

## 5.18 NINTEDANIB

**100 mg capsule, 60; 150 mg capsule, 60**  
**Ofev®, Boehringer Ingelheim Pty Ltd**

### 1 Purpose of Application

- 1.1 To request Authority Required listing for nintedanib for treatment of idiopathic pulmonary fibrosis (IPF).

### 2 Requested listing

- 2.1 The submission requested that the PBAC consider listing on the basis of 'rule of rescue'. The following table details the rule of rescue criteria and summary of the response.

**Responses to the four factors relevant to the consideration of the 'rule of rescue'**

Rule of rescue factor (Guidelines, version 4.4, p258)	Submission response	Comment
(1) No alternative exists in Australia to treat patients with the specific circumstances of the medical condition meeting the criteria of the restriction. This means that there are no non-pharmacological or pharmacological interventions for these patients.	<ul style="list-style-type: none"> <li>No specific disease modifying pharmacological interventions are available for patients with IPF.</li> <li>Current recommended treatment for IPF is BSC: providing information and support, symptom relief, management of comorbidities and withdrawal of therapies that may be suspected to be ineffective or causing harm.</li> <li>Lung transplant, while potentially curative, is only an option for a limited number of patients.</li> </ul>	<ul style="list-style-type: none"> <li>Although no disease modifying pharmacological interventions for IPF are available in Australia, pirfenidone has been approved for use in Europe (2011), Canada (2012) and the USA (2014). [REDACTED]</li> <li>Given the lack of available treatments for IPF, patients may access pirfenidone treatment via the TGA special access scheme.</li> </ul>
(2) The medical condition defined by the requested restriction is severe, progressive and expected to lead to premature death. The more severe the condition, or the younger the age at which a person with the condition might die, or the closer a person with the condition is to death, the more influential the rule of rescue might be in consideration by the PBAC.	<ul style="list-style-type: none"> <li>Approximately 50% of patients die within the first 3.5 years of diagnosis.</li> </ul>	<ul style="list-style-type: none"> <li>The clinical course of IPF is highly variable, characterised by a patient population of fast and slow progressors.</li> <li>The submission indicates that variability in IPF progression results in a proportion of patients (approximately 20% who have not experienced an acute exacerbation) with survival of up to 10 years.</li> </ul>

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Rule of rescue factor (Guidelines, version 4.4, p258)	Submission response	Comment
(3) The medical condition defined by the requested restriction applies to only a very small number of patients. Again, the fewer the patients, the more influential the rule of rescue might be in the consideration by PBAC. However, PBAC is also mindful that the PBS is a community-based scheme and cannot cater for individual circumstances.	<ul style="list-style-type: none"> <li>The submission estimates that the prevalence of IPF in Australia is 11.37/100,000, based on an average of prevalence rates identified in 12 publications (range: 1.25/100,000 to 27.9/100,000).</li> <li>Incidence rates ranged from 0.22/100,000 to 9.13/100,000.</li> </ul>	<ul style="list-style-type: none"> <li>There is limited epidemiological evidence to reliably determine the prevalence of IPF in Australia. Methods used by the submission are likely to underestimate the prevalence of IPF.</li> </ul>
(4) The proposed medicine provides a worthwhile clinical improvement sufficient to qualify as a rescue from the medical condition. The greater the rescue, the more influential the rule of rescue might be in the consideration by the PBAC.	<ul style="list-style-type: none"> <li>Nintedanib is a disease modifying pharmacological intervention for IPF.</li> <li>Nintedanib is associated with: a significant reduction in the rate of pulmonary decline; statistically significant reduction in the proportion of patients that experienced an FVC%Pred decline; reduced incidence of acute IPF exacerbations; and trend towards improved survival.</li> </ul>	<ul style="list-style-type: none"> <li>The impact upon patient relevant outcomes is limited (refer to clinical claim): <ul style="list-style-type: none"> <li>No statistically significant difference was observed for overall survival (treated set analysis) or disease specific measures (SGRQ).</li> <li>FVC as a surrogate measure for mortality has not been adequately validated.</li> </ul> </li> </ul>

Abbreviations: BSC = best supportive care; IPF = idiopathic pulmonary fibrosis; St George's Respiratory Questionnaire = SGRQ. Source: pp226-229 of the submission

2.2 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
NINTEDANIB 100 mg capsule, 60	1	5	\$ [redacted] (\$ [redacted] after rebate)	Ofev® BY
150 mg capsule, 60	1	5	\$ [redacted] (\$ [redacted] after rebate)	

<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Severity:</b>	Mild to moderate
<b>Condition:</b>	Idiopathic pulmonary fibrosis
<b>PBS Indication:</b>	<i>Mild to moderate</i> idiopathic pulmonary fibrosis
<b>Treatment phase:</b>	Initial <i>treatment</i>
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined

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<b>Treatment criteria:</b>	<i>Must be treated by a respiratory physician or specialist physician experienced in the management of patients with idiopathic pulmonary fibrosis.</i>
<b>Clinical criteria:</b>	<p><del>Initial PBS subsidised treatment with nintedanib prescribed by a respiratory physician or specialist physician experienced in the management of patients with idiopathic pulmonary fibrosis. Adult patient aged 40 years and over to satisfy the following criteria:</del></p> <p><del>—————</del> <i>Diagnosis of idiopathic pulmonary fibrosis confirmed and documented by a respiratory physician, or specialist physician as part of a multidisciplinary team. The diagnosis should be less than 5 years old, or greater than 5 years old where there is confirmed progressive disease.</i></p> <p><del>AND</del></p> <p><i>Patient must have a confirmed and documented diagnosis of idiopathic pulmonary fibrosis that is less than 5 years old; OR</i></p> <p><i>Patient must have a confirmed and documented diagnosis of idiopathic pulmonary fibrosis that is greater than 5 years old where there is confirmed progressive disease,</i></p> <p><del>AND</del></p> <p><i>Patient must have chest high resolution computed tomography (HRCT) consistent with diagnosis of idiopathic pulmonary fibrosis within the previous 12 months,</i></p> <p><del>AND</del></p> <p><i>Patient must have forced vital capacity (FVC) greater than 50% of predicted normal for age, gender and weight, and FEV1/FVC ratio &gt;0.7,</i></p> <p><del>AND</del></p> <p><i>Patient must have diffusing capacity for carbon monoxide (DLCO) corrected for haemoglobin greater than 30%,</i></p> <p><del>AND</del></p> <p><i>Patient must not have interstitial lung disease due to other known causes including domestic and occupational environmental exposures, connective tissue disease, and drug toxicity.</i></p>
<b>Population criteria:</b>	<p><del>PBS subsidy does not apply to other known causes of interstitial lung disease due to domestic and occupational environmental exposures, connective tissue disease, and drug toxicity</del></p> <p><i>Patient must be aged 40 years or older.</i></p>
<b>Administrative advice</b>	<i>Special Pricing Arrangements apply.</i>
<b>Administrative advice</b>	<p><i>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</i></p> <p><i>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at <a href="http://www.humanservices.gov.au">www.humanservices.gov.au</a></i></p> <p><i>Applications for authority to prescribe should be forwarded to:</i></p> <p><i>Department of Human Services</i></p> <p><i>Prior Written Approval of Complex Drugs</i></p> <p><i>Reply Paid 9826</i></p> <p><i>GPO Box 9826</i></p> <p><i>HOBART TAS 7001</i></p>

