Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2331

nintedanib 100mg and 150mg soft capsules (Ofev®)

Boehringer Ingelheim

07 May 2021

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 NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission considered under the orphan equivalent process:

nintedanib (Ofev®) is accepted for use within NHSScotland.

Indication under review: in adults for the treatment of chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype other than idiopathic pulmonary fibrosis (IPF).

Nintedanib, compared with placebo, slowed the decline in forced vital capacity (FVC) in adults with non-IPF progressive fibrosing ILD.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

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

Chairman
Scottish Medicines Consortium

Indication

In adults for the treatment of chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype other than idiopathic pulmonary fibrosis (IPF).[1]

Dosing Information

Nintedanib 150mg orally twice daily administered with food approximately 12 hours apart. The capsules should be swallowed whole with water, and should not be chewed or crushed. The 100mg twice daily dose is only recommended to be used in patients who do not tolerate the 150mg twice daily dose. Dose adjustment to manage adverse events are detailed in the summary of product characteristics (SPC).
Treatment should be initiated by physicians experienced in the management of diseases for which nintedanib is approved.[1]

Product availability date

13 July 2020
Nintedanib meets SMC orphan equivalent criteria.

Summary of evidence on comparative efficacy

Nintedanib is a tyrosine kinase inhibitor that blocks vascular endothelial growth factor receptors 1-3, fibroblast growth factor receptors 1-3 and platelet-derived growth factor receptors α and β kinase, thereby inhibiting the proliferation, migration and transformation to myofibroblast of lung fibroblasts.[1]

A double-blind phase III study (INBUILD) recruited adults with physician-diagnosed progressive fibrosing ILD (PF-ILD), which was not IPF. They had fibrosing disease affecting at least 10% of lung volume, disease progression within the preceding two years despite standard treatment, forced vital capacity (FVC) ≥45% predicted and carbon monoxide diffusion capacity (DLco) ≥30% to <80% predicted. Randomisation was stratified by presence of usual interstitial pneumonia (UIP) on centrally-reviewed high resolution computed tomography and patients were equally assigned to double-blind treatment with nintedanib 150mg orally twice daily or placebo until all patients had completed at least 52 weeks of treatment. The primary outcome, annual rate of decline in FVC, was assessed over the first 52 weeks in patients who received at least one dose of study drug in two primary populations: the overall study population and the subgroup with UIP.[2, 3]

In the overall population and the UIP subgroup the annual rate of FVC decline was significantly smaller within the nintedanib group compared with placebo as detailed in Table 1 below. Results in the other fibrotic pattern (non-UIP) subgroup are also detailed, although this was not one of the primary analyses populations. All other outcomes were exploratory and not formally tested. Two of the main secondary outcomes, time to first acute exacerbation or death and time to death, are detailed in Table 2.[2, 3]

Table 1: Annual decline in forced vital capacity (FVC) in INBUILD study.[2, 3]

	Number of patients		Rate of decline in FVC at week 52 (mL/year)		
	Nintedanib	Placebo;	Nintedanib	Placebo	Difference (95% CI)
Overall population	332	331	-80.8	-187.8	107.0 (65.4; 148.5)*
UIP subgroup	206	206	-82.9	-211.1	128.2 (70.8; 185.6)*
Other fibrosis subgroup	126	125	-79.0	-154.2	75.3 (15.5; 135.0)

CI = confidence interval; FVC = forced vital capacity; UIP = usual interstitial pneumonia; * p<0.001

Table 2: Main secondary outcomes in INBUILD study.[2, 3]

	Nintedanib		Placebo		Hazard ratio (95% confidence interval)
	N	Events	N	Events	
Acute exacerbation or death at week 52					
Overall population	332	26	331	32	0.80 (0.48 to 1.34)
UIP subgroup	206	17	206	25	0.67 (0.36 to 1.24)
Death at week 52					
Overall population	332	16	331	17	0.94 (0.47 to 1.86)
UIP subgroup	206	11	206	16	0.68 (0.32 to 1.47)

CI = confidence interval; N = number of patients; UIP = usual interstitial pneumonia

