

**5.20 REGORAFENIB**  
**40 mg tablet, 84;**  
**Stivarga®; Bayer Australia Ltd**

**1 Purpose of Application**

1.1 The submission sought section 85, Authority required listing for regorafenib for treatment of gastrointestinal stromal tumours (GIST).

**2 Requested listing**

2.1 The requested listing is outline below. Suggestions and additions proposed by the Secretariat to 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
REGORAFENIB 40 mg tablet, 84	1	2	\$ [REDACTED] (effective price: \$ [REDACTED])	Stivarga® BN

<b>Category / Program</b>	GENERAL – General Schedule (Code 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>Episodicity:</b>	<del>Until disease progression</del>
<b>Severity:</b>	<i>Metastatic or unresectable</i>
<b>Condition:</b>	<i>Malignant gastrointestinal stromal tumour</i>
<b>PBS Indication:</b>	<i>Metastatic or unresectable malignant gastrointestinal stromal tumour</i>
<b>Treatment phase:</b>	<del>Initial (new patient) who has not received any PBS-subsidised treatment with regorafenib for gastrointestinal stromal tumour.</del>
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input checked="" 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 type="checkbox"/> Streamlined

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<b>Treatment criteria:</b>	<p>Patient with metastatic or unresectable malignant gastrointestinal stromal tumour after failure of or intolerance to imatinib mesylate</p> <p>and</p> <p>after failure of sunitinib treatment.</p> <p>The treatment must be as monotherapy.</p> <p>Patients who have failed to respond or are intolerant to imatinib and sunitinib are no longer eligible to receive PBS subsidised imatinib and sunitinib.</p>
<b>Clinical criteria:</b>	<p>The patient must have unresectable metastatic gastrointestinal stromal tumour,</p> <p>The treatment must be as monotherapy,</p> <p>AND</p> <p>Patient must have previously failed or be intolerant after failure of or intolerance to imatinib mesylate,</p> <p>AND</p> <p>Patient must have previously failed or be intolerant to sunitinib,</p> <p>AND</p> <p>Patient must have a WHO performance status of 0 or 1.</p>
<b>Population criteria:</b>	<p>Patient must be aged 18 years or older <del>an adult</del>.</p>
<b>Prescriber Instructions</b>	<p>Patients who fail to demonstrate a response to treatment with regorafenib or who progress while on regorafenib will not be eligible to receive further PBS-subsidised treatment with this drug for this condition.</p>
<b>Prescriber Instructions</b>	<p>Applications for authorisation must be in writing and must include:</p> <p>(1) a completed authority prescription form; and</p> <p>(2) a completed regorafenib (Stivarga) PBS Authority Application for Use in the Treatment of gastrointestinal stromal tumour. Supporting Information Form [may be downloaded from the Medicare Australia website (<a href="http://www.medicareaustralia.gov.au">www.medicareaustralia.gov.au</a>)]; and</p> <p>(3) a signed patient acknowledgement indicating they understand and acknowledge that they will not be eligible to receive further PBS-subsidised treatment with this drug for this condition if they fail to demonstrate a response to treatment with regorafenib or who progress while on regorafenib.</p>

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<b>Administrative Advice</b>	<p>Applications for continuing treatment may be made by telephone (1800 700 270, hours of operation 8 a.m. to 5 p.m. EST Monday to Friday)/</p> <p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at <a href="http://www.humanservices.gov.au">www.humanservices.gov.au</a></p> <p>Applications for authority to prescribe should be forwarded to:          Department of Human Services          Prior Written Approval of Complex Drugs          Reply Paid 9826          GPO Box 9826          HOBART TAS 7001</p>
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<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
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<b>Episodicity:</b>	<del>Until disease progression</del>
<b>Severity:</b>	<i>Metastatic or unresectable</i>
<b>Condition:</b>	<i>malignant gastrointestinal stromal tumour</i>
<b>PBS Indication:</b>	<i>Metastatic or unresectable malignant gastrointestinal stromal tumour</i>
<b>Treatment phase:</b>	<del>Continuing PBS-subsidised treatment as monotherapy of a patient with a metastatic or unresectable malignant gastrointestinal stromal tumour.</del>
<b>Restriction Level / Method:</b>	<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
<b>Treatment criteria:</b>	<del>Patient must have previously been issued with an authority prescription for regorafenib and who does not have progressive disease.</del>
<b>Clinical criteria:</b>	<p><i>Patient must have previously received PBS-subsidised therapy with this drug for this condition,</i></p> <p><del>The patient must have unresectable metastatic gastrointestinal stromal tumour</del></p> <p>AND</p> <p><i>The treatment must be as monotherapy,</i></p> <p>AND</p> <p><del>Patient must not have had disease progression while on regorafenib receiving treatment with this drug,</del></p> <p>AND</p> <p><i>Patient must have a WHO performance status of 0 or 1.</i></p>
<b>Population criteria:</b>	<del>Patient must be an adult.</del>

<b>Prescriber Instructions</b>	Patients who fail to demonstrate a response to treatment with regorafenib or who progress while on regorafenib will not be eligible to receive further PBS-subsidised treatment with this drug for this condition.
<b>Administrative Advice</b>	Authority applications for continuing treatment may be made by telephone to the Department of Human Services on 1800 700 2707 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

- 2.2 The pre-sub-committee response (PSCR) accepted the suggested revisions to the restriction for PBAC consideration, including the addition of a criterion requiring the patient to have a WHO performance status of 0 or 1, in line with the eligibility criteria in the trial.
- 2.3 The submission sought a listing based on the cost-effectiveness of regorafenib compared with best supportive care (BSC).

