7.05 NINTEDANIB
100 MG CAPSULE, 60, 150 MG CAPSULE, 60
OFEV®, BOEHRINGER INGELHEIM PTY LTD.

1 Purpose of Application

1.1 Authority required listing for nintedanib for treatment of idiopathic pulmonary fibrosis (IPF).

2 Requested listing

2.1 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®	BY
Oral, Capsule 100 mg, 60	1	5			
Oral, Capsule 150 mg, 60	1	5			

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐ Dental ☒ Medical Practitioners ☐ Nurse practitioners ☐ Optometrists ☐ Midwives
Episodicity:	-
Severity:	Mild to moderate
Condition:	Idiopathic pulmonary fibrosis
PBS Indication:	Mild to moderate idiopathic pulmonary fibrosis
Treatment phase:	Initial treatment
Restriction Level / Method:	☐ Restricted benefit ☒ Authority Required - In Writing ☐ Authority Required - Telephone ☐ Authority Required – Emergency ☐ Authority Required - Electronic ☐ Streamlined
Treatment criteria:	Patient must be treated by a respiratory physician or specialist physician experienced in the management of patients with idiopathic pulmonary fibrosis.

Clinical criteria: *(To be finalised)*	• Patient must have a confirmed and documented diagnosis of idiopathic pulmonary fibrosis~~; through a multidisciplinary team (comprising at least respiratory, radiology and where required, pathology)~~. **AND** • Patient must have a confirmed and documented diagnosis of idiopathic pulmonary fibrosis that is less than 5 years old; **OR** • 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, **AND** • Patient must have chest high resolution computed tomography (HRCT) consistent with the 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 weight, and FEV1/FVC ratio greater than 0.7, **AND** • Patient must have diffusing capacity *of the lungs* for carbon monoxide (DL_{CO}) 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.
Population criteria:	Patient must be aged 40 years or older.
Prescriber Instruction 1 *(To be finalised)*	*If attendance is not possible, because of geographical isolation, consultation with a multidisciplinary team may be necessary in the diagnosis of idiopathic pulmonary fibrosis (IPF). The multidisciplinary team may comprise of at least a pulmonologist, radiologist and where required, pathologist.*
Administrative Advice 1 **Administrative Advice 2** **Administrative Advice 3**	*No applications for increase in the maximum quantities 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 HOBART TAS 7001 Special Pricing Arrangements apply.

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Episodicity:	-
Severity:	Mild to moderate

Condition:	Idiopathic pulmonary fibrosis
PBS Indication:	Mild to moderate idiopathic pulmonary fibrosis
Treatment phase:	Continuing treatment
Restriction Level / Method:	☐ Restricted benefit ☒ Authority Required - In Writing ☒ Authority Required - Telephone ☒ Authority Required – Emergency ☒ Authority Required - Electronic ☐ Streamlined
Treatment criteria:	*Must be treated by a respiratory physician or specialist physician experienced in the management of patients with idiopathic pulmonary fibrosis.*
Clinical criteria: *(To be finalised)*	• Patient must have previously received PBS-subsidised treatment with this drug for this condition. **AND** • Patient must have a confirmed and documented diagnosis of idiopathic pulmonary fibrosis that is less than 5 years old; **OR** • 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.
Population criteria:	Patient must be aged 40 years or older.
Prescriber Instructions	-
Administrative Advice 1 **Administrative Advice 2** **Administrative Advice 3**	*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). *Special Pricing Arrangements apply.*
Cautions	-

2.2 The re-submission sought listing on the basis of a cost utility analysis (CUA) comparing nintedanib to best supportive care (BSC).

2.3 The re-submission revised the following key aspects of the requested restriction:

- Effective price: the re-submission proposed an effective price of $[redacted] and $[redacted] for nintedanib 100mg and 150mg, respectively. This represented an [redacted]% decrease from the effective price included in the March 2015 submission ($[redacted]: 100mg; $[redacted]: 150mg).
- Clinical criteria (initial treatment): at the March 2015 meeting, the PBAC indicated that the restriction should include the role of a multidisciplinary team in diagnosing IPF (paragraph 7.3, Nintedanib for IPF PSD, March 2015). The re-submission 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). Accurate diagnosis of IPF is important as some treatments (eg corticosteroids) can be harmful. The multidisciplinary team described in the Prescriber instruction in the restriction needs careful consideration as to whether it is sufficiently detailed to prevent misdiagnosis. An additional clinical criteria required eligible

patients to have a FEV1/FVC>0.7. The amendment was consistent with the inclusion/exclusion criteria used in the pivotal trials (Trials 30, 32 and 34).

- Clinical criteria (continuing treatment): the re-submission simplified to the clinical criteria for continuing treatment, limiting requirements to prior PBS subsidised treatment and documentation of an IPF diagnosis less than 5 years or greater than 5 years where progression has been confirmed. The ESC discussed the difficulty of having a continuation rule for IPF treatment based on response. The purpose of treatment is to prevent progression of the disease, as once patients progress there can be no further gains in lung function. There is no way to know if patients are responding to treatment, only that they are not getting worse. The PSCR (p.1) suggested the patient's treating specialist may be best placed to determine whether continuing treatment with nintedanib is appropriate, considering factors such as quality of life and daily activities (e.g. walking) in addition to lung function.
- Administrative advice: given the complexity associated with the diagnosis of IPF and the potential for misclassification of other fibrotic lung conditions, the PBAC considered that strategies for managing risk of leakage to other indications through the wording for the requested write in initial authority be considered (paragraph 7.3, Nintedanib for IPF PSD, March 2015). While the requested restriction indicated the use of an authority application form no further details were provided in the re-submission.

