

**7.05 SORAFENIB**  
**200 mg, tablet;**  
**Nexavar<sup>®</sup>; Bayer Australia Ltd**

**1 Purpose of Application**

1.1 The resubmission sought section 85, Authority required listing for sorafenib for the 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.

**2 Requested listing**

2.1 The requested listing is outlined below. Suggestions and additions proposed by the Secretariat 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
SORAFENIB 200 mg tablet	120	2	\$ [REDACTED] (effective price: \$ [REDACTED])	Nexavar <sup>®</sup> BN

<b>Category / Program</b>	Section 85 General Schedule (GE)
<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 <del>and</del> or metastatic
<b>Condition:</b>	<del>Radioactive iodine refractory</del> differentiated thyroid cancer
<b>PBS Indication:</b>	Locally advanced or metastatic differentiated thyroid cancer
<b>Treatment phase:</b>	Initial treatment
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
<b>Treatment criteria:</b>	<del>Patient must have symptomatic progressive disease prior to treatment.</del> <del>Patient must have thyroid stimulating hormone adequately repressed.</del>

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<b>Clinical criteria:</b>	<p>Patient must have symptomatic progressive disease prior to treatment,</p> <p>AND</p> <p>Patient must have thyroid stimulating hormone adequately repressed,</p> <p>AND</p> <p>Patient must be naive to drug treatment (except for prior low dose chemotherapy for radio-sensitisation) for this condition,</p> <p>AND</p> <p>Patient must have a WHO performance status of 2 or less,</p> <p>AND</p> <p>Patient must be one in whom surgery is inappropriate,</p> <p>AND</p> <p>The patient must not be a candidate for radiotherapy with curative intent,</p> <p>AND</p> <p>The condition must be refractory to radioactive iodine,</p> <p>AND</p> <p>The treatment must be the sole PBS-subsidised therapy for this condition.</p>
<b>Population criteria:</b>	<del>Patient must be an adult</del>
<b>Definitions</b>	<p>Definition of radioactive iodine refractory:</p> <ul style="list-style-type: none"> <li>- A lesion without iodine uptake on a radioactive iodine (RAI) scan, or</li> <li>- Receiving cumulative RAI <math>\geq</math> 600 mCi, or</li> <li>- Experiencing a progression after a RAI treatment within 16 months of enrolment, or</li> <li>- After two RAI treatments within 16 months of each other</li> </ul>
<b>Prescriber Instructions</b>	<p><del>Patients must have stable or responding disease according to Response Evaluation Criteria in Solid Tumours (RECIST) criteria to be eligible for continuing PBS subsidy.</del></p> <p><del>Patients who fail to demonstrate stable disease or response to treatment with sorafenib or who progress while on sorafenib will not be eligible to receive further PBS-subsidised treatment with this drug for this condition.</del></p>
<b>Administrative Advice</b>	<p>NOTE: No increase in the maximum quantity or number of units may be authorised.</p> <p>NOTE: No increase in the maximum number of repeats may be authorised.</p> <p>NOTE: Special Pricing Arrangements apply.</p>

<b>Category / Program</b>	Section 85 General Schedule (GE)
<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 and/or metastatic

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<b>Condition:</b>	Radioactive iodine refractory differentiated thyroid cancer
<b>PBS Indication:</b>	Locally advanced or metastatic differentiated thyroid cancer
<b>Treatment phase:</b>	Continuing treatment
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
<b>Treatment criteria:</b>	<p><del>Patient must have previously been issued with an authority prescription for sorafenib for radioactive iodine refractory differentiated thyroid cancer and who does not have progressive disease according to Response Evaluation Criteria in Solid Tumours (RECIST) criteria.</del></p> <p>Continuing PBS-subsidised treatment as monotherapy.</p>
<b>Clinical criteria:</b>	<p>Patient must have previously been issued with an authority prescription for sorafenib,</p> <p>AND</p> <p>Patient must have stable or responding disease according to the Response Evaluation Criteria In Solid Tumours (RECIST),</p> <p>AND</p> <p>The treatment must be the sole PBS-subsidised therapy for this condition.</p>
<b>Population criteria:</b>	<del>Patient must be an adult</del>
<b>Prescriber Instructions</b>	<p><del>Patients must have stable or responding disease according to Response Evaluation Criteria in Solid Tumours (RECIST) criteria to be eligible for continuing PBS subsidy.</del></p> <p><del>Patients who fail to demonstrate stable disease or response to treatment with sorafenib or who progress while on sorafenib will not be eligible to receive further PBS-subsidised treatment with this drug for this condition.</del></p>
<b>Administrative Advice</b>	<p><i>Response Evaluation Criteria In Solid Tumours (RECIST) is defined as follows:</i></p> <p><i>Complete response (CR) is disappearance of all target lesions.</i></p> <p><i>Partial response (PR) is a 30% decrease in the sum of the longest diameter of target lesions.</i></p> <p><i>Progressive disease (PD) is a 20% increase in the sum of the longest diameter of target lesions.</i></p> <p><i>Stable disease (SD) is small changes that do not meet above criteria.</i></p> <p>NOTE: No increase in the maximum quantity or number of units may be authorised.</p> <p>NOTE: No increase in the maximum number of repeats may be authorised.</p> <p>NOTE: Special Pricing Arrangements apply.</p>

