

## 7.10 REGORAFENIB, Tablet 40 mg (as monohydrate), Stivarga<sup>®</sup>, Bayer Australia Ltd

### 1 Purpose of submission

- 1.1 The standard re-entry resubmission requested a General Schedule, Authority Required (STREAMLINED) listing for regorafenib for the treatment of patients with metastatic colorectal cancer (mCRC) who have been previously treated with, or are not considered suitable candidates for, available therapies including fluoropyrimidine, oxaliplatin and irinotecan-based chemotherapy, anti-vascular endothelial growth factor (VEGF) therapy and if RAS wildtype, anti-epidermal growth factor receptor (EGFR) therapy.
- 1.2 Listing was requested based on a cost minimisation approach versus trifluridine/tipiracil.

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

Component	Description
Population	Patients with mCRC who have been previously treated with, or are not considered suitable candidates for, fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if RAS wild type, an anti-EGFR therapy.
Intervention	Regorafenib 40 mg oral tablets; administered as four tablets at the same time each day (total daily dose of 160 mg) for three weeks on therapy (21 days) followed by one week off therapy (7 days) to comprise a cycle of four weeks (28 days).
Comparator	Trifluridine/tipiracil oral tablets (trifluridine 15 mg + tipiracil 6.14 mg & trifluridine 20 mg + tipiracil 8.19 mg) given at 35 mg/m <sup>2</sup> (based on the trifluridine component) twice daily on days 1 to 5 and days 8 to 12 of a 28-day cycle.
Outcomes	Primary outcome: OS Secondary and other outcomes: PFS; QoL; Safety
Clinical claim	In patients with mCRC who have failed, or who are not considered suitable for, available first- and second-line therapies, regorafenib is non-inferior in its effectiveness compared to trifluridine/tipiracil, with a non-inferior safety profile.

Source: Table 1-1, p4 of the resubmission.

EGFR = epidermal growth factor receptor, mCRC = metastatic colorectal cancer, OS = overall survival, PFS = progression-free survival, QoL= quality of life, VEGF = vascular endothelial growth factor.

### 2 Background

#### Registration status

- 2.1 Regorafenib was TGA registered on 29<sup>th</sup> November 2013 for the following indications:
- The treatment of patients with mCRC who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if RAS wild type, an anti-EGFR therapy.

- The treatment of patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) who progressed on or are intolerant to prior treatment with imatinib and sunitinib.
- The treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

### ***Previous PBAC consideration***

- 2.2 Regorafenib was previously considered by the PBAC for the treatment of patients with mCRC following failure of, or intolerance to, other treatment options.
- 2.3 At the July 2014 meeting, regorafenib was not recommended on the basis that compared with best supportive care (BSC) “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” (paragraph 7.1, regorafenib, Public Summary Document, July 2014 PBAC meeting).
- 2.4 Table 2 summarises the key matters of concern regarding the previous submission and how the resubmission has addressed those concerns.

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

<b>Component</b>	<b>Matter of concern</b>	<b>How the resubmission addresses it</b>
<b>Restriction</b>		
Requested PBS listing	Risk of use outside the requested listing, in patients with WHO performance status >1 and in the post-progression setting (Para 7.4, July 2014 PSD)	Not addressed. However, this was consistent with the listing of trifluridine/tipiracil.
<b>Clinical evidence</b>		
Clinical effectiveness	The PBAC noted the small gain in median PFS of 0.2 months and median OS of 1.4 months compared with BSC in the CORRECT trial (para 7.6, July 2014 PSD).	The resubmission presented additional data from the CONCUR trial. The resubmission presented an indirect comparison of regorafenib and trifluridine/tipiracil.
Clinical safety	The PBAC noted the severe adverse effects associated with regorafenib, particularly hepatotoxicity and hand-foot skin reactions (para 7.7, July 2014 PSD)	The resubmission presented post hoc safety analyses from CORRECT and CONCUR trials.
Quality of Life	The PBAC noted that no patients in the CORRECT trial had a complete response and that EQ-5D data showed no improvement in QoL with regorafenib (para 7.6, July 2014 PSD).	The resubmission presented post hoc analyses of patient reported outcomes from CORRECT and CONCUR, by treatment cycle.
<b>Economic evaluation</b>		
Economic evaluation	The PBAC considered that use of regorafenib was associated with an unacceptably high ICER (para 7.8, July 2014 PSD).	A cost minimisation to trifluridine/tipiracil was presented based on indirect comparison.
Inclusion of cost associated with the management and monitoring of adverse events	The ESC considered that the cost of adverse events was likely to be underestimated as the model does not include palliative care costs or costs associated with adverse events that require hospitalisation (para 6.22, July 2014 PSD).	The resubmission did not include the costs for the management and monitoring of adverse events.
<b>Financial estimates</b>		
Financial impact	The PBAC noted that the sensitivity analysis showed that there is considerable variation in the financial estimates of cost to the Commonwealth (para 7.9, July 2014 PSD).	A market share approach in reference to trifluridine/tipiracil was used. No consideration of additional costs to the Commonwealth. No sensitivity analyses of financial estimates were presented.

Source: Executive summary, ppxv-xxvi of the resubmission; Regorafenib Public Summary Document, July 2014 PBAC meeting.

BSC = best supportive care, EQ-5D = Euro QoL, 5-dimensional QoL measurement, ICER = incremental cost-effectiveness ratio, OS = overall survival, PFS = progression free survival, QoL = Quality of Life.

### 3 Requested listing

- 3.1 The submission requested a listing consistent with that of trifluridine/tipiracil for mCRC.

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Name, Restriction, Manner of administration and form	Max. Qty (packs)	Max. Qty (units)	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
REGORAFENIB 40 mg (as monohydrate) oral tablets, 28	3	84	2	\$ [REDACTED] published price Effective price to be determined	Stivarga® Bayer Australia Ltd
<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>Severity:</b>	Metastatic				
<b>Condition:</b>	Metastatic colorectal cancer				
<b>PBS Indication:</b>	Metastatic colorectal cancer				
<b>Treatment phase:</b>	Initial treatment				
<b>Restriction:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required – Telephone, Electronic <input checked="" type="checkbox"/> Streamlined				
<b>Clinical criteria:</b>	Patient must have a WHO performance status of 1 or less, <b>AND</b> Patient must have previously received treatment with fluoropyrimidine, oxaliplatin, irinotecan-based chemotherapies, an anti-vascular endothelial growth factor (anti-VEGF) agent and an anti-epidermal growth factor receptor (anti-EGFR) agent for this condition, <b>OR</b> Patient must not be a suitable candidate for treatment with fluoropyrimidine, oxaliplatin, irinotecan-based chemotherapies, an anti-VEGF agent and an anti-EGFR agent for this condition, <b>AND</b> The treatment must be the sole PBS-subsidised therapy for this condition.				
<b>Prescriber Instructions:</b>	The patient's WHO performance status and body weight must be documented in the patient's medical records at the time the treatment cycle is initiated.				
<b>Treatment phase:</b>	Continuing treatment				
<b>Restriction:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required – Telephone, Electronic <input checked="" type="checkbox"/> Streamlined				
<b>Clinical criteria:</b>	Patient must have previously been treated with PBS-subsidised treatment with this drug for this condition, <b>AND</b> Patient must not develop progressive disease whilst receiving PBS-subsidised treatment with this drug for this condition, <b>AND</b> The treatment must be the sole PBS-subsidised therapy for this condition.				
<b>Prescriber Instructions:</b>	Patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug.				
<b>Treatment phase:</b>	Grandfathering treatment				