Supportive analyses over the whole double-blind period of time to acute exacerbation or death indicated hazard ratio (HR) of 0.67 (95% confidence interval [CI]: 0.46 to 0.98) in the overall study population and 0.62 (95% CI: 0.39 to 0.97) in the UIP subgroup. Similar analyses of overall survival indicated HR of 0.70 (95% CI: 0.43 to 1.15) in the overall study population and 0.63 (95% CI: 0.36 to 1.10) in the UIP.[2, 4]

Health Related Quality of Life was assessed using the King's Brief Interstitial Lung Disease (K-BILD) questionnaire, the third main secondary outcome, and the Living with Pulmonary Fibrosis Symptoms and Impact Questionnaire (L-PF). There were small changes from baseline to week 52 in the K-BILD scores in both the nintedanib and placebo groups, but changes in the dyspnoea and cough symptom domains of L-PF suggest possible benefits with nintedanib. Results are detailed in Table 3.

Table 3: Quality of life outcomes in INBUILD study.[2]

	Number of patients		Mean change		Difference
	Nintedanib	Placebo	Nintedanib	Placebo	95% CI
Adjusted Mean Change from baseline to week 52 in K-BILD Total Score					
Overall population	332	330	0.55	-0.79	1.34 (-0.31 to 2.98)
UIP subgroup	206	205	0.75	-0.79	1.53 (-0.68 to 3.74)
Adjusted Mean Change from baseline to week 52 L-PF Dyspnoea Domain					
Overall population	329	323	4.28	7.81	-3.53 (-6.14 to -0.92)
UIP subgroup	204	201	4.14	8.32	-4.18 (-7.48 to -0.88)
Adjusted Mean Change from baseline to week 52 L-PF Cough Domain					
Overall population	327	320	-1.84	4.25	-6.09 (-9.65 to -2.53)
UIP subgroup	203	199	-3.20	4.09	-7.28 (-11.86 to -2.71)

CI = confidence interval; K-BILD = King's Brief Interstitial Lung Disease questionnaire (range 0 to 100, with higher score indicating better health); L-PF = Living with Pulmonary Fibrosis Symptoms and Impact Questionnaire (range 0 to 100, with higher score indicating greater impairment); UIP = usual interstitial pneumonia

To support the economic analysis, an assumption was made within the submission that disease progression in patients with PF-ILD and the effect of nintedanib on overall survival will be similar to that in patients with IPF. This was supported by a published report of a comparison between the placebo groups of the INBUILD study (in PF-ILD) and INPULSIS-1 and -2 studies (in IPF), which

suggested that there is a relationship between decline in FVC and overall survival in the INPULSIS studies and in the INBUILD study within the overall population and UIP subgroup. There were too few deaths in the non-UIP subgroup to draw conclusions on a relationship with FVC.[5] Also presented were Bayesian analyses of overall survival, which were informed via a matched (by propensity scoring) comparison of the INBUILD study[2, 3] with four studies of nintedanib in patients with IPF: the IMPULSIS-1 and -2, IMPULSIS-ON and TOMORROW.[6-8]

Summary of evidence on comparative safety

The European Medicines Agency (EMA) review noted that the safety profile of nintedanib in the INBUILD study overall was consistent with its known safety profile in IPF including post-marketing data. In the INBUILD study the mean duration of treatment over 52 weeks was 10.3 months in the nintedanib group and 11.2 months in the placebo group (median 12.2 months in both groups). Within the respective groups 96% (317/332) and 89% (296/331) had a treatment-emergent adverse events, which were treatment-related in 79% and 38% of patients and were serious in 32% and 33% of patients. Within the nintedanib group, compared with placebo, there were higher rates of adverse events leading to permanent dose reduction, 33% versus 4.1% and study discontinuation, 20% versus 10%, respectively. Fatal adverse events occurred in 3.3% and 5.1% of patients in the respective groups and fatal adverse events excluding progression of ILD occurred in 3.0% and 4.2% of patients, respectively.[2, 3]

