NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Nerandomilast for treating idiopathic pulmonary fibrosis or progressive pulmonary fibrosis

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using nerandomilast in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

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Note that this document is not NICE's final guidance on nerandomilast. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using nerandomilast in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 10 September 2026
- Second evaluation committee meeting: TBC
- Details of the evaluation committee are given in section 4**.**

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1 Recommendations

1.1 Nerandomilast should not be used to treat idiopathic pulmonary fibrosis (IPF) or progressive pulmonary fibrosis (PPF) in adults.

1.2 This recommendation is not intended to affect treatment with nerandomilast 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 healthcare professional consider it appropriate to stop.

What this means in practice

These are NICE's draft recommendations. If these recommendations become final, nerandomilast would not be required to be funded and should not be used routinely in the NHS in England for the conditions and populations in the recommendations.

This is because there is not enough evidence to determine whether nerandomilast offers benefit and value for money in these populations.

Why the committee made these recommendations

Usual treatment for IPF and PPF includes antifibrotic treatment and best supportive care. Antifibrotic treatment for IPF depends on lung function, measured by forced vital capacity (FVC). This is usually expressed as a percentage of the value expected for a healthy person (FVC % predicted). For IPF, pirfenidone or nintedanib is used when FVC % predicted is between 50% and 80%, and nintedanib is used when FVC % predicted is 80% or more. For PPF, nintedanib is the only antifibrotic treatment option, regardless of FVC % predicted.

For this evaluation, the company asked for nerandomilast to be considered only for use alone with best supportive care for treating:

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- IPF in people with an FVC % predicted of 50% or more, or
- PPF.

This does not include everyone it is licensed for.

Clinical trial evidence suggests that people may live longer with nerandomilast than with placebo for both IPF and PPF. But this is uncertain. Nerandomilast has not been directly compared in a clinical trial with pirfenidone or nintedanib for IPF, or with nintedanib for PPF. Indirect comparisons suggest no clear differences between nerandomilast and these treatments on slowing lung function decline, improving how long people live or reducing the risk of acute exacerbations. But this is also uncertain.

In addition, there are uncertainties in the economic model, including:

- the way that lung function and how long people live are modelled
- how treatment effects should be modelled when people stop treatment.

Because of the uncertainties in the clinical evidence and the economic model, it is not possible to determine the most likely cost-effectiveness estimates for nerandomilast. So, nerandomilast should not be used.

2 Information about nerandomilast

Marketing authorisation indication

2.1 Nerandomilast (Jascayd, Boehringer Ingelheim) is indicated for 'the treatment of adult patients with Idiopathic Pulmonary Fibrosis (IPF) or Progressive Pulmonary Fibrosis (PPF)'.

Dosage in the marketing authorisation

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

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Price

2.3 The list price for a pack of 60x18 mg (company submission) or 60x9 mg tablets (company communication) is £3,825.

2.4 The company has a commercial arrangement, which would have applied if nerandomilast had been recommended.

Carbon Reduction Plan

2.5 Information on the Carbon Reduction Plan for UK carbon emissions for Boehringer Ingelheim will be included here when guidance is published.

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.

The condition

3.1 Idiopathic pulmonary fibrosis (IPF) and progressive pulmonary fibrosis (PPF) are chronic, progressive, fibrosing, interstitial lung conditions characterised by irreversible scarring of the lungs. IPF is a specific fibrotic condition of unknown cause. PPF describes progressive fibrosis that can occur in several underlying conditions despite appropriate treatment. The clinical experts explained that IPF and PPF have different underlying causes. But, once fibrosis becomes progressive, they have similar clinical trajectories, with worsening symptoms, declining lung function and poor survival. The patient experts explained that pulmonary fibrosis has a profound impact on all aspects of people's lives. They described progressive breathlessness, persistent cough, fatigue and increasing dependence on others, as well as anxiety caused by uncertainty about progression of their condition and limited treatment options. The committee concluded that IPF and PPF can substantially reduce quality of life and life expectancy.

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Assessing disease progression

3.2 Forced vital capacity (FVC) is the maximum volume of air a person can breathe out after taking the deepest breath possible. It is commonly reported as a percentage of the predicted value for a healthy person of the same age, sex, height and ethnicity (FVC % predicted). The clinical experts explained that FVC is an important measure of lung function and disease progression in both IPF and PPF. But they emphasised that treatment decisions are based on overall clinical presentation, including symptoms, imaging, oxygen needs and pattern of disease progression over time, rather than a single FVC measurement. They also explained that the clinical significance of changes depends on the person and the stage of pulmonary fibrosis. So, there is no universally accepted minimum clinically important difference in FVC. They explained that an FVC % predicted decline of around 10% over 12 months is associated with a substantially increased risk of death. The committee concluded that FVC is an important measure of disease progression, and prognosis in IPF and PPF. But it thought that FVC should be interpreted alongside the person's overall clinical condition rather than used in isolation.

