Cost-effectiveness of nintedanib (Ofev®) for the treatment of adults with chronic progressive fibrosing interstitial lung disease (PF-ILD)

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of nintedanib (Ofev®). Following assessment of the Applicant's submission, the NCPE recommends that nintedanib (Ofev®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments*.

The HSE asked the NCPE to carry out an assessment of the Applicant's (Boehringer Ingelheim) Health Technology Assessment 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.

**This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.*

National Centre for Pharmacoeconomics **June** **2021**

Summary

In November 2020, Boehringer Ingelheim submitted a dossier which investigated the clinical effectiveness, cost effectiveness and potential budget impact of nintedanib (Ofev®) for the treatment of adults with chronic, progressive fibrosing interstitial lung disease (PF-ILD), other than idiopathic pulmonary fibrosis (IPF). Reimbursement is sought for this indication under the High Tech Drug Arrangement.

Nintedanib received marketing authorisation from the EMA for the treatment of PF-ILD in March 2020, having been licensed for the treatment of IPF since January 2015 and systemic sclerosis associated interstitial lung disease since February 2020. In February 2016, nintedanib was not recommended for reimbursement for the treatment of IPF following assessment by the NCPE. Nintedanib was subsequently reimbursed by the HSE, in June 2017, for the treatment of IPF following confidential price negotiations.

Nintedanib is a small molecule that inhibits a distinct spectrum of tyrosine kinases, whose downstream signalling cascades have been shown to be involved in the pathogenesis of fibrotic tissue remodelling. Nintedanib is taken orally at a dose of 150mg twice daily. Treatment interruptions or dose reductions to 100mg twice daily are allowed in the event of an adverse reaction; once resolved, the full dose (150mg twice daily) can be recommenced.

Nintedanib is the only licensed therapy for PF-ILD. Best supportive care (BSC) in PF-ILD in Irish clinical practice comprises unlicensed therapies such as high-dose corticosteroids and immunomodulators (such as rituximab and mycophenolate). Nintedanib is intended to be used as an add-on therapy to BSC in clinical practice.

1. Comparative effectiveness of nintedanib

The clinical efficacy of nintedanib in adults with PF-ILD was investigated over 52 weeks in a double-blind, placebo-controlled, phase III trial, INBUILD. Patients with PF-ILD affecting ≥10% of lung volume and with fibrosis that has demonstrated progression over the past 24 months were recruited. Unlicensed therapies used to treat PF-ILD in clinical practice (such as high-dose corticosteroids, mycophenolate and rituximab) were prohibited in the weeks prior to recruitment and were restricted in both treatment arms for the first six months of

the trial. As such, participants in both treatment arms had limited treatment options that the Review Group do not consider to be fully reflective of BSC in Ireland.

The trial population (n=663) was planned to be enriched with participants who had a usual interstitial pneumonia (UIP)-like fibrotic pattern (n=412) compared with patients who had other fibrotic patterns (n=251). However, no active intervention was required to achieve this. Participants were randomised in a 1:1 ratio to receive nintedanib 150mg twice daily (n=332) or placebo (n=331). The primary efficacy endpoint was annual rate of decline in forced vital capacity ((FVC); ml/year)) at week 52, measured in both co-primary populations (i.e. the overall trial population and those with a UIP-like fibrotic pattern). A statistically significant result was achieved if the analyses (primary efficacy endpoint) in both co-primary populations were significant at the two-sided 5% level, or if the analysis in either co-primary population was statistically significant at the two-sided 2.5% level. Secondary exploratory endpoints included ILD-specific, health-related quality of life measured using the K-BILD questionnaire, time to first acute exacerbation or death and time to death over 52 weeks. The majority of INBUILD participants were male (54%) and the mean age was 65.8 years. Baseline characteristics were balanced across treatment groups. The primary efficacy endpoint was significant at the two-sided 5% level in both co-primary populations (Table 1). However, the reduction in the annual rate of FVC decline was not as large in the population with other fibrotic patterns, although this was an exploratory endpoint and did not undergo formal hypothesis testing.