2.4 The requested restriction did not specify whether nintedanib should be used as sole therapy for the treatment of IPF. Combination treatment was not permitted in the pivotal trials. Given the complex pathology of IPF, combination treatment with nintedanib and pirfenidone has been suggested in the literature as a possible future regimen for patients with definite or probable IPF (Wuyts 2014, Wells 2015). The ESC agreed with the PSCR (p. 1) that the combination of nintedanib and pirfenidone is not supported by clinical evidence and a note should be added to the Cautions in the PBS listing to advise prescribers that the combination should not be used.

2.5 No discontinuation criterion was included in the requested restriction. The recent ATS clinical practice guideline for IPF (Raghu 2015) states that the current available evidence for nintedanib does not allow suggestions about the optimal duration of therapy, and it is unknown how long treatment effect endures with ongoing therapies.

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

3 Background

3.1 Nintedanib for the treatment of IPF was previously considered by the PBAC in March 2015. TGA approval for the indication of IPF and advanced, metastatic or recurrent non-small cell lung cancer (NSCLC) of adenoncarcinoma tumour histology after failure of first line chemotherapy was received on 27th August 2015.

3.2 At the March 2015 meeting, the PBAC rejected the submission 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 (paragraph

7.1, Nintedanib for IPF PSD, March 2015). The PBAC identified the following key clinical and economic issues:

- Clinical evaluation – relationship between forced vital capacity (FVC) and survival: the PBAC considered that while it was clear that lower FVC was associated with a higher risk of mortality, quantifying the relationship between change in FVC from nintedanib and change in mortality (and resulting survival gain) was challenging (paragraph 7.7, Nintedanib for IPF PSD, March 2015). The re-submission 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 (R^2 = [redacted]), the hazard ratios for time to death across the trials were not statistically significant. In October 2015, the ESC noted that the PSCR (p. 2) presented the analysis of the relationship between treatment difference in FVC and hazard ratio for time to death across the pirfenidone and nintedanib trials (Figure 1 PSCR). The confidence intervals on the hazard ratios for time to death are very wide across all trial observations.
- Modelled evaluation – rationale: the PBAC considered that the CUA presented in the submission was inappropriate given the non-statistically significant point estimates for overall survival (OS) and no significant difference in quality of life (paragraph 7.10, Nintedanib for IPF PSD, March 2015). There were no substantive changes to the design and structure of the economic model in the re-submission (refer to Economic analysis below for comments).
- Modelled evaluation – extrapolation of survival benefit: the PBAC considered that the base case ICER ($105,000-$200,000/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 (paragraph 7.10, Nintedanib for IPF PSD, March 2015). The PBAC concluded that a re-submission should present a revised model including the more conservative methodology for extrapolation of survival benefit recommended by the evaluation (paragraph 7.12, Nintedanib for IPF PSD, March 2015). This involved the use of Kaplan Meier survival estimates to 21 months, followed by adjustment of the nintedanib survival curve for the gradient of the best supportive care curve (paragraph 6.28, Nintedanib for IPF PSD, March 2015). The re-submission only partially adopted this advice. 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 (refer to Economic analysis below for comments).
- Modelled evaluation – time horizon: the PBAC considered that the modelled time horizon was inappropriate given the uncertainty regarding extrapolation of non-significant survival over 10 years (paragraph 7.10, Nintedanib for IPF PSD, March 2015). The re-submission's model continued to use a 10 year time horizon (refer to Economic analysis below for comments).

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. There is a high degree of variability in IPF disease progression (median

survival: 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 As in the March 2015 submission, the re-submission proposed nintedanib is used in combination with BSC to slow disease progression associated with IPF.

5 Comparator

5.1 As in the March 2015 submission, the re-submission nominated BSC as the main comparator. The PBAC previously accepted BSC as the appropriate comparator and also noted another novel agent, pirfenidone, for the treatment of IPF (paragraph 7.5, March 2015). Pirfenidone for the treatment of IPF is being considered by the PBAC in the November 2015 meeting. The re-submission presented the same indirect comparison of nintedanib and pirfenidone as was presented in the March 2015 submission.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (50), health care professionals (5) and organisations (3) via the Consumer Comments facility on the PBS website. The comments described the benefits of treatment with nintedanib in patients with IPF in slowing down the progression of IPF and improving the quality of life. The comments also requested the PBAC eligibility for the drug include patients with FVC <50% because the patients with FVC 40-50% may still be functional, though they were excluded from clinical trials. It was further commented that confirmation of diagnosis via a designated tertiary hospital would make it difficult to access the drug for respiratory physicians working outside the metropolitan areas.