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

2.3 The requested PBS listing differed from the previous submission because it included: a definition for 'refractory to radioactive iodine' (RAI-R) that aligns with the definition

used in the DECISION trial; a requirement that the patient has had thyroid stimulating hormone adequately repressed; and a requirement that the patient must have symptomatic progressive disease prior to treatment. The evaluation considered that these changes were consistent with the changes requested by the PBAC in its July 2014 consideration of sorafenib.

- 2.4 The resubmission stated that sorafenib should not be restricted to use in patients with stage III or stage IV disease on the basis that this would exclude all patients aged less than 45 years. The pre-PBAC response stated that ‘if staging is included in the restriction, patients under 45 years but at high risk (bulky tumour, growing local metastases) would be excluded’. This is because patients aged less than 45 years with papillary or follicular cancer and distant metastases are stage II, not stage IV. The pre-PBAC response further noted that only 3.8% of patients in the sorafenib arm of the key trial had stage I or II disease.

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

### 3 Background

- 3.1 **TGA status:** Sorafenib was approved for registration by the TGA for treatment of patients with locally advanced or metastatic, progressive, differentiated thyroid cancer refractory to radioactive iodine in May 2014. Sorafenib was granted Orphan Drug Status on 4 March 2013 for the above indication.

- 3.2 The table below compares the previous submission to the PBAC for sorafenib in RAI-R DTC with the current resubmission.

#### Summary of the previous submission and current resubmission

	Submission for sorafenib and July 2014 PBAC comment	Current resubmission
Requested PBS listing	<p>Section 85 Authority required</p> <p>Treatment for patients with locally advanced or metastatic, progressive, differentiated thyroid carcinoma (DTC) refractory to radioactive iodine.</p> <p><b>PBAC Comment:</b> the PBAC considered the following with regard to the restriction:</p> <ol style="list-style-type: none"> <li>1. That the patient must have thyroid stage III or IV (since only 3.8% of patients in the sorafenib arm of the trial had thyroid stage I or II).</li> <li>2. That “locally advanced” be removed and the metastases defined as “distant”.</li> <li>3. That a definition for RAI-R be included, i.e. a) A lesion without iodine uptake on a radioactive iodine (RAI) scan, or b) Receiving cumulative RAI ≥ 600 mCi, or c) Experiencing a progression after a RAI treatment within 16 months of enrolment, or d) After two RAI treatments within 16 months of each other.</li> <li>4. That the patient must had thyroid stimulating hormone adequately repressed.</li> <li>5. That the patient must have had symptomatic progressive disease prior to treatment.</li> </ol>	<p>The resubmission’s proposed restriction included a definition for ‘refractory to radioactive iodine’ (RAI-R) and a requirement that the patient has had thyroid stimulating hormone adequately repressed and that patient must have symptomatic progressive disease prior to treatment.</p> <p>The resubmission did not include the requirement for stage III or stage IV disease to be present. The resubmission claimed that doing so would exclude patients who are under 45 and in need of sorafenib.</p>
Requested price	\$ (published) \$ (effective)	\$ (published) \$ (effective)

