

## 7.15 TRIFLURIDINE with TIPIRACIL

**Tablet, 15 mg trifluridine with 6.14 mg tipiracil, 20 mg trifluridine with 8.19 mg tipiracil, LONSURF®, Servier Laboratories (Australia) Pty Ltd**

### 1 Purpose of Application

- 1.1 The minor submission sought an Authority Required (STREAMLINED) listing for trifluridine with tipiracil (hereafter 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 submission requested the following new listing:

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 6.14 mg tablet, 20	3	2	\$ [REDACTED] <sup>a</sup>	LONSURF	Servier
Trifluridine 20 mg + tipiracil 8.19 mg tablet, 20	4	2	\$ [REDACTED] <sup>b</sup>		Laboratories

<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 Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required <input checked="" type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	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.
<b>Administrative Advice</b>	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.

<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>	Continuing treatment
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required <input checked="" type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	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.
<b>Prescriber Instructions</b>	A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug.
<b>Administrative Advice</b>	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.

<sup>a</sup> Effective price = \$ [REDACTED] (including [REDACTED]% rebate) <sup>b</sup> Effective price = \$ [REDACTED] (including [REDACTED]% rebate)

2.2 At its July 2017 meeting, the PBAC considered the request for no repeats in the proposed listing for trifluridine with tipiracil to be inappropriate, noting that this would impose undue burden on clinicians and lacks precedent for other PBS-listed oral antineoplastic agents with similar toxicity profiles. In response to the PBAC advice, the minor resubmission requested two repeats in the proposed listing.

### 3 Background

- 3.1 The PBAC first considered trifluridine/tipiracil as a major submission at its 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, November 2016 Public Summary Document).
- 3.2 A minor resubmission for trifluridine/tipiracil was considered at the March 2017 PBAC meeting where it was again not recommended for listing. While the PBAC noted the revised lower incremental-cost effectiveness ratio (ICER) presented, it considered that the ICER remained high and uncertain, and remained concerned regarding the modest benefits observed in clinical practice remained (paragraph 5.1, March 2017 Public Summary Document (PSD)). Further, the PBAC considered that the proposed rebates of ■■■% and ■■■% for utilisation over the financial caps were insufficient to address the significant financial impact to the PBS (paragraph 5.8, March 2017 Public Summary Document).
- 3.3 A minor resubmission for trifluridine/tipiracil was considered again at the July 2017 PBAC meeting. The PBAC did not recommend the listing of trifluridine/tipiracil based on a modest clinical benefit in the context of substantial toxicity, and high and uncertain ICER given the extent of benefit observed in the trial and model may not be realised in clinical practice (paragraph 5.1, July 2017 PSD). The PBAC noted that the increase in the proposed rebate (■■■%) decreased the ICER from \$45,000/QALY - \$75,000/QALY to \$45,000/QALY - \$75,000/QALY. However, the PBAC considered that the base case ICER presented in the submission likely represented a best case scenario where the benefit observed in the trial setting is reflected in clinical practice and the true ICER would be higher than \$45,000/QALY - \$75,000/QALY and therefore not cost-effective at the price proposed (paragraph 5.6, July 2017 Public Summary Document).

### 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 PBAC noted and welcomed the input from health care professionals (2) and one organisation via the Consumer Comments facility on the PBS website. The health care professionals commented on the modest survival advantage and manageable toxicity profile of trifluridine/tipiracil and noted that it is currently the only option for third line treatment in mCRC.
- 4.3 Bowel Cancer Australia described the impact of, and treatment options for, bowel cancer on patients' quality of life. Bowel Cancer Australia emphasised the importance of prolonging quality life for individuals and their families, and expressed their support for greater availability of treatment options for metastatic bowel

cancer such as trifluridine/tipiracil. The statement also included a case summary of one patient's experience with trifluridine/tipiracil for advanced bowel cancer, who experienced a number of toxicities but did not appear to derive direct clinical benefit from the drug combination.

- 4.4 The Medical Oncology Group of Australia (MOGA) reiterated its support for the trifluridine/tipiracil minor 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)<sup>1</sup>, based on a comparison with placebo.

### ***Clinical trials***

- 4.5 As a minor submission, no clinical trials were presented in the resubmission.