6.3 The PBAC noted the advice received from Lung Foundation Australia, Department of Respiratory and Sleep Medicine, RPA hospital NSW, and Department of Respiratory Medicine, Eastern Health Victoria clarifying the likely use of nintedanib in clinical practice. The organisations provided advice in support of PBS listing given the anti-fibrotic treatments improve the prognosis for patients, with The Lung Foundation noting these drugs been shown to alter the natural history of IPF. However, Department of Respiratory and Sleep Medicine, RPA hospital NSW stated that 20% of patients referred to the Australian IPF Registry were over-diagnosed with IPF. Thus, it was strongly recommended to restrict this medication to specialist centres only, where an accurate IPF diagnosis could be made via specialist interstitial lung disease (ILD) multidisciplinary team. This would enable controlled prescription to patients with accurate IPF diagnosis and prevent over-prescription by non-ILD specialists.

6.4 The PBAC noted that this advice was supportive of the evidence provided in the submission.

Clinical trials

6.5 As with the March 2015 submission, the re-submission was based on three head-to-head randomised trials comparing nintedanib to placebo: Trial 30 (n=432), Trial 32 (n=515) and Trial 34 (n=551). An indirect comparison of nintedanib and pirfenidone, the same as that presented in the March 2015 submission, was presented in an attachment to the re-submission. Additional evidence presented by the re-submission included: (1) further discussion of the handling of missing data in Trial 30; (2) consideration of methods used to derive the minimally clinically important difference (MCID) and a trial based analysis of MCID for FVC%Pred; (3) long term efficacy data from Trial 30 for up to 80 weeks of treatment with nintedanib; (4) the development safety uptake report (DSUR).

6.6 Details of the trials presented in the re-submission are provided in the table below.

Table 1: Trials and associated reports presented in the re-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, p31-32 of the re-submission

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

Table 2: 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^	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

6.8 Meta-analyses of results from Trial 30, 32 and 34 are presented by the re-submission. The PBAC has previously questioned the appropriateness of including Trial 30 in the meta-analyses due to differences in the handling of missing data (last observation carried forward; LOCF) and comparability of the trial populations (March 2015, paragraph 7.6).

6.9 The re-submission justified the robustness of the LOCF approach on the basis of sensitivity analyses conducted in IPF clinical trials investigating high dose acetylcysteine (Demedts 2005) and pirfenidone (Lederer 2015). Although the comparison of LOCF to alternative statistical methods indicated similarities in relative FVC outcomes, these observations were in scenarios where treatment discontinuations were comparable across treatment and placebo arms. Given that discontinuation rates from Trial 30 were considerably higher in nintedanib treated patients (38%) in comparison to placebo (28%), this is of greater consequence to the appropriateness of the LOCF method. Consequently, the evaluation considered the re-submission had not adequately demonstrated the robustness of the LOCF method in situations where there are notable differences in patient discontinuations.

Comparative effectiveness

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

Table 3: 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	Investigator reported	RR (95% CI) = 0.48 (0.18, 1.30)

Outcome		Meta analyses (Trial 30, 32 & 34)
IPF exacerbation	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, pp123-124 of the re-submission

6.11 At the March 2015 meeting, 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. The PBAC previously acknowledged the challenge in demonstrating survival gain in this population (March 2015, paragraph 7.7).

6.12 The ESC noted the reduction in FVC%Pred is close to the minimally clinically important difference (MCID) as calculated by the anchor based method and the distribution based method (see table below).

Table 4: Trial based derivation of MCID for FVC%Pred

MCID method		FVC%Pred
Anchor based: SGRQ subgroups, mean (95% CI)	Deterioration (≥4 points) vs Stable (+/- <4 points)	-3.00 (-4.31, -1.69)
	Improvement (≤ -4 points) vs Stable (+/- <4 points)	2.41 (0.97, 3.86)
Distribution based: Effect size = 0.2	Trial 30 (SD = 17.9)	3.58
	Trial 32 and 34 (SD = 17.82)	3.56

Abbreviations: FVC%Pred = forced vital capacity % predicted; MCID = minimally clinically important difference; SD = standard deviation; SGRQ = Saint George's Respiratory Questionnaire.
Source: Table B.5-4, Table B.5-5, pp80-81 of the re-submission

6.13 A brief summary of results from the indirect comparison with pirfenidone is provided in the table below. The ESC noted that the point estimates favour nintedanib.

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

Outcome		Indirect Comparison: NTB vs Pirfenidone	
		NTB ITT population vs CAPACITY	NTB 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 re-submission applies a post hoc adjustment to the nintedanib results via a matched patient cohort based on the ASCEND inclusion criteria. The re-submission states (Attachment 1, p1-) that there was a lack of comparability between the baseline characteristics of the trial populations. This was attributed to the ASCEND trial recruiting 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; ITT = intention to treat; NR = not reported; NTB = nintedanib; RR = relative risk. Source: Attachment 1 of the re-submission

6.14 Although the reduction in FVC in the placebo groups of the pirfenidone studies are similar, as noted in the FDA report in the NEJM (see figure below), it is important to note that the CAPACITY studies were over 72 weeks and the ASCEND over 52 weeks, the same as nintedanib. The ESC considered it clear that the pirfenidone

studies recruited patients with more accelerated decline in FVC than the nintedanib studies, especially the ASCEND study.

