Cost-effectiveness of nintedanib (Ofev®) for the treatment of Idiopathic Pulmonary Fibrosis

The NCPE has issued a recommendation regarding the cost-effectiveness of nintedanib (Ofev®). Following NCPE assessment of the applicant's submission, nintedanib (Ofev®) is not considered cost-effective for the treatment of Idiopathic Pulmonary Fibrosis and therefore it is not recommended for reimbursement at the submitted price.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant's (Boehringer Ingelheim Ltd) economic dossier on the cost-effectiveness of nintedanib (Ofev®). 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 **February 2016**

Summary

In September 2015, Boehringer Ingelheim Ltd submitted a dossier for nintedanib (Ofev®) for reimbursement under the High Tech Drug Scheme. Nintedanib (Ofev®) is indicated in adults for the treatment of IPF. The only other licensed therapy is pirfenidone which is indicated in adults for the treatment of mild to moderate IPF. Current guidelines do not provide recommendations for one treatment regimen over another. Furthermore, it is anticipated that there will also be a small number of patients that will not be suitable for either agent and will be managed with best supportive care (BSC).

Nintedanib (Ofev®) is a small molecule tyrosine kinase inhibitor of PDGFRα and β, FGFR 1-3, and VEGFR 1-3. It was designated as an Orphan medicinal product in April 2013. The recommended dose for the treatment of IPF is 150mg orally twice daily. The 100mg twice daily dose is only recommended for use in patients who cannot tolerate the 150mg twice daily dose. Treatment is recommended to continue unless there are unacceptable adverse events.

1. **Comparative effectiveness of nintedanib**

- Evidence submitted to support the efficacy of nintedanib was derived from the phase II TOMORROW study and the phase III INPULSIS-1 and INPULSIS-2 studies. TOMORROW was a multicentre phase II randomised double blind placebo controlled study assessing efficacy and safety of four oral doses of nintedanib using a dose-escalation scheme (n=432). The primary endpoint was annual rate of FVC decline evaluated from baseline until 12 months of treatment. Key secondary endpoints included: acute exacerbations, quality of life (St George's Respiratory Questionnaire (SGRQ score)), total lung capacity and survival. In the group receiving the 150mg twice daily dose of nintedanib, FVC declined by 0.06 litres per year, as compared with 0.19 litres per year in the placebo group, a 68.4% reduction in the rate of loss with nintedanib ($p = 0.06$ with the closed testing procedure for multiplicity correction; $p = 0.01$ with the hierarchical testing procedure). A significant difference was also seen for this dose versus placebo in some clinically important secondary outcomes, including a lower proportion of patients experiencing acute exacerbation (2.4 vs. 15.7 per 100 patient-years, $p = 0.02$) and a significantly improved SGRQ

score.

INPULSIS-1 and INPULSIS-2 were two replicate randomised, double blind, placebo-controlled phase III studies evaluating the efficacy and safety of 150mg nintedanib twice daily across 205 sites across 24 countries (n=1,066). The primary endpoint was annual rate of FVC decline evaluated from baseline until 12 months of treatment. Key secondary endpoints included: time to first acute exacerbation (investigator reported) and quality of life (SGRQ score). All investigator reported acute exacerbations were confirmed and categorised by a blinded adjudication committee (Adjudicated Acute IPF exacerbations). Nintedanib significantly reduced the decline in FVC compared with placebo at 12 months. The results were statistically significant both when the studies were analysed individually and in a pre-specified analysis of the pooled data. Fewer people randomised to nintedanib died compared with placebo, but this difference was not statistically significant. The time to first acute exacerbation was inconsistent across the trials. The INPULSIS trials were not powered to detect the effect of nintedanib on acute exacerbations. Decline in FVC over one year has been shown to be associated with overall prognosis in patients with IPF and is correlated with survival time. A reduction in the rate of decline in FVC is widely considered to be consistent with a slowing of disease progression and it is now the preferred primary end point in IPF treatment trials. Although it is not a proven surrogate for mortality, the FDA recently highlighted that the relationship between FVC and mortality trends, in both the nintedanib and pirfenidone clinical trials, improves the reliability of FVC as a clinically relevant efficacy measure in IPF.

- There is no direct comparative evidence investigating effectiveness and safety of nintedanib versus the primary comparator pirfenidone. Therefore, the evidence for the safety and effectiveness of nintedanib versus its comparators for the economic model was derived from a network meta-analysis (NMA). The NMA included the three nintedanib trials and five placebo controlled trials of pirfenidone (SP2, SP3, CAPACITY 1, CAPACTIY 2 and ASCEND). The NMA was implemented in a Bayesian framework, using both fixed-effect and random-effect models. The results of the NMA suggest that nintedanib was more effective than pirfenidone at reducing loss of lung function and comparable in terms of overall survival; fewer acute exacerbations were demonstrated with nintedanib compared with pirfenidone. The review group

have a number of concerns with the results of this indirect comparison, in particular with regard to heterogeneity and potential sources of bias from included studies. Of note, the results of an independent NMA (Loveman et al) were more favourable for pirfenidone than nintedanib in terms of overall survival, loss of lung function and acute exacerbations. The impact of excluding studies from the NMA, when heterogeneity was identified, was determined in sensitivity analysis. Another limitation of the evidence derived from the NMA is that there is no direct evidence with which to assess consistency. An assessment of consistency between direct and indirect evidence can help to validate the findings of the NMA. In the absence of direct evidence, it must be accepted that inconsistency may be present.

