

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

1 Purpose of Application

1.1 The submission requested 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	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
NINTEDANIB				Ofev BI
100 mg capsules, 60	2	3	\$ [REDACTED]	
150 mg capsules, 60	1	3	\$ [REDACTED]	

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Locally advanced or metastatic
Condition:	non-small cell lung cancer
PBS Indication:	Locally advanced or metastatic non-small cell lung cancer
Treatment phase:	Initial treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required - Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Clinical criteria:	The treatment must be in combination with docetaxel AND The condition must be non-small cell lung cancer of adenocarcinoma tumour histology AND The treatment must be after failure of first-line chemotherapy AND Patient must have a WHO-ECOG performance status of 2 or less
Administrative Advice	Special Pricing Arrangements apply. No increase in the maximum quantity or number of units may be authorised.

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Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Locally advanced or metastatic
Condition:	non-small cell lung cancer
PBS Indication:	Locally advanced or metastatic non-small cell lung cancer
Treatment phase:	Continuing treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required - Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
Clinical criteria:	Patient must have previously been issued with an authority prescription for this drug for this condition AND Patient must not have progressive disease
Administrative Advice	Special Pricing Arrangements apply. No increase in the maximum quantity or number of units may be authorised.

- 2.2 The re-submission sought listing on the basis of a cost-minimisation analysis comparing nintedanib and docetaxel combination therapy to pemetrexed monotherapy.
- 2.3 The re-submission requested that a rebate to the requested published price be applied through a special pricing arrangement (SPA) to result in an effective price of \$ [REDACTED] and \$ [REDACTED] for the requested maximum quantities of the 100mg and 150mg capsules, respectively. The ESC noted the significant reduction (of around [REDACTED]%) in the requested effective price of nintedanib compared with the requested effective price in the previous submission (\$ [REDACTED]).
- 2.4 The TGA Product Information for nintedanib stated that the recommended maximum daily dose of 400 mg should not be exceeded for this indication. The Pre-Sub-Committee Response (PSCR, p1) noted that an additional Administrative Advice to the restriction, stating “No increase in the maximum quantity or number of units may be authorised” would be acceptable, subject to PBAC approval.

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

3 Background

- 3.1 Nintedanib plus docetaxel was registered by the TGA for NSCLC in September 2015.
- 3.2 This will be the second consideration of nintedanib for the treatment of NSCLC by the PBAC. The first submission was rejected by the PBAC in March 2015.
- 3.3 The following table presents a comparison of the March 2015 submission and the current re-submission.

Table 1: Summary of the previous submission and current re-submission

Component	Nintedanib March 2015	Current re-submission
Requested PBS listing	<ul style="list-style-type: none"> •Initial and continuing treatment of locally advanced or metastatic non-small cell lung cancer in combination with docetaxel. •The treatment must be after failure of first line chemotherapy; and •Patient must have a WHO performance status of 2 or less •For continuing treatment, patient must have previously been issued with an authority prescription for this drug; and •Patient must not have progressive disease <p>PBAC Comment: none</p>	<ul style="list-style-type: none"> •Same as March 2015.
Requested price	<ul style="list-style-type: none"> •DPMQ of \$ [REDACTED] (effective price: \$ [REDACTED]) for: •150mg capsules with a maximum quantity of 60, and •100mg capsules with a maximum quantity of 120. 	<ul style="list-style-type: none"> •DPMQ of \$ [REDACTED] (effective price \$ [REDACTED]) for 150 mg capsule, with a maximum quantity of 60 •DPMQ of \$ [REDACTED] (effective price \$ [REDACTED]) for 100 mg capsules with a maximum quantity of 120.
Main comparator	<ul style="list-style-type: none"> •Docetaxel monotherapy and pemetrexed monotherapy <p>PBAC Comment: 'The PBAC did not accept docetaxel monotherapy as an appropriate comparator...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.' (paragraph 7.3)</p>	<ul style="list-style-type: none"> •Pemetrexed
Clinical evidence	<ul style="list-style-type: none"> •LUME Lung 1 comparing nintedanib plus docetaxel to docetaxel monotherapy (n=1314) and JME1 trial comparing pemetrexed to docetaxel monotherapy (n=571). 	<ul style="list-style-type: none"> •Same as March 2015.
Key effectiveness data	<ul style="list-style-type: none"> •Direct comparison of nintedanib plus docetaxel versus docetaxel. •Indirect comparison of nintedanib plus docetaxel versus pemetrexed via docetaxel as a common comparator with OS HR (95% CI) of [REDACTED] ([REDACTED], [REDACTED]) and PFS HRs (95% CIs) of [REDACTED] ([REDACTED], [REDACTED]) and [REDACTED] ([REDACTED], [REDACTED]) using the LUME Lung 1 primary and final analyses, respectively. •The minimum clinically important difference (MCID) used to assess non-inferiority of 1.33 was the upper bound of a hazard ratio confidence interval (CI). <p>PBAC Comment: '...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.' (paragraph 7.8)</p> <p>'... the upper confidence limits for the indirect comparison of progression free survival ([REDACTED]) and overall survival ([REDACTED]) 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.' (paragraph 7.9)</p>	<ul style="list-style-type: none"> •No MCID used in indirect comparison of nintedanib plus docetaxel versus pemetrexed.

