


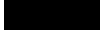
**5.17 NINTEDANIB**  
**100 mg capsule, 60, 150 mg capsule, 60;**  
**Ofev®; Boehringer Ingelheim Pty Ltd.**

**1 Purpose of Application**

- 1.1 To request Authority Required listing for nintedanib in combination with docetaxel for second line treatment of non-small cell lung cancer (NSCLC) in patients with adenocarcinoma histology.

**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	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
NINTEDANIB				Ofev BI
Nintedanib, 100 mg, capsules, 60	2	3		
Nintedanib, 150 mg, capsules, 60	1	3		

<b>Category / Program</b>	Efficient Funding of Chemotherapy – Section 100 Arrangements
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Severity:</b>	Locally advanced, or metastatic <del>or recurrent</del>
<b>Condition:</b>	Non-small cell lung cancer (NSCLC)
<b>PBS Indication:</b>	Locally advanced, or metastatic <del>or recurrent</del> non-small cell lung cancer (NSCLC) of <del>adenocarcinoma tumour histology</del>
<b>Treatment phase:</b>	Initial treatment
<b>Restriction Level / Method:</b>	Authority Required - In Writing Authority Required - Telephone Authority Required – Emergency Authority Required - Electronic
<b>Clinical criteria:</b>	The treatment must be in combination with docetaxel  AND  The condition must be non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology  AND  The treatment must be after failure of first line chemotherapy  AND

Public Summary Document – March 2015 PBAC Meeting

	The Patient must have a WHO/ECOG performance status of 2 or less
<b>Administrative Advice</b>	<i>Special Pricing Arrangements apply.</i>
<b>Category / Program</b>	Efficient Funding of Chemotherapy – Section 100 Arrangements
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Severity:</b>	Locally advanced, metastatic or recurrent
<b>Condition:</b>	Non-small cell lung cancer (NSCLC)
<b>PBS Indication:</b>	Locally advanced, or metastatic or recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology
<b>Treatment phase:</b>	Continuing treatment
<b>Restriction Level / Method:</b>	Authority Required - In Writing Authority Required - Telephone Authority Required – Emergency Authority Required - Electronic
<b>Clinical criteria:</b>	Patient must have previously been issued with an authority prescription for this drug  AND  Patient must not have progressive disease
<b>Administrative Advice</b>	<i>Special Pricing Arrangements apply.</i>

- 2.2 The Pre-Sub-Committee Response (PSCR) accepted the suggested revisions to the restriction for PBAC consideration.
- 2.3 The submission sought listing on the basis of a cost-utility analysis comparing nintedanib and docetaxel combination therapy to a weighted comparator (87% pemetrexed and 13% docetaxel monotherapy).
- 2.4 The submission proposed an effective price of \$ [REDACTED] for both 100mg x 60 capsules and 150mg x 60 capsules dosages of nintedanib for the NSCLC listing. While this effective price was applied in the economic evaluation and the financial estimates, a special pricing arrangement (SPA) was also requested across the idiopathic pulmonary fibrosis (IPF) and NSCLC indications as summarised in the following table.

**Special pricing arrangement for nintedanib**

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

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

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

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

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

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

**3 Background**

- 3.1 The submission was lodged under TGA/PBAC Parallel Process with the Delegate’s consideration expected in July 2015. The Round 1 Clinical Evaluation Report was received on 26 February 2015.
- 3.2 This was the first consideration by the PBAC of nintedanib for the treatment of NSCLC.

**4 Clinical place for the proposed therapy**

- 4.1 NSCLC is a fatal lung disease consisting of heterogeneous, malignant tumours that generally affect cells lining the bronchi and other airways. Adenocarcinoma NSCLC develops in the mucus developing cells of the bronchioles and alveoli. Adenocarcinoma is the most common type of lung cancer in non-smokers, but smoking is also a leading cause of this type of lung cancer. Patients of the adenocarcinoma type who have previously failed first line chemotherapy, and are not selected for EGFR or ALK mutations are currently treated with pemetrexed or docetaxel.
- 4.2 Nintedanib combination therapy will likely mostly replace pemetrexed in second-line therapy. The evaluation considered that there is potential for replacement of docetaxel monotherapy.

**5 Comparator**

- 5.1 The submission nominated docetaxel monotherapy and pemetrexed as comparators. The PBAC had previously considered that pemetrexed was an appropriate comparator for adenocarcinoma NSCLC patients on second line therapy (crizotinib PSD, November 2013). Pemetrexed may be the only appropriate comparator.

