7.21 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 resubmission sought an 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 submission requested the following new listing:

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

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Severity:	Metastatic
Condition:	Metastatic colorectal cancer
PBS Indication:	Metastatic colorectal cancer
Treatment phase:	Initial treatment
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒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:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Severity:	Metastatic
Condition:	Metastatic colorectal cancer
PBS Indication:	Metastatic colorectal cancer
Treatment phase:	Continuing treatment
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☒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)

2.2 The proposed restriction was unchanged from the November 2017 minor resubmission. The minor resubmission (p13) indicated that the sponsor would be willing to further amend the restriction to align with the RECOURSE trial eligibility criteria if required.

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 [PSD]).

3.2 A minor resubmission for trifluridine/tipiracil was considered at the March 2017 PBAC meeting where it was 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 as concerns 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 [redacted]% and [redacted]% for utilisation over the financial caps were insufficient to address the significant financial impact to the PBS (paragraph 5.8, March 2017 PSD).

3.3 A minor resubmission for trifluridine/tipiracil was considered 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 proposed rebate ([redacted]%) decreased the ICER from $45,000-$75,000 per QALY gained to $45,000-$75,000 per QALY gained. 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 PSD).

3.4 At its November 2017 meeting, the PBAC again considered a minor resubmission for trifluridine/tipiracil where it did not recommend the requested listing for the treatment of mCRC. The PBAC noted that the submission presented a 'worst case' scenario sensitivity analysis however, considered that 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)

(paragraph 5.9, November 2017, PSD).

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 (5) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described the manageable toxicity profile of trifluridine/tipiracil, the convenience of the treatment as an oral therapy and potential benefit though the treatment may not extend survival significantly.

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 long term health outcomes and prolonging quality life for individuals, 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 valued the convenience and independence the trifluridine/tipiracil tablets offered over intravenous chemotherapy.

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)[1] , based on a comparison with placebo. The PBAC noted that although the MOGA supported the minor submission, it indicated that the submission was of a lower priority for PBS listing on the basis of its low ESMO-MCBS rating.

Clinical trials

4.5 As a minor resubmission, no clinical trials were presented.

[1] Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 28:2340-2366, 2017

Comparative effectiveness

4.6 At its November 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 RECOURSE 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 RECOURSE trial was modest. The PBAC also recalled that the results of the J003 trial (n=169) were similar to those of the RECOURSE trial.

4.7 The minor resubmission (p7-8) reiterated that differences in mean PFS and 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 reflects the difference in PFS or OS at 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 RECOURSE and J003 OS survival gain) in the progression-free health state).

4.8 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 PSD).

Special pricing arrangement

4.9 The proposed special pricing arrangement (SPA) remained unchanged from the November 2017 minor resubmission, which proposed a rebate of [redacted]% of the published dispensed price for maximum quantity (DPMQ). There is a small increase in the dispensed prices from the November 2017 minor resubmission due to an increase in the administration, handling and infrastructure (AHI) fee (from $70.92 to $72.43). A summary of the proposed SPA is presented below.

Table 1: Summary of the special pricing arrangement proposed (unchanged from November 2017)

Presentation	Published AEMP	Effective AEMP	Published DPMQ	Effective DPMQ	% Rebate on DPMQ (published)
Trifluridine 15 mg + tipiracil 6.14 mg tablet, 20 (Max Qty 3)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	[redacted]%
Trifluridine 20 mg + tipiracil 8.19 mg tablet, 20 (Max Qty 4)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	

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

Economic analysis

4.10 As per the previous submissions, the minor resubmission presented a trial-based economic evaluation. There were no structural changes to the economic model presented in the previous submissions.

4.11 There were no changes to the base case economic evaluation except for the average total drug costs due to an increase in the AHI fee (see paragraph 4.9 above). The results of the economic analysis are presented below.

Table 2: Results of the economic analysis

	Trifluridine/tipiracil arm	Placebo arm	Increment
Costs			
Average total drug costs	$[redacted]	$0.00	$[redacted]
Average cost per patient to manage AEs	$[redacted]	$0.00	$[redacted]
Clinician visits	$[redacted]	$[redacted]	$[redacted]
Monitoring costs	$[redacted]	$0.00	$[redacted]
Total costs	$[redacted]	$[redacted]	$[redacted]
Outcomes			
Mean OS (in months)	[redacted]	[redacted]	[redacted]
Mean OS (in years)	[redacted]	[redacted]	[redacted]
Mean QALYs	0.54	0.39	0.15
Incremental cost of trifluridine/tipiracil vs placebo per LY gained:			$[redacted]
Incremental cost of trifluridine/tipiracil vs placebo per QALY gained:			**$[redacted]**

Abbreviations: AE = adverse event; OS = overall survival; QALY = quality adjusted life year
Source: Economic & financial analyses – LONSURF – Mar 2018 resub Excel workbook provided with the submission

4.12 The revised economic analysis which incorporates the proposed [redacted]% rebate and increased drug costs (due to increased AHI fee) resulted in a base case ICER of $45,000-$75,000 per QALY gained.