<b>Clinical criteria:</b>	<p>Patient must have previously received treatment with fluoropyrimidine, oxaliplatin, irinotecan based chemotherapies, an anti-vascular endothelial growth factor (anti-VEGF) agent and an anti-epidermal growth factor receptor (anti-EGFR) agent for this condition,  <b>AND</b>                  Patient must not be a suitable candidate for treatment with fluoropyrimidine, oxaliplatin, irinotecan-based chemotherapies, an anti-VEGF agent and an anti-EGFR agent for this condition,  <b>AND</b>                  Patient must have been receiving non-PBS-subsidised treatment with this drug for this condition prior to (date to be determined)  <b>AND</b>                  Patient must not have developed progressive disease while receiving non-PBS-subsidised treatment with this drug for this condition  <b>AND</b>                  The treatment must be the sole PBS-subsidised therapy for this condition.</p>
<b>Prescriber Instructions:</b>	<p>A Grandfathered patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the continuing treatment criteria.</p>

- 3.2 The resubmission proposed that the effective price of regorafenib would need to be calculated based on cost-minimisation to trifluridine/tipiracil effective price.
- 3.3 The requested listing was aligned with the inclusion criteria in the CORRECT trial, which was the pivotal clinical trial evidence for regorafenib. Other differences between the previous and the current restriction included the addition of the following statement: ‘treatment must be the sole PBS-subsidised therapy for this condition’ and the restrictions for the Grandfathering phase. The PBAC previously noted that there was “a risk of use outside the requested listing, in patients with a WHO performance status greater than 1 and in the post-progression setting” (paragraph 7.4, regorafenib, Public Summary Document, July 2014 PBAC meeting). In addition, the requested restriction does not limit the potential use of regorafenib in a subsequent line of treatment beyond the third line (e.g., after trifluridine/tipiracil).
- 3.4 The Pre-Sub-Committee Response (PSCR) argued the risk of leakage to patients with a WHO performance status >1 was managed through the trifluridine/tipiracil risk sharing arrangement (RSA) and further argued the risk of sequential use could be managed through the RSA. The Sponsor indicated a willingness to join existing arrangements. The ESC considered this was reasonable and could be adequately addressed through regorafenib joining the existing trifluridine/tipiracil RSA, should regorafenib be recommended for listing.

## 4 Population and disease

- 4.1 The target population are patients with metastatic colorectal cancer (mCRC). Colorectal cancer is a progressive multistep genetic cancer of the colon or rectum. Around 16% of colorectal cancer patients are diagnosed with mCRC (Stage IV). The overall 5-year survival rate in mCRC is around 13% (Cancer Australia 2020; AIHW 2021). The majority of mCRC patients will not have disease that can be surgically

resected with curative intent. Thus, the goal of care is generally palliative to prolong survival and maintain quality of life.

- 4.2 The clinical management algorithm was based on Cancer Council Australia 2017 guidelines for the management of mCRC and Price *et al* (2020). The resubmission proposed regorafenib as an alternative to trifluridine/tipiracil in the third line of treatment in mCRC patients who failed, or who are not candidate for, standard chemotherapy, anti-VEGF therapy, and, if RAS wild type, an anti-EGFR therapy. Regorafenib is recommended in Cancer Council Australia guidelines in the third line of mCRC treatment.
- 4.3 Regorafenib is an oral anti-tumour agent that potently blocks multiple protein kinases, including kinases involved in tumour angiogenesis (VEGFR1, -2, -3, TIE2), oncogenesis (KIT, RET, RAF-1, BRAF), metastasis (VEGFR3, PDGFR, FGFR) and tumour immunity (CSF1R). By directly inhibiting the tyrosine kinases, regorafenib reduces the subsequent signalling through downstream pathways involved in angiogenesis, oncogenesis and stromal interactions, and thereby inhibits tumour growth and disease progression.

## 5 Comparator

- 5.1 The resubmission nominated trifluridine/tipiracil as the main comparator. The nominated comparator in the previous submission was BSC. The main arguments supporting this change were as follows:
  - The mCRC population targeted for regorafenib is identical to that currently considered eligible on the PBS for treatment with trifluridine/tipiracil.
  - The proposed clinical place in therapy for regorafenib is identical to that for trifluridine/tipiracil, which is PBS listed for the management of mCRC patients as a third line of treatment.
- 5.2 The choice of trifluridine/tipiracil as the comparator was appropriate. Other subsequent therapy (e.g., chemotherapy) could also be replaced in practice, which occurred in the clinical trials but wasn't considered in the economic analysis and financial estimates.

## 6 Consideration of the evidence

### ***Sponsor hearing***

- 6.1 The sponsor requested a hearing for this item. The clinician stated that regorafenib provides a genuine benefit in terms of progression free survival in advanced, incurable and non-resectable colorectal cancer and also stated that in their clinical experience the adverse events of regorafenib can be satisfactorily managed in practice, such as through dose adjustments or a lower starting dose. The PBAC noted a lower starting

dose of regorafenib was not consistent with the current TGA dosing recommendations.

### **Consumer comments**

- 6.2 The PBAC noted and welcomed the input from Bowel Cancer Australia which broadly supported the application to increase choices for patients.

### **Clinical trials**

- 6.3 There were no head-to-head trials of regorafenib and trifluridine/tipiracil for the treatment of patients with mCRC. Therefore, the resubmission conducted an indirect treatment comparison of regorafenib and trifluridine/tipiracil, using placebo as a common reference. The submission identified a total of five trials, two trials comparing regorafenib with placebo (CORRECT and CONCUR trials) and three trials comparing trifluridine/tipiracil with placebo (RECOURSE, TERRA and J003 trials). The CORRECT trial was considered by the PBAC as a part of the previous regorafenib submission in July 2014. Although not considered in the original regorafenib submission, RECOURSE and J003 have been previously considered in the submission for trifluridine/tipiracil in November 2016. Data from CONCUR and TERRA trials have not been considered by the PBAC.
- 6.4 Details of the included trials presented in the submission are provided in the Table 3.

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

Trial ID	Protocol title/ Publication title	Publication citation
CORRECT	A randomised, double-blind, placebo-controlled phase III study of regorafenib plus BSC versus placebo plus BSC in patients with metastatic colorectal cancer (CRC) who have progressed after standard therapy. Grothey A, Cutsem EV, Sobrero A et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial.	January 2014  <i>Lancet</i> (London, England) 2013; 381(9863): 303-312.
CONCUR	A randomised, double-blind, placebo-controlled phase III study of regorafenib plus best supportive care (BSC) versus placebo plus BSC in Asian subjects with metastatic colorectal cancer (CRC) who have progressed after standard therapy (CONCUR). Li J, Qin S, Xu R et al. Regorafenib plus BSC versus placebo plus BSC in Asian patients with previously treated metastatic colorectal cancer (CONCUR): a randomised, double-blind, placebo-controlled, phase 3 trial. Li J, Qin S, Yau T et al. Concur: a Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of Regorafenib Monotherapy in Asian Patients with Previously Treated Metastatic Colorectal Cancer (MCRC).	January 2016  <i>The Lancet Oncology</i> 2015; 16(6): 619-629.  <i>Annals of Oncology</i> 2014; 25: ii114-.
RECOURSE	Mayer RJ, Cutsem EV, Falcone A et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. Yoshino T, Mayer R, Falcone A et al. Results of a Multicenter, Randomized, Double-Blind, Phase III Study of TAS-102 vs. Placebo, with Best Supportive Care (BSC), in Patients (PTS) with Metastatic Colorectal Cancer (MCRC) Refractory to Standard Therapies (RECOURSE).	<i>NEJM</i> 2015; 372(20): 1909-1919.  <i>Annals of Oncology</i> 2014; 25: ii114.
TERRA	Xu J, Kim TW, Shen L et al. Results of a randomized, double-blind, placebo-controlled, phase III trial of trifluridine/tipiracil (TAS-102) monotherapy in Asian patients with previously treated metastatic colorectal cancer: the TERRA study. Kim TW, Shen L, Xu JM et al. TERRA: a randomized, double-blind, placebo-controlled phase 3 study of TAS-102 in Asian patients with metastatic colorectal cancer	<i>JCO</i> 2018; 36(4): 350-358.  <i>Annals of Oncology</i> 2016; 27: vi153.
J003	Yoshino T, Mizunuma N, Yamazaki K et al. TAS-102 monotherapy for pretreated metastatic colorectal cancer: a double-blind, randomised, placebo-controlled phase 2 trial.	<i>The Lancet Oncology</i> 2012; 13(10): 993-1001.