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

### 3 Background

- 3.1 **TGA status:** The submission was made under TGA/PBAC Parallel Process. The TGA Delegate's overview, received on 17 December 2014, considered the benefit/risk profile to be positive. The application was reviewed by the Advisory Committee on Prescription Medicines (ACPM) on 6 February 2015. The ACPM outcome, received on 4 March 2015, agreed with the delegate and considered regorafenib to have an overall positive benefit-risk profile for the treatment of patients with unresectable or metastatic GIST who progressed on or are intolerant to prior treatment with imatinib and sunitinib.
- 3.2 The ESC noted the PBAC previously considered a submission requesting listing of regorafenib for the treatment of metastatic colorectal cancer in July 2014. The PBAC rejected that submission on the basis that the observed improvement in comparative effectiveness associated with regorafenib was of uncertain clinical significance especially in the context of the increase in serious adverse effects associated with treatment. The PBAC considered that even if the small incremental survival gain was considered to be clinically significant, the most reliable estimate of the incremental cost-effectiveness ratio for regorafenib compared to best supportive care was unacceptably high. (Public Summary Document, regorafenib, July 2014 PBAC meeting).
- 3.3 The PBAC further noted that the UK Cancer Drug Fund (CDF) recently considered that the median drug cost of regorafenib was of insufficient value for retention within the CDF (CDF decision summary, Regorafenib for the treatment of previously treated gastrointestinal stromal tumours, Jan 2015, <http://www.england.nhs.uk/wp-content/uploads/2015/01/ncdf-summ-regorafnb-2nd-gist.pdf>).

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

#### **4 Clinical place for the proposed therapy**

- 4.1 GISTs are rare and occur in the muscular layer of the digestive tract. Surgery has been the sole treatment for primary localised GIST and most patients after surgery are observed ('watchful waiting'). However, surgery alone is not curative for the majority of patients.
- 4.2 The treatment options for metastatic GIST include imatinib (first-line treatment) and sunitinib (second-line treatment). The submission proposed regorafenib as a third-line treatment.

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

#### **5 Comparator**

- 5.1 The submission nominated BSC as the comparator for regorafenib. The ESC considered this was appropriate.

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

#### **6 Consideration of the evidence**

##### **Sponsor hearing**

- 6.1 There was no hearing for this item.

##### **Consumer comments**

- 6.2 The PBAC noted and welcomed the input from an individual (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with regorafenib including slowed progression of disease and improved quality of life.

##### **Clinical trials**

- 6.3 The submission was based on one randomised, double-blind, placebo-controlled, multi-centre, crossover phase 3 trial (GRID), comparing regorafenib to placebo. A total of 199 patients were randomised in a 2:1 ratio to either: regorafenib + BSC (133 patients) or placebo + BSC (66 patients). All patients had prior imatinib and sunitinib treatment. This was appropriate and consistent with the proposed PBS restriction.
- 6.4 Details of the trial presented in the submission are provided in the following table.

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

Trial ID	Protocol title/ Publication title	Publication citation
<b>Direct randomised trial(s)</b>		
Grid	Bayer Amended Clinical Study Report No. A59137. 05 October 2012.	CSR October 2012.
	Bayer Clinical Study Report OS update Database cut-off 31.01.2014.	CSR Jan 2014.
	Demetri GD, Reichardt P, Kang .K, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial.	<i>Lancet</i> 2013; 381(9863):295-302.
	Demetri GD, Jeffers M, Reichardt P, et al. Detection of oncogenic kinase mutations in circulating plasma DNA and correlation with clinical benefit in the phase III GRID study of regorafenib vs placebo in TKI-refractory metastatic GIST. In: Proceedings of the 104th Annual Meeting of the American Association for Cancer Research; 2013 Apr 6-10; Washington, DC. Philadelphia (PA): AACR;	Cancer Res 2013;73(8 Suppl): Abstract nr LB-295. doi:10.1158/1538-7445.AM2013-LB-295
	Poole CD, Connolly MP, Chang J, et al. Health utility of patients with advanced gastrointestinal stromal tumors (GIST) after failure of imatinib and sunitinib: findings from GRID, a randomized, double-blind, placebo-controlled phase III study of regorafenib versus placebo.	Gastric Cancer (2014). Date of Publication: 24 Jun 2014.

Source: Table B-4, p68 of the submission.