Table 1 Annual rate of decline in FVC (mL/year) over 52 weeks in the INBUILD trial

Treatment	Adjusted rate of decline of FVC over 52 weeks (mL/year)	Comparison vs. placebo		
		Adjusted difference*	95% CI	p-value
Overall population				
Placebo, n=331	-187.78			
Nintedanib 150mg b.d., n=332	-80.82	106.96	(65.42, 148.50)	<0.0001
Patients with a UIP-like fibrotic pattern				
Placebo, n=206	-211.07			
Nintedanib 150mg b.d., n=206	-82.87	128.2	(70.81, 185.59)	<0.0001
Patients with other fibrotic patterns				
Placebo, n=125	-154.24			
Nintedanib 150mg b.d., n=126	-78.97	75.28	(15.54, 135.01)$^{\alpha}$	

FVC=forced vital capacity; **CI**=confidence interval; **UIP**=usual interstitial pneumonia; **b.d**.=twice daily

[*]Based on a random coefficient regression with fixed effects for treatment, high-resolution computed tomography pattern (only for the overall population) and baseline FVC[mL], and including treatment-by-time and baseline-by-time interactions. Within-patient errors were modelled by an unstructured variance-covariance matrix.
[α]Nominal p-value 0.0137

In the overall population, an acute exacerbation or death over 52 weeks was experienced in 7.8% of the nintedanib group compared with 9.7% of the placebo group; time to acute exacerbation or death hazard ratio ((HR) = 0.80, 95% CI 0.48 to 1.34). Similarly, no treatment benefit with regards time to death was observed for nintedanib over 52 weeks in the overall population (HR 0.94, 95% CI 0.47 to 1.86). In the cost-effectiveness analysis, results from database lock two, which occurred approximately four months after all patients had completed 52 weeks (Table 2), were used to inform efficacy parameters.

Table 2 Additional endpoints from the INBUILD trial assessed during period until database lock two (11 September 2019)

Endpoint	**Nintedanib (N = 332)**	**Placebo (N = 331)**	**HR (95% CI)**
Acute exacerbation or death (no. with event/total no. [%])			
Overall population	46/332 (13.9%)	65/331 (19.6%)	0.67 (0.46, 0.98)
Patients with UIP-like fibrotic pattern	31/206 (15%)	47/206 (22.8%)	0.62 (0.39, 0.97)
Death (no. with event/total no. [%])			
Overall population	36/332 (10.8%)	45/331 (13.6%)	0.78 (0.50, 1.21)
Patients with UIP-like fibrotic pattern	25/206 (12.1%)	36/206 (17.5%)	0.66 (0.40, 1.10)

CI=confidence interval; **UIP**=usual interstitial pneumonia; **HR**=Hazard Ratio.

The Review Group had concerns about the generalisability of efficacy results from the placebo arm of the INBUILD trial to Irish clinical practice, given that unlicensed therapies used as part of BSC were restricted for the first six months of the trial. In addition, the efficacy of nintedanib is driven by efficacy in the population with a UIP-like fibrotic pattern. Also, INBUILD did not have sufficient follow-up and was not statistically powered to detect significant differences in overall survival (OS) between treatment groups.

2. Safety of nintedanib

The safety profile of nintedanib in the population with PF-ILD is generally consistent with the known safety profile of nintedanib in the population with IPF. Safety analyses in the PF-ILD population were based on all patients who received at least one dose of trial medication in the INBUILD trial (n=663). Data from database lock two indicated the mean duration of exposure was 15.6 months (SD 7.2 months) for nintedanib compared with 16.8 months (SD 5.8 months) for placebo. Premature discontinuation was more common in the nintedanib group (25.3%) compared with the placebo group (17.2%). The most frequently reported