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<b>Severity</b>	Mild to moderate
<b>Condition:</b>	Idiopathic pulmonary fibrosis
<b>Indication:</b>	<i>Mild to moderate</i> idiopathic pulmonary fibrosis
<b>Phase of treatment:</b>	Continuing treatment
<b>Restriction:</b>	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	<p><i>Patient must have previously received PBS-subsidised treatment with nintedanib for this condition.</i></p> <p>AND</p> <p><i>Patient must have a confirmed and documented diagnosis of idiopathic pulmonary fibrosis that is less than 5 years old; OR</i>  <i>Patient must have a confirmed and documented diagnosis of idiopathic pulmonary fibrosis that is greater than 5 years old where there is confirmed progressive disease.</i></p> <p><del>Adult patient aged 40 years and over to satisfy the following criteria:</del></p> <ul style="list-style-type: none"> <li><del>— Initial diagnosis documented and treatment initiated by a respiratory physician experienced in the management of patients with idiopathic pulmonary fibrosis, or specialist physician as part of a multidisciplinary team. The diagnosis should be less than 5 years old or greater than 5 years old where there is confirmed progressive disease.</del></li> </ul> <p>AND</p> <ul style="list-style-type: none"> <li><del>— Chest high resolution computed tomography (HRCT) at diagnosis consistent with idiopathic pulmonary fibrosis</del></li> </ul> <p>AND</p> <ul style="list-style-type: none"> <li><del>— Forced vital capacity (FVC) greater than or equal to 50% of predicted normal at diagnosis</del></li> </ul> <p>AND</p> <ul style="list-style-type: none"> <li><del>— Diffusing capacity for carbon monoxide (DL<sub>CO</sub>) corrected for haemoglobin greater than 30% at diagnosis</del></li> </ul>
<b>Population criteria</b>	<del>PBS subsidy does not apply to other known causes of interstitial lung disease due to domestic and occupational environmental exposures, connective tissue disease, and drug toxicity</del>
<b>Administrative advice</b>	<i>Authority applications for continuing treatment may be made by telephone to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</i>

2.3 The Pre-Sub-Committee Response (PSCR) accepted the suggested revisions to the restriction for PBAC consideration. In addition, the evaluation questioned the intent of requiring that continuing patients have a diagnosis that is less than 5 years old (or greater than 5 years old where there is confirmed progressive disease). The Pre-PBAC Response indicated that the intent of this criterion was to attempt to ensure that patients with long-standing IPF could have access to nintedanib where the treating physician has confirmed disease progression.

2.4 The ESC considered that the restriction could be revised to include the:

- role of a multi-disciplinary team in diagnosing the condition (NICE Guideline January 2015);

- criteria for enrolment in the two phase 3 trials including: IPF being diagnosed based on most recent and appropriate guidelines (Raghu 2011, as outlined in the submission); and surgical biopsy to confirm suspected IPF; and
  - patient to have FEV1/FVC ratio of greater than 0.7.
- 2.5 The Pre-PBAC Response accepted the inclusion of the role of a multi-disciplinary team in initial diagnosis. However, the Pre-PBAC Response did not accept that it was necessary for the listing to require biopsy for confirmation of diagnosis given the clinical symptoms of IPF, the availability of high resolution computed tomography (HRCT), and that biopsy is invasive and can therefore lead to morbidity and mortality in elderly IPF patients.
- 2.6 The ESC also considered whether it would be desirable to include stopping rules in case of a lack of efficacy. However, it was acknowledged that it would be difficult to define a lack of response in relation to FVC in a progressive, irreversible and fatal condition with heterogeneous patient progression.
- 2.7 The submission sought listing on the basis of a cost utility analysis comparing nintedanib to best supportive care.
- 2.8 The submission proposed an effective price of \$ [REDACTED] for nintedanib 100mg x 60 capsules and \$ [REDACTED] for nintedanib 150mg x 60 capsules for the IPF listing. While this effective price was applied in the economic evaluation and the financial estimates, a special pricing arrangement (SPA) was also requested across the IPF and non-small cell cancer (NSCLC) indications as summarised in the following table.

**Special pricing arrangement for nintedanib**

Nintedanib		Public DPMQ <sup>^</sup>	Confidential Rebate	Effective price <sup>*</sup>	SPA: IPF and NSCLC
IPF	100mg, 60 capsules x 1	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	Effective ex-manufacturer price after SPA rebate*: 100mg, 60 capsules: \$ [REDACTED] 150mg, 60 capsules: \$ [REDACTED]
	150mg, 60 capsules x 1	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	
NSCLC	100mg, 60 capsules x 2	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	
	150mg, 60 capsules x 1	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	

\* [REDACTED] are proposed for the IPF and NSCLC indications. The submission claims (p221) this corresponds to [REDACTED] for nintedanib 100mg x 60 and [REDACTED] for nintedanib 150mg x 60.

<sup>^</sup> The submission states (p221) that the DPMQ for IPF and NSCLC indications are the same. This is inconsistent with the public DPMQs presented in the IPF and NSCLC submissions for the 100mg strength: NSCLC: 60 capsules x 2 requested (public DPMQ = \$ [REDACTED]); IPF: 60 capsules x 1 requested (public DPMQ = \$ [REDACTED])

Abbreviations: IPF = idiopathic pulmonary fibrosis; NSCLC = non-small cell lung cancer; SPA = special pricing arrangement.

Source: F.2-1, p221 of the submission

- 2.9 The submission proposed [REDACTED] of \$ [REDACTED] (100mg × 60 capsules) and \$ [REDACTED] (150mg × 60 capsules) across the IPF and NSCLC listings.

*For more detail on PBAC’s view, see section 7 “PBAC outcome”*

### 3 Background

- 3.1 **TGA status:** The submission was made under TGA/PBAC Parallel Process with the Delegate’s consideration expected in July 2015. The Round 1 Clinical Evaluation Report was received on 26 February 2015.