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	Submission for sorafenib and July 2014 PBAC comment	Current resubmission
Main comparator	Best supportive care (BSC) <b>PBAC Comment:</b> The PBAC accepted BSC (placebo) as the appropriate comparator.	Best supportive care
Clinical evidence	One randomised, head-to-head trial comparing sorafenib to placebo plus BSC (n=417). (DECISION) <b>PBAC Comment:</b> Overall survival was confounded by substantial crossover following progression or at the end of the double-blind period. The DECISION trial allowed continued post-progression use of sorafenib. Therefore OS with sorafenib may be lower in clinical practice if the PBS restriction does not allow post-progression use of sorafenib.	DECISION trial  The resubmission presented additional ad hoc analysis to address this issue.
Key effectiveness data	-A significant increase in median PFS compared with placebo from 5.8 months (placebo) to 10.8 months (sorafenib): HR 0.587 (0.454 - 0.758). Censoring of patients who ceased sorafenib early due to side effects without progression may bias this result towards sorafenib; -A significant increase in 'Disease Control', which comprises complete response, partial response and stable disease. The disease control rate was 74.6% in the placebo arm compared with 86.2% in the sorafenib arm: RD 0.12 (0.04-0.19); -The comparison of sorafenib with placebo did not result in a statistically significant difference in OS for the intention to treat population. The unadjusted HR for OS was 0.80 (0.54 – 1.19). This result may have been affected by the significant crossover (from placebo to open-label sorafenib after disease progression) that occurred in the trial. <b>PBAC Comment:</b> The PBAC noted that the outcomes from the DECISION trial showed a gain in PFS of 5 months. Due to the design of the trial, any gain in OS was uncertain. The PBAC considered that it was uncertain whether a gain in PFS was clinically meaningful in this type of cancer, in the absence of evidence of a benefit in OS, noting that before progression, health related quality of life data from the trial favoured placebo compared with sorafenib.	Same. Additionally, the resubmission presented updated OS, based on May 2013 data cut-off. The results showed no statistical difference was observed in OS between the sorafenib arm and the placebo arm: [REDACTED]. The pre-sub-committee response (PSCR) (p6) reported RPSFT [REDACTED]. The resubmission presented additional information to address the crossover issue.
Key safety data	On the basis of the direct evidence presented in the submission, for every 100 patients treated with sorafenib in comparison with placebo, approximately: 38 additional patients will have at least one Grade 3 or higher adverse event (AE). 20 additional patients will have Grade 3 or higher hand-foot skin reaction. 7 additional patients will have Grade 3 or higher hypertension. 40 additional patients will have sorafenib treatment interrupted due to AE. 55 additional patients will have sorafenib treatment reduced due to AE. 15 additional patients will have sorafenib treatment stopped due to AE. This is based on a period of 10 – 12 months of treatment with sorafenib (compared with 8 – 9 months of observation in the placebo+BSC arm). <b>PBAC Comment:</b> The PBAC accepted that sorafenib has inferior safety compared with BSC (placebo).	Same.
Clinical claim	The submission describes sorafenib as superior in terms of comparative effectiveness and inferior in terms of comparative safety over placebo. <b>PBAC Comment:</b> The PBAC only accepted the claim of inferior safety profile.	Same.
Economic evaluation	Cost-utility model with cost/QALY of \$ [REDACTED] <b>PBAC Comment:</b> The PBAC agreed with the ESC that it was not reasonable to attach utilities to the post-progression health state as it may result in bias against BSC.	Cost-utility model with cost/QALY of \$ [REDACTED].

	Submission for sorafenib and July 2014 PBAC comment	Current resubmission
Number of patients	<p>█ in Year 1 increasing to █ in Year 5.</p> <p><b>PBAC Comment:</b> The PBAC agreed with the DUSC that the financial estimates were highly uncertain.</p>	<p>█ in Year 1 increasing to █ in Year 5.</p>
Estimated cost to PBS	<p>\$█ in Year 1 increasing to \$█ in Year 5.</p> <p><b>PBAC Comment:</b> The PBAC agreed with the DUSC that the financial estimates were highly uncertain.</p>	<p>\$█ in Year 1 increasing to \$█ in Year 5.</p>
PBAC decision	<p>Rejected, on the basis of high and uncertain cost effectiveness, a sub-optimally defined patient population and uncertain clinical benefit.</p>	-

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.

#### 5 Comparator

- 5.1 The submission nominated best supportive care (placebo) as the comparator for sorafenib. The PBAC had previously accepted best supportive care (placebo) as the appropriate comparator.

#### 6 Consideration of the evidence

##### Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician presented clinical case studies and discussed the natural history of the disease, including that it is generally difficult to predict the natural course of the condition in individual patients. The clinician also outlined how sorafenib would be used in practice, including that it may be used after progression as the condition may worsen once sorafenib is ceased.

##### Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with sorafenib including an improvement in quality of life.
- 6.3 The PBAC also noted the '*Differentiated Thyroid Cancer Patient Survey*', which was received through the Consumer Comments facility and was conducted by Commercial Eyes in consultation with Rare Cancer Australia, and funded by Bayer. The results of the patient survey included that patients considered DTC to be a 'life-altering condition' and 'expressed a willingness to accept moderate to severe toxicities of cancer treatment to delay disease progression, even if that delay was 5 to 6 months in duration'.

## Clinical trials

- 6.4 The resubmission was based on one randomised, head-to-head trial comparing sorafenib to placebo plus best supportive care (BSC) (n=417).
- 6.5 Details of the trial presented in the submission are provided in below.