Source: Table 2-6, pp46-48 of the resubmission.

BSC = best supportive care, CRC = colorectal cancer.

6.5 The key features of the direct randomised trials are summarised in the Table 4.

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

Trial	N	Design/ Mean duration of treatment	Risk of bias	Patient population	Outcome(s)
<b>Regorafenib vs. placebo</b>					
CORRECT	760	R, DB, MC, MN, PC 12.08 weeks	Low	mCRC, failed ≥ 2 standard therapies	OS, PFS, HrQoL
CONCUR	204	R, DB, MC, MN, PC 17.27 weeks	Low	mCRC, failed ≥ 2 standard therapies	OS, PFS, HrQoL
Meta-analysis	961	Included CORRECT and CONCUR; assessed OS and PFS			
<b>Trifluridine/tipiracil vs. placebo</b>					
RECOURSE	800	R, DB, MC, MN, PC 12.7 weeks	Low	mCRC, failed ≥ 2 standard therapies	OS, PFS
TERRA	406	R, DB, MC, MN, PC 14.93 weeks	Low	mCRC, failed ≥ 2 standard therapies	OS, PFS
J003	172	R, DB, MC, PC NR	Low	mCRC, failed ≥ 2 standard therapies	OS, PFS
Meta-analysis	1378	Included RECOURSE, TERRA and J003; assessed OS and PFS			

Source: Table 2-7, pp55-57, Table 2-11, pp74-77, Table 2-13, p79 of the resubmission.

DB = double blind, HrQoL = health related quality of life, MC = multi-centre, mCRC = metastatic colorectal cancer, MN = multi-national, NR = not reported, OS = overall survival, PC = placebo-controlled, PFS = progression-free survival, R = randomised.

6.6 Overall, the risk of bias across the five trials was low. In the 2014 consideration of regorafenib, the PBAC considered that the CORRECT trial had a low risk of bias. In November 2016 consideration of trifluridine/tipiracil, the PBAC considered that the RECOURSE and J003 trials had a low risk of bias.

### **Comparative effectiveness**

6.7 The resubmission presented an indirect comparison between regorafenib and trifluridine/tipiracil using placebo as a common reference based on the outcomes of the CORRECT (regorafenib vs placebo) and RECOURSE (trifluridine/tipiracil vs placebo) trials. An indirect comparison between regorafenib and trifluridine/tipiracil with placebo as a common reference was presented in a previous trifluridine/tipiracil submission. The PBAC previously noted that “the efficacy of trifluridine/tipiracil appears to be similar to that for regorafenib, but that trifluridine/tipiracil appears to be better tolerated” (paragraph 7.7, trifluridine/tipiracil, Public Summary Document, November 2016 PBAC meeting).

6.8 The results of the main indirect comparison are summarised in Table 5.

**Table 5: Results of indirect comparison of regorafenib and trifluridine/tipiracil**

Trial	Outcome	Regorafenib n/N (%)	Placebo n/N (%)	Absolute difference	HR (95% CI)
CORRECT	Death events	275/505 (54.5%)	157/255 (61.6%)	-	-
	Median OS (months) (95% CI)	6.4 (3.6, 11.8)	5.0 (2.8, 10.4)	1.4 months	<b>0.77 (0.64, 0.94)</b>
	Progression events	430/505 (85.1%)	241/255 (94.5%)	-	-
	Median PFS (months) (95% CI)	1.9 (1.6, 3.9)	1.7 (1.4, 1.9)	0.2 month	<b>0.49 (0.42, 0.58)</b>
Comparators		Trifluridine/tipiracil n/N (%)	Placebo n/N (%)	Absolute difference	HR (95% CI)
RECOURSE	Death events	364/534 (68.2%)	210/266 (78.9%)	-	-
	Median OS (months) (95% CI)	7.1 (6.5, 7.8)	5.3 (4.6, 6.0)	1.8 months	<b>0.68 (0.58, 0.81)</b>
	Progression events	472/534 (88.4%)	251/266 (94.4%)	-	-
	Median PFS (months) (95% CI)	2.0 (1.9, 2.1)	1.7 (1.7, 1.9)	0.3 month	<b>0.48 (0.41, 0.57)</b>
Indirect comparison regorafenib vs. trifluridine/tipiracil for OS					1.13 (0.88, 1.46)
Indirect comparison regorafenib vs. trifluridine/tipiracil for PFS					1.02 (0.82, 1.28)

Sources: Table 2-17, p93, Table 2-18, p94, Table 2-25, p103, Table 2-26, p104, Table 2-48, p148 and Table 2-49, p149 of the resubmission. CI = confidence interval, HR = hazard ratio, n = number of participants reporting data, N = total participants in group, OS = overall survival, PFS = progression-free survival.

**Bold** indicates statistically significant results.

Shaded cells include data presented to PBAC before.

- 6.9 The indirect analyses of regorafenib and trifluridine/tipiracil showed no statistically significant difference in OS or PFS. However, the resubmission did not specify a non-inferiority margin, which makes it difficult to assess the non-inferiority claim.
- 6.10 The resubmission excluded the CONCUR trial as well as the TERRA and J003 trail from the main indirect comparison. Subgroup analyses showed that differences in patient characteristics did not have significant treatment modification effect. Furthermore, there was low heterogeneity in the pooled results of the RECOURSE, TERRA and J003. In the trifluridine/tipiracil 2016 consideration, the PBAC considered that the exclusion of J003 might not have been warranted as patients in J003 would still qualify for treatment under the proposed PBS listing (paragraph 6.5, trifluridine/tipiracil, Public Summary Document, November 2016 PBAC meeting). Sensitivity analyses of the indirect comparison using alternative combinations of trials are presented in Table 6.

