

## 7.03 REGORAFENIB, Tablet 40 mg (as monohydrate), Stivarga<sup>®</sup>, Bayer Australia Limited.

### 1 Purpose of Application

- 1.1 The resubmission requested a Section 85, Authority Required (STREAMLINED) listing for regorafenib for treatment of patients with unresectable hepatocellular carcinoma (HCC) who progressed following treatment with sorafenib. The first submission was rejected by the PBAC at its March 2018 meeting.
- 1.2 The resubmission presented one head to head clinical trial (RESORCE) which formed the basis of a cost-effectiveness analysis against best supportive care (BSC).

**Table 1: Key components of the clinical issue addressed by the resubmission**

Component	Description
Population	Patients with advanced HCC who have progressed after treatment with sorafenib.
Intervention	Regorafenib 40 mg oral tablet administered four times daily (total 160 mg) at the same time each day for three weeks (21 days) followed by one week off therapy (7 days) to comprise a cycle of four weeks.
Comparator	Best supportive care (BSC).
Outcomes	Primary: OS Secondary: PFS; TTP; ORR; disease control rate (CR + PR + SD); duration of response; duration of stable disease. Tertiary: HRQoL and utility values; pharmacokinetics (PK); biomarker evaluation.
Clinical claim	Regorafenib is superior to BSC for the treatment of advanced (unresectable) HCC, providing a statistically significant and clinically significant increase in OS but is associated with a higher incidence of drug related adverse events which were well tolerated and with no clinically significant impact on QoL. The clinical claim was supported by the data presented with respect to OS but may not be supported with respect to the impact of adverse events on QoL.

Abbreviations: BSC= Best supportive care; CR= complete response; HCC= Hepatocellular carcinoma; HRQoL= health related quality of life; ORR= objective tumour response rate; OS= overall survival; PFS= progression free survival; PR= partial response; QoL= quality of life; SD= stable disease; TTP= time to progression

Source: Table 1-1 p. 16 of the resubmission, Executive summary p. vi of the resubmission.

### 2 Requested listing

- 2.1 The requested restriction is summarised below and is largely consistent with the RESORCE trial.

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Name, Restriction, Manner of administration and form	Max. Qty (packs)	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
REGORAFENIB (STIVARGA®) 40 MG ORAL TABLET, 28	3	2	\$ [REDACTED] published effective	Stivarga	Bayer
Category/Program:	GENERAL				
PBS indication:	For the treatment of patients with hepatocellular carcinoma (HCC) who have progressed on sorafenib treatment				
Treatment phase:	Initial and continuing				
Restriction:	Authority Required (STREAMLINED)				
Treatment criteria:	The treatment must be the sole PBS-subsidised therapy for this condition				
Clinical criteria:	<p><u>Initial:</u> Patient must have a WHO PS of 1 or less, must have Child Pugh class A, must have received prior treatment with sorafenib for a minimum of 20 days at a minimum dose of 400 mg QD and patient must have progressed on sorafenib treatment</p> <p><u>Continuation:</u> The patient must have previously been treated with PBS-subsidised regorafenib AND The patient must only be treated until disease progression OR until no further clinical benefit is observed.</p> <p>Clinical benefit defined as:</p> <ul style="list-style-type: none"> <li>- the absence of deterioration of ECOG status (e.g. ECOG should not deteriorate from baseline status: 0 to 2 or higher, from 1 to 3 or higher)</li> <li>- and/or absence of deterioration of liver function (jaundice, uncontrolled ascites, encephalopathy).</li> </ul>				

Abbreviations: HCC= hepatocellular carcinoma; Max= maximum; PS= performance status; QD= once daily; Qty= quantity; Rpts= repeats; WHO= World Health Organization

2.2 The resubmission proposed a special pricing arrangement (SPA), with price [REDACTED] % lower than had been proposed in the March 2018 submission (DPMQ \$ [REDACTED]).

2.3 The restriction proposed in the resubmission may not reflect the eligible population in Australia and may represent differences in the circumstances of use due to:

- Differences in the severity of Barcelona Clinic Liver Cancer between the proposed restriction (stage C only) and the RESORCE trial study entry (stage A, B and C);
- Differences in the proposed performance status (PS) criterion. The RESORCE trial enrolled patients with an ECOG  $\leq 1$ , the proposed restriction is WHO PS  $\leq 1$  while the current PBS listing for sorafenib is a WHO PS  $\leq 2$  (ECOG has the same scoring levels as WHO PS). Therefore, the proposed PBS patient population is limited to patients healthier than those eligible for sorafenib. The ESC noted that patients progressing on sorafenib with a WHO PS of 2 would not be eligible for treatment with regorafenib, thus limiting treatment to a healthier subset of the sorafenib population.
- The proposed restriction stated patients should be treated only until disease progression OR until no further clinical benefit is observed. The PBAC had requested that the proposed PBS listing should not permit use in patients beyond disease progression (paragraph 7.3 regorafenib PSD, March 2018 PBAC meeting). Including a criterion based on 'no further clinical benefit' may be difficult to administer in clinical practice. Although the resubmission did define 'clinical benefit', testing for changes in these performance factors (on an ongoing basis or

when deterioration is suspected) may not be practical for clinicians and patients to follow. The ESC considered that ‘clinical benefit’ was not sufficiently defined in the revised restriction and noted that it was unclear whether the WHO PS and liver function status that form the basis of this criteria would be impacted by treatment rather than specifically reflecting the underlying disease. The ESC considered that the listing should not allow treatment beyond progression. The ESC considered that treatment beyond progression is unlikely to benefit patients overall and is unlikely to be cost-effective. The ESC noted that clinical progression is not always equivalent to radiological progression. A criterion of “patient must only be treated until disease progression” would allow clinicians to determine when disease progression has occurred and treatment should be discontinued. The pre-PBAC response indicated that the sponsor accepted the simpler continuation criteria recommended by ESC if the PBAC considers it is more appropriate.

- The ESC noted that the resubmission stated the sponsor was amenable to including a criterion related to patients’ HIV status: “Patients must not be HIV immunocompromised”. The ESC considered this may be appropriate in order to align the patient population with the trial population.

2.4 The PSCR confirmed that the sponsor intends to grandfather patients on existing therapy and these patients were accounted for in the estimated financial impact. The sponsor requested that a grandfathering clause be included in the listing notes. Patients treated with regorafenib in an access program prior to PBS listing still need to qualify for PBS treatment under initial restriction criteria. It is unclear if patients who have previously been treated with lenvatinib in an access program would qualify under the initial restriction criteria or if a separate initial restriction is required.

*For more detail on the PBAC’s view, see section 7 PBAC outcome.*

### 3 Background

#### **Registration status**

3.1 Regorafenib was TGA approved for advanced HCC on 21 December 2017.

#### **Previous PBAC consideration**

3.2 A summary of the matters of concern raised with respect to the March 2018 submission, and how they have been addressed in the November 2018 resubmission is provided in Table 2.

**Table 2: Summary of outstanding matters of concern**

Component	Matter of concern	How the resubmission addresses it
Applicability issues	The PBAC noted that the RESORCE trial enrolled patients with an ECOG ≤1 while the current PBS listing for sorafenib is for patients with WHO PS ≤2.	Addressed by clarifying that the performance status is WHO 1 or less. A discrepancy remains between the WHO PS for sorafenib and that proposed for regorafenib.

