

5.15 REGORAFENIB, tablet, 40 mg, Stivarga[®], Bayer Australia Limited

1 Purpose of Application

- 1.1 Authority required listing of initial or continuing treatment of metastatic colorectal cancer following failure of, or intolerance to, other treatment options.

2 Requested listing

2.1

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
REGORAFENIB tablet 40mg (as monohydrate)	84	2	Stivarga [®]	BN

Section 85. Authority Required (STREAMLINED)

Initial PBS-subsidised treatment as monotherapy, of a patient with a WHO performance status of 0 or 1 with metastatic colorectal cancer, following failure of, or intolerant to, approved standard chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy.

Continuing PBS-subsidised treatment, as monotherapy, of a patient with metastatic colorectal cancer who has previously received PBS-subsidised treatment with regorafenib and who does not have progressive disease.

- 2.2 The PBAC considered that a telephone Authority rather than a Streamlined Authority would be more appropriate.

- 2.3 Listing was sought on a cost-utility basis compared with best supportive care (BSC).

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

3 Background

- 3.1 Regorafenib was approved by the TGA on 29th November 2013 for 'the treatment of patients with metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine,-oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy and, if KRAS wild type, an anti-EGFR therapy'.

- 3.2 Regorafenib was initially rejected by the TGA (May, 2013). The TGA delegate's overview considered that the increase in overall survival (OS) was not clinically significant and not supported by secondary endpoints. Following an appeal from the sponsor the TGA subsequently approved the listing of regorafenib. The reviewing delegate stated that there was "evidence of statistically significant and consistent, albeit modest, benefit in terms of OS and PFS in heavily pre-treated patients with mCRC where there is no approved treatment alternative."

- 3.3 Similarly, a submission was made in Europe (May, 2012) that was initially rejected due to a negative benefit-risk profile. On review of updated survival data (CORRECT trial as presented in this submission) and consideration of sub-group analyses the European Assessment Summary (EAS) found that "the results are of potential clinical relevance considering the target population is patients for which no other treatment

options are available. However, the absolute gain of 1.4 months is rather modest” (EAS, p4).

3.4 This drug has not been considered by PBAC previously.

4 Clinical place for the proposed therapy

4.1 Regorafenib is an oral tumour deactivation agent that blocks multiple protein kinases, including those involved in angiogenesis, oncogenesis and the tumour microenvironment. The current treatment algorithm is dependent on *KRAS* status. Regorafenib is proposed for use after failure of oxaliplatin or irinotecan based regimens and after failure of treatment with bevacizumab or cetuximab (if *KRAS* WT).

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

5 Comparator

5.1 The submission nominates best supportive care (BSC) as the main comparator.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (1) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described benefits of treatment with regorafenib including a clinical need for new treatment options and equitable access to such cancer treatments.

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

Clinical trials

6.3 The submission is based on one double-blind randomised trial, the CORRECT trial, comparing regorafenib plus BSC to placebo plus BSC, shown below.

Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials		
CORRECT	A randomized, double-blind placebo-controlled phase III study of regorafenib plus BSC versus placebo plus BSC in patients with mCRC who have progressed after standard therapy Axel Grothey et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial.	19 March 2012 The Lancet. Published online 22 November 2012 pp. 1-10.

Source: Table B.2.3, p82 of the submission

- 6.4 The ESC noted that the trial data were mature with no cross-over in the trial and the subsequent therapy was relatively balanced between treatment arms.

Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
regorafenib vs. BSC						
CORRECT trial	760 (2:1 allocation)	R, DB 12 months	Low	Metastatic, failed ≥ 2 lines chemotherapy	OS, PFS	OS,PFS extrapolated

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

Source: compiled during the evaluation

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

Comparative effectiveness

- 6.5 Regorafenib treatment was associated with a statistically significant OS and PFS benefit compared with BSC (placebo). The median OS improvement was 1.4 months and median PFS improvement was 0.2 months.

