4.02 NINTEDANIB, 100 mg capsule, 60, 150 mg capsule, 60, Ofev®, Boehringer Ingelheim Pty Limited.

1 Purpose of Application

1.1 Resubmission to request Authority Required listing for nintedanib for the treatment of patients with idiopathic pulmonary fibrosis (IPF).

2 Requested listing

2.1 An abbreviated version of the requested restriction is below. 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	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
NINTEDANIB				Ofev® Boehringer Ingelheim Pty Ltd
CAPSULE, ORAL, 100 MG, 60	1	5	$[redacted] (effective price: $[redacted])	
CAPSULE, ORAL, 150 MG, 60	1	5	$[redacted] (effective price: $[redacted])	

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Severity:	Mild to moderate
Condition:	Idiopathic pulmonary fibrosis
PBS Indication:	Mild to moderate idiopathic pulmonary fibrosis
Restriction Level / Method:	☒Authority Required - In Writing
Treatment phase:	Initial treatment
Treatment criteria:	Must be treated by a respiratory physician *with expertise* in the management of idiopathic pulmonary fibrosis, *OR* *Must be treated by a specialist physician with expertise in the management of idiopathic pulmonary fibrosis* *AND* *Must be treated in a centre with expertise in idiopathic pulmonary fibrosis, OR* *Must be treated in consultation with a centre with expertise in idiopathic pulmonary fibrosis if attendance is not possible due to geographic isolation*
Clinical criteria:	~~Patient must have a confirmed and documented diagnosis of idiopathic pulmonary fibrosis through a multidisciplinary team.~~ ~~AND~~ Patient must have a chest high resolution computed tomography (HRCT) consistent with diagnosis of idiopathic pulmonary fibrosis within the previous 12 months,

	AND Patient must have forced vital capacity (FVC) equal to or greater than 50% predicted for age, gender and *height*, and forced expiratory volume in 1 second (FEV1)/FVC ratio greater than 0.7, AND Patient must have diffusing capacity of the lungs for carbon monoxide (DLCO) corrected for haemoglobin equal to or greater than 30%, AND Patient must not have interstitial lung disease due to other known causes including domestic and occupational environmental exposures, connective tissue disease, and drug toxicity. *AND* *The treatment must not be in combination with PBS-subsidised pirfenidone.*
Population criteria:	Patient must be aged 40 years or older.
Prescriber Instructions	Applications for authorisation must be in writing and must include: 1. A completed authority prescription form; 2. A completed IPF ~~Nintedanib~~ Authority Application Supporting Information Form; 3. A copy for the result for HRCT; 4. The result for the baseline ~~%~~*per cent* predicted FVC; 5. The result for FEV1/FVC ratio; 6. The result for DLCO corrected for haemoglobin *7. A signed patient acknowledgement* A baseline measurement of *per cent*~~%~~ predicted FVC must be documented *prior to commencement of treatment*. FVC must be measured, where possible, in an accredited pulmonary function laboratory. Patient must have no acute respiratory infection at the time of FVC testing. PBS treatment with nintedanib *must* be discontinued if disease progresses (a confirmed absolute decline in ~~%~~*per cent* predicted FVC of 10% or more within any 12-month period while receiving treatment).

Treatment phase:	Continuing treatment
Treatment criteria:	<*As per initial treatment*>
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with *this drug* for this condition. AND *Patient must not have had an absolute decline in per cent predicted FVC of 10% or more within any 12-month period while receiving treatment.* *AND* *The treatment must not be in combination with PBS-subsidised pirfenidone*
Population criteria:	Patient must be aged 40 years or older.
Prescriber instructions:	*Applications for authorisation must be in writing and must include:* *1. A completed authority prescription form;* *2. A completed IPF Authority Application Supporting Information Form* *3. The result for the percent predicted FVC;* *FVC must be measured, where possible, in an accredited pulmonary function laboratory. Patient must have no acute respiratory infection at the time of FVC testing.* *The absolute decline in per cent predicted FVC is determined by subtracting the most recent % predicted FVC value from the per cent predicted FVC value measured 12 months ago.* *PBS treatment with nintedanib must be discontinued if disease progresses (a confirmed absolute decline in percent predicted FVC of 10% or more within any 12-month period while receiving treatment).*

Treatment phase:	*Grandfathering treatment*
Treatment criteria:	<*As per initial treatment*>
Clinical criteria:	Patient must have previously received non-PBS subsidised treatment with *this drug for this condition* prior to [listing date] AND *The treatment must not be in combination with PBS-subsidised pirfenidone*
Population criteria:	Patient must be aged 40 years or older.
Prescriber instructions:	<*As per initial treatment*>

2.2 The current resubmission sought listing on the basis of a cost utility analysis (CUA) comparing nintedanib with best supportive care (BSC). As in the previous submissions, the current resubmission proposed a Special Pricing Arrangement (SPA) such that the effective DPMQ of nintedanib is $[redacted] and $[redacted] for one pack of 100 mg and 150 mg capsules, respectively.

2.3 The current resubmission included a continuation rule that: "treatment with nintedanib should be discontinued if disease progresses (a confirmed absolute decline in % predicted forced vital capacity (FVC) of 10% or more within any 12-month period while receiving treatment)." The proposed continuation rule differed from the one proposed in the November 2015 pre-PBAC response with the addition of the word "absolute" in defining disease progression. The Pre-Sub-Committee Response (PSCR, p1) proposed that the following wording be added after the presentation of the continuation rule: 'The absolute decline in % predicted FVC is determined by

subtracting the most recent % predicted FVC value from the % predicted FVC value measured 12 months ago'.

2.4 The ESC noted that for those patients who breach the proposed continuation rule, the sponsor proposed to fund nintedanib, where deemed appropriate, under the direction of a specialist physician. The ESC noted that in its consideration of pirfenidone in March 2016, the PBAC considered that implementing a stopping rule would be difficult in clinical practice (March 2016 pirfenidone PSD, paragraph 5.2). In this regard, the ESC considered that it may be preferable to manage the risk of continuing treatment with nintedanib in patients who have experienced a significant decline in lung function through other methods (e.g. a risk sharing arrangement (RSA)).

2.5 The pre-PBAC response (p2) acknowledged and accepted the majority of the Secretariat's proposed changes to the restriction wording for nintedanib, subject to approval by the PBAC.

2.6 The pre-PBAC response (p2), Australian Pulmonary Fibrosis Consortium and the Australian IPF Registry Steering Committee noted the importance of a clear diagnosis of IPF within the setting of an established specialist multidisciplinary team meeting for increased accuracy in diagnosis. The Australian IPF Registry further advised that the multidisciplinary team should be defined as a respiratory physician, radiologist and, where histological material is considered, a pathologist.

2.7 The Australian IPF Registry Steering Committee also advised that:

- the criterion specifying that the patient must be treated by a respiratory/specialist physician with expertise in the management of IPF be removed, given the absence of a definition of expertise; and
- the requirement for HRCT scan results confirming diagnosis of IPF be removed and replaced with a requirement for evidence that a HRCT scan has been performed.

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

3 Background

3.1 **TGA status at time of PBAC consideration:** Nintedanib was registered on the ARTG for the treatment of IPF on 1 September 2015.

3.2 The PBAC previously considered major submissions for nintedanib for IPF in March 2015 and November 2015. Table 1 provides a detailed summary of the November 2015 resubmission, relevant PBAC comments and changes in the current resubmission.

3.3 The PBAC also previously considered (but did not recommend) submissions for pirfenidone for the treatment of patients with IPF at the November 2015 and March 2016 meetings.

