

**4.05 SORAFENIB
tablet, 200 mg
Nexavar®, Bayer Australia Ltd.**

1 Purpose of Application

1.1 Section 85, Authority Required listing for sorafenib for treatment of locally advanced or metastatic, radioactive iodine refractory differentiated thyroid cancer (RAI-R DTC). The first submission was considered at the July 2014 PBAC Meeting, a re-submission was considered at the March 2015 PBAC meeting and a minor re-submission was withdrawn prior to the July 2015 PBAC meeting.

2 Requested listing

2.1 The abridged proposed listings of sorafenib are shown below.

Scenario 1: disallows PBS-subsidised use of sorafenib after progression.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
SORAFENIB TABLET 200 mg	120	2	\$ [REDACTED] (\$ [REDACTED]) ^a	Nexavar® Bayer Australia

Authority required (Streamlined)

^a Updated DPMQ using 1 July 2015 pharmacy mark-ups

Scenario 2: allows PBS-subsidised use of sorafenib after progression.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
SORAFENIB TABLET 200 mg	120	2	\$ [REDACTED] (\$ [REDACTED]) ^a	Nexavar® Bayer Australia

Authority required (Streamlined)

^a Updated DPMQ using 1 July 2015 pharmacy mark-ups

2.2 The current re-submission sought a listing based on the cost-effectiveness of sorafenib compared with best supportive care (BSC).

2.3 The requested restriction for Scenario 1 was the same as suggested by the Secretariat for the March 2015 re-submission. The restriction for Scenario 2 differed in that it would allow the use of sorafenib post progression (i.e. the requirement of stable or responding disease for continuing treatment was removed). The Sponsor's rationale for Scenario 2 was that the sorafenib treatment duration accepted by the PBAC for use in the economic model (17.55 months; 7.9, ratified PBAC minutes, sorafenib March 2015) includes the post-progression use of sorafenib.

2.4 The re-submission did not address the PBAC's previous considerations that stage III or stage IV disease patients should be specified in the restriction and that the restriction should define the subset of high-risk patients aged less than 45 years who should be included. The PSCR (p.1) argued that restricting use to stage III or IV

disease would exclude patients who are under 45 years, and claimed that the requested restriction wording requires patients to be at risk.

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

3 Background

- 3.1 Sorafenib was TGA registered on May 2014 for locally advanced or metastatic, progressive, differentiated thyroid carcinoma refractory to radioactive iodine. Sorafenib was granted Orphan Drug Status on 4 March 2013 for this indication.
- 3.2 The PBAC has previously considered sorafenib for this indication twice.
- 3.3 The table below compares the March 2015 re-submission to the PBAC for sorafenib in RAI-R DTC with the current re-submission.

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

	Sorafenib, March 2015 re-submission	Current re-submission
Requested PBS listing	Treatment of RAI-R DTC. PBAC Comment: "The PBAC considered that the restriction should define the subset of high risk patients aged less than 45 years who should be included" (7.3, PBAC PSD, sorafenib March 2015).	Scenario 1: use post progression not allowed, same as the March 2015 re-submission. Scenario 2: use post progression allowed. <i>Defining these high-risk patients was not addressed.</i>
Requested price	\$ [redacted] (published) \$ [redacted] (effective)	Scenario 1: effective DPMQ \$ [redacted] (with updated mark-ups \$ [redacted]) Scenario 2: effective DPMQ of \$ [redacted] (with updated mark-ups \$ [redacted]) Same published DPMQ
Main comparator	Best supportive care. PBAC Comment: The PBAC accepted BSC (placebo) as the appropriate comparator (7.5, PBAC PSD, sorafenib March 2015).	Same
Clinical evidence	One head-to-head trial (DECISION) comparing sorafenib to placebo plus best supportive care (BSC) (n=417). PBAC Comment: Overall survival (OS) was confounded by substantial crossover (6.7, PBAC PSD, sorafenib March 2015).	Same
Key effectiveness data	- Increase in median PFS from 5.8 months (placebo) to 10.8 months (sorafenib); HR 0.587 (95% CI 0.454 - 0.758) - OS, unadjusted HR: 0.80 (95% CI 0.54 – 1.19) (August 2012 data cut-off, ITT); 0.88 (95% CI 0.63-1.24) (May 2013 data cut-off, ITT) PBAC Comment: The PBAC could not conclude whether the RPSFT estimate would be less biased than the unadjusted survival estimate...the PBAC concluded that the ITT results, which did not show a statistically significant improvement in OS, were more informative than the adjusted analyses (7.10, PBAC PSD, sorafenib March 2015).	Same
Key safety data	Sorafenib is associated with an increase in Grade ≥3 treatment emergent AEs, including hand-foot skin reaction and hypertension (6.17, PBAC PSD, sorafenib March 2015).	Same
Clinical claim	Superior in terms of comparative effectiveness but inferior in terms of comparative safety profile. PBAC Comment: The PBAC accepted that sorafenib has inferior safety compared with BSC (7.8, PBAC PSD, sorafenib March 2015). The claim of superior comparative effectiveness was adequately supported by the data for PFS, but not for OS (6.19, PBAC PSD, sorafenib March 2015).	Same
Economic evaluation	Cost/QALY: \$ [redacted] PBAC Comment: The PBAC considered for the purposes of its deferral that the sensitivity analysis in which the gain in PFS is the same as the gain in OS should be the base case. The ICER for this sensitivity analysis was \$ [redacted]/QALY (7.13, PBAC PSD, sorafenib March 2015).	Scenario 1: Cost/QALY \$ [redacted]. Scenario 2: Cost/QALY \$ [redacted].
Number of patients	[redacted] in Year 1 increasing to [redacted] in Year 5. PBAC Comment: The re-submission's estimate (approximately [redacted] patients per annum) was reasonable (7.15, PBAC PSD, sorafenib March 2015).	[redacted] in Year 1 increasing to [redacted] in Year 5.
Estimated cost to PBS	\$ [redacted] in Year 1 increasing to \$ [redacted] in Year 5, \$ [redacted] over the first 5 years.	Scenario 1: \$ [redacted] in Year 1; \$ [redacted] in Year 5; \$ [redacted] over the first 5 years. Scenario 2: \$ [redacted] in Year 1; \$ [redacted] in Year 5; \$ [redacted] over the first 5 years.
PBAC decision	Deferral. The submission had not provided a reliable estimate of the cost-effectiveness of sorafenib. The PBAC wished to see the results of its request for a price reduction to the otherwise accepted sensitivity analysis in which the gain in OS was the same as the gain in PFS (7.1, PBAC PSD, sorafenib March 2015).	-