Analysis of Forced Vital Capacity and All-Cause Mortality.*

Study	Forced Vital Capacity			All-Cause Mortality		
	Change from Baseline (ml)		Treatment Difference (95% CI)	No. of Deaths (%)		Hazard Ratio for Time to Death (95% CI)
	study drug	*placebo*		*study drug*	*placebo*	
Pirfenidone study 2 (November 2008)	−318	−475	157 (3 to 311)	14 (8.0)	20 (11.5)	0.65 (0.33 to 1.29)
Pirfenidone study 3 (November 2008)	−379	−373	−6 (−178 to 167)	18 (10.5)	17 (9.8)	1.07 (0.55 to 2.08)
Pirfenidone study 1 (re-submitted; February 2014)	−235	−428	193 (96 to 289)	12 (4.3)	21 (7.6)	0.57 (0.28 to 1.16)
Nintedanib study 1 (June 2010)	−60	−191	131 (27 to 235)	7 (8.1)	9 (10.3)	0.73 (0.27 to 1.98)
Nintedanib study 2 (October 2013)	−115	−240	125 (78 to 173)	13 (4.2)	13 (6.4)	0.63 (0.29 to 1.36)
Nintedanib study 3 (October 2013)	−114	−207	94 (45 to 143)	22 (6.7)	20 (9.1)	0.74 (0.40 to 1.35)

* The studies are listed in chronologic order by drug, with study numbers as referenced in the product labels and the months in which enrolment ended. Data for forced vital capacity are the absolute values for the change from baseline to week 52 for pirfenidone study 1, to week 72 for pirfenidone studies 2 and 3, and to week 52 for all nintedanib studies; the change from baseline for pirfenidone studies was based on descriptive statistics, and the change from baseline for nintedanib studies was based on regression analysis. Mortality data are from the vital status analysis (from randomization to the time of death) and include all deaths irrespective of the cause and of whether the patient had continued treatment. Hazard ratios for time to death are based on Cox proportional-hazards regression analysis. CI denotes confidence interval.

Source: 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):p 1190.

6.15 During the evaluation, results from a network meta-analyses published by Loveman et al 2015 were located[1]. While pirfenidone and nitendanib 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).

6.16 The ESC considered that the data from the meta-analysis, by Loveman 2015, is valuable in not only providing another approach to the meta-analysis of the data and reassurance that the trials had similar patients but suggesting that pirfenidone is inferior to nintedanib, with respect to slowing the decline in FVC. The ESC noted in the review by Loveman 2015, there is conflicting data where pirfenidone has a trend to better overall survival but nintedanib has a trend to better prevention of exacerbations.

Comparative harms

6.17 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

	Meta-analysis (Trial 30, 32 & 34): RR (95% CI)
Overall safety outcomes	

[1] Loveman E, Copley VR, Scott DA, Colquitt JL, Clegg AJ and O'Reilly. Comparing new treatments for idiopathic pulmonary fibrosis-a network meta-analysis. BMC Pulmonary Medicine, 2015; 15:37.

	Meta-analysis (Trial 30, 32 & 34): RR (95% CI)
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, pp109-110 and Table B.8-1, pp123-124 of the re-submission

6.18 At the March 2015 meeting, 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 (March 2015, paragraph 7.9). A statistically significant difference was also observed for arterial thromboembolic events (RR = [redacted], 95% CI: [redacted]) in the pooled analysis of the phase 3 trials.

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, in comparison to placebo, nintedanib was associated with:

- Approximately a 3.31% reduction in absolute change in forced vital capacity percent 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 support a significant difference in OS.

6.21 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 52 week duration of follow-up.
- Approximately 9 additional patients would have vomiting over 52 week duration of follow-up.
- Approximately 4 fewer patients would have dyspnoea over 52 week duration of follow-up.

Clinical claim

6.22 The re-submission 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.

6.23 The effectiveness claim is identical to that presented in the March 2015 submission. At that meeting, 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 independent adjudicated acute IPF exacerbations. While it was noted that lower FVC was associated with a higher risk of mortality, the PBAC concluded that quantification of the relationship was challenging given the lack of demonstration of a statistically significant impact on survival or quality of life in the trial (March 2015, paragraph 6.22).

6.24 In comparison to the March 2015 submission, the re-submission altered the context surrounding the 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'. 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 (RR = 2.45, 95% CI: 2.12, 2.83), with an absolute difference of 42% (RD% = 41.9, 95%CI: 36.8, 47.1). The PBAC considered that a claim of inferior comparative safety was reasonable (March 2015, paragraph 6.23).

6.25 In November 2015, the PBAC agreed with the clinical claim of effectiveness and safety, noting the FDA review[2] of perfinidone and nintedinab studies suggests that FVC is a valid surrogate for mortality in IPF.

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

[2] 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

Economic analysis

6.26 The re-submission presents an updated economic model to evaluate the cost-effectiveness of nintedanib versus BSC. In comparison to the March 2015 submission, no substantive changes have been made to the structure or rationale of the economic model (refer to Table 9, below). Given that the economic model continues to rely on non-statistically significant extrapolations of survival (refer to paragraph 6.24 for further details), it is unlikely that the PBAC's concerns regarding the appropriateness of the CUA (paragraph 7.10, Nintedanib for IPF PSD, March 2015) have been adequately resolved by the re-submission.

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	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 from month 0-21, followed by Weibull extrapolations to 10 years.
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.