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Component	Nintedanib March 2015	Current re-submission
Key safety data	<ul style="list-style-type: none"> LUME Lung 1 data showed higher rates of diarrhoea and nausea in the nintedanib combination group versus docetaxel alone. Nintedanib plus docetaxel was also associated with statistically significant higher risk of neutropenia, febrile neutropenia and diarrhoea (grades 3/4/5) in comparison with pemetrexed. 	<ul style="list-style-type: none"> Same as March 2015 except additional discussion of exposure adjustments for fatal adverse events, and brief discussion of periodic benefit-risk evaluation report data (Section B.7).
Clinical claim	<ul style="list-style-type: none"> Superior efficacy and inferior safety to docetaxel monotherapy. Non-inferior efficacy and inferior safety to pemetrexed. <p>PBAC Comment: The PBAC considered that the claim of non-inferior comparative effectiveness to pemetrexed was not adequately supported.' (paragraph 6.20) 'The PBAC considered that the claim of inferior comparative safety to pemetrexed was reasonable.' (paragraph 6.21)</p>	<ul style="list-style-type: none"> Same as March 2015.
Economic evaluation	<ul style="list-style-type: none"> Cost-utility model of weighted comparator (docetaxel and pemetrexed) with nintedanib plus docetaxel dominating the weighted comparator. <p>PBAC Comment: '...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...' (paragraph 7.11) '...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.' (paragraph 7.12)</p>	<ul style="list-style-type: none"> Cost-minimisation: Nintedanib, 344.84 mg/day on days 2 to 21 of a 21 day treatment cycle in combination with docetaxel, 132.44 mg on day 1 of 21 is equivalent to pemetrexed 859.40 mg on day 1 of 21.
Number of patients	<ul style="list-style-type: none"> Less than 10,000 in Year 1 increasing to less than 10,000 in Year 5. 	<ul style="list-style-type: none"> Less than 10,000 in Year 1 increasing to less than 10,000 in Year 5.
Estimated cost to PBS	<ul style="list-style-type: none"> \$Less than \$10 million saved in Year 1 to \$10 - \$20 million saved in Year 5 for a total of \$60 - \$100 million saved over the first 5 years of listing. 	<ul style="list-style-type: none"> Less than \$10 million saved in Year 1 increasing to \$20 - \$30 million saved in Year 5 - total of more than \$100 million over the first 5 years.
PBAC decision	<ul style="list-style-type: none"> Reject <p>PBAC Comment: 'The PBAC rejected the request to list nintedanib (in combination with docetaxel)...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' (paragraph 7.1)</p>	-

Source: Compiled during the evaluation

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

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 (which is a sub-type of non-squamous 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 The PSCR (p1) argued that the clinical need for new treatments for NSCLC remains significant, especially in patients who progress and who have a poor prognosis.

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

5 Comparator

- 5.1 The re-submission nominated pemetrexed as the comparator and no longer included docetaxel as a comparator (compared with the previous submission where docetaxel was included as an additional main comparator). It is likely that nintedanib combination therapy will mostly replace pemetrexed in second-line therapy. The PBAC previously considered that pemetrexed was the appropriate comparator (March 2015 PBAC PSD, paragraph 7.3).

For more details 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 the Lung Foundation Australia via the Consumer Comments facility on the PBS website. The Lung Cancer Foundation Australia recommended that lung cancer patients receive early access to any treatments for which the evidence shows benefit.

Clinical trials

- 6.3 As in the March 2015 submission, the re-submission was based on an indirect comparison of two head-to-head trials:
- LUME Lung 1, comparing nintedanib in combination with docetaxel to docetaxel monotherapy (n=1314); and
 - JMEI, comparing pemetrexed to docetaxel monotherapy (n=571).
- 6.4 Details of the trials presented in the re-submission are provided in the following table.