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Component	Matter of concern	How the resubmission addresses it
	The PBAC considered that the listing should be for patients with WHO PS $\leq$ 1. (p. 2.3 Mar-18 PSD)	
Applicability issues: proposed restriction vs. eligible population	The RESORCE trial excluded patients with a known history of HIV. The pre-PBAC response noted the sponsor was amenable to including a criterion related to patients' HIV status, for example, "Patients must not be HIV immunocompromised" (p. 2.3 Mar-18 PSD).	The resubmission noted the sponsor was amenable to including a criterion related to patients' HIV status: "Patients must not be HIV immunocompromised".
Applicability issues: proposed restriction vs. eligible population	The PBAC noted that 'Patients must only be treated until disease progression' as the use of regorafenib beyond progression is unlikely to be cost effective (p. 7.3 PSD Mar-18).	The resubmission included a revised restriction that permitted use in patients with ongoing clinical benefit. This does not reflect the PBAC request.
Applicability issues: proposed restriction vs. eligible population	The PBAC noted that a higher proportion of patients in Doyle et al (2016) compared to patients in the RESORCE trial had worse liver function and worse ECOG performance status. The PBAC also noted that patients in the RESORCE trial had an average treatment duration with sorafenib of 7.8 months compared with 5.3 months in the SHARP trial (the pivotal trial for sorafenib in HCC). The PBAC considered that patients recruited into the RESORCE trial are likely to be younger and fitter, tolerate systemic therapies better, and have longer survival, compared to the Australian population for the requested listing (p 6.8 Mar-18 PSD).	The resubmission stated that aligning the proposed PBS restriction to the eligibility criteria for the RESORCE trial would ensure that Australian patients accessing regorafenib are comparable to those in the clinical evidence.
Clinical claim/ Safety issues	The PBAC considered that the evidence presented in the submission did not support the submission's initial claim of no significant impact of regorafenib toxicity on QoL, and that the claim of inferior safety compared with BSC was appropriate. The PBAC considered that overall, regorafenib was associated with a range of substantial AEs, which may be more frequent and severe in the proposed Australian population compared with the trial population (p 7.8 PSD Mar-18).	The resubmission included a revised claim of "inferior safety".
Trial data	A resubmission should be based on the latest available data from the RESORCE trial (p. 7.12 Mar-18 PSD)	The resubmission presented the latest available data (Cut-off: 23JAN17).
Economic Issues	The ESC advised that additional univariate analyses and multivariate analyses testing the following assumptions would be informative: <ul style="list-style-type: none"> <li>• extrapolating <u>both</u> regorafenib and BSC arms;</li> <li>• applying extrapolations from different time points, including from the point of median follow-up;</li> <li>• using all observed survival data (i.e. from day 1) to inform the parametric function used to undertake the extrapolations; and</li> <li>• applying trial-based within treatment group utility values.</li> </ul> (p 6.43 Mar-18 PSD).	The resubmission has <ul style="list-style-type: none"> <li>• Extrapolated both the regorafenib and BSC arms;</li> <li>• Used all observed survival data (i.e. from day 1) to inform the parametric function used to undertake the extrapolations; and</li> <li>• Applied trial-based utility values.</li> </ul> However, extrapolations were applied from the point of median survival, and not median follow-up.

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Component	Matter of concern	How the resubmission addresses it
Economic Issues	The PBAC had requested that the base case ICER should be less than \$██████/QALY to reflect the substantial toxicity of the drug (Mar-18 PSD, Section 7.12).	The resubmission presented an ICER that decreased from \$██████/QALY (in pre-PBAC response in March 2018) to \$██████/QALY. A further 42% price reduction from the price in the resubmission would result in an ICER of \$██████/QALY (effective DPMQ of \$██████).
Financial Impact Issues	Financial estimates were over-estimated due to: an overestimated eligible patient pool and uptake rates, inclusion of patients with ECOG PS>1, and the assumption of treatment beyond progression (p 7.11 Mar-18 PSD).	The resubmission assumed a lower proportion in terms of patient eligibility (60% as compared to 70% in the March 2018 submission) to account for the sorafenib clinical criteria (ECOG ≤ 2) being broader than proposed for regorafenib (WHO PS ≤ 1). The resubmission did not adjust for the potential impact on the estimated cost to Government of restricting PBS treatment to those without disease progression.
Financial Impact Issues	The PBAC noted that treatment related costs for medical visits, pathology, diagnostics and AEs were included in the economic model but no costs to the MBS were included in the financial estimates. The PBAC advised that costs to the MBS should be included in the financial estimates (p 6.58 Mar-18 PSD).	This was not addressed in the resubmission noting that: “costs to the MBS were not included in the financial estimates because the drug-related TEAEs are assumed to require hospitalisation based on their severity”. An argument could be made that there will be increased service use due to ongoing survival beyond the impact on AE treatment. This is likely to have a negligible impact on the costs to Government.

Source: Regorafenib Mar-18 Public Summary Document and resubmission Mar-18 – see right-hand column for exact location details.  
Abbreviations: BSC= Best supportive care; CR= complete response; DPMQ= dispensed price maximum quantity; ECOG= Eastern Cooperative Oncology Group; HCC= Hepatocellular carcinoma; ESC= Economics Sub Committee; HIV= human immunodeficiency virus; HRQoL= health related quality of life; ICER= incremental cost effectiveness ratio; OS= overall survival; PBAC= Pharmaceutical Benefits Advisory Committee; PFS= progression free survival; PR= partial response; PS= performance score; PSCR= pre-subcommittee response; PSD= public summary document; QALY= quality adjusted life years; QoL= quality of life; SD= stable disease; TTP= time to progression; vs= versus; WHO= World Health Organization

*For more detail on the PBAC’s view, see section 7 PBAC outcome.*

## **4 Population and disease**

- 4.1 HCC is the second-commonest cause of cancer-related death worldwide. It is more common in males and approximately 90% of cases are associated with underlying chronic liver disease and liver cirrhosis. The most common aetiologies include chronic hepatitis B and C virus (HBV, HCV), alcohol abuse, and aflatoxin exposure. A reduction in the number of HCV cases progressing to cirrhosis (and potentially HCC) since new antiviral therapies became available on the PBS could reduce the future incidence of HCC. The prevalence of HCC closely mirrors the annual incidence, which is consistent with the presentation of patients with HCC typically at a late stage with poor survival prognosis.
- 4.2 Regorafenib is only registered for use following sorafenib therapy and the proposed PBS listing is as a second line treatment of patients who progress following treatment with sorafenib. Lenvatinib is an alternative first line treatment which was deferred at the July 2018 PBAC meeting and was considered at the November 2018 meeting. The proposed listing for regorafenib would not allow patients treated with lenvatinib to access second line regorafenib and this may create an incentive for patients to preferentially be treated with sorafenib in the first line setting. The ESC noted that lenvatinib is likely to be the preferred first line therapy for advanced HCC if available on the PBS. The ESC advised that the proposed restriction for regorafenib should be revised to allow use following either lenvatinib or sorafenib, although noted there are no clinical trials assessing the use of regorafenib following lenvatinib, and that lenvatinib and sorafenib are sufficiently different that it may not be appropriate to assume that treatment with regorafenib after lenvatinib failure would be equivalent to treatment after sorafenib failure. The ESC further noted that guidelines currently recommend regorafenib as second line treatment in HCC after sorafenib, however it is likely that in the next few years other drugs will become available for second line treatment of HCC, such as cabozantinib. The PBAC noted that nivolumab, pembrolizumab and ramucirumab are included as second line treatments in NCCN guidelines (version 4.2018) and may also become available for second line treatment of HCC. The pre-PBAC response acknowledged that other drugs will become available in this setting but maintained that it would not be appropriate to allow use of regorafenib following lenvatinib, claiming that the sequence of sorafenib and regorafenib offers the most cost-effective and evidence-based option for advanced HCC.

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

## 5 Comparator

- 5.1 The resubmission nominated BSC as the main comparator. The RESORCE trial defined BSC as any intervention including concomitant medications, medical procedures, psychotherapy, growth factors, palliative surgery or any other symptomatic therapy except for anti-tumour agents or anti neoplastic chemotherapy, or hormonal or immunotherapy. The ESC considered this was appropriate.

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

## 6 Consideration of the evidence

### **Sponsor hearing**

- 6.1 There was no hearing for this item.

### **Consumer comments**

- 6.2 The PBAC noted that no consumer comments were received for this item.
- 6.3 The PBAC noted input from Eisai (the sponsor for lenvatinib) requesting that regorafenib not be limited to use after initial treatment with sorafenib but rather after progression on or intolerance to a first line TKI. The letter also noted that Eisai is currently undertaking a clinical study of initial lenvatinib followed by the treatment of physicians' choice, including regorafenib, sorafenib or cabozantinib, which would investigate the clinical benefit of sequential use of TKIs.
- 6.4 The Medical Oncology Group of Australia (MOGA) expressed its strong support for the regorafenib submission, categorising it as one of the therapies of "high priority for PBS listing" on the basis of the RESORCE trial. The PBAC noted that the MOGA presented the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for regorafenib, which was limited to 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)<sup>1</sup>, based on a comparison with placebo.

### **Clinical trials**

- 6.5 The resubmission was based on one head to head trial comparing regorafenib with BSC, RESORCE trial (n=573). Details of the trial presented in the resubmission are provided in Table 3. The resubmission noted that this has been published in 25 publications (see Table 2-10, p. 50-52 of the resubmission for details).