Clinical management

Treatment pathway

3.3 Management of IPF and PPF includes best supportive care, with or without antifibrotic treatment. Best supportive care is tailored to the person's needs. It may include symptom management, pulmonary rehabilitation, smoking cessation support, vaccination, oxygen therapy, management of comorbidities, psychological support and palliative care. The clinical experts explained that current antifibrotic treatments slow disease progression but do not stop or reverse fibrosis or restore lung function. For IPF, NICE recommends:

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- nintedanib for people with an FVC % predicted of between 50% and 80% (see NICE's technology appraisal guidance on nintedanib for treating idiopathic pulmonary fibrosis, from here TA379)
- nintedanib for people with an FVC % predicted of 80% or more (see NICE's technology appraisal guidance on nintedanib for treating idiopathic pulmonary fibrosis when forced vital capacity is above 80% predicted)
- pirfenidone for people with an FVC % predicted of between 50% and 80% (see NICE's technology appraisal guidance on pirfenidone for treating idiopathic pulmonary fibrosis, from here TA504).

Only the recommendations for nintedanib in TA379 and pirfenidone in TA504 include stopping criteria based on a decline in FVC % predicted of 10% or more within any 12-month period (see section 3.2). For PPF, NICE recommends nintedanib, regardless of baseline FVC % predicted (see NICE's technology appraisal guidance on nintedanib for treating progressive fibrosing interstitial lung diseases).

The clinical experts explained that treatment decisions are made by specialist multidisciplinary teams. They explained that current antifibrotic treatments are generally thought to have similar effects on slowing disease progression. So, treatment choice is usually based on tolerability, comorbidities and patient preference rather than differences in efficacy. The clinical and patient experts explained that adverse effects can substantially affect quality of life and often lead to dose reductions, stopping treatment or reluctance to start treatment. The committee concluded that current treatments slow disease progression but do not prevent it. It also concluded that there is a high unmet need for additional treatments that are both effective and well tolerated.

Positioning of nerandomilast and comparators

3.4 Nerandomilast has a marketing authorisation for treating IPF and PPF in adults without restrictions according to baseline FVC % predicted (see

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section 2.1). For this evaluation, the company limited its evidence submission to nerandomilast used alone with best supportive care rather than with other antifibrotic treatments.

For IPF, the company proposed positioning nerandomilast for people with an FVC % predicted of 50% or more. This reflects the eligibility criteria in existing NICE recommendations for nintedanib and pirfenidone (see section 3.3). For PPF, the company did not propose restricting treatment according to baseline FVC. The committee noted that FIBRONEER-IPF (IPF) and FIBRONEER-ILD (PPF) only included people with an FVC % predicted of 45% or more (see section 3.5). The clinical experts explained that people with IPF or PPF could benefit from treatment that slows disease progression regardless of disease severity, including people with more advanced condition. The committee acknowledged that people with an FVC % predicted of less than 45% may benefit from antifibrotic treatment. But, because people with an FVC % predicted of less than 45% were not included in either FIBRONEER trials, it had not seen evidence to establish the clinical and cost effectiveness of nerandomilast in this group. So, it concluded that, for both IPF and PPF, the population considered in the evaluation should be people with an FVC % predicted of 45% or more, with no upper FVC threshold.

The company identified nintedanib, pirfenidone and best supportive care as comparators for IPF, and nintedanib and best supportive care as comparators for PPF. The clinical experts agreed that these represented the treatments most likely to be used in NHS practice. The committee concluded that the company's choice of comparators was appropriate.

The clinical experts explained that pirfenidone and nintedanib are not used in combination in NHS practice, and that there are no national guidelines recommending combination antifibrotic treatment. They noted that healthcare professionals may wish to use nerandomilast with another antifibrotic treatment in some circumstances. The committee noted that

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the company had not submitted evidence for nerandomilast used with other antifibrotic treatments. So, it concluded that it could only consider nerandomilast used alone in this evaluation.

Clinical effectiveness

FIBRONEER trials

3.5 The key clinical-effectiveness evidence for nerandomilast came from 2 multinational, phase 3, randomised, double-blind, placebo-controlled trials:

- FIBRONEER-IPF for IPF (1,177 people)
- FIBRONEER-ILD for PPF (1,178 people).

Both trials compared nerandomilast (18 mg or 9 mg twice daily) plus best supportive care with placebo plus best supportive care. People enrolled in both trials had an FVC % predicted of 45% or more and a predicted diffusing capacity of the lung for carbon monoxide (DLCO) of 25% or more. Background antifibrotic treatment was allowed if the condition was stable. In FIBRONEER-IPF, this could be nintedanib or pirfenidone, and in FIBRONEER-ILD, it was limited to nintedanib. The primary outcome in both trials was the change from baseline in FVC (ml) at week 52. Secondary outcomes included acute exacerbations, disease progression, mortality, health-related quality of life and safety.

Because this evaluation considered nerandomilast used alone (see section 3.4), the company focused on prespecified subgroups of people not having background antifibrotic treatment and having the licensed 18 mg dose. These analyses included 174 people in FIBRONEER-IPF and 442 people in FIBRONEER-ILD. The company also presented results from the full analysis set (FAS). This included all randomised participants who had at least 1 dose of study treatment, analysed according to the treatment they were randomised to. The FAS included both people who were having background antifibrotic treatment and people who were not.

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FIBRONEER results

3.6 In the FAS, the FIBRONEER trials showed that:

- Nerandomilast (18 mg) statistically significantly reduced decline in lung function compared with placebo at week 52 in both IPF and PPF. In IPF, the adjusted mean change from baseline in FVC was −114.7 ml with nerandomilast compared with −183.5 ml with placebo. This was a 37% relative reduction in FVC decline ($p<0.001$). In PPF, the adjusted mean change from baseline in FVC was −98.6 ml with nerandomilast compared with −165.8 ml with placebo. This was a 41% relative reduction in FVC decline ($p<0.001$).
- Nerandomilast did not statistically significantly improve the key secondary composite endpoint of time to first acute exacerbation, respiratory hospitalisation or death compared with placebo in either IPF or PPF.
- The company did not present the results for overall survival as an individual endpoint. Instead, deaths were reported within the key secondary composite endpoint, and were numerically lower with nerandomilast than with placebo in both IPF and PPF.