Table 2: Trials and associated reports presented in the re-submission

Trial ID	Reports	Publication citation
Nintedanib plus docetaxel		
Trial 1199.13 (LUME Lung 1)	Clinical Trial Report BI Trial 1199.13 (Final OS Analysis) 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)	26 Aug 2013
	Clinical Trial Report BI Trial 1199.13 (Primary PFS Analysis) 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)	19 Sep 2012
	Reck M; Kaiser R; Mellemgaard A; Douillard JY; Orlov S; Krzakowski M; Pawel J von; Gottfried M; Bondarenko I; Liao M; Gann CN; Barrueco J; Gaschler-Markefski B; Novello S; 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.	Lancet Oncol. 2014; 15(2):143-155.
Pemetrexed		
JMEI	Hanna N, Shepherd FA, Fossella FV, et al.: Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. Scagliotti G, Hanna N, Fossella F, et al.: The differential efficacy of pemetrexed according to NSCLC histology: A review of two phase III studies.	J. Clinic. Oncol., 22:1589-1597. Oncologist, 2009; 14:253-263.

Source: p34-35 of the re-submission.

- 6.5 The key features of the randomised trials included in the indirect comparison are summarised in the table below.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes
Nintedanib and docetaxel versus docetaxel					
LUME Lung 1	1314	R, DB, MC	Low	2 nd line NSCLC	PFS/OS
Pemetrexed versus docetaxel					
JMEI	571	R, OL	High	2 nd line NSCLC	PFS/OS

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 following table presents the results of the indirect comparison against pemetrexed.

Table 4: Results of the indirect comparison – OS, PFS and ORR

	LUME Lung 1			JMEI			Indirect estimate of effect ^c HR (95% CI)
	Treatment effect ^a HR (95% CI)	Nintedanib plus docetaxel n/N (%)	Docetaxel n/N (%)	Docetaxel n/N (%)	Pemetrexed n/N (%)	Treatment effect ^b 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, 2.78)	

Source: Tables B.30, p99 and B.36, p114 and B.42, p124 of the re-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

^a Nintedanib plus docetaxel over docetaxel

^b Pemetrexed over docetaxel

^c Nintedanib plus docetaxel over pemetrexed

- 6.7 The March 2015 submission used a minimum clinically important difference (MCID) of 1.33 to assess non-inferiority, which the submission claimed was the upper bound of a hazard ratio confidence interval. The PBAC considered that ‘...the MCID selected in the submission of 1.33 from Novello 2007 was not the upper confidence interval 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’ (March 2015 PBAC PSD, paragraph 7.8). The PBAC further considered in March 2015 that the upper confidence limits for the indirect comparison of progression free survival (1.29) and overall survival (1.26) were at the borderline of MCIDs used in similar settings, including the JMEI study (1.21) and a review of non-inferiority cancer trials (mean 1.25; range 1.10 to 1.50) (Riechelmann 2011). Consequently, the PBAC considered that non-inferiority was not adequately supported (March 2015 PBAC PSD, paragraph 7.9).
- 6.8 The re-submission did not present a MCID on the basis of PBAC decisions regarding other tyrosine kinase inhibitors for NSCLC, referring to the July 2013 PSD for afatinib and the July 2013 PSD for erlotinib. No new evidence was presented in the re-submission further supporting non-inferiority except for reference to PBAC precedence for the absence of MCIDs in relation to afatinib, gefitinib, and erlotinib.
- 6.9 The PSCR (p2) argued that the assessment of the results versus MCIDs “is based on using a MCID for head-to-head clinical trials where outcomes are directly compared and the analysis is powered for such precision”. In addition, the PSCR argued that “the point estimates for both PFS and OS outcomes indicate a consistent numeric trend in favour of nintedanib compared with pemetrexed”. Accordingly, the PSCR argued that an expectation of a similar precision in an indirect treatment comparison is not reasonable and requested that the PBAC make a pragmatic decision without reference to a MCID.

Comparative harms

6.10 There was no change in the safety data since the March 2015 submission. The key safety outcomes from the indirect comparison are presented in the following table.