Source: Compiled during the evaluation

4 Clinical place for the proposed therapy

- 4.1 With treatment, thyroid cancer generally has a good prognosis. However, patients with locally advanced or distant metastatic differentiated thyroid cancer, who fail to respond to radioactive iodine, have a survival of only 2.5 to 3.5 years. Currently, there is no active treatment available for this group of patients.
- 4.2 The re-submission proposed sorafenib is used in patients who progress after treatment with radioactive iodine. Lenvatinib was discussed at the November 2015 PBAC meeting for the same patient population.

5 Comparator

- 5.1 Best supportive care (placebo). The PBAC has previously accepted best supportive care (placebo) as the appropriate comparator. The PBAC also noted that the concurrent submission for lenvatinib in essentially the same population meant that lenvatinib was also an appropriate comparator.

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

6 PBAC consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC welcomed the input from an organisation (1) via the Consumer Comments facility on the PBS website. The comment described that there are patients who are willing to accept moderate to severe toxicities of cancer treatment to delay disease progression and that there was a need for better understanding and support for DTC.

Clinical trials

- 6.3 The re-submission was based on one head-to-head trial comparing sorafenib to placebo (n=417).
- 6.4 Details of the trials presented in the re-submission are provided in the table below.

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

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trial		
DECISION	Clinical Study Report No. A57578. A double-blind, randomized, phase III trial evaluating the efficacy and safety of sorafenib compared to placebo in patients with locally advanced/ metastatic RAI-refractory, differentiated thyroid cancer. May 2013	Year: 2013 14295 Clinical study report NCT00984282 in clinicaltrials.gov
	Brose MS, Nutting CM, Sherman SI <i>et al</i> Rationale and design of decision: a double-blind, randomized, placebo-controlled phase III trial evaluating the efficacy and safety of sorafenib in patients with locally advanced or metastatic radioactive iodine (RAI)-refractory, differentiated thyroid cancer.	<i>BMC Cancer</i> . 2011 Aug 11;11:349