**Table 6: Results of sensitivity analyses of regorafenib and trifluridine/tipiracil: OS and PFS**

Analysis	Direct HR (95% CI)		Indirect HR (95% CI)
	REG vs. placebo	T/T vs. placebo	REG vs. T/T
<b>OS</b>			
OS (main)	0.77 (0.64, 0.94)	0.68 (0.58, 0.8)	1.132 (0.881, 1.455)
OS (sensitivity1)	0.67 (0.48, 0.93)	0.69 (0.6, 0.8)	0.971 (0.677, 1.393)
OS (sensitivity 2)	0.77 (0.64, 0.94)	0.69 (0.6, 0.8)	1.116 (0.878, 1.419)
OS (sensitivity 3)	0.55 (0.40, 0.76)	0.69 (0.6, 0.8)	0.797 (0.561, 1.133)
<b>PFS</b>			
PFS (main)	0.49 (0.42, 0.58)	0.48 (0.41, 0.56)	1.021 (0.816, 1.278)
PFS (sensitivity 1)	0.4 (0.25, 0.63)	0.46 (0.4, 0.52)	0.87 (0.538, 1.406)
PFS (sensitivity 2)	0.49 (0.42, 0.58)	0.46 (0.4, 0.52)	1.065 (0.865, 1.311)
PFS (sensitivity 3)	0.31 (0.22, 0.44)	0.46 (0.4, 0.52)	<b>0.674 (0.465, 0.976)</b>

Source: Table 2-48, p148 and Table 2-49, p149 of the resubmission.

CI = confidence interval, HR = hazard ratio, OS = overall survival, PFS = progression-free survival, REG = regorafenib, T/T = trifluridine/tipiracil.

Main analysis compared CORRECT vs RECOURSE.

Sensitivity analysis 1 compared the meta-analysis of CORRECT and CONCUR vs the meta-analysis of RECOURSE, TERRA and J003.

Sensitivity analysis 2 compared CORRECT vs the meta-analysis of RECOURSE, TERRA and J003.

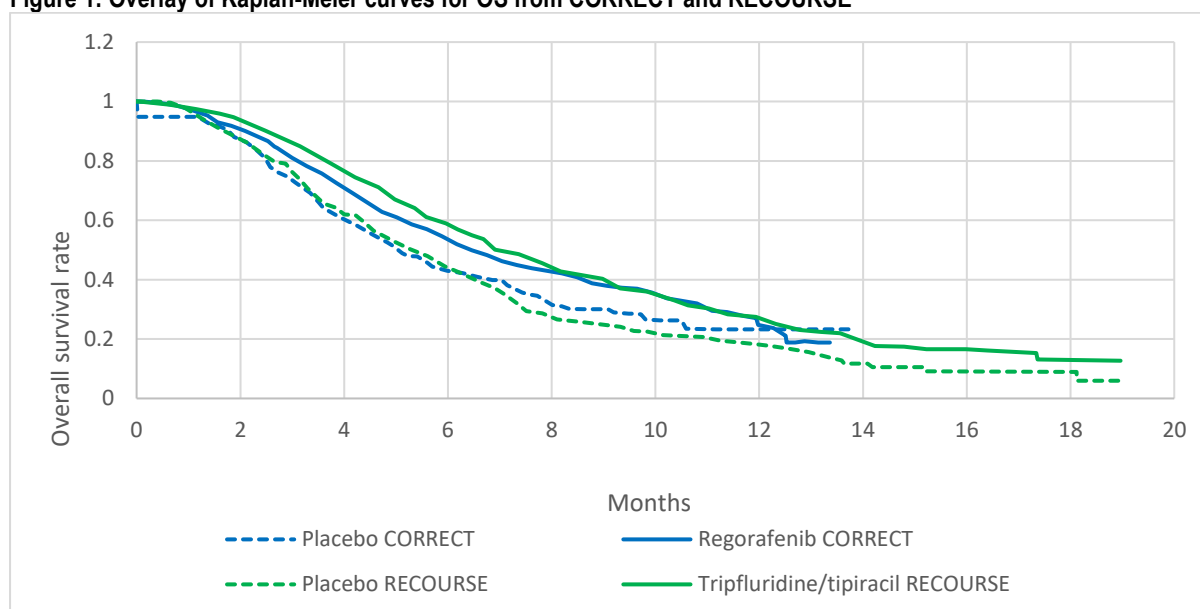
Sensitivity analysis 3 compared CONCUR vs the meta-analysis of RECOURSE, TERRA and J003.

**Bold** indicates statistically significant results.

6.11 The sensitivity analyses showed no statistically significant differences in OS between regorafenib and trifluridine/tipiracil. Similarly, there were no significant differences in PFS between regorafenib and trifluridine/tipiracil, except sensitivity analysis 3.

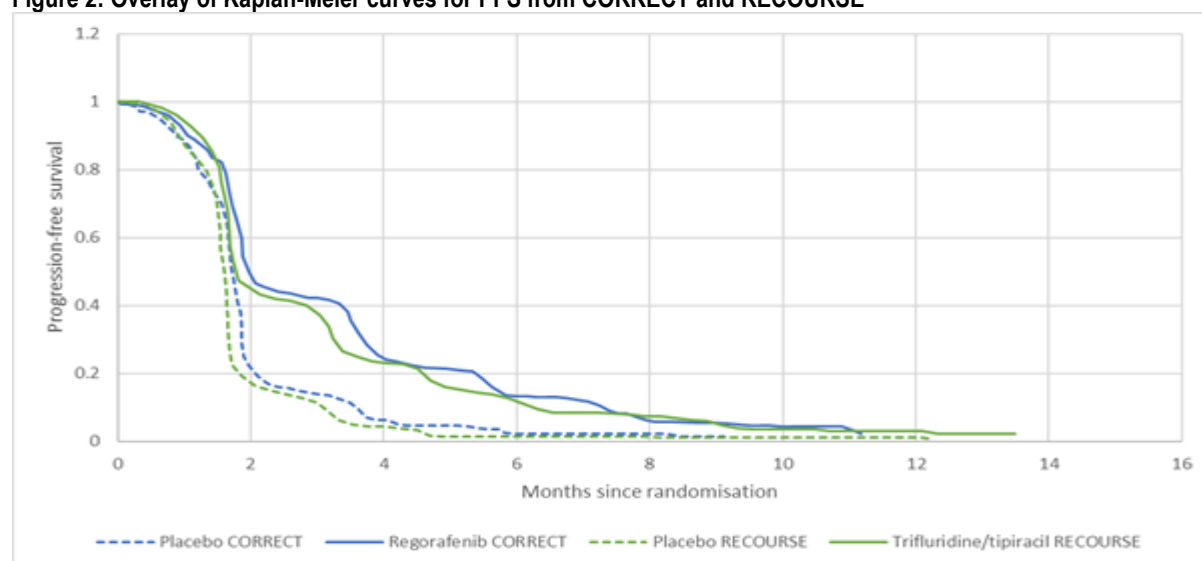
6.12 The overlay of Kaplan Meier curves for OS and PFS are presented in Figure 1 and Figure 2, respectively.

**Figure 1: Overlay of Kaplan-Meier curves for OS from CORRECT and RECOURSE**



Source: Figure 2-38, p148 of the resubmission.

Figure 2: Overlay of Kaplan-Meier curves for PFS from CORRECT and RECOURSE



Source: Figure 2-39, p149 of the resubmission.

6.13 The overlay of KM curves for OS from CORRECT and RECOURSE trials suggested that the median duration of survival was longer for trifluridine/tipiracil when compared with regorafenib (7.1 months vs 6.4 months). The presented PFS curves suggested that regorafenib had a longer median PFS compared with trifluridine/tipiracil, which was not accurate because the median PFS of trifluridine/tipiracil in the RECOURSE trial was 2.0 months compared with a median PFS of 1.9 months for regorafenib in the CORRECT trial.

6.14 The resubmission also presented patient reported outcomes from the CORRECT and the CONCUR trials as summarised in Table 7.