Table 1: Summary of the November 2015 submission and current resubmission

Component	November 2015 resubmission	Current resubmission
Requested PBS listing	•Mild to moderate IPF where the patient must have a predicted forced vital capacity (FVC) ≥50%, and a predicted carbon monoxide diffusing capacity (DLCO) ≥ 30%. •The resubmission provided further details of the multidisciplinary team (comprising at least respiratory, radiology and where required, pathology) and extenuating circumstances where consultation may be necessary (geographical isolation). •The resubmission added an additional clinical criteria required eligible patients to have a FEV1/FVC>0.7	•The resubmission included a continuation rule as follows: treatment with nintedanib should be discontinued if disease progresses (a confirmed absolute decline in % predicted forced vital capacity (FVC) of 10% or more within any 12 month period while receiving treatment).
Requested price	100mg, $[redacted] (effective) 150mg, $[redacted] (effective)	100mg, $[redacted] (effective) 150mg, $[redacted] (effective)
Main comparator	• Best supportive care. Same as March 2015 submission; indirect comparison with nintedanib also presented. **PBAC Comment:** The PBAC reaffirmed that best supportive care was the appropriate main comparator for nintedanib for IPF (paragraph 7.5, November 2015 PBAC Public Summary Document (PSD))	•Same as previous submission
Clinical evidence	• Trial 30 (n=432), Trial 32 (n=515) and Trial 34 (n=551 Same as March 2015 submission with additional information provided regarding: handling of missing data in Trial 30; consideration of methods used to derive the minimally clinically important difference (MCID) and a trial based analysis of MCID for FVC%Pred; long term efficacy data from Trial 30 for up to 80 weeks of treatment with nintedanib; and the development safety uptake report (DSUR)	•Same as previous submission with additional long-term efficacy analyses for INPULSIS ON (Trial 33), the extension study of Trials 32 and 34, that had not been previously available
Key effectiveness data	•The resubmission presented additional evidence indicating a linear trend between FVC and survival benefit across the nintedanib (Trial 30, 32 and 34) and pirfenidone trials (ASCEND, CAPACITY-1, CAPACITY-2). While there was a high degree of correlation was observed in the analysis (R2 = [redacted]), the hazard ratios for time to death across the trials were not statistically significant. •During the evaluation, results from a network meta-analyses published by Loveman et al 2015 were located While pirfenidone and nintedanib both demonstrated beneficial effects, the authors concluded that nintedanib appeared to have a superior benefit for slowing decline in FVC (OR = 0.67, 95% CI: 0.51, 0.88).	•Same as previous submission (with additional interim data from an extension study). •The PSCR identified an additional meta-analysis by Rogliani et al 2016 – the results were consistent with the conclusions in Loveman et al 2015.
Key safety data	•Same as March 2015 submission. Nintedanib was associated with statistically significantly higher instances of drug related adverse events and gastrointestinal adverse events including diarrhoea, nausea and vomiting. A statistically significant difference was also observed for arterial thromboembolic events (RR = 3.54, 95% CI: 1.04, 12.06) in the pooled analysis of the phase 3 trials.	•Same as previous submission
Clinical claim	•As in the March 2015 submission, the resubmission described nintedanib as superior to placebo for the treatment of patients with IPF but associated with a slightly higher incidence of drug related adverse events. •The resubmission altered the context surrounding the	•Same as previous submission

Component	November 2015 resubmission	Current resubmission
	claim of a higher occurrence of drug-related adverse events, emphasising 'slightly higher' incidence as opposed to 'insignificance in discontinuations and adequacy of the management of adverse events' **PBAC Comment:** The description of 'slightly higher' incidence is questionable considering that nintedanib treated patients had over double the frequency of drug related adverse events in comparison to placebo. (paragraph 6.24, November 2015 PBAC PSD) The PBAC agreed with the clinical claim of superior effectiveness and inferior safety, noting the FDA review of pirfenidone and nintedanib studies suggests that FVC is a valid surrogate for mortality in IPF. (paragraph 6.25, November 2015 PBAC PSD) The PBAC considered nintedanib and pirfenidone to likely be similarly clinically effective. (paragraph 7.11, November 2015 PBAC PSD)	
Economic evaluation	•Cost-utility model with cost/QALY of $75,000 - $105,000. There were no substantive changes to the design and structure of the economic model in the resubmission •Mortality risk from Weibull extrapolations were applied beyond the trial based period (21 months to 10 years) and were responsible for the majority of survival gains estimated in the economic model. •The effective price used in the model was based on the RSA proposal to cap expenditure **PBAC Comment:** Overall, the resubmission presented limited adjustments to predicted survival and it is likely that the economic model continues to overestimate the incremental benefits associated with nintedanib (paragraph 6.30, November 2015 PBAC PSD) The PBAC proposed that the sponsor consider how the use of the continuation rule may impact on the ICER. (paragraph 7.15, November 2015 PBAC PSD) The PBAC considered any effective price used in the model cannot be based on the RSA proposal to cap expenditure. (paragraph 7.13, November 2015 PBAC PSD)	•Cost-utility model with cost/QALY of $75,000 - $105,000. •RSA pricing removed from the effective price used in the model. •Continuation rule included into the model
Number of patients	Less than 10,000 in Year 1 increasing to less than 10,000 in Year 5.	Less than 10,000 in Year 1 increasing to less than 10,000 in Year 5.
Estimated cost to PBS	•RSA: Less than $10 million in Year 1 increasing to $20 - $30 million in Year 5 for a total of $60 - $100 million over the first 5 years of listing. •DUSC utilisation: $10 - $20 million in Year 1 increasing to $30 - $60 million in Year 5 for a total of more than $100 million over the first 5 years of listing. **PBAC Comment:** Overall, the resubmission applied a highly conservative approach to the RSA, given that the IPF prevalence and nintedanib uptake rates were considered by DUSC to be potential underestimates. If prevalence in the PBS population is towards the higher estimates as reported in Raghu 2014 (145.7/100,000 in patients aged ≥65 years	•RSA: Less than $10 million in Year 1 increasing to $10 - $20 million in Year 5 for a total of $60 - $100 million over the first 5 years of listing. DUSC utilisation: $10 - $20 million in Year 1 increasing to $20 - $30 million in Year 5 for a total of more than $100 million over the first 5 years of listing

Component	November 2015 resubmission	Current resubmission
	in 2011), the proposed RSA may limit the potential risk associated with the estimation of the eligible patient pool.	
PBAC decision	•Deferred **PBAC Comment:** The PBAC deferred the decision to recommend nintedanib for PBS listing for IPF subject to a revised base case ICER of approximately $60,000/QALY, re-specified to incorporate a continuation rule and a price reduction which does not take into account any consequence of the proposed RSA. The sponsor is also asked to consider a managed access program to compare the proportion of PBS patients who discontinue against the proportion established by the clinical trials and agree a basis to vary the price to maintain cost-effectiveness reflecting the extent that the PBS observed proportion might differ from the proportion established by the clinical trials and/or the model. (November 2015 PSD, paragraph 7.1)	-

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

4 Clinical place for the proposed therapy

4.1 IPF is a specific form of chronic, progressive, fibrosing, idiopathic interstitial pneumonia (IIP). It is the most common IIP and the most severe and frequently occurring of the broader category of all interstitial lung diseases (ILD). IPF is an irreversible and fatal disease with considerable variability in disease progression and median survival ranging from 3 to 5 years. IPF causes a progressive decline in lung function, which increasingly restricts routine physical activity due to breathlessness from disrupted alveolar-capillary barrier architecture, leading to impaired gas exchange and increased work of breathing due to reduced compliance of the lungs. Lung transplant is the only potentially curative intervention for IPF.