- 3.2 This was the first consideration by the PBAC of nintedanib for the treatment of IPF.

*For more detail on PBAC’s view, see section 7 “PBAC outcome”*

### 4 Clinical place for the proposed therapy

- 4.1 IPF is a non-neoplastic irreversible fatal lung disease resulting from abnormal remodelling of lung tissue leading to fibrosis and a progressive degradation of lung function. The clinical course is unpredictable and there is a high degree of variability in IPF disease progression. Median survival after diagnosis is 3.5 years. Lung transplant is the only potentially curative intervention for IPF. No other medications are listed on the PBS specifically for the treatment of IPF.

- 4.2 The submission proposed that nintedanib be used in combination with best supportive care to slow disease progression associated with IPF.

- 4.3 The ESC noted the significant clinical need for an effective treatment for IPF.

*For more detail on PBAC’s view, see section 7 “PBAC outcome”*

### 5 Comparator

- 5.1 The submission nominated best supportive care as the main comparator. The evaluation considered this was appropriate.

- 5.2 Additionally, the submission indicated that the sponsor was aware of another novel agent for the treatment of IPF, pirfenidone, which was not TGA approved or PBS-listed at the time of PBAC consideration. A summary of available evidence and an indirect comparison with nintedanib was provided in an attachment to the submission.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

## **6 Consideration of the evidence**

### **Sponsor hearing**

- 6.1 The sponsor requested a hearing for this item. The respiratory clinician discussed the relevance of FVC as a surrogate clinical outcome for morbidity and mortality. In addition, the clinician claimed that FVC, or change in FVC, is a clinically important end point in itself in monitoring whether a patient's condition has stabilised or has continued to progress. The clinician also discussed the appropriateness of the modelled time horizon of 10 years to the natural history of the disease. The context in which nintedanib should be responsibly prescribed for IPF was addressed, including the role of a multi-disciplinary care team in diagnosis.
- 6.2 The PBAC considered that the hearing was informative as it provided a clinical perspective on treating this disease for which no other treatment was currently available on the PBS.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

### **Consumer comments**

- 6.3 The PBAC noted and welcomed the input from individuals (3) and organisations (1) via the Consumer Comments facility on the PBS website. The comments emphasised the benefits of nintedanib including an increase in life expectancy and quality of life.
- 6.4 The PBAC noted the advice received from the Australian IPF Registry Steering Committee that stressed the clinical need for a medication for IPF. The organisation indicated that it is confident that nintedanib is proved to successfully slow down the progression of IPF and may improve the quality and length of life. The PBAC specifically noted the advice that prescribers should be aware of the criteria for prescribing, the side effects of the drug and ideally be experienced with supervising use of nintedanib. The Steering Committee recommended that authority to prescribe nintedanib could be applied for, and prescription be coordinated through only those hospitals regarded as having expertise in IPF diagnosis and management. The PBAC noted that this advice was supportive of the evidence provided in the submission.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

## Clinical trials

- 6.5 The submission was based on three head-to-head randomised trials, which compared nintedanib to placebo: Trial 30 (n=432), Trial 32 (n=515) and Trial 34 (n=551).
- 6.6 Details of the trials presented in the submission are provided in the following table.

### Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
<b>Direct randomised trials</b>		
Trial 30	<p>A 52 week, double blind, randomized, placebo-controlled trial evaluating the effect of BIBF 1120 administered at oral doses of 50mg qd, 50mg bid, 100mg bid and 150mg bid on Forced Vital Capacity decline during one year, in patients with Idiopathic Pulmonary Fibrosis, with optional active treatment extension until last patient out.</p> <p>Richeldi L, Costabel U, Selman M, Kim DS, Hansell DM, Nicholson AG, Brown KK, Flaherty KR, Noble PW, Raghu G, Brun M, Gupta A, Juhel N, Klüglich M, du Bois RM. Efficacy of a tyrosine Kinase Inhibitor in Idiopathic Pulmonary Fibrosis</p>	<p>25 February 2011</p> <p><i>The New England Journal of Medicine.</i> 2011; 365 (12): 1079-1087</p>
Trial 32	<p>A 52 weeks, double blind, randomized, placebo-controlled trial evaluating the effect of oral BIBF 1120, 150mg twice daily, on annual Forced Vital Capacity decline, in patients with Idiopathic Pulmonary Fibrosis (IPF)</p> <p>Richeldi L, Cottin V, Flaherty KR, Kolb M, Inoue Y, Raghu G, Taniguchi H, Hansell DM, Nicholson AG, Le Maulf F, Stowasser S, Collard HR. Design of the INPULSIS™ trials: two phase 3 trials of nintedanib in patients with idiopathic pulmonary fibrosis.</p> <p>Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, Cottin V, Flaherty KR, Hansell DM, Inoue Y, Kim DS, Kolb M, Nicholson AG, Noble PW, Selman M, Taniguchi H, Brun M, Le Maulf F, Girard M, Stowasser S, Schlenker-Herceg R, Disse B, Collard HR; INPULSIS Trial Investigators. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis</p>	<p>08 April 2014</p> <p><i>Respiratory Medicine.</i> 2014; 108(7): 1023-1030</p> <p><i>The New England Journal of Medicine.</i> 2014; 370(22): 2071-2082</p>
Trial 34	<p>A 52 weeks, double blind, randomized, placebo-controlled trial evaluating the effect of oral BIBF 1120, 150mg twice daily, on annual Forced Vital Capacity decline, in patients with Idiopathic Pulmonary Fibrosis (IPF)</p> <p>Richeldi L, Cottin V, Flaherty KR, Kolb M, Inoue Y, Raghu G, Taniguchi H, Hansell DM, Nicholson AG, Le Maulf F, Stowasser S, Collard HR. Design of the INPULSIS™ trials: two phase 3 trials of nintedanib in patients with idiopathic pulmonary fibrosis.</p> <p>Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, Cottin V, Flaherty KR, Hansell DM, Inoue Y, Kim DS, Kolb M, Nicholson AG, Noble PW, Selman M, Taniguchi H, Brun M, Le Maulf F, Girard M, Stowasser S, Schlenker-Herceg R, Disse B, Collard HR; INPULSIS Trial Investigators. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis</p>	<p>08 April 2014</p> <p><i>Respiratory Medicine.</i> 2014; 108(7): 1023-1030</p> <p><i>The New England Journal of Medicine.</i> 2014; 370(22): 2071-2082</p>