Table 7: Summary of patient-reported outcomes

Outcome	LS mean (95% CI)		Difference (95% CI)
	Regorafenib	Placebo	
<b>CORRECT</b>			
EORTC QLQ-C30	56.93 (54.79, 59.08)	58.13 (55.72, 60.53)	-1.19 (-3.13, 0.75)
EQ-5D			
-Index score	0.67 (0.64, 0.70)	0.67 (0.64, 0.70)	0.00 (-0.03, 0.03)
-VAS	60.62 (58.62, 62.63)	61.84 (59.59, 64.09)	-1.21 (-3.04, 0.61)
<b>CONCUR</b>			
EORTC QLQ-C30	60.70 (58.81, 62.71)	61.16 (58.48, 63.83)	-1.19 (-3.13, 0.75)
EQ-5D			
-Index score	0.70 (0.67, 0.73)	0.74 (0.70, 0.78)	-0.03 (-0.08, 0.01)
-VAS	69.28 (67.48, 71.08)	70.46 (68.01, 72.91)	-1.18 (-4.01, 1.66)

Sources: Table 2-19, p96 and Table 2-23, p101 of the resubmission.

CI = confidence interval, EORTC = European Organisation for Research and Treatment of Cancer, EQ-5D = Euro QoL, 5-dimensional QoL measurement, LS = least square, VAS = visual analogue scale.

6.15 Although not statistically significant, the least square means for EORTC QLQ-C30, EQ-5D index score and EQ-5D VAS were lower in the regorafenib arm when compared to the placebo arm across the CORRECT and CONCUR trials, indicating a negative impact

of regorafenib on quality of life. Patient-reported outcomes were not available for the trifluridine/tipiracil trials, RECOURSE, TERRA and J003.

### Comparative harms

6.16 The resubmission presented safety data for regorafenib based on the data from the CORRECT and CONCUR trials, and safety data for trifluridine/tipiracil based on the RECOURSE, TERRA and J003 trials.

6.17 Summary of key adverse events is summarised in Table 8.

**Table 8: Summary of key adverse events in the randomised trials**

Trial ID	Proposed drug n with event/N (%)	Placebo n with event/N (%)	OR (95% CI)	RR (95% CI)	RD (95% CI)
<b>Regorafenib trials vs. Placebo</b>					
<b>CORRECT</b>					
Study drug related severe (≥Grade 3) TEAE	275/500 (55.00%)	35/253 (13.83%)	<b>7.61 (5.11, 11.33)</b>	<b>3.98 (2.89, 5.46)</b>	<b>0.41 (0.34, 0.49)</b>
• Hypertension	36/500 (7.20%)	2/253 (0.79%)	<b>9.74 (2.33, 40.78)</b>	<b>9.11 (2.21, 37.53)</b>	<b>0.06 (0.03, 0.10)</b>
• Fatigue	48/500 (9.60%)	13/253 (5.14%)	<b>1.96 (1.04, 3.69)</b>	<b>1.87 (1.03, 3.38)</b>	0.04 (0.00, 0.09)
• Hand-foot skin reaction	83/500 (16.60%)	1/253 (0.40%)	<b>50.16 (6.94, 362.54)</b>	<b>42.00 (5.88, 299.94)</b>	<b>0.16 (0.11, 0.21)</b>
• Rash/desquamation	29/500 (5.80%)	0/253 (0.00%)	Not estimable	Not estimable	<b>0.06 (0.03, 0.09)</b>
• Diarrhoea	36/500 (7.20%)	2/253 (0.79%)	<b>9.74 (2.33, 40.78)</b>	<b>9.11 (2.21, 37.53)</b>	<b>0.06 (0.03, 0.10)</b>
<b>Trifluridine/tipiracil vs. Placebo</b>					
<b>RECOURSE</b>					
Study drug related severe (≥Grade 3) TEAE	261/533 (48.97%)	26/265 (9.81%)	<b>8.82 (5.69, 13.68)</b>	<b>4.99 (3.43, 7.26)</b>	<b>0.39 (0.32, 0.46)</b>
• Neutropenia	107/533 (20.08%)	0/265 (0.00%)	Not estimable	Not estimable	<b>0.20 (0.15, 0.25)</b>
• Anaemia	65/533 (12.20%)	5/265 (1.89%)	<b>7.22 (2.87, 18.16)</b>	<b>6.46 (2.63, 15.86)</b>	<b>0.10 (0.06, 0.14)</b>
• WBC decreased	52/533 (9.76%)	0/265 (0.00%)	Not estimable	Not estimable	<b>0.10 (0.06, 0.13)</b>

Source: Table 2-31, p115; Table 2-33, p118; Table 2-37, p126 and Table 2-39, p129, of the resubmission.

CI = confidence interval, n = number of participants reporting data, N = total participants in group, OR = odds ratio, RD = risk difference, RR = relative risk, TEAE = treatment emergent adverse event, WBC = white blood cells.

**Bold** indicates statistically significant results.

6.18 The safety profiles of regorafenib and trifluridine/tipiracil are different. The most common adverse events (AEs) of Grade ≥3 of regorafenib in the CORRECT trial were hand-foot skin reaction, fatigue, diarrhoea, hypertension and rash/desquamation,

whereas myelosuppression (e.g., neutropenia and anaemia) was the most common AE of Grade  $\geq 3$  reported for trifluridine/tipiracil in the RECURSE trial.

- 6.19 In the July 2014 consideration of regorafenib for patients with mCRC, the PBAC considered regorafenib to be, ‘inferior in comparative safety to BSC and noted severe adverse effects associated with the drug, particularly hepatotoxicity and hand-foot skin reactions,’ (paragraph 7.7, regorafenib, Public Summary Document, July 2014 PBAC meeting). The regorafenib Product Information carries a warning of severe drug induced hepatotoxicity with fatal outcomes.
- 6.20 The results of the indirect comparison of regorafenib and trifluridine/tipiracil with respect to Worst Grade toxicities reported by patients in the CORRECT and RECURSE is presented in Table 9.

**Table 9: Indirect comparison of regorafenib vs. trifluridine/tipiracil via Placebo: Worst Grade toxicities reported in the CORRECT and RECURSE studies**

Worst Grade reported	Outcome measure	Direct estimate (95% CI)		Indirect estimate (95% CI)
		REG vs Placebo	T/T vs Placebo	REG vs T/T
Any Grade	OR	8.13 (1.17, 38.58)	4.24 (1.88, 9.58)	1.92 (0.28, 13.19)
	RR	1.03 (1.01, 1.05)	1.05 (1.02, 1.09)	0.98 (0.94, 1.02)
	RD	0.03 (0.01, 0.04)	0.05 (0.02, 0.08)	-0.02 (-0.05, 0.01)
Max Grade 1 or 2	OR	0.30 (0.22, 0.42)	0.57 (0.42, 0.78)	<b>0.53 (0.34, 0.82)</b>
	RR	0.45 (0.37, 0.56)	0.70 (0.57, 0.85)	<b>0.64 (0.48, 0.86)</b>
	RD	-0.26 (-0.33, -0.19)	-0.13 (-0.20, -0.06)	<b>-0.13 (-0.23, -0.03)</b>
Max Grade 3	OR	3.53 (2.54, 4.92)	1.88 (1.38, 2.55)	<b>1.88 (1.2, 2.95)</b>
	RR	2.11 (1.70, 2.63)	1.44 (1.20, 1.74)	<b>1.47 (1.1, 1.95)</b>
	RD	0.30 (0.23, 0.36)	0.15 (0.08, 0.22)	<b>0.15 (0.05, 0.25)</b>
Max Grade 4	OR	1.10 (0.63, 1.91)	3.12 (1.79, 5.43)	<b>0.35 (0.16, 0.77)</b>
	RR	1.09 (0.65, 1.81)	2.77 (1.66, 4.61)	<b>0.39 (0.19, 0.81)</b>
	RD	0.01 (-0.03, 0.05)	0.11 (0.06, 0.15)	<b>-0.10 (-0.16, -0.04)</b>
Max Grade 5	OR	0.90 (0.59, 1.39)	0.26 (0.14, 0.48)	<b>3.46 (1.63, 7.33)</b>
	RR	0.92 (0.63, 1.33)	0.28 (0.16, 0.50)	<b>3.29 (1.66, 6.49)</b>
	RD	-0.01 (-0.07, 0.04)	-0.08 (-0.12, -0.04)	<b>0.07 (0, 0.14)</b>

Source: Table 2-52, p159 of the resubmission.