4.13 The resubmission also presented the same sensitivity analysis presented in the previous November 2017 minor submission which attempted to stimulate a 'worse 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).

The resulting ICER from the sensitivity analysis was $45,000-$75,000 per QALY gained.

4.14 The PBAC previously 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 (paragraph 5.9, November 2017, PSD).

Drug cost/patient/course: $[redacted]

4.15 The resubmission stated (p15) that the average effective dispensed cost per patient per cycle (one month) is approximately $[redacted][2]. This estimate is based on the minor resubmission's estimate of total net financial implications over 6 years ($[redacted]) divided by the estimated total number of patients over 6 years ([redacted]), divided by the average number of cycles per patient (3.42). *Based on this per cycle cost and an average of 3.42 cycles of treatment per patient, the total effective dispensed cost would be $[redacted].*

Estimated PBS usage & financial implications

4.16 The 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 [redacted]% rebate on the DPMQs.

4.17 The resubmission's estimated financial implications have not been evaluated. The estimated financial implications are similar to those presented in the November 2017 submission ($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).

[2] The average effective dispensed price per cycle based on the individual patient data was $[redacted] (sourced from the 'Recourse IPD – summary' worksheet of the economic and financial workbook submitted with the minor resubmission

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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients receiving 15 mg x 20 x 1 pack per cycle	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Number of patients receiving 15 mg x 20 x 2 packs per cycle	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Number of patients receiving 15 mg x 20 x 3 packs per cycle	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Number of patients receiving 20 mg x 20 x 1 pack per cycle	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Number of patients receiving 20 mg x 20 x 2 packs per cycle	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Number of patients receiving 20 mg x 20 x 3 packs per cycle	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Number of patients receiving 20 mg x 20 x 4 packs per cycle	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Average number of cycles of treatment per patient	[redacted]						
Total dispensed cost	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	
Total rebates paid	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	$[redacted]	
General patient co-payments	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	
Concessional patient co-payments	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	-$[redacted]	
Net financial implications for PBS budget	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Proposed subsidisation caps (current minor resubmission)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Proposed subsidisation caps (November 2017)	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Source: Table 8, page 22 of the submission, Table 4 November 2017 Minutes

The redacted table shows that the total estimated number of patients was 10,000 - 50,000 and the net cost to the PBS would be $60 – $100 million.

Financial Management – Risk-sharing Arrangements

4.18 The minor resubmission proposed a rebate of [redacted] for any expenditure that exceeds the annual subsidisation caps. The proposed subsidisation caps are set at volumes less than the estimated utilisation and are lower than those proposed in the November 2017 submission (see Table 4 above). The minor resubmission estimated that these proposed caps would limit PBS expenditure to $30-$60 million. The minor resubmission stated (p2) that the subsidisation caps equate to [redacted] of its estimated volumes of use of trifluridine/tipiracil and claimed that these estimates were accepted by the PBAC in at the July 2017 meeting. At its July 2017 meeting, the PBAC noted that the minor resubmission reduced the uptake rate (of patients treated in the first-line setting for mCRC) from [redacted]% to [redacted]% in the first year after listing and

from [redacted]% to [redacted]% in subsequent years. The PBAC considered that the revised utilisation was more likely to reflect actual uptake (paragraph 5.8, July 2017 PSD).

4.19 The resubmission (p14) claimed that the proposed risk-sharing arrangement would further reduce the average effective price of trifluridine/tipiracil per cycle of treatment and the associated ICER. The minor resubmission presented its estimates of the impact of the proposed annual caps on the ICER by utilisation, as shown below.

Figure 1: The minor resubmission's estimate of the impact of proposed annual caps on the ICER

Source: 'Financial implications summary' worksheet of the economic and financial analyses workbook accompanying the minor resubmission

4.20 The minor resubmission argued that if utilisation exceeds its proposed caps, the effective ICER would reduce accordingly. The PBAC noted that these estimates have not been verified. However, the minor resubmission's argument for the reduced ICERs relies on the proposed annual caps to be exceeded into the future. Furthermore, although there is a [redacted]% rebate for use exceeding the agreed caps, the Commonwealth would nonetheless incur increased expenditure in the period between each dispensing of the medicine and the payment of the associated rebate by the sponsor. The pre-PBAC Response advised it would be prepared to work with the Department to identify potential solutions for reducing the time between Government payments to pharmacists dispensing trifluridine/tipiracil and the payment of rebates by Servier.