4.2 No other medications are currently listed on the PBS specifically for the treatment of IPF. A resubmission for pirfenidone for the treatment of IPF was also considered by the PBAC at the November 2016 meeting.

4.3 Nintedanib is a small molecule tyrosine kinase inhibitor which blocks intracellular signalling associated with the proliferation, migration and transformation of fibroblasts, which are mechanisms of IPF pathology. By comparison, the complete mechanism of action of pirfenidone is yet to be fully established; however, existing data indicates anti-fibrotic, anti-inflammatory and anti-oxidant properties in a variety of in vitro systems and animal models of pulmonary fibrosis.

4.4 As in the March and November 2015 submissions, the current resubmission proposed nintedanib to be used in combination with BSC for the treatment of IPF.

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

5 Comparator

5.1 As in the March and November 2015 submissions, the current resubmission nominated BSC as the main comparator. In November 2015, the PBAC reaffirmed that BSC was the appropriate main comparator for nintedanib for IPF, and noted that pirfenidone was also a relevant comparator (November 2015 nintedanib PSD, paragraph 7.5).

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 sponsor made arguments in support of the submission including the high clinical need for a PBS-subsidised drug for IPF, the impact of the disease on quality of life and survival, and the impact of the drug on outcomes such as exacerbations and decline in lung function. The sponsor reiterated its proposed continuation rule and RSA. In response to a question from the PBAC, the sponsor stated that it believed the uptake rates in the submission (of [redacted]% in Year 1 to [redacted]% in Year 5) were reasonable despite advice from DUSC that these rates were underestimated, and noted that the proposed RSA will provide financial certainty to government.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (33), health care professionals (5) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described a range of potential benefits of treatment with nintedanib including the ability to slow disease progression and improve quality of life. The comments also described the unmet need for an effective and PBS-subsidised treatment for IPF, the financial burden associated with purchasing non-PBS subsidised nintedanib and the risk of patients acquiring cheaper versions of nintedanib online for which the safety and efficacy are uncertain.

6.3 The PBAC noted the advice received from the Lung Foundation Australia and the Australian Pulmonary Fibrosis Consortium that treatment with nintedanib may slow disease progression and improve quality of life. The PBAC specifically noted the advice that the only access to relatively affordable medication for IPF (i.e. nintedanib or pirfenidone) is through importation. The advice noted that alternative treatment consists of non-pharmacological interventions, such as pulmonary rehabilitation and oxygen therapy and, in a small proportion of patients, lung transplantation. The PBAC noted that this advice was supportive of the evidence provided in the submission.

Clinical trials

6.4 As in the November 2015 resubmission, the current resubmission was based on three head-to-head trial randomised trials comparing nintedanib with placebo: Trial 30 (n=432), Trial 32 (n=515) and Trial 34 (n=551). An indirect comparison of

nintedanib and pirfenidone (as per the November 2015 resubmission) was presented in an attachment to the current resubmission.

6.5 Details of the trials presented in the resubmission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Nintedanib trials		
Trial 30	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.	25 February 2011
	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	*The New England Journal of Medicine.* 2011; 365 (12): 1079-1087
Trial 32	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)	08 April 2014
	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.	*Respiratory Medicine*. 2014; 108(7): 1023-1030
	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	*The New England Journal of Medicine.* 2014; 370(22): 2071-2082
Trial 34	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)	08 April 2014
	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.	*Respiratory Medicine*. 2014; 108(7): 1023-1030
	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	*The New England Journal of Medicine.* 2014; 370(22): 2071-2082

Source: Table B.2-2, p38-39 of the current resubmission

6.6 The key features of the direct randomised trials are summarised in Table 3.

Table 3: Key features of the included evidence

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

^ High risk of bias associated with the analyses of FVC change from baseline. 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.

Comparative effectiveness

6.7 Direct comparison with placebo: Key results from the meta-analyses are presented in the table below; these have not changed since the March 2015 submission.

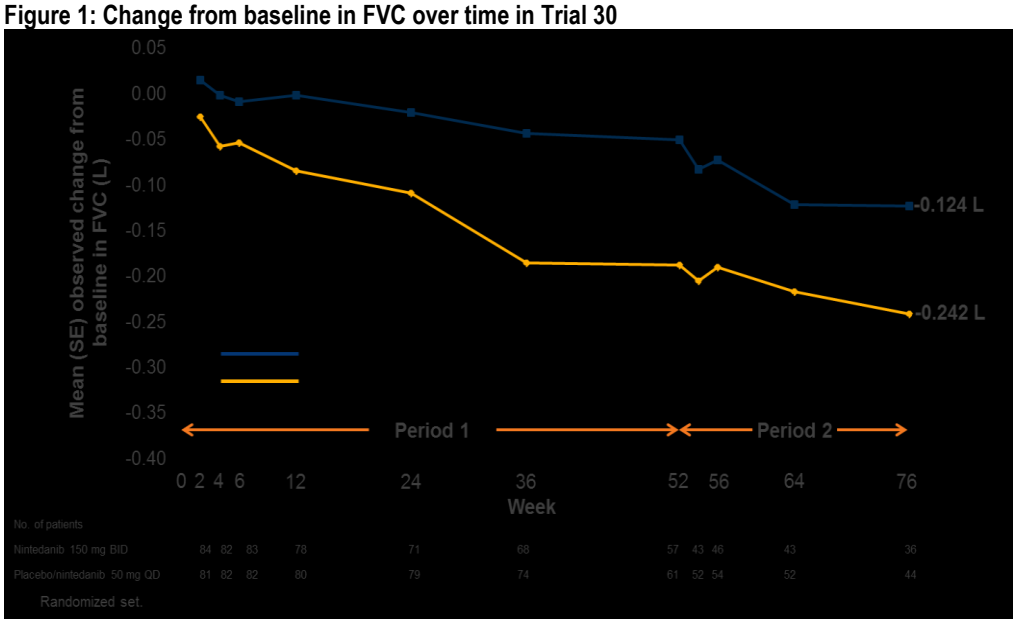
Table 4: Summary of the meta-analyses of key efficacy outcomes from the nintedanib trials

Outcome		Meta analyses (Trial 30, 32 & 34)
Annual rate of decline in FVC (ml/year)		MD (95% CI) = 118.89 (79.57, 144.21)
Absolute change in FVC%pred from baseline to week 52		MD (95% CI) = 3.31 (2.46, 4.16)
Proportion of patients with a decline in FVC%pred <5% over 52 weeks		RR (95% CI) = 1.39 (1.23, 1.57)
Incidence of acute IPF exacerbation	Investigator reported	RR (95% CI) = 0.48 (0.18, 1.30)
	Independent adjudication (Trial 32 & 34)	RR (95% CI) = 0.35 (0.13, 0.94)
Survival: all-cause mortality over 52 weeks		RR (95% CI) = 0.72 (0.48, 1.09)
SGRQ: change from baseline over 52 weeks		MD (95% CI) = -2.41 (-5.26, 0.45)

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, p139 of the current submission