In the nerandomilast-alone subgroup analyses, the FIBRONEER trials showed that:

- Nerandomilast (18 mg) statistically significantly reduced decline in lung function compared with placebo at week 52 in PPF, but not in IPF. The difference in absolute mean change from baseline in FVC was 69.4 ml (95% confidence interval [CI] −12.3 to 151.2) for IPF and 58.9 ml (95% CI 12.1 to 105.8) for PPF. The company considers the exact results for FVC % predicted confidential, so they cannot be reported here.
- Nerandomilast nominally significantly prolonged time to death compared with placebo in both IPF and PPF. The hazard ratios (HR) were 0.26 (95% CI 0.07 to 0.91) in IPF and 0.44 (95% CI 0.24 to 0.80) in PPF..

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- Nerandomilast nominally significantly improved the composite endpoint of time to first acute exacerbation, first respiratory hospitalisation or death compared with placebo in PPF (HR 0.65, 95% CI 0.46 to 0.92). In IPF, the hazard ratio numerically favoured nerandomilast, but the result was not nominally significant (HR 0.62, 95% CI 0.35 to 1.10).

The EAG noted that the nerandomilast-alone subgroup analyses were prespecified, but the smaller subgroup sample sizes meant they were not powered to detect differences with the same precision as the full trial populations. It also noted that some of the time-to-event analyses were exploratory and should be interpreted with caution. The committee noted that, in the full trial populations, nerandomilast statistically significantly slowed decline in lung function compared with placebo in both IPF and PPF. It also noted that the results from the nerandomilast-alone subgroup, , particularly for the time-to-event outcomes and for IPF, were less certain because of the wider confidence intervals and because some endpoint analyses were exploratory. The committee concluded that the FIBRONEER trials showed that nerandomilast slowed decline in lung function compared with placebo in the full trial populations for both IPF and PPF. But it also concluded that there was greater uncertainty about the size of the treatment effect when nerandomilast was used alone, particularly for IPF.

Indirect treatment comparisons

3.7 There were no head-to-head trials comparing nerandomilast with nintedanib or pirfenidone. So, the company did indirect treatment comparisons (ITCs) to estimate the relative effectiveness of nerandomilast against these treatments for IPF and PPF. The company had access to individual patient data for nerandomilast and nintedanib but only aggregate data for pirfenidone. So, it did an individual patient data network meta-regression (IPD-NMR) to compare nerandomilast with nintedanib. It used data from FIBRONEER-IPF and INPULSIS 1 and 2 for IPF, and from FIBRONEER-ILD and INBUILD for PPF. It also did

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exploratory pooled IPD-NMR analyses combining the IPF and PPF trial populations for selected outcomes, including mortality and safety. For the comparison with pirfenidone in IPF, the company did a Bayesian network meta-analysis (NMA) using data from the ASCEND, CAPACITY 1 and 2, and JAPICCTI-050121 trials.

The company and the EAG agreed that the IPD-NMR was the most robust method for comparing nerandomilast with nintedanib. This was because it allowed adjustment for differences in baseline characteristics and treatment-effect modifiers between trials. But they differed in their preferred approach for comparing nerandomilast with pirfenidone because only aggregate data was available (see section 3.12).

The committee noted that the comparator trials included in the ITCs compared nintedanib or pirfenidone used alone with placebo. So, they were broadly comparable with the FIBRONEER nerandomilast-alone subgroup because participants did not have another antifibrotic as background treatment. It noted that previous antifibrotic use was not consistently reported across the comparator trials. This meant that it was unclear whether all participants had not had antifibrotic treatment before. But the committee noted that neither the company nor the EAG identified differences in previous or background antifibrotic use as an important source of heterogeneity between the trials. The committee concluded that the IPD-NMR and Bayesian NMA were appropriate methods for comparing nerandomilast with nintedanib and pirfenidone, respectively. It also concluded that despite some uncertainty about previous antifibrotic use across the trials, the ITCs were appropriate for decision making.

ITC results for the nerandomilast-alone subgroup

3.8 The results of the ITCs showed:

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- For IPF, there were no statistically significant differences between nerandomilast and nintedanib or pirfenidone for the following individual end points:
  - change from baseline in FVC at week 52
  - time to first acute exacerbation
  - time to a decline of more than 10% in FVC % predicted
  - time to death.

  The point estimates numerically favoured nerandomilast for mortality but favoured nintedanib and pirfenidone for acute exacerbations. The company considers the exact results confidential, so they cannot be reported here.

- For PPF, there were no statistically significant differences between nerandomilast and nintedanib the following individual end points:
  - change from baseline in FVC at week 52
  - time to first acute exacerbation
  - time to a decline of more than 10% in FVC % predicted
  - time to death.

  The company considers the exact results confidential, so they cannot be reported here.