Results of OS and PFS across the direct randomised trials

Trial ID	Proposed drug n with event/N (%) [or mean \pm SD]	Main comparator n with event/N (%) [or mean \pm SD]	Absolute difference RD \pm NNT [or mean difference] (95% CI)	Relative difference RR/HR [or results of statistical testing] (95% CI)
CORRECT				
OS	275/505(54.5)	157/255(61.6)	0.07(0.14,0.00)	0.774(0.636,0.942)
PFS	430/505(85.1)	241/255(94.5)	0.09(0.14,0.05)	0.494(0.419,0.582)

Source: Table B.6.1, Table B.6.2, Section B, p 17-18 of the commentary.

- 6.6 The ESC agreed that regorafenib was superior in terms of comparative effectiveness to BSC alone.
- 6.7 The TGA (and European Medicines Agency, EMA) has previously questioned the clinical meaningfulness of the OS advantage of 1.4 months, particularly as it was not supported by a meaningful difference in PFS (0.2 months) or an improvement in quality of life over BSC. The submission provided additional information in the form of sub-group analyses and expert opinion. On review both the TGA and EMA considered that “there is evidence of statistically significant and consistent, albeit modest, benefit in terms of overall survival and progression free survival”.

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

Comparative harms

- 6.8 More patients in the regorafenib arm than the placebo arm experienced Grade 3-4 drug-related, treatment-emergent serious adverse events (SAEs), experienced adverse events leading to discontinuation and had dose modifications. The most common treatment emergent AEs of grade 3 or higher in the regorafenib arm included hand-foot skin reaction, fatigue, diarrhoea, hypertension and hyperbilirubinaemia. There were five drug related deaths, due to hepatotoxicity, haemorrhage and vascular events related to regorafenib use. Regorafenib was approved by the FDA with a boxed warning describing the risk of hepatotoxicity.
- 6.9 The ESC considered that regorafenib is inferior in terms of comparative safety to BSC (placebo), which is understated by the phrase ‘slightly worse’.

6.10 The TGA considered that the safety profile is “in line with those seen in other similar drugs approved for use in metastatic solid tumours. The effect of these toxicities can be mitigated, but not eliminated, through skilled management”.

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

Summary of comparative benefits and harms for regorafenib and BSC

Trial	regorafenib	BSC	RR (95% CI)	Event rate/100 patients*		RD (95% CI)	
				regorafenib	BSC		
Benefits							
Dichotomous Outcome 1							
Deaths	275/505	157/255	0.774 (0.636,0.942)	54.4	61.6	7.2 (3.0, 14)	
Median (mths) [IQR]	6.4(3-11.8)	5.0 (2.8-10.4)	-	-	-	1.4 months	
Dichotomous Outcome 2							
Progression	430/505	241/255	0.494 (0.419,0.582)	85.1	94.5	9.4 (4.0,13.0)	
Median (mths) [IQR]	1.9(1.6-3.9)	1.7(1.4-1.9)	-	-	-	0.2 months	
Continuous Outcome I: change from baseline EQ-5D							
	regorafenib			BSC			Mean difference*: regorafenib vs. BSC (95% CI)
	n	Mean Δ baseline EQ-5D	SD	n	Mean Δ baseline EQ- 5D	SD	
Cycle 2	354	-0.075	0.25	187	-0.071	0.243	0.004 (NR)
EOT	262	-0.159	0.294	136	-0.20	0.300	0.041(NR)
Harms (\geq Grade 3)							
	regorafenib	BSC	RR (95% CI)	Event rate/100 patients*		RD	
				regorafenib	BSC		
Adverse event I							
Diarrhoea	42/500(0.08)	5/253 (0.01)	3.99 (1.66,9.98)	8.4	1.97	6.42	
Adverse event II							
Hand/foot	83/500(0.16)	1/253(0.004)	36.16 (5.06,158.33)	16.6	0.4	16.2	

* CORRECT trial = approximately 12 months

Abbreviations: PBO = placebo; RD = risk difference; RR = risk ratio

Source: Compiled during the evaluation/Table Table B.6.1, Table B.6.2, Section B, p 17-18, Attachment B of the commentary.