2. Safety of nintedanib

- The most common adverse effect of nintedanib is diarrhoea. Overall nintedanib has a better tolerability profile and reduced dosing frequency compared with pirfenidone.
- In both INPULSIS trials, the proportion of patients with serious adverse events (SAEs) was similar in the nintedanib and placebo groups. AEs leading to study discontinuation were higher in the nintedanib group compared to placebo: 19% (123/638) versus 13% (55/423). Liver enzymes were elevated in 13.6% of nintedanib treated patients, this was reversible and not associated with clinically manifest liver disease. Arterial thromboembolic events were infrequently reported (0.7% of patients in the placebo group and 2.5% in the nintedanib treated group).
- The safety of nintedanib was compared to pirfenidone and placebo in the NMA. Serious cardiac event estimates for nintedanib and pirfenidone were similar to placebo. Nintedanib had a higher rate of gastrointestinal adverse events than placebo, whereas pirfenidone was similar to placebo for this outcome. Nintedanib reported a higher overall discontinuation compared to pirfenidone but less discontinuation due to adverse events.

3. Cost-effectiveness of nintedanib

Methods

- The model was a Markov model that estimated costs and health benefits over the

lifetime of the cohort. The main clinical outcomes represented in the model were overall survival, acute exacerbations and loss of lung function (FVC%Pred) which were derived from the available evidence from the INPULSIS trials. A 10-point categorization of FVC%Pred was used in the model, based on evidence from the literature and clinical opinion. The cohort entered the model at different FVC%Pred health states without exacerbation and could transition to: death, loss of lung function (progression to a health state with lower FVC%Pred), exacerbation, loss of lung function combined with exacerbation or remain in the same health state. The perspective of the HSE under the High Tech Drugs Arrangements was presented. A lifetime time horizon was applied with cycle lengths of three month and a half cycle correction was appropriately applied to all costs and benefits.

- The baseline risk of mortality (OS), acute exacerbations and decline of lung function (progression based on FVC%Pred) was derived from patients in the placebo arm of the TOMORROW and INPULSIS trials (representing BSC). The risk of those events was extrapolated beyond the period of the clinical trial follow-up using parametric survival analysis. The plausibility of the extrapolated portions of parametric survival models was assessed through the use of external data and/or clinical validity. The relative effectiveness of nintedanib and pirfenidone was obtained from a NMA performed on those matching outcomes. Similar to the efficacy parameters, the BSC overall discontinuation risk was calculated based on parametric modelling extrapolation of the clinical trial data, while the discontinuation risks for the active treatments were estimated using the ORs from the NMA. Furthermore, the incidence of serious cardiac events and serious GI events for the BSC arm was estimated from the placebo arm of the INPULSIS studies. The SAE risk for the active comparators were estimated using the ORs from the NMA. GI perforation events experienced in nintedanib treated patients, and photosensitivity reaction and rash in pirfenidone treated patient were also included.
- Health benefit was measured in quality adjusted life years (QALYs). Utility decrements related to acute exacerbation events were derived from the phase III INPULSIS trials. Disutilities for adverse events included serious cardiac events, serious GI events, skin disorders and GI perforation. The disutility for serious GI events was derived from the INPULSIS study and those for the other adverse events

were derived from a systematic review of the literature.

- Cost of active treatment includes drug acquisition costs for nintedanib and pirfenidone. Liver function tests were assumed to be performed on patients receiving pirfenidone and nintedanib every 3 months. Health state costs were estimated for each FVC%Pred category. The per-cycle probability of incurring resources (hospitalisation, A&E visits, outpatient visits and procedures) was calculated for each FVC%Pred group. The cost of an acute exacerbation included hospitalisation, A&E visit, GP visit and specialist visit. It was assumed that patients with an FVC%Pred <80% would receive supportive long-term oxygen supplementation. An end of life cost was applied for all patients who die in their last year of life. Costs of adverse events were also included.

Results

- The base case deterministic analysis demonstrated that nintedanib dominates pirfenidone (i.e. less costly and more effective). Pirfenidone was assessed by the NCPE in 2013 and cost-effectiveness was not demonstrated at the proposed price. It was reimbursed after a confidential discount was negotiated.
- The ICER of nintedanib versus BSC was €200,802/QALY and pirfenidone versus BSC was €278,330/QALY. Therefore, neither pirfenidone (at the list price) nor nintedanib at the proposed list price were found to be cost-effective versus BSC at the current willingness to pay (WTP) threshold of €45,000/QALY.

Sensitivity analysis

- The uncertainty associated with the ICERs were explored using one-way sensitivity analysis. The model results were particularly sensitive to the price of pirfenidone, baseline risk of overall survival, mortality probabilities and risk of discontinuation. When the model was run using the results from the independent NMA by Loveman et al, nintedanib was less costly and less effective than pirfenidone.
- All model input parameters were varied in probabilistic sensitivity analysis (PSA). The cost-effectiveness acceptability curve demonstrates that there is greater than 60% probability that nintedanib is cost-effective compared with pirfenidone at any threshold value. However, PSA results of nintedanib and pirfenidone versus BSC

demonstrate 0% probability that either active treatment is cost-effective at a WTP threshold of €45,000/QALY.

4. Budget impact of nintedanib

- Nintedanib is submitted for reimbursement under the High-tech drug scheme. The proposed ex-manufacturer price of nintedanib is €2,733.17 (60 x 100mg and 60 x 150mg). The annual cost of nintedanib and pirfenidone per patient is estimated at €32,788.36 and €38,340.36 respectively. Based on the applicant's estimate of the current eligible population, the projected cumulative gross budget impact over the first five years is almost €20 million (€543,100 in Year 1 rising to €6.74 million in Year 5).
- The applicant estimated that there would be net savings based on cost-offsets due to displacement of prescriptions for pirfenidone. However, this does not take into account the confidential discount on the price of pirfenidone.

5. Conclusion

Following NCPE assessment of the company submission, nintedanib (Ofev®) is not considered cost-effective for the treatment of IPF and therefore is not recommended for reimbursement at the submitted price.