6.8 The results of Periods 1 and 2 of Trial 30 are presented in Figure 1.

Figure 1: Change from baseline in FVC over time in Trial 30



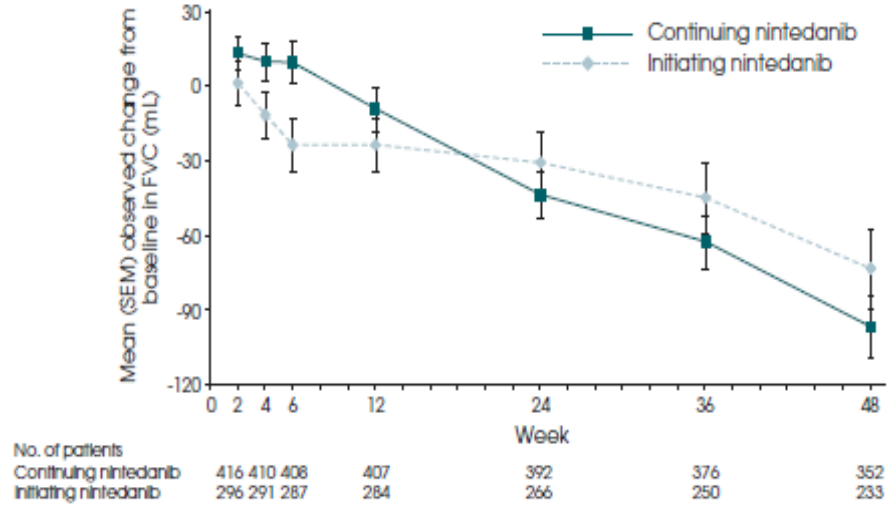
Source: Figure B.6.3, p116 of the current submission.

6.9 In November 2015, the PBAC considered a FDA[1] review of pirfenidone and nintedanib studies which suggested that FVC is a valid surrogate for mortality in IPF. This review gave the PBAC more confidence that the lack of statistical significance in overall survival may be an issue of lack of power in the trials. It was further noted that the poor prognosis of patients with IPF combined with the observed trend in survival benefit imposes ethical limitations on any further placebo-controlled trials given the nature of the disease. This makes it difficult to generate prospective and placebo-controlled evidence of a statistically significant overall survival benefit with nintedanib.

6.10 The current resubmission included additional interim long-term efficacy analyses for INPULSIS-ON (Trial 33), the extension study of Trials 32 and 34. Figure 2 illustrates the results of INPULSIS-ON.

[1] Karimi-Shah BA, Chowdhury BA. Forced vital capacity in idiopathic pulmonary fibrosis-FDA review of pirfenidone and nintedanib. The New England Journal of Medicine. 2015;372(13):1189-91.

Figure 2: Change from baseline in FVC over time in INPULSIS-ON



Source: Figure B.6.4, p116 of the current submission.

6.11 The resubmission stated that all patients experienced decline in FVC over time with a mean decrease of 87.1 mL to week 48 in INPULSIS-ON, which was similar to the change seen in Trials 32 and 34. The resubmission also stated that the change from baseline in FVC (mean decrease of 87.1 mL) over 48 weeks in INPULSIS-ON was consistent with the results seen in Trial 30, and that these data confirmed that benefits were maintained beyond the 52 week trial period.

6.12 Indirect comparison with pirfenidone: A brief summary of results from the indirect comparison with pirfenidone is provided in Table 5.

Table 5: Summary of results for the indirect comparison of nintedanib and pirfenidone

Outcome		nintedanib mITT population vs CAPACITY	nintedanib matched patient population^ vs ASCEND
Overall survival	HR (95% CI)	1.03 (0.53, 1.97)	[redacted]
Exacerbations – Investigator reported	RR (95% CI)	0.64 (0.15, 2.76)	NR
Progression free survival	HR (95% CI)	1.00 (0.71, 1.39)	
FVC%pred: 10 point decline	RR (95% CI)	0.86 (0.61, 1.23)	
FVC%pred: 10 point decline or death (52 weeks)	RR (95% CI)	NR	[redacted]

^ The resubmission applies a post hoc adjustment to the nintedanib results via a matched patient cohort based on the ASCEND inclusion criteria. The ASCEND trial recruited patients with an increased risk of disease progression. In comparison to the inclusion criteria applied in the nintedanib phase 3 trials, the ASCEND trial required patients to have: (1) Clinical symptoms consistent with IPF of ≥ 12 months and diagnosis of IPF at least 6 months and no more than 48 months before randomisation; (2) Increased hurdle requirements for the diagnosis of IPF: patients with possible usual interstitial pneumonia without surgical lung biopsy were excluded. Abbreviations: FVC = forced vital capacity; HR = hazard ratio; mITT = modified intention to treat; NR = not reported; NTB = nintedanib; RR = relative risk. Source: Attachment 1 of the current submission.

6.13 In November 2015, the PBAC considered that interpretation of the indirect comparison with pirfenidone was difficult given the differences in the trial populations and the outcomes. A network meta-analysis published by Loveman et al 2015 provided conflicting data which suggested a trend to better overall survival for pirfenidone (OR = 1.39, 95% CI: 0.70, 2.82), but a superior benefit in slowing FVC decline for nintedanib (OR = 0.67, 95% CI: 0.51, 0.88) and a trend to better

prevention of exacerbations with nintedanib (no OR provided but only nintedanib had a superior result to placebo). The PBAC considered both drugs are likely to be similarly clinically effective (nintedanib November 2015 PSD, paragraph 7.11).

6.14 The resubmission identified a Bayesian meta-analysis by Rochwerg[2] et al (2016) which compared treatments for IPF, and graded the available evidence using GRADE criteria. The authors concluded that there was no significant difference in mortality between nintedanib and pirfenidone, and that the certainty of the evidence for this was moderate. These results were consistent with those of Loveman (2015).

6.15 The PSCR identified an additional meta-analysis, Rogliani et al 2016[3], which compared nintedanib, pirfenidone and N-acetylcysteine patients with IPF. The PSCR stated that the findings in this publication are consistent with the conclusions in Loveman 2015, suggesting a signal for greater effectiveness for nintedanib in slowing decline in FVC, compared with pirfenidone. The PSCR also stated that nintedanib was the only treatment to result in a statistically significant reduction in the risk of acute IPF exacerbations and mortality, compared with placebo. The ESC noted the concluding statement in the paper that "the precautionary approach of…not strongly recommending specific medication for use in IPF is understandable. Further precaution should be taken in transposing the results obtained from different meta-analysis in every day clinical practice…methodological discrepancies across meta-analysis may led [sic] to different results."

Comparative harms

6.16 Key results from the meta-analyses of safety outcomes are presented in Table 6.

Table 6: Summary of the meta-analyses of key safety outcomes from the nintedanib trials

Safety outcomes	Meta-analysis (Trial 30, 32 & 34): RR (95% CI)
Overall safety outcomes	
Number of patients with any AEs	1.06 (1.03, 1.10)
Drug related AEs	2.45 (2.12, 2.83)
Common adverse events (>5%)	
Diarrhoea	3.41 (2.81, 4.15)
Nausea	3.41 (2.42, 4.81)
Vomiting	3.82 (2.22, 6.58)
Dyspnoea	0.66 (0.46, 0.93)

Abbreviations: AE = adverse event; SAE = serious adverse event.
Source: Table B.6-15, p118 and Table B.8-1, p139 of the current submission.

6.17 In November 2015, the PBAC noted there were higher incidences of thromboembolic events (3.8% vs 2.4%) and hypertension (5.2% vs 4.0%) in the nintedanib treatment arms, with a statistically significant difference in arterial thromboembolic events (RR = [redacted], 95% CI: [redacted], [redacted]). The PBAC also considered that no evidence was available to determine whether these cardiovascular/thromboembolic safety signals would have any substantial impact upon long-term patient risks (November 2015

[2] Rochwerg B, Neupane B, Zhang Y, Garcia CC, Raghu G, Richeldi L, Brozek J, Beyene J, and Schünemann. Treatment of idiopathic pulmonary fibrosis: a network meta-analysis. BMC Medicine, 2016; 14: 18
[3] Rogliani P, Calzetta L, Cavalli F et al. Pirfenidone, nintedanib and N-acetylcysteine for the treatment of idiopathic pulmonary fibrosis: A systematic review and meta-analysis. Pulmonary Pharmacology & Therapeutics 40(2016): 95-103.