6.12 The PBAC noted on the basis of direct comparison of regorafenib with BSC:

- the improvement in median progression-free survival was approximately 6 days, and the improvement in median overall survival was approximately 43 days.
- for every 100 patients treated with regorafenib compared with BSC:
 - 1 patient would die from a treatment-related adverse event.
 - 16 patients would experience hand/foot adverse events.
 - 6 patients would experience diarrhoea.
- at the end of treatment, the quality of life of participants in both arms of the study fell as measured by EQ-5D, with patients on regorafenib falling approximately

0.041 more than patients on BSC. However, the area under curve (AUC) analysis over the 12 months of the trial period showed no significant difference in overall quality of life (Mean difference 0.00 95%CI -0.03,0.03) between the regorafenib and BSC arms. However, it is feasible that the on-treatment differences may reflect a clinically important dis-utility associated with higher adverse events that the EQ-5D was not powered to detect. Utility differences between on-treatment arms are considered in the economic evaluation.

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

Clinical claim

- 6.13 The submission describes regorafenib as superior in terms of comparative effectiveness and ‘slightly worse’ in terms of comparative safety over BSC (placebo).
- 6.14 The PBAC considered that the claim of a statistically significant improvement in survival was reasonable, but was not convinced a gain in PFS of a median 0.2 months and OS of a median of 1.4 months (approximately 43 days) is clinically significant.
- 6.15 The PBAC agreed with the ESC that the claim of ‘slightly worse’ comparative safety is understated and considered that a claim of inferior comparative safety was reasonable.

Economic analysis

- 6.16 A summary of the model structure and key drivers of the model are shown below.

Summary of model structure and rationale

Time horizon	5 years in the model base case versus approximately 13 months (400days) for PFS and OS in the trial.
Outcomes	LYG and QALYs
Methods used to generate results	Directly trial-based, using log-normal and log-logistic and area under the curve analysis.
Cycle length	1 week (based on chemotherapy cycles). Half cycle correction are applied to outcomes (not costs)
Transition probabilities	Calculated by survival analysis.
Discount rate	5% for costs and outcomes
Software package	Excel 2007.

Source: compiled during the evaluation

Key drivers of the model

Description	Method/Value	Impact
Time horizon	5 years; assumed from approximately 12 month trial duration	High, favours regorafenib
Extrapolated OS assumptions	Based on modelled OS using log-normal	High, favours regorafenib

Source: compiled during the evaluation

- 6.17 The ESC agreed with the Commentary, that if BSC was accepted as the comparator, then patients in the placebo group would not receive chemotherapy at progression. The assumption that BSC patients do receive chemotherapy is therefore inappropriate and favours regorafenib. On this basis, post-progression chemotherapy costs in the BSC should be excluded from the economic evaluation. The ESC agreed that the revised base-case ICER range of \$45,000/QALY to \$75,000/QALY should be

used for testing all other sensitivity analyses. In the pre-PBAC response, the sponsor agreed with this approach.

Results of the stepped economic evaluation^a

Component	Incremental costs	Incremental effectiveness	Incremental cost-effectiveness ^a
Within trial			
IC/LYS revised	██████████	██████	██████████
IC/QALY revised	██████████	██████	██████████
Extrapolated to 5 years			
IC/LYS revised	██████████	██████	██████████
IC/QALY Revised (<i>revised base-case accepted by ESC</i>)	██████████	██████	██████████

^a revised base-case assumes no post-progression costs (refer p47 of the commentary). Source: pp50-51 of the commentary.