- 5.2 The PSCR argued that the submission adopted a conservative approach by selecting both pemetrexed and docetaxel as comparators. The PSCR noted, however, that the sponsor would accept the ESC and PBAC feedback on the appropriate comparator(s). The ESC considered that pemetrexed was the appropriate comparator given the precedent for crizotinib and the dominance of pemetrexed as second-line treatment for advanced NSCLC.

*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 that no consumer comments were received for this item.

### **Clinical trials**

- 6.3 The submission was based on one head-to-head trial, LUME Lung 1, comparing nintedanib in combination with docetaxel to docetaxel monotherapy (n=1314) and an indirect comparison using LUME Lung 1 and one head-to-head trial (JME1) comparing pemetrexed to docetaxel monotherapy (n=571).
- 6.4 Details of the trials presented in the submission are provided in the table below.

**Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Nintedanib vs. docetaxel</b>		
Trial 1199.13 LUME Lung 1	Clinical Trial Report BI Trial 1199.13 Multicentre, randomised, double-blind, Phase III trial to investigate the efficacy and safety of oral BIBF 1120 plus standard docetaxel therapy compared to placebo plus standard docetaxel therapy in patients with stage IIIB/IV or recurrent non-small-cell lung cancer after failure of first line chemotherapy. (LUME Lung 1)	Sep 11 2012
	Mellemgaard, A et al. Analysis of overall survival in adenocarcinoma NSCLC patients receiving 2nd line combination treatment with nintedanib (BIBF 1120) + docetaxel in the LUME-Lung 1 trial: a randomized, double-blind, placebo-controlled phase 3 study	Eur. J. Cancer (2013); 49(Supplement 2):S798., 27 Sep - 1 Oct 2013
	Novello, S et al. LUME-Lung 1 Study Group. Analysis of patient-reported outcomes from the LUME-lung 1 trial: a randomized, double-blind, placebo-controlled phase III study in second-line advanced non-small cell lung cancer (NSCLC) patients.	15th World Conference on Lung Cancer, Sydney; 27 - 30 Oct 2013 (Poster)
	Novello, S et al. Impact of tumor burden on the overall survival analysis of the Lume-Lung 1 study: a randomized, double-blind phase 3 trial of nintedanib (BIBF 1120) + docetaxel in NSCLC patients progressing after first-line chemotherapy.	J. Thorac. Oncol. (2013); 8(Suppl. 2):S196. 27 - 30 Oct 2013