Source: Table B.2-2, p26 of the submission

6.7 The key features of the direct randomised trials are summarised in the table below.

**Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Trial 30	432	R, DB, MC, MN, phase 2 dose finding trial; 52 weeks	High <sup>^</sup>	IPF	FVC: annual rate of decline, absolute change from baseline;	Kaplan Meier survival analysis: parametric extrapolation
Trial 32	515	R, DB, MC, MN, phase 3	Low	IPF	FVC responder; Acute IPF exacerbation; Survival; SGRQ	Kaplan Meier survival analysis: parametric extrapolation; transition probabilities, cycle probabilities of adverse events; utilities: EQ-5D
Trial 34	551					

<sup>^</sup> High risk of bias associated with the analyses of FVC change from baseline and incidence of acute IPF exacerbations. Abbreviations: DB=double blind; FVC=forced vital capacity; IPF=idiopathic pulmonary fibrosis. MC=multi-centre; MN=multinational; R=randomised; SGRQ=St George’s Respiratory Questionnaire. Source: compiled during the evaluation

6.8 Meta-analyses of results from Trial 30, 32 and 34 were presented by the submission. The inclusion of the phase 2 Trial 30 in the meta-analyses was questionable, due to differences in the handling of missing data (last observation carried forward approach) and the comparability of the trial populations (differing diagnostic criteria was applied for the diagnosis of IPF).

6.9 The PSCR acknowledged ‘the potential bias as a result of the difference in the handling of missing data’. The PSCR argued, however, that the inclusion or exclusion of Trial 30 did not significantly alter the conclusions and that ‘despite the difference in diagnostic criteria there were no clinically significant differences between the trial populations’. The ESC noted that the diagnostic criteria used in Trial 30 were the more recent updated criteria (Raghu 2011).

*For more detail on PBAC’s view, see section 7 “PBAC outcome”*

**Comparative effectiveness**

6.10 Key results from the meta-analyses are presented in the table below.

**Summary of the meta-analyses of key efficacy outcomes from the nintedanib trials**

Outcome	Meta analyses (Trial 30, 32 & 34)
Annual rate of decline in FVC (ml/year)	MD (95% CI) = [redacted]
Absolute change in FVC%Pred from baseline to week 52	MD (95% CI) = [redacted]
Proportion of patients with a decline in FVC%pred <5% over 52 weeks	RR (95% CI) = [redacted]
Incidence of acute IPF exacerbation	RR (95% CI) = [redacted]
Survival: all-cause mortality over 52 weeks	RR (95% CI) = [redacted]
SGRQ: change from baseline over 52 weeks	MD (95% CI) = [redacted]

Abbreviations: FVC = forced vital capacity; IPF = idiopathic pulmonary fibrosis; MD = mean difference; RR = relative risk; SGRQ = St George’s Respiratory Questionnaire. Source: Table B.8-1, pp107-108 of the submission

6.11 The impact of the statistically significant difference across measures of change in FVC over 52 weeks upon patient relevant outcomes is addressed in the clinical claim.

- 6.12 The table below presents the results of the incidence of investigator reported and adjudicated acute IPF exacerbations. Results for the incidence of acute IPF exacerbations were inconsistent across the trials and acute IPF exacerbations in Trial 30 were based on investigator-assessed outcomes reporting. The PSCR acknowledged that, given the subjectivity associated with the assessment of acute IPF exacerbation, the independent adjudication process used in Trials 32 and 34 was less subject to bias. The statistically significant risk ratio for the incidence of adjudicated acute IPF exacerbations indicated an approximately 65% reduction associated with nintedanib treatment. The ESC noted the absolute numbers of adjudicated acute IPF exacerbations were small, with 12 out of 638 participants experiencing an acute exacerbation event in the nintedanib arm compared with 24 of 423 participants in the placebo arm.

**Incidence of acute IPF exacerbations: investigator reported; adjudicated events**

Trial	Incidence of acute IPF exacerbations: n/N (%)		Treatment effect		
	Nintedanib	Placebo	HR (95% CI)	RR (95% CI)	RD (95% CI)
<b>Incidence of investigator reported acute IPF exacerbations</b>					
Trial 30	2/86 (2.3)	12/87 (13.8)	<b>0.16 (0.03, 0.71)</b>	<b>0.17 (0.04, 0.73)</b>	<b>-0.11 (-0.19, -0.04)</b>
Trial 32	19/309 (6.1)	11/204 (5.4)	1.15 (0.54, 2.42)	1.14 (0.55, 2.35)	0.01 (-0.03, 0.05)
Trial 34	12/329 (3.6)	21/219 (9.6)	<b>0.38 (0.19, 0.77)</b>	<b>0.38 (0.19, 0.76)</b>	<b>-0.06 (-0.10, -0.02)</b>
Meta-analysis			Trial 32 & 34: ██████████	██████████	██████████
Heterogeneity			NA	I <sup>2</sup> = ██████	I <sup>2</sup> = ██████
<b>Incidence of adjudicated acute IPF exacerbations</b>					
Trial 32	7/309 (2.3)	8/204 (3.9)	0.55 (0.20, 1.54)	0.58 (0.21, 1.57)	-0.02 (-0.05, 0.01)
Trial 34	5/329 (1.5)	16/219 (7.3)	<b>0.20 (0.07, 0.56)</b>	<b>0.21 (0.08, 0.56)</b>	<b>-0.06 (-0.09, -0.02)</b>
Meta analysis			██████████	██████████	██████████
Heterogeneity			NA	I <sup>2</sup> = ██████	I <sup>2</sup> = ██████

Figures in bold indicate results that are statistically significant

Abbreviations: IPF = idiopathic pulmonary fibrosis.

Source: Table 3.2.1.3: 1, p85 and Table 3.2.1.3: 2, p89, Summary of Clinical Efficacy (U13-2383-01); Table B.6-7, p84, Table B.6-8, p85 of the submission.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

**Comparative harms**

- 6.13 Key results from the meta-analyses of safety outcomes are presented in the following table.

**Summary of the meta-analyses of key safety outcomes from the nintedanib trials**

	Meta-analysis (Trial 30, 32 & 34): RR (95% CI)	
<b>Overall safety outcomes</b>		
Number of patients with any AEs		
Drug related AEs		
Patients with AEs leading to discontinuation		
Patients with SAEs		
<b>Common adverse events (&gt;5%)</b>		
Diarrhoea		
Nausea		
Vomiting		
Dyspnoea		

Abbreviations: AE = adverse event; SAE = serious adverse event.