### Key trial presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
<b>Direct randomised trial</b>		
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>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.</i>	Year: 2011 BMC Cancer. 2011 Aug 11;11:349.
	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.	Lancet. 2014 Jul 26;384(9940):319-28. doi: 10.1016/S0140-6736(14)60421-9. Epub 2014 Apr 24.
	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.	Journal of Clinical Oncology (2014) 32:15 SUPPL. 1. Date of Publication: 20 May-14
	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.	Journal of Clinical Oncology (2014) 32:15 SUPPL. 1. Date of Publication: 20 May-14
	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.	Journal of Clinical Oncology (2014) 32:15 SUPPL. 1. Date of Publication: 20 May-14
	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.	Thyroid (2013) 23 SUPPL. 1 (A49-A50). Date of Publication: October 2013

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.	Onkologie (2013) 36 SUPPL. 7 (184). Date of Publication: October 2013
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.	European Journal of Cancer (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.	Journal of Clinical Oncology (2013) 31:18 SUPPL. 1. Date of Publication: 20

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

**Key features of the included evidence**

Trial	N	Design/ duration <sup>a</sup>	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
<b>Sorafenib versus placebo</b>						
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.

Source: compiled during the evaluation

<sup>a</sup>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.

6.7 Overall survival (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.

6.8 The extent of attrition bias during the double-blind period for PFS was unclear. There were 75 discontinuations in the sorafenib arm compared with 22 discontinuations in the placebo arm.

**Comparative effectiveness**

6.9 At the time of the first data cut-off (31 August 2012), median overall survival had not yet been reached (23.7% of patients had experienced an event). Approximately one quarter of patients were still receiving sorafenib at the data cut-off date.

**Results for the DECISION trial (data cut-off 31 August 2012)**

Trial ID	Sorafenib Median survival ± SD (months)	Placebo+BSC Median survival ± SD (months)	Absolute difference (months)	Relative effect HR (95% CI)
PFS – central review	10.8 (9.1, 12.9)	5.8 (5.3, 7.8)	5.0	
OS	Median not yet reached		Not calculable	

BSC = best supportive care; PFS=progression-free survival; OS=overall survival.

Source: Table 34, p75 and Table 38, p81 of the submission

- 6.10 The resubmission provided updated OS data, based on the data cut-off at 31 May 2013.

**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, without censored values):unadjusted	1.9-31.8	0.9-36.5
Hazard ratio with 95% CI (sorafenib/placebo): unadjusted		
p-value (one-sided from stratified log-rank test): unadjusted		
Hazard ratio (95% CI): adjusted for crossover, RPSFT method		
Hazard ratio (95% CI): adjusted for crossover, IPE method		

Source: Table B.34, p133 of the resubmission

Note: FAS=full analysis set (this is the same as ITT); CI=confidence interval; A=value cannot be estimated due to censored data.

- 6.11 The submission and pre-sub-committee response (PSCR) adjusted the OS estimates for crossover using iterative parameter estimation (IPE) and rank preserving structural failure time (RPSFT) models. The ESC considered that these methods were appropriate, with a preference for the RSPFT over the IPE in this case because the IPE is more sample intensive and relies on parametric assumptions that cannot be verified.
- 6.12 The ESC noted that the sponsor stated in the PSCR “Since crossover patients are more likely to have a smaller treatment effect since they begin treatment later in time and at a later stage of the disease (after progression), the RPSFT and IPE methods will underestimate the treatment effect actually received by the patients randomised to the experimental arm, meaning that these methods will give a conservative estimate of the true treatment effect.” The ESC agreed that switching patients in the control arm may have a smaller treatment effect than the experimental arm, but did not agree that the RPSFT and IPE methods generally give a conservative estimate of the true treatment effect in such a scenario. No justification or reference for the sponsor’s claim was provided. The ESC highlighted a recent simulation study, which reported that use of the RPSFT, and IPE methods consistently resulted in overestimation of the true treatment effect when switching patients received a reduced treatment effect (Latimer 2012 <http://etheses.whiterose.ac.uk/3720/>). Furthermore the sponsor did not specify exactly which component of the RPSFT adjustment was used as proxy for the treatment effect. (The pre-PBAC response

subsequently advised that the “tumour growth rate” was used.) If the acceleration factor derived from the RPSFT model was presumed to capture the treatment effect, then the treatment effect in the experimental arm would be underestimated. Conversely if counterfactual survival times in the control arm were used and compared to survival times observed in the experimental arm, then the treatment effect in the experimental would be overestimated.

