NICE National Institute for Health and Care Excellence

NICE guidance

Nintedanib for treating idiopathic pulmonary fibrosis when forced vital capacity is above 80% predicted

Technology appraisal guidance
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www.nice.org.uk/guidance/ta864

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

This guidance partially replaces TA379.

1 Recommendations

1.1 Nintedanib is recommended as an option for treating idiopathic pulmonary fibrosis in adults, only if:

- they have a forced vital capacity of above 80% predicted
- the company provides it according to the commercial arrangement.

1.2 This recommendation is not intended to affect treatment with nintedanib that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

This technology appraisal is for treating idiopathic pulmonary fibrosis in people with a forced vital capacity (FVC) above 80% predicted. Nintedanib is also recommended for people with an FVC between 50% and 80% predicted (NICE technology appraisal guidance 379). Currently, the only option for people with idiopathic pulmonary fibrosis with an FVC above 80% predicted is best supportive care.

Clinical trial evidence shows that nintedanib slows the decrease of lung function compared with placebo in people with idiopathic pulmonary fibrosis with an FVC above 80% predicted. Also, long-term evidence suggests that the effect of nintedanib is maintained over time.

The most likely cost-effectiveness estimates are within what NICE considers an acceptable use of NHS resources. So, nintedanib is recommended.

2 Information about nintedanib

Marketing authorisation indication

2.1 Nintedanib (Ofev, Boehringer Ingelheim) is indicated 'for the treatment of idiopathic pulmonary fibrosis'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for nintedanib.

Price

2.3 The price of nintedanib is £2,151.10 per pack of 60 capsules, each containing 150 mg (excluding VAT; BNF online accessed October 2022).

2.4 The company has a commercial arrangement. This makes nintedanib available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The evaluation committee considered evidence submitted by Boehringer Ingelheim, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

Review objectives

3.1 The committee reviewed existing and new data on the clinical and cost effectiveness of nintedanib. It also considered evidence on the nature of idiopathic pulmonary fibrosis and the benefits of nintedanib for people with the condition and clinical experts. The committee also took into account the effective use of NHS resources. This evaluation reviews part of NICE's previous technology appraisal guidance on nintedanib. This is to take into account new evidence relating to people with a forced vital capacity (FVC) above 80% predicted. This review only considers part of nintedanib's marketing authorisation (people with a FVC above 80% predicted).

The condition

Unmet need

3.2 Idiopathic pulmonary fibrosis is a chronic, progressive lung disease characterised by scarring (fibrosis) of lung tissues. Most people with idiopathic pulmonary fibrosis experience breathlessness and coughing, which are associated with a progressive decline in lung function. The median survival from diagnosis is 2 to 5 years. Patient experts explained that the physical symptoms of the condition severely impacts people's quality of life affecting mobility, mental health, and ability to complete usual activities. The committee discussed the treatments for idiopathic pulmonary fibrosis in current NHS practice. The clinical experts explained that they offer treatment with pirfenidone (NICE's technology appraisal guidance on pirfenidone for treating idiopathic pulmonary fibrosis) or nintedanib (NICE's technology appraisal guidance on nintedanib for

treating idiopathic pulmonary fibrosis, from now TA379) to people with an FVC between 50% and 80% predicted. This reflects NICE's technology appraisal guidance on pirfenidone and nintedanib for treating idiopathic pulmonary fibrosis. The clinical experts noted that they would offer best supportive care to people with an FVC above 80% predicted because NICE does not recommend pirfenidone or nintedanib in this population. Clinicians would like to offer active treatments to people with an FVC above 80% predicted. The committee concluded that the only treatment option for people with idiopathic pulmonary fibrosis who have an FVC above 80% predicted is best supportive care. It recognised the unmet need of these people.

Clinical effectiveness

Evidence sources

3.3 The company did an updated systematic literature review to identify new data available since TA379. Data from relevant subgroups within 5 identified trials comparing nintedanib with placebo were included in the company's submission:

- phase 3 INPULSIS 1 and 2 randomised controlled trials (RCTs)
- phase 2 TOMORROW RCT
- INPULSIS-ON open-label extension study
- TOMORROW open-label extension study.