- For the pooled IPD-NMR analyses (combining the IPF and PPF trials), there were no statistically significant differences in FVC decline between nerandomilast and nintedanib. The exploratory analyses showed a statistically significant reduction in time to death and statistically significant improvements in time to treatment discontinuation. Also, several tolerability outcomes favoured nerandomilast (see section 3.9). The company considers the exact results confidential, so they cannot be reported here.

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The EAG noted that the ITCs, particularly the condition-specific analyses, were based on the nerandomilast-alone subgroups. So, they included relatively few clinical events, especially deaths and acute exacerbations. This resulted in wide confidence intervals and substantial uncertainty around the relative effectiveness estimates. The committee agreed that the condition-specific ITCs did not provide sufficient evidence to distinguish the relative clinical effectiveness of nerandomilast from that of nintedanib or pirfenidone. It noted that the evidence did not consistently favour either treatment across the key clinical outcomes and that clinically important differences in either direction could not be excluded.

The EAG acknowledged that pooling the IPF and PPF trial populations increased the sample size and improved the precision of the mortality estimates. But it thought that this did not, by itself, establish that pooling the 2 conditions was clinically or statistically appropriate. The committee thought that the pooled IPF and PPF analyses were potentially informative because they included more people and more events than the condition-specific analyses. It also acknowledged the clinical experts' view that pooling IPF and PPF was appropriate (see section 3.1). But it noted that the exploratory pooled IPD-NMR comparing nerandomilast with nintedanib showed no clear difference in FVC decline despite suggesting a reduction in mortality. Because worsening lung function is associated with poorer survival (see section 3.2), the committee thought that the available evidence did not adequately explain this finding. Together with the small number of deaths and the exploratory nature of the pooled analyses, it thought that uncertainty remained about the relative mortality estimates.

The committee thought that analyses using the full FIBRONEER trial populations (over 2,300 people) could provide more informative evidence on the relationship between FVC decline and mortality than analyses

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using the nerandomilast-alone subgroup. It also thought that further evidence was needed to determine whether:

- background antifibrotic treatment modified this relationship
- whether the mortality estimates were robust to small changes in the number and timing of deaths.

The committee requested:

- additional evidence to support pooling the IPF and PPF nerandomilast-alone subgroup populations for the mortality analyses
- analyses using individual patient data from the full FIBRONEER trial populations to investigate the relationship between FVC decline and mortality separately for IPF and PPF, and in the pooled population if appropriate
- assessment of whether background antifibrotic treatment modified the relationship between FVC decline and mortality
- sensitivity analyses exploring the robustness of the mortality estimates to small changes in the number and timing of deaths.

The committee concluded that these analyses would help resolve the uncertainty around the mortality benefit. It thought that the available evidence was insufficient to conclude that nerandomilast improved overall survival compared with nintedanib or pirfenidone.

Adverse events

3.9 The committee considered whether nerandomilast offered any advantages over existing antifibrotic treatments in terms of tolerability. The clinical experts explained that the side-effect profiles of the available antifibrotics differ. Key side effects affecting people are photosensitivity, rash and loss of appetite with pirfenidone, and diarrhoea with nintedanib.

The results from the ITCs suggested that nerandomilast had a more favourable gastrointestinal tolerability profile than nintedanib. In both IPF

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and PPF, nerandomilast was associated with statistically significantly longer time to treatment discontinuation and fewer gastrointestinal adverse events than nintedanib. In PPF, nerandomilast was also associated with statistically significantly fewer treatment discontinuations because of adverse events and less diarrhoea. In IPF, the corresponding estimates numerically favoured nerandomilast but were not statistically significant. The company considers the exact estimates confidential, so they cannot be reported here (see section 3.8).

The clinical and patient experts explained that there was often greater urgency with diarrhoea associated with nintedanib than with diarrhoea associated with nerandomilast. They explained that diarrhoea with nerandomilast was usually mild to moderate and generally occurred within the first 3 months of treatment. But diarrhoea with nintedanib can continue throughout treatment, so could have a greater impact on people's daily activities and willingness to continue treatment. They thought that this difference in tolerability could be meaningful in clinical practice.

The committee recalled that adverse effects commonly lead to dose reductions and stopping treatment in NHS practice (see section 3.3). It noted that uncertainty remained about the relative clinical effectiveness of nerandomilast compared with the active comparators (see section 3.8). But it thought that improvements in tolerability could represent an important benefit for people with IPF or PPF. The committee concluded that the available evidence suggested that nerandomilast may offer a clinically relevant tolerability advantage over nintedanib.

Economic model

Company's modelling approach

3.10 The company provided separate state-transition Markov cohort models to estimate the cost effectiveness of nerandomilast compared with the relevant comparators for adults with IPF and PPF. The models included 9

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health states defined by FVC % predicted, in 10%-point intervals, and a death state. People entered the models according to the baseline FVC distributions seen in the FIBRONEER-IPF and FIBRONEER-ILD nerandomilast-alone subgroups. During each model cycle, they could remain in the same FVC health state, move to a lower FVC health state or move to the death health state. Acute exacerbations, stopping treatment and death were modelled independently of FVC progression.

Health-state occupancy determined health-related quality of life and management costs of the condition. The modelled populations had a mean age of 70.4 years in IPF, of whom 76% were men, and 66.2 years in PPF, of whom 49.8% were men. The EAG thought that the FIBRONEER trial populations were broadly representative of people who would be offered nerandomilast in NHS clinical practice and were appropriate for defining the modelled cohorts. The models used 3-month cycles, applied a half-cycle correction and adopted a lifetime time horizon. The committee thought that the overall model structure was appropriate for decision making. But it noted that there were uncertainties around modelling FVC progression and overall survival independently (see section 3.11).