In addition, the re-censoring of data applied by the RPSFT may further under- or over-estimate the treatment effect depending upon exactly when during the observation period this occurred. Without details of these two properties of the RPSFT, the ESC was unable to confirm the sponsor’s claim that the RPSFT and the related IPE adjustments specifically underestimated the treatment effect. In the absence of convincing evidence or justification to support the sponsor’s claim, the ESC advised that when treatment effect is reduced for switchers in the control arm (relative to that received by the experimental arm), the available evidence suggests that RPSFT and IPE methods are more likely to give an overestimate than an underestimate of the true treatment effect. The PBAC noted that the important estimate for interpretation in this context was of any incremental OS for sorafenib over BSC alone, and that the sponsor’s arguments did not convincingly address this estimate.

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

### **Comparative harms**

- 6.13 The comparative harms were unchanged from the previous 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.
- 6.14 More than 70% of patients receiving sorafenib experienced at least one Grade 3 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%). The evaluation noted that these were all considerably more common in the sorafenib arm compared with placebo+BSC.

### **Benefits/harms**

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

**Summary of comparative benefits and harms for sorafenib and placebo+BSC**

<b>Benefits</b>						
<b>Progression-free survival / Overall survival<sup>a</sup></b>						
	<b>Sorafenib</b>	<b>PBO+BSC</b>	<b>Absolute difference</b>	<b>HR (95% CI)</b>		
<b>cut-off 31 May 2013</b>						
OS			-			
Median (months)	A (A; A)	1110 (979; A)	Not evaluable			
<b>cut-off 31 August 2012</b>						
PFS			-			
Median (months)	10.8 (9.1, 12.9)	5.8 (5.3, 7.8)	5.0	-		
OS			-			
Median (months)	Median not yet reached		Not evaluable			
<b>Trial</b>	<b>Sorafenib</b>	<b>PBO+BSC</b>	<b>RR (95% CI)</b>	<b>Event rate/100 patients</b>		<b>RD (95% CI)</b>
				<b>Sorafenib</b>	<b>PBO</b>	
<b>Disease control rate (CR + PR + SD) – per protocol analysis set, cut-off 31 August 2012</b>						
DECISION						
<b>Harms, cut-off 31 August 2012</b>						
	<b>Sorafenib</b>	<b>PBO+BSC</b>	<b>RR (95% CI)</b>	<b>Event rate<sup>b</sup>/100 patients</b>		<b>RD (95% CI)</b>
				<b>Sorafenib</b>	<b>PBO</b>	
<b>Treatment-emergent AE, Grade 3 or higher</b>						
DECISION						
<b>Hand-foot skin reaction, Grade 3 or higher</b>						
DECISION						
<b>Hypertension, Grade 3 or higher</b>						
DECISION						

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

<sup>b</sup> the proportion of patients who experience 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; A: value cannot be estimated due to censored data; RPSFT = rank-preserving structural failure time; IPE = iterative parameter estimation

- 6.16 On the basis of direct randomised evidence presented by the submission, for patients treated with sorafenib in comparison to placebo+BSC, there would be:
- Approximately 5 months difference in median progression-free survival.
  - An unknown possible difference in median overall survival.
- 6.17 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

- 6.18 The submission described sorafenib as superior in terms of comparative effectiveness and inferior in terms of comparative safety over BSC. The evaluation considered that this claim may not be adequately supported.
- The magnitude of benefit in terms of extension of life derived from sorafenib is difficult to ascertain due to crossover following progression.
  - The magnitude of benefit in terms of progression-free survival is likely to be overestimated due to the inappropriate censoring of patients who withdraw from treatment, which occurred more frequently in the sorafenib arm.
- 6.19 The PBAC considered that the claim of superior comparative effectiveness was adequately supported by the data for PFS, but not for OS.

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

## Economic analysis

- 6.20 The resubmission presented a modelled economic evaluation (cost-utility analysis). The economic evaluation was largely the same as in the previous submission. The key changes were: the assumed duration of treatment was increased to 17.55 months and the dispensed price of sorafenib was reduced to a new proposed effective price of \$ [REDACTED] (DPMQ for 120 x 200 mg tablets). The model structure is summarised below.

### 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	Life-years gained and quality-adjusted life-years gained
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 progression-free survival and overall survival curves

Source: compiled during the evaluation

- 6.21 Key model components were the two extrapolation models: one model extrapolated PFS for sorafenib, which included a fitted treatment effect parameter to estimate PFS for BSC; the second model extrapolated OS for sorafenib, applying the hazard ratio estimated from the RPSFT analysis (the less conservative approach) to the extrapolated estimate of OS for BSC.
- 6.22 The model used OS data from the August 2012 data cut-off adjusted for crossover using the RPSFT method, rather than the more recent data from the May 2013 data cut-off.
- 6.23 Model drivers are summarised in the table below.