Public Summary Document – November 2015 PBAC Meeting

Trial ID	Protocol title/ Publication title	Publication citation
	Note: this publication is for the protocol for DECISION. One abstract of the results presented at ASCO has been identified; however there is no peer reviewed publication.	
	Brose MS, Nutting CM, Jarzab B, Elisei R, Siena S, Bastholt L, de la Fouchardiere C, Pacini F, Paschke R, Shong YK, Sherman SI, Smit JW, Chung J, Kappeler C, Peña C, Molnár I, Schlumberger MJ; DECISION investigators. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial.	<i>Lancet</i> . 2014 Jul 26;384(9940):319-28
	Population PK modelling and exposure-response analyses of sorafenib in patients with radioactive iodine-refractory differentiated thyroid cancer (RAI-rDTC) in the phase III DECISION trial. Bastholt L. Brose M.S. Jarzab B. Schlumberger M. Siena S. De La Fouchardiere C. Paschke R. Deshpande H.A. Shi Y. Elisei R. Gao M. Li L. Prins K. Walker H. Mitchell D.Y. Lettieri J.T. Molnar I. Kappeler C. Pena C.E.	<i>Journal of Clinical Oncology</i> (2014) 32:15 SUPPL. 1
	Updated overall survival analysis of patients with locally advanced or metastatic radioactive iodine-refractory differentiated thyroid cancer (RAI-rDTC) treated with sorafenib on the phase 3 DECISION trial. Brose M.S. Jarzab B. Elisei R. Siena S. Bastholt L. De La Fouchardiere C. Pacini F. Paschke R. Nutting C. Shong Y.K. Sherman S.I. Smit J.W.A. Chung J.W. Kappeler C. Molnar I. Schlumberger M.	<i>Journal of Clinical Oncology</i> (2014) 32:15 SUPPL. 1
	Safety and tolerability of sorafenib for treatment of locally advanced or metastatic radioactive iodine-refractory differentiated thyroid cancer (RAI-rDTC): Detailed analyses from the phase III DECISION trial. Worden F.P. Fassnacht M. Shi Y. Hadjieva T. Bonichon F. Gao M. Fugazzola L. Ando Y. Hasegawa Y. Park D.J. Nutting C. Sherman S.I. Shong Y.K. Smit J.W.A. Chung J.W. Kappeler C. Molnar I. Schlumberger M. Brose M.S.	<i>Journal of Clinical Oncology</i> (2014) 32:15 SUPPL. 1
	Phase III randomized, double-blinded, placebo controlled trial of sorafenib in locally advanced or metastatic patients with radioactive iodine (RAI)-refractory differentiated thyroid cancer (DTC)-exploratory analyses of patient-reported outcomes. Schlumberger M. Jarzab B. Elisei R. Siena S. Bastholt L. De La Fouchardiere C. Pacini F. Paschke R. Worden F. Bockisch A. Nutting C. Shong Y. Sherman S.I. Smit J. Chung J. Kappeler C. Molnar I. Keating K. Cella D. Brose M.S.	<i>Thyroid</i> (2013) 23 SUPPL. 1 (A49-A50)
	Sorafenib in locally advanced or metastatic patients with radioactive iodine-refractory differentiated thyroid cancer: The phase 3 DECISION trial. Paschke R. Brose M.S. Nutting C. Jarzab B.J. Elisei R. Siena S. Bastholt L. De La Fouchardiere C. Pacini F. Shong Y.K. Sherman S.I. Smit J.W.A. Chung J. Siedentop H. Molnar I. Schlumberger M.	<i>Onkologie</i> (2013) 36 SUPPL. 7 (184)
	Association between tumor BRAF and RAS mutation status and clinical outcomes in patients with radioactive iodine (RAI)-refractory differentiated thyroid cancer (DTC) randomized to sorafenib or placebo: Sub-analysis of the phase III DECISION trial. Brose M.S. Nutting C. Shong Y.K. Sherman S.I. Smit J.W.A. Chung J. Molnar I. Jeffers M. Pena C. Schlumberger M.	<i>European Journal of Cancer</i> (2013) 49 SUPPL. 2 (S745)
	Sorafenib in locally advanced or metastatic patients with radioactive iodine-refractory differentiated thyroid cancer: The phase III DECISION trial. Brose M.S. Nutting C. Jarzab B. Elisei R. Siena S. Bastholt L. De La Fouchardiere C. Pacini F. Paschke R. Shong Y.K. Sherman S.I. Smit J.W.A. Chung J.W. Siedentop H. Molnar I. Schlumberger M.	<i>Journal of Clinical Oncology</i> (2013) 31:18 SUPPL. 1
	<i>Sorafenib: a review of its use in patients with radioactive iodine-refractory, metastatic differentiated thyroid carcinoma. Blair H.A., Plosker G.L</i>	<i>Targeted Oncology</i> (2015), 10 (1) (pp 171-178)

Trial ID	Protocol title/ Publication title	Publication citation
	Sorafenib in locally advanced or metastatic patients with radioactive iodine-refractory differentiated thyroid cancer (DTC): The phase III DECISION trial. Bockisch A, Brose MS, Nutting C, Jarzab B, Elisei R, Siena S, Bastholt L, De La Fouchardiere C, Pacini F, Paschke R, Shong YK, Sherman SI, Smit JW, Chung JW, Kappeler C, Molnar I, Schlumberger M.	Experimental and clinical endocrinology & diabetes 122(3)
	Sorafenib for the treatment of thyroid cancer: An updated review. Krajewska J., Handkiewicz-Junak D., Jarzab B.	Expert Opinion on Pharmacotherapy. 16 (4) (pp 573-583)

Source: Table B.5, p82-83 of the March 2015 re-submission

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

Table 3: Key features of the included evidence

Trial	N	Design/ duration ^a	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Sorafenib versus Placebo						
DECISION	417	R, DB, MC 46.1 weeks (sorafenib) 28.3 weeks (placebo)	Low	Progressed, radioactive iodine refractory	PFS, OS	PFS OS – adjusted for crossover

DB=double blind; MC=multi-centre; OS=overall survival; PFS=progression-free survival; R=randomised; BSC=best supportive care.

