Cost-effectiveness of Pirfenidone (Esbriet®) for the treatment of Idiopathic Pulmonary Fibrosis.

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1. Pirfenidone is indicated in adults for the treatment of mild to moderate Idiopathic Pulmonary Fibrosis (IPF). Pirfenidone was granted Orphan Drug status by the EMA and received Marketing Authorisation in February 2011. Intermune submitted an economic evaluation to the NCPE for the use of pirfenidone for the treatment of IPF compared to best supportive care (BSC) and triple therapy on 26th November 2012. The perspective of the analysis was that of the Health Service Executive (HSE).

2. IPF is defined as a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, and associated with the histopathologic and/or radiologic pattern of usual interstitial pneumonia (UIP). The estimated median survival time for patients with IPF is two to five years. Therapeutic treatment options are limited and, other than pirfenidone, there is currently no licensed therapy for IPF.

3. Evidence for the efficacy of pirfenidone includes three phase 3 RCTs (CAPACITY 004, CAPACITY 006 and the Japanese Shionogi study SP3), one phase 2 RCT (the Japanese study SP2) and an open label extension study to the CAPACITY studies (RECAP). Patient level data from the CAPACITY studies were used to inform the effectiveness of pirfenidone in the economic model. The primary outcome measure in the CAPACITY studies was the change in percent predicted forced vital capacity (FVC) from baseline to week 72.

4. The economic dossier was a cost utility analysis comparing pirfenidone with a pooled comparator of BSC and triple therapy (prednisolone, azathioprine and N-acetylcysteine) under the High Tech Drug (HTD) Scheme. It is estimated that triple therapy is prescribed for approximately 5% of IPF patients in specialist centres and 30% of IPF patients outside specialist centres in Ireland. Triple therapy is an unlicensed treatment option and the interim results of the PANTHER study showed increased mortality and hospitalisations with triple therapy compared with placebo. Consequently, the use of triple therapy is declining and it is no longer

recommended by professional organisations such as the British Thoracic Society. It is estimated that the use of triple therapy will decline to 0% over the next two years. Consequently, it will not be an appropriate comparator for pirfenidone in the long term. Pirfenidone was also compared with BSC separately in a scenario analyses.

5. The base case results of the manufacturer submission were derived from the subgroup of patients with mild to moderate disease and excluding patients with borderline obstructive disease (as defined by FEV1/FVC <0.8). The reason for this was to avoid confounding of treatment effect, due to an imbalance observed in CAPACITY 006 in patients with borderline obstructive disease. The presence of obstructive physiology and emphysema are associated with less decline in lung volume despite similar progression of fibrosis in the lungs. Such patients demonstrate an attenuated rate of decline in FVC which can mask the true effect of treatment on progression of IPF in terms of FVC changes. The NCPE Review Group have concerns in relation to the robustness of this subgroup analysis which is based on a post-hoc analysis.

6. A microsimulation model was constructed to estimate incremental costs and benefits in this population of patients. Patient level data was used to estimate the empirical relationship between FVC and 6 minute walk distance (6MWD) which was measured in the trials and the probability of IPF-related mortality and health related quality of life (HRQoL) which was required for the model. The placebo arms of CAPACITY trials were used to inform the regression equations that were used for the model. Patient level data from the INSPIRE study, comparing interferon-gamma with placebo in patients with mild to moderate IPF, was used to enrich the data set and provide more IPF-related mortality events. It was assumed that the treatment effect at 72 weeks would continue over a lifetime horizon.

7. There was no patient level data available for triple therapy and no direct evidence of the effectiveness of pirfenidone compared with triple therapy. The indirect effect was derived by multiplying the all-cause mortality

hazard ratio (HR) of placebo compared to triple therapy from the PANTHER trial (HR=0.11) by the IPF-related mortality HR of pirfenidone compared to placebo (HR=0.34) from the CAPACITY studies. The Review Group note that cautious interpretation of the indirect comparison with triple therapy is required, given the lack of robust evidence for relative effectiveness of triple therapy versus pirfenidone.

8. HRQoL was measured in the CAPACITY trials with the St Georges Respiratory Questionnaire (SGRQ) and WHO score for HRQoL and data was available up to 72 weeks. The utility values in the economic model were estimated by mapping the SGRQ scores predicted in the model onto the EQ5D. Long term data was predicted by linear regression using FVC and 6MWD as independent variables.

9. The base case ICER for pirfenidone (reimbursed under the HTDS) versus a pooled comparator of triple therapy and BSC was **€81,588/QALY**. Over a lifetime horizon, a patient receiving pirfenidone accrued 4.548 QALYs at a cost of €198,189. Patients receiving BSC accrued 3.114 QALYs at a cost of €49,365. Patients receiving triple therapy accrued 0.262 QALYs at a cost of €27,030. The ICERs for pirfenidone versus BSC and triple therapy were **€103,761/QALY** and **€39,935/QALY** respectively. The Review Group note that cautious interpretation of the base case analysis is required as it is based on a post-hoc subgroup analysis of patients with mild to moderate IPF excluding obstructive disease. The ICER for pirfenidone versus BSC in the full mild to moderate population was **€131,263/QALY**.

10. One-way and probabilistic sensitivity analysis (PSA) were appropriately conducted. The ICER for the base case scenario (mild to moderate patients excluding obstructive disease and comparing pirfendione with a pooled comparator) was most sensitive to the regression coefficient for IPF related mortality with the ICER increasing from €81,558/QALY (base case) to **€133,764/QALY** at the lower limit of the 95% confidence interval. The results were sensitive to a number of other parameters including the

QoL SGRQ mapping coefficient and the daily dosage of pirfenidone. The PSA demonstrates that there is a 0% probability that pirfenidone versus the pooled comparator is cost-effective in all mild to moderate patients excluding obstructive disease at a willingness to pay of €45,000/QALY.

11. The total number of patients anticipated to receive pirfenidone is estimated to be 97 in year one, increasing to 207 in year five. At a cost of €32,700 per patient per year, the gross budget impact was estimated to range from approximately €3.16 million in year 1 to approximately €6.76 million by year 5. The net budget impact was estimated to increase from € 3.0 million in year 1 to €6.34 million by year 5. This includes the cost offsets from replacing prescriptions for triple therapy and reduced length of stay in hospital for patients treated with pirfenidone.

12. The ICERs for pirfenidone versus a pooled comparator of triple therapy and BSC range from €81,558 to €131,263/QALY. These ICERs exceed the willingness to pay threshold of €45,000/QALY. Pirfenidone has been shown to have a modest but measurable effect on slowing decline in lung function in patients with mild to moderate IPF. This is a condition which has to date responded poorly or not at all to current therapeutic algorithms. Whilst pirfenidone may represent an important treatment option for patients with IPD there are significant uncertainties, including the absence of long term health outcome data.

13. In view of the high drug acquisition cost, the significant budget impact, the absence of long term clinical data and the fact that the product is not cost-effective we cannot recommend reimbursement of pirfenidone at the submitted price of €32,700 per patient per year. A mechanism such as a performance based risk sharing scheme and/or a significant reduction in price could facilitate access to pirfenidone for patients with IPF.