

7.10 TRIFLURIDINE with TIPIRACIL

Tablet containing 15 mg trifluridine with 6.14 mg tipiracil (as hydrochloride),

Tablet containing 20 mg trifluridine with 8.19 mg tipiracil (as hydrochloride),

Lonsurf[®], Servier Laboratories (Australia) Pty Ltd.

1 Purpose of Application

- 1.1 Authority Required / Authority Required (STREAMLINED) listing for trifluridine with tipiracil (thereafter referred to as trifluridine/tipiracil) for the treatment of patients with metastatic colorectal cancer (mCRC) who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine, oxaliplatin and irinotecan-based chemotherapy, anti-VEGF therapy and anti-EGFR therapy.

2 Requested listing

- 2.1 The requested restriction is presented below, including initial and continuing criteria.
- 2.2 The minor resubmission requested both Authority Required and Authority Required (STREAMLINED) listings. The pre-PBAC response (p1) indicated preference for an Authority Required (STREAMLINED) listing. The PBAC considered the risk of leakage to indications other than mCRC to be small and hence that a STREAMLINED authority may be acceptable.

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Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Manufacturer	Name and
TRIFLURIDINE + TIPIRACIL					
Trifluridine 15 mg + tipiracil tablet, 20	6.14 mg 3	2	\$ [REDACTED] ^a	LONSURF	Servier Laboratories
Trifluridine 20 mg + tipiracil tablet, 20	8.19 mg 4	2	\$ [REDACTED] ^b		

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	-
Severity:	Metastatic
Condition:	Metastatic colorectal cancer
PBS Indication:	Metastatic colorectal cancer
Treatment phase:	Initial treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	Patient must have a WHO performance status of 1 or less, AND Patient must have previously received treatment with fluoropyrimidine, oxaliplatin, irinotecan-based chemotherapies, an anti-VEGF agent and an anti-EGFR agent, OR Patient must not be a candidate for treatment with fluoropyrimidine, oxaliplatin, and irinotecan-based chemotherapies, anti-VEGF agents and anti-EGFR agents.
Administrative Advice	The prescribed dose is not permitted to be increased once it has been reduced. No increase in maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised.

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	-
Severity:	Metastatic
Condition:	Metastatic colorectal cancer
PBS Indication:	Metastatic colorectal cancer
Treatment phase:	Continuing treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input checked="" type="checkbox"/> Authority Required – Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	Patient must have previously been issued with an authority prescription for this drug for this condition, AND Patient must not have progressive disease while on this drug, AND The treatment must be the sole PBS-subsidised therapy for this condition.
Prescriber Instructions	A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug.
Administrative Advice	The prescribed dose is not permitted to be increased once it has been reduced. No increase in maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised.

^a Effective price = \$ [redacted] (including [redacted] % rebate)

^b Effective price = \$ [redacted] (including [redacted] % rebate)

3 Background

- 3.1 A major submission for trifluridine/tipiracil was previously considered by the PBAC at the November 2016 meeting. The major submission was made under the TGA/PBAC parallel process. The TGA clinical evaluator’s first round report was received prior to the November 2016 PBAC meeting. The TGA Delegate’s overview (for the April 2017 meeting of Advisory Committee on Medicines) was not available one week prior to the PBAC meeting.
- 3.2 At the November 2016 meeting, trifluridine/tipiracil was not recommended for listing on the basis of a modest clinical benefit, high and uncertain incremental cost-effectiveness ratio, and concern that the extent of benefit as observed in the clinical trial would not be realised in clinical practice (paragraph 7.1 of the November 2016 Public Summary Document).