**Model drivers**

Description	Method/Value	Impact
OS benefit of sorafenib over BSC	Adjustment of OS in the BSC arm due to crossover to sorafenib post-progression (methods of adjustment and the 95% CI of hazard ratio in the same adjustment analysis) leading to a finding that OS benefit is greater than PFS benefit.	High, favours sorafenib
Time horizon	10 years; assumed from 2 years trial duration.	Low, favours sorafenib
Duration of sorafenib treatment	Average number of cycles of treatment observed in the double-blind and post-progression period of the DECISION trial.	Low
Dose intensity of sorafenib treatment	Dose intensity observed in the DECISION trial, assuming no wastage.	Moderate, favours sorafenib
Utilities of health states	Trial-based utility values without disutility associated with continued post-progression sorafenib treatment.	Likely to be low, depending on the duration of continued post-progression treatment, favours sorafenib.

OS = overall survival; BSC = best supportive care

Source: compiled during the evaluation

6.24 The results of the economic evaluation are summarised below.

**Results of the economic evaluation**

Component	Sorafenib	BSC	Increment
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LYs	3.62	2.67	0.95
QALYs	2.39	1.80	0.59
<b>Incremental cost per LY gained</b>			\$ [REDACTED]
<b>Incremental cost per QALY gained</b>			\$ [REDACTED]

BSC = best supportive care; LY = life year; QALY = quality-adjusted life year.

Note: table compiled during evaluation.

6.25 The base case ICER (sorafenib vs. BSC) was lower than the previous submission (\$45,000/QALY – \$75,000/QALY versus \$45,000/QALY – \$75,000/QALY, the revised base case). This was mainly because of a [REDACTED]% reduction in the price of sorafenib.

6.26 The base case predicted a difference in mean OS of [REDACTED] months, which was 50% greater than the predicted difference in mean PFS of [REDACTED] months.

6.27 The key results of the sensitivity analyses presented by the submission and conducted during the evaluation are summarised below. The ESC was concerned that, in view of the higher ICERs generated from the sensitivity analyses, the ICERs that would be generated using updated OS data could be even higher. The ESC requested that the sponsor provide sensitivity analyses based on the updated OS data in its pre-PBAC response, however, these were not provided.

6.28 The model was most sensitive to the modelled gain in OS. The commentary provided a sensitivity analysis that assumed there was no incremental post-progression benefit, which effectively assumed that the modelled gain in OS is the same magnitude as the gain in PFS reported in the trial. This was conducted by setting the utility for the post-progression health state to zero. The ICER for this sensitivity analysis was \$105,000/QALY – \$200,000/QALY, which was double the base case ICER of \$45,000/QALY – \$75,000/QALY.

- 6.29 The pre-PBAC response stated that setting the utility for the post-progression health state to zero was an “inaccurate interpretation of the model and that it is “clinically unrealistic to assume that patients in the post-progression state have no quality of life”. However, the PBAC noted that the purpose of this sensitivity analysis was to assume that, for health outcomes, there was no difference in the post-progression course (no additional gain in OS after progression). However, the sensitivity analysis overestimated the ICER for sorafenib for the scenario in which there was no additional gain in OS after disease progression because the model included the costs of post-progression interventions.
- 6.30 When the ITT results for OS (unadjusted for crossover) were used, the ICER was \$105,000/QALY – \$200,000/QALY. The ICER was also sensitive to the time horizon and assumptions around dose intensity.

**Results of univariate sensitivity analyses (discounted)**

Univariate analyses		ICER (\$/QALY)	Difference
<b>Sensitivity analysis</b>		<b>Base case</b>	<b>0%</b>
Time horizon	5 years	\$ [REDACTED]	+27.4%
	20 years	\$ [REDACTED]	-5.1%
OS estimate	Unadjusted OS estimate	Adjusted OS	+84.5%
Extrapolation	Log-normal for PFS	Weibull for PFS and OS	-1.1%
	Log-normal for OS	Weibull for PFS and OS	+1.2%
Discount rate	0% for both cost and health outcome	5%	-69.0%
	7% for both cost and health outcome		+7.6%
Utility value for post-progression health state	[REDACTED]	[REDACTED]	-4.8%
	[REDACTED]	[REDACTED]	+12.2%
	0 <sup>a</sup>	[REDACTED]	+102.7%
Treatment duration	Treatment till progression only	Treatment also after progression	-14.6%
Dose intensity	60%	81%	-26.2%
	100%		+22.8%

Source: Table D.8 p262 of the resubmission.

Note: items in italics were constructed during evaluation.

<sup>a</sup> When the utility was set to zero, the model assumed there was no incremental post-progression benefit as outlined in paragraph 6.28.