Public Summary Document – March 2015 PBAC Meeting

Trial ID	Protocol title/ Publication title	Publication citation
	<p>Novello S, et al. Analysis of patient-reported outcomes from the LUME-lung 1 trial: a randomized, double-blind, placebo-controlled phase 3 study in second-line advanced non-small cell lung cancer (NSCLC) patients. 15th World Conf on Lung Cancer, Sydney, 27 - 30 Oct 2013 Abstr P3.11-040 J Thorac Oncol 2013; 8(Suppl 2):S1207</p> <p>Reck, M et al LUME-Lung 1 Study Group. Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial.</p> <p>Reck, M et al. LUME-Lung 1 Study Group. Nintedanib (BIBF 1120) + docetaxel as second-line therapy in patients with stage IIIB/IV or recurrent NSCLC: results of the phase III, randomised, double-blind LUME-Lung 1 trial.</p> <p>Reck, M et al. LUME-Lung 1 Study Group. Nintedanib (BIBF 1120) + docetaxel as second-line therapy in patients with stage IIIB/IV or recurrent NSCLC: results of the phase III, randomised, double-blind LUME-Lung 1 trial.</p> <p>Reck, M et al. Nintedanib (BIBF 1120) + docetaxel as 2nd-line therapy in patients with stage IIIB/IV or recurrent NSCLC: results of the phase III, randomised, double-blind LUME-Lung 1 trial. (for the LUME-Lung 1 study group).</p> <p>Reck, M et al. LUME-Lung 1 Study Group. Antiangiogenic-specific adverse events in patients with non-small cell lung cancer (NSCLC) treated with nintedanib (BIBF 1120) and docetaxel.</p>	<p>15th World Conf on LungCancer, Sydney, 27 - 30 Oct 2013 Abstr P3.11-040 J Thorac Oncol 2013; 8(Suppl 2):S1207</p> <p>Lancet Oncol. 2014; 15(2):143-155.</p> <p>BTOG 2014, 12th Ann Conference of the British Thoracic Oncology Group (BTOG), Dublin, 29 - 31 Jan 2014 Abstr 30 Lung Cancer 2014; 83(Suppl 1):S12.</p> <p>4th European Lung Cancer Conference (ELCC), Geneva, 26 - 29 Mar 2014 (Poster)</p> <p>4th European Lung Cancer Conference (ELCC), Geneva, 26 - 29 Mar 2014 Abstr 97PD J. Thorac. Oncol. 2014; 9(4, Suppl 1):S39-S40.</p> <p>50th Annual Mtg of the American Society of Clinical Oncology (ASCO), Chicago, 30 May - 3 Jun 2014 (Poster).</p>
<b>Pemetrexed vs. docetaxel</b>		
JMEI	<p>De Marinis, F et al. Lung cancer symptom scale outcomes in relation to standard efficacy measures: An analysis of the phase III study of pemetrexed versus docetaxel in advanced non-small cell lung cancer.</p> <p>Hanna, N et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy.</p> <p>Scagliotti, G et al. The differential efficacy of pemetrexed according to NSCLC histology: A review of two phase III studies.</p> <p>Peterson, P et al. Is pemetrexed more effective in adenocarcinoma and large cell lung cancer than in squamous cell carcinoma? A retrospective analysis of a phase III trial of pemetrexed vs docetaxel in previously treated patients with advanced non-small-cell lung cancer (NSCLC).</p>	<p><i>Journal of Thoracic Oncolog</i>, 2008; 3:30-36.</p> <p><i>J. Clinic. Oncol.</i>, 22:1589-1597</p> <p><i>Oncologist</i>, 2009; 14:253-263</p> <p><i>J. Thoracic Oncol.</i> 2007; 2(8, Suppl. 4): S851 (Abstract P2-328).</p>

Source: Table B.5, pp.51-3 of the submission

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

**Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
<b>Nintedanib and docetaxel versus docetaxel</b>						
LUME Lung 1	1314	R, DB, MC	Low	2 <sup>nd</sup> line NSCLC	PFS/OS	OS PFS adenocarcinoma subgroup
<b>Pemetrexed versus docetaxel</b>						
JMEI	571	R, OL	High	2 <sup>nd</sup> line NSCLC	PFS/OS	OS PFS adenocarcinoma subgroup

DB=double blind; MC=multi-centre; OL=open label; OS=overall survival; PFS=progression-free survival; R=randomised  
Source: compiled during the evaluation

**Comparative effectiveness**

6.6 The submission claimed superior efficacy and inferior safety to docetaxel. A summary of the efficacy results of the LUME Lung 1 trial is presented in the following table. A primary analysis was conducted when a sufficient number of events occurred to power progression-free survival analysis, and a final analysis was conducted after a sufficient number of events for the overall survival analysis.

**Results of OS and PFS in the LUME Lung 1 trial adenocarcinoma subgroup**

Outcome	Nintedanib n/N (%)	Docetaxel n/N (%)	Difference in medians	Relative difference HR (95% CI)
<b>Primary analysis</b>				
Patients with PFS event	NR	NR	-	0.77 (0.62, 0.96)
<b>Final analysis</b>				
Patients with OS event	259/322 (80.4)	276/336 (82.1)	--	0.83 (0.70, 0.99)
Median OS in months(IQR)	12.6 (5.5, 24.2)	10.3 (5.5, 19.9)	2.3	--
Patients with PFS event	255/322 (79.2)	267/336 (79.5)	--	0.84 (0.71, 1.00)
Median PFS in months(IQR)	4.2 (2.1, 6.9)	2.8 (1.4, 4.9)	1.4	--

Source Tables B.32, B.33, and B.34, pp97, 101 and 103 of the submission  
CIR=Central Independent Review; HR=hazard ratio; IQR=interquartile range; NR=not reported; OS=overall survival; PFS=progression-free survival

6.7 The submission also claimed non-inferior efficacy and inferior safety to pemetrexed. Efficacy results of the indirect comparison against pemetrexed are presented in the table below. The economic evaluation was based on a hazard ratio (0.77), for which no Kaplan Meier data were presented.