treatment-emergent adverse events in the nintedanib group over the 52 weeks of the INBUILD trial were diarrhoea (59%), nausea (23.8%), vomiting (12.3%), decreased appetite (11.1%) and alanine aminotransferase elevation (10.8%). Most gastrointestinal adverse events were of mild to moderate intensity and were managed with anti-diarrhoeal therapy, dose reduction or treatment interruption. Adverse events that led to a permanent dose reduction and treatment discontinuation, respectively, were reported in substantially higher proportions in the population treated with nintedanib (33.1% and 19.6% respectively) compared with the placebo group (4.2% and 10.3% respectively). As per the SPC, liver enzymes should be measured prior to commencing nintedanib and at regular intervals throughout treatment.

3. Cost effectiveness of nintedanib

The cost effectiveness of nintedanib was assessed using a Markov model with a cycle length of three months and a lifetime horizon. The model defined nine health states based on differing levels of FVC percentage predicted (FVC%Pred), as well as a death state. The model health states were further stratified by whether or not patients had experienced an acute exacerbation event. The comparator in the model was BSC, with efficacy data informed by the placebo arm of INBUILD. The distribution of patients across health states at baseline was informed by INBUILD. Transitions to health states of lower FVC%Pred were based on a model for lung function decline using data from INBUILD. Mortality was modelled based on a standard parametric survival extrapolation using data from INBUILD combined with an informative prior using data from trials in patients with IPF.

Treatment effectiveness was modelled through slower progression of lung function decline, reduced risk of experiencing an acute exacerbation and reduced risk of mortality. Patients discontinuing nintedanib were assumed to maintain the reduced risk of mortality associated with nintedanib. The rationale provided by the Applicant for this assumption was that participants in the INBUILD trial who discontinued nintedanib were also included in the generation of the OS extrapolation for nintedanib. However, as survival benefits for nintedanib mainly accumulate over the extrapolated portion of the model, the Review Group noted there was considerable uncertainty associated with assuming a continued survival benefit in patients who discontinue nintedanib. This was explored in scenario analysis. The Review Group did not consider the Applicant's chosen extrapolation of OS

(Bayesian Weibull model) to be appropriate due to concerns about using data from patients with IPF to predict likely OS outcomes in patients with PF-ILD. The Review Group note that having a UIP-like fibrotic pattern is an essential diagnostic criterion associated with IPF, whereas this is not the case in PF-ILD. While 62% of the INBUILD trial population had a UIP-like fibrotic pattern, there is uncertainty over whether the use of data from patients with IPF is reflective of fibrotic patterns observed in the population with PF-ILD in clinical practice. In the NCPE adjusted base case, a Frequentist Weibull model based on extrapolation of the OS INBUILD trial data (database lock two) was chosen to inform OS in the cost-effectiveness model. An exponential model was used to extrapolate time to discontinuation data from INBUILD, yielding a constant rate. The Review Group did not consider a constant rate to be appropriate and considered that discontinuation was likely to be overestimated, based on clinical opinion obtained by the Review Group. In the NCPE adjusted base case, the discontinuation rate was adjusted downwards in order to capture a discontinuation plateau. The Applicant further assumed a decrement in utility following an acute exacerbation event to occur for a period of one month. In the NCPE adjusted base case, this decrement was extended to a continuous reduction (at half the value of the initial reduction beyond one month).

EQ-5D utility data were collected as part of the INBUILD trial for modelling purposes only but did not form part of the CHMP assessment of nintedanib. EQ-5D data were categorised by FVC%Pred group, as per the health state descriptions. EQ-5D-5L data were mapped onto the EQ-5D-3L using the Van Hout mapping algorithm. The Review Group noted uncertainty arising from the lack of transparency in analytic methods that were used to obtain mean utility values for each health state. In addition, comparatively small sample sizes informed utility values. Costs relating to drug acquisition, adverse events and liver function tests were applied, with healthcare utilisation data sourced from INBUILD.