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

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

- 6.31 The estimated total drug cost of \$ [REDACTED] per patient per course is based on [REDACTED] year duration of treatment and a dose intensity of 81%.

**Estimated PBS usage & financial implications**

6.32 This resubmission was not considered by DUSC. The resubmission’s approach was different from the previous submission. The previous submission had used Australian and international DTC epidemiological statistics to estimate the market size of sorafenib, however the DUSC considered that this method substantially overestimated the eligible population and suggested a mortality approach based on AIHW mortality statistics (6.2 sorafenib 07-13 DUSC ADV). The resubmission followed the DUSC’s advice. Under the new mortality approach, the resubmission estimated the potential eligible RAI-R DTC population to be less than less than 10,000 persons per annum over 5 years, which was lower than the previous estimate of less than 10,000 per year. The evaluation considered that this was appropriate.

**Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5
<b>Estimated extent of use</b>					
Treatment eligible patients					
Total utilisation (120 x 200 mg packs) <sup>a</sup>					
<b>Estimated net cost to PBS/RPBS</b>					
Net cost to PBS	\$	\$	\$	\$	\$
Net cost to RPBS	\$	\$	\$	\$	\$
<b>Estimated total net cost</b>					
Net cost to PBS/RPBS	\$	\$	\$	\$	\$
Average cost of managing TEAEs	\$	\$	\$	\$	\$
Estimated total cost to Government	\$	\$	\$	\$	\$

Source: Compiled during the evaluation

6.33 The estimated net cost to the PBS/RPBS and government health budgets of listing sorafenib was expected to increase from approximately less than \$10 million in Year 1 to around less than \$10 million in Year 5. The cumulative budget impact, over the first five years of listing sorafenib was estimated to be \$10 - \$20 million over 5 years.

**Quality Use of Medicines**

6.34 The sponsor stated that, should sorafenib be reimbursed on the PBS, the company would undertake activities to support patients who experience the hand foot skin reaction (including providing a [redacted], a [redacted], a [redacted] and [redacted]) as well as [redacted]. This was unchanged from the previous submission.

**Financial Management – Risk Sharing Arrangements**

6.35 The submission requested an effective dispensed price for maximum quantity (DPMQ) of \$ [redacted], compared with a published DPMQ of \$ [redacted]. The effective DPMQ was used in both the economic evaluation and financial estimates in the submission.

- 6.36 The pre-PBAC response proposed a risk sharing arrangement with a financial cap based on a ■% increase in the uptake rates, and an ■% rebate for expenditure above the financial cap in each year of listing. The PBAC would support the inclusion of a risk sharing arrangement, noting that thyroid cancer outside the intended population is an indolent cancer which tends to be over diagnosed.

*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 because the submission had not provided a reliable estimate of the cost-effectiveness of sorafenib in this setting, and wished to see the results of its request for a price reduction to an otherwise accepted sensitivity analysis of the submitted modelled economic evaluation. The PBAC considered that the clinical data did not adequately demonstrate a statistically significant gain in OS and therefore the life-years gained (LYG) of ■ months in the economic evaluation was implausible. The PBAC considered that, in this case, the modelled incremental LYG should not be greater than the incremental PFS reported in the clinical trial (5 months) as was reflected in the PBAC-accepted sensitivity analysis performed for the evaluation of the submission.
- 7.2 As previously, the PBAC noted that RAI-R DTC can be asymptomatic and treatment may not be needed. The PBAC considered that sorafenib should only be used in patients with a symptomatic progressive disease and agreed with the sponsor's proposal to specify this in the restriction.
- 7.3 The PBAC noted that if PBS use is restricted to patients with Stage III or IV disease, then patients aged less than 45 years but at high risk (bulky tumour, growing local metastases) would not be eligible for sorafenib. The PBAC considered that the restriction should define the subset of high risk patients aged less than 45 years who should be included.
- 7.4 The PBAC considered 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. However, the PBAC noted that, even with the revised restriction, it would be difficult to limit use of sorafenib to this group.
- 7.5 The PBAC considered that there would be a high risk of usage outside the requested restriction, including a risk that sorafenib would be continued beyond progression.
- 7.6 As previously, the PBAC considered that BSC was the appropriate comparator.