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

**Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
<b>Regorafenib + BSC vs. Placebo + BSC</b>						
GRID	199	R, DB 22.94 weeks (regorafenib) 6.98 weeks (placebo)	Low for PFS, High for OS	GIST	PFS, OS	PFS OS – adjusted for crossover

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

Source: compiled during the evaluation

6.6 Overall survival (OS) was confounded by substantial crossover: 85% of patients in the placebo + BSC group crossed over to open-label regorafenib treatment after progression, leaving just 10 patients in the comparator arm of the trial to contribute data to the methods used to adjust for this crossover. The ESC considered that the GRID intention to treat (ITT) OS results therefore effectively examined early versus late regorafenib treatment as opposed to regorafenib versus placebo.

6.7 Selection bias for crossover was a possibility. The PSCR acknowledged this, but argued that ‘the selection of patients for crossover to active treatment would most likely have been for those patients who were deemed suitable/well enough to receive active treatment, which would be expected to be similar to the approaches taken in patient selection in clinical decision making’.

6.8 The submission 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. However, the ESC also noted that both of these methods may result in more biased estimates than the ITT estimate if the ‘common treatment effect’ assumption does not sufficiently hold. If the treatment effect for switchers is less than that of the experimental group, this would likely result in an overestimate of the adjusted survival benefit. The ESC considered that reduced efficacy of switchers may be more likely than increased efficacy, although there appeared to be no evidence to suggest either with respect to this specific drug in this specific setting. Therefore, the extent and direction of bias of the adjusted estimates was unknown.

- 6.9 The pre-PBAC response argued that “[i]t is less clinically plausible that the treatment effect on switchers is greater. The more plausible situation would be that the treatment effect is less; if this effect for switchers is less, then Bayer’s methods would likely result in an underestimate of the adjusted benefit using the IPE/RPSFT methods.” The PBAC noted that the important estimate for interpretation in this context was of any incremental OS for regorafenib over BSC alone, and that this argument did not convincingly address this estimate.
- 6.10 The January 2012 data cut-off had immature OS data. Twenty-nine OS events (21.8%) occurred in the regorafenib + BSC group and 17 events (25.8%) occurred in the placebo + BSC group). The January 2014 data cut-off had more mature OS data with 139 events: 91 (68.4%) in the regorafenib group and 48 (72.7%) in the placebo group (before any crossover adjustment). The January 2012 data were originally used in the economic model. The PSCR updated the economic model with the more mature OS data.
- 6.11 The PSCR argued the PBAC recommendation for sunitinib provides a precedent where issues of immature OS data and confounding by and adjustment for crossover were accepted. The ESC advised that the PBAC compare all relevant factors between this regorafenib submission and the nominated sunitinib precedent, not just the immaturity and contamination of OS data.

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

### **Comparative effectiveness**

- 6.12 The table below summarises the main results for progression-free survival (PFS), based on the ITT population, and stratified as per the randomisation. Median PFS time was longer in the regorafenib + BSC group (147 days) than in the placebo + BSC group (28 days). The risk of progression or death in the regorafenib + BSC group was lower than in the placebo + BSC group with a hazard ratio of 0.268 (95% CI: 0.185 to 0.388).

**Primary analysis of progression-free survival (ITT, January 2012 data cut-off)**

	<b>Regorafenib + BSC group (N = 133)</b>	<b>Placebo + BSC group (N = 66)</b>
Number of patients (%) with event	81 (60.9%)	63 (95.5%)
Number of patients (%) censored	52 (39.1%)	3 (4.5%)
Median PFS, days (95% CI)	147 (122, 173)	28 (28, 32)
Median PFS, months	4.8	0.9
Range (without censored values)	(6-281)	8-169
Hazard ratio (regorafenib/placebo)	0.268	
95% CI for hazard ratio	(0.185, 0.388)	
p value (one sided from log rank test)	<0.000001	

Abbreviations: BSC=best supportive care; CI=confidence interval; ITT=intention to treat; PFS=progression-free survival.  
Source: Table B-18, p108 of the submission.

- 6.13 The PSCR argued that ‘the link between PFS and OS in GIST is strong. An analysis by Keyser et al (2011) of studies in advanced and/or metastatic GIST indicates a strong correlation between PFS and OS benefits in 2nd and 3rd line therapy; the authors concluding “PFS benefits may be indicative of OS benefits in this indication” (Keyser, Tranbarger, Freier, Hoaglin, Tzivelekis, & Ozer-Stillman, 2011).’ The ESC questioned the validity of this analysis, noting that it was an abstract of a poster presentation with minimal details of methods and results, and that it included observational studies.
- 6.14 A third of patients in the regorafenib group in GRID trial remained on regorafenib after progression. The PSCR argued that the post-progression treatment time was relatively short at around 2 weeks, compared with the median duration of therapy of 23 weeks.
- 6.15 The following table presents the interim analysis of OS, both unadjusted and adjusted for crossover. At time of data cut-off (January 2012), median OS had not yet been reached.