### ***Comparative effectiveness***

- 4.6 At its July 2017 meeting, the PBAC recalled that the median increase in PFS of 0.3 months (HR 0.49; CI: 0.42, 0.58) compared with best supportive care in the RECURSE trial (n=800) was small and that the majority of patients (i.e. 53% of patients in the trifluridine/tipiracil treatment arm and 79% of patients in the best supportive care arm) had progressed by week 8. The PBAC also recalled that the median gain in OS was 2.0 months (HR 0.69; CI: 0.59, 0.81) in the RECURSE trial was modest, and that a substantial proportion of the estimated gain in overall survival was in the post-progression state associated with poorer quality of life. The PBAC also recalled that the results of the J003 trial (n=169) were similar to those of the RECURSE trial.
- 4.7 The PBAC previously considered that the mean increase in OS is informative because at the end of the trial follow-up period most patients had died (87% of patients randomised to trifluridine/tipiracil and 94% of patients randomised to placebo) and hence the survival data were near complete (paragraph 7.5, November 2016 Public Summary Document).
- 4.8 The minor resubmission (p9-10) argued that differences in mean PFS and mean OS are more relevant to consider in relation to the magnitude of benefit associated with trifluridine/tipiracil compared with placebo, rather than the median, which is a single point on the Kaplan-Meier curve. Based on means, the minor resubmission argued that the majority of survival gain in the trials was in the progression free health state (with 1.8 months [70%] of the 2.6 month gain in OS (pooled RECURSE and J003 OS survival gain) in the progression-free health state).

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

### Special pricing arrangement

4.9 The submission proposed a special pricing arrangement (SPA) where the sponsor would rebate the Commonwealth ██████% of the published dispensed price for maximum quantity (DPMQ). The submission noted that while the proposed rebate was less than the ██████% rebate proposed in the July 2017 submission, a ██████% reduction in the published approved ex-manufacturer price (AEMP) is also proposed. A summary of the special pricing arrangements proposed in the July 2017 and current submission are presented below in Table 1.

**Table 1: Summary of July 2017 and November 2017 special pricing arrangements**

Presentation	Published AEMP	Effective AEMP	Published DPMQ	Effective DPMQ	% Rebate on DPMQ (published)
<b>July 2017 Submission</b>					
Trifluridine 15 mg + tipiracil 6.14 mg tablet, 20 (Max Qty 3)	██████	██████	██████	██████	██████
Trifluridine 20 mg + tipiracil 8.19 mg tablet, 20 (Max Qty 4)	██████	██████	██████	██████	
<b>November 2017 Submission</b>					
Trifluridine 15 mg + tipiracil 6.14 mg tablet, 20 (Max Qty 3)	██████	██████	██████	██████	██████
Trifluridine 20 mg + tipiracil 8.19 mg tablet, 20 (Max Qty 4)	██████	██████	██████	██████	

Abbreviations: AEMP= approved ex-manufacturer price; DPMQ=dispensed price for maximum quantity  
Source: Table 1 & Table 2, page 7 of the submission

4.10 The proposed ██████% rebate on the published DPMQ (consisting of ██████% reduction in the published AEMP from July 2017) equates to a further ██████% and ██████% reduction in the effective AEMP proposed in the July 2017 submission for trifluridine 20 mg + tipiracil 8.19 mg tablet and tipiracil 15 mg + tipiracil 6.14 mg tablet respectively. The minor resubmission (p5) explained that the percentage reduction in effective AEMP for trifluridine/tipiracil 15 mg is less because wholesaler margin and dispensing fee are not affected by price reductions and changes in rebates.

### Economic analysis

4.11 As per the March 2017 and July 2017 resubmissions, the minor resubmission presented a trial-based economic evaluation. There were no structural changes to the economic model presented in the previous submissions.

4.12 The minor resubmission made the following changes to the base case economic evaluation presented in the July 2017 submission:

- The updated dispensing fee of \$7.15 as at 1 July 2017 was applied.
- Updated the proposed rebate on the DPMQs to ██████% from ██████%.
- The revised effective AEMPs are applied.

4.13 Results of the revised economic analysis are presented in Table 2.

**Table 2: Results of the economic analysis**

	Trifluridine/tipiracil arm	Placebo arm	Increment
<b>Costs</b>			
Average total drug costs	██████	████	██████
Average cost per patient to manage AEs	██████	████	██████
Clinician visits	██████	██████	██████
Monitoring costs	████	████	████
<b>Total costs</b>	██████	████	██████
<b>Outcomes</b>			
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:			██████
Incremental cost of trifluridine/tipiracil vs placebo per QALY gained:			██████