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<sup>1</sup> Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017

**Table 3: Trials and associated reports presented in the resubmission**

Trial ID	Protocol title/ Publication title	Publication citation
RESORCE	A randomised, double blind, placebo-controlled, multicenter phase III study of regorafenib in patients with hepatocellular carcinoma (HCC) after sorafenib	Bayer Healthcare AG: Clinical Study Report: 23 September 2016 ClinicalTrials.gov identifier: NCT01774344  Clinical study report cut-off 23 January 2017.
	Key publication: Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial.	Bruix J et al. 2017. Lancet, 389, 56-66.

Source: Table 2-10, p. 50-52 of the resubmission.

6.6 The key features of the direct randomised trial are summarised in Table 4.

**Table 4: Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
<b>Regorafenib vs. BSC</b>						
Bruix 2017	573	R, DB, MC 33 months (Feb-16 cut-off) 46 months (Jan-17 cut-off)	Low	Progressed following sorafenib.	OS, PFS	Survival and progression free gain.

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

6.7 The trial design had a low risk of selection, performance, detection, attrition and reporting bias. The resubmission acknowledged that hand-foot reaction is a known adverse event for tyrosine kinase inhibitors, so its occurrence was a potential unmasking factor associated with regorafenib treatment. Patients in RESORCE were permitted to continue treatment beyond progression, at the discretion of the clinical investigator. The ESC noted that 48% of patients in RESORCE were treated post progression, and 37% were treated for 7 days or more after radiological progression.

6.8 The resubmission presented updated OS and PFS results (cut-off date 23<sup>rd</sup> January 2017) which provided 11 additional months of data from the primary analysis (cut-off date 29<sup>th</sup> February 2016). These data were presented in the PSCR and Pre-PBAC Response for the March 2018 submission but were not independently evaluated prior to PBAC consideration in March 2018. No updated information was provided for time to progression (TTP) or Quality of Life (QoL). The resubmission presented updated safety information concerning HFSR adverse events.

### **Comparative effectiveness**

6.9 A significant increase in terms of OS, PFS and TTP was observed for regorafenib compared to BSC. For OS, the estimated hazard ratio was 0.614 (95% CI: 0.501 – 0.753), which implied a 39% reduced risk of death in the regorafenib group compared with the BSC group. For PFS, the estimated hazard ratio was 0.455 (95% CI: 0.372 – 0.557), which implied a 55% reduced risk of progression or death in the regorafenib

group compared with the BSC group. The benefit of regorafenib mainly comes from patients achieving stable disease (54.4% versus 32.0% in the BSC group).

Table 5: Results of overall survival, progression free survival and time to progression in the RESORCE trial

Trial ID: RESORCE	Reg n/N with event (%)	Reg Median time to event (95% CI)	BSC n/N with event (%)	BSC Median time to event (95% CI)	Difference months (95% CI)	P value (log rank test)	HR (95% CI)
Submission Mar-18							
OS	233/379 (61.5%)	10.6 (9.1–12.1)	140/194 (72.2%)	7.8 (6.3–8.8)	2.8 (2.8 – 3.3)	< 0.0001	<b>0.627</b> (0.500 - 0.785)
PFS	293/379 (77.3%)	3.1 (2.8–4.2)	181/194 (93.3%)	1.5 (1.4–1.6)	1.6 (0 – 2.6)	< 0.0001	<b>0.455</b> (0.371 - 0.558)
TTP	274/379 (72.3%)	3.2 (2.9–4.2)	173/194 (89.2%)	1.5 (1.4–1.6)	1.7 (0.1 – 0.9)	< 0.00001	<b>0.442</b> (0.358 - 0.545)
Resubmission Nov-18							
OS	290/379 (76.5%)	10.7 (9.1–12.2)	169/194 (87.1%)	7.9 (6.4–9)	2.8 (2.7 – 3.2)	< 0.00001	<b>0.614</b> (0.501 – 0.753)
PFS	313/379 (82.6%)	3.1 (2.8–4.2)	183/194 (94.3%)	1.5 (1.4–1.6)	1.6 (1.4 – 2.6)	< 0.000001	<b>0.455</b> (0.372 - 0.557)

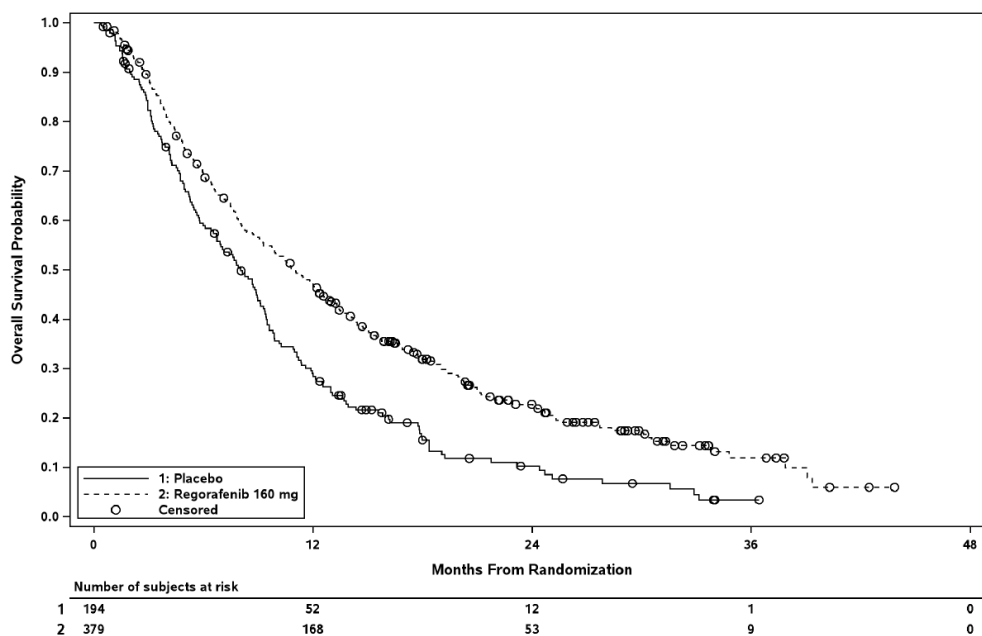
Abbreviations: BSC= Best supportive care; CI = confidence interval; HR = Hazard ratio; OS= overall survival; PFS= progression free survival; TTP= time to progression.

Source: Table 2-27, Table 2-29 to 2-30, p. 86 to 92 of the resubmission.

Note: Bold text indicates a statistically significant value.

6.10 The Kaplan-Meier data are presented in Figure 1. The gain in median OS was 2.8 months.

Figure 1: Kaplan Meier curve for overall survival (Full Analysis Set): 23<sup>rd</sup> January 2017



Source: Figure 2-9, p. 88 of the resubmission.

6.11 The results from the RESORCE trial showed that there were no statistically significant differences in QoL between regorafenib and BSC, despite improved PFS. However, on

average, lower QoL values were observed for regorafenib compared with BSC for all QoL questionnaires. These were statistically significantly lower for the FACT-HEP and Trial Outcomes Index, but did not achieve the minimally important differences for those questionnaires. These lower QoL average values for regorafenib could be explained by the increased toxicity associated with regorafenib. A summary of key QoL outcomes is presented in Table 6.

**Table 6: Results for patient reported outcomes (HRQoL) in the RESORCE trial**

LSM time-adjusted AUC (95% CI)	Reg	BSC	Difference	P value	MID
EQ-5D 3L index	0.76 (0.75-0.78)	0.77 (0.75-0.79)	-0.01 (-0.03-0.02)	0.4695	0.1
EQ-5D VAS	71.68 (70.46-72.90)	73.45 (71.84-75.06)	-1.77 (-3.58-0.04)	0.0558	10
FACT-General	75.14 (74.12-76.16)	76.55 (75.20-77.90)	-1.41 (-2.93-0.11)	0.0698	6-7
FACT-Hep total	129.31 (127.84-130.79)	133.17 (131.21-135.12)	<b>-3.85</b> (-6.06 - -1.65)	0.0006	8-9
Trial outcome index	91.47 (90.30-92.64)	95.52 (93.98-97.07)	<b>-4.05</b> (-5.79 - -2.31)	<0.0001	7-8

Abbreviations: AUC= area under the curve; CI= confidence intervals; FACT= Functional assessment cancer therapy; LSM= least squares mean; MID= minimally important difference; VAS= visual analogue scale.

Source: Table 2-35, p. 100 – 101 of the resubmission.

Note: Bold text indicates a statistically significant value.