3.3 A summary of the November 2016 major submission and March 2017 minor resubmission is presented in Table 1.

Table 1: Summary of the November 2016 major submission and the March 2017 minor resubmission

	November 2016 major submission	March 2017 minor resubmission
Requested PBS listing	Authority Required (STREAMLINED) listing for the treatment of patients with mCRC who have been treated with/not considered candidates for available therapies.	Both an Authority Required and Authority Required (STREAMLINED) listing was requested.
Requested effective DPMQs	Trifluridine 15 mg + tipiracil 6.14 mg tablet, 20: \$ [REDACTED] Trifluridine 20 mg + tipiracil 8.19 mg tablet, 20: \$ [REDACTED] *Prices include [REDACTED] % rebate	\$ [REDACTED] \$ [REDACTED] *Prices include [REDACTED] % rebate
Main comparator	Best supportive care PBAC Comment: (paragraph 7.4) The PBAC considered best supportive care to be the appropriate comparator.	No change
Clinical evidence	Primary trial: RECURSE (n=800), head to head, randomised double blind trial (used in economic model). Supportive trial: J003 trial (n=169), considered only as supportive because of Asian ethnicity of recruited patients (not used in economic model as required ECOG data not reported). PBAC Comment: (paragraph 7.5) the results of the J003 trial were similar to those for the RECURSE trial.	Pooled analysis of RECURSE and J003 trials used in economic model as a revised model based on PFS which was reported in both trials.
Key effectiveness data	RECURSE trial <u>Mean overall survival, months (95% CI)</u> trifluridine/tipiracil: 9.7 (9.2, 10.3); placebo: 7.2 (6.6, 7.9) difference: 2.5 months <u>Mean time to deterioration of ECOG-PS to ≥2, months (95% CI)</u> trifluridine/tipiracil: 6.5 (6.1, 6.9), placebo: 4.8 (4.3, 5.3) difference: 1.7 months	Pooled RECURSE and J003 trials <u>Mean overall survival, months</u> trifluridine/tipiracil: 10.0, placebo: 7.4, difference: 2.6 <u>Mean progression-free survival, months</u> trifluridine/tipiracil: 3.7, placebo: 1.9, difference: 1.8 months
Clinical claim	Superior in terms of efficacy and inferior in terms of safety to best supportive care (placebo). PBAC Comment: (paragraphs 7.5, 7.6 and 7.8) <u>Efficacy:</u> claim of superior efficacy adequately supported by the data, although the magnitude of the benefit may not be realised in clinical practice. <u>Safety:</u> claim of inferior safety reasonable. The toxicity associated with trifluridine/tipiracil was predictable, with myelosuppression being the key adverse event.	No change
Economic evaluation, model structure	Trial based analysis (no extrapolation) using data from RECURSE with OS partitioned based on ECOG-PS. Utility values: ECOG 0,1 = 0.81, ECOG 2,3 = 0.70 (based on transformation of ECOG-PS scores, data not specific to mCRC) PBAC Comment: (paragraph 7.13) the PBAC considered that any resubmission should include an economic model with health states based on progression, and the utility values from the regorafenib mCRC trial should be applied to these health states.	Trial based analysis (no extrapolation) using data from RECURSE and J003 with OS partitioned based on PFS. Utility values: pre-progression = 0.75, post-progression = 0.59. Based on regorafenib mCRC trial with a 2.5% increase (from 0.73 to 0.75) to the pre-progression value to account for better safety profile of trifluridine/ tipiracil compared to regorafenib.