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

Source: Table 3, page 14 of the submission

- 4.14 The revised economic analysis, which incorporates the proposed █████% rebate, resulted in a base case ICER of \$45,000/QALY - \$75,000/QALY.
- 4.15 At its November 2017 meeting, the PBAC noted that 9.4% of patients in the RECURSE trial received granulocyte colony stimulating factors (G-CSF) which would not be routinely used in Australian clinical practice. The PBAC considered that in clinical practice, neutropenia would likely lead to dose reductions and delays which would impact on efficacy (paragraph 7.8 November, 2016 Public Summary Document).
- 4.16 The resubmission attempted to address the PBAC's concerns regarding the use of G-CSF in the RECURSE trial and its impact on the applicability of the clinical data to Australian clinical practice with a sensitivity analysis. The sensitivity analysis attempted to simulate a 'worst case' scenario assuming:
- No benefit of treatment in patients who received granulocyte colony stimulating factors (G-CSF). Placebo outcomes were applied for the 9.4% of patients in the trifluridine/tipiracil arm treated with G-CSF, and the costs for G-CSF were also removed.
  - Quality of life for patients treated with trifluridine/tipiracil is considered to be no better than for patients treated with regorafenib. The utility value applied to patients in the progression-free health state is the unadjusted regorafenib trial utility value for the progression-free health state of 0.73 without the adjustment of a 2.5% increase (utility value for progression-free health state in the base-case analysis is 0.75).
- 4.17 The results of the sensitivity analysis are presented below in Table 3.

**Table 3: Results of the sensitivity analysis**

	Trifluridine/tipiracil arm	Placebo arm	Increment
<b>Costs</b>			
Average total drug costs	██████████	██████	██████████
Average cost per patient to manage AEs	██████	██████	██████████
Clinician visits	██████████	██████████	██████████
Monitoring costs	██████	██████	██████████
<b>Total costs</b>	██████████	██████████	██████████
<b>Outcomes</b>			
Mean OS (in months)	10.0	7.4	2.6
Mean OS (in years)	0.82	0.62	0.20
Mean QALYs	0.52	0.39	0.14
Incremental cost of trifluridine/tipiracil vs placebo per LY gained:			██████████
Incremental cost of trifluridine/tipiracil vs placebo per QALY gained:			██████████

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

Source: Table 4, page 15 of the submission

4.18 When the unadjusted utility value (0.73) for the progression free health state from the CORRECT (regorafenib) trial was applied in the model and the benefit of treatment removed for 9.4% of patients in the trifluridine/tipiracil arm, the ICER increased to \$45,000/QALY - \$75,000/QALY from \$45,000/QALY - \$75,000/QALY.

**Drug cost/patient/course: \$ ██████████**

4.19 The minor resubmission stated (p14) that the average effective dispensed cost per patient per cycle (one month) is \$ ██████████. This estimate is based on an average dose of 60 mg, and the effective dispensed price for 3 packs of 20 tablets of the 20 mg strength. The submission stated that based on a per cycle cost of \$ ██████████ and an average 3.42 cycles of treatment per patient, the total effective dispensed cost would be \$ ██████████.

**Estimated PBS usage & financial implications**

4.20 The minor resubmission estimated a net cost to the PBS of \$10 - \$20 million in Year 6 of listing, with a total net cost to the PBS of \$60 - \$100 million over the first 6 years of listing. The revised financial estimates incorporated the proposed ██████████% rebate on the DPMQs. The submission’s revised estimated PBS usage and financial implications are shown below in Table 4.

4.21 The estimated PBS usage and financial implications presented in the minor resubmission have not been evaluated. The estimated net cost to the PBS in the July 2017 submission was \$60 - \$100 million over the first 6 years of listing.

**Table 4: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Total
Likely number of patients in each year	■	■	■	■	■	■	
Number of patients receiving 15 mg x 20 x 1 pack per cycle	■	■	■	■	■	■	
Number of patients receiving 15 mg x 20 x 2 packs per cycle	■	■	■	■	■	■	
Number of patients receiving 15 mg x 20 x 3 packs per cycle	■	■	■	■	■	■	
Number of patients receiving 20 mg x 20 x 1 pack per cycle	■	■	■	■	■	■	
Number of patients receiving 20 mg x 20 x 2 packs per cycle	■	■	■	■	■	■	
Number of patients receiving 20 mg x 20 x 3 packs per cycle	■	■	■	■	■	■	
Number of patients receiving 20 mg x 20 x 4 packs per cycle	■	■	■	■	■	■	
Average number of cycles of treatment per patient	3.42						
Total dispensed cost	■	■	■	■	■	■	
Total rebates paid	■	■	■	■	■	■	
General patient co-payments	■	■	■	■	■	■	
Concessional patient co-payments	■	■	■	■	■	■	
<b>Net financial implications for PBS budget</b>	■	■	■	■	■	■	■
<b>Proposed subsidisation caps</b>	■	■	■	■	■	■	■

Source: Table 5, page 16 of the submission

The redacted table shows that at year 5, the estimated number of patients was less than 10,000 per year.