Source: Table B.6-12, pp93-94 and Table B.8-1, pp107-108 of the submission

- 6.14 Nintedanib was associated with statistically significantly higher instances of drug related adverse events and gastrointestinal adverse events including diarrhoea, nausea and vomiting compared with best supportive care. Additionally, there was a significant reduction in the incidence of dyspnoea. The ESC noted that the reduction in the incidence of dyspnoea could be considered a benefit of treatment as opposed to an adverse event.
- 6.15 In the pooled analysis of the phase 3 trials (Appendix 9 of the submission), for adverse events of special interest, there were higher incidences of thromboembolic events (█% vs █%) and hypertension (█% vs █%) in the nintedanib treatment arms. A statistically significant difference was observed for arterial thromboembolic events (RR = █, 95% CI: █, █). No evidence was available to determine whether the above cardiovascular/thromboembolic safety signals would have any substantial impact upon long term patient risks.
- 6.16 The ESC noted that the draft Product Information stated that ‘a higher percentage of patients experienced myocardial infarctions in the nintedanib group (1.6%) compared to the placebo group (0.5%). Use caution when treating patients at higher cardiovascular risk including known coronary artery disease. Treatment interruption should be considered in patients who develop signs or symptoms of acute myocardial ischaemia.’ This risk was also a discussion point in the published versions of the trials (NEJM).

*For more detail on PBAC’s view, see section 7 “PBAC outcome”*

**Benefits/harms**

- 6.17 A summary of the comparative benefits and harms for nintedanib and placebo are presented in the following table.

Summary of comparative benefits and harms for nintedanib and placebo

Trial	Nintedanib	Placebo	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				Nintedanib	Placebo	
<b>Benefits</b>						
<b>All-cause mortality over 52 weeks</b>						
Trial 30, 32 & 34	42/724	42/510	█	5.8	8.2	█
<b>Acute IPF exacerbation: investigator reported</b>						
Trial 30, 32 & 34	33/724	44/510	█	4.6	8.6	█
<b>Acute IPF exacerbation: adjudicated</b>						
Trial 32 & 34	12/638	24/423	0.35 (0.13, 0.94)	1.9	5.7	-0.04 (-0.08, 0.01)
	<b>Nintedanib</b>		<b>Placebo</b>		<b>Mean difference (95% CI)</b>	
	<b>n</b>	<b>Mean Δ baseline (SE)</b>	<b>n</b>	<b>Mean Δ baseline (SE)</b>		
<b>Annual rate of decline in FVC (ml/year)</b>						
Trial 30	84	-60 (39)	83	-190 (36)	█	
Trial 32	250	-114.65 (15.33)	204	-239.91 (18.71)		
Trial 34	269	-113.59 (15.73)	219	-207.32 (19.31)		
<b>Absolute change in FVC%Pred from baseline to week 52</b>						
Trial 30	84	-1.04 (0.99)	84	-6.00 (1.02)	█	
Trial 32	250	-2.76 (0.41)	165	-5.98 (0.47)		
Trial 34	269	-3.09 (0.43)	180	-6.15 (0.51)		
<b>Harms</b>						
	Nintedanib	Placebo	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				Nintedanib	Placebo	
<b>Diarrhoea</b>						
Trial 30, 32 & 34	445/723	91/508	3.41 (2.81, 4.15)	61.5	17.9	█
<b>Vomiting</b>						
Trial 30, 32 & 34	85/723	15/508	3.82 (2.22, 6.58)	11.8	3.0	█
<b>Dyspnoea</b>						
Trial 30, 32 & 34	55/723	59/508	0.66 (0.46, 0.93)	7.6	11.6	█

\* Duration of follow-up: Trial 30, 32 & 34 – 52 weeks. Abbreviations: FVC = forced vital capacity; IPF = idiopathic pulmonary fibrosis; RD = risk difference; RR = risk ratio, SE = standard error. Source: Compiled during the evaluation

- 6.18 On the basis of direct evidence presented by the submission, in comparison to placebo, nintedanib was associated with:
- Approximately a 118.9 ml/year reduction in the annual rate of decline in FVC.
  - Approximately a 3.31% reduction in absolute change in FVC%Pred (proportion of predicted normal FVC for age, gender and weight) from baseline to week 52.
  - No significant difference was observed for all-cause mortality over 52 weeks.
  - No significant difference was observed for the incidence of acute investigator reported IPF exacerbations.
  - Approximately 65% reduction in adjudicated acute exacerbations of IPF.
- 6.19 On the basis of direct evidence presented by the submission, for every 100 patients treated with nintedanib in comparison to placebo:
- Approximately 43 additional patients would have diarrhoea over a 52 week duration of follow-up.
  - Approximately 9 additional patients would have vomiting over a 52 week duration of follow-up.

- Approximately 4 fewer patients would have dyspnoea over a 52 week duration of follow-up.

### Clinical claim

6.20 The submission described nintedanib as superior in efficacy when compared with placebo for the treatment of IPF. Although a statistically significant difference was observed for measures of change in FVC over 52 weeks, proportion of FVC responders and adjudicated acute exacerbations, impact upon most patient relevant outcomes was limited due to the following reasons:

- No statistically significant difference was observed for overall survival, acute investigator reported IPF exacerbations, or disease specific quality of life measures (St George's Respiratory Questionnaire (SGRQ)). The ESC noted that the SGRQ was originally designed for patients with chronic obstructive pulmonary disease and is not a disease-specific instrument for IPF. The ESC also acknowledged the statistically significant difference in adjudicated acute IPF exacerbations and the small absolute numbers of acute exacerbations and death over the time period, noting that the submission claimed that a longer trial period and extensive recruitment (potentially up to n=6000) would be necessary to provide statistical demonstration of an improvement in survival.
- FVC has not been validated as a surrogate measure for mortality. The PSCR argues that the submission presented evidence from the literature which demonstrates a higher risk of death in IPF patients who have a greater than or equal to 10% decline in FVC. The ESC acknowledged that there are epidemiologically based data showing that FVC, change in FVC and change in FVC%Pred are associated with mortality.
- The submission claimed a minimally clinically important difference (MCID) for change in FVC%Pred of 2-6%. The MCID was sourced from du Bois et al 2011a which used a distribution method based on the standard error of the measurement (SEM) of FVC%Pred from baseline to a range of alternative time intervals (e.g. week 48, SEM = 3.4, 95% CI: 3.2, 3.5). The evaluation noted that SEM is representative of a minimal detectable effect that is unlikely to be attributable to random measurement error. The evaluation considered that, as the distribution method was primarily based on statistical reasoning, there was a lack of clinical or patient input in determining the MCID. Alternatively, application of the anchor method in du Bois et al 2011a resulted in a MCID of 3.3% or 3.7%. The evaluation considered that the use of anchor methods, which are based on the patient assessment of improvement/decline, were a more suitable means of calculating the MCID given the focus of the analysis is directly linked to patient relevant outcomes. The meta-analysis of the phase 3 trials (██████████) did not reach this alternative benchmark. The PSCR argued that 'the authors concluded that a decline of 2-6% in FVC%Pred represents a clinically important difference... The authors based this range on several approaches to triangulate the results, rather than a point-estimate based on one method.'