**Interim analysis of overall survival (ITT, January 2012 data cut-off)**

	<b>Regorafenib + BSC group (N=133)</b>	<b>Placebo + BSC group (N=66)</b>
Number of patients with event (%)	29 (21.8)	17 (25.8)
Number of patients (%) censored	104 (78.2)	49 (74.2)
Hazard ratio (95% CI): unadjusted	0.772 (0.423, 1.408)	
p-value	0.198896	
Hazard ratio (95% CI): adjusted for crossover, RPSFT method	0.537 (0.286, 1.007)	
p-value	0.024725	
Hazard ratio (95% CI): adjusted for crossover, IPE method	0.565 (0.302, 1.055)	
p-value	0.034931	

Abbreviations: BSC=best supportive care; CI=confidence interval; IPE=iterative parameter estimation; ITT=intention to treat; RPSFT=rank preserving structural failure time.  
Source: Table B-22, p115 of the submission.

- 6.16 The submission provided an updated OS analysis, based on the data cut-off at January 2014. These data were not used in the economic model in the submission; however, they were presented in a revised economic evaluation in the PSCR.

**Summary of overall survival (ITT, January 2014 data cut-off)**

	<b>Regorafenib + BSC group (N=133)</b>	<b>Placebo + BSC group (N=66)</b>
Number of patients with event (%)	91 (68.4)	48 (72.7)
Number of patients (%) censored	42 (31.6)	18 (27.3)
Median (95% CI) (days)	529 (454, 614)	529 (373, 640)
Median OS, months	17.4	17.4
Median OS, months: adjusted for crossover, RPSFT method	17.4	8.7
Median OS, months: adjusted for crossover, IPE method	17.4	10.1
Hazard ratio (95% CI): unadjusted	0.849 (0.597, 1.206)	
p-value	0.179856	
Hazard ratio (95% CI): adjusted for crossover, RPSFT method	0.388 (0.259, 0.580)	
p-value	0.000001	
Hazard ratio (95% CI): adjusted for crossover, IPE method	0.508 (0.352, 0.734)	
p-value	0.000119	

Abbreviations: BSC=best supportive care; CI=confidence interval; IPE=iterative parameter estimation; ITT=intention to treat; RPSFT=rank preserving structural failure time; OS=overall survival.

Source: Table B-24, Table B-25 and Table B-26, p119-p121 of the submission.

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

**Comparative harms**

- 6.17 During the double-blind period, dose modifications were required for 72.0% of regorafenib-treated patients and 25.8% of placebo-treated patients. Among the placebo + BSC patients who crossed over to open-label treatment with regorafenib + BSC, dose modifications were required for 72.7% of patients.
- 6.18 More drug-related grade 3 treatment-emergent adverse events (TEAEs) were reported for patients who received regorafenib + BSC (77 events (58.3%)) compared to patients who received placebo + BSC (5 events (7.6%)). The most common grade 3 drug-related TEAEs that had a higher incidence ( $\geq 5$  percentage points) in the regorafenib + BSC treatment group included: hypertension (22.7% vs. 3.0%), Palmar-Plantar Erythrodysesthesia Syndrome (hand food skin reaction (HFSR)) (19.7% vs. 0%), and diarrhoea (5.3% vs. 0%). Grade 3 events that resulted in discontinuation of treatment were infrequent and occurred at similar rates in each treatment group (1.5% and 4.5%) for regorafenib + BSC and placebo + BSC, respectively.

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

**Benefits/harms**

- 6.19 A summary of the comparative benefits and harms for regorafenib versus placebo is presented in the following table.

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

<b>Benefits</b>						
<b>Progression-free survival / Overall survival</b>						
	<b>Regorafenib + BSC</b>	<b>PBO + BSC</b>	<b>Absolute difference</b>	<b>HR (95% CI)</b>		
<b>cut-off January 2012</b>						
PFS	81/133	63/66		0.268 (0.185, 0.388)		
Median	147 days (122, 173)	28 days (28, 32)	119			
OS	29/133	17/66		0.772 (0.423, 1.408)		
Median (months)	Median not yet reached					
<b>cut-off January 2014</b>						
OS	91/133	48/66		0.849 (0.597, 1.206)		
Median (months)	17.4	17.4	0			
<b>Harms, cut-off January 2012</b>						
<b>Trial</b>	<b>Regorafenib + BSC</b>	<b>PBO+BSC</b>	<b>RR (95% CI)</b>	<b>Event rate/100 patients</b>		<b>RD (95% CI)</b>
				<b>Regorafenib</b>	<b>PBO</b>	
<b>Treatment-emergent AE, Grade 3 or higher</b>						
GRID	79/132	6/66	6.6 (3, 14.3)	60	9	-0.5 (-0.6, -0.38)
<b>HFSR, Grade 3 or higher</b>						
GRID	26/132	0/66	26.6 (1.7, 431.4)	20	0	-0.2 (-0.27, -0.11)
<b>Hypertension, Grade 3 or higher</b>						
GRID	30/132	2/66	7.5 (1.8, 30.4)	23	3	-0.2 (-0.3, -0.1)

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

Source: Table B-18, p108 Table B-39, p138 and Table B-40, p139 of the submission.