^a Median duration of treatment in the double-blind period (data cut-off 31 August 2012). Treatment with sorafenib continued into open label study for 55 patients in the sorafenib arm and overall median duration of treatment at data cut-off 31 August 2012 was 56.9 weeks.

Source: compiled during the evaluation

6.6 OS was confounded by substantial crossover: 71% of patients in the placebo + BSC group crossed over to open-label sorafenib treatment after progression or at the end of the double-blind period, leaving 63 patients in the comparator arm of the trial to contribute data to the methods used to adjust for this crossover. The re-submission did not address further the issues identified by the March 2015 PBAC meeting concerning the contamination of the overall survival results, instead simply assuming that the hazard ratio for overall survival adjusted using the rank preserving structural failure time (RPSFT) model should be further adjusted back towards the null by 10%.

6.7 The extent of attrition bias during the double-blind period for PFS was unclear. There were 75 discontinuations (49 censored without a PFS event) in the sorafenib arm compared with 22 (17 censored without a PFS event) discontinuations in the placebo arm.

Comparative effectiveness

6.8 The comparative benefits are unchanged from the March 2015 re-submission.

Table 4: Progression free survival, central assessment (FAS), first cut-off 31 August 2012

DECISION	Sorafenib (N = 207)	Placebo (N = 210)
Number of subjects (%) with event	113 (54.6%)	137 (65.2%)
Number of subjects (%) censored	94 (45.4%)	73 (34.8%)
Median PFS (days) [95% CI]	329 [278, 393]	175 [160, 238]
Median PFS (months) ^a	10.8	5.8
PFS range (days; without censored values)	20 - 728	14 - 728
Hazard ratio (sorafenib/placebo)	0.587	
95% CI for hazard ratio	[0.454, 0.758]	
p-value (one-sided from stratified log-rank test)	<0.0001	

Note: CI = confidence interval; FAS = full analysis set; PFS = progression-free survival.

^a Months = days/30.4

Source: Table B.1, p.27 of the re-submission

Table 5: Overall survival (FAS), first cut-off 31 August 2012

	Sorafenib (N=207)	Placebo (N=210)
Number of subjects (%) with event	45 (21.7%)	54 (25.7%)
Number of subjects (%) censored	162 (78.3%)	156 (74.3%)
Median overall survival (days)	Cannot be estimated due to censored data	
Range (days, without censored values): uncorrected	57 - 771	26 - 766
Range (months ^a , without censored values): uncorrected	1.9 - 25.3	0.9 - 25.2
Hazard ratio (sorafenib/placebo): uncorrected	0.802	
95% CI for hazard ratio: uncorrected	[0.539, 1.194]	
p-value (one-sided from stratified log-rank test): uncorrected	0.1381	
Adjusted for crossover: RPSFT	0.613 (CI: 0.398, 0.944; one-sided p = 0.0125)	
Adjusted for crossover: IPE	0.698 (CI: 0.467, 1.043; one-sided p = 0.0388)	

Note: CI = confidence interval; FAS = full analysis set, IPE = iterative parameter estimation, RPSFT = rank preserving structural failure time.

^a Months = days/30.4.

Source: Table B.2, p.27 of the re-submission

Table 6: Overall survival (FAS), latest cut-off 31 May 2013

	Sorafenib (N=207)	Placebo (N=210)
Number of subjects (%) with event	66 (31.9%)	72 (34.3%)
Number of subjects (%) censored	141 (68.1%)	138 (65.7%)
Median overall survival (days) [95% CI]	A (A;A)	1110 (979;A)
Range (days, without censored values): unadjusted	57 - 967	26 - 1110
Range (months ^a , without censored values):unadjusted	1.9 - 31.8	0.9 - 36.5
Hazard ratio with 95% CI (sorafenib/placebo): unadjusted	0.884 (0.633, 1.236)	
p-value (one-sided from stratified log-rank test): unadjusted	0.2359	
Hazard ratio (95% CI): adjusted for crossover, RPSFT method	0.69 (0.49, 0.99)	
Hazard ratio (95% CI): adjusted for crossover, IPE method	0.79 (0.57, 1.11)	

Note: A = value cannot be estimated due to censored data; CI = confidence interval; FAS = full analysis set, IPE = iterative parameter estimation, RPSFT = rank preserving structural failure time.

^a Months = days/30.4.

Source: Paragraph 6.10, p.10, 7.5 sorafenib ratified minutes, March 2015

Comparative harms

- 6.9 The comparative harms were unchanged from the March 2015 re-submission. Dose modifications were common among patients who received sorafenib (86.0%) with 60% of patients requiring two or more interruptions to the study medication.