Results of the indirect comparison – OS, PFS and ORR

	LUME Lung 1			JMEI			Indirect estimate of effect <sup>c</sup> HR (95% CI)
	Treatment effect <sup>a</sup> HR (95% CI)	Nintedanib plus docetaxel n/N (%)	Docetaxel n/N (%)	Docetaxel n/N (%)	Pemetrexed n/N (%)	Treatment effect <sup>b</sup> HR (95% CI)	
OS	0.83 (0.70, 0.99)	259/322 (80.4)	276/336 (82.1)	NR	NR	0.92 (0.69, 1.22)	█
PFS (primary analysis)	0.77 (0.62, 0.96)	NR	NR	NR	NR	0.83 (0.65, 1.06)	█
PFS (final analysis)	0.84 (0.71, 1.00)	255/332 (79.2)	267/336 (79.5)	NR	NR	0.83 (0.65, 1.06)	█
ORR	1.32 (0.61, 2.93)	15/322 (4.7)	12/336 (3.6)	NR	NR	1.35 (0.65 to 2.78)	█

Source: Tables B.50 and B.51 p141 and p143 of the submission. CI=confidence interval; n=number with event; N=number in group; NR=not reported; ORR=overall/objective response rate; OS=overall survival; PFS=progression-free survival; RR=relative risk

\*odds ratio

<sup>a</sup> Nintedanib plus docetaxel over docetaxel

<sup>b</sup> pemetrexed over docetaxel

<sup>c</sup> Nintedanib plus docetaxel over pemetrexed

- 6.8 On the basis of the indirect evidence presented by the submission, for patients treated with nintedanib in combination with docetaxel, in comparison to pemetrexed:
- There was no statistically significant difference in overall survival
  - There was no statistically significant difference in progression-free survival.
- 6.9 The minimum clinically important difference (MCID) used to assess non-inferiority was the upper bound of a HR confidence interval (1.33). This was significantly higher than the median upper bound found in the literature (1.21 from the JMEI trial and 1.25 from a review on non-inferiority of cancer trials (Riechelmann 2011)). With more conservative MCID's, non-inferiority between nintedanib and pemetrexed was not demonstrated. The ESC considered that the level selected in the submission of 1.33 (Novello 2007) was not the upper CI in that study but the HR to be tolerated when using an experimental single drug regimen compared to two drugs for stable Stage IV NSCLC. The ESC noted that the hazard ratio in Novello (2007) had to be significantly higher than the more appropriate MCIDs (between 1.21 and 1.25) given that the three cycles had to be substantially more effective to justify extra exposure to toxicity. This clinical justification is only appropriate because of the known, fixed extra exposure and the specific context of the Novello trial. This reasoning is not appropriate for setting an MCID in the current indirect comparison.
- 6.10 The ESC considered the upper confidence limits for the indirect comparison of progression-free survival (█) and overall survival (█) are at the borderline of MCID used in the JMEI pemetrexed-docetaxel study (1.21) and a review of non-inferiority cancer trials (mean 1.25; range 1.10 to 1.50).

- 6.11 The ESC questioned the use of hazard ratios in isolation in determining the effectiveness of oncology medicines. The PBAC has required estimates of both relative and absolute benefit for progression-free survival or overall survival as a more informative statistical analysis in oncology.

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

### Comparative harms

- 6.12 Key safety outcomes from the direct and indirect comparisons are presented in the table below.

**Key safety outcomes from the direct and indirect comparisons**

Adverse event	RR (95% CI)
<b>Direct Comparison: nintedanib versus docetaxel</b>	
Diarrhoea (all grades)	1.76 (1.41, 2.21)
Nausea (all grades)	1.61 (1.20, 2.14)
<b>Indirect comparison: nintedanib versus pemetrexed.</b>	
Febrile Neutropenia	
Neutropenia	
Diarrhoea (grades 3/4/5)	

Source: Tables B.41-B.43, p119-126 and Table B.52, p145 of the submission  
CI=confidence interval; RR=relative risk