CI = confidence interval, OR = odds ratio, REG = regorafenib, RD = risk difference, RR = risk ratio, T/T = trifluridine/tipiracil.

**Bold** indicates statistically significant results.

- 6.21 The indirect comparison of Worst Grade toxicity showed that statistically significantly fewer patient treated with regorafenib had Grade 4 (i.e., serious) AEs than the patients treated with trifluridine/tipiracil. However, more patients treated with regorafenib suffered Grade 3 (i.e., severe) and Grade 5 (i.e., death) AEs than the patients treated with trifluridine/tipiracil. In the November 2016 consideration of trifluridine/tipiracil, the PBAC noted that trifluridine/tipiracil appears to be better tolerated when

compared to regorafenib (paragraph 7.7, trifluridine/tipiracil, Public Summary Document, November 2016 PBAC meeting).

- 6.22 The resubmission did not present sensitivity analyses to include other clinical trials in the indirect comparison of safety.
- 6.23 The PSCR stated regorafenib and trifluridine/tipiracil have distinct adverse event profiles and reiterated the results of the indirect comparison which indicated regorafenib may be associated with more grade 3 events, while trifluridine/tipiracil may be associated with more grade 4 adverse events. The ESC noted the available evidence indicated regorafenib may also be associated with more grade 5 (i.e. fatal) adverse events. The ESC was of the view that the haematological adverse effects of trifluridine/tipiracil are generally easier to manage than the severe dermatological reactions with regorafenib.
- 6.24 The Pre-PBAC Response (p1) disagreed with the ESC and argued the dermatological adverse events associated with regorafenib can be managed by a dose titration strategy and the use of topical creams. Furthermore, the sponsor also argued dose titration is now included in some treatment guidelines and adopted to mitigate the incidence of early onset grade III adverse events without compromising efficacy<sup>1</sup> and stated that a dose titration approach would also reduce the drug costs associated with regorafenib. The PBAC noted options for lower starting doses appeared to be contrary to the approved TGA Product Information for regorafenib.
- 6.25 The Pre-PBAC Response (p1) noted the results of a meta-analysis (Zhao and Zhao 2017<sup>2</sup>) that assessed the risk of regorafenib-related hepatotoxicity in 2,213 subjects across its range of approved indications, which found the incidence of life-threatening hepatic failure was extremely small. The PBAC noted that the TGA included the rare cases of fatal hepatotoxicity in a black box warning.

### **Clinical claim**

- 6.26 The resubmission described regorafenib as non-inferior in terms of effectiveness compared to trifluridine/tipiracil. The evaluation identified the key issues of uncertainty with this claim were:
- The lack of a statistically significant difference in the primary outcome in the indirect comparison is not sufficient to establish non-inferiority in the absence of a non-inferiority margin; and

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<sup>1</sup> T. J., Jacobs, N. L., Pasche, B. C., Cleary, J. M., Meyers, J. P., Desnoyers, R. J., McCune, J. S., Pedersen, K., Barzi, A., Chiorean, E. G., Sloan, J., Lacouture, M. E., Lenz, H. J., & Grothey, A. (2019). Regorafenib dose-optimisation in patients with refractory metastatic colorectal cancer (ReDOS): a randomised, multicentre, open-label, phase 2 study. *The Lancet. Oncology*, 20(8), 1070–1082. [https://doi.org/10.1016/S1470-2045\(19\)30272-4](https://doi.org/10.1016/S1470-2045(19)30272-4)

<sup>2</sup> Zhao B., Zhao H. Incidence and risk of regorafenib-induced hepatotoxicity. *Oncotarget*. 2017; 8: 84102-84111.

- The results of the indirect comparison may be subject to potential confounders, particularly the use of systemic therapies after progression on regorafenib or trifluridine/tipiracil.
- 6.27 The PSCR reiterated the view expressed in the submission that the results of the main indirect comparison are consistent with that previously considered by the PBAC for trifluridine/tipiracil. Although the PBAC had previously noted that the efficacy of trifluridine/tipiracil may be similar to that of regorafenib, the ESC noted this was a broad observation rather than a definitive conclusion on the comparative efficacy of these therapies based on a formal comparison.
- 6.28 The resubmission described regorafenib as non-inferior in terms of safety compared to trifluridine/tipiracil. The evaluation concluded this claim was not adequately supported. The key issues were:
- Post hoc statistical comparisons for selected adverse events were presented; and
  - The indirect comparisons of specific adverse events are not informative because regorafenib and trifluridine have distinct adverse events profiles.
- 6.29 Whilst there were uncertainties in the clinical comparison, the ESC considered that, on balance, the claim of non-inferior comparative effectiveness versus trifluridine/tipiracil may be reasonable, however agreed the lack of a specified non-inferiority margin exacerbated the uncertainties.
- 6.30 On balance, the ESC considered regorafenib may have a worse safety profile than trifluridine/tipiracil and noted this view appeared to be supported by the PBAC's prior expressed view relating to trifluridine/tipiracil, and the fact regorafenib is subject to a TGA black boxed warning, whilst trifluridine/tipiracil is not.
- 6.31 The PBAC considered that the claim of non-inferior comparative effectiveness to trifluridine/tipiracil was, on balance, likely to be reasonable.
- 6.32 The PBAC considered that the claim of non-inferior comparative safety to trifluridine/tipiracil was not adequately supported.

### ***Economic analysis***

- 6.33 The resubmission presented a cost-minimisation analysis against trifluridine/tipiracil. In the previous submission, a cost-utility analysis was presented against BSC.
- 6.34 The equi-effective doses were estimated as:
- 11,088 mg regorafenib (administered over 3.3 28-day cycles) to 4,104 mg of trifluridine/tipiracil (administered over 3.42 28-day cycles), or equivalently
  - 2.702 mg regorafenib is equi-effective to 1.000 mg trifluridine/tipiracil.
- 6.35 The equi-effective doses of regorafenib and trifluridine/tipiracil were based on the recommended usage in the respective TGA Product Information and were consistent

with the average number of treatment cycles completed by patients in the CORRECT and RECOURSE trials. These were 3.3 cycles for regorafenib in the CORRECT trial and 3.42 cycles for trifluridine/tipiracil in the RECOURSE trial. The same cycle numbers were used in the regorafenib previous submission, and in trifluridine/tipiracil November 2017 submission (paragraph 4.19, trifluridine/tipiracil, Public Summary Document, November 2017 PBAC meeting). However, the mean duration of treatment in the CORRECT trial was 12.08 weeks, which is 3.02 cycles (i.e., 12.08/4), and the mean duration of treatment in the RECOURSE trial was 12.7 weeks, which is 3.18 cycles (i.e., 12.7/4). Assuming fewer cycles on average for regorafenib versus trifluridine/tipiracil results in a higher price for regorafenib. If it is assumed that there are 3.3 cycles for both treatments the cost minimised AEMP for regorafenib reduces from \$ [REDACTED] to \$ [REDACTED]. The PSCR noted the Sponsor was amenable to aligning the number of cycles for the two treatments as part of the CMA. The ESC considered it was appropriate to align the number of treatment cycles for regorafenib and trifluridine/tipiracil in the CMA. The ESC further noted the cost minimised price for regorafenib would be the same using either 3.3 or 3.02 cycles if the number of treatment cycles were aligned for both treatments.