- 6.10 More than 70% of patients receiving sorafenib experienced at least one Grade 3 adverse reaction or higher compared with 33% of patients receiving placebo+BSC. The most common treatment-emergent adverse events associated with sorafenib were hypertension (40.6%), fatigue (49.8%), weight loss (46.9%), hand-foot skin reaction (76.3%) and diarrhoea (68.6%).

Benefits/harms

- 6.11 A summary of the comparative benefits and harms for sorafenib versus placebo+BSC is presented below.

Table 7: Summary of comparative benefits and harms for sorafenib and placebo+BSC

Benefits						
Progression-free survival / overall survival^a						
	Sorafenib	PBO+BSC	Absolute difference	HR (95% CI)		
PFS (31 August 2012)	113/207	137/210	-	0.587 (0.454, 0.758)		
Median (95% CI), months	10.8 (9.1, 12.9)	5.8 (5.3, 7.8)	5.0	-		
OS (31 August 2012)	45/207	54/210	-	0.802 (0.539, 1.194)		
Median (95% CI), months	Median not yet reached		Not evaluable			
OS (31 May 2013)	66/207	74/210	-	0.884 (0.633, 1.236)		
Median (95% CI), months	Median not yet reached		Not evaluable			
Trial	Sorafenib	PBO+BSC	RR (95% CI)	Event rate^b/100 patients		RD (95% CI)
				Sorafenib	PBO	
Disease control rate (CR + PR + SD) – per protocol analysis set						
DECISION	169/196	150/201	1.16 (1.05, 1.27)	86.2	74.6	0.12 (0.04, 0.19)
Harms						
	Sorafenib	PBO+BSC	RR (95% CI)	Event rate^b/100 patients		RD (95% CI)
				Sorafenib	PBO	
Treatment-emergent AE, Grade 3 or higher						
DECISION	147/207	69/209	2.15 (1.74, 2.66)	71.0	33.0	0.38 (0.29, 0.47)
Hand-foot skin reaction, Grade 3 or higher						
DECISION	42/207	0/209	Not calculable	20.3	0	0.20 (0.14, 0.26)
Hypertension, Grade 3 or higher						
DECISION	20/207	5/209	4.04 (1.54, 10.56)	9.7	2.4	0.07 (0.03, 0.12)

^a PFS and OS were measured to data cut-off of 31 August 2012, at which time median exposure to the drug in the sorafenib arm was 46.1 weeks under double-blind conditions and 56.9 weeks including the open-label use of sorafenib. Median exposure to placebo was 28.3 weeks under double-blind conditions.

^b The proportion of patients who experienced at least one adverse event.

Abbreviations: PBO = placebo; RD = risk difference; BSC = best supportive care; RR = risk ratio; AE = adverse event; CR = complete response; PR = partial response; SD = stable disease; PFS = progression-free survival; OS = overall survival.

Source: Compiled during the evaluation from Table 34, p75, Table 38, p81, Table 40, p85, Table 51, p96, Table 53, pp99-100 of the March 2015 re-submission.

- 6.12 On the basis of direct randomised evidence presented by the submission, for patients treated with sorafenib in comparison to placebo+BSC, there would be:
- an approximate difference in median progression-free survival of 5 months
 - an unknown possible difference in median overall survival.
- 6.13 On the basis of direct randomised evidence presented by the submission, for every 100 patients treated with sorafenib in comparison to placebo+BSC:
- approximately 38 additional patients would experience at least one treatment-emergent adverse event of Grade 3 or greater severity over a period of 10 – 12

months of treatment with sorafenib (compared to 8 – 9 months of observation in the placebo+BSC arm)

- approximately 20 additional patients would experience a hand-foot skin reaction of at least Grade 3 severity over a period of 10 – 12 months of treatment with sorafenib (compared to 8 – 9 months of observation in the placebo+BSC arm)
- approximately 7 additional patients would experience hypertension of at least Grade 3 severity over a period of 10 – 12 months of treatment with sorafenib (compared to 8 – 9 months of observation in the placebo+BSC arm).

Clinical claim

- 6.14 The re-submission described sorafenib as superior in terms of comparative effectiveness and inferior in terms of comparative safety over BSC.
- The PBAC has previously accepted the claim of superiority for PFS, but not for OS. The PBAC noted the magnitude of benefit in terms of extension of life derived from sorafenib is difficult to ascertain due to crossover following progression.
 - The PBAC has previously accepted that sorafenib has inferior safety compared with BSC.