6.21 The submission described nintedanib as being associated with a higher incidence of drug-related adverse events, which are well managed and did not lead to a significantly higher incidence of discontinuation. Although gastrointestinal adverse events were generally mild to moderate in intensity, notable differences in the duration of diarrhoea (134-139 days vs. 6.5-9.0 days) and nausea (5-8 days vs. 1 day) was observed for the comparison of nintedanib and placebo.

6.22 The PBAC considered that the claim of superior comparative effectiveness was adequately supported in terms of measures of change in FVC over 52 weeks, proportion of FVC responders and adjudicated acute exacerbations. The PBAC considered that it is clear that lower FVC is associated with a higher risk of mortality. However, the PBAC considered that quantifying the relationship between change in FVC from nintedanib and a change in mortality risk (and resulting survival gain) is challenging given the lack of demonstration of a statistically significant impact on survival or quality of life in the trial.

6.23 The PBAC considered that the claim of inferior comparative safety was reasonable.

*For more detail on PBAC’s view, see section 7 “PBAC outcome”*

### Economic analysis

6.24 The submission presented a modelled economic evaluation using a cost utility analysis. The risk sharing arrangement (RSA) proposed by the sponsor was incorporated into the economic evaluation (see paragraph 6.40).

6.25 The ESC questioned whether there was sufficient clinical evidence to proceed to a modelled economic evaluation, particularly a cost utility analysis, given:

- non-significant overall survival or quality of life outcomes;
- uncertain clinical significance of surrogate outcome of rate of FVC decline; and
- uncertain statistical and clinical significance of FVC%Pred outcome (compared with MCID).

#### Summary of model structure and rationale

Component	Summary
Time horizon	10 years in the model base case versus 12 months in the nintedanib trials. The ESC questioned whether 10 years was the clinically appropriate time horizon for this condition, given a median survival of 3.5 years
Outcomes	Cost/LYG; Cost/QALY (trial based EQ-5D utilities)
Methods used to generate results	Markov state transition model separated into two parts: ‘no exacerbation’ and ‘exacerbations’. Patients may either remain stable or transition via a one-step decline in FVC%Pred health state according to ‘no exacerbation’ or ‘exacerbation’ status. Discontinuation probabilities are also applied to the nintedanib arm of the model. Upon discontinuation of treatment, the economic model applied relevant transition probabilities associated with BSC. Patients could transition to the self-absorbing death health state at any time, as determined by the Kaplan Meier estimates (trial based economic evaluation) or Weibull extrapolations to 10 years (modelled evaluation).
Health states	8 FVC%Pred health states and death
Cycle length	0.25 years; half cycle correction applied
Transition probabilities	On the basis of pooled data from Trial 32 and Trial 34, a logistic function was used to determine the probability for progressing to a worse FVC%Pred health state

Source: compiled during the evaluation

Abbreviations: BSC = best supportive care, IPF = idiopathic pulmonary fibrosis, LYG = life year gained, QALY = quality adjusted life years.

6.26 With the exception of survival extrapolations, the economic model utilised a constant hazards approach in which the transition probabilities moved to a worse FVC%Pred health state and the risks of exacerbation remained constant throughout the 10 year modelled timeframe. The risk of disease progression and exacerbation could alter

over the course of the disease. Overall, the constant hazards approach may inadequately represent the clinical course of IPF progression over time.

6.27 Key drivers of the model are summarised in the table below.

**Key drivers of the model**

Description	Method/Value	Impact
Survival extrapolation	Parametric extrapolation to 10 years	High, favours nintedanib
Time horizon	10 years; assumed from 12 month trial duration	High, favours nintedanib

Source: compiled during the evaluation

6.28 The reliability of the economic model was significantly compromised by the submission's assumption that non-statistically significant survival benefits associated with nintedanib persist for the 10 year time horizon. The evaluation considered this was a highly optimistic interpretation of the evidence. Overall, the Weibull extrapolations were incapable of representing potential long term survival benefits, considering that the treatment effect estimated from the trials was not statistically significant. A more acceptable, but conservative, approach would have been the use of trial based Kaplan Meier survival estimates to 21 months (provided in an appendix to the submission) followed by adjustment of the nintedanib survival curves for the gradient of the best supportive care curve. The modelled economic evaluation was highly sensitive to this re-specification of the survival extrapolations (ICER more than \$200,000/QALY).

6.29 The PSCR argued that the approach proposed above was not appropriate. The ESC considered that the submission's approach (with a base case ICER of \$105,000/QALY – \$200,000/QALY) was optimistic as it used non-significant survival and quality of life benefits extrapolated from 12 months to 10 years to estimate LYs and QALYs gained. However, the ESC also considered that using the trial based Kaplan Meier survival estimates to 21 months (resulting in an ICER of more than \$200,000/QALY) would be a conservative approach.

6.30 The Pre-PBAC Response argued that the modelled 10 year time horizon was reasonable compared with the time horizons used in evaluation of IPF therapies considered by NICE (60 years) and SMC (18.5 years). Furthermore, the Pre-PBAC Response argued that the time horizon was clinically appropriate as the predicted median survival of 3.3 years over the 10 year time horizon was almost identical to the published median survival of 3.5 years and indicated that the modelled survival was similar to that observed in clinical practice.

6.31 The results of the stepped economic evaluation are provided in the following table.

**Results of the stepped economic evaluation**

Step and component	Nintedanib	BSC	Increment
<b>Step 1: trial based economic evaluation: 52 weeks</b>			
Costs	\$ [REDACTED]	\$416.00	\$ [REDACTED]
LYG	[REDACTED]	[REDACTED]	[REDACTED]
<b>Incremental cost/LYG</b>			\$ [REDACTED]
<b>Step 2: modelled economic evaluation include healthcare resource utilisation: 52 weeks</b>			
Costs	\$ [REDACTED]	\$3,073.00	\$ [REDACTED]
LYG	[REDACTED]	[REDACTED]	[REDACTED]
<b>Incremental cost/LYG</b>			\$ [REDACTED]
<b>Step 3: modelled economic evaluation including extrapolation (10 years)</b>			
Costs	\$ [REDACTED]	\$10,230.03	\$ [REDACTED]
LYG	[REDACTED]	[REDACTED]	[REDACTED]
<b>Incremental cost/LYG</b>			\$ [REDACTED]
<b>Step 4: modelled economic evaluation including utilities (10 years)</b>			
Costs	\$ [REDACTED]	\$10,230.03	\$ [REDACTED]
QALY	[REDACTED]	[REDACTED]	[REDACTED]
<b>Incremental cost/QALY</b>			\$ [REDACTED]