PSD, paragraph 7.10). No new comparative safety evidence was presented in the current resubmission.

6.18 Common (>5%) adverse events associated with pirfenidone include photosensitivity reaction, rash and gastrointestinal disorders (pirfenidone, November 2015 PSD, paragraphs 6.19 and 6.22).

Benefits/harms

6.19 A summary of the comparative benefits and harms for nintedanib and placebo is presented in the following table.

Table 7: 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	
Benefits						
All-cause mortality over 52 weeks						
Trial 30, 32 & 34	42/724	42/510	0.72 (0.48, 1.09)	5.8	8.2	-0.02 (-0.05, 0.01)
Acute IPF exacerbation: adjudicated acute IPF exacerbation						
Trial 32 & 34	12/638	24/423	0.35 (0.13, 0.94)	1.9	5.7	-0.04 (-0.08, 0.01)
	Nintedanib		**Placebo**		**Mean difference (95% CI)**	
	N	**Mean Δ baseline (SE)**	**n**	**Mean Δ baseline (SE)**		
Absolute change in FVC%Pred from baseline to week 52						
Trial 30	84	-1.04 (0.99)	84	-6.00 (1.02)	3.31 (2.46, 4.16)	
Trial 32	250	-2.76 (0.41)	165	-5.98 (0.47)		
Trial 34	269	-3.09 (0.43)	180	-6.15 (0.51)		
Harms						
	Nintedanib	**Placebo**	**RR (95% CI)**	**Event rate/100 patients***		**RD (95% CI)**
				Nintedanib	**Placebo**	
Diarrhoea						
Trial 30, 32 & 34	445/723	91/508	3.41 (2.81, 4.15)	61.5	17.9	0.43 (0.39, 0.48)
Vomiting						
Trial 30, 32 & 34	85/723	15/508	3.82 (2.22, 6.58)	11.8	3.0	0.09 (0.06, 0.12)
Dyspnoea						
Trial 30, 32 & 34	55/723	59/508	0.66 (0.46, 0.93)	7.6	11.6	-0.04 (-0.07, -0.01)

* 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

6.20 On the basis of direct evidence presented by the submission (for baseline to week 52), in comparison to placebo, nintedanib was associated with:

- 3.31% reduction in absolute change in FVC%Pred (forced vital capacity predicted for age, gender and weight).
- 65% reduction in the risk of independently adjudicated acute IPF exacerbations.
- No significant difference in all-cause mortality.

6.21 On the basis of direct evidence presented by the submission, for every 100 patients treated with nintedanib in comparison to placebo, over a 52 week duration of follow-up, approximately:

- 43 additional patients would have diarrhoea.
- 9 additional patients would have vomiting.
- 4 fewer patients would have dyspnoea.

Clinical claim

6.22 As in the November 2015 submission, the current resubmission described nintedanib as superior to placebo for the treatment of patients with IPF but associated with a slightly higher incidence of drug related adverse events. The PBAC previously agreed with the clinical claim of superior effectiveness and inferior safety (November 2015 PSD, paragraph 6.25).

6.23 As in the previous resubmission, the current resubmission did not make an explicit clinical claim against pirfenidone. In November 2015, the PBAC considered that "interpretation of the indirect comparison with pirfenidone is difficult given the differences in the trial populations and the outcomes... However, PBAC considered both drugs are likely to be similarly clinically effective" (November 2015 PSD, paragraph 7.11).

6.24 The ESC considered that no new evidence was presented that would be sufficient to change the PBAC's previous conclusion that nintedanib and pirfenidone are likely to be similarly clinically effective.

6.25 The PBAC reaffirmed that the claim of superior effectiveness and inferior safety, compared with placebo, was reasonable. The PBAC also reaffirmed that nintedanib and pirfenidone are likely to be similarly clinically effective.

Economic analysis

6.26 The current resubmission presented an updated economic model to evaluate the cost-effectiveness of nintedanib versus BSC. As requested by the PBAC (November 2015 PSD, paragraph 7.13), the impact of the proposed caps on expenditure through a RSA on the effective price was removed and a continuation rule was incorporated into the model. No other substantive changes were made to the structure or rationale of the economic model (refer to Table 8, below).

Table 8: Summary of model structure and rationale

Component	Summary
Time horizon	10 years in the model base case versus 21 months maximum follow-up in the nintedanib trials
Outcomes	LYG and QALYs (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. Included stopping rule to limit treatment to patients progressing on treatment.
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 34, a logistic function was used to determine the probability for progressing to a worse FVC%Pred health state. Probability of adjudicator defined acute IPF exacerbation and nintedanib discontinuation was determined from exponential functions. Probability of death determined by the Kaplan Meier estimates from month 0-21, followed by Weibull extrapolation to 10 years.
Discount rate	5% for costs and outcomes
Software package	Microsoft Excel

Source: compiled during the evaluation.

6.27 The continuation rule was incorporated into the economic model based on observations of FVC % predicted decline in any 3-month interval of Trials 32 and 34. Out of a total of [redacted] observations, [redacted] had a FVC % predicted decline of [redacted]% or more ([redacted]%). This probability was applied to all nintedanib patients in each model cycle. The current resubmission acknowledged that this method assumed the same risk of failing to meet the continuation criteria regardless of FVC health state. The current resubmission also acknowledged that the distribution of patients who do not meet the continuation rule will necessarily be more weighted towards worse pulmonary function health states, while the health state distribution of patients who remain on PBS subsidised treatment will be weighted towards better health states.

6.28 The current resubmission considered that in order to model the continuation rule more accurately, each patient would need to be modelled individually. The evaluation acknowledged that more precise modelling of the continuation rule would require restructuring of the model, but considered it may not be necessary to model patients individually. It was difficult to estimate the extent to which more precise modelling of the continuation rule would affect the ICER without testing a restructured model. Nevertheless, for framing purposes, extreme value sensitivity analyses were conducted during the evaluation on the cycle probability of failing to meet the continuation criteria. The analyses suggested that even in extreme cases, estimates of patients continuing treatment had a moderate effect on the ICER. The PSCR (p2) agreed with the evaluation but noted that the "3-month probability for the FVC per cent predicted health states 40-49 through to 110-119 is reasonably constant, ranging between 3% and 4%". The ESC agreed that a higher probability of decline would be more likely for worse health states but considered that the simplifying assumption may have been reasonable in this case.