Economic analysis

- 6.15 The re-submission presented a cost-utility analysis. The economic evaluation was largely unchanged from the March 2015 re-submission. The key changes were: the assumed duration of treatment was reduced to 13.44 months in Scenario 1 (it remained at 17.55 months for Scenario 2), the dispensed price of sorafenib was reduced to an effective price of \$ [REDACTED] in Scenario 1 and \$ [REDACTED] in Scenario 2, and the adjusted HR for OS was changed from 0.613 to 0.68. This adjustment was based on the RPSFT model which was previously not accepted by the PBAC. The model structure is summarised below.

Table 8: Summary of model structure and rationale

Component	Summary
Time horizon	10 years (130 cycles) in the model base case versus 2 years in the trial
Outcomes	LYG and QALYs
Methods used to generate results	Cohort expected value analysis
Health states	Progression-free, progressed and death
Cycle length	28 days
Transition probabilities	The proportion of patients in each health state is based on the modelled PFS and OS curves

LYG = life years gained; QALY = quality-adjusted life-year; PFS = progression free survival; OS = overall survival.

Source: compiled during the evaluation

- 6.16 The key driver for the economic model was the OS benefit with sorafenib over BSC.
- 6.17 The results of the economic evaluation are summarised below. The re-submission sought to address the uncertainty regarding the incremental gain in OS by changing the adjusted OS HR by 10% (from 0.613 to 0.68). The ESC considered that this adjustment was arbitrary and not adequately justified by the submission. Additionally, the ESC noted that the adjusted OS HR used (0.613) was from the first data cut-off – at the latest data cut-off, the adjusted OS HR was 0.69. The analysis requested by the PBAC with the post-progression utility value set to zero (so that the modelled

gain in OS approximates the gain in PFS) was not included in the re-submission. This analysis was undertaken during the evaluation. An additional analysis was undertaken during the evaluation whereby the HR for OS was adjusted so that the gain in OS was the same as the gain in PFS.

Table 9: Incremental results of the economic evaluation

	Analysis	DPMQ	Model parameters: Treatment duration (months) OS HR Post-progression utility	PFS	LY	QALY	Cost	Cost/QALY gained
March 2015 re-submission								
Sorafenib	Base case	\$ [REDACTED]	Treatment duration: 17.55 OS HR: 0.613 Utility: 0.637 ^b	1.10	3.62	2.39	\$ [REDACTED]	\$ [REDACTED]
BSC				0.62	2.67	1.80	\$6	
Difference				0.48	0.95	0.59	\$ [REDACTED]	
Sorafenib	Post progression utility of 0	\$ [REDACTED]	Treatment duration: 17.55 OS HR: 0.613 Utility: 0	1.10	NA	0.79	\$ [REDACTED]	\$ [REDACTED]
BSC				0.62	NA	0.50	\$6	
Difference				0.48	NA	0.29	\$ [REDACTED]	
Listing Scenario 1 (post-progression use of sorafenib not allowed)								
Sorafenib	Base case	\$ [REDACTED] ^a	Treatment duration: 13.44 OS HR: 0.680 Utility: 0.637 ^b	1.10	3.62	2.39	\$ [REDACTED]	\$ [REDACTED]
BSC				0.62	2.86	1.92	\$6	
Difference				0.48	0.76	0.47	\$ [REDACTED]	
Sorafenib	Analysis requested by PBAC	\$ [REDACTED] ^a	Treatment duration: 13.44 OS HR: 0.613 Utility: 0	1.10	NA	0.79	\$ [REDACTED]	\$ [REDACTED]
BSC				0.62	NA	0.50	\$6	
Difference				0.48	NA	0.29	\$ [REDACTED]	
Sorafenib	OS HR changed so that OS gain equals PFS gain	\$2065.77 ^a	Treatment duration: 13.44 OS HR: 0.788 ^c Utility: 0.637 ^b	1.10	3.62	2.39	\$ [REDACTED]	\$ [REDACTED]
BSC				0.62	3.14	2.10	\$6	
Difference				0.48	0.48	0.29	\$ [REDACTED]	
Listing Scenario 2 (post-progression use of sorafenib allowed)								
Sorafenib	Base case	\$ [REDACTED] ^a	Treatment duration: 17.55 OS HR: 0.680 Utility: 0.637 ^b	1.10	3.62	2.39	\$ [REDACTED]	\$ [REDACTED]
BSC				0.62	2.86	1.92	\$6	
Difference				0.48	0.76	0.47	\$ [REDACTED]	
Sorafenib	Analysis requested by PBAC	\$ [REDACTED] ^a	Treatment duration: 17.55 OS HR: 0.613 Utility: 0.	1.10	NA	0.79	\$ [REDACTED]	\$ [REDACTED]
BSC				0.62	NA	0.50	\$6	
Difference				0.48	NA	0.29	\$ [REDACTED]	
Sorafenib	OS HR changed so that OS gain equals PFS gain	\$ [REDACTED] ^a	Treatment duration: 17.55 OS HR: 0.788 ^c Utility: 0.637 ^b	1.10	3.62	2.39	\$ [REDACTED]	\$ [REDACTED]
BSC				0.62	3.14	2.10	\$6	
Difference				0.48	0.48	0.29	\$ [REDACTED]	

^a Updated DPMQ

^b Post-progression utility values from March 2015 re-submission, spreadsheet 'Sorafenib in DTC Section D Workbook-base case-FINAL_for_March 2015'

^c Calculated by setting OS gain to equal PFS gain using "Goal Seek" function on HR for OS.