Source: Table D.5-1, Table D.5-2, Table D.5-3 and Table D.5-4, pp192-194 of the submission

- 6.32 The submission claimed that the estimated ICER presented for nintedanib might be considered reasonable, especially since it argued that all criteria for the ‘rule of rescue’ are met. The evaluation and the ESC considered that the applicability of the ‘rule of rescue’ for nintedanib was compromised due to concerns regarding the extent of clinical impact (refer to the clinical claim) and the severity of the disease. The ESC noted that the clinical course of IPF is highly variable, characterised by a patient population of fast and slow progressors. Although a median survival of 3.5 years was estimated for patients with IPF, approximately 20% of patients who have not experienced an acute exacerbation will be alive at 10 years. The PBAC agreed that the criteria for the ‘rule of rescue’ were not met for nintedanib due to the extent and heterogeneity of the clinical impact and the severity of the disease as well as lack of a true ‘rescue’ effect of the drug.
- 6.33 The PBAC noted that the application of the trial based disutilities for acute IPF exacerbations and adverse events in the model would result in some double counting of the trial based utilities for FVC%Pred health states. However, the PBAC noted that the model was relatively insensitive to the removal of these disutilities.

*For more detail on PBAC’s view, see section 7 “PBAC outcome”*

**Drug cost/patient/year: \$ [REDACTED]**

- 6.34 The estimated usage per patient was based on an expected compliance rate of 96.4%, as observed in Trials 32 and 34. This results in an average of 11.73 nintedanib prescriptions per patient per year. The submission assumed a proportional distribution of nintedanib 150mg and 100mg (76%/24%) consistent with usage reported in Trials 32 and 34.

**Estimated PBS usage & financial implications**

- 6.35 The estimated use and financial implications to the PBS in the submission, based on the effective price, are presented in the below table. The submission estimated a cost

of \$30 - \$60 million per year over the first five years of listing. The submission did not include the RSA in the estimated financial implications for the PBS/RPBS. The submission indicated that it was not possible to determine accurately the exact value of the RSA and it was not further considered in the analysis.

**Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5
<b>Estimated extent of use</b>					
Patients treated with nintedanib	█	█	█	█	█
Nintedanib prescriptions	█	█	█	█	█
<b>Net cost to PBS/RPBS</b>					
Total	\$ █	\$ █	\$ █	\$ █	\$ █

Source: Table E.2-5, Table E.2-6, pp212-213 of the submission

- 6.36 The redacted table above shows that there is estimated to be less than 10,000 patients treated per year by year 5. The estimated financial expenditure is less than \$10 million in year 1 increasing to \$10 - \$20 million per year in year 5.
- 6.37 There was limited epidemiological evidence to reliably determine the prevalence of IPF in Australia. Epidemiological studies located by the submission reported prevalence rates that varied from 1.25/100,000 to 27.9/100,000. While an average prevalence rate (█) was applied in the financial estimates, this was likely to be underestimated given the inclusion of non-population based studies in the analysis. In addition, the uptake rate applied by the submission was highly conservative (█% in Year 1 increasing to █% in Year 5). No other specific IPF therapies are readily available in the Australian market. The accuracy of the estimated net costs may be further compromised by the prevalence only approach used in the financial model which applied an average prevalence rate of █ per year. Without an incident population, the financial model was unable to estimate the number of new IPF patients that would enter the PBS population each year or consider the expected treatment duration over the 5 year estimates.
- 6.38 This submission was considered by the DUSC. The DUSC considered that the submission had underestimated the likely utilisation and budget impact resulting from the proposed listing of nintedanib for IPF due to the following:
- The prevalence of IPF and the rate of uptake of nintedanib are likely to be higher than proposed. Limiting the analysis to population based studies resulted in an average prevalence of 14.4 per 100,000.
  - The submission applied an “Accuracy of diagnosis” rate of 87% to the estimated prevalent IPF population. The DUSC considered that this reduction was not necessary as the studies used to estimate prevalence only included diagnosed patients.
  - Given that IPF is a progressive and ultimately fatal disease, with no other specific therapies available in Australia, the DUSC considered that uptake in the eligible population would be substantial. The DUSC recommended a revised uptake rate of 60% in Year 1 increasing to 100% in Year 5.
- The DUSC considered that the net cost to the PBS for listing nintedanib could be approximately triple the submission Year 1 estimates and approximately double the submission Year 5 estimates.

- 6.39 In addition, the ESC noted that estimates of use and financial implications were based on uncertain incidence and prevalence of IPF in Australia. The ESC considered that incidence and prevalence of IPF to date may be underestimated given the absence of an effective treatment and the limited use of the major diagnostic test, HRCT chest scanning. The ESC noted that Raghu et al (2014) analysed a 5% random sample of US Medicare beneficiaries (age >65) from 2000 to 2011 and found a stable incidence rate of 93.7 per 100,000 person years and increasing prevalence from 202 per 100,000 in 2001 to 494 per 100,000 in 2011, with median survival increasing from 3.3 years to 4.0 from 2001 to 2007.
- 6.40 The Pre-PBAC Response accepted that the prevalence rate of 14.4/100,000 suggested by the DUSC was reasonable. The Pre-PBAC Response presented revised financial estimates incorporating this revised prevalence rate and diagnosis and uptake rates and methodology recommended by the DUSC to account for the proposed RSA. The listing of nintedanib on the PBS for IPF was estimated in the revised estimates to be \$ [REDACTED] in Year 1 (with less than 10,000 patients treated), increasing to \$ [REDACTED] in Year 5 (with less than 10,000 patients).

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

#### **Financial Management – Risk Sharing Arrangement**

- 6.41 For the IPF submission, a RSA was proposed involving a [REDACTED]% rebate for nintedanib use in patients with a FVC less than [REDACTED]% of predicted normal. The proposed restriction requires that patients must have a FVC%Pred of greater than 50%.
- 6.42 Data from the Australian IPF registry indicated that [REDACTED]% of patients with IPF have a FVC%Pred of [REDACTED]%. The submission considered that use of nintedanib in patients with a FVC%Pred of <50% would be minimal.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

#### **Quality Use of Medicines**

- 6.43 The submission indicated that the sponsor would support education activities for prescribers and patients.
- 6.44 The DUSC considered that diagnosis of IPF is complex, and despite the restriction requiring diagnosis of IPF by a respiratory physician or a specialist physician as part of a multi-disciplinary team, that there may be misclassification of other fibrotic lung conditions (i.e. false positives).
- 6.45 Based on the number of patients requiring at least one dose reduction due to tolerability issues in the clinical trials, the submission estimated that 24% of patients would be on the 100mg dose. The DUSC noted that side effects were common at the 150mg dose with 60% of patients experiencing diarrhoea, 25% nausea and 12% vomiting. The DUSC recommended that if nintedanib is listed on the PBS for IPF that the Predicted versus Actual utilisation review should assess the proportion of use of the 100mg dose, and the duration of dose reductions or interruptions.