5 PBAC Outcome

5.1 The PBAC decided not to recommend trifluridine with tipiracil for the treatment of patients with metastatic colorectal cancer (mCRC) who have been treated previously or are not considered suitable for current available therapies, on the basis of modest clinical benefit and moderate toxicity. The PBAC reiterated its view that in clinical practice the modest benefit observed in the clinical trial was unlikely to be realised to the same extent and therefore considered that the cost effectiveness of trifluridine with tipiracil was uncertain and the incremental cost-effectiveness ratio was likely underestimated. The PBAC noted the proposed expenditure caps, however considered that given the uncertainty around the estimated utilisation of trifluridine with tipiracil, the caps were not an appropriate approach to ensure cost effectiveness.

5.2 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). The PBAC noted that although the MOGA supported the minor submission, it indicated that the submission was of a lower priority for PBS listing on the basis of its low ESMO-MCBS rating.

5.3 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 a 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.

5.4 The PBAC recalled that the median increase in progression free survival (PFS) of 0.3 months (HR 0.49; CI: 0.42, 0.58) compared with best supportive care in the RECOURSE 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) of 2.0 months (HR 0.69; CI: 0.59, 0.81) in the RECOURSE trial was modest. The PBAC also recalled that the results of the J003 trial (n=169) were similar to those of the RECOURSE trial. The PBAC agreed with the minor resubmission that the mean increase in OS is informative given the survival data were near complete (87% of patients randomised to trifluridine/tipiracil and 94% of patients randomised to placebo had died at the end of RECOURSE trial follow-up). The PBAC noted that the minor resubmission emphasised that the majority of survival gain (1.8 months of 2.6 months) was in the progression free health state. Overall however, the PBAC reaffirmed its view that the magnitude of clinical benefit observed from the trial may not be realised in clinical practice.

5.5 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 RECOURSE trial and therefore an important factor in the assessment of cost-effectiveness of trifluridine/tipiracil.

5.6 The PBAC considered that patients treated with trifluridine/tipiracil in clinical practice would generally have a poorer prognosis compared with patients enrolled in the RECOURSE trial. In the absence of adequate data supporting the comparability of the trial population to the eligible PBS population, the PBAC maintained that 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 treatment.

5.7 The PBAC noted that as there were no changes to the base case economic evaluation apart from a small increase in average total drug costs due to an increase in administrative fees (see paragraph 4.9 above), the resulting base case ICER of $45,000 -$75,000 per QALY gained, which also incorporates the previously proposed [redacted]% rebate, was not substantially different from that of the previous submission. The PBAC recalled that it previously considered that the base case ICER should not exceed $45,000 -$75,000 per QALY gained. However, as the PBAC considered that the benefit observed in the clinical trial setting may not be realised to the same extent in clinical practice, the Committee considered the true ICER would be higher than $45,000 -$75,000 per QALY gained.

5.8 The PBAC noted the submission's revised expenditure caps in the proposed Risk Sharing Arrangement (RSA) was based on half the utilisation estimated by the minor resubmission, and resulted in an estimated net financial impact of $30 -$60 million over 6 years. The PBAC noted while this was less than the financial impact of $30 - $60 million in the previous submission, it was nevertheless a substantial cost to Government and therefore represented a significant opportunity cost.

5.9 The PBAC recalled that at its July 2017 meeting, it considered that the reduced uptake rate applied in the utilisation estimates was more likely to reflect actual uptake. However, the PBAC reaffirmed there was still uncertainty in the estimated number of patients, and considered that the data presented on variation in uptake rate in other jurisdictions (ranging 33% to 88% of the estimated number of patients in Year 1) was indicative of this uncertainty. The PBAC noted the minor resubmission emphasised that the greater the utilisation of trifluridine/tipiracil above the proposed annual caps, the further the "effective ICER" would decrease below $45,000 -$75,000 /QALY. However, the PBAC considered that this was premised on estimated utilisation that was uncertain and likely overestimated. For assessments of cost-effectiveness to rely on RSA rebates, the PBAC advised that it would need to

have a high level of confidence in the utilisation estimates underpinning the RSA. As such, the PBAC considered that the proposed RSA was not an appropriate approach to achieve cost-effectiveness.

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.