- 6.13 On the basis of the indirect evidence presented by the submission, for every 100 patients treated with nintedanib in combination with docetaxel, in comparison to pemetrexed:
- Approximately 28 to 42 more patients suffered at least one neutropenia event.
  - Approximately 3 to 9 more patients suffered at least one severe (grade 3/4/5) diarrhoea event.
- 6.14 Nintedanib plus docetaxel was associated with statistically significant increases in the risk of diarrhoea and nausea compared with docetaxel alone.
- 6.15 Nintedanib plus docetaxel was also associated with a statistically significant higher risk of neutropenia, febrile neutropenia and diarrhoea (grades 3/4/5) in comparison with pemetrexed.
- 6.16 The PSCR dismissed the increase in toxicity of nintedanib added to docetaxel and stated that the toxicity of nintedanib alone compared to pemetrexed is not substantial. The ESC disagreed with the PSCR and considered that nintedanib is associated with higher toxicity compared to pemetrexed. In relation to the combination use of nintedanib with docetaxel, the ESC noted the results from Reck 2014, where grade 3 or worse adverse events were more common in the docetaxel plus nintedanib group than in the docetaxel plus placebo group. The ESC further considered that it was unreasonable to discount the adverse events associated with docetaxel, as nintedanib is only given in combination with docetaxel.

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

### **Clinical claim**

- 6.17 The submission claimed superior effectiveness and inferior safety in comparison with docetaxel monotherapy. These claims were supported by overall survival and progression-free survival outcomes as well as safety outcomes of the LUME Lung 1 trial evidence. The ESC considered this claim was well supported but irrelevant given that it considered pemetrexed to be the appropriate comparator.
- 6.18 The submission claimed non-inferior effectiveness and inferior safety in comparison with pemetrexed. The MCID level proposed by the submission was likely too high, and with a lower MCID, nintedanib failed to demonstrate non-inferior efficacy to pemetrexed. The safety claim was supported by higher frequency across several comparable AEs as well as a generally worse safety profile in comparison to docetaxel.
- 6.19 With respect to the claim that nintedanib-docetaxel is non-inferior in efficacy to pemetrexed, the upper confidence limits for the indirect comparison of progression-free survival (■■■■) and overall survival (■■■■) are at the borderline of MCIDs used in similar settings including the JME1 pemetrexed-docetaxel study (1.21) and a review of non-inferiority cancer trials (mean 1.25; range 1.10 to 1.50) (Riechelmann 2011). Overall, the ESC considered the claim of non-inferior clinical effectiveness to pemetrexed to be border-line and the claim of inferior safety to pemetrexed to be appropriate.
- 6.20 The PBAC considered that the claim of non-inferior comparative effectiveness to pemetrexed was not adequately supported.
- 6.21 The PBAC considered that the claim of inferior comparative safety to pemetrexed was reasonable.

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

### **Economic analysis**

- 6.22 Because the clinical claim is non-inferior efficacy and inferior safety in comparison to pemetrexed, there is no basis for modelling cost-effectiveness using the pemetrexed component of the model. The PSCR argued that a CUA is appropriate as it quantified differences in adverse events given the inferior safety of nintedanib. The ESC considered the CUA used in the submission was not consistent with the clinical claim of non-inferior efficacy (or borderline inferiority), and inferior safety of nintedanib to pemetrexed.
- 6.23 The submission included a cost-utility analysis (CUA) of nintedanib in combination with docetaxel versus a weighted comparator comprised of pemetrexed (87%) and docetaxel (13%). The ESC considered the weighted comparator to be inappropriate. More recent data suggested that pemetrexed use in the proposed setting is closer to 90% (PSCR). Given these utilisation estimates, pemetrexed alone is the appropriate comparator.
- 6.24 The ESC considered that without additional justification, a cost-minimisation analysis may also be an inappropriate methodology given that the currently available indirect

evidence did not demonstrate non-inferiority for nintedanib and docetaxel compared with pemetrexed.

6.25 The following table presents a summary of the structure and rationale of the model.

**Summary of model structure and rationale**

Component	Summary
Time horizon	5 years in the model base case versus 43 weeks in trial
Outcomes	PfLYG, LYG and QALYs
Methods used to generate results	Trial based, survival extrapolations using Weibull curves to inform a Markov model.
Health states	Progressed, non-progressed, dead and utility decrements for specific AEs
Cycle length	3 weeks
Transition probabilities	Weibull curves extrapolated from LUME Lung 1, and indirect comparison hazard ratio

Source: compiled during the evaluation. AE=adverse event; LYG=Life years gained, PfLYG=progression-free life years gained; QALY=quality-adjusted life years