6.18 The ESC considered that a time horizon of 3 years may be more appropriate for modelling this stage of disease. The ESC noted that additional sensitivity analyses of models extrapolating the OS outcomes were provided in table 2 of the PSCR (p5). From the base case ICER presented in the submission of \$45,000/QALY to \$75,000/QALY, the ESC noted that the ICER varied between \$45,000/QALY to \$75,000/QALY (Reference curve and HR, Log logistic) and \$75,000/QALY to \$105,000/QALY (Independent Curves, Exponential).

6.19 The submission presents univariate sensitivity analysis. The key drivers are the estimates of OS, extrapolation and the time on treatment.

Key sensitivity analyses

Sensitivity analysis	Base Case	Worst Case	
	Value	Value	Cost/QALY
Base Case ICER = \$██████████			
95% CI OS HR	██████	██████	██████████
Weeks on regorafenib treatment	██████	██████	██████████
Assuming no treatment effect beyond trial /trial based ICER	██████████	██████████	██████████

6.20 The economic evaluation used values from the EQ-5D from the CORRECT trial. The ESC noted that CORRECT also collected cancer specific quality of life data using QLQ-C30. ESC noted that a sensitivity analysis could have been undertaken by transforming the QLQ-C30 values to utility scores.

6.21 Regarding whether a sustained treatment effect is clinically feasible for these patients, the PSCR (p3) argued that ‘...the treatment effect cannot readily be equalized between groups beyond the trial period without imposing an artificial assumption that patients in the regorafenib group have a greater hazard of death in the post-trial period than those in the BSC group’. The ESC considered that a sensitivity analysis as proposed in the Commentary would be informative to assess the ‘worst case’.

6.22 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. All adverse event costs in the model are inappropriately applied as a one-off cost during the first cycle of the model.

- 6.23 The ESC noted that the evaluation has tested the impact of higher costs associated with the management of adverse events in the sensitivity analysis and the impact is low.
- 6.24 The PSCR (p3-4) argues that the alternative scenario considered by the evaluator in a revised sensitivity analysis, in which every patient with Grade 3 or 4 diarrhoea would incur an admitted episode of hospitalization is simply not plausible. Noting that this may be extreme, the ESC agreed that it would be appropriate to consider a ‘worst case’ scenario of the costs associated with adverse events that require hospitalisation, as a counter point to the submission which has assumed a ‘best case’ by assuming no hospitalisations.

Results of uni-variate sensitivity analyses- evaluation

	INC Costs	INC QALYs	INC LYS	ICER/QALY	ICER/LYS
Base- Case	████████	██████	█████	██████	██████
Within trial results	████████	██████	█████	██████	██████
Revised base case- no post-progression costs.	████████	██████	█████	██████	██████
SA1 revised AE costs- including hospitalisation DRG-G60B \$████████ + revised basecase.	████████	██████	█████	██████	██████
SA2- assuming no treatment effect beyond 12 months / trial based ICER	████████	██████	█████	██████	██████

Developed as part of the evaluation.

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

Drug cost/patient/course: \$██████ /per patient/per course.

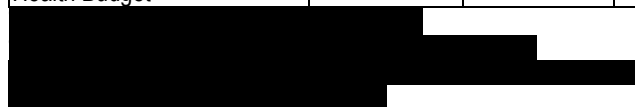
Estimated PBS usage & financial implications

- 6.25 This submission was not considered by DUSC.
- 6.26 The submission’s estimates of PBS usage and the financial implications are summarised in the table below:

Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Number treated	█████	█████	█████	█████	█████
Uptake Rate	█████	█████	█████	█████	█████
Scripts ^a	█████	█████	█████	█████	█████
Estimated net cost to PBS/RPBS/MBS					
Net cost to PBS	████████	████████	████████	████████	████████
Revised net cost to PBS ^b	████████	████████	████████	████████	████████
Net cost to Government for MBS	████████	████████	████████	████████	████████
Revised Net cost to Government for MBS ^c	████████	████████	████████	████████	████████
Estimated total net cost					
Net cost of regorafenib to Government Health Budget	████████	████████	████████	████████	████████
Revised net cost of	████████	████████	████████	████████	████████

	Year 1	Year 2	Year 3	Year 4	Year 5
regorafenib to Government Health Budget					



6.27 The submission has indicated that the Sponsor is willing to enter into a special pricing arrangement with a published and effective price.