6.36 The resubmission assumed the dose intensity of both regorafenib and trifluridine/tipiracil to be 100% rather than the average dose intensity reported in CORRECT (78.9%) and RECOURSE (89.0%) trials. Furthermore, the resubmission did not consider the recommendations from the ReDOS trial and eviQ guidelines to reduce the dose of regorafenib in the first cycle. This is conservative.

6.37 The results of the cost-minimisation analysis are presented in Table 10.

**Table 10: Results of the cost-minimisation analysis**

Row	Component	Regorafenib	Trifluridine/tipiracil
A	Cost per pack AEMP <sup>a</sup> (\$)	[REDACTED]	\$942.86
B	Mg required per 28-day treatment cycle	3360	1200
C	Number of mg per pack	3360	400
D	Number of packs per 28-day treatment cycle (B/C)	1	3
E	Mean number of cycles per treatment course	3.3	3.42
F	Total cost of treatment per patient per treatment course (AXDXE) (\$)	[REDACTED]	\$9,673.74

Source: Table 3-3, p186 of the resubmission.

<sup>a</sup>The 20mg pack of trifluridine/tipiracil has been applied in these calculations for simplicity. However, the cost per mg for the 15mg and 20 mg dose strength of Lonsurf are equal. Hence the above calculations if applying the 15 mg dose total mg per pack would be equal.

6.38 On the basis of cost-minimisation analysis, the proposed published AEMP for regorafenib was \$ [REDACTED] and the proposed published DPMQ was \$ [REDACTED].

6.39 Sensitivity analyses for economic analysis were not presented in the resubmission and have been calculated as a part of the evaluation. The results of the sensitivity analyses are presented in Table 11.

**Table 11: Results of sensitivity analyses**

Component	Regorafenib	Trifluridine/tipiracil
<b>Base case</b>		
Cost per pack AEMP (\$)		\$942.86
DPMQ (\$)		\$3,932.70
<b>Assuming the mean number of cycles were equal at 3.3</b>		
Cost per pack AEMP (\$)		\$942.86
DPMQ (\$)		\$3,932.70
<b>Assuming the mean number of cycles was based on the mean duration of treatment reported in the CORRECT and RECURSE trials</b>		
Cost per pack AEMP (\$)		\$942.86
DPMQ (\$)		\$3,932.70

Source: Calculated during evaluation

<sup>a</sup> Number of cycles for regorafenib was 3.02 cycles (12.08/4) and trifluridine/tipiracil was 3.18 cycles (12.7/4).

- 6.40 The sensitivity analyses showed that using a lower number of regorafenib treatment cycles compared with trifluridine/tipiracil resulted in an increased regorafenib price.
- 6.41 The resubmission acknowledged that regorafenib and trifluridine/tipiracil have distinct AE profiles, but it did not include the costs for the management and monitoring of adverse events. Costs associated with regorafenib AEs include the costs to manage hand-foot skin reaction, hypertension and diarrhoea. The TGA recommends monitoring for abnormal liver function tests before initiation of treatment with regorafenib and every two weeks during first two months of treatment, then monthly as clinically indicated. The exclusion of these costs likely underestimates the economic cost associated with the use of regorafenib.
- 6.42 The cost-minimisation approach is only appropriate if the non-inferiority claims regarding comparative effectiveness and safety between regorafenib and trifluridine/tipiracil are accepted.
- 6.43 The cost-minimisation approach must establish that the cost per patient for treatment with regorafenib would be no more than the cost per patient of trifluridine/tipiracil. The cost per patient takes into account the mean equi-effective doses of the new intervention and the alternative therapy, and also accounts for any difference in the mean duration of treatment. Where these cost per patient calculations are uncertain, the guiding principle is that the Australian Government should not bear the financial risk of this uncertainty because the Australian population already has access to therapy that is at least as effective and safe. In this regard, the assumed short treatment duration and exclusion of the management and monitoring of adverse events are uncertainties that should be considered.
- 6.44 The PSCR (p5) argued not including adverse event costs in the CMA was conservative on the basis many of the known adverse events associated with regorafenib could be managed prophylactically with low cost topical creams or pain relief for hand, foot and/or skin reactions, antihypertensive therapies and anti-diarrhoea medication; whilst adverse events associated with trifluridine/tipiracil may require prophylactic

administration of expensive growth factors or blood transfusions. The ESC did not accept the argument in the PSCR and reiterated that regorafenib appeared to have a worse safety profile than trifluridine/tipiracil (paragraph 6.27 refers) and therefore the cost of managing adverse events should have been included in the CMA.

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

6.45 This submission was not considered by DUSC.

6.46 The resubmission used a market share approach to assess the financial impact of listing regorafenib. The key inputs for financial estimates are summarised in Table 12.

**Table 12: Key inputs for financial estimates**

Parameter	Value applied and source	Comment
<b>Treatment utilisation</b>		
Uptake rate	█% in Year 1 increasing to █% of trifluridine/tipiracil share in Year 6. Assumed by the resubmission.	Based on the assumption that trifluridine/tipiracil will lose █% of its market share to regorafenib in Year 1, █% in Year 2, and █% in subsequent years.
Projected use of trifluridine/tipiracil	█ <sup>1</sup> scripts. Assumed to be constant from 2020 onwards.	Use of trifluridine/tipiracil was assumed to remain the same from year 1 to year 6. This is uncertain because it was based on historical data over a short period of two years.
<b>Costs</b>		
Proposed medicine	\$█. Requested price by the submission.	The cost minimised price was based on the assumption of non-inferiority in safety and effectiveness compared with trifluridine/tipiracil, which is highly uncertain. It did not include additional costs associated with management and monitoring of adverse events.
Comparator	\$2282.58 (trifluridine/tipiracil – 15 mg) \$3932.62 (trifluridine/tipiracil – 20 mg) PBS listed drugs (published prices)	The effective price of trifluridine/tipiracil in the Special Pricing Arrangement is unknown to the sponsor.
Patient co-payment	\$18.87. PBS statistics.	A weighted average patient co-payment was calculated using current trifluridine/tipiracil usage data by co-pay types as a basis.

Source: Section 4.1, pp187-191 of the resubmission.

The redacted values correspond to the following ranges:

<sup>1</sup> 500 to < 5,000

6.47 The source of the market share of █% proposed was not clear. Moreover, the assumption of a stable market share over time was not well justified.