Source: compiled during the evaluation

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

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
Weighted effective price	The price of nintedinab in the model is based on the proposed RSA which adjusts the price by applying a cap on expenditure beyond the March 2015 predictions of utilisation.	Moderate/High, favours nintedanib

Source: compiled during the evaluation

6.28 The economic model continued to be based on a 10 year time horizon. Although the re-submission presented epidemiological evidence reporting 20-30% survival for IPF patients at 10 years, the choice of time horizon continued to disregard the PBAC concerns regarding the uncertainty associated with the extrapolation of non-significant survival (paragraph 7.10, Nintedanib for IPF PSD, March 2015). From this perspective, it is unlikely that head to head trial evidence (unchanged in the re-submission) can adequately support the modelling of health outcomes over the natural history of IPF. The ESC considered that the key issue with this is not the time horizon but the extrapolation of a non-statistically significant treatment benefit beyond the trial period (see table below, which provides more detail of how the model has been adjusted from the previous submission).

Table 10: Summary of results of pre-modelling studies and their uses in the economic evaluation

Pre-modelling study	Results	Use in Section D/Comment
Extrapolation pre-modelling studies		
Transition probabilities: survival	Kaplan Meier estimates applied to 21 months, followed by mortality risk from the Weibull extrapolation over 10 years.	The PBAC considered that a revised model should use the more conservative methodology of survival recommended in the evaluation (March 2015, paragraph 7.12). This involved the application of the Kaplan Meier estimate of survival to month 21, followed by the adjustment of the nintedanib survival curve for the gradient of BSC. Consequently, the re-submission has only partially adopted this advice with mortality risk from the Weibull extrapolations applied to 10 years following the trial based period. Given the unreliability of the Weibull extrapolations (based on non-statistically significant differences in survival), it is unlikely that long term survival can be adequately estimated by the economic model.
Transition probabilities: exacerbations	Exponential model: risk of adjudicator defined acute IPF exacerbation.	P (adjudicator defined exacerbation): Nintedanib = 0.005; BSC = 0.013. The re-submission applies adjudicator defined exacerbations as opposed to the investigator defined exacerbations used in the March 2015 model. This is appropriate, given the reduced risk of bias associated with adjudicator defined exacerbations. In regard to the suitability of the exponential model, the re-submission has not entirely justified the assumption of constant hazards, with analysis of hazard ratios over time suggesting that risks associated with BSC increase over time. Overall, the use of the exponential model compromises the model's ability to adequately represent the clinical course of IPF.
Transformation pre-modelling studies		
Transition probabilities: FVC%Pred	Logistic function: probability for progressing to a worse FVC%Pred health state.	Transition probabilities are unchanged in the re-submission (refer to Table C.5-2, pp191 of the re-submission). Additional analyses conducted by the re-submission indicated that there was no statistical significance for time when included as a covariate for the logistic model. Consequently, there appears to be a reasonable basis for continued application of the transition probabilities for FVC%Pred as used in the March 2015 economic model.
Estimation of utilities and disutilities	Trial based EQ-5D utilities (FVC%Pred health state) and disutilities (acute IPF exacerbation, adverse events)	Trial based utilities for FVC%Pred health states continue to be applied in the economic model. In response to the PBAC's conclusion that disutilities are exacerbations and adverse events resulted in some double counting of utilities from the FVC%Pred health states (March 2015, paragraph 7.10), the re-submission claims (p221) that disutilities have been removed from the economic model. A review of the economic model indicated that only disutilities for adverse events were excluded (refer to Section C.2).

Source: Table C.3.1 from the Commentary

6.29 The table below summarises the revisions to parameters in the economic model applied in the re-submission.

Table 11: Summary of revisions to parameters in the economic model presented in the re-submission

		March 2015 submission	November 2015 re-submission
Transition probabilities	Death	Weibull parametric extrapolation	Kaplan-Meier estimate: month 0-21; then mortality risk-Weibull extrapolation to Year 10
	Acute IPF	Investigator defined exacerbation	Adjudicator defined exacerbation

		March 2015 submission	November 2015 re-submission
	exacerbation	Trial 32 & 34: exponential model	Trial 32 & 34: exponential model
Disutilities	Acute IPF exacerbation	Investigator defined exacerbation; EQ-5D: Trial 32 & 34	Adjudicator defined exacerbation; EQ-5D: Trial 32 & 34
	Adverse events	Diarrhoea, nausea, vomiting; EQ-5D: Trial 32 & 34	Not included
Healthcare resource items – utilisation and costs	Nintedanib	$[redacted]/day	$[redacted]/day (inclusive of RSA)
	BSC	$1.21/day	$1.28/day: July 2015 PBS schedule
	LFTs	Not included	Nintedanib: $13.65 every 3 months
	Tests & procedures	Resource items and frequency of utilisation dependent on FVC%Pred health state	
		Trial 32 and 34: MBS items	Australian IPF registry: MBS items
	Adverse events	Diarrhoea, nausea, vomiting; Trial 32 & 34: Nintedanib: $[redacted]/cycle, BSC: $4.34/cycle	Diarrhoea, severe diarrhoea, nausea, vomiting; Trial 32 & 34: Nintedanib: $[redacted]/cycle; BSC: $10.22/cycle