Modelling treatment benefit

3.11 The company modelled treatment benefit through 3 clinical outcomes:

- disease progression, represented by movement between FVC % predicted health states
- acute exacerbations
- overall survival.

Acute exacerbations generated additional healthcare costs, temporary quality-of-life decrements and increased mortality. Overall survival determined life expectancy and the duration over which quality-adjusted life years (QALYs) accrued.

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Because the ITCs did not show a statistically significant difference in FVC progression between nerandomilast and the active comparators (see section 3.8), the company assumed identical FVC transitions across treatment arms. But it retained differential treatment effects on acute exacerbations and overall survival for nerandomilast compared with nintedanib, modelling these independently of FVC progression. In particular, deterioration through the FVC % predicted health states did not increase a person's underlying mortality risk in the model. For pirfenidone, the company assumed the same treatment effects on acute exacerbations and overall survival as for nintedanib (see section 3.12). This was because the company thought that FVC did not capture all clinically relevant aspects of pulmonary fibrosis, and that treatment could influence survival and acute exacerbations through pathways not fully reflected by changes in lung function.

The EAG thought that disease progression, acute exacerbations and mortality are related manifestations of pulmonary fibrosis. It questioned the structural consistency of modelling FVC progression and mortality independently, particularly because deterioration through the FVC health states did not increase the underlying risk of death. It thought that this approach needed robust clinical evidence or a clear justification for survival benefits occurring independently of lung function.

The committee recalled that FVC is an important marker of disease progression and prognosis (see section 3.2). The clinical experts explained that FVC is an imperfect surrogate for mortality because it does not capture all factors influencing the risk of death. The committee acknowledged that treatment could plausibly influence survival through mechanisms not fully captured by FVC. But it noted that FVC-defined health states represented disease progression in the model. So, it thought that the relationship between FVC progression and mortality should either

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be explicitly represented or that there should be stronger evidence to support modelling them independently. It would have preferred the company to explore modelling mortality according to FVC health state if this relationship could be robustly characterised (see section 3.8). It concluded that modelling treatment effects on FVC progression, acute exacerbations and overall survival independently introduced uncertainty about the internal consistency of the model. It took this uncertainty into account in its decision making.

Relative treatment effects

3.12 In its base case, the company assumed equivalent treatment effects for nerandomilast, nintedanib and pirfenidone on FVC progression. For overall survival and acute exacerbations, it used treatment-effect estimates from the IPD-NMR for comparisons between nerandomilast and nintedanib. Because comparable individual patient data was not available for pirfenidone, the company assumed that pirfenidone had the same treatment effects on overall survival, acute exacerbations and stopping treatment as nintedanib.

The EAG accepted the use of the IPD-NMR estimates for comparisons between nerandomilast and nintedanib. But it preferred to use the available Bayesian NMA estimates for pirfenidone rather than assuming equivalence with nintedanib. The EAG thought that, although the NMA estimates were uncertain, it was preferable to reflect this uncertainty probabilistically than to assume identical treatment effects.

The EAG also noted uncertainty in the estimation of treatment effects on acute exacerbations. It thought that death was a competing risk for acute exacerbations and that a competing-risks approach would have been more appropriate than the standard survival analysis used by the company. But it noted that alternative assumptions for acute exacerbations had little effect on the cost-effectiveness results and concluded that the impact of this issue was likely to be small.

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The committee recalled that the available ITC evidence did not establish clear differences in efficacy between nerandomilast, nintedanib and pirfenidone (see section 3.8). It also recalled that the clinical experts thought the available antifibrotic treatments have broadly similar efficacy, with treatment choice primarily driven by differences in tolerability (see section 3.3 and section 3.9). It noted that, in its base case, the company assumed equivalent effects on FVC progression but retained treatment-specific effects on overall survival and acute exacerbations. This generated much of the incremental health benefit associated with nerandomilast. The committee thought that the available evidence was not sufficiently robust to support these differential treatment effects. It would have preferred to see a scenario analysis assuming equivalent treatment effects for nerandomilast, nintedanib and pirfenidone on FVC progression, acute exacerbations and overall survival. It would also have preferred that the differences in cost effectiveness had arisen principally from adverse events, stopping treatment, health-related quality of life and costs. The committee concluded that this scenario would have better reflected the available clinical evidence and current NHS practice.

Treatment discontinuation and treatment waning

3.13 The company modelled treatment discontinuation using parametric time-to-treatment discontinuation curves estimated from the FIBRONEER trials. Treatment costs stopped when treatment was stopped. But people who stopped treatment continued to accrue treatment effects on disease progression and overall survival until 1 year after the maximum follow up in the relevant FIBRONEER trial. After this point, people who had stopped treatment followed best supportive care transition probabilities for disease progression and mortality.

The company explained that treatment effects were estimated from intention-to-treat analyses, which included people who stopped treatment during follow up. It thought that continuing treatment effects for a limited

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period after treatment discontinuation was more appropriate than assuming that people immediately reverted to best supportive care. The company also explained that it was not assuming that there would be a persistent treatment effect for an individual after stopping treatment. Rather, it was using this approach to account for the potential underestimate of treatment effect for the cohort because some people stopped treatment sooner. The company argued that this approach was consistent with previous NICE technology appraisals of antifibrotic treatments. It also argued that the key uncertainty was related to the duration of treatment waning rather than whether treatment benefit persisted after treatment discontinuation.