6.48 The estimated use and financial implications associated with the use of regorafenib are summarised in Table 13.

**Table 13: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of scripts dispensed <sup>a</sup>	■ <sup>1</sup>	■ <sup>1</sup>	■ <sup>1</sup>	■ <sup>1</sup>	■ <sup>1</sup>	■ <sup>1</sup>
<b>Estimated financial implications of regorafenib</b>						
Cost to PBS/RPBS less co-payments	■ <sup>2</sup>	■ <sup>2</sup>	■ <sup>2</sup>	■ <sup>2</sup>	■ <sup>2</sup>	■ <sup>2</sup>
<b>Estimated financial implications for trifluridine/tipiracil</b>						
Cost to PBS/RPBS less co-payments	■ <sup>2</sup>	■ <sup>2</sup>	■ <sup>2</sup>	■ <sup>2</sup>	■ <sup>2</sup>	■ <sup>2</sup>
<b>Net financial implications</b>						
Net cost to PBS/RPBS less co-payments	■ <sup>2</sup>	■ <sup>2</sup>	■ <sup>2</sup>	■ <sup>2</sup>	■ <sup>2</sup>	■ <sup>2</sup>
<b>Previous submission July, 2014</b>						
Net cost to PBS/RPBS	■ <sup>2</sup>	■ <sup>2</sup>	■ <sup>2</sup>	■ <sup>2</sup>	■ <sup>2</sup>	NR
Revised net cost to PBS/PRBS	■ <sup>2</sup>	■ <sup>2</sup>	■ <sup>2</sup>	■ <sup>2</sup>	■ <sup>2</sup>	NR

Source: Table 4-8, p192; Table 4-9, p193; Table 4-10, p194 of the resubmission; Table E.4.1, p231 of the previous submission and Table E.4.1, p64 of 5.15 regorafenib COM 07-14.

NR = not reported

Shaded cells include data presented to PBAC before.

The redacted values correspond to the following ranges:

<sup>1</sup> 500 to < 5,000

<sup>2</sup> \$0 to < \$10 million

- 6.49 The net financial impact of listing regorafenib was estimated to be \$0 to < \$10 million in Year 6, with a total of \$0 to < \$10 million in the first 6 years of listing.
- 6.50 Based on the claim of non-inferiority in effectiveness and safety, the resubmission did not estimate any impact on the MBS or the financial implication for the broader health budget. This was not appropriate because this ignores the additional costs associated with the monitoring and management of the different types of AEs associated with regorafenib and trifluridine/tipiracil.
- 6.51 The resubmission assumed that regorafenib would substitute trifluridine/tipiracil in the third line of mCRC treatment; however, regorafenib and trifluridine/tipiracil may be used before or after each other in practice. If regorafenib is used in subsequent lines of therapy, then the substitution cost-offsets might be overestimated, and overall financial impact of regorafenib listing might be underestimated.
- 6.52 The listing of regorafenib may affect the utilisation of chemotherapy and palliative care in subsequent lines of treatment. This was not included in the analysis.
- 6.53 The risk of leakage to use in patients with a WHO performance status of >1 cannot be excluded, which may increase the overall financial cost of regorafenib.
- 6.54 The PSCR argued that excluding the costs of adverse event management was reasonable as these are often managed through dose modifications for both regorafenib and trifluridine/tipiracil. The ESC considered this was not appropriate as

regorafenib may have a worse safety profile than trifluridine/tipiracil and the cost of managing adverse events for these therapies was different.

### **Financial Management – Risk Sharing Arrangements**

- 6.55 There is currently a Special Pricing Arrangement and a Risk sharing Agreement in place for trifluridine/tipiracil in the mCRC therapeutic area.

## **7 PBAC Outcome**

- 7.1 The PBAC did not recommend the listing of regorafenib for the treatment of metastatic colorectal cancer (mCRC) after treatment with two or more prior therapies, on the basis that the evidence presented indicated regorafenib is toxic and would adversely impact patients' overall quality of life, whilst having a limited impact on prognosis. The PBAC considered while there was a clinical need for additional safe and effective later-line therapies in mCRC, the modest efficacy and poor safety profile of regorafenib meant it did not fulfil this need.
- 7.2 The PBAC noted there appeared to be limited support amongst clinicians or patients for the PBS listing of regorafenib in this population, given only one comment was received, from Bowel Cancer Australia, which was in general support for additional choices for patients. The Committee also noted the Medical Oncology Group of Australia (MOGA) did not include regorafenib in its list of supported applications.
- 7.3 The PBAC considered the nominated comparator of trifluridine/tipiracil was reasonable, as the only other PBS-listed option in this line of therapy for mCRC.
- 7.4 The PBAC noted there were no head-to-head trials of regorafenib and trifluridine/tipiracil for the treatment of patients with mCRC after two or more prior therapies. Therefore, the resubmission conducted an indirect treatment comparison (ITC) of regorafenib and trifluridine/tipiracil, using placebo as a common reference.
- 7.5 The PBAC considered that, whilst there were uncertainties with the ITC and variability in the sensitivity analyses, the evidence presented may support a claim of non-inferior comparative effectiveness in terms of overall survival and progression-free survival of regorafenib to trifluridine/tipiracil. However, the Committee considered in this late stage setting, the magnitude of benefit appeared to be small and of borderline clinical meaningfulness.
- 7.6 The PBAC noted the evidence presented indicated regorafenib is associated with significant risk of adverse events, including many of grade III or higher severity. The PBAC was particularly concerned about the high number of hand-foot skin reactions of this severity (16.6% in the CORRECT trial) and the impact on patients' ability for self-care. It was also noted more than 7% of patients experienced diarrhoea at this level of severity, which may require hospitalisation. The PBAC also noted the TGA black box warning for rare cases of fatal hepatotoxicity.

- 7.7 The Committee considered regorafenib and trifluridine/tipiracil have distinct adverse event profiles, however it was the view of the Committee that the haematological adverse effects of trifluridine/tipiracil are generally easier to manage than the severe dermatological reactions with regorafenib, and regorafenib was associated with statistically significantly higher rates of adverse events leading to treatment discontinuation. Based on the available evidence, the PBAC did not agree with the submission claim of non-inferior comparative safety to trifluridine/tipiracil and considered regorafenib was likely inferior. The Committee also noted the Pre-PBAC Response and sponsor hearing suggested dose modification and lower dose regimens may be used in practice to address the risk and severity of adverse events; however, the PBAC noted that the recommended dosing in Australian Product Information only includes a starting dose of 160mg per day.
- 7.8 The PBAC considered the cost minimisation approach inappropriately did not account for differing costs of managing adverse events of regorafenib and trifluridine with tipiracil.
- 7.9 The PBAC considered that the uptake of regorafenib was likely overestimated, given the poor safety profile and likely modest effectiveness of regorafenib after two or more prior therapies in mCRC. The Committee was of the view that the use of regorafenib would likely be very low in practice if listed on the PBS. The PBAC noted the sponsor had also indicated a willingness to join the trifluridine/tipiracil Risk Sharing Arrangement.
- 7.10 The PBAC noted that this submission is for an Independent Review.

**Outcome:**

Not recommended

## **8 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

## **9 Sponsor's Comment**

Bayer is disappointed that the Pharmaceutical Benefits Advisory Committee (PBAC) did not recommend the reimbursement of Stivarga® (regorafenib) for the treatment of patients with metastatic colorectal cancer (mCRC). Bayer remains of the view that

Stivarga® is an effective treatment option for patients with mCRC and has a manageable adverse events profile, where tolerability can be maintained by dose modifications, while maintaining quality of life.