Abbreviations: BSC = best supportive care; EQ-5D = EuroQol 5-Dimensional Quality of Life questionnaire; FVC = forced vital capacity; IPF = idiopathic pulmonary fibrosis; LFTs = liver function tests; RSA = risk sharing arrangement. Source: constructed during the evaluation

6.30 In March 2015, the PBAC considered that a revised economic model incorporate the more conservative estimate of survival recommended in the evaluation (Kaplan Meier estimate to month 21, followed by the adjustment of the nintedanib survival curve for the gradient of BSC; March 2015, paragraph 6.28, 7.12). The re-submission only partially adopted this advice through the incorporation of Kaplan Meier estimates during the trial based period (21 months). This was followed by unadjusted mortality risk from the Weibull extrapolations applied to 10 years. As noted in the results of the stepped economic evaluation, the extrapolated period is responsible for the majority of accrued LYGs and QALYs. The PBAC has previously noted that Weibull extrapolations were incapable of representing potential long term survival benefits (March 2015, paragraph 6.28). Overall, the re-submission presented limited adjustments to predicted survival and it is likely that the economic model continues to overestimate the incremental benefits associated with nintedanib. The economic model was highly sensitive to alternative methods for the estimation of long term survival.

6.31 The ESC considered the issue with the time horizon is not whether it is reasonable in terms of modelling the progression of disease, but whether it is reasonable to extrapolate non-statistically significant survival benefits from 12 months to 10 years; this is unchanged from the previous submission. It may be reasonable to consider that a reduction in FVC decline, and a reduction in exacerbations if sustained, will translate to survival benefits. However, it is important to consider Figure 2 below which suggests that the extent of treatment benefit may not be maintained at Week 80 compared with Week 52.

Figure.2: Change in FVC over time: Trial 30 periods 1 and 2

Source: Figure B.6-3, p105 of the re-submission

6.32 Nintedanib cost/day in the economic model ($ /day) was based on a weighted effective price that incorporated the RSA. The weighted effective price is dependent on the differential between the 5 year uptake rates for nintedanib in the RSA cap (Year 1-5: %) and the estimated expected utilisation as per the DUSC suggested parameters (Year 1 to 5: %). Given that the weighted effective price was based on estimates over 5 years there is an underlying disconnect with the 10 year time frame used in the economic model. If the price of nintedanib was to revert to the effective price after Year 5 (i.e. uptake rates for year 6-10 = 100%), this would result in a nintedanib cost/day of $. The economic model was highly sensitive to this revised weighted effective price.

6.33 The ESC considered the use of the weighted effective price in the model to be inappropriate as this approach links the actual ICER to the difference between the DUSC estimates and submission estimates. While this limits the risk in terms of overall cost, it does not provide a stable estimate of cost-effectiveness if there are differences in utilisation.

6.34 Sensitivity analyses indicated that other changes to the economic model were of negligible impact to the estimated ICER: risk of acute IPF exacerbation calculated from adjudicator defined events; removal of disutility for adverse events; inclusion of costs associated with severe diarrhoea and liver function tests; utilisation rates for tests and procedures derived from the Australian IPF registry.

6.35 Results of the stepped economic evaluation are provided in the table below.

Table 12: Results of the stepped economic evaluation

Step and component	Nintedanib	BSC	Increment
Step 1: trial based economic evaluation (21 months)			
Costs	$	$695	$
LYG		1.4912	
Incremental cost/LYG			$
Step 2: modelled economic evaluation including healthcare resource utilisation (21 months)			
Costs	$	$4955	$

Step and component	Nintedanib	BSC	Increment
LYG	[redacted]	1.4912	[redacted]
Incremental cost/LYG			$[redacted]
Step 3: modelled economic evaluation including extrapolation (10 years)			
Costs	$[redacted]	$9,724	$[redacted]
LYG	[redacted]	2.7798	[redacted]
Incremental cost/LYG			$[redacted]
Step 4: modelled economic evaluation including utilities (10 years)			
Costs	$[redacted]	$9,724	$[redacted]
QALY	[redacted]	2.1432	[redacted]
Incremental cost/QALY			$[redacted]
Step 5: modelled economic evaluation including proposed RSA (10 years)			
Costs	$[redacted]	$9,724	$[redacted]
QALY	[redacted]	2.1432	[redacted]
Incremental cost/QALY			**$**[redacted]

Abbreviations: BSC = best supportive care. Source: Table D.5-1 to D.5-6, pp252-255 of the re-submission

6.36 The estimated base case ICER ($75,000/QALY - $105,000 /QALY) has decreased in comparison to the March 2015 submission ($105,000/QALY – $200,000/QALY). This change in the ICER is driven by the reduction in incremental costs due to the weighted effective price for nintedanib (inclusive of the RSA), which dominates the reduction in incremental QALYs. The following key observations were noted from the univariate sensitivity analyses:

- Alternative estimates of long term survival: utilisation of the entire Weibull function (optimistic approach) resulted in LYGs of [redacted], with the application of Kaplan Meier estimates (base case) and the adjustment of the nintedanib survival according to a linear decline in the treatment co-efficient or the gradient of the BSC (conservative approach), reducing LYGs to [redacted], [redacted] and [redacted], respectively. Corresponding ICERs ranged from a 13% reduction (Weibull function; $75,000/QALY - $105,000/QALY) to an approximate doubling (Kaplan Meier plus gradient of the BSC; $105,000/QALY – $200,000/QALY) of the base case estimate.
- Nintedanib weighted effective price: adjustment of the weighted effective price assuming 100% uptake from Years 6 to 10 (refer to Section D.4) and removal of the RSA resulted an increase in the ICER of 33% ($105,000/QALY – $200,000/QALY) and 58% ($105,000/QALY – $200,000/QALY), respectively, when compared to the base case estimate.