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	November 2016 major submission	March 2017 minor resubmission
Economic evaluation, results	Incremental costs: \$ Incremental time with ECOG of 0 or 1: 0.14 years Incremental difference in mean overall survival: 0.21 years Incremental difference in mean QALYs: 0.16 ICER: <ul style="list-style-type: none"> \$45,000 - \$75,000 per LY gained \$75,000 - \$105,000 per QALY gained 	Incremental costs: \$ Incremental difference in mean PFS: 0.15 years Incremental difference in mean overall survival: 0.22 years Incremental difference in mean QALYs: 0.15 ICER: <ul style="list-style-type: none"> \$15,000 - \$45,000 per LY gained \$45,000 - \$75,000 per QALY gained (\$45,000 - \$75,000 using unadjusted utility value of 0.73 for progression-free).
Number of patients and estimated net cost to PBS	Patient numbers: Year 1: less than 10,000, Year 6: less than 10,000 Net PBS cost: Year 1: \$20 - \$30m, Year 6: \$30 - \$60m PBAC Comment: (paragraph 7.12) the submission's estimate of the number of patients to be treated and the associated financial impact is likely to have been overestimated.	Revised financial estimates not presented. The sponsor maintained that the utilisation estimates in the November 2016 submission are reasonable.
Risk share	Acknowledged but no details proposed.	A further % rebate (total %) for any expenditure that exceeds the annual subsidisation caps by ≤ 20%. An additional % rebate (total %) for any expenditure that exceeds the annual subsidisation caps by > 20%.
Advice for resubmission	PBAC Comment: (paragraph 7.13) any resubmission should include an economic model with health states based on progression, and the utility values from the regorafenib mCRC trial should be applied to these health states. The PBAC considered that the base case ICER for this scenario should not exceed \$50,000 per QALY gained.	ICER is \$45,000 - \$75,000 per QALY gained.

Abbreviations: CI = confidence interval; ECOG-PS = Eastern Cooperative Oncology Group Performance Status; ICER = incremental cost-effectiveness ratio; LY = life year; mCRC = metastatic colorectal cancer; OS = overall survival; PFS = progression free survival; QALY = quality adjusted life year

Source: compiled from the November 2016 PBAC Minutes and the March 2017 minor submission.

For more detail on PBAC's view, see section 5 "PBAC outcome".

4 Consideration of the evidence

Sponsor hearing

4.1 There was no hearing for this item as it was a minor submission.

Consumer comments

4.2 The Medical Oncology Group of Australia (MOGA) expressed support for the trifluridine/tipiracil submission. It was noted that the indication for this item represents an area of unmet need after failure of standard prior therapies and trifluridine/tipiracil has a proven survival benefit in a phase 3 trial. The PBAC noted that the MOGA

presented the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for trifluridine/tipiracil, which was limited to 2 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)¹, based on a comparison with placebo.

Clinical trials

4.3 As a minor submission, no new clinical trials were presented in the submission.

Comparative effectiveness

4.4 The November 2016 major submission used results from the RECURSE trial for the primary analysis. A second trial, J003, was excluded from primary analysis based on the assumption that (a) the Asian ethnicity of recruited patients influenced the comparative efficacy of trifluridine/tipiracil; and that (b) recruited patients were less heavily pre-treated than those in the RECURSE trial to all potentially available treatment options for mCRC (based on exposure to bevacizumab and EGFR inhibitors) (paragraph 6.5, November 2016 Public Summary Document).

4.5 The minor resubmission pooled the results of overall survival (OS) and progression free survival (PFS) from the RECURSE and J003 trials. The pooled results are presented in Table 2.

Table 2: Results of the pooled analysis for PFS and OS applied in the revised economic analysis

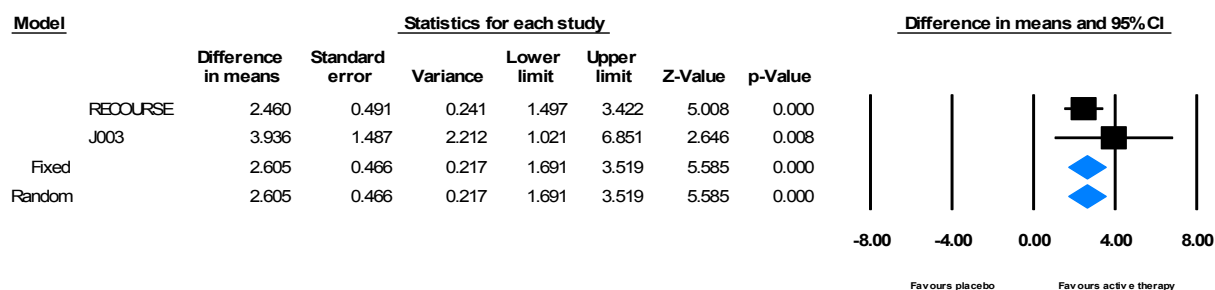
Outcome	Trifluridine/tipiracil	Placebo	Difference
Mean PFS (months)	3.7	1.9	1.8
Mean OS (months)	10.0	7.4	2.6