6.29 Key drivers of the model are summarised in Table 9.

Table 9: Key drivers of the model

Description	Method/Value	Impact
Survival extrapolation	Parametric extrapolation from month 21 to year 10	High, favours nintedanib
Time horizon	10 years; assumed from maximum 21 month follow-up in the nintedanib trials	High, favours nintedanib
Continuation rule	A cycle probability of 3.8% failing to meet continuation rule was applied to nintedanib arm of the model based on individual patient data from INPULSIS	Low to moderate, unclear impact

Source: compiled during the evaluation

6.30 Results of the stepped economic evaluation are provided in Table 10.

Table 10: Results of the stepped economic evaluation

Step and component	Nintedanib	BSC	Increment
Step 1: trial based economic evaluation (21 months)			
Costs	$ [redacted]	$ [redacted]	$ [redacted]
LYG	[redacted]	[redacted]	[redacted]
Incremental cost/LYG			$ [redacted]
Step 2: modelled economic evaluation including healthcare resource utilisation (21 months)			
Costs	$ [redacted]	$ [redacted]	$ [redacted]
LYG	[redacted]	[redacted]	[redacted]
Incremental cost/LYG			$ [redacted]
Step 3: modelled economic evaluation including extrapolation (10 years)			
Costs	$ [redacted]	$ [redacted]	$ [redacted]
LYG	[redacted]	[redacted]	[redacted]
Incremental cost/LYG			$ [redacted]
Step 4: modelled economic evaluation including utilities (10 years)			
Costs	$ [redacted]	$ [redacted]	$ [redacted]
QALY	[redacted]	[redacted]	[redacted]
Incremental cost/QALY			$ [redacted]
Step 5: modelled economic evaluation including effect of continuation rule (10 years)			
Costs	$ [redacted]	$ [redacted]	$ [redacted]
QALY	[redacted]	[redacted]	[redacted]
Incremental cost/QALY			**$** [redacted]

Abbreviations: BSC = best supportive care, LYG = life years gained, QALY = quality adjusted life years.
Source: Table D.5-1, Table D.5-2, Table D.5-3, Table D.5-4, Table D.5-5, p283-286 of the current submission

6.31 The base case ICER increased in comparison to the November 2015 resubmission ($75,000/QALY - $105,000/QALY). This change in the ICER was driven by the removal of RSA linked pricing from the economic model. In November 2015, the PBAC considered that any effective price used in the model cannot be based on an RSA proposal to cap expenditure; this approach linked the ICER to the difference between the DUSC and submission estimates of utilisation and therefore did not provide a stable estimate of cost-effectiveness.

6.32 The base case ICER of $75,000/QALY - $105,000/QALY in the current submission is higher than $60,000, as previously requested by the PBAC (November 2015 PSD, paragraph 7.1). The PSCR (p1) stated that it is not possible to provide a further price reduction to achieve such an ICER, as well as agreeing to a financial RSA that the

DUSC and the evaluation agree significantly underestimates the likely usage of nintedanib on the PBS. In addition, the PSCR argued that the base case ICER was reasonable in the context of high clinical need for (and to provide equity of access to) a PBS listed treatment for IPF, and given the limited long term survival associated with the condition.

6.33 The ESC noted that the model was sensitive to the incorporation of the continuation rule in the current model; this decreased the ICER from $105,000/QALY - $200,000/QALY to the base case of $75,000/QALY - $105,000/QALY. The ESC noted that the November 2015 base case did not include the impact of the continuation rule; accordingly, an ICER that incorporated the RSA caps and the continuation rule would have been lower than $75,000/QALY - $105,000/QALY. The PBAC considered that if nintedanib were to be listed without the continuation rule, the risk of continued treatment in patients whose condition has progressed such that the incremental benefit of treatment is likely to be smaller (and will therefore be less cost effective, compared with earlier in the course of their disease) should be managed through a RSA.

6.34 Overall, no new variables of high sensitivity were identified in the current submission, compared with the previous submission.

6.35 The current resubmission stated that the PBAC had accepted the arguments in the November 2015 pre-PBAC response (p2-3) regarding the extrapolation of survival of nintedanib. However, the ESC noted that the model remained highly sensitive to estimates of long-term overall survival (modelled based on FVC % predicted health states).

6.36 The ESC and the PBAC noted the challenges of making comparisons across the nintedanib and pirfenidone submissions for IPF given that the two submissions adopted distinct modelling approaches. The PBAC reiterated that the available comparative evidence suggested that the two drugs are likely to be similarly clinically effective. Accordingly, the PBAC considered that any difference in incremental life years gained between the nintedanib and pirfenidone models contradicted the clinical evidence and was an artefact of the different modelling approaches. The PBAC considered that the only inputs that should result in a difference in the cost effectiveness of nintedanib and pirfenidone are the proposed drug costs and, potentially, any differences in costs or quality of life associated with differences in comparative safety.

6.37 In its comparative assessment of the outcomes of the nintedanib and pirfenidone models, the PBAC considered that extrapolation of survival may have not favoured nintedanib as initially suggested by ESC. Rather, the nintedanib model may have resulted in an underestimate of incremental benefit (of 0.1519 life years) and thus an overestimate of the ICER per QALY. In this regard, the PBAC considered that the ICER per QALY for nintedanib may be closer to a range that it would typically consider to be reasonably cost effective for a relatively small patient population with high clinical need. Accordingly, the PBAC considered the cost effectiveness of nintedanib would be acceptable in conjunction with risk sharing measures to provide additional certainty (see paragraphs 6.47-6.48).

Drug cost/patient/year: $[redacted]

6.38 The estimated usage per patient was based on an expected compliance rate of 96.4% (observed in Trial 32 and 34), resulting in an average of 11.7 nintedanib prescriptions/patient/year. Proportional distribution of nintedanib 150mg and 100mg (76.33%/23.67%) was assumed to be consistent with usage reported in Trial 32 and 34. At the effective prices of $[redacted] for one pack of the 100mg and $[redacted] for the 150mg, the drug cost per patient per year was estimated to be $[redacted].

Estimated PBS usage & financial implications

6.39 The resubmission was considered by DUSC. The resubmission updated the estimated extent of use and financial implications associated with the requested listing for nintedanib. At Year 5, the submission estimated that the number of patients treated with nintedanib (adjusted for the continuation rule) would be less than 10,000 and the net cost to the PBS would be $10 – 20 million per year.

6.40 The one major change in the approach to estimating financial implications was the incorporation of the continuation rule: those who experience a decline in FVC%Pred of 10 percentage points or more in the past 12 months will be discontinued from PBS subsidised treatment. The current resubmission relied on the annual probability of failing to meet the continuation rule calculated for the economic evaluation ([redacted]%) for Years 2-5, and assumed that this probability would be half ([redacted]%) in Year 1.

6.41 DUSC considered the estimates presented in the submission to be underestimated. The main issues were:

- As the number of Australian IPF patients was derived from prevalence estimates consistent with the restriction, rather than population prevalence, DUSC considered that it was unnecessary to further reduce the population based on FVC. Therefore, DUSC considered the eligible patient pool was slightly underestimated.
- DUSC confirmed its opinion that the proposed uptake rates in the resubmission were underestimated (nintedanib March 2015 PSD, paragraph 6.38). Given that IPF is fatal and there are limited treatment options, and nintedanib is an oral therapy, DUSC considered it reasonable that uptake may reach 100% within the first five years of listing. However, DUSC considered that tolerability in practice might be lower than in the clinical trials, meaning patients may not persist with therapy.
- DUSC noted that the resubmission financial model did not consider that patients may discontinue and recommence treatment.
- DUSC considered that a compliance rate of 96.4% seemed high for a medicine where 44% of people experience diarrhoea to the extent that it requires treatment for 158 days.