The EAG raised concerns that the inclusion and exclusion criteria in the company's systematic literature review were unclear, which may have caused relevant observational studies to be excluded. In particular, the EAG raised concerns about excluding Lancaster et al. (2020), which reports the results of a phase 3b clinical trial comparing nintedanib with placebo. The company explained that this was excluded from the literature review because it is not a pivotal trial and because of methodological limitations caused by protocol amendments. For example, the company noted that the primary analysis was done at 6 months instead of 52 weeks, which may have introduced bias into

the study. However, the EAG believed that limitations of the study would not significantly bias the results and the data could have been used to inform survival estimations in the model. The company explained that the results of Lancaster et al. are consistent with data from the TOMORROW and INPULSIS studies. Because of this, the company considered that including the data from Lancaster et al. (2020) would have a minimal effect on the results in its submission. The committee concluded that further transparency on the company's systematic literature review methodology would have been useful to reduce uncertainty, but there was enough evidence for reasonable decision making.

Results

3.4 The results for the clinical effectiveness of nintedanib in people with idiopathic pulmonary fibrosis with an FVC above 80% predicted came from post-hoc subgroup analyses of the INPULSIS and TOMORROW trials (see section 3.3). The pooled results from the INPULSIS trials showed a reduced decline in FVC of 128.4 ml per year for nintedanib compared with placebo in people with idiopathic pulmonary fibrosis with an FVC above 80% predicted. Results from the TOMORROW trial showed a reduced decline in FVC of 176 ml per year for nintedanib compared with placebo in people with idiopathic pulmonary fibrosis with an FVC of above 80% predicted. There was no statistically significant difference in the reduction in decline for the FVC above 80% predicted subgroup compared with the whole population. The committee noted that the annual rate of decline in FVC in INPULSIS-ON was consistent with what was observed in the INPULSIS trials, which suggested that the effects of nintedanib persist beyond 4 years. The results from the TOMORROW open-label extension also showed similar results. Long-term efficacy in reducing disease progression was also sustained in people who needed dose adjustments. The committee concluded that results from all the trials indicated that nintedanib gave a sustained improvement in patient outcomes compared with placebo in people with an FVC above 80% predicted.

Survival modelling

Overall survival population

3.5 The company stated that the network meta-analysis (NMA) done as part of TA379 had not been updated for this evaluation. The company said that this was because no new relevant nintedanib RCTs had been identified. However, unlike the previous evaluation, only results for the comparison with placebo were considered relevant to this population and considered within this evaluation. The EAG noted that the NMA was done for the whole trial population and not specifically for people with an FVC above 80% predicted. The company explained that this was because no significant treatment effect by subgroup was observed for primary or secondary endpoints (see section 3.4). This meant the results for the overall population are expected to be similar to those expected in people with an FVC above 80% predicted. The EAG noted that the INPULSIS trials were not designed to investigate the effects of nintedanib in subgroups and so it is plausible that the non-significant results are because of a lack of statistical power. Also, the EAG suggested that overall survival for people with an FVC above 80% predicted should have been used to reflect the lower mortality rate in this group. Because of this, the EAG preferred to include overall survival results for people with an FVC above 80% predicted in its base case. The committee recognised that analysis of people with an FVC above 80% predicted may be more relevant, but also noted that subgroup analysis would reduce sample sizes and increase uncertainty. So, the committee concluded that scenarios with both EAG and company approaches would be relevant to consider in decision making.

Overall survival extrapolation

3.6 The committee noted that the duration of follow-up data for nintedanib is about 5.5 years (which is longer than in the analyses used in TA379). The EAG explained that in the data for people with an FVC above 80% predicted, the survival curves were similar in the nintedanib group and the best supportive care group at 52 weeks. At this point in the trials, people having placebo were allowed to switch to nintedanib, significantly

reducing the number of people having placebo and available for survival analysis beyond this point. The EAG noted that this increased the uncertainty of survival data in the placebo arm. Therefore, the EAG's preferred approach was to assume that survival in the nintedanib arm and the best supportive care arm was equivalent until the average predicted FVC of the subgroup reached that of the whole trial population. After this point, survival in the best supportive care arm was assumed to follow the extrapolated curve from the whole trial population for the best supportive care arm. This was modelled to happen after 5.5 years in the EAG's base case. However, the EAG also presented scenario analyses assuming that overall survival remained the same in both treatment groups for 1 year and for 3 years. The company disagreed with the EAG's survival data extrapolation. It believed that the approach did not match with real-world data. Also, the company suggested that modelling equal survival for nintedanib and the best supportive care arm implied that nintedanib was not effective for the first 5.5 years. It noted that lung function decline is a key predictor of survival. So, assuming equal survival in both arms does not take into account the data showing that nintedanib reduces the rate of lung function decline (see section 3.4). The committee noted that nintedanib showed a higher survival probability at 5 years (60% instead of 40%) than was predicted in the original evaluation. It considered that the EAG's approach may be conservative because the trial results suggested there could be a survival difference between the arms. The committee also noted that, despite the survival data in the placebo arm being more uncertain, the length of follow up was typical for a technology appraisal and the nintedanib arm had far more data than was usual. The committee concluded that both the company's approach and the EAG's approach should be considered.