6.26 The model extrapolated progression-free survival and survival from Weibull curves for the entirety of the model period, and not a post-trial (post 43 month) extrapolation phase. This application of Weibull curves favours nintedanib. Given that the extrapolated treatment effect based on the Weibull survival function generated fewer progression-free life years in the weighted comparator than what the trial-based Kaplan Meier estimates show patients to have actually lived, the Weibull extrapolation is likely unreasonable. If Kaplan Meier estimates were used for the trial period, the weighted comparator would no longer be cost-saving. The PSCR (p3) argued that Kaplan Meier survival data were not available for pemetrexed and that Kaplan Meier analysis is not a proportional hazards model; i.e. the HR cannot be applied to the observed Kaplan Meier data for nintedanib plus docetaxel. However the ESC noted that the resulting survival curve is based on a hazard ratio point estimate, which is neither well supported by the evidence, nor consistent with the clinical claim of non-inferiority made by the submission. This issue is crucial because, even though the hazard ratio is higher than in the nintedanib versus docetaxel direct comparison, the model is weighted heavily towards the pemetrexed comparison (87%).

6.27 The table below presents a summary of the key drivers of the model.

**Key drivers of the model**

Description	Method/Value	Impact
Time horizon	5 years; assumed from 43 week trial duration	High, favours nintedanib
Extrapolation	Weibull curves applied to entire model duration	High, favours nintedanib
Weighting of comparators	Pemetrexed weighted at 87%	High, favours nintedanib

Source: compiled during the evaluation

6.28 The results of the submission's stepped economic evaluation, as well as final results for each comparator, are provided in the following table.

Results of the stepped economic evaluation

Step and component	Nintedanib + docetaxel	Weighted comparator	Increment
<b>Step 1: trial-based costs and outcomes</b>			
Costs	\$ [REDACTED]	\$12,299.78	[REDACTED]
Progression-free LYG	[REDACTED]	0.39	[REDACTED]
<b>Incremental cost/PfLYG</b>			Dominant
LYG	[REDACTED]	1.19	[REDACTED]
<b>Incremental cost/LYG</b>			Dominant
<b>Step 2: Incorporating costs of third line therapies and disease monitoring</b>			
Costs	\$ [REDACTED]	\$27,413.21	\$ [REDACTED]
Progression-free LYG	[REDACTED]	0.39	[REDACTED]
<b>Incremental cost/PfLYG</b>			\$ [REDACTED]
LYG	[REDACTED]	1.19	[REDACTED]
<b>Incremental cost/LYG</b>			\$ [REDACTED]
<b>Step 3: extrapolation to 5 years</b>			
Costs	\$ [REDACTED]	\$27,977.67	-\$ [REDACTED]
Progression-free LYG	[REDACTED]	0.38	[REDACTED]
<b>Incremental cost/PfLYG</b>			Dominant
LYG	[REDACTED]	1.22	[REDACTED]
<b>Incremental cost/LYG</b>			Dominant
<b>Step 4: Transformation to utilities vs. docetaxel</b>			
	<b>Nintedanib + docetaxel</b>	<b>Docetaxel</b>	
Costs	\$ [REDACTED]	\$17,777.99	\$ [REDACTED]
QALYS	[REDACTED]	0.66	[REDACTED]
<b>Incremental cost/extra QALYs gained</b>			\$ [REDACTED]
<b>Step 4: Transformation to utilities vs. pemetrexed</b>			
	<b>Nintedanib + docetaxel</b>	<b>Pemetrexed</b>	
Costs	\$ [REDACTED]	\$29,510.02	-\$ [REDACTED]
QALYS	[REDACTED]	0.69	[REDACTED]
<b>Incremental cost/extra QALYs gained</b>			Dominant
<b>Step 4: Transformation to utilities vs. weighted comparator (13% docetaxel; 87% pemetrexed)</b>			
	<b>Nintedanib + docetaxel</b>	<b>Weighted comparator</b>	
Costs	\$ [REDACTED]	\$27,977.67	-\$ [REDACTED]
QALYS	[REDACTED]	0.69	[REDACTED]
<b>Incremental cost/extra QALYs gained</b>			Dominant

Source: Tables D.14-D.17, pp241-3 of the submission; 'Nintedanib Economic Evaluation (Final).xlsx'  
 LYG= life years gained; PfLYG=progression-free life years gained; QALY= quality-adjusted life years

- 6.29 While the ESC considered the presentation of a cost-utility model in the submission to be inappropriate, it also noted the following concerns regarding the model:
- The use of non-statistically significant hazard ratio point estimates (from an indirect comparison) as the basis of the pemetrexed transition probabilities (over five years) in the modelled evaluation was not appropriate
  - The model generated more progression-free life years, life years and quality adjusted life years (QALYs) for the nintedanib arm than the pemetrexed arm. This was inconsistent with the submission's clinical claim of non-inferior efficacy and inferior safety between nintedanib and pemetrexed, and lacked face validity.