Table 5: Key safety outcomes from the indirect comparison of nintedanib plus docetaxel versus pemetrexed

Adverse event	RR (95% CI)	RD (95% CI)
Febrile neutropenia		
Neutropenia		
Diarrhoea (grades 3/4/5)		

Source: Tables B.43-B.46, p131 to p139 and Tables B.43-B.46, p131 to p139 of the re-submission
 CI=confidence interval; RR=relative risk

6.11 Nintedanib plus docetaxel was associated with statistically significant higher risk of neutropenia, febrile neutropenia and diarrhoea (grades 3/4/5) in comparison with pemetrexed. 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.

Clinical claim

6.12 The re-submission described nintedanib as non-inferior in terms of comparative effectiveness and inferior in terms of comparative safety compared to pemetrexed.

6.13 The ESC noted that the claim of inferior safety accurately reflects the evidence. With regard to the efficacy claim, the re-submission no longer specified an MCID through which to rule out inferiority and justified this omission by referencing positive PBAC decisions for other tyrosine kinase inhibitors where no MCID was presented. The ESC considered that the literature on what the MCID should be had been inappropriately ignored, that not presenting a MCID did not change the evidence; therefore the previous conclusion drawn should not change.

6.14 Consideration of Paesmans’ (2014) discussion of MCIDs did cast further doubt, however, on the reliability of the JMEI trial’s conclusion of non-inferiority to docetaxel in the first place, as it was found that the JMEI trial failed to meet its primary definition of non-inferiority. In this regard, the ESC noted the poor quality and high bias of the JMEI trial.

6.15 The PSCR requested that the PBAC make a pragmatic decision without reference to a MCID. However, the ESC noted that should the PBAC accept a claim of non-inferior efficacy, nintedanib’s basis for listing remains unclear, as it provides no efficacy benefit and is comparatively more harmful than pemetrexed.

6.16 The PBAC considered that the claim of non-inferior comparative effectiveness was not adequately supported by the data.

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

Economic analysis

6.18 The re-submission presented a cost-minimisation analysis of nintedanib plus docetaxel versus pemetrexed. There is limited support for this analysis, given inadequate support for the claim of non-inferior efficacy, and inferior safety. The cost-minimisation took into account drug costs, administration costs, monitoring costs and costs of adverse events.

6.19 Equi-effective doses were calculated as 344.83mg/ day of nintedanib on days 2 to 21 of a 21-day treatment cycle in combination with 132.44mg IV infusion of docetaxel on day 1 of a 21-day treatment cycle was equivalent to 869.40mg IV infusion of pemetrexed on day 1 of a 21-day treatment cycle. The equi-effective dosing was based on LUME Lung 1 trial data and the TGA product information of each agent.

6.20 The equi-effective dose was calculated on a per cycle basis, rather than a per course basis. This ignored the fact that pemetrexed was expected to have significantly shorter treatment duration than nintedanib, and consequently overestimated the increment in drug costs.

6.21 The table below provides the results of the cost-minimisation analysis as well as the results of an analysis conducted during the evaluation adjusting for pemetrexed treatment duration.

Table 6: Results of the cost minimisation analysis

Presentation	Nintedanib + docetaxel	Pemetrexed	Incremental cost
Total cost per cycle (submission base case)	\$ [REDACTED]	\$3,164.43	-\$ [REDACTED]
Total cost per course*	\$ [REDACTED]	\$12,657.74	-\$ [REDACTED]
Total cost per cycle adjusted for treatment duration**	\$ [REDACTED]	\$1,689	-\$ [REDACTED]

Source: compiled during evaluation.

*The analysis assumes 4.8 months (6.988 cycles) of treatment for nintedanib and 4 cycles of treatment for pemetrexed. The evaluation conducted the conversion as follows: 4.827 x 30.4/21. This method was selected to be consistent with the method of calculating cycle risks in the re submission's modelling of adverse events.

**This adjustment was made by dividing the total per course costs by the number of cycles of nintedanib. This is for indicative purposes only, as it does not account for the separate treatment duration of docetaxel.

6.22 Adjusting for treatment duration had a significant effect on the estimated cost-savings, decreasing the incremental savings per cycle by [REDACTED] %.

6.23 Applying the re-submission's sensitivity analysis that increased adverse events in nintedanib to an alternative base case, which accounted for alternative treatment duration, led to nintedanib costing over \$ [REDACTED] more per course than pemetrexed. Even if the re-submission's sensitivity analysis of adverse events was overly conservative, nintedanib was unlikely to be cost-saving.