- 6.20 On the basis of direct randomised evidence presented by the submission, for patients treated with regorafenib in comparison to BSC, there would be:
- Approximately 119 days (3.9 months) difference in median PFS.
  - An unknown possible difference in median OS.
- 6.21 On the basis of direct randomised evidence presented by the submission, for every 100 patients treated with regorafenib in comparison to BSC:
- Approximately 51 additional patients would experience at least one treatment-emergent adverse event of Grade 3 or greater severity.
  - Approximately 20 additional patients would experience a HFSR of at least Grade 3 severity.
  - Approximately 20 additional patients would experience hypertension of at least Grade 3 severity.

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

**Clinical claim**

- 6.22 The submission described regorafenib as superior in terms of comparative effectiveness and inferior in terms of comparative safety over BSC.
- 6.23 The ESC considered this claim is adequately supported for PFS. However, the ESC noted that insufficient basis was provided to show that PFS is a valid surrogate for predicting the extent of any effect on OS in GIST. Furthermore, the method of adjustment for crossover may overestimate the effect on OS. Accordingly, the existence and magnitude of any benefit in terms of OS derived from regorafenib is difficult to ascertain due to crossover following progression.

6.24 The PBAC considered that the claim of superior comparative effectiveness was adequately supported by the data for PFS, but not for OS.

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

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

### Economic analysis

6.26 The submission presented a modelled economic evaluation (cost utility analysis) based on claim of superior efficacy against placebo (BSC). The model structure is summarised below.

#### Summary of model structure and rationale

Component	Summary
Time horizon	5 years in the model base case versus 147 days in trial (PFS)
Outcomes	Life-years gained, quality-adjusted life-years gained
Methods used to generate results	Expected value analysis. Cost utility model with three health states: progression-free, progression and death.
Cycle length	28 days, with half-cycle correction. This is reasonable.
Transition probabilities	A time-dependent health state distribution models used. Kaplan-Meier estimates of probability being alive and alive in progression-free state used from GRID trial patient-level data; parametric extrapolation used for estimates beyond the duration of the trial.
Discount rate	5% for costs and outcomes
Software package	Excel 2010
Utility values	EQ-5D results from GRID: Progression-free state (regorafenib or placebo): 0.767 Post-progression state (regorafenib or placebo): 0.647 The omission of disutility values for regorafenib-related adverse events in the submission is not reasonable.

Abbreviations: PFS=progression-free survival.

Source: compiled during the evaluation

#### Key drivers of the model

Description	Method/Value	Impact
Time horizon	5 years; assumed from 147 days in trial	High, favors regorafenib
OS adjustment (cross over)	IPE and RPSFT	High, favours regorafenib (compared with ITT)
Regorafenib post-progression cost	Not included	Unknown (likely relatively modest), favours regorafenib

Abbreviations: IPE=iterative parameter estimation; RPSFT=rank preserving structural failure time; OS=overall survival.

Source: compiled during the evaluation

#### Results of the economic evaluation

Component	Regorafenib	Placebo	Increment
Costs	\$ [REDACTED]	\$27.18	\$ [REDACTED]
LYs	2.165	1.552	0.613
QALYs	1.467	1.018	0.449
<b>Incremental cost per LY gained</b>			\$ [REDACTED]
<b>Incremental cost per QALY gained</b>			\$ [REDACTED]

Abbreviations: LY=life year; QALY=quality-adjusted life year.

Source: Section D regorafenib.xls

**Results of sensitivity analyses carried out during the evaluation**

Analysis parameter	Base case ICER: \$ [REDACTED]	
	Value	ICER
Time horizon	3 years	\$ [REDACTED]
	10 years	\$ [REDACTED]
Discount rate	7%	\$ [REDACTED]
	3%	\$ [REDACTED]
OS adjustment (cross over)	Unadjusted	\$ [REDACTED]
	RPSFT	\$ [REDACTED]
PFS data	PFS	\$ [REDACTED]
PFS/TTP extrapolation	Log logistic	\$ [REDACTED]
	Weibull	\$ [REDACTED]
OS extrapolation	Log logistic	\$ [REDACTED]
	Weibull	\$ [REDACTED]
PFS utilities (+/- 20%)	0.6136	\$ [REDACTED]
	0.9204	\$ [REDACTED]
PPS utilities (+/-20%)	0.5176	\$ [REDACTED]
	0.7764	\$ [REDACTED]
PFS utilities (by treatment group) from Section C.3 of the commentary	PF (placebo): 0.583 PF (regorafenib): 0.702 Progressed disease (both groups): 0.649	\$ [REDACTED]
Regorafenib cost +/-10%	\$ [REDACTED]	\$ [REDACTED]
	\$ [REDACTED]	\$ [REDACTED]
Dose intensity %	100%	\$ [REDACTED]
	80%	\$ [REDACTED]
PFS background cost (REG; BSC)	\$200; \$100	\$ [REDACTED]
	\$100; \$200	\$ [REDACTED]
PPS background cost	\$200	\$ [REDACTED]