- The extrapolated treatment effect based on the Weibull survival function generates fewer life years in the weighted comparator than the trial-based Kaplan Meier estimates show that patients to have actually lived. This unreasonably, and significantly, favours nintedanib treatment.
- Adverse event disutilities and costs were estimated based on the proportion of patients at risk of an adverse event in each cycle (cycle risk), which was a function of treatment duration. This did not adequately capture repeat adverse events, or time for which patients temporarily interrupted nintedanib treatment.

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

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

6.30 The drug cost of nintedanib is \$ [REDACTED] per year, based on a DPMQ of \$ [REDACTED] and [REDACTED] prescriptions per year. The estimate of [REDACTED] prescriptions per year is based on a based on the maximum of 30 days treatment for 1 prescription and a dose intensity of 91.2%. The costs are the same regardless of dose.

**Estimated PBS usage & financial implications**

6.31 This submission was not considered by DUSC. The submission took an epidemiological approach to estimating usage, based on AIHW and market research data, as well as NSCLC survival data from Yang 2005.

6.32 The estimated net costs, based on the effective price, are provided in the table below.

**Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5
<b>Estimated extent of use</b>					
Number treated	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Scripts <sup>a</sup>	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Total nintedanib and docetaxel scripts	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
<b>Estimated net cost to PBS/RPBS/MBS</b>					
Net cost to PBS/RPBS	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]
Net cost to MBS	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Net cost to other budgets	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]	-\$ [REDACTED]
<b>Estimated total net cost</b>					
<b>Net cost to PBS/RPBS/MBS</b>	<b>-\$ [REDACTED]</b>	<b>-\$ [REDACTED]</b>	<b>-\$ [REDACTED]</b>	<b>-\$ [REDACTED]</b>	<b>-\$ [REDACTED]</b>

<sup>a</sup> Assuming 11.10 scripts per year as estimated by the submission.  
Source: Tables E.2 and E.5, p248 and p250 of the submission

6.33 At year 5, the estimated number of scripts was less than 10,000 and the estimated net cost to the PBS/RPBS was a cost saving of \$10 – \$20 million.

- 6.34 The evaluation stated that the estimates are generally well supported, and reasonable. Overall, financial estimates are most sensitive to the relative usage weights of docetaxel or pemetrexed due to the significant price differential between the two comparators. The ESC considered that the pemetrexed weighting (87%) for relative use in comparison to docetaxel was not appropriate.

### **Financial Management – Risk Sharing Arrangements**

- 6.35 The IPF submission proposed a SPA across both the NSCLC and IPF indications (see paragraph 2.4 for further details). There was no specific risk sharing arrangement proposed for NSCLC.

## **7 PBAC Outcome**

- 7.1 The PBAC rejected the request to list nintedanib (in combination with docetaxel) for the treatment of patients with NSCLC on the basis that the submission did not demonstrate non-inferior effectiveness compared with pemetrexed and that the economic analysis was inconsistent with the clinical claim.
- 7.2 The PBAC noted that the submission was made under the TGA/PBAC Parallel Process with the Delegate's consideration expected in July 2015. Accordingly, the PBAC noted that it was only able to defer or reject the submission. However, the PBAC noted that even if a positive Delegate's overview been available, it would have been minded to reject the submission due to the lack of clinical benefit and inadequately supported comparative effectiveness to pemetrexed.
- 7.3 The PBAC did not accept docetaxel monotherapy as an appropriate comparator and noted that the Pre-PBAC Response indicated that the sponsor would accept the recommendation of the PBAC. The PBAC considered that pemetrexed was the appropriate comparator given the dominance of pemetrexed as second-line treatment for advanced NSCLC due to its superior effectiveness compared with docetaxel monotherapy. The PBAC recalled the acceptance of pemetrexed as the appropriate comparator for adenocarcinoma NSCLC patients on second-line therapy.
- 7.4 The PBAC further considered that replacing an I.V. infusion (pemetrexed) with a combination of oral medication (nintedanib) and I.V. infusion (docetaxel) would have disadvantages for the patient.
- 7.5 In forming a view of their recommendation, the PBAC noted that nintedanib should be placed in the context of a number of trials of oral angiokinase inhibitors (in combination with other chemotherapy) for NSCLC that have not produced meaningful outcomes. For example, a trial of vandetanib in combination with docetaxel compared with docetaxel monotherapy (Herbst et al, *The Lancet Oncology*, July 2010, 11: p619-626) did not produce clinically meaningful outcomes, and the LUME Lung 2 trial (Hanna et al, *Proc Am Soc Clin Oncol* 2013; 31 (suppl) abstr 8034) demonstrated that nintedanib did not have additional benefit when added to pemetrexed.