6.24 The PSCR (p3) noted a discrepancy in the use of mean number of months of treatment of nintedanib and median months of pemetrexed. Taking into account the PSCR's concerns that "the use of different measures of central tendency significantly biases the results against nintedanib," alternative cost-minimisation results are presented in Table 7. As shown in the table, adjusting the mean and median number

of cycles of the treatments does not change the overall conclusions of the evaluation that cost-savings are significantly overestimated in the re-submission's base case, and that accounting for differential treatment duration and increased adverse events challenges the claim of nintedanib's cost-savings.

Table 7: Alternative cost-minimisation results with median and mean treatment durations

Component	Nintedanib plus docetaxel	Pemetrexed	Incremental cost
Commentary estimates			
Treatment duration	4.827 months (mean) =6.988 cycles	4.00 cycles (median)	-
Nintedanib/pemetrexed	\$ [REDACTED]	\$11,829.93	-\$ [REDACTED]
Docetaxel	\$ [REDACTED]	\$0.00	\$ [REDACTED]
Drug administration	\$ [REDACTED]	\$432.20	\$ [REDACTED]
Monitoring costs	\$ [REDACTED]	\$213.80	\$ [REDACTED]
Adverse events	\$ [REDACTED]	\$181.81	\$ [REDACTED]
Total cost per course	\$ [REDACTED]	\$12,657.74	-\$ [REDACTED]
Sensitivity analysis with nintedanib AEs for entire cycle	\$ [REDACTED]	\$12,657.74	\$ [REDACTED]
Nintedanib/pemetrexed mean treatment duration			
Treatment duration	4.827 months =6.988 cycles	4.39 cycles	-
Nintedanib/pemetrexed	\$ [REDACTED]	\$12,983.34	-\$ [REDACTED]
Docetaxel	\$ [REDACTED]	\$0.00	\$ [REDACTED]
Drug administration	\$ [REDACTED]	\$474.34	\$ [REDACTED]
Monitoring costs	\$ [REDACTED]	\$234.64	\$ [REDACTED]
Adverse events	\$ [REDACTED]	\$199.54	\$ [REDACTED]
Total cost per course	\$ [REDACTED]	\$13,891.86	-\$ [REDACTED]
Sensitivity analysis with nintedanib AEs for entire cycle	\$ [REDACTED]	\$13,891.86	\$ [REDACTED]
Nintedanib/pemetrexed median treatment duration			
Treatment duration	3.517 months = 5.091 cycles	4.0 cycles	-
Nintedanib/pemetrexed	\$ [REDACTED]	\$11,829.93	-\$ [REDACTED]
Docetaxel	\$ [REDACTED]	\$0.00	\$ [REDACTED]
Drug administration	\$ [REDACTED]	\$432.20	\$ [REDACTED]
Monitoring costs	\$ [REDACTED]	\$213.80	\$ [REDACTED]
Adverse events	\$ [REDACTED]	\$181.81	\$ [REDACTED]
Total cost per course	\$ [REDACTED]	\$12,657.74	-\$ [REDACTED]
Sensitivity analysis with nintedanib AEs for entire cycle	\$ [REDACTED]	\$12,657.74	\$ [REDACTED]

6.25 The PSCR (p3) further argued that if a t-test was conducted after adjusting for differences in progression free survival for nintedanib and pemetrexed, the differences between means shows no statistically significant differences in the number of treatment cycles. The ESC considered that this analysis was insufficiently justified, noting that:

- the t-test presumes underlying normality in the distribution of treatment cycles and no formal test of skew is presented, as such it was unclear how reliable the calculations were without seeing distributions of treatment duration for either pemetrexed or nintedanib; and
- the PSCR did not justify why the mean PFS of pemetrexed should be estimated based on the ratio of mean to median cycles multiplied by the median PFS.

6.26 Overall, the ESC considered it was unclear whether the █% reduction in the effective price of nintedanib represented value for money in the context of the inadequately supported non-inferiority claim and the adverse events associated with this combination treatment, compared with pemetrexed.

Drug cost/patient/course: \$█

6.27 The drug cost of nintedanib per patient per course is \$█ based on a per cycle cost of nintedanib of \$█ and 6.988 cycles of treatment based on the LUME Lung 1 trial data.

Estimated PBS usage & financial implications

6.28 This re-submission was not considered by DUSC.

6.29 The re-submission took an epidemiological approach to estimating usage, based on AIHW and market research data as well as NSCLC survival data from Yang 2005.