Source: Table D-8, p214, of the submission

- 6.27 The one-way sensitivity analyses suggested that the model was most sensitive to the comparative effect of treatment on OS (i.e. choice to adjust OS estimates), time horizon of the analysis, and the OS extrapolation method. However, the submission did not use the available utility values from QLQ-C30, or EQ-5D split by health states. Monitoring and maintenance cost for regorafenib-related symptoms (such as liver testing) were also not included.
- 6.28 The submission underestimated the cost of regorafenib-related mentoring cost for liver tests, and haemorrhage symptoms (as indicated in the Australian Product Information). These costs may double in Year 1, and be substantially higher than estimated by the submission in Years 2 to 5.
- 6.29 The PSCR presented a revised economic evaluation which included updated OS data (January 2014), noting that the best fitting parametric model for the updated OS data was log logistic, rather than exponential. The revised model also included symptom-related management costs, post-progression regorafenib, and changes to the extrapolation area. The revised model presented a reduced base case ICER of \$15,000/QALY - \$45,000/QALY (compared with \$45,000/QALY – \$75,000/QALY in the submission).

**Results of the updated economic evaluation presented in the PSCR**

Component	Regorafenib	Placebo	Increment
Costs	\$ [REDACTED]	\$17.33	\$ [REDACTED]
LYs	1.921	0.970	0.951
QALYs	1.309	0.642	0.668
<b>Incremental cost per LY gained</b>			\$ [REDACTED]
<b>Incremental cost per QALY gained</b>			\$ [REDACTED]

Abbreviations: LY=life year; PSCR = pre-sub-committee response; QALY=quality-adjusted life year.  
Source: PSCR.

**Comparison of the regorafenib original model, with the model presented in the PSCR**

Analysis	Value		ICER	Δ from the base case in original submission
	Original Submission	New model provided in PSCR		
Original model (base case)	January 2012	-	\$ [REDACTED]	
PSCR updated OS data and analysis (base case)	-	January 2014	\$ [REDACTED]	-9%
Breakdown of parameter impact on the old model				
Symptom management cost	\$0	\$100	\$ [REDACTED]	3%
Post-progression regorafenib	Not included	Included	\$ [REDACTED]	32%
OS parametric extrapolation	Exponential	Log logistic	\$ [REDACTED]	25%
OS data extrapolation	End of trial data	Entirely parametric	\$ [REDACTED]	-8%

Abbreviations: ICER=incremental cost effectiveness ratio; OS=overall survival; PSCR = pre-sub-committee response.  
Source: PSCR, revised GIST model spreadsheet.

6.30 The ESC noted that:

- The regorafenib-related symptom management costs had little impact on the ICER; the impact of \$100 increases the ICER slightly, by 3%.
- The ICER was sensitive to the inclusion of post-progression regorafenib, and to the choice of OS data extrapolation point.
- To a lesser extent, the ICER was also sensitive to the choice of the OS parametric extrapolation. (Note that the Akaike's Information Criteria<sup>1</sup> values for extrapolation could not be verified because the raw data was not provided.)

6.31 Adverse event related disutility values were not included in the economic analysis. This omission favoured regorafenib. The PSCR presented sensitivity analyses on the updated economic evaluation of varying the utility for regorafenib patients on treatment. Reducing the regorafenib utility from 0.767 to 0.717 increased the ICER from \$15,000/QALY - \$45,000/QALY (base case) to \$45,000/QALY – \$75,000/QALY.

6.32 The ESC considered that, given the large number of changes to the model in the PSCR, it was difficult to assess the validity and impact of all the individual changes. In particular, the choice of the parametric model (including supportive evidence) and the inclusion of post-progression regorafenib were unable to be evaluated as the details and justification for the changes were unclear.

6.33 The PBAC considered that the economic analysis was overly optimistic. The QALY gain was considered to be overestimated, as it was based on adjusted OS data that

<sup>1</sup> K.P. Burnham and D.R. Anderson, Multimodel Inference: Understanding AIC and BIC in Model Selection, Sociological methods and research, 33 (2004), 261–304.

could not be relied upon and did not take account of disutilities associated with adverse events.

- 6.34 The PBAC considered that a worst case scenario would only consider the QALY gain resulting from the difference in median PFS (a gain of 0.027531 QALYs). This scenario would result in an ICER in the order of more than \$200,000/QALY. As a pragmatic way forward in this instance, the PBAC also proposed that an upper estimate with the observed trial-based 3.9 month gain in median PFS translated into a 3.9 month incremental OS in the model. In this case, the QALY gained (of 0.310) would translate to an ICER of around \$75,000/QALY – \$105,000/QALY. The PBAC noted that if this scenario was applied in the model, a significant reduction in the price of regorafenib would be required to result in a sufficiently cost-effective ICER.