The EAG agreed that treatment effects should not be extrapolated indefinitely. But it thought that treatment waning should be linked to stopping treatment rather than to a fixed time from starting treatment. Given the short half-lives of the available antifibrotic treatments, it thought that assuming people moved to best supportive care shortly after stopping treatment was clinically plausible. The clinical experts explained that they did not expect the treatment effect to continue after treatment is stopped. But they thought that people would retain the benefit accrued while on treatment.

The committee agreed that it was important to distinguish between accrued benefit and an ongoing treatment effect after treatment was stopped. It did not consider that the intention-to-treat analyses provided sufficient evidence that treatment-specific effects persisted after treatment discontinuation. Although it acknowledged that treatment discontinuation was not random, it noted the company had not presented analyses using the full FIBRONEER trial populations to assess whether treatment-specific effects persisted after treatment discontinuation. The committee was also not persuaded that previous NICE technology appraisals established a precedent for assuming continued treatment benefit after stopping

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treatment. This was because those appraisals considered how any residual benefit should wane, rather than whether treatment-specific effects persisted after treatment stopped.

The committee considered the clinical experts' view that the treatment effect is unlikely to continue after treatment is stopped. It concluded that the most appropriate approach was for treatment-specific effects to stop at treatment discontinuation, while preserving any benefit accrued while on treatment. After treatment discontinuation, people should follow the disease progression of the best supportive care arm, starting from the FVC health state they had reached when treatment was stopped. This would mean that no additional treatment-specific benefit should accrue after treatment discontinuation. But any benefit already gained while on treatment should not be removed immediately. The committee acknowledged that the company's current model structure could not implement this approach. This was because treatment effects were estimated from intention-to-treat analyses rather than conditional on treatment exposure. It concluded that the company should revise its model so that treatment-specific effects stop when treatment is stopped, while preserving the benefit accrued during treatment. It also thought that a scenario analysis should be provided exploring alternative assumptions about the persistence of a treatment effect after discontinuation.

Treatment sequencing

3.14 The company assumed that all antifibrotic treatments were used as first-line treatments. It did not model subsequent treatment with a different antifibrotic (that is, the company did not model treatment sequencing). After stopping treatment, people were assumed to only have best supportive care. The company explained that there was insufficient evidence to estimate the clinical effectiveness or costs of subsequent antifibrotic treatment.

The EAG thought that excluding treatment sequencing did not reflect NHS

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practice. This was because people may switch to another antifibrotic treatment, particularly because of intolerance. It noted that treatment sequencing could affect costs and health outcomes. But it agreed that there may be insufficient evidence to model the clinical effectiveness of subsequent antifibrotic treatment. It thought that the direction and magnitude of any resulting bias in the cost-effectiveness estimates was uncertain.

The clinical experts explained that treatment sequencing occurs in NHS practice and that treatment choice is often driven by tolerability (see section 3.3 and section 3.9). They also explained that people may benefit from switching to a treatment with a different mechanism of action. But they added that there is uncertainty about the clinical effectiveness of subsequent antifibrotic treatment, particularly in people with more advanced pulmonary fibrosis.

The committee agreed that treatment sequencing is relevant to NHS practice. It noted that the full FIBRONEER trial populations included people who had had previous antifibrotic treatment (see section 3.5). It would have preferred to see analyses exploring whether nerandomilast retained its clinical effectiveness in these people to reduce the uncertainty around treatment sequencing. But it acknowledged that the available evidence may be insufficient to model treatment sequencing robustly. It concluded that treatment sequencing could not reliably be included in the economic model and took this uncertainty into account in its decision making.

Modelling dose reductions

3.15 The committee recalled that adverse effects can lead to dose reductions in clinical practice (see section 3.9). For nerandomilast, the recommended dose of 18 mg twice daily can be reduced to 9 mg twice daily to manage tolerability. The clinical experts explained that dose reductions are also used with existing antifibrotic treatments and may allow people to remain

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on treatment rather than stopping it.

The committee noted that the company had not explicitly modelled dose reductions for nerandomilast or the comparator treatments. It assumed 100% dose intensity for all active treatments when calculating treatment acquisition costs. Also, it did not account for any effect of dose reductions on treatment effectiveness. So, although the model captured adverse events and treatment discontinuation, it did not capture dose reductions in people who remained on treatment.

The EAG noted that the proportion of people in the FIBRONEER trials who reduced their nerandomilast dose from 18 mg to 9 mg twice daily was not reported. It also noted that outcomes for people randomised to 9 mg twice daily could not be assumed to represent outcomes for people who started treatment at 18 mg twice daily and subsequently reduced their dose because of intolerance.

The committee thought that dose reductions could affect treatment costs, duration and clinical effectiveness. It also thought that frequency, duration and effects may differ between nerandomilast, nintedanib and pirfenidone. It concluded that not modelling dose reductions was an additional source of uncertainty in the cost-effectiveness estimates. It would have preferred to see a scenario analysis accounting for the impact of dose reductions across all antifibrotic treatments on clinical effectiveness, treatment duration and costs.