### **Financial Management – Risk-sharing Arrangements**

4.22 The submission proposed a rebate of ■% for any expenditure that exceeds the annual subsidisation caps. In contrast to the July 2017 submission, the proposed subsidisation caps are set at volumes less than the estimated utilisation (see Table 4 above). The submission estimated that these proposed caps would limit PBS expenditure to \$30 - \$60 million over the first 6 years of listing.

## **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 or are not considered suitable for current available therapies. The PBAC based its decision on the modest clinical benefit and moderate toxicity, noting that the clinical benefit observed in the trial may not be realised in clinical practice. The PBAC was concerned that the financial impact of listing was substantial, with a total net cost to the PBS of \$30 - \$60 million over the first 6 years of listing. The PBAC considered that this represented a significant opportunity cost for the Commonwealth.

- 5.2 The PBAC considered that the proposed PBS restriction was appropriate.
- 5.3 The PBAC noted that the Medical Oncology Group of Australia (MOGA) reiterated its 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 reiterated its view that as metastatic cancer is rarely cured and treatments aim to relieve symptoms or delay death, there will always be an unmet clinical need for additional effective and well-tolerated therapies. In this context, the PBAC noted the modest benefit and moderate toxicity and considered that this clinical need would not be discernibly addressed by the availability of trifluridine/tipiracil.
- 5.5 The PBAC recalled that the median increase in PFS of 0.3 months (HR 0.49; CI: 0.42, 0.58) compared with best supportive care in the RECURSE trial (n=800) was small, and that the majority of patients (i.e. 53% of patients in the trifluridine/tipiracil treatment arm and 79% of patients in the best supportive care arm) had progressed by week 8. The PBAC recalled that the median gain in overall survival (OS) was 2.0 months (HR 0.69; CI: 0.59, 0.81) in the RECURSE trial was modest. The PBAC also recalled that the results of the J003 trial (n=169) were similar to those of the RECURSE trial.
- 5.6 The PBAC recalled that the toxicity associated with trifluridine/tipiracil was similar to other oral antineoplastic agents listed on the PBS, with myelosuppression being a key adverse event. The PBAC considered that while the toxicity associated with trifluridine/tipiracil may be manageable, it was important in the context of the modest gain in PFS and OS observed in the RECURSE trial.
- 5.7 The PBAC considered that patients treated with trifluridine/tipiracil in clinical practice would, in general, have a poorer prognosis compared with patients enrolled in the RECURSE trial. Thus the benefits observed in the trial may not be fully realised in clinical practice, at least in part because of a reduced ability to tolerate the side effects associated with the treatment.
- 5.8 The PBAC noted that the minor resubmission proposed a revised rebate for trifluridine/tipiracil, equating to a further [REDACTED]% and [REDACTED]% reduction in the effective AEMP proposed in the previous submission for trifluridine 20 mg + tipiracil 8.19 mg tablet and tipiracil 15 mg + tipiracil 6.14 mg tablet respectively. The PBAC noted that incorporating the reduced effective price into the economic model resulted in a revised ICER of \$45,000/QALY - \$75,000/QALY. The revised ICER did not differ substantially from that of the previous submission \$45,000/QALY - \$75,000/QALY).
- 5.9 The PBAC noted the sensitivity analysis presented in the resubmission, which was stated to be a 'worst case' scenario, in which (i) no benefit in the proportion of patients (9.4%) which received granulocyte colony stimulating factors (G-CSF) in the RECURSE trial was assumed and; (ii) quality of life for patients treated with trifluridine/tipiracil was assumed to be the same as for patients treated with regorafenib (the unadjusted utility value of 0.73 for the progression-free health state is applied). The ICER increased to \$45,000/QALY - \$75,000/QALY. The PBAC considered this analysis addressed only one aspect of the potential differences

between the trial and likely PBS population (i.e. that G-CSF is not routinely used in Australia in patients with metastatic disease), and it did not adequately address that the PBS population are likely to have additional and/or more extensive comorbidities compared with the trial patients.

- 5.10 The PBAC noted that the reduced effective price and rebate proposed by the resubmission resulted in an estimated net financial impact of \$30 - \$60 million over 6 years. The PBAC considered that although this was less than the financial impact of \$60 - \$100 million over 6 years estimated in the previous submission, it was still a substantial financial impact to Government. The PBAC further considered that as the minor submission may have overestimated the utilisation of trifluridine/tipiracil, expenditure caps may not be reached. Therefore, the difference between the total expenditure and the proposed caps may not have a real or significant impact in the PBS setting. Given the modest clinical benefit of trifluridine/tipiracil, the PBAC considered that a PBS listing represented a significant opportunity cost.
- 5.11 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.