The key driver of the model was the probability of mortality, as derived from the extrapolation of OS. A further key driver was that patients who discontinue nintedanib would maintain a mortality benefit rather than reverting to the same risk as for BSC.

Results

Deterministic incremental cost-effectiveness ratios (ICERs) generated under the NCPE adjusted base case and the Applicant's base case assumptions are shown in Table 3 and Table 4 respectively.

Table 3: Deterministic results from NCPE adjusted base case cost-effectiveness analysis

Treatment	Incremental Costs (€)	Incremental QALYs	ICER (€ per QALY)
BSC	-	-	-
Nintedanib	95,271	1.18	80,804

ICER = incremental cost-effectiveness ratio; **QALY** = quality-adjusted life year; **BSC** = best supportive care;
Note: A discount rate of 4% on costs and outcomes is applied. Figures in the table are rounded, and so calculations will not be directly replicable.

Table 4: Deterministic results from Applicant's base case cost-effectiveness analysis

Treatment	Incremental Costs (€)	Incremental QALYs	ICER (€ per QALY)
BSC	-	-	-
Nintedanib	81,999	1.93	42,382

ICER = incremental cost-effectiveness ratio; **QALY** = quality-adjusted life year; **BSC** = best supportive care;
Note: A discount rate of 4% on costs and outcomes is applied. Figures in the table are rounded, and so calculations will not be directly replicable.

Probabilistic ICERs were similar to the deterministic ICERs. In the NCPE adjusted base case, the probability of nintedanib being cost-effective compared with BSC was 3.8% at a threshold of €45,000 per QALY and 0% at a threshold of €20,000 per QALY.

The Review Group consider the assumption that patients who discontinue nintedanib will continue to follow the survival trajectory associated with nintedanib in the long-term to be highly uncertain, given the mean exposure time on nintedanib was 15.6 months. Scenario analyses conducted on the NCPE adjusted base case indicated that, should patients who discontinue nintedanib revert to the same risk of mortality as the BSC treatment arm, the ICER would be substantially higher (€188,517 per QALY).

4. Budget impact of nintedanib

The price to wholesaler of a pack of 60 x 150mg nintedanib capsules is €2,278.89, while the price to wholesaler of 60 x 100mg capsules is €1,872.30. The Applicant anticipates that 79% of patients on nintedanib will be treated at a dose of 150mg twice daily, while the remaining proportion will take nintedanib at a dose of 100mg twice daily, which the Review Group consider a plausible estimation. The weighted annual treatment cost per patient was estimated to be €28,117.95, inclusive of pharmacy fees and rebate. The Applicant estimates that 24 patients will be treated in year one, rising to 114 in year five. BSC was the only comparator in the budget impact estimates, with a treatment cost of zero assumed, as nintedanib is considered an add-on therapy. The Review Group did not agree with the Applicant's estimated mortality rate and considered it more appropriate to use the mortality rate observed across both treatment arms in the INBUILD trial. Using an annual

discontinuation rate of 19.6%, the Review Group estimated the five-year cumulative gross (and net) drug budget impact to be €12.69 million. The Review Group consider that the market share assumed for nintedanib is underestimated given that it is the only licensed therapy for PF-ILD. Sensitivity analyses regarding market share estimates conducted by the Review Group indicated the drug budget impact could increase noticeably if there was a moderate increase in nintedanib's market share. If current market share estimates were to increase by 60% (equivalent to nintedanib having market share of 11.2% in year one (n=38), rising to 51.2% in year five (n=183)), the five-year cumulative drug budget impact of nintedanib could be in excess of €20 million.

5. Patient submissions

A Patient Organisation Submission was received from the Irish Lung Fibrosis Association during the course of this assessment and will form part of the data that the HSE considers.

6. Conclusion

Following assessment of the Applicant's submission, the NCPE recommends that nintedanib (Ofev®) not be considered for reimbursement unless cost effectiveness can be improved relative to existing treatments*.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.