6.12 Patients treated with regorafenib were 3 times more likely to suffer any grade 3 or 4 adverse event compared to BSC (Table 7). The data from the RESORCE trial showed that more patients treated with regorafenib (31.6%) reported infections and infestations than patients treated with BSC (17.24%) however the benefit-risk balance in the assessed patient population was positive (TGA Delegate’s Overview regorafenib, Section 4.3, p. 11). This was acknowledged by the TGA and a precautionary warning was included in the PI.

**Table 7: Summary of key adverse events in the RESORCE trial**

	Regorafenib N = 374 (100%)	BSC N = 193 (100%)	Relative risk (95% CI)	Risk difference (95% CI)
<b>Any drug-related AE</b>	<b>346 (92.5%)</b>	<b>100 (51.8%)</b>	<b>1.79 (1.55, 2.05)</b>	<b>0.41 (0.33, 0.48)</b>
Worst CTCAE grade:				
Grade 3	173 (46.3%)	31 (16.1%)	<b>2.88 (2.05, 4.05)</b>	<b>0.30 (0.23, 0.37)</b>
Grade 4	14 (3.7%)	1 (0.5%)	7.22 (0.96, 54.53)	<b>0.03 (0.01, 0.05)</b>
Grade 5 (death)	7 (1.9%)	2 (1.0%)	1.81 (0.38, 8.61)	0.01 (-0.01, 0.03)
Grade 3 or 4	187 (50.0%)	32 (16.6%)	<b>3.02 (2.16, 4.20)</b>	<b>0.33 (0.26, 0.41)</b>
Grade 3, 4 or 5	194 (51.9%)	34 (17.6%)	<b>2.99 (2.17, 4.12)</b>	<b>0.35 (0.28, 0.42)</b>
Serious	39 (10.4%)	5 (2.6%)	<b>4.03 (1.61, 10.05)</b>	<b>0.08 (0.04, 0.12)</b>
Leading to dose modification	202 (54.0%)	20 (10.4%)	<b>5.21 (3.41, 7.97)</b>	<b>0.44 (0.37, 0.50)</b>
Leading to permanent discontinuation of study drug	39 (10.4%)	7 (3.6%)	2.58 (0.57, 11.66)	0.02 (-0.01, 0.04)

Abbreviations: AE= adverse event; BSC= best supportive care; CI = confidence interval; CTCAE= Common Terminology Criteria for Adverse Events; n = number of participants reporting data; N = total participants in group; RD = risk difference; RR = relative risk

Source: Table 2-36, p. 102 of the resubmission.

Note: Bold text indicates a statistically significant value.

### Comparative harms

6.13 Safety data presented in the resubmission were obtained from the RESORCE trial and are summarised in Table 8. There is a boxed warning for hepatotoxicity associated with regorafenib and included as a warning on the PI. The rates of liver-related adverse events and liver failure with regorafenib in the RESORCE trial were not higher when compared with other regorafenib trials (for a different indication). The PI states that in clinical studies, no relevant differences in safety or efficacy were observed between patients with mild hepatic impairment (Child-Pugh A) and normal hepatic function and that close monitoring of overall safety is recommended in patients with moderate hepatic impairment (Child-PughB) as limited data are available in these patients.

**Table 8: Summary of key drug-related TEAEs in the RESORCE trial (more than 5% in either treatment group)**

CTCAE drug related TEAEs	Regorafenib N=374 (100%)			BSC N=193 (100%)			Relative risk (95% CI)	Risk difference (95% CI)
	Grade 3	Grade 4	Total (Grade 3+4)	Grade 3	Grade 4	Total (Grade 3+4)		
Hypertension	48 (12.8%)	0	48 (12.8%)	6 (3.1%)	0	6 (3.1%)	<b>4.13</b> <b>(1.80, 9.47)</b>	<b>0.10</b> <b>(0.06, 0.14)</b>
HFSR	46 (12.3%)	0	46 (12.3%)	1 (0.5%)	0	1 (0.5%)	<b>23.74</b> <b>(3.30, 170.82)</b>	<b>0.12</b> <b>(0.08, 0.15)</b>
Blood bilirubin increased	19 (5.1%)	0	19 (5.1%)	2 (1.0%)	0	2 (1.0%)	<b>4.90</b> <b>(1.15, 20.83)</b>	<b>0.04</b> <b>(0.01, 0.07)</b>
AST increased	17 (4.5%)	3 (0.8%)	20 (5.3%)	9 (4.7%)	1 (0.5%)	10 (5.2%)	1.03 (0.49, 2.16)	0.00 (-0.04, 0.04)

Abbreviations: BSC = best supportive care; CI = confidence interval; CTCAE = Common Terminology Criteria Adverse Event; HFSR= hand-foot skin reaction; n = number of participants reporting data; N = total participants in group; RD = risk difference; RR = relative risk; TEAE = treatment-emergent adverse events.

Source: Table 2-37, p. 104 of the resubmission.

Note: Bold text indicates a statistically significant value.

## Benefits/harms

6.14 A summary of the comparative benefits and harms for regorafenib versus BSC is presented in the table below.

**Table 9: Summary of comparative benefits and harms for regorafenib and best supportive care (BSC) - RESORCE**

Benefits						
Event:	Regorafenib, N=379	BSC, N=194	Absolute difference	HR (95% CI)		
<b>Progression</b>						
PFS at 6 months (%)	28.0%	8.5%	19.5%	<b>0.455 (0.372, 0.557)</b>		
PFS at 12 months (%)	12.7%	2.5%	10.2%			
PFS at 18 months (%)	6.6%	1.2%	5.4%			
PFS at 24 months (%)	4.4%	1.2%	3.2%			
<b>Survival</b>						
Alive at 12 months (%)	46.6%	27.9%	18.7%	<b>0.614 (0.501, 0.753)</b>		
Alive at 18 months (%)	31.9%	15.5%	16.4%			
Alive at 24 months (%)	10.2%	21.9%	11.7%			
Alive at 30 months (%)	16.0%	6.7%	9.3%			
<b>Harms</b>						
RESORCE trial	Regorafenib n/N	BSC n/N	RR (95% CI)	Event rate/100 patients <sup>c</sup>		RD (95% CI)
				Regorafenib	BSC	
Hypertension <sup>a</sup>	49/374	15/193	<b>4.13 (1.80, 9.47)</b>	13.1	7.8	<b>0.10 (0.06, 0.14)</b>
HFSR (grade 3)	47/374	1/193	<b>23.74 (3.30, 170.82)</b>	12.6	<1	<b>0.12 (0.08, 0.15)</b>
HFSR (any grade) <sup>b</sup>	198/374	15/193	6.81 (n.r.)	52.9	7.8	<b>0.45 (n.r.)</b>
Blood bilirubin increased <sup>a</sup>	25/374	4/193	<b>4.90 (1.15, 20.83)</b>	6.7	2.1	<b>0.05 (-0.03, 0.14)</b>
AST increased <sup>a</sup>	19/374	10/193	1.03 (0.49, 2.16)	5.1	5.2	0.00 (-0.04, 0.04)

Notes: <sup>a</sup> Only grade 3 and 4 adverse events are reported. <sup>b</sup> Unknown whether statistically significant due to data being unavailable.

<sup>c</sup> Median duration of follow-up OS: RESORCE Trial = 7 months, Maximum duration of follow-up OS: RESORCE Trial = 33 months.

Abbreviations: AST= aspartate aminotransferase; BSC= best supportive care; HFSR= Hand-foot skin reaction; HR = hazard ratio; n.r.=not reported; RD = risk difference; RR = risk ratio

Source: Table 2-27, Table 2-29, Table 2-37, p. 86 to 89, 104 of the resubmission, Table 14.2.1/1 p6 of 79 (OS) and Table 14.2.1/1 p3 of 10 (PFS) of the updated CSR to the resubmission. HFSR (any grade) calculated from Table 2 data within reference in resubmission: Bruix Updated overall survival analysis (ESMO 19<sup>th</sup> World Congress on Gastrointestinal Cancer) - July 2017

Note: Bold text indicates a statistically significant value.

6.15 On the basis of the direct evidence presented by the resubmission, for every 100 patients treated with regorafenib in comparison to BSC:

- Approximately 5 more patients will remain progression free after 18 months of treatment.
- Approximately 16 more patients will remain alive after 18 months of treatment.
- Approximately 10 more patients will experience hypertension over a duration of exposure of 7 months.
- Approximately 12 more patients will experience a grade 3 HFSR over a duration of exposure of 7 months.

- Approximately 45 more patients will experience a HFSR (any grade) over a duration of exposure of 7 months.