6.30 Compared with the March 2015 submission, the re-submission assumed a relative use weight of 100% for pemetrexed. Additionally, the re-submission changed its source of administration costs and included monitoring costs. The re-submission also included adverse event costs in its financial estimates. The table below presents the estimated use and financial implications presented in the re-submission.

Table 8: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated	█	█	█	█	█
Number treated (March 2015)	█	█	█	█	█
Nintedanib and docetaxel scripts	█	█	█	█	█
Nintedanib and docetaxel scripts (March 2015)	█	█	█	█	█
Estimated net cost to PBS/MBS					
Net cost to PBS/RPBS (after rebate)	\$█	\$█	\$█	-\$█	-\$█
Net cost to MBS	\$█	\$█	\$█	\$█	\$█
Net cost to other budgets	\$█	\$█	\$█	\$█	\$█
Estimated total net cost					
Net costs to Government	\$█	-\$█	-\$█	\$█	-\$█
Net costs to Government (March 2015)	-\$█	-\$█	-\$█	-\$█	-\$█

Source: Compiled during the evaluation.

Note: As with the cost-minimisation analysis, financial estimates were updated during the evaluation to account for the increase in the efficient funding for chemotherapy preparation fee from \$█ to \$█.

The redacted table shows that at year 5, the estimated number of patients was less than 10,000 per year and the net savings to PBS in the range of \$10 - \$20 million.

6.31 As in the cost-minimisation analysis, the financial estimates did not adjust for the differential treatment duration of nintedanib and pemetrexed and the base case

potentially underestimated adverse event net costs. Consequently, the cost savings were likely to have been significantly overestimated. The PSCR (p4) argued that the “rationale for including different treatment durations by the Commentary is incorrect and probably misleading” for the same reason that it considered the evaluation’s cost-minimisation analysis incorrect. The ESC considered it was unclear whether the cost savings estimated in the submission were reliable. The ESC considered that the cost of adverse events associated with nintedanib and docetaxel combination therapy may have been underestimated.

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

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 resubmission did not demonstrate non-inferior effectiveness and safety compared with pemetrexed.
- 7.2 The PBAC recalled that it rejected the March 2015 submission for nintedanib for 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. At that time, the PBAC considered that, should the sponsor wish to pursue the request for listing of nintedanib for NSCLC, 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.
- 7.3 The PBAC recalled that it previously accepted pemetrexed as the main comparator given the dominance of pemetrexed as second-line treatment for advanced NSCLC, due to its superior effectiveness compared with docetaxel monotherapy.
- 7.4 In March 2015, the PBAC 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. In addition, the PBAC previously considered that nintedanib should be placed in the context of a number of trials of oral angiokinase inhibitors (in combination with other chemotherapy) for NSCLC which have not produced meaningful outcomes. Overall, the PBAC did not consider there was a clinical need for PBS subsidised access to this drug for the treatment of NSCLC.
- 7.5 The pre-PBAC response appealed to the PBAC to take into account the significant improvement in overall survival for nintedanib with docetaxel compared with docetaxel alone. 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.

- 7.6 The PBAC agreed with ESC that the resubmission did not present new clinical evidence to support the claim of non-inferior effectiveness of nintedanib with docetaxel, compared with pemetrexed, and that the literature on what the MCID should be had been inappropriately ignored. The PBAC therefore considered the clinical claim of non-inferior efficacy was not adequately supported.
- 7.7 The PBAC reiterated that nintedanib was associated with statistically significantly higher instances of neutropenia, febrile neutropenia and diarrhoea events. Accordingly, the PBAC considered that the claim of inferior comparative safety was appropriate. The PBAC considered these side effects would be expected to lead to substantial costs to patients and the health system.
- 7.8 The PSCR requested that the PBAC make “a pragmatic decision without reference to a MCID”. The PBAC considered that it was not minded to make a pragmatic recommendation in this instance, particularly in the context of the higher rate adverse events associated with nintedanib with docetaxel, compared with pemetrexed.
- 7.9 The PBAC noted the resubmission presented a cost-minimisation analysis of nintedanib plus docetaxel versus pemetrexed and the significant reduction in the requested effective price compared with the previous submission. The PBAC reiterated its view that a cost-minimisation analysis was inappropriate given that the currently available indirect evidence did not demonstrate non-inferior efficacy for nintedanib with docetaxel, compared with pemetrexed.
- 7.10 The PBAC agreed with the ESC that the cost of adverse events associated with nintedanib and docetaxel combination therapy may have been underestimated. Accordingly, the cost-savings estimated by the submission were likely to have been overestimated.
- 7.11 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.