Economic model

Model structure

3.7 The company presented a Markov model to estimate the cost effectiveness of nintedanib compared with standard care in people with idiopathic pulmonary fibrosis with an FVC above 80% predicted. The

structure of the model was the same as was submitted in TA379. The model used a lifetime horizon and a cycle length of 3 months. The health states in the model used 2 measures: predicted FVC (separated by 10 percentage point increments) and the occurrence of an acute exacerbation. People changed health states if they experienced a loss of lung function, exacerbation, both a loss of lung function and exacerbation, or death. People who moved to a lower predicted FVC health state could not move back to a higher health state. Similarly, people who experienced exacerbation were unable to move back to a non-exacerbation health state. The model also allowed for people to experience adverse events. The EAG considered the model structure reasonable. However, it noted that the company model does not include general population mortality and uses a 50-year time horizon. The EAG suggested that a 35-year time horizon may be more suitable because the starting age of the patient population in the model was 67 years old. The committee concluded that the company's model was acceptable for decision making, but noted that it was more appropriate to use a 35-year time horizon.

Stopping rule

3.8 In TA379, a stopping rule was implemented for people whose predicted FVC percentage decreased by 10% or more in a 12-month period. This stopping rule was not implemented by the company in this evaluation of people with an FVC above 80% predicted. The committee recalled that in TA379, nintedanib could not be considered cost effective without a stopping rule. In this evaluation, the company removed the stopping rule from their analyses and explained that expert clinical advice input suggested that the stopping rule would be difficult to implement. It was also noted that in NICE's technology appraisal guidance on nintedanib for treating progressive fibrosing interstitial lung diseases, clinical experts advised they would stop treatment with nintedanib if disease progression was not sufficiently slowed, even without a formal stopping rule. Clinical experts advised the EAG that people tend to stop taking nintedanib because of tolerability issues or advancing disease with high symptom burden. Also, they advised that predicted FVC was not usually used as the only measure for stopping treatment with nintedanib. They noted that predicted FVC can vary significantly for an individual patient. The

EAG also did scenario analysis including the stopping rule. The committee acknowledged the expert opinion and concluded that if nintedanib was a cost-effective use of NHS resources without a formal stopping rule in this evaluation, then no stopping rule would be applied.

Cost-effectiveness estimates

Results

3.9 The company's base-case incremental cost-effectiveness ratio (ICER) compared with best supportive care was below £20,000 per quality-adjusted life-year (QALY) gained, when commercial arrangements for nintedanib and all the comparators were included. The exact ICERs are considered confidential and cannot be reported here. Also, the ICER was below £30,000 per QALY gained when considering the EAG's base case which used:

- the survival data from the subgroup of people with an FVC above 80% predicted (see section 3.5)
- the same extrapolation for the nintedanib and placebo arms for the first 5.5 years of the model (see section 3.6)
- a time horizon of 35 years (see section 3.7).

The committee agreed with the EAG's use of the survival data for the subgroup with an FVC above 80% predicted (see section 3.5) and the reduced time horizon (see section 3.7). However, the committee believed that the EAG's extrapolation of the survival data may be conservative (see section 3.6). The committee also considered key scenario analysis such as different extrapolations of survival data. To understand the level of uncertainty, it considered probabilistic sensitivity analyses on both the corrected company base case and the EAG's base case. The results indicated that, using the corrected company base case, nintedanib was likely to be cost effective at a threshold of £20,000 per QALY gained. Even with the conservative approach taken by the EAG, nintedanib was likely to be cost effective at a threshold of £30,000 per QALY gained. Overall, the committee concluded that nintedanib was likely to be a cost-effective use of NHS resources.

Other factors

Equality issues

3.10 No equality issues were identified. NICE's advice about conditions with a high degree of severity did not apply.

Conclusion

Recommendation

3.11 All the ICERs considered by the committee were in the range normally considered a cost-effective use of NHS resources. So, nintedanib is recommended for treating idiopathic pulmonary fibrosis in people with an FVC above 80% predicted.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has idiopathic pulmonary fibrosis with a forced vital capacity above 80% predicted and the doctor responsible for their care thinks that nintedanib is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal evaluation committees are standing advisory committees of NICE. This topic was considered by committee D.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Stephen Smith
Chair, technology appraisal evaluation committee D

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser and a project manager.

George Millington
Technical lead

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