### ***Clinical claim***

- 6.16 The resubmission claimed that regorafenib was superior to BSC for the treatment of advanced HCC, providing a statistically and clinically significant increase in OS; and that regorafenib was associated with a higher incidence of drug related adverse events which were well tolerated and with no clinically significant impact on QoL. The clinical claim was supported by the data presented with respect to OS, and the ESC considered that the clinical claim of superior efficacy to BSC was reasonable. The clinical claim may not be supported with respect to the impact of adverse events on QoL and the ESC considered that regorafenib has inferior safety to BSC. Patients treated with regorafenib are 3 times more likely to suffer any grade 3 or 4 adverse event compared to BSC; there were no data presented which showed that these events did not result in a diminution of patients' QoL. The submission acknowledged that patients on regorafenib are more likely to experience significant toxicity and the PSCR revised the clinical claim to inferior safety compared with placebo. The ESC agreed that this was appropriate and noted that the economic model accounted for this inferior safety by using utility values based on treatment groups and applying disutility values for adverse events.
- 6.17 The PBAC considered that the claim of superior comparative effectiveness was reasonable.
- 6.18 The PBAC considered that the claim of inferior comparative safety was reasonable.

### ***Economic analysis***

- 6.19 The economic evaluations presented were a cost-effectiveness analysis (CEA) and cost-utility analysis (CUA). Health benefits were reported as life years gained (LYGs) and QALYs gained, respectively. The latest OS and PFS data were used for the economic analysis (cut-off 23<sup>rd</sup> January 2017). This was appropriate and provided an additional 11 months of follow-up data from the March 2018 submission.

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**Table 10: Key components of the economic evaluation**

Component	Description
Perspective	Health care perspective
Type of analysis	CEA and CUA
Outcomes	LYGs and QALYs
Time horizon	<u>Mar-18 submission</u> : 5 years in the base case vs 2.77 years (33 months) in the RESORCE trial. Only costs and outcomes in the regorafenib arm, not BSC were extrapolated out to five years. This was not appropriate. <u>Nov-18 resubmission</u> : 5 years base case vs 3.8 years (46 months) in the RESORCE trial. Costs and outcomes for both treatment arms were extrapolated out to five years. This was appropriate.
Methods used to generate results	Partitioned survival model
Health states	Progression Free (PFS), Progressive Disease (PD) and Dead.
Cycle length	28 days
Utility values	Treatment specific utility values from RESORCE: PF: 0.776 (Regorafenib) & 0.783 (BSC) PD: 0.738 (Regorafenib) & 0.741 (BSC)
Discounting	5% per year for costs and benefits
Area under the curve (AUC)	<u>Mar-18 submission</u> : The KM estimates for PFS and OS were derived directly from the RESORCE trial, with extrapolations thereafter for the regorafenib arm only using a piecewise model. <u>Nov-18 resubmission</u> : The KM estimates for PFS and OS were derived directly from the RESORCE trial, with extrapolation applied to both arms from median PFS and OS. However, the PBAC had requested extrapolation from the median point of follow-up (p 6.43, Mar-18 PSD), rather than median survival timepoints.
Software package	Microsoft Excel 2016

Abbreviations: AUC= area under the curve; BSC= best supportive care; KM= Kaplan-Meier; LYG= life years gained; N/A= not applicable; OS= overall survival; PD= progressive disease; PFS= progression free survival; QALYs= quality adjusted life years.

Source: Table 3-1, p. 132 of the resubmission.

6.20 A summary of the key drivers of the model is shown in Table 11.

**Table 11: Key drivers of the model**

Description	Method/Value	Impact (Base case ICER: \$ ██████ per QALY)
Application of extrapolation	Extrapolation was applied to both OS and PFS, as an independent model, for both treatment groups.	Moderate The ICER ranged from \$ ██████ to \$ ██████ per QALY depending on the choice of extrapolation function (see Table 12).
Disease costs	The model included ongoing disease management costs for HCC, including for medical services and TEAE management. The ESC considered it appropriate for these costs to be included in the model.	Moderate, favoured BSC. An analysis which excluded ongoing disease management costs reduced the ICER to \$ ██████.

Source: Table 3-26, p. 204 of the resubmission.

Abbreviations: BSC= best supportive care; ICER= incremental cost effectiveness ratio.

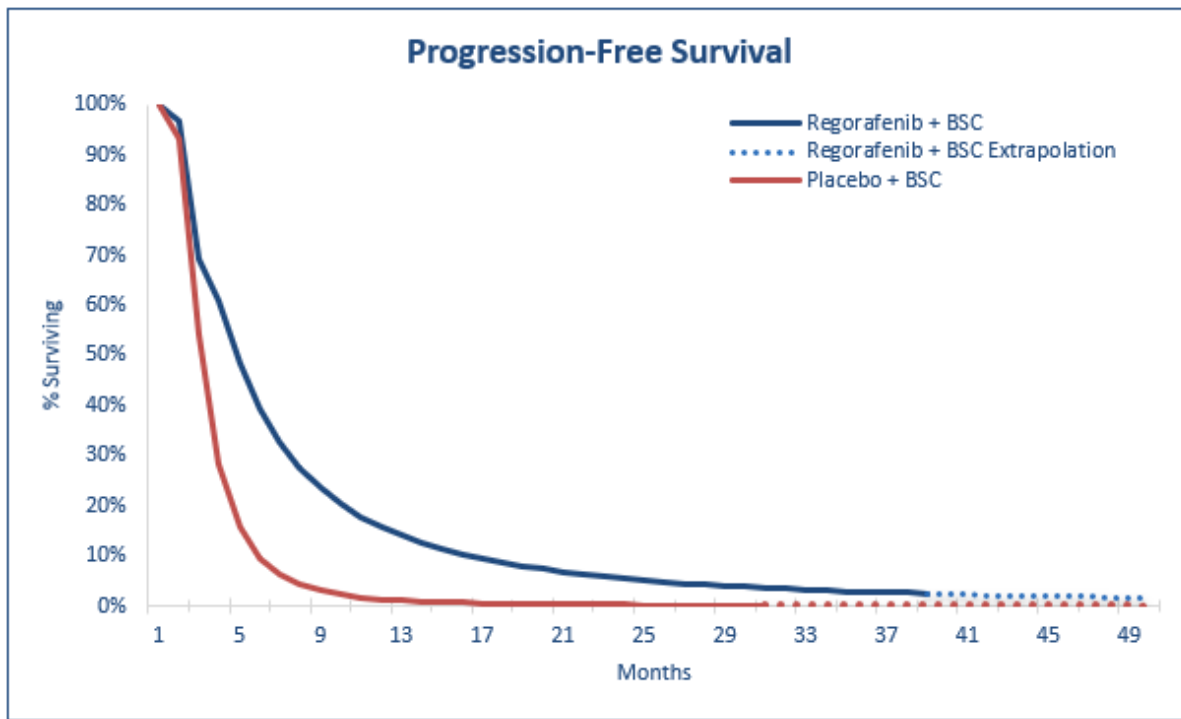
6.21 In line with the proposed restriction, patients in the trial could continue receiving treatment after progression was established if, in the opinion of the investigator, the treatment was still providing clinical benefit. The PBAC had requested that the proposed PBS listing should not permit use in patients beyond disease progression (paragraph 7.3 regorafenib PSD, March 2018 meeting). Adopting such a restriction criterion may result in survival outcomes that are less than those observed in

RESORCE; the PBAC has previously considered that use beyond progression is unlikely to be cost-effective (paragraph 2.3 regorafenib PSD, March 2018 meeting). The resubmission utilised the observed outcomes and health care use from the RESORCE trial without adjusting for use beyond progression. The ESC noted that use beyond disease progression in the RESORCE trial has implications for the applicability of the clinical data in the economic modelling. The PSCR stated that it was not possible to 'adjust' the economic analysis or corresponding financial impact to reflect this restriction wording because the economic and financial impact were aligned with the evidence base of the RESORCE trial. The ESC considered that if use beyond progression is not cost-effective, using the observed outcomes and healthcare use from the RESORCE trial in the model may give an appropriately conservative estimate of the ICER for regorafenib in Australian practice where used to progression only.