- 7.7 As previously, the PBAC noted the DECISION trial reported a gain in median PFS of 5 months. Most progression events were assessed using radiological evaluation, with 60.9% and 78.1% of investigator-assessed progression being 'radiologically defined' in the sorafenib and placebo arms, respectively. The PBAC considered that it was difficult to assess the clinical meaningfulness of asymptomatic progression, particularly in the context of the disutilities associated with sorafenib use (a [REDACTED] disutility was applied to sorafenib treatment). However, in the context of the high clinical need for an effective treatment, the PBAC concluded that PFS may be clinically meaningful in RAI-R DTC. The PBAC therefore accepted that sorafenib is more effective than BSC in terms of PFS.
- 7.8 As previously, the PBAC accepted that sorafenib has inferior safety compared with BSC.
- 7.9 With regard to OS, the results were not statistically significant for the ITT analyses, with a HR for OS of [REDACTED] at the August 2012 data cut-off and [REDACTED] at the May 2013 data cut-off. Median OS had not been reached.
- 7.10 Given the high degree of crossover, the submission adjusted the OS results for crossover using both the RPSFT and IPE methods. However, the PBAC considered that the adjusted results did not provide a reliable estimate of the OS. In forming this view, the PBAC considered a range of factors including:
- the high degree of crossover; with 71.4% of patients from the placebo arm of the trial crossing over to sorafenib
  - the small number of patients upon which the adjustment methods are based, with only 60 of the 210 patients randomised to placebo who did not crossover to sorafenib
  - most progression events, which were the trigger for many crossovers, were assessed using radiological evaluation rather than symptomatic events
  - BSC patients had long post-progression survival relative to other cancers and to progression-free survival, so any variation to the hazard ratio for OS would have a larger consequence for incremental OS
  - the ITT results did not show a statistically significant improvement in OS
  - no corroborating evidence was provided to support the use of PFS as a surrogate measure for OS in this specific condition
  - the assumptions underlying the presented adjustment methods were not shown to be fulfilled. The ESC advised that the RPSFT method for adjusting for crossover was more technically appropriate than the IPE method in this case. The sample size in the placebo arm was considered too small to permit the IPE method to work optimally and to properly assess a parametric survival time distribution. However, the validity of the underlying assumption upon which RPSFT is based – the common treatment effect assumption – was not fulfilled. That is, it was unclear whether patients have an equal likelihood of responding to sorafenib irrespective of whether or not they received placebo first. Accordingly, the PBAC could not conclude whether the RPSFT estimate would be less biased than the unadjusted survival estimate.

In view of these factors, the PBAC concluded that the ITT results, which did not show a statistically significant improvement in OS, were more informative than the adjusted

analyses.

- 7.11 The PBAC considered that the modelled OS gain of ■ months in the resubmission's economic evaluation was implausible given that the trial had observed no statistically significant gain in OS in the ITT analysis and only a 5 month gain in median PFS.
- 7.12 The PBAC considered the potential range within which the estimate of any gain in OS could plausibly fit. The lower estimate would only consider the trial-based OS gain, so in this case, the modelled QALY gain would be derived entirely from the 5 month delay in median time to progression (i.e. no LYG in the model). As a pragmatic way forward, the PBAC also proposed an upper estimate with the observed trial-based 5 month gain in median PFS translated into an incremental OS of 5 months. Given the issues outlined in paragraph 7.10, the PBAC considered that such an assumption would be highly favourable to sorafenib, however the PBAC considered that this upper estimate would be appropriate in this particular case in order to facilitate subsidised access to an effective new therapy in an area of unmet clinical need. The PBAC further noted that the PFS data were mature, with more than 50% of patients in both arms experiencing a progression event.
- 7.13 The PBAC noted that the sensitivity analysis outlined in paragraph 6.28 provided an approximation of the cost-effectiveness of sorafenib in the scenario in which there is no further gain in OS beyond progression (i.e. a scenario in which the observed trial-based 5 month gain in median PFS is translated into an incremental OS of 5 months in the model). The PBAC considered for the purposes of its deferral that this should be the base case for the economic evaluation. The ICER for this sensitivity analysis was \$105,000/QALY – \$200,000/QALY at the price proposed.
- 7.14 The PBAC considered that sorafenib would likely be cost-effective at a reduced price generating an ICER less than \$45,000/QALY – \$75,000/QALY by this sensitivity analysis in which the gain in OS is of the same magnitude as the gain in PFS observed in the trial. Any request from the sponsor to reconsider sorafenib on another basis would require a major resubmission.
- 7.15 The PBAC acknowledged the difficulties associated with estimating utilisation in this patient population, and considered that the resubmission's estimate (approximately less than 10,000 patients per annum) was reasonable.
- 7.16 In light of the uncertain patient numbers and the risk of use of sorafenib outside the requested restriction, the PBAC noted that a risk-sharing arrangement would be required should sorafenib be recommended for listing in this patient population in the future. The PBAC considered that a financial cap would be required, based on the patient numbers outlined in the 'Estimated use and financial implications' table in paragraph 6.32, with a 100% rebate for expenditure above the cap.

**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 intends to continue working with the PBAC to make sorafenib available to those Australian patients with RAI-DTC that could benefit from the product.