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

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

- 6.35 The total cost for regorafenib per patient per year was estimated to be \$ [REDACTED]. This cost was based on the requested effective dispensed price for maximum quantity (DPMQ) of \$ [REDACTED] and the average number of packs per patient per year 11.39 (based on estimated 13.04 packs per patient per year with a dose intensity of 87%).

**Estimated PBS usage & financial implications**

- 6.36 This submission was not considered by DUSC. The submission used a mixed market share and epidemiological approach.
- 6.37 The submission presented drug cost per year for the five years. The submission used the requested effective DPMQ of \$ [REDACTED] to estimate the total cost of regorafenib in Year 1 to Year 5. The number of regorafenib eligible patients treated per year was used to estimate the total number of packs dispensed per year.

**Net cost of regorafenib to government health budgets**

	Year 1	Year 2	Year 3	Year 4	Year 5
Patients treated with regorafenib	█	█	█	█	█
Uptake rate (regorafenib)	█%	█%	█%	█%	█%
Estimated number of packs per year per patient	█	█	█	█	█
Dose intensity	█%	█%	█%	█%	█%
Average packs per year per patient	█	█	█	█	█
Number of packs dispensed per year (regorafenib 40 mg tablet, pack of 84 tablets)	█	█	█	█	█
<b>Total cost of regorafenib (DPMQ)</b>	\$█	\$█	\$█	\$█	\$█
Cost to PBS/RPBS for drugs to treat regorafenib-related AEs	\$█	\$█	\$█	\$█	\$█
<b>Net cost to PBS/RPBS</b>	\$█	\$█	\$█	\$█	\$█
Net cost to MBS	\$█	\$█	\$█	\$█	\$█
Net cost to for DHS processing	\$█	\$█	\$█	\$█	\$█
<b>Net cost of regorafenib to government health budgets</b>	\$█	\$█	\$█	\$█	\$█

Source: Tables E-9 and E-10, pp 229-230, of the submission

The redacted table above shows that in Year 5, the estimated number of regorafenib packs would be less than 10,000 and the net cost to Government would be less than \$10 million per year.

- 6.38 The estimated number of patients eligible for third-line therapy was dependent on the method used. The submission used UK disease prevalence estimates to estimate imatinib (first-line treatment) patients in Years 1 to 5 (less than 10,000 patients in Year 5). The evaluation indicated that a linear projection of PBS 10% sample data provided by DUSC resulted in a larger number of imatinib patients (with less than 10,000 in Year 5) and therefore a larger number of patients eligible for second- (sunitinib) and third-line (regorafenib) treatment. The PSCR noted that the sponsor was willing to discuss the most relevant approach during the post-approval process.
- 6.39 The uptake rates (65% in year 1) for regorafenib use may be underestimated, given that this is the only treatment option for third-line therapy.
- 6.40 It is possible that leakage may occur outside of the proposed listing, in post-progression; since 30.8% in the regorafenib group in GRID trial received regorafenib post-progression. This was not considered in the economic analysis or the financial implications. The PSCR argued that the treatment time post-progression was relatively short at around 2 weeks (compared with the median duration of therapy of 23 weeks).
- 6.41 At year 5, the estimated number of patients would be less than 10,000 and the net cost to the PBS would be less than \$10 million.

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

## Quality Use of Medicines

- 6.42 The sponsor stated that, should regorafenib be reimbursed on the PBS, it would undertake activities to support patients who experience HFSR (including providing a patient information booklet, a urea-based moisturising cream, a pair of cotton gloves and cotton foot gloves).

## Financial Management – Risk Sharing Arrangements

- 6.43 The submission requested an effective 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. No risk sharing arrangements were proposed.

## 7 PBAC Outcome

- 7.1 The PBAC rejected the request to list regorafenib for the treatment of patients with GIST on the basis of uncertain efficacy and cost-effectiveness. The PBAC accepted that regorafenib provides a clinical benefit to patients in terms of PFS, but considered that the adjusted estimates of OS could not be relied upon and the adverse effect profile of regorafenib was not adequately reflected in the model. Given the small clinical benefit due to PFS and the unfavourable safety profile of regorafenib, the PBAC considered that the ICER per QALY gained was highly uncertain.
- 7.2 The PBAC noted the proposed restriction and agreed that the addition of a criterion requiring the patient to have a WHO performance status of 0 or 1, in line with the eligibility criteria in the trial, was appropriate.
- 7.3 The PBAC accepted the clinical place for regorafenib for GIST as third-line treatment following failure with or intolerance to imatinib and sunitinib.
- 7.4 The PBAC agreed that BSC was the appropriate comparator.
- 7.5 The PBAC noted that the TGA Clinical Evaluation Report (CER) stated that the benefit of regorafenib, demonstrated by an improvement in PFS and suggested improvement in OS, outweighs its unfavourable safety profile. The CER stated that regorafenib is associated with well-documented common adverse effects including HFSR, fatigue, diarrhoea, and hypertension and serious adverse effects of acute hepatic toxicity with fatal occurrences, sudden cardiac death, gastrointestinal perforation and bleeding risk.
- 7.6 The PBAC noted the submission presented the results of a randomised, double-blind, placebo-controlled, multi-centre, crossover phase 3 trial (GRID), comparing regorafenib + BSC (n=133) to placebo + BSC (n=66). The primary outcomes were PFS and OS. With regard to OS, the results were not statistically significant for the ITT analyses, with a HR for OS of 0.772 (95% CI: 0.423, 1.408) at the January 2012 data cut-off and 0.849 (95% CI: 0.597, 1.206) at the January 2014 data cut-off. Median OS had been reached at the January 2014 cut-off, with both treatment arms recording 17.4 months median OS.
- 7.7 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 85% of patients crossing over from placebo to regorafenib at progression;
- the small number of patients upon which the adjustment methods are based, with only 10 patients randomised to placebo who did not crossover to regorafenib;
- progression events, which were the trigger for crossover, were assessed using radiological review 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; and
- 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 regorafenib 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 results for OS.