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

7 PBAC Outcome

- 7.1 The PBAC rejected the submission on the basis that the observed improvement in comparative effectiveness associated with regorafenib was of uncertain clinical significance especially in the context of the increase in serious adverse effects associated with treatment. Even if the small incremental survival gain was considered to be clinically significant, the most reliable estimate of the incremental cost-effectiveness ratio for regorafenib compared to best supportive care was unacceptably high.
- 7.2 The PBAC noted the consumer comments regarding the importance of effective treatments for bowel cancer. However, the PBAC considered that the comparative effectiveness of this drug was small and that treatment was associated with significant adverse effects.
- 7.3 The PBAC accepted that BSC (placebo) was an appropriate comparator.
- 7.4 The PBAC noted that there is a risk of use outside the requested listing, in patients with a WHO performance status greater than 1 and in the post-progression setting. Leakage would further worsen the cost-effectiveness of this medicine.
- 7.5 The PBAC considered that the clinical evidence from the key clinical trial CORRECT trial data was mature, there was no cross-over and subsequent therapy was relatively balanced between treatment arms. For this reason, the CORRECT trial was unlikely to have underestimated the effectiveness of regorafenib compared with BSC.
- 7.6 The PBAC noted the small gain in median PFS of 0.2 months and median OS of 1.4 months in CORRECT. The Committee also expressed concern at the inconsistency between the relatively larger (although still numerically small) gain in OS compared to PFS, noting the initial TGA delegate’s overview that considered that the increase in OS was not supported by secondary endpoints. The PBAC noted that no patients in the CORRECT trial had a complete response and that EQ-5D data showed no improvement in quality of life with regorafenib.
- 7.7 The PBAC agreed that regorafenib was inferior in comparative safety to BSC and noted the severe adverse effects associated with the drug, particularly hepatotoxicity and hand-foot skin reactions.
- 7.8 The PBAC accepted the ESC advice about the modelled evaluation including:
 - Time Horizon: the submission assumes a sustained treatment effect with a time horizon of 5 years. This extrapolation was not accepted, noting that most patients with metastatic colorectal cancer would not survive to 5 years. The revised model truncated the time horizon to 3 years.

- Inclusion of post-progression costs in the economic evaluation: the revision to post progression costs of chemotherapy as recommend by ESC was accepted by the sponsor in the Pre-PBAC response.
- Costs associated with adverse effects requiring hospitalisation: the submission did not consider costs associated with adverse effects that require hospitalisation. The PBAC agreed that the exclusion of these costs may underestimate the cost of managing adverse events.
- Palliative care costs: the submission did not include palliative costs in the model. The PBAC considered that while it is possible that regorafenib may delay palliation, it is also possible that palliative care costs may begin to accrue before treatment with regorafenib is completed, and that these should be included in the model.
- The use of cetuximab to calculate third-line treatment costs: the current restriction for cetuximab suggests that it would be used second-line rather than third-line and the requested restriction requires that anti-EGFR antibody be used prior to regorafenib. Therefore the PBAC did not accept it appropriate to include cetuximab in the analysis.

The PBAC considered that these issues, combined with the estimate of the small overall effect of regorafenib, resulted in an unacceptably high ICER. While some inputs to the model might be adjusted to address the PBAC concerns, the overall question of the likely value to patients of the small gain in survival compared to the increase in adverse effects would not be able to be resolved by amending the economic model.

7.9 The PBAC noted that the sensitivity analysis showed that there is considerable variation in the financial estimates of cost to the Commonwealth.

7.10 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected.

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

The sponsor had no comment.