Abbreviations: OS= Overall Survival; PFS= Progression-free Survival

Source: Table 2, page 7 of the minor submission

4.6 The pooled results of OS from the RECURSE and J003 trials were presented as part of supporting analyses in the November 2016 major submission, re-presented in Figure 1.

Figure 1: Results of meta-analysis of outcomes for mean OS in the trifluridine/tipiracil trials*



* Based on an analysis of individual patient data (IPD) that were made available for the May 2014 datacut of RECURSE trial and IPD of OS outcomes in J003

Source: Figure B.5-7, p131 of the November 2016 major submission.

¹ Cherny NI, Sullivan R, Dafni U, et al: A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). Ann Oncol 26:1547-73, 2015

- 4.7 The PBAC noted at its November 2016 meeting that the results of the secondary analysis for OS including J003 were similar to those based on the RECURSE trial only (mean gain in OS of 2.5 months) (paragraph 6.5 and 7.5, November 2016 Public Summary Document).
- 4.8 At its November 2016 meeting, the PBAC noted that approximately 63% and 57% of patients in the RECURSE and J003 trials respectively, had an ECOG performance status of 0, and considered that a higher proportion of patients with an ECOG performance status of 1 may be treated in clinical practice (paragraph 7.8, November 2016 Public Summary Document). The minor resubmission (p7) acknowledged that, at launch, the patients treated with trifluridine/tipiracil will reflect a prevalent pool of patients, which may include patients with worse performance status. However, it argued that this would not be different to the period over which the RECURSE and J003 trials were conducted, where the population recruited to the trials would have been a sample of the prevalent patients at the time.
- 4.9 The PBAC also noted at its November 2016 meeting that, 9.4% of patients in the RECURSE trial received granulocyte colony stimulating factors (GCSF) for neutropenia. It considered that in Australian clinical practice, GCSF would not be routinely used and neutropenia would lead to dose reductions and delays which may impact on efficacy (paragraph 7.8, November 2016 Public Summary Document). The minor resubmission argued (p8) that if dose reductions and delays occurred, it would result in lower costs of trifluridine/tipiracil and that the costs of administering GCSF would not be incurred. The minor resubmission further argued that if efficacy and costs are simultaneously reduced then the impact on the ICER is likely to be minor.

Clinical claim

- 4.10 The November 2016 major submission claimed superior efficacy and inferior safety of trifluridine/tipiracil compared with placebo. There were no changes to the clinical claim in the minor resubmission.
- 4.11 The PBAC again accepted the submission's claim of superior comparative effectiveness of trifluridine/tipiracil over placebo as it had at the November 2016 meeting. However, the PBAC considered the benefit to be modest, and possibly smaller in clinical practice.
- 4.12 The PBAC again considered the claim of inferior safety compared with placebo to be reasonable as it had at the November 2016 meeting.

Economic analysis

- 4.13 The minor resubmission presented a trial-based economic evaluation, with no structural changes to the economic model presented in the November 2016 major submission. The differences in modelling in the minor resubmission compared with the November 2016 major submission are presented in Table 3.

Table 3: Differences in key components of the economic evaluation in the March 2017 minor resubmission versus the November 2016 major submission

	November 2016 major submission	March 2017 minor resubmission
Time horizon	Based on time horizon of RECOURSE trial.	Based on time horizons of Recourse and J003 trials.
Clinical data	IPD from the RECOURSE trial.	KM pooled analysis of RECOURSE and J003 trials.
Partitioned survival analysis	ECOG-PS <1, ECOG ≥2, dead.	Progression-free, progressing disease, dead.
Utilities	Utility values (ECOG 0,1= 0.81; ECOG 2,3= 0.70) were transformed from ECOG-PS scores based on the Teckle et al., 2011 publication which were not specific to mCRC.	Utility values were based on the CORRECT (regorafenib) trial with an adjustment of a 2.5% increase* (from 0.73 to 0.75) to the progression-free health state, and 0.59 for progressing disease. *The submission claimed that this was applied to account for the better safety profile of trifluridine/tipiracil compared to regorafenib.