- 7.8 The PBAC noted that unadjusted median OS to January 2014 was 17.4 months in both treatment groups. Due to the issue of crossover (as discussed in paragraph 7.7), the OS ITT results are effectively a comparison of early versus late treatment with regorafenib. The PBAC considered that it could not conclude that regorafenib improves OS compared with BSC on the basis of the RPSFT adjusted estimates of median OS (of 17.4 months for the regorafenib treatment group and 8.7 months for placebo).
- 7.9 The PBAC considered the gain in median PFS of 119 days (or 3.9 months) associated with regorafenib treatment was clinically meaningful. The PBAC also noted that treatment with regorafenib was associated with a higher incidence of treatment-emergent adverse events, HSFR, and hypertension (all of grade 3 or greater severity) compared with placebo (see paragraphs 6.15 and 6.18).
- 7.10 The submission described regorafenib as superior in terms of comparative effectiveness and inferior in terms of comparative safety over BSC. The PBAC considered that, given the discussion outlined in paragraphs 7.7 to 7.9, this claim was adequately supported for superior comparative effectiveness in terms of PFS and inferior comparative safety, compared with BSC. However, the claim of superior comparative effectiveness was not adequately supported for OS. While regorafenib has some clinical benefits, these appear to be largely negated by clinical harms.

- 7.11 The PBAC noted that the PSCR presented a revised economic model that used the more mature OS data to January 2014 and included symptom-related management costs, post-progression regorafenib, OS parametric extrapolation and changes to the extrapolation area. The PBAC noted that the ESC considered that, given the large number of changes to the model in the PSCR, it was difficult to assess the validity and impact of all the individual changes.
- 7.12 The PBAC noted that the cost utility analyses presented in the submission and PSCR were not reasonable as they were based on QALYs gained resulting from the adjusted OS estimates that could not be relied upon. The PBAC considered that the modelled gain in median OS of 8.7 months in the PSCR's economic evaluation was implausible given that the trial had observed no statistically significant gain in median OS in the ITT analysis and a 3.9 month gain in median PFS. Accordingly, the ICER presented in the PSCR of \$15,000/QALY - \$45,000/QALY gained was considered to be a significant underestimate. Furthermore, the PBAC considered that the omission of adverse event related disutility values in the economic analysis was not reasonable, particularly given the unfavourable side effects profile of the drug, and overestimated the QALY gain associated with treatment with regorafenib.
- 7.13 The PBAC considered the potential range within which any OS estimate 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 3.9 month delay in median time to progression (i.e. no LYs gained in the model, leaving a 0.027 gain in QALYs). As a pragmatic way forward, in this instance, the PBAC also proposed an upper estimate with the observed trial-based 3.9 month gain in median PFS translated into incremental OS of 3.9 months in the model. Given the issues outlined in paragraph 7.7, the PBAC considered that such an assumption would be highly favourable to regorafenib, however the PBAC considered that the benefit of the doubt in this upper estimate would be appropriate in this particular case (see paragraph 6.34) 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.
- 7.14 The PBAC noted that the estimates of utilisation of regorafenib may have been underestimated. The pre-PBAC response indicated that the sponsor "is willing to discuss the most relevant approach during the post-approval process".
- 7.15 The PBAC considered that a major resubmission would be required to request further consideration of recommending listing of regorafenib for GIST. The resubmission should present the updated model that was presented in the PSCR for evaluation under less optimistic assumptions regarding incremental OS. As discussed in paragraph 7.13, a pragmatic way forward could be to propose an upper estimate for modelled incremental OS to be translated directly from the observed gain in median PFS. In addition, the PBAC considered that the resubmission should include adverse event related disutilities in the economic analysis. If these changes are made to the model, the PBAC noted that a significant reduction in the price of regorafenib may be required to result in a sufficiently cost-effective ICER.

7.16 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.