- 6.22 In the economic model presented previously, only the regorafenib arm was extrapolated. The ESC noted that both the regorafenib and BSC arms were now extrapolated as requested by the PBAC. The base case model extrapolated OS and PFS for both regorafenib and BSC from the median OS and PFS points. This was inconsistent with the claim made in the resubmission that 'extrapolation was applied from the median points of follow-up'. The PBAC previously requested extrapolation from the median point of follow-up (paragraph 6.43, regorafenib PSD, March 2018 meeting), so the extrapolation points used in the resubmission model were inappropriate. PFS was extrapolated using an independent model with a generalised-gamma distribution for regorafenib and a log-logistic distribution for BSC treatment arms. OS was extrapolated using a dependent (no-piecewise) generalised-gamma survival model. The PSCR clarified that the median points of follow-up for BSC and regorafenib arms in the RESORCE trial were 229 days (7.5 months) and 313 days (10.3 months) respectively. The PSCR reported that the use of these data as the basis for extrapolation resulted in an ICER of \$45,000 - \$75,000 per QALY (2.1% increase from the resubmission base case). The ESC noted that this estimate could not be replicated, but that this different point for extrapolation had little impact on the ICER. The ESC noted that the choice of extrapolation approach does not have a large impact on the ICER as data from RESORCE are almost complete with death events in 77% of patients in the regorafenib arm and in 87% of patients in the placebo arm.
- 6.23 At the end of study follow-up, the updated Kaplan-Meier analysis (cut-off 23 January 2017) for PFS estimated that only 1% and 3% of patients treated with BSC and regorafenib were free of disease progression and still alive at 30 and 39 months respectively. With respect to OS, the Kaplan-Meier analysis estimated that 3% of patients treated with BSC survived beyond 40 months and 6% of patients treated with regorafenib survived beyond 46 months. The low proportion of patients still alive by the end of trial follow-up was given as the reason for the time horizon of 5 years. ESC had stated this was reasonable in its consideration of the March 18 submission (paragraph 6.35, regorafenib PSD, March 2018 meeting).

6.24 The modelled results for OS and PFS and the source Kaplan-Meier estimates are presented in Figure 2 and Figure 3.

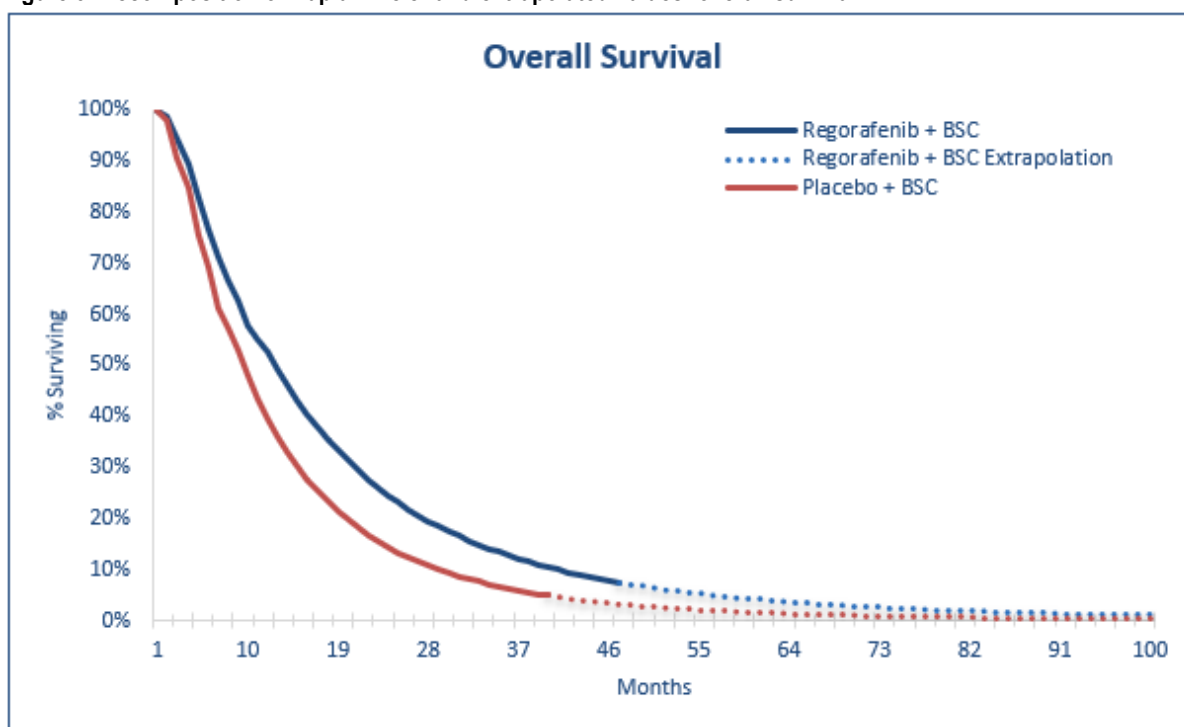
Figure 2: Decomposition of Kaplan-Meier and extrapolated values: progression free survival



Source: Figure 3-15, p. 193 of the resubmission.

Note: The broken line represents extrapolation beyond the trial follow-up however extrapolation is actually applied from median PFS.

Figure 3: Decomposition of Kaplan-Meier and extrapolated values: overall survival



Source: Figure 3-14, p. 191 of the resubmission.

Note: The broken line represents extrapolation beyond the trial follow-up however extrapolation is actually applied from median OS.

- 6.25 The ESC noted that in Figures 2 and 3 above, the broken line shows extrapolation beyond the trial follow up. However, as noted in paragraph 6.22 the model extrapolated for regorafenib and BSC from the points of median OS (10.7 months and 7.9 months, respectively) and PFS (3.1 months and 1.5 months). As such extrapolation is from a much earlier point than is indicated in the figures above.
- 6.26 A stepped economic evaluation was presented (see Table 12). Step 1 was a trial-based economic evaluation with only the costs of primary treatment (medicines) considered. Step 2 extrapolated results to a 5-year time horizon. Step 3 in the resubmission included all resource use in addition to the drug price. Finally, Step 4 transformed the trial outcome (LYG) to QALYs.

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Table 12: Results of the stepped economic evaluation

Step	Cost			Outcomes			ICER
	Reg	BSC	Inc	Reg	BSC	Inc	
Step 1. RESORCE trial (time horizon 46 months)	\$██████	\$0	\$██████	1.18	0.90	0.28	\$██████ /LYG
Step 2. RESORCE trial extrapolated to 5 years	\$██████	\$0	\$██████	1.23	0.92	0.31	\$██████ /LYG
Step 3. RESORCE trial extrapolated to 5 years including all resource use	\$██████	\$5,941	\$██████	1.23	0.92	0.31	\$██████ /LYG
Step 4. RESORCE trial extrapolated to 5 years including all resource use and transformed to QALY's	\$██████	\$5,941	\$██████	0.93	0.69	0.24	\$██████ /QALY

Abbreviations: ICER= incremental cost effectiveness ratio; Inc= incremental; LYG= life years gained; QALYs= quality adjusted life years; Reg= regorafenib

Source: Table 3-25, p. 203 of the resubmission.

*The redacted table shows ICERs in the range of \$15,000 - \$75,000 per LY or QALY gained.*

- 6.27 In accordance with the advice provided by PBAC (paragraph 6.43, regorafenib PSD, March 2018 meeting), the utility values used in the resubmission base case model were based on those from the within treatment-arm values in RESORCE, instead of using an average utility per health state as in the March 2018 submission. The utility values for both treatment arms are directly used from the RESORCE clinical trial. The ESC considered this was appropriate, and noted that the impact of this was small.
- 6.28 The transformation of the outcome from LYG to QALYs, had an important impact on the cost-effectiveness results, the ICER was increased from \$45,000/LYG - \$75,000/LYG to \$45,000/QALY - \$75,000/QALY (24%).
- 6.29 The resubmission applied appropriate methodology to estimate the total expected costs. The sources for valuing health resources were appropriate. The cost of a hospital admission for each TEAE was derived from the relevant AR-DRG. This was appropriate.