- 6.18 Changing the OS HR by 10% (from 0.613 to 0.68) reduced the incremental LYGs from 0.95 years (11.4 months) to 0.76 years (9.12 months). The corresponding incremental gain in PFS was 0.48 years (5.76 months). This was the base case presented in the re-submission and the ICERs were between \$45,000/QALY – \$75,000/QALY for Scenario 1 and \$45,000/QALY – \$75,000/QALY for Scenario 2.
- 6.19 When OS is set to equal PFS, the ICER for Scenario 1 is approximately \$45,000/QALY – \$75,000/QALY, regardless of the method used. The ICER is less than that in the March 2015 re-submission (\$105,000/QALY - \$200,000/QALY) because the DPMQ for sorafenib was reduced from \$ [REDACTED] to \$ [REDACTED] and the

treatment duration was reduced from 17.55 months to 13.44 months. When OS is set to equal PFS, the ICER for Scenario 2 is approximately \$75,000/QALY - \$105,000/QALY, regardless of the method used. The ICER is less than that in the March 2015 re-submission (\$105,000/QALY - \$200,000/QALY) because the DPMQ for sorafenib was reduced from \$ [REDACTED] to \$ [REDACTED].

- 6.20 The ESC noted that post-progression costs were included in the analysis in which the post-progression utility is set to zero. Although the effect on the ICER was not expected to be large, the ESC considered that an additional analysis where these costs were set to zero would be informative.

Drug cost/patient/course: \$ [REDACTED] (Scenario 1) and \$ [REDACTED] (Scenario 2)

- 6.21 Scenario 1: the re-submission estimated the cost of sorafenib per patient based on the effective DPMQ of \$ [REDACTED] (for 120 * 200 mg tablets), a dose of 400 mg twice daily, an average treatment duration of 1.12 years and a dose intensity of 81% ($\$ [REDACTED] * (365/30) * 1.12 * 0.81$).
- Scenario 2: the re-submission estimated the cost of sorafenib per patient based on the effective DPMQ of \$ [REDACTED] (for 120 * 200 mg tablets), a dose of 400 mg twice daily, an average treatment duration of 1.46 years and a dose intensity of 81% ($\$ [REDACTED] * (365/30) * 1.46 * 0.81$).

Estimated PBS usage & financial implications

- 6.22 This re-submission was not considered by DUSC. The re-submission’s approach for estimating the financial implications was the same as in the March 2015 re-submission. Separate financial estimates were provided for Scenario 1 and Scenario 2. Changes from the March 2015 re-submission included the reduced effective DPMQs, longer treatment duration for Scenario 2 (1.46 years; the same treatment duration of 1.12 years was used for Scenario 1) and higher uptake rates (100% by Year 5). The March 2015 re-submission assumed treatment duration of 1.12 years and uptake reaching 80% by Year 5.

Table 10: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated – Scenario 1 ^a	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Number treated – Scenario 2 ^b	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Number treated - March 2015	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Uptake rate – Scenario 1 and 2	80%	85%	90%	95%	100%
Uptake rate March 2015	60%	65%	70%	75%	80%
Estimated total net cost					
Net cost PBS/RPBS – Scenario 1	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost PBS/RPBS – Scenario 2	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Net cost PBS/RPBS March 2015	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

^a Scenario 1 patients received 11.03 packs per course of treatment.

^b Scenario 2 patients received 14.41 packs per course of treatment (9.85 in initial year and 4.56 in continuing year).

Source: Compiled during the evaluation

The redacted table above shows that the number of patients treated with sorafenib in Scenario 1 and Scenario 2 is estimated to be less than 10,000 per year at a net cost of less than \$10 million per year.

- 6.23 The re-submission's financial estimates were based on higher uptake rates and consequently larger patient numbers than the March 2015 re-submission. Therefore, despite the reduction in the requested price for sorafenib, the estimated cost to the PBS/RPBS was similar (Scenario 1) or higher (Scenario 2) than in the March 2015 re-submission.
- 6.24 Scenario 1 attributed all the costs of treatment in one year despite treatment duration of 1.12 years. This overestimated the financial costs, especially in the initial years of listing. The treatment duration for Scenario 2 was 1.46 years and the cost of one year of treatment (68% of the total cost) was assigned to the initial year of treatment. This overestimated the financial costs, especially in the initial years of listing.