Abbreviations: IPD = individual patient data; ECOG-PS = Eastern Cooperative Oncology Group Performance Status; mCRC = metastatic colorectal cancer;

Source: Table 1, pages 5-8 of the minor submission and Table 3, page 11 of the minor submission

- 4.14 A summary of the costs and outcomes of the economic analysis are presented in Table 4 below.

Table 4: Results of the economic analysis

	Trifluridine/tipiracil arm	Placebo arm	Increment
Costs			
Average total drug costs	\$ █████	\$0.00	\$ █████
Average cost per patient to manage AEs	\$ █████	\$0.00	\$ █████
Clinician visits	\$ █████	\$ █████	\$ █████
Monitoring costs	\$ █████	\$0.00	\$ █████
Total costs:	\$ █████	\$ █████	\$ █████
Outcomes			
Mean OS (in months)	10.0	7.4	2.6
Mean OS (in years)	0.84	0.62	0.22
Mean QALYs	0.54	0.39	0.15
Incremental cost of trifluridine/tipiracil vs placebo per LY gained:			\$15,000 - \$45,000
Incremental cost of trifluridine/tipiracil vs placebo per QALY gained:			\$45,000 - \$75,000

Abbreviations: AE = adverse event; OS = overall survival; PFS = progression free survival; QALY = quality adjusted life year

Source: Table 4, page 12 of the minor submission

- 4.15 The revised economic analysis, which incorporates the proposed █████% rebate, resulted in a base case incremental cost-effectiveness ratio (ICER) of \$45,000 - \$75,000 per QALY gained.
- 4.16 When the unadjusted utility value for the progression free health state (0.73) from the CORRECT (regorafenib) trial was applied to the model, the ICER increased to \$45,000 - \$75,000. If the utility weight in the progression-free health state is adjusted

to be 5% better for trifluridine/tipiracil-treated patients compared with regorafenib-treated patients, the ICER decreased to \$45,000 - \$75,000.

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

- 4.17 The average effective dispensed cost per patient per cycle (one month) is \$ [REDACTED]. This estimate is based on an average dose of 60 mg, and represents the cost for 3 packs of 20 tablets of the 20 mg strength. This cost is based on the proposed effective dispensed price and includes the proposed [REDACTED]% rebate to the Commonwealth. On average, a patient would be dispensed drug for 3.42 cycles of treatment, representing a total cost of \$ [REDACTED].

Estimated PBS usage & financial implications

- 4.18 The sponsor stated that no changes were made to estimates of utilisation and associated financial implications from those presented in the November 2016 major submission, and argued that its original estimates are reasonable. However, the minor resubmission proposed different pricing arrangements from the November 2016 major submission, including a [REDACTED]% rebate (increased from [REDACTED]%) on the dispensed price for maximum quantity and a staged risk share arrangement .
- 4.19 The sponsor provided an updated financial analyses workbook reflecting the proposed pricing arrangements, and the estimated use and financial implications for years 1 to 6 in its pre-PBAC response. The estimated net cost to the PBS was approximately \$20-\$30 million in Year 6 of listing, with a total net cost to the PBS of approximately more than \$100 million over the first 6 years of listing. The PBAC noted that these estimates had not been verified.
- 4.20 The sponsor indicated in the pre-PBAC response that grandfathering of patients would not be required as the duration of treatment is relatively short.