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Table 13: Results of sensitivity analyses

	Cost	Outcomes	ICER
	Incremental Reg vs BSC	Incremental Reg vs BSC	(\$/QALY)
<b>Base case</b>			
Base case	\$ [REDACTED]	0.24	\$ [REDACTED]
<b>One Way Sensitivity analysis</b>			
OS – Loglogistic	\$ [REDACTED]	0.22	\$ [REDACTED]
OS – Weibull	\$ [REDACTED]	0.25	\$ [REDACTED]
OS – LogNormal	\$ [REDACTED]	0.23	\$ [REDACTED]
OS – Gompertz	\$ [REDACTED]	0.25	\$ [REDACTED]
OS – Exponential	\$ [REDACTED]	0.26	\$ [REDACTED]
Regorafenib PFS – Loglogistic	\$ [REDACTED]	0.23	\$ [REDACTED]
Regorafenib PFS – Weibull	\$ [REDACTED]	0.23	\$ [REDACTED]
Regorafenib PFS – LogNormal	\$ [REDACTED]	0.23	\$ [REDACTED]
Regorafenib PFS – Gompertz	\$ [REDACTED]	0.24	\$ [REDACTED]
Regorafenib PFS – Exponential	\$ [REDACTED]	0.23	\$ [REDACTED]
BSC PFS – Weibull	\$ [REDACTED]	0.23	\$ [REDACTED]
BSC PFS – LogNormal	\$ [REDACTED]	0.23	\$ [REDACTED]
BSC PFS – Gompertz	\$ [REDACTED]	0.23	\$ [REDACTED]
BSC PFS – Exponential	\$ [REDACTED]	0.23	\$ [REDACTED]
BSC PFS – Gamma	\$ [REDACTED]	0.23	\$ [REDACTED]
Disease monitoring (MBS Benefit)	\$ [REDACTED]	0.24	\$ [REDACTED]
Exclude disease monitoring	\$ [REDACTED]	0.24	\$ [REDACTED]
Exclude TEAEs	\$ [REDACTED]	0.24	\$ [REDACTED]
Utility (Literature-PFS: 0.76; PD: 0.68)	\$ [REDACTED]	0.23	\$ [REDACTED]
Utility (IPD PFS: 0.778; PD: 0.720)	\$ [REDACTED]	0.24	\$ [REDACTED]
Time horizon 3 years	\$ [REDACTED]	0.19	\$ [REDACTED]
Time horizon 4 years	\$ [REDACTED]	0.22	\$ [REDACTED]
Discount rate: 0%	\$ [REDACTED]	0.26	\$ [REDACTED]
Discount rate: 3.5%	\$ [REDACTED]	0.24	\$ [REDACTED]
<b>Additional sensitivity analysis</b>			
ICER=\$ [REDACTED]/QALY (effective DPMQ of \$ [REDACTED])	\$ [REDACTED]	0.24	\$ [REDACTED]

Abbreviations: AE= adverse event; BSC= best supportive care; ICER= incremental cost effectiveness ratio; OS= overall survival; PD= progressive disease; PFS= progression free survival; QALYs= quality adjusted life years; Reg= regorafenib; SPA= special price agreement; TEAEs= treatment emergent adverse event.

Source: Table 3-28, p. 207 of the resubmission.

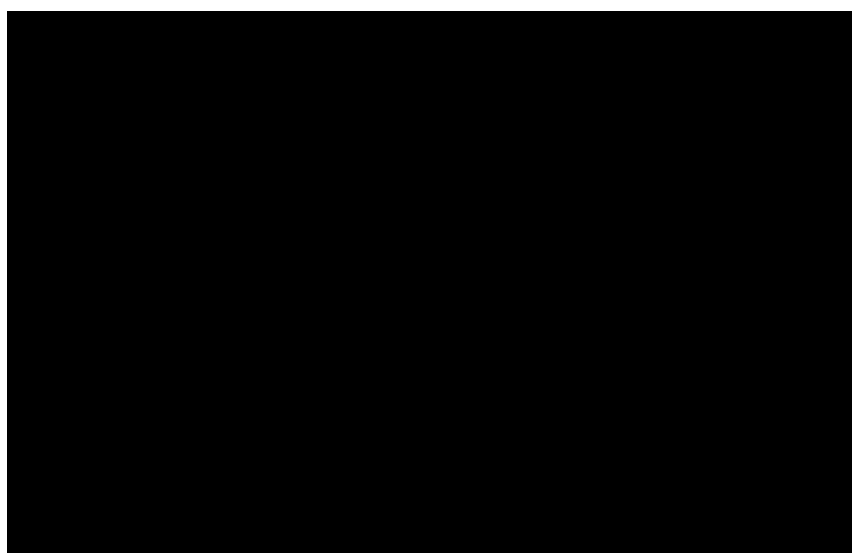
*The redacted table shows ICERs in the range of \$15,000/QALY - \$75,000/QALY.*

6.30 The results from the sensitivity analyses provided in the resubmission, showed that the ICER estimates were most sensitive to variations in the type of extrapolation function adopted and in the manner in which ongoing treatment and AE costs were included.

6.31 The PBAC had requested that the base case ICER should be \$15,000 - \$45,000 per QALY gained to reflect the substantial toxicity of the drug (Section 7.12 regorafenib PSD, March 2018 meeting). A further 42% price reduction from the effective price

requested in the resubmission would result in an ICER of \$15,000 - \$45,000 per QALY gained (effective DPMQ of \$ [REDACTED] compared to \$ [REDACTED]). The PSCR stated that the sponsor was unable to reduce the price sufficiently to achieve the ICER of \$15,000 - \$45,000 using the model inputs previously considered appropriate by the PBAC. Figure 4 shows the relationship between the effective DPMQ and the ICER. In the pre-PBAC response the sponsor reiterated that it was unable to reduce the price of regorafenib to the extent required to decrease the ICER to \$15,000 - \$45,000 per QALY. Instead, the sponsor offered an approximate 10% discount on the effective price for sorafenib in first line advanced HCC, contingent on recommendation of regorafenib and acceptance of the proposed restriction that regorafenib initiation is subsequent to sorafenib treatment.

Figure 4: Relationship between the effective DPMQ and incremental cost-effectiveness ratio.



### ***Drug cost/patient/course***

6.32 Based on the estimated treatment exposure (5.41 packs) from the RESORCE trial, the expected cost per patient course was \$ [REDACTED].

### ***Estimated PBS usage & financial implications***

6.33 This submission was not considered by DUSC. The predicted use of regorafenib was estimated using an epidemiological approach. The resubmission used an analysis based on the 10% Medicare sample to estimate the rate of regorafenib uptake after sorafenib progression for the six years following listing.

6.34 Since the nominated comparator for this condition was BSC, there are no PBS-listed medicines substituted by the proposed medicine, noting that administration of BSC needs to be maintained while on regorafenib treatment.

6.35 If lenvatinib is PBS listed in this indication this would significantly decrease the patient utilisation numbers for its comparator, sorafenib, and this would be expected to

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decrease the potential patient utilisation of regorafenib if listed after first line sorafenib treatment. This was not accounted for in the estimates presented in the resubmission. The PSCR presented a scenario in which lenvatinib assumes 20% of the market share. In this scenario the total cost to the government health budget is reduced to less than \$100 million in 2019 to less than \$10 million in year 2024. The ESC noted that there was no basis for the 20% market share and it was unclear how these estimates were calculated as the net cost to the Government in these estimates was reduced by more than 20%.

6.36 Overall, a listing for regorafenib is expected to result in an incremental cost to the PBS/RPBS of less than \$10 million in 2019 (Year 1), increasing to less than \$10 million in 2024 (Year 6). The total financial implications to the PBS over 6 years of subsidising regorafenib were \$10 - \$20 million. This has decreased by 39% since the March-2018 submission (\$30 - \$60 million). The total financial implication to the government health budget over 6 years of subsidising regorafenib was \$20 - \$30 million.

**Table 14: Estimated use and financial implications**

	6-year time horizon considering SPA					
	2019	2020	2021	2022	2023	2024
<b>Estimated extent of use</b>						
Number of patients treated	█	█	█	█	█	█
Number of scripts dispensed <sup>a</sup>	█	█	█	█	█	█
<b>Estimated financial implications of regorafenib</b>						
Cost to PBS/RPBS	\$█	\$█	\$█	\$█	\$█	\$█
Co-payments	\$█	\$█	\$█	\$█	\$█	\$█
<b>Net financial implications</b>						
Net cost to PBS/RPBS	\$█	\$█	\$█	\$█	\$█	\$█
Net cost to State and Territory Governments	\$█	\$█	\$█	\$█	\$█	\$█ <sup>^</sup>
Overall net cost to Government Health Budget	\$█	\$█	\$█	\$█	\$█	\$█ <sup>^</sup>

Note: <sup>a</sup>Assuming 5.41 packs per year as estimated by the resubmission. <sup>^</sup>Correct value reported here due to an error made in the Cost Model 'AE's management tab' of the resubmission.

Abbreviation: SPA= special price agreement.

Source: Table 4-11, 4-14 and 4-15, p. 225 – 229 and cost model of the resubmission.