Drug cost/patient/year: $[redacted]

6.37 The estimated usage per patient was based on an expected compliance rate of 96.4% (observed in Trials 32 and 34), resulting in an average of 11.73 nintedanib prescriptions/patient/year. Proportional distribution of nintedanib 150mg and 100mg (76%/24%) was assumed to be consistent with usage reported in Trials 32 and 34.

Estimated PBS usage & financial implications

6.38 This submission was not considered by DUSC. The re-submission updates the estimated extent of use and financial implications associated with the requested listing for nintedanib, with the estimated eligible patient pool calculated using parameters consistent with the DUSC advice (IPF prevalence = 14.4/100,000, diagnosis rate for IPF = 100%). Adverse event (diarrhoea, nausea, vomiting) and liver monitoring costs were also included in the updated estimates.

6.39 The re-submission focused on estimates calculated from uptake rates (Year 1-5: [redacted]% to [redacted]%) that form the basis of the cap proposed in the RSA. The re-submission indicated (p295) that in the scenario where the uptake rate for nintedanib occurs as predicted by DUSC (Year 1-5: 60% to 100%), this would result in an incremental rebate equivalent to the difference between the capped and actual Commonwealth expenditure. During the evaluation it was considered that the DUSC estimates were a proxy for the expected utilisation of nintedanib. Estimated extent of use of nintedanib based on DUSC utilisation rates are presented in addition to the RSA capped estimates in the table below. The presentation of costs is based on the requested effective price for nintedanib.

Table 13: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Eligible patient pool –prevalence rate of 14.4/100,000; diagnosis rate for IPF = 100%					
November 2015 re-submission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
March 2015 submission	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RSA – uptake rates: year 1-5; 25% to 65%					
Total prescriptions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net costs to PBS/RPBS – RSA	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Expected utilisation – uptake rates: year 1-5; 60% to 100% (DUSC)					
Total prescriptions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net costs to PBS/RPBS	$[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	$45,414	$73,900	$103,309	$114,546	$126,080
Net financial implications to government health budgets					
Expected utilisation^	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
RSA rebate	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
RSA	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
March 2015 submission	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

^ The re-submission'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 – expected utilisation + adverse events net cost to the PBS/RPBS (base case analysis) + net cost to the MBS. Abbreviations: RSA = risk sharing arrangement. Source: Table E.2-2 and Table E.2-3, p278; Table E.2-8, p285; Table E.4-2 and Table E.4-3, p284; 'DUSC PBS-RPBS Cost' and 'Epidemiology and patient number' worksheets, Nintedanib IPF Financial Implications.xlsx of the re-submission

The redacted table above shows that the number of patients treated with nintedanib is estimated to be less than 10,000 per year at a net cost of $60 - $100 million over five years.

6.40 Overall, the re-submission 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 in 2011), the proposed RSA may limit the potential risk associated with the estimation of the eligible patient pool.

Quality Use of Medicines

6.41 The re-submission indicated that sponsor will support education activities for prescribers and patients.

Financial Management – Risk Share Arrangement

6.42 In the context of the results of the economic evaluation (Step 4: ICER = $105,000/QALY – $200,000/QALY), the re-submission proposed an RSA to improve the cost effectiveness of nintedanib for the treatment of IPF. A summary of the RSA is located in the table below.

Table 14: Proposed RSA

Risk sharing arrangement	Rebate	Data source
Rebate the cost of all nintedanib use beyond the utilisation estimates presented in the re-submission.	100% of the effective IPF DPMQ, co-payment adjusted	Department of Human Services, adjusted for rebate for public versus effective DPMQ minus co-payment

Abbreviations: IPF = idiopathic pulmonary fibrosis. Source: Table F.2-4, p296 of the re-submission

6.43 In comparison to the March 2015 submission, the RSA is no longer based on a rebate for patients with a FVC%Pred < [redacted]% and has been restructured to incorporate a cap in expenditure according to the RSA utilisation estimates. Given the potential that substantial usage may occur beyond expectations within the requested restriction the RSA may serve to lessen the financial risks associated with the listing of nintedanib for IPF.

6.44 On the basis of the capped expenditure (RSA) and expected utilisation of nintedanib (actual number of prescriptions) a weighted DPMQ of $[redacted] for nintedanib 150mg and $[redacted] for nintedanib 100mg across the first 5 years of listing was calculated by the re-submission. This was applied in the last step of the economic model, reducing the estimated ICER to $[redacted]/QALY.

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

7 PBAC Outcome

7.1 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. Discussions with the Department of Health should take place prior to a future major resubmission.

7.2 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.