Table 11: November 2016 resubmission financial estimates for nintedanib use

	Year 1	Year 2	Year 3	Year 4	Year 5
Patients					
Eligible prevalent patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated patients (base case uptake [redacted] - [redacted]%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated patients (base case uptake [redacted] - [redacted]%) adjusted for continuation rule	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treated patients (uptake [redacted]% - [redacted]%) adjusted for continuation rule	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prescriptions					
Total prescriptions (uptake [redacted] - [redacted]%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total prescriptions (uptake [redacted] - [redacted]%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to PBS/RPBS					
Net costs to PBS/RPBS and proposed RSA expenditure caps (base case uptake [redacted] - [redacted]%)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net costs to PBS/RPBS (uptake [redacted] - [redacted]%)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Adverse event costs (diarrhoea, nausea and vomiting)					
Net cost to the PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Liver function tests					
Net cost to the MBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net financial implications to government health budgets					
Cost to government (uptake [redacted] - [redacted]%)^	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost to government with proposed RSA expenditure caps	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Source: modified from Table 10, 4.02.COM.13; Abbreviations: RSA = risk sharing arrangement.
^ The resubmission's financial model does not present net financial implications to the government health budgets with the removal of the RSA. During the evaluation this was calculated on the basis of nintedanib net costs to the PBS/RPBS (with 60-100% uptake) + adverse events net cost to the PBS/RPBS (base case analysis) + net cost to the MBS.

The redacted table above shows that at year 5, the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be less than $10 - $20 million per year.

Quality Use of Medicines

6.42 The resubmission indicated that the sponsor will support education activities for prescribers and patients, including those patients who breach the proposed continuation rule.

6.43 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. DUSC previously noted that side effects were common at the 150 mg dose with 60% of patients experiencing diarrhoea, 25% nausea and 12% vomiting. DUSC recommended that if nintedanib is listed on the PBS for IPF, that a predicted versus actual utilisation review should assess the proportion of

100mg use and the duration of dose reductions or interruptions (nintedanib March 2015 PSD, paragraph 6.45).

Financial Management – Risk Sharing Arrangements

6.44 As in the November 2015 resubmission, the current resubmission proposed an SPA and an RSA which implemented subsidisation caps based on the submission's financial estimates.

6.45 The current resubmission stated that, at the proposed effective price, the associated capped expenditure in Year 1 was less than $10 million, increasing to between $10 million and $20 million in Year 5. Alternatively, the current resubmission proposed class expenditure caps, which were based on the same prevalence rates but have adjusted uptake rates to account for the listing of multiple therapies. No detail was supplied of how the uptake rates were adjusted. In this case the effective expenditure was $10 - $20 million in Year 1, increasing to $20 - $30 million in Year 5. Given the estimates were conducted in the context of no other available treatments, the DUSC considered that the class subsidisation caps would be expected to be consistent with nintedanib subsidisation caps.

6.46 DUSC considered there would be potential for use of nintedanib outside the requested restriction in other subtypes of interstitial lung disease, which also have limited treatment options. While this risk would likely be mitigated by the suggested authority listing and the requirement for diagnosis by a multidisciplinary team, DUSC considered a tight RSA was important.

6.47 In November 2015, the PBAC asked the sponsor to consider a managed access program to compare the proportion of PBS patients who discontinue against the proportion established by the clinical trials. They were asked to agree a basis to vary the price to maintain cost-effectiveness reflecting the extent that the PBS observed proportion might differ from the proportion established by the clinical trials and/or model (November 2015 PSD, paragraph 7.1). The current resubmission (p326) considered that a managed access program would likely further delay access to nintedanib and be "unlikely to address any uncertainties that have not already been addressed by the proposed continuation criteria and the financial RSA."

6.48 The PBAC considered that implementing a continuation rule for nintedanib would be difficult in practice and recommended that the risk of continued treatment in patients whose condition has deteriorated (and may no longer be cost effective) should be managed through the RSA.

6.49 The PBAC recommended an RSA, which would cap Government financial expenditure based on the submission's estimates for treated patients (uptake of [redacted] - [redacted]%) and adjusted for the continuation rule. A 100% rebate should apply to any Government expenditure beyond the financial cap. The PBAC further recommended that any other drugs recommended for the treatment of IPF in the future should be included within the same financial caps.

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

7 PBAC Outcome

7.1 The PBAC recommended the listing of nintedanib for the treatment of idiopathic pulmonary fibrosis (IPF) under certain conditions (see recommended listing). The PBAC was satisfied that nintedanib provides, for some patients, a significant improvement in effectiveness compared with best supportive care (BSC).

7.2 The PBAC recalled that in November 2015 it deferred making a decision for nintedanib subject to a revised base case ICER of approximately $60,000 per QALY, re-specified to incorporate a continuation rule and a price rebatetion that does not take into account any consequence of the proposed RSA.

7.3 As per its previous considerations in March 2015 and November 2015, the PBAC recognised the high clinical need for an effective treatment for IPF and the significant debilitating effects of the disease on quality of life, as noted in the consumer comments received for this item. The PBAC noted that the American Thoracic Society guidelines for the treatment of IPF (2015 update[4]) conditionally recommend the use of nintedanib and pirfenidone for the treatment of IPF (with moderate confidence in the effect estimates for both drugs).

7.4 The PBAC noted that IPF is a heterogeneous disease with different clinical courses but ultimately a poor prognosis. In noting the difficulty of diagnosis of IPF and the comments from the Australian IPF registry steering committee, the PBAC recommended that the restriction should include a criterion requiring diagnosis by a multidisciplinary team, defined as a respiratory physician, radiologist and, where histological material is considered, a pathologist. The PBAC also recommended the following additional changes to the requested Authority Required (in-writing) restriction:

- Removal of the continuation rule for nintedanib as it would be difficult to implement in practice, with the risk of continued use in patients who have progressed and are likely to receive a relatively smaller benefit of treatment to be managed through the recommended financial cap. The PBAC noted that in progressive conditions like IPF, deterioration in lung function is not inconsistent with a treatment benefit and that no continuation rule was implemented in the clinical trials.
- Remove “mild to moderate” from the severity, as this is captured in the clinical criteria in the initial treatment restriction and is no longer appropriate in the continuing treatment restriction with the removal of the continuation rule.
- Retain the requirement for a chest HRCT scan to be consistent with diagnosis of IPF.
- Removal of the population criterion restricting use to patients aged 40 years and over.

7.5 The PBAC reaffirmed that best supportive care was an appropriate comparator for nintedanib for IPF. Another novel agent for the treatment of IPF, pirfenidone, was also considered at the November 2016 PBAC meeting and was a relevant secondary comparator.

[4] *An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis. An Update of the 2011 Clinical Practice Guideline.* Raghu et al. April 2015. https://www.thoracic.org/statements/resources/interstitial-lung-disease/IPF-Full-length.pdf.

7.6 The PBAC noted the resubmission presented the same three head-to-head randomised trials comparing nintedanib to placebo as in the March 2015 and November 2015 submissions: Trial 30 (n=432), Trial 32 (n=515) and Trial 34 (n=551). On the basis of a meta-analysis of this direct evidence versus placebo, nintedanib was associated with:

- Approximately a 3.31% reduction in absolute decline in forced vital capacity per cent predicted (FVC%Pred) from baseline to week 52.
- Approximately a 65% reduction in the risk of independently adjudicated acute IPF exacerbations over 52 weeks.
- Insufficient evidence to directly support a significant difference in OS (although the PBAC noted that the trials were not powered for survival and the duration of the trials was likely insufficient to detect an OS benefit).

7.7 The PBAC recalled that in November 2015 it noted that loss of lung function was a more critical clinical issue than exacerbations and an FDA review of pirfenidone and nintedanib studies that suggested that FVC is a valid surrogate for mortality in IPF. It was further noted that the poor prognosis of patients with IPF combined with the observed trend in survival benefit imposes ethical limitations on any further placebo-controlled trials given the nature of the disease. This makes it difficult to generate prospective and placebo-controlled evidence of a statistically significant OS benefit with nintedanib. Overall, PBAC considered there may be indirect grounds to conclude that nintedanib would likely improve OS, compared with BSC.