*The redacted table shows that at Year 6, the estimated number of patients was less than 10,000 per year.*

6.37 A 100% PBS sample of patients receiving sorafenib was made available by the DUSC Secretariat for analysis during the evaluation of the March 2018 submission. The estimated number of patients was similar in the early years (2010-2013) to those presented in the resubmission (based on 10% PBS sample). A difference was observed

in later years where use reported for sorafenib in the 100% PBS sample from 2015 to 2016 was lower than that from the 10% sample.

- 6.38 The proposed restriction is for use in patients with ECOG  $\leq 1$  (in accordance with the RESORCE trial). However, the estimates presented in the resubmission allowed for a proportion of patients with worsened performance status to access treatment with regorafenib. The sponsor has attempted to address the potential discrepancies and uncertainties in the differences between the patient populations in the RESORCE trial and in the Australian clinical setting by reducing the proportion of eligible patients from 70% (Mar-18 submission) to 60% in the resubmission. The ESC considered that this was appropriate.
- 6.39 The financial estimates were based on treatment exposure in RESORCE, which included some patients continuing treatment with regorafenib beyond progression. Regorafenib use on the PBS may thus be overestimated given the PBAC's proposed restriction limiting access to those without treatment progression.
- 6.40 The PBAC had requested that treatment-related MBS costs for medical visits, pathology, diagnostics and AEs should be included in the financial estimates (paragraph 6.58 regorafenib PSD, March 2018 meeting). The resubmission claimed that drug related TEAEs (grade 3 and 4) were assumed to require hospitalisation and included these in its costs to Government. However, other MBS costs were not included and given the assumed longer-term survival of regorafenib treated HCC patients, it is reasonable that they would incur additional medical service use (e.g. specialist and diagnostic services) and therefore that the financial estimates were underestimated. The PSCR provided estimates of the MBS costs associated with the incremental OS. The PSCR stated that the impact on the MBS costs would be minimal, ranging from \$ [REDACTED] in 2019 to \$ [REDACTED] in 2024.

### ***Quality Use of Medicines***

- 6.41 The most common and/or important adverse events in the RESORCE trial were hypertension, hand-foot skin reaction (HFSR), fatigue, and diarrhoea. Although common, most were manageable by dose modification. Detailed advice, warnings and recommendations are provided in the Product Information. The resubmission presented a QUM plan focused on the management of HFSR directed to patients and training sessions for nurses and physicians.

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

## **7 PBAC Outcome**

- 7.1 The PBAC did not recommend the listing of regorafenib for the treatment of hepatocellular carcinoma for patients who have progressed on first line treatment with a sorafenib. The PBAC considered that regorafenib provided a modest survival benefit in some patients, however treatment was also associated with substantial

- toxicity. The PBAC considered that at the proposed price, the incremental cost-effectiveness ratio for regorafenib was unacceptably high.
- 7.2 The PBAC reiterated patients should only be treated with regorafenib until disease progression and the restriction criteria should not allow treatment beyond disease progression. The PBAC noted that in the pre-PBAC response the sponsor indicated it would accept inclusion of this criterion. The PBAC noted that the requested listing was for patients with BCLC stage C, however the RESORCE trial also included patients with BCLC stage B. The PBAC considered that it would be appropriate to include patients with BCLC stage B and C in the listing for regorafenib consistent with the population in the RESORCE trial. The PBAC considered that it would not be clinically appropriate to include an eligibility criterion excluding patients who are HIV immunocompromised as clinicians should be allowed to make individual treatment decisions for these patients.
- 7.3 The PBAC noted that lenvatinib was considered for first line treatment of HCC at the November 2018 meeting. The proposed listing for regorafenib would not allow patients treated with lenvatinib to access second line regorafenib and this may create an incentive for patients to preferentially be treated with sorafenib in the first line setting. The PBAC considered that it was not clinically appropriate for the availability of regorafenib as a second line treatment to impact on the choice of the first line treatment for HCC. The PBAC noted that NCCN guidelines recommend sorafenib or lenvatinib as the preferred first line systemic therapies and regorafenib, cabozantinib, ramucirumab, nivolumab, sorafenib (after first line lenvatinib) or pembrolizumab for subsequent therapy after disease progression. The PBAC agreed with the ESC that if it were to be listed the restriction for regorafenib should be revised to allow use following treatment with a TKI. Currently this would only include sorafenib, however if lenvatinib is PBS listed this restriction would allow for regorafenib to be used following treatment with either sorafenib or lenvatinib.
- 7.4 The PBAC considered that the comparator of BSC, as previously accepted, remained appropriate for the resubmission.
- 7.5 The PBAC noted that the resubmission presented an updated data set from the RESORCE trial (cut-off date Jan 23, 2017) with an additional 11 months follow-up. The PBAC noted that the magnitude of the OS and PFS benefit remained the same as presented in the March 2018 submission based on the earlier data cut, with a 2.8 month improvement in median overall survival and a 1.6 month improvement in median PFS. PBAC maintained that the claim of superior comparative effectiveness was reasonable and that regorafenib showed modest clinical benefit, though it was associated with substantial toxicity and no improvement in quality of life.
- 7.6 The PBAC noted that patients treated with regorafenib were 3 times more likely to suffer any grade 3 or 4 adverse event compared with BSC. The submission acknowledged that patients on regorafenib are more likely to experience significant toxicity and the PSCR revised the clinical claim to inferior safety compared with BSC.

The PBAC agreed with the ESC and maintained that the clinical claim of inferior safety compared with BSC was appropriate.

- 7.7 The PBAC noted that the economic analysis presented in the resubmission addressed the majority of the PBAC concerns, with the exception of the point of extrapolation being the median PFS rather than the median follow-up. The PSCR provided an estimate of the ICER using the median points of follow-up which showed that this factor had little impact on the ICER. The PBAC considered that the model inputs and structure of the economic analysis presented in the resubmission were appropriate.
- 7.8 In March 2018 the PBAC requested a revised economic analysis with a cost per QALY of \$15,000 - \$45,000 to reflect the modest OS benefit and considerable toxicity associated with regorafenib. While the resubmission addressed the majority of the PBAC and ESC concerns in the approach to the economic model, the resulting ICER was \$45,000 - \$75,000 per QALY. The resubmission offered a [REDACTED] % discount in the DPMQ from the March 2018 submission (\$ [REDACTED]). To achieve an ICER of \$15,000 - \$45,000, a further 42% price reduction would be required (effective DPMQ of \$ [REDACTED] compared to the proposed \$ [REDACTED]). The sponsor indicated that it was unable to reduce the price of regorafenib to the extent required to decrease the ICER to \$15,000 - \$45,000 per QALY gained. Instead, the sponsor offered an approximate 10% discount on the effective price for sorafenib for first line advanced HCC, contingent on recommendation of regorafenib and acceptance of the proposed restriction that regorafenib initiation is subsequent to sorafenib treatment. The PBAC considered that the proposed reduction in the effective sorafenib price did not address the requirement to establish an acceptable level of cost-effectiveness for regorafenib.
- 7.9 The PBAC noted that the ICER accepted as appropriate when sorafenib was listed (>\$75k per QALY, July 2008 meeting, sorafenib PSD) may no longer be appropriate given the increasing availability of other treatments for HCC and the changing clinical algorithm.
- 7.10 The PBAC noted that if lenvatinib is PBS listed in this indication this would significantly decrease the patient utilisation numbers for its comparator, sorafenib. This was not accounted for in the estimates presented in the resubmission. The PSCR presented a scenario in which lenvatinib assumes 20% of the market share and patients treated with lenvatinib do not receive second line regorafenib, which was not consistent with the restriction considered appropriate by the PBAC if lenvatinib is PBS listed. The PBAC also noted that the estimates should be adjusted to exclude use post-progression, consistent with the PBAC's recommendation on the restriction. The PBAC considered that the utilisation estimates presented in the submission and in the pre-PBAC response did not reflect the listing considered appropriate by the PBAC.
- 7.11 The PBAC considered that, given the economic analysis presented in the resubmission addressed the majority of the PBAC concerns, the cost-effectiveness of regorafenib would be acceptable with a reduction in price that resulted in an ICER consistent with

that previously advised by the PBAC, of \$15,000 - \$45,000 per QALY. The PBAC considered that a resubmission addressing price only could be submitted as a minor submission.

7.12 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**

Bayer has proposed an ICER within the 45,000-75,000 ICER band, which we consider appropriate for an originally designated orphan population and recognized unmet need. Bayer also maintains its proposed restriction is consistent with the current available evidence and HTA principles.

Bayer is currently assessing the feasibility of re-submitting to PBAC for further consideration.