7.3 The PBAC welcomed the Pre-PBAC response (p1) suggestion for the following continuation rule: "treatment with nintedanib should be discontinued if disease progresses (a confirmed decline in % predicted FVC of 10% or more within any 12-month period while receiving treatment)". This proposed rule had recently been requested for nintedanib by the National Institute for Health and Care Excellence (through the appraisal consultation document process) and the Canadian Drug Expert Committee. PBAC considered a future resubmission should explore the likelihood of the stopping rule proving effective by exploring the numbers of patients who may discontinue treatment based on the clinical trial evidence and the proposed model.

7.4 Other suggested wording changes to the restriction in the Pre-PBAC response (p1) included "Prescriber Instruction 1" be made clearer to read: "Documented diagnosis through a multidisciplinary team which comprises of at least a pulmonologist, radiologist and where required, pathologist. If attendance is not possible, because of geographical isolation, consultation with a multidisciplinary team is necessary in the diagnosis of idiopathic pulmonary fibrosis (IPF)". PBAC agreed with the suggested wording, noting the letter received from the Australian IPF Registry Steering Committee (1 July 2015) which endorsed the requirement for a written authority prescription for anti-fibrotic therapy, including the need for diagnosis to have been made at a multidisciplinary team meeting. Such meetings were described by the Steering Committee as likely be held in association with respiratory departments in large public hospitals. The PBAC agreed that a one-off requirement for diagnosis by the multidisciplinary team for initiating therapy would be appropriate.

7.5 The PBAC reaffirmed that best supportive care was the appropriate main comparator for nintedanib for IPF. Another novel agent for the treatment of IPF, pirfenidone, was considered at the same November 2015 PBAC meeting and, although not currently registered by TGA, pirfenidone was considered to be a relevant secondary comparator. PBAC noted its concern that should both drugs become PBS subsidised in the future, the risk of concomitant use would need to be addressed.

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 submission: 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 118.89 mL/year reduction in the annual rate of decline in FVC.
- Approximately a 3.31% reduction in absolute decline in forced vital capacity percent predicted (FVC%Pred) from baseline to week 52.
- Approximately a 65% reduction in the risk of independently adjudicated acute IPF exacerbations over 52 weeks, but no significant difference in investigator-reported acute IPF exacerbations.
- No significant difference in disease specific quality of life.
- Insufficient evidence to support a significant difference in OS.

7.7 The PBAC noted that loss of lung function was a more critical clinical issue than exacerbations and that the 3.31% absolute decline in reduction in FVC was close to

the MCID calculated by the anchor based method and the distribution based method (see Table 4 above).

7.8 The FDA review[3] of pirfenidone and nintedanib studies suggests that FVC is a valid surrogate for mortality in IPF. This review gave the PBAC more confidence that the lack of statistical significance in OS may be an issue of lack of power in the trials. It was further noted, from the Pre-PBAC response (p2), 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.

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. A statistically significant reduction in dyspnoea was observed.

7.10 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 = 3.54, 95% CI: 1.04, 12.06). No evidence was available to determine whether these cardiovascular/thromboembolic safety signals would have any substantial impact upon long term patient risks.

7.11 Interpretation of the indirect comparison with pirfenidone is difficult given the differences in the trial populations and the outcomes. The network meta-analysis from Loveman et al 2015[4] suggests 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). However, PBAC considered both drugs are likely to be similarly clinically effective.

7.12 The PBAC noted the revisions to the economic model only partially adopted advice from the March 2015 PBAC. The PBAC accepted the arguments relating to time horizon and methodology for extrapolation in the pre-PBAC response (p2-3) as the suggested approach for extrapolation beyond the trial period was not supported by the additional long-term efficacy data from Trial 30, which showed a statistically significant difference in FVC rate of decline (mL/year) over 80 weeks. The Pre-PBAC response (p3) also noted ESC's concern that the additional follow-up data from Trial 30 over 80 weeks suggest a reduction in difference in the annual rate of decline in FVC between nintedanib and placebo over the longer period and have incorporated this into the model, resulting in an ICER of approximately $75,000/QALY - $105,000/QALY, up from an estimated base case ICER of $75,000/QALY - $105,000/QALY.

[3] 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

[4] Loveman E, Copley VR, Scott DA, Colquitt JL, Clegg AJ and O'Reilly. Comparing new treatments for idiopathic pulmonary fibrosis-a network meta-analysis. BMC Pulmonary Medicine, 2015; 15:37.

7.13 The above ICERs use a weighted effective price for nintedanib of $[redacted]/day based on the proposed RSA which adjusts the price by applying a cap on expenditure beyond the March 2015 predictions of utilisation. The PBAC agreed with the ESC that this was inappropriate. Removal of the RSA from the price resulted in $[redacted]/day and an ICER of $105,000/QALY – $200,000/QALY compared to $75,000/QALY - $105,000/QALY. The PBAC considered any effective price used in the model cannot be based on the RSA proposal to cap expenditure.

7.14 The PBAC also noted the model was very sensitive to the estimates of long-term survival.

7.15 The cost-effectiveness of the assumed long-term benefit of nintedanib may be partially supported by effective implementation of the continuation rule, as subsidised treatment would not continue for those patients with FVC%Pred deteriorating 10% or more within any 12-month period. The PBAC proposed that the sponsor consider how the use of the continuation rule may impact on the ICER and discuss further with the Department of Health how the benefits of treatment may be monitored in practice and the price potentially aligned to reflect a pay for performance scenario.

Outcome:
Deferred

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.