Costs

Cost of generic nintedanib

3.16 In May 2026, NHS England informed NICE that confidential Medicines Procurement and Supply Chain (MPSC) prices had become available for generic nintedanib. The exact prices are commercial in confidence and unavailable to the company. The EAG provided a confidential appendix

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incorporating these confidential MPSC prices into the cost-effectiveness analyses before the committee meeting.

The company thought that it was unfair to place substantial weight on the generic prices because they became available shortly before the committee meeting. It also questioned whether the prices reflected current NHS costs because generic nintedanib had only recently become available.

The committee noted that the NICE scope stated that generic prices would be considered when relevant. It thought that its decision making should reflect the most relevant current costs to the NHS because the guidance would apply prospectively. It concluded that the MPSC prices for generic nintedanib should be used in the cost-effectiveness analyses.

Resource use

3.17 The company included the costs of treatment acquisition, managing the condition, acute exacerbations, adverse events, monitoring and end-of-life care in the model. It included routine liver-function monitoring costs for nintedanib and pirfenidone but not for nerandomilast. This was because routine drug-specific liver-function monitoring is not required for nerandomilast.

The company thought that the model underestimated the benefits of avoiding routine liver-function monitoring. This was because it did not capture the burden of repeated blood tests and hospital visits for people with fibrotic lung conditions or the associated demands on specialist interstitial lung disease services. The EAG accepted the monitoring costs included in the model. But it did not think that the company's proposed utility decrement for liver-function monitoring was adequately supported by the available evidence. It preferred not to include a monitoring disutility. The clinical and patient experts agreed that avoiding routine liver-function monitoring would reduce the burden for patients and specialist interstitial

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lung disease services.

The committee agreed that the model appropriately captured treatment-specific adverse-event costs, adverse-event disutilities and routine monitoring costs. It also agreed with the EAG that the proposed monitoring disutility was not appropriate. But it thought that the practical benefits of avoiding routine liver-function monitoring for patients and specialist interstitial lung disease services had likely not been fully captured in the model (see section 3.26). It concluded that these were additional benefits of nerandomilast that were not reflected in the cost-effectiveness estimates and took them into account in its decision making.

Stopping rules

3.18 In its base case, the company applied a stopping rule for all antifibrotic treatments by which treatment was stopped after an absolute decline of 10% or more in FVC % predicted within any 12-month period. This reflected the stopping criteria in the existing NICE technology appraisals guidance recommendations for IPF and was also applied in PPF for consistency (see section 3.3). The company also explored a scenario without the stopping rule. The EAG thought that the stopping rule had an important effect on the cost-effectiveness results. This was because it interacted with the company's assumptions about treatment discontinuation (see section 3.13).

The committee questioned whether stopping treatment after a 10% decline in FVC % predicted over 12 months was clinically appropriate. The clinical experts explained that this threshold predicts poor prognosis rather than treatment failure. They also explained that people whose lung function continues to decline are still likely to benefit from treatment. In addition, they explained that the stopping rule is not routinely applied in NHS practice and that treatment is generally continued if it is well tolerated. The committee concluded that an FVC-based stopping rule did not reflect current NHS clinical practice and preferred analyses without it.

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Minor model corrections

3.19 The EAG identified several minor technical issues in the company's economic model, including:

- correcting the application of acute exacerbation disutilities
- updating the adverse-event assumptions to include gastrointestinal perforation
- correcting the associated costs and utility decrements
- applying the appropriate NHS reference costs for physiotherapy and occupational therapy visits.

The company accepted these amendments at the committee meeting. The committee agreed that they improved the accuracy of the model and should be incorporated into the cost-effectiveness analyses. It noted that they only had a minimal effect on the results and did not materially affect the key uncertainties in the economic model.

Severity

3.20 The committee considered the severity of IPF and PPF using the severity modifier described in NICE's technology appraisal and highly specialised technologies guidance manual. The company and the EAG both concluded that the absolute and proportional QALY shortfall estimates (that is, the extent to which the quality and length of life of people with IPF or PPF differs from that of the general population) did not meet the threshold for applying a severity weighting.

The committee recognised that IPF and PPF are serious, progressive conditions associated with substantial morbidity and premature mortality. It understood the patient experts' concern that not applying a severity modifier could give the impression that these were not severe conditions. But the severity modifier is determined by the QALY shortfall criteria, which were not met in this evaluation. The committee concluded that a severity modifier should not be applied.

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Cost-effectiveness estimates

Committee's preferred assumptions

3.21 The committee noted that neither the company's nor the EAG's base cases or scenario analyses included all its preferred assumptions. These were:

- using the nationally available generic price for nintedanib (see section 3.16)
- assuming equivalent treatment effects for nerandomilast, nintedanib and pirfenidone on FVC progression, acute exacerbations and overall survival (see section 3.11 and section 3.12)
- modelling treatment effects while people are on treatment and stopping treatment-specific effects when treatment is stopped, while preserving any benefit accrued during treatment (see section 3.13)
- excluding a utility decrement associated with routine liver-function monitoring (see section 3.17)
- excluding FVC-based stopping rules for all treatments (see section 3.18)
- including the EAG's accepted minor technical corrections to the economic model (see section 3.19).

