volume of gas in the lungs at end expiration during tidal breathing. There were three primary outcomes; assessment of PD15 density at TLC alone, FRC alone and a combined assessment of the sum of both TLC and FRC.

The RAPID trial results showed a statistically significant 34% reduction in the annual rate of decline in CT-measured lung density at TLC with human A1PI (Respreeza ®) versus placebo (-1.45 versus -2.19 grams/Litre/year; p=0.03). The primary outcome was not met when measured at FRC or FRC and TLC combined. In a pre-defined subgroup analyses, treatment differences in rate of decline in lung density (g/L) by various baseline parameters at the TLC state were performed. Treatment benefit with human A1PI (Respreeza ®) versus placebo was observed and significant in females (mean difference of +1.45 grams/Litre/year, 95% CI: 0.382 to 2.526, p=0.004) and observed but non-significant in males (mean difference of +0.267 grams/Litre/year, 95% CI: -0.616 to 1.4148, p=0.275). An interim analysis of the open labelled RAPID extension study showed a 36% reduction in the rate of lung density loss when patients were switched from placebo to human A1PI (Respreeza ®) (-2.06 versus -1.31 grams/Litre/year; p=0.021) when measured at TLC. Although not powered to detect a treatment effect, there was a numerical worsening in annual number and relative duration of exacerbations, FEV1 and single breath diffusion capacity in the human A1PI arm (Respreeza ®) versus placebo in the RAPID trial which were not statistically significant.

2. Safety of human A1PI (Respreeza ®)

Overall, the proportion of subjects with a treatment-emergent adverse event (TEAE) were similar between the human A1PI (99%) and placebo (99%) groups in the RAPID study. The most commonly reported TEAE were infections and infestations which occurred in 77 subjects (83%) in the human A1PI arm and 76 subjects in the placebo arm (87%). The important identified risks in the EMA Risk Management are allergic reactions including anaphylaxis. Important potential risks identified include transmission of infectious agents, increased or unknown risks with home-based self-administration and medication error.

3. Cost effectiveness of human A1PI (Respreeza ®)

A cohort based semi-Markov model with a 43 year time horizon, programmed in Microsoft Excel® was constructed for the cost-effectiveness analysis comparing human A1PI (Respreeza ®) with best supportive care to evaluate the impact of human A1PI (Respreeza ®) on costs, QALYs and survival.

In the base case analysis of the submitted HTA dossier, human A1PI (Respreeza ®) was associated with an incremental cost of €712,563 and an incremental QALY gain of 1.2 giving a calculated base case incremental cost-effectiveness ratio (ICER) of €581,322 cost per QALY. However the RG note that there is considerable uncertainty associated with this ICER, mainly due to the lack of clinical evidence of survival benefit. There is uncertainty associated with the analysis in that a significant relationship between rate of lung density decline and mortality in A1PI deficiency has not yet been robustly established. The RG view that extrapolating treatment effects on mortality based on lung density decline over a lifetime is associated with a great deal of uncertainty. There is also uncertainty in the predicted estimates of lung transplantation in the economic model.

Both deterministic and probabilistic sensitivity analyses were presented, and a number of scenario analyses were explored by the Review Group.

4. Budget impact of human A1PI (Respreeza ®)

The cost of treatment in the HTA submission is estimated based on the average number of vials required per patient per week (5.2 vials) and a cost per vial of €312. The annual acquisition cost of human A1PI (Respreeza ®) per person excluding VAT is € 84,364.80 and €103,768.70 when VAT is included.

The gross budget impact presented by the applicant was estimated at €7,063,937 in year 1, €7,315,699 in year 2, €7,550,679 in year 3, €7,766,530 in year 4 and €7,964,808 in year 5. The NCPE's preferred scenario of administration which minimises potential risks identified by the EMA, infusions being administered in nurse-led clinics at a local hospital yields a gross

budget impact of €6,949,813 in year 1, €7,201,651 in year 2, €7,432,987 in year 3, €7,645,490 in year 4 and €7,840,693 in year 5. The cumulative 5 year budget impact is €37,070,632.

There remains uncertainty in terms of optimal dosing with human A1PI (Respreeza ®). Studies are currently underway to investigate whether patients would benefit from higher dosing i.e. 120mg/kg per week dose (double the licensed dose) which could in a 'worst case' scenario double the budget impact estimates.

5. Patient submissions

A patient submission was received from the Alpha- 1 Foundation.

6. Conclusion

Following The NCPE assessment of the applicant's submission, cost effectiveness of human alpha-1 proteinase inhibitor (Respreeza®) has not been demonstrated, at a threshold of €45,000/QALY, and therefore is not recommended for reimbursement.