Verification of estimates

- 4.21 The November 2016 major submission (unchanged in the minor submission) adopted a market share approach and analysed a 10% sample of PBS data for patients treated with first and second line therapies for mCRC from January 2011 to 2015, scaled up to the Australian population, to inform an estimation of the likely number of patients to be treated. At its October 2016 meeting, the ESC noted that the estimates could not be verified because details of the analysis using the 10% PBS sample were not provided (paragraph 6.41, November 2016 Public Summary Document). The November 2016 pre-PBAC response clarified that the estimates were based on incident patients and that the sample included bevacizumab, panitumumab, cetuximab, oxaliplatin and irinotecan. As the item codes were not stated it is unknown if the analysis had captured all the relevant listings. The November 2016 pre-PBAC response stated that oxaliplatin and irinotecan were included as they were only registered for mCRC. While this is true for irinotecan, oxaliplatin has several other registered indications, including the treatment of:
- adjuvant treatment of stage III (Duke's C) colon cancer in combination with fluoropyrimidine agent. The pre-PBAC response (p1) provided additional information regarding the analysis steps used to distinguish patients treated in the adjuvant setting versus those in the mCRC setting

- advanced colorectal cancer in combination with fluorouracil and folinic acid.
- advanced oesophagogastric cancer in combination with epirubicin and either capecitabine or fluorouracil. The pre-PBAC response (p1) estimated the use of oxaliplatin and epirubicin to be relatively low.

- 4.22 As oxaliplatin is not listed on the PBS for a specific indication, the sponsor’s analysis was likely to have overestimated the treated population by capturing the use of oxaliplatin for other indications.
- 4.23 A full description of the methods used to extract the 10% sample was not provided for the November 2016 major submission. The pre-PBAC response for this minor resubmission provided the Authority codes used to identify patients with mCRC.

Assumptions used to forecast the first-line mCRC population

- 4.24 At its October 2016 meeting, the ESC was uncertain of whether a decline in the first-line mCRC population from mid-2013 to 2015 presented in the November 2016 major submission was the result of the submission’s method or if it was a real trend in PBS use (paragraph 6.41 November 2016 Public Summary Document). Actual PBS data to December 2015 was presented in the financial estimates. More recent data is available which the minor resubmission could have used to address the ESC’s concern of whether the first-line mCRC population is continuing to decline and if its assumption of continuing linear growth in treated patients was justified.
- 4.25 The November 2016 major submission applied an assumption for annual growth to forecast the number of patients receiving trifluridine/tipiracil as first-line treatment of mCRC. The annual growth assumption is highly sensitive to the period used to derive this estimate. The submission used an early period (January 2011 to January 2012) for its growth rate assumption of 7.4% (Cell B11, sheet “Servier CRC Regimens – Patients”, of excel workbook “3. Financial analyses – LONSURF – mCRC – Nov 2016.xlsx”). In addition to the uncertainty of whether growth at this time reflects more current use, the assumption is based on estimated patient figures (‘Check application growth rate’, row 10) rather than the actual patient numbers (‘Patients receiving 1st-line treatment for mCRC, row 3).
- 4.26 The growth trends over time based on the actual patient numbers in row 3 is presented in Table 5.

Table 5: mCRC first-line patient growth trends over time based on actual patient numbers

Period	Growth
Jan 2011 to Jan 2012	15.6%
Jan 2012 to Jan 2013	4.8%
Jan 2013 to Jan 2014	-9.2%
Jan 2014 to Jan 2015	19.3%

Source: Derived from excel workbook “3. Financial analyses – LONSURF – mCRC – Nov 2016.xlsx” presented in the November 2016 submission, sheet “Servier CRC Regimens – Patients”, row 3.

- 4.27 While the growth rates are highly variable, the average over the four periods is similar to the submission’s assumption (7.6% vs. 7.4%, respectively).