Quality Use of Medicines

- 6.25 The sponsor stated that, should sorafenib be reimbursed on the PBS, the company would undertake activities to support patients who experience hand foot skin reaction. This remains unchanged from the March 2015 re-submission.

Financial Management – Risk Sharing Arrangements

- 6.26 The submission requested an effective DPMQ of \$ [REDACTED] (\$ [REDACTED]) for Scenario 1 and \$ [REDACTED] (\$ [REDACTED]) for Scenario 2 compared with a published DPMQ of \$ [REDACTED]. The effective DPMQ was used in the economic evaluation and financial estimates in the re-submission.
- 6.27 The sponsor agreed to a Risk Sharing Arrangement in general, however, requested the financial cap and level of rebate be finalised following a positive recommendation by the PBAC.
- 6.28 The PBAC considered that the financial cap should be based on the estimated patient numbers provided in the March 2015 sorafenib re-submission ([REDACTED] patients in Year 1 compared with [REDACTED] patients in Year 1 in the current re-submission).

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

7 PBAC Outcome

- 7.1 The PBAC deferred its decision on sorafenib for the treatment of locally advanced or metastatic RAI-R DTC as the re-submission had not provided a reliable estimate of the cost-effectiveness of sorafenib in this setting, and wished to see the results of its preferred re-specifications for the base case of the economic model. The PBAC considered, as previously, that the clinical data did not adequately demonstrate a statistically significant gain in OS and therefore the incremental life-years gained of 9.12 months (0.76 years) estimated by the modelled economic evaluation was implausibly large.

- 7.2 The PBAC reiterated its view that there is a clinical need for an effective treatment for patients with locally advanced or metastatic RAI-R DTC who have rapid, symptomatic progression. The PBAC noted that it would be challenging to limit use of sorafenib to this group of patients, and that the restriction would need further work to capture the appropriate eligible population. The PBAC also noted that the restriction should define the subset of high risk patients aged less than 45 years who should also be included.
- 7.3 As previously, the PBAC considered that BSC was the appropriate comparator. The PBAC also noted that the concurrent submission for lenvatinib in essentially the same population meant that lenvatinib was also an appropriate comparator. In this regard, the PBAC noted that the Endocrine Society of Australia expressed no preference between sorafenib and lenvatinib.
- 7.4 The PBAC reiterated its view that sorafenib is more effective than BSC in terms of PFS and that sorafenib has a worse safety profile than BSC.
- 7.5 The PBAC reaffirmed its view from March 2015 that the adjusted OS results for crossover presented by the re-submission did not provide a reliable estimate of the OS. The PBAC considered that the modelled incremental OS gain of 9.12 months (0.76 years) in the re-submission's economic evaluation was implausibly large, especially in the context of the modelled incremental PFS gain of 5.76 months (0.48 years). The PBAC recalled that it had previously proposed a pragmatic way forward to value the accepted and clinically meaningful gain in PFS, where the trial-based 5-month gain in median PFS translated into an gain in median OS of the same duration, however the re-submission had not presented this either as its base case or as a sensitivity analysis.
- 7.6 The PBAC noted advice from the Endocrine Society of Australia that patients should be able to continue therapy as long as there is thought to be clinical benefit. The PBAC thus considered that the preferred listing of sorafenib would be as per Scenario 2, where use beyond progression is permitted. The PBAC noted that the ICER for Scenario 2 presented in this re-submission was \$45,000/QALY – \$75,000/QALY, however this base case was not considered reliable and did not use the sensitivity analysis as requested by the PBAC in March 2015, in which the gain in OS was of the same magnitude as the gain in PFS observed in the trial.
- 7.7 The PBAC did not consider that sorafenib was cost-effective at either price proposed in the re-submission for either listing scenario, noting that the more relevant model was for Scenario 2, and that the treatment duration in this scenario was based on the trial. The PBAC recalled that an ICER threshold of \$[REDACTED]/QALY had been set at the March 2015 PBAC meeting in the context of uncertainty in the extent of incremental overall survival, and noted that the evaluation of the re-submission had estimated an incremental QALY gain of 0.29 by setting the incremental overall survival gain as the same as the more confidently estimated incremental progression-free survival gain. The Committee proposed that a pragmatic approach could consider the base case of the modelled economic evaluation be re-specified to have an incremental QALY denominator in the ICER of 0.2, and thus to identify a price of sorafenib such that the ICER is less than \$[REDACTED]/QALY. The two proposed approaches to justifying a cost-effective price were broadly consistent because there can be more confidence that at least the smaller incremental QALY would be realised

in practice.

- 7.8 The PBAC considered that a major resubmission would be required should the sponsor not wish to accept either of the proposed re-specifications of the base case of the modelled economic evaluation.
- 7.9 The PBAC noted that the re-submission provided revised estimates of utilisation, however the PBAC advised its preference for the estimated numbers from the March 2015 re-submission which were considered a more reasonable estimate.

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.