Within the nintedanib group, compared with placebo, gastrointestinal adverse events were reported more frequently, 81% versus 45%, including diarrhoea (67% versus 24%), nausea (29% versus 9.4%), vomiting (18% versus 5.1%) and abdominal pain (10% versus 2.4%). Abnormal liver function (5.7% versus 0.9%) and elevated liver enzymes were reported at higher rates in the nintedanib group compared with placebo: 13% versus 3.6% for alanine aminotransferase; 11% versus 3.6% for aspartate aminotransferase; and 5.7% versus 2.1% for gamma-glutamyltransferase, respectively.[2]

Summary of clinical effectiveness issues

PF-ILD comprises a range of fibrosing ILD with various aetiologies (hypersensitivity pneumonitis, autoimmune conditions, interstitial pneumonia that is non-specific or unclassifiable) that have a progressive phenotype. There are no defined standard criteria for diagnosis, which is usually made by specialists. It has been managed with corticosteroids (first-line) and immunosuppressants, which are used off-label.[2] Prior to nintedanib, there were no medicines licensed for treatment of PF-ILD. Clinical experts consulted by SMC note that there is an unmet need for effective medicines that are licensed for the treatment of PF-ILD.

Nintedanib is likely to be added to existing treatments for PF-ILD and may reduce the use of these. It meets SMC orphan equivalent criteria in this indication.

In the INBUILD study nintedanib, compared with placebo, was associated with a significant decrease in the annual rate of decline in FVC of 107mL/year in the total study population and

128mL/year in the UIP subgroup. Within the other fibrotic pattern (non-UIP) subgroup, which the study was not designed to assess, there appears to be a possible benefit with nintedanib of about 75mL/year.[2, 3]

The death rates were low over 52 weeks (5.1% and 4.8% in the nintedanib and placebo groups, respectively) and over the whole double-blind period (8.1% and 11%). These outcomes were not formally tested and the data do not support definitive conclusions. Potential effects of nintedanib, compared with placebo, appear smaller in the analyses over 52 weeks, compared with the supportive analyses over the whole double-blind period for time to acute exacerbation or death and for overall survival.[2, 3]

The population recruited to the INBUILD study was highly selected and not fully representative of patients eligible within the PF-ILD indication; for example, only 5% of patients had environmental or occupational fibrosing lung diseases, only 1.8% had sarcoidosis and patients with idiopathic pneumonia with autoimmune features were not enrolled. Also, in the group with autoimmune ILD, the majority had rheumatoid arthritis. An ad hoc expert group convened during the EMA review considered that extrapolation of data to under- and not-represented groups was a realistic option, especially due to the similar pathological mechanisms and feasibility issues for conducting studies in rare conditions. However, the expert group considered sarcoidosis separately as a special case as it is more common than many of the other diseases and noted that using nintedanib in preference to other second-line therapies for sarcoidosis may not be beneficial and this should be reflected in the review. The expert group also noted that although the INBUILD study only included patients with disease progression on standard treatment, there should be no need to explicitly limit the indication to first- or second-line treatment. The EMA recommended that nintedanib could be indicated for patients with fibrosing ILD with a progressive phenotype, but recommended that further data in post-marketing setting for different phenotypes should be generated.[2]

Patients with significant pulmonary hypertension and cardiovascular disease were excluded from the INBUILD study. The SPC recommends that nintedanib should not be used in patients with severe pulmonary hypertension and close monitoring is recommended in mild to moderate pulmonary hypertension.[2] Caution should be used when treating patients at higher cardiovascular risk including known coronary artery disease.[1]

In the INBUILD study rheumatoid arthritis and connective tissue disease medications were allowed at stable doses at baseline and during the study with the exception of the following (less frequently used) medications: azathioprine, cyclosporine, tacrolimus, high dose steroids, rituximab, cyclophosphamide and mycophenolate mofetil. These were not allowed during the initial six months in the study but could be initiated after that at the discretion of the investigator in the case of significant deterioration. However, there is no information on the efficacy and safety of nintedanib in combination with them in patients with PF-ILD.