Estimate of uptake

- 4.28 At its November 2016 meeting, the PBAC considered that the submission's estimate of the number of patients to be treated was likely to have been overestimated. In particular the uptake of trifluridine/tipiracil was considered to have been overestimated, as to be suitable for treatment, patients are required to be fit and healthy with a good performance status despite having received a number of previous treatments for their mCRC (paragraph 7.12, November 2016 Public Summary Document).
- 4.29 The minor resubmission has included the clinical criteria that patients must have a WHO performance status of ≤ 1 ; however, the submission has not justified its view that the uptake assumptions from the November 2016 submission should be retained.

Financial implications to manage adverse events

- 4.30 At its November 2016 meeting, the PBAC noted that based on data from the RECURSE trial, 9.4% of patients will require treatment for neutropenia, which would incur additional hospital based costs (paragraph 6.45, November 2016 Public Summary Document). Costs to the MBS were included in the economic model for physician visits and for full blood count determinations but these were excluded from the financial estimates. The pre-PBAC response for this minor resubmission (p4) estimated the net implications for the MBS to be less than \$10 million in Year 1 increasing to less than \$10 million by Year 6.

Financial Management – Risk-sharing Arrangements

- 4.31 The minor resubmission proposed a further ■% rebate (total ■%) for any expenditure that exceeds the annual subsidisation caps by up to 20%, and an additional ■% rebate (total ■%) for any expenditure that exceeds the annual subsidisation caps by more than 20%. The minor resubmission did not propose what the annual subsidisation caps should be. The pre-PBAC response indicated that the proposed subsidisation caps correspond to the estimated net cost to the PBS.

For more detail on PBAC's view, see section 5 "PBAC outcome"

5 PBAC Outcome

- 5.1 The PBAC did not recommend the listing of trifluridine with tipiracil on the PBS for treatment of patients with metastatic colorectal cancer (mCRC) who have been treated previously with or are not considered suitable for currently available therapies on the basis of a modest clinical benefit, moderate toxicity and a high and uncertain incremental cost-effectiveness ratio given the extent of benefit observed in the trial setting may not be realised in clinical practice.
- 5.2 The PBAC reiterated its view that there is an unmet clinical need for additional effective and well-tolerated therapies for patients with mCRC who have failed or are unsuitable for the currently available therapies.

- 5.3 The PBAC noted MOGA expressed support for the trifluridine/tipiracil submission, and based on the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) the rating was limited to 2 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement).
- 5.4 The PBAC noted that the minor resubmission was made under the TGA/PBAC parallel process, and that the TGA Delegate's overview (for the April 2017 meeting of Advisory Committee on Medicines) was not available one week prior to the PBAC meeting.
- 5.5 The PBAC noted that the minor resubmission was based on the pooled analysis of the RECURSE and J003 (previously presented as supportive evidence) trials, and that the estimated mean OS gain for the pooled analysis was similar to that based on the RECURSE trial only (2.6 months and 2.5 months, respectively). The PBAC considered the magnitude of the benefit to be modest. The PBAC reiterated its previous concern that the magnitude of benefit observed in the trials may not be realised in clinical practice.
- 5.6 The PBAC noted the revised economic model partitioned overall survival based on progression and applied utility values based on the regorafenib mCRC trial as advised by the PBAC at its November 2016 meeting.
- 5.7 The PBAC considered the base case ICER of \$45,000 - \$75,000 per QALY gained presented in the resubmission to be unacceptably high and uncertain given concerns over the likely modest benefits observed in clinical practice.
- 5.8 The PBAC considered the estimated financial impact of more than \$100 million over 6 years to be significant. The PBAC noted that no changes to the utilisation estimates were presented in the minor resubmission compared with the original submission. The PBAC considered utilisation likely to be overestimated given the modest efficacy observed. Although the PBAC considered the financial caps were unlikely to be reached, the proposed rebates of ■% and ■% were considered to be insufficient.
- 5.9 The PBAC advised that any resubmission should be made subsequent to TGA approval, the benefit likely to be realised in clinical practice should be considered, and any risk share arrangement should more adequately contain the financial risk to the Commonwealth.
- 5.10 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Rejected

6 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.

7 Sponsor's Comment

The sponsor had no comment.