- 7.6 Given that the PBAC did not accept docetaxel monotherapy as an appropriate comparator, it considered that the statistically significant differences between nintedanib in combination with docetaxel and docetaxel monotherapy demonstrated in the LUME Lung 1 trial were not clinically meaningful in this context.
- 7.7 The PBAC noted that on the basis of the indirect evidence presented by the submission, there was no statistically significant difference in progression-free survival or overall survival for patients treated with nintedanib in combination with docetaxel, in comparison to treatment with pemetrexed.
- 7.8 The PBAC agreed with the ESC that the MCID selected in the submission of 1.33 from Novello 2007 was not the upper CI in that study but the HR to be tolerated when using an experimental single drug regimen compared to two drugs for stable Stage IV NSCLC. The PBAC noted the arguments made in the PSCR and the Pre-PBAC Response relating to the selection of the non-inferiority margins and considered that the reasoning was not appropriate for setting a MCID in the current indirect comparison.
- 7.9 With respect to the claim that nintedanib and docetaxel is non-inferior in efficacy to pemetrexed, the upper confidence limits for the indirect comparison of progression free survival (■■■■) and overall survival (■■■■) were at the borderline of MCIDs used in similar settings, including the JME1 pemetrexed-docetaxel study (1.21) and a review of non-inferiority cancer trials (mean 1.25; range 1.10 to 1.50) (Riechelmann 2011). Accordingly, the PBAC considered that the claim of non-inferior comparative effectiveness to pemetrexed was not adequately supported.
- 7.10 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. Accordingly, the PBAC considered that the claim of inferior comparative safety was appropriate. The Pre-PBAC response emphasised that nintedanib (in combination with docetaxel) resulted in only a small toxicity burden compared to docetaxel alone and that the management of diarrhoea is inexpensive. The Pre-PBAC Response further stated that the absolute event rates are low (eg 7% febrile neutropenia, 6.6% diarrhoea) and that the relative risks over-emphasise the adverse events. The PBAC did not agree with the interpretation of this data in the Pre-PBAC Response, noting that nintedanib (in combination with docetaxel) had ■■■■ times the risk of grade 3/4/5 diarrhoea and ■■■■ times the risk of febrile neutropenia compared to pemetrexed. These side effects would be expected to lead to substantial costs to patients and the health system.
- 7.11 The PBAC agreed with the ESC that the use of a CUA in the submission was not consistent with the clinical claim of non-inferiority efficacy and inferior safety of nintedanib (in combination with docetaxel) to pemetrexed (see paragraph 6.22). Furthermore, the clinical claim and the outcomes generated by the model were inconsistent as more progression-free life years, life years and QALYs were gained in the nintedanib treatment group compared with pemetrexed. The PBAC also agreed with the other concerns that the ESC had regarding the model (outlined in paragraph 6.29).
- 7.12 The PBAC noted that the sponsor presented a cost-minimisation analysis against pemetrexed in its Pre-PBAC Response. However, the PBAC considered that a cost-

minimisation analysis would also be inappropriate given that the currently available indirect evidence did not demonstrate non-inferiority for nintedanib and docetaxel compared with pemetrexed.

- 7.13 The ESC considered that the pemetrexed weighting (87%) for relative use in comparison to docetaxel in the financial estimates was not appropriate.
- 7.14 Should the sponsor wish to pursue the request for listing of nintedanib (for the treatment of patients with NSCLC), the PBAC considered that a major resubmission would need to demonstrate non-inferior comparative effectiveness in PFS and OS, compared with pemetrexed, and include a consideration of the patient quality of life and costs associated with the management of adverse events.
- 7.15 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**

Rejected

**8 Context for Decision**

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

**9 Sponsor's Comment**

The Sponsor had no comment.