7.8 The PBAC noted that no new comparative safety evidence was presented in the current resubmission. The PBAC previously noted that nintedanib was associated with statistically significantly higher instances of drug-related adverse events and gastrointestinal adverse events including diarrhoea, nausea and vomiting. The PBAC also previously noted the higher incidences of thromboembolic events and hypertension (see paragraph 6.17).

7.9 The PBAC recalled that it previously considered nintedanib and pirfenidone to be similarly clinically effective (see paragraph 6.13). No new evidence was presented to change the PBAC's previous consideration.

7.10 The PBAC considered that, on balance, the nintedanib model may have resulted in an underestimate of incremental benefit and thus an overestimate of the ICER per QALY. The PBAC concluded that the cost effectiveness of nintedanib would be acceptable in conjunction with risk sharing measures to provide additional certainty.

7.11 The PBAC considered that a remaining area of uncertainty is the rate of uptake of nintedanib. DUSC's estimates of the eligible patient population, of less than 10,000 patients per annum compared with the submission's estimates of treated patients (including the impact of the continuation rule), of less than 10,000 in year 1, increasing to less than 10,000 in year 5). The PBAC considered that uncertainty in costs arising from the submission and DUSC estimates of uptake should be addressed through the recommended RSA.

7.12 The PBAC recommended that nintedanib should not be treated as interchangeable on an individual patient basis with any other currently PBS listed drugs.

7.13 The PBAC advised that nintedanib is not suitable for prescribing by nurse practitioners.

7.14 The PBAC considered the Early Supply Rule should apply to nintedanib.

7.15 The PBAC noted that no basis was provided to assess the clinical effectiveness, safety and cost-effectiveness of combined use of nintedanib and pirfenidone for the treatment of IPF. Accordingly, the PBAC recommended that if both nintedanib and pirfenidone are PBS-subsidised in the future, a clinical criterion should be added to the nintedanib restriction stating that "The treatment must not be in combination with PBS-subsidised pirfenidone" (and vice versa for the pirfenidone restriction). Any financial risk of concomitant use of PBS-subsidised pirfenidone and nintedanib despite this criterion would be managed through the recommended financial caps. The PBAC also noted that switching rules between the two drugs would be necessary.

7.16 The PBAC noted that this submission is not eligible for an Independent Review because the PBAC has made a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
NINTEDANIB			Ofev® Boehringer Ingelheim Pty Ltd
CAPSULE, ORAL, 100 MG, 60	1	5	
CAPSULE, ORAL, 150 MG, 60	1	5	

Category/Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Condition:	Idiopathic pulmonary fibrosis
PBS Indication:	Idiopathic pulmonary fibrosis
Restriction Level / Method:	☒Authority Required - In Writing
Treatment phase:	Initial 1: new patient
Treatment criteria:	Must be treated by, or in consultation with, a respiratory physician or specialist physician.
Clinical criteria:	The condition must be diagnosed through a multidisciplinary team. AND Patient must have a chest high resolution computed tomography (HRCT) consistent with diagnosis of idiopathic pulmonary fibrosis within the previous 12 months AND Patient must have forced vital capacity (FVC) greater than or equal to 50% predicted for age, gender and height

	AND Patient must have a forced expiratory volume in 1 second (FEV1)/FVC ratio greater than 0.7 AND Patient must have diffusing capacity of the lungs for carbon monoxide (DLCO) corrected for haemoglobin equal to or greater than 30% AND Patient must not have interstitial lung disease due to other known causes including domestic and occupational environmental exposures, connective tissue disease, or drug toxicity.
Prescriber Instructions	A multidisciplinary team is defined as comprising of at least a specialist respiratory physician, a radiologist and, where histological material is considered, a pathologist. If attendance is not possible, because of geographical isolation consultation with a multidisciplinary team is required for diagnosis. Application for authorisation for initial treatment must be in writing and must include: 1. A completed authority prescription form 2. A completed IPF Authority Application Supporting Information Form; and 3. A signed patient acknowledgement. Patient must not have an acute respiratory infection at the time of FVC testing.
Administrative Advice	Special Pricing Arrangements apply. No increase in the maximum quantity will be authorised No applications for increased repeats will be authorised 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). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au Applications for authority to prescribe should be forwarded to: Department of Human Services Prior Written Approval of Complex Drugs Reply Paid 9826 GPO Box 9826 HOBART TAS 7001

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
NINTEDANIB			Ofev® Boehringer Ingelheim Pty Ltd
CAPSULE, ORAL, 100 MG, 60	1	5	
CAPSULE, ORAL, 150 MG, 60	1	5	

Category/Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Condition:	Idiopathic pulmonary fibrosis
PBS Indication:	Idiopathic pulmonary fibrosis

Restriction Level / Method:	☐Restricted benefit ☒Authority Required - In Writing ☒Authority Required - Telephone ☐Authority Required - Emergency ☐Authority Required - Electronic ☐Streamlined
Treatment phase:	Continuing treatment
Treatment criteria:	Must be treated by, or in consultation with, a respiratory physician or specialist physician.
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition.
Administrative Advice	Special Pricing Arrangements apply. No increase in the maximum quantity will be authorised No applications for increased repeats will be authorised 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).

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
NINTEDANIB			Ofev® Boehringer Ingelheim Pty Ltd
CAPSULE, ORAL, 100 MG, 60	1	5	
CAPSULE, ORAL, 150 MG, 60	1	5	

Category/Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Condition:	Idiopathic pulmonary fibrosis
PBS Indication:	Idiopathic pulmonary fibrosis
Restriction Level / Method:	☐Restricted benefit ☒Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required - Emergency ☐Authority Required - Electronic ☐Streamlined
Treatment phase:	Initial 2 - Grandfathering treatment
Treatment criteria:	Must be treated by, or in consultation with, a respiratory physician or specialist physician.
Clinical criteria:	Patient must have previously received non-PBS-subsidised treatment with this drug for this condition prior to [listing date]. AND The condition must have been diagnosed through a multidisciplinary team. AND Patient must have had a forced vital capacity (FVC) greater than or equal to 50% predicted for age, gender and height at the time treatment with this drug for this condition was initiated. AND Patient must have had a forced expiratory volume in 1 second (FEV1)/FVC ratio greater than 0.7 at the time treatment with this drug for this condition was initiated. AND

	Patient must have had diffusing capacity of the lungs for carbon monoxide (DLCO) corrected for haemoglobin equal to or greater than 30% at the time treatment with this drug for this condition was initiated. AND Patient must not have interstitial lung disease due to other known causes including domestic and occupational environmental exposures, connective tissue disease, or drug toxicity.
Prescriber Instructions	A multidisciplinary team is defined as comprising of at least a specialist respiratory physician, a radiologist and where histological material is considered, a pathologist. If attendance is not possible, because of geographical isolation consultation with a multidisciplinary team is required for diagnosis. Application for of initial treatment authorisation must be in writing and must include: 1. A completed authority prescription form 2. A completed IPF Authority Application Supporting Information Form; and 3. A signed patient acknowledgement. Patient must not have an acute respiratory infection at the time of FVC testing.
Administrative Advice	Special Pricing Arrangements apply. No increase in the maximum quantity will be authorised No applications for increased repeats will be authorised 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). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au Applications for authority to prescribe should be forwarded to: Department of Human Services Prior Written Approval of Complex Drugs Reply Paid 9826 GPO Box 9826 HOBART TAS 7001

9 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.

10 Sponsor's Comment

The sponsor had no comment.