The Bayesian analyses that informed overall survival estimates in the economic case had some limitations, including data immaturity and observed differences between the UIP and non-UIP subgroups of the INBUILD study in placebo group overall survival and nintedanib therapeutic effects. The matching process within the Bayesian analyses included demographic variables (age, race, sex) smoking status, time since diagnosis, percent predicted FVC, percent predicted DLco and

underlying diagnosis group, but did not account for differences across the studies in fibrotic pattern, which may be particularly relevant for the non-UIP subgroup as they differ in this respect from both the UIP subgroup and IPF patients (who have UIP identified during diagnosis of IPF). Also, the INBUILD study had no or under representation of some types of PF-ILD.

Clinical experts consulted by SMC considered that nintedanib is a therapeutic advancement as it is the first anti-fibrotic medicine licensed for PF-ILD. They considered that its place in therapy would be in addition to standard care and the introduction of this medicine would have minimal impact on service delivery.

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 nintedanib, as an orphan-equivalent medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- PF-ILD are a range of pulmonary diseases characterised by progressive irreversible fibrotic lung damage, increasing difficulties with breathing and physical activities, leading to dependence on oxygen and assistance from family with activities of daily living. Patients can have exacerbations, which require hospitalisation and PF-ILD markedly reduces their life expectancy. They may have to give up work and social activities and often suffer anxiety and depression.
- The disease has a devastating impact and patients are often aware (through support groups and social media) of the benefits of nintedanib in patients with one particular PF-ILD, IPF for which this medicine is available within NHS Scotland. They can feel an acute sense of injustice and unfairness in not being able to receive this medicine and accessing this medicine would provide reassurance they are receiving optimum treatment.
- There are no other medicines licensed for PF-ILD and it is currently managed with corticosteroids and immunosuppressants, which have a poorer safety profile compared with nintedanib. There is an unmet need for effective treatments for PF-ILD, which stabilise or slow progression.
- Nintedanib reduces the rate of decline in respiratory function in patients with PF-ILD and may have the potential to reduce exacerbations and prolong life. It may extend the period when patients are independent and able to work and socialise, thereby improving quality of life for the patient's life and their carers.

Additional Patient and Carer Involvement

We received a patient group submission from Action for Pulmonary Fibrosis, which is a registered charity. Action for Pulmonary Fibrosis has received 8% pharmaceutical company funding in the past two years, including from the submitting company. A representative from Action for

Pulmonary Fibrosis Scotland participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The submitting company provided a cost-utility analysis evaluating nintedanib for the treatment of chronic fibrosing ILDs with a progressive phenotype other than IPF. This compared nintedanib versus best supportive care (BSC) on the basis that there are no alternative therapies licensed for the treatment of PF-ILD within NHSScotland.

A *de novo* economic model was created in the form of a Markov state-transition cohort model, stratified by prior exacerbation status, covering a total of 6 core health states. Health states were primarily defined according to patients' % of their predicted FVC and were categorised as follows (30-39.9, 40-49.9, 50-99.9, 100-109.9 and ≥110). Patients could transition to the absorbing state of death at any time. A three-month cycle length was used with a lifetime time horizon.

Clinical effectiveness data were primarily obtained from the phase 3 randomised INBUILD study[3], which informed initial health state distribution, health state transition probabilities, time to first acute exacerbation, overall survival, treatment discontinuation and adverse events among others parameters. Health state transition probabilities were estimated using a multivariate mixed effects logistic regression analysis and the per-cycle probability of experiencing an exacerbation was estimated by fitting the exponential distribution, which was selected for a combination of statistical fit and model simplicity. To estimate overall survival, the company adopted a Bayesian analytic framework, combining data from the INBUILD study with longer-term follow-up data on nintedanib for patients with IPF. Based on feedback from clinicians and a visual comparison of the fitted curves versus registry data, the Bayesian Weibull distribution was selected by the submitting company to extrapolate survival beyond the study follow-up period.

The majority of utility values were estimated from a pooled analysis of EQ-5D-3L data collected during the INBUILD study. Utility values were estimated separately for individual health states. A utility decrement was applied to the proportion of patients experiencing an exacerbation per cycle. No adjustments were made for covariates and disutilities were estimated for gastrointestinal events.