Acceptable ICER

3.22 NICE's manual on health technology evaluations notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £25,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee noted that there remained substantial uncertainty in both the clinical evidence and the economic modelling. In particular, that:

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- the comparative clinical-effectiveness evidence was based on exploratory nerandomilast-alone subgroup analyses that were not powered for hypothesis testing and included relatively few clinical events, particularly deaths and acute exacerbations
- the ITCs did not robustly establish clinically meaningful differences in efficacy between nerandomilast and the comparators
- the relationship between FVC decline and overall survival remained uncertain, and the model estimated treatment effects on disease progression, acute exacerbations and mortality independently
- the committee's preferred approach to modelling treatment discontinuation, in which treatment effects apply only while people are having treatment and stop when treatment is discontinued while preserving any accrued benefit, could not be implemented in the current model.

The committee also noted that the current model structure meant that it was not possible to implement all its preferred assumptions simultaneously. So, there was no single cost-effectiveness analysis that fully reflected the committee's preferred assumptions, which increased the uncertainty in the cost-effectiveness estimates.

Taking these factors, along with any uncaptured benefits (see section 3.26) into account, the committee concluded that the ICER would need to be towards the lower end of the range normally considered a cost-effective use of NHS resources (£25,000 to £35,000 per QALY gained) before it could recommend nerandomilast for routine use.

Areas needing clarification and further analyses

3.23 The committee agreed that there were several areas of uncertainty (see section 3.22). It would like the company to provide:

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- Further evidence to support pooling the IPF and PPF nerandomilast-alone subgroup populations for the mortality analyses. This should include:
  - analyses using individual patient data from the full FIBRONEER trial populations to investigate the relationship between FVC decline and mortality separately for IPF and PPF, and in the pooled population if appropriate
  - assessment of whether background antifibrotic treatment modifies this relationship
  - sensitivity analyses exploring the robustness of the mortality estimates to small changes in the number and timing of deaths (see section 3.8).
- Revised economic analyses using a consistent approach to modelling treatment benefit across FVC progression, acute exacerbations and overall survival. This should include a scenario assuming equivalent treatment effects for nerandomilast, nintedanib and pirfenidone across all 3 outcomes, with the differences in cost effectiveness arising principally from adverse events, treatment discontinuation, health-related quality of life and costs (see section 3.11 and section 3.12).
- A revised approach to treatment discontinuation, in which treatment-specific effects stop when treatment is stopped, while preserving any benefit accrued during treatment. The company should also provide scenario analyses exploring alternative assumptions about the persistence of treatment effect after discontinuation (see section 3.13).
- Analyses exploring whether nerandomilast retains its clinical effectiveness in people who have previously had antifibrotic treatment to help to address the uncertainty around treatment sequencing (see section 3.14).
- Further information on dose reductions for nerandomilast. This should include the proportion of people in the FIBRONEER trials who reduced their dose from 18 mg to 9 mg twice daily. If available, it should also include the duration of dose reduction and associated clinical

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outcomes. The company should also provide a scenario analysis accounting for the impact of dose reductions across all antifibrotic treatments on clinical effectiveness, treatment duration and costs (see section 3.15).

- Revised cost-effectiveness analyses. These should:
  - incorporate the nationally available generic price for nintedanib (see section 3.16)
  - exclude an FVC-based stopping rule (section 3.18)
  - incorporate the EAG's resource use and accepted minor model corrections (section 3.17 and section 3.19).

Cost-effectiveness estimates

3.24 The company and the EAG each presented base-case analyses and a range of scenario analyses. None of these analyses fully reflected the committee's preferred assumptions (see section 3.21). Also, none resulted in ICERs that were within the range that the committee thought would represent a cost-effective use of NHS resources, given the remaining uncertainty. The exact ICERs cannot be reported because they include confidential commercial information.

Other factors

Equality

3.25 Stakeholders highlighted regional inequalities in access to specialist interstitial lung disease services. They noted that people living in areas of greater socioeconomic deprivation or further from specialist centres may have reduced access to specialist care. The committee recognised these inequalities but concluded that they reflected variation in service provision that could not be addressed through its recommendations. So, they did not affect the committee's recommendations.

Uncaptured benefits

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3.26 The committee considered whether there were any benefits of nerandomilast that were not fully captured in the economic model. It recalled that avoiding routine liver-function monitoring could reduce treatment burden for people with IPF or PPF and demands on specialist interstitial lung disease services. Although the evidence did not support the company's proposed monitoring disutility, the committee thought that these practical benefits were not fully reflected in the cost-effectiveness estimates (see section 3.17). It took these benefits into account when considering the acceptable ICER.

Conclusion

Recommendation

3.27 The committee acknowledged the substantial burden of IPF and PPF and the need for additional treatment options that are effective and well tolerated. It noted that nerandomilast slowed decline in lung function compared with placebo in the full trial populations. But it noted that its clinical effectiveness compared with available antifibrotic treatments remained uncertain because the evidence was based on exploratory nerandomilast-alone subgroup analyses and ITCs. The committee acknowledged that nerandomilast may offer practical advantages because its use does not need routine liver-function monitoring and it may have tolerability advantages over nintedanib (see section 3.9). But these benefits were not sufficient to overcome the uncertainty in the clinical- and cost-effectiveness evidence. Taking into account the cost-effectiveness estimates, the remaining uncertainties and the acceptable ICER, the committee concluded that nerandomilast could not be recommended as a cost-effective use of NHS resources for treating IPF or PPF.

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4 Evaluation committee members and NICE project team

Evaluation committee members

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

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

Charles Crawley

Chair, technology appraisal committee B

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, a project manager and an associate director.

Sharlene Ting

Technical lead

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Technical adviser

Jeremy Powell

Project manager

Emily Crowe

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