- 6.46 The Australian IPF Registry Steering Committee, in correspondence to the PBAC, indicated that it is 'well placed to assist the PBAC in collecting information on medications and disease outcomes in a timely and cost effective manner'.

## **7 PBAC Outcome**

- 7.1 The PBAC rejected the request to list nintedanib for the treatment of patients with IPF on the basis of an uncertain estimate of comparative effectiveness, as measured by the effect on clinically relevant outcomes, including acute IPF exacerbations and overall survival, and a resulting very high and uncertain estimate of cost effectiveness.
- 7.2 The PBAC noted that the submission was made under TGA/PBAC Parallel Process with the Delegate's consideration expected in July 2015. Accordingly, the PBAC noted that it was only able to defer or reject the submission. However, the PBAC noted that even if a positive Delegate's overview been available, it would have been minded to reject the submission due to high and uncertain cost effectiveness.
- 7.3 The PBAC noted the proposed restriction and agreed that it should include the role of a multi-disciplinary team in diagnosing the condition as recommended by the ESC and the Australian IPF Registry Steering Committee, and proposed by the sponsor. The Australian IPF Registry Steering Committee also recommended that authority to prescribe nintedanib could be applied for and prescription be coordinated through only those hospitals regarded as having expertise in IPF diagnosis and management. The PBAC noted that if nintedanib was to be listed on the PBS, the finalisation of a restriction (including consideration of the other suggestions raised by ESC in paragraph 2.4) would require consultation with relevant clinicians and other stakeholders (including the Australian IPF Registry Steering Committee). The PBAC noted the DUSC advice that diagnosis of IPF is complex and there may be misclassification of other fibrotic lung conditions. Due to the difficulty in diagnosis, the PBAC considered that strategies for managing the risk of leakage to other indications, such as the wording for the requested write-in initial authority, should be considered if nintedanib is recommended for listing.
- 7.4 The PBAC noted the high clinical need for an effective treatment for IPF.
- 7.5 The PBAC agreed that best supportive care was the appropriate comparator for nintedanib for IPF and accepted the clinical place. The PBAC noted that another novel agent for the treatment of IPF, pirfenidone, was not currently TGA approved or listed on the PBS.
- 7.6 The PBAC noted the submission was based on three head-to-head randomised trials comparing nintedanib to placebo. The PBAC questioned the appropriateness of including Trial 30 in the meta-analyses due to differences in the handling of missing data and the comparability of the trial populations (as discussed in paragraphs 6.8 and 6.9).
- 7.7 The PBAC noted that a statistically significant difference was observed in terms of change in FVC over 52 weeks and proportion of FVC responders. There were no statistically significant differences in overall survival, acute investigator reported IPF

exacerbations or disease specific quality of life measures, although the PBAC acknowledged the challenge in demonstrating a survival gain in this population. The PBAC considered that while it was clear that lower FVC is associated with a higher risk of mortality, quantifying the relationship between change in FVC from nintedanib and change in mortality (and resulting survival gain) is challenging.

- 7.8 The PBAC considered that, while there was no statistically significant difference in acute *investigator reported* exacerbations, the statistically significant risk ratio for *adjudicated* acute exacerbations (indicating an approximately 65% reduction associated with nintedanib treatment) was pivotal evidence in favour of nintedanib. In this regard, the PBAC noted that, given the subjectivity associated with the assessment of acute IPF exacerbations, the independently adjudicated acute exacerbations were less subject to bias than the investigator reported exacerbations. The PBAC noted that the relationship between mortality and FVC was much more certain in patients with an acute exacerbation.
- 7.9 The PBAC noted that nintedanib was associated with statistically significantly higher instances of drug related adverse events and gastrointestinal adverse events including diarrhoea, nausea and vomiting.
- 7.10 The PBAC noted the following issues with the economic model:
- The CUA presented in the submission was inappropriate given the non-statistically significant point estimates for OS and no significant difference in quality of life.
  - The base case ICER (of \$105,000-\$200,000 per QALY) was unacceptably high and likely to be optimistic as it used non-significant survival and quality of life benefits extrapolated from 12 months to 10 years to estimate life years and QALYs gained. The ESC presented a more conservative ICER of more than \$200,000 per QALY which was based on extrapolation of the Kaplan Meier survival estimates to 21 months.
  - The risks of exacerbation remained constant in the economic model and therefore considered that it inadequately represented the clinical course of IPF progression over time.
  - The application of the trial based disutilities for exacerbations and adverse events in the model resulted in some double counting of the trial based utilities for FVC%Pred health states. Although, the PBAC noted that the model was relatively insensitive to the removal of these disutilities.
  - The modelled time horizon should be determined in the context of both the natural history of the disease and the duration over which it is reasonable to model a benefit. In this regard, the PBAC agreed with the ESC that the time horizon was inappropriate given the uncertainty regarding extrapolation of non-significant survival over 10 years.
- 7.11 The PBAC noted the challenges in identifying the appropriate patient population and that the Pre-PBAC Response accepted the DUSC recommended prevalence rate of 14.4 per 100,000. The PBAC also noted the revised financial estimates in the Pre-PBAC Response were roughly in line with the DUSC's consideration that the net cost to the PBS for listing nintedanib could be approximately triple the submission Year 1 estimates and approximately double the submission Year 5 estimates.

- 7.12 The PBAC considered that a major resubmission would be required to seek listing of nintedanib for IPF on the PBS. The resubmission should present a revised model that addresses the issues outlined in paragraph 7.10, including the use of the more conservative methodology for extrapolation of survival benefit associated with nintedanib recommended by the evaluation (see paragraph 6.28). The PBAC noted that a price reduction would likely be required to result in nintedanib being considered sufficiently cost-effective for the treatment of IPF. Alternatively, the PBAC considered that another way forward could be to present a new model that examined the impact of treatment with nintedanib for patients with IPF on acute exacerbations.
- 7.13 The PBAC considered that the criteria for the 'rule of rescue' were not met for nintedanib due to the extent and heterogeneity of the clinical impact and the severity of the disease as well as lack of a true 'rescue' effect of the drug.
- 7.14 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**

Rejected

**8 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

**9 Sponsor's Comment**

The Sponsor had no comment.