Medicine acquisition costs for nintedanib were included in the analysis however no costs were included for BSC. The dose and duration of nintedanib was assumed to be 150mg twice daily indefinitely and no administration costs were included for nintedanib on the basis that it is an oral therapy. Resource use was estimated using data collected during the INBUILD study; a post-hoc analysis of the data allowed the type and intensity of resource use to be calculated according to a patient's health state. Where data on resource use were not available from this study (e.g. acute exacerbation, frequency of liver function tests) data from a study of nintedanib in patients with IPF (INPULSIS)[6] were used or assumed to be equal to that stated in the summary of product characteristics. Adverse events were assumed to require a GP visit to resolve and patients who discontinued treatment with nintedanib were assumed to incur costs equal to that for BSC.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price. The base-case economic results for nintedanib versus BSC at list price was an incremental cost-effectiveness ratio (ICER) of £44,013.

SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish these results. As such, only the without-PAS figures can be presented.

Disaggregated analyses indicate that incremental costs associated with nintedanib are primarily from purchase of the medicine itself as well as greater costs associated with patient monitoring and oxygen use. The majority of incremental QALYs associated with nintedanib appear to be from anticipated improvements in life expectancy for nintedanib relative to BSC.

Key scenario analyses at list price are shown in Table 4 and indicate that the cost-effectiveness of nintedanib is upwardly sensitive to the use of alternative frequentist survival extrapolations and different discontinuation assumptions.

Table 4: Key scenario analyses (list price)

Scenario	Description		ICER (£/QALY)
0	Base case		44,013
1	Time horizon	10 years	53,302
2		20 years	41,816
3	No impact of nintedanib on declining lung function		44,390
4	Discontinuation	INBUILD study	52,950
5		None	92,697
6	Alternative utility values from IPF population		39,384
7	Frequentist survival analysis	Exponential	97,330
8		Generalised gamma	91,462
9		Log-normal	34,647
10		Log-logistic	45,877
11		Weibull	63,229
12	Bayesian survival analysis	Gamma	48,623
13		Log-logistic	40,563

Abbreviations: QALY, quality adjusted life year; ICER, Incremental cost-effectiveness ratio; IPF, idiopathic pulmonary fibrosis; NR, not reported

The following limitations are noted regarding the economic evaluation:

- The analysis used to inform the relative effectiveness of nintedanib versus BSC at reducing deterioration in lung function in the economic evaluation finds no statistically significant effect. This is inconsistent with findings from the INBUILD study but reflects that fact that data have been transformed and analysed differently for use in the economic evaluation. Furthermore, a scenario analysis where no difference in effectiveness on lung function is

assumed has minimal impact on results (scenario 3) suggesting that the incremental QALYs associated with nintedanib are the result of an estimated increase in life expectancy.

- In the absence of directly demonstrated survival benefit, the company used a novel Bayesian analytic framework to estimate overall survival. This is reliant on the assumption of similar disease trajectories for patients with PF-ILD and IPF, which is associated with uncertainty. Use of a standard frequentist analytic framework for overall survival produced a range of results (table 4, scenarios 7-11).
- The patient population enrolled in the INBUILD study was highly selected and it was noted that not all types of ILDs with progressive behavior were sufficiently represented in the study. It is therefore unclear how valid cost-effectiveness estimates based on this study will be for the PF-ILD population in general.

The Committee considered the benefits of nintedanib in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as nintedanib is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted nintedanib for use in NHSScotland.

*Other data were also assessed but remain confidential.**

Additional information: guidelines and protocols

There are no guidelines for the management of PF-ILD.

Additional information: comparators

There are no other medicines licensed for PF-ILD.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
Nintedanib	100mg or 150mg orally twice daily	26,100

Costs from BNF online on 14.01.21. Costs do not take patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 81 patients eligible for treatment with nintedanib in each year, to which confidential estimates of treatment uptake were applied.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain confidential.**

References

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This assessment is based on data submitted by the applicant company up to and including 11 March 2021.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine 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.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

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.