5.16 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 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. Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Initial treatment

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
Episodicity:	-
Severity:	Metastatic
Condition:	Metastatic colorectal cancer
PBS Indication:	Metastatic colorectal cancer
Treatment phase:	Initial treatment ~~(new patients)~~
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,~~ AND~~ oxaliplatin,~~ AND~~irinotecan-based chemotherapies, ~~AND~~an anti-VEGF agent ~~AND~~and an anti-EGFR agent, OR Patient must not be a candidate for treatment with ~~any of the following:~~ 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.*

Continuing treatment

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
Episodicity:	-
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. ~~A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug.~~

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.*

Abbreviations: Max. = maximum; Qty =quantity; Rpts = repeats; DPMQ = dispensed price for maximum quantity; SE = Servier.

3 Background

3.1 TGA status at time of PBAC meeting: The submission was made under the TGA/PBAC parallel process. The TGA clinical evaluator's first round report was received prior to the PBAC meeting. The final (second round) TGA clinical evaluator's report and the TGA delegate's overview were not available at the time of the PBAC meeting.

3.2 Trifluridine/tipiracil has not been previously considered by the PBAC.

3.3 The National Institute for Health and Care Excellence (NICE) in the UK published their appraisal of trifluridine/tipiracil for the treatment of patients with previously treated mCRC on 24 August 2016[1]. The primary differences in the PBAC and NICE submissions related to the structure of the economic model and the utility values applied.

3.4 In July 2014 the PBAC rejected a submission for regorafenib for patients with mCRC who had received and failed (or were intolerant of) prior therapy. While outcome measures in the submission for trifluridine/tipiracil are broadly similar to the ones presented in the regorafenib submission, the magnitude of effect (and safety profile) was different.

4 Clinical place for the proposed therapy

4.1 Colorectal cancer is the second most commonly diagnosed cancer in Australia. The 5-year survival rate for those newly diagnosed with colorectal cancer (CRC) is estimated to be 68%. Median overall survival (OS) in patients who are newly diagnosed with mCRC in Australia is approximately two years.

4.2 The submission positioned trifluridine/tipiracil as last-line therapy for patients with mCRC who have failed on first and second line treatment, or are intolerant of, or not candidates for approved standard chemotherapy, an anti-vascular endothelial growth factor (VEGF) therapy, and, if RAS wild-type, an anti-epidermal growth factor receptor (EGFR) therapy.

4.3 Trifluridine/tipiracil is an orally active combination agent containing the drugs trifluridine and tipiracil. Trifluridine is a cytotoxic pyrimidine analogue, whilst tipiracil is an inhibitor of the enzyme that metabolises trifluridine and therefore increases its

[1] Trifluridine–tipiracil for previously treated metastatic colorectal cancer. NICE Final Appraisal Determination. Available from https://www.nice.org.uk/guidance/TA405/chapter/1-Recommendations . Accessed 05 September 2016.

bioavailability. Trifluridine and 5-FU (and its derivatives) inhibit thymidylate synthase (TS), a central enzyme in DNA synthesis inducing DNA dysfunction and a cytotoxic effect. The submission described the key differences between the trifluridine/tipiracil combination and the 5-FU-based fluoropyrimidines - inhibition of TS is the primary mechanism by which the 5-FU derivatives exert their effect, whereas the primary cytotoxic mechanism of action of trifluridine/tipiracil is DNA incorporation.

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

5 Comparator

5.1 The submission nominated best supportive care (BSC) as the main comparator given the proposed positioning of trifluridine/tipiracil as a last-line anticancer therapy. The evaluation considered this the appropriate comparator.

5.2 The ESC considered that BSC was the appropriate comparator, noting that BSC was previously accepted by PBAC as the comparator for regorafenib for the last line treatment of mCRC at the July 2014 PBAC meeting. The PBAC agreed with the ESC that BSC was the appropriate 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 health care professionals (6) and organisations (2) via the Consumer Comments facility on the PBS website. The comments from health care professionals described their experience in prescribing trifluridine/tipiracil for their patient(s), including the benefits and harms of treatment. The health care professionals also stated that there were currently limited treatment options for patients with mCRC, and that trifluridine/tipiracil represented an additional treatment option in an area of need.

6.3 Bowel Cancer Australia indicated its support for greater availability of treatment options for metastatic bowel cancer, such as trifluridine/ tipiracil, given the limited treatment options that are currently available through the PBS. The Medical Oncology Group of Australia (MOGA) also expressed its support for the trifluridine/tipiracil submission, on the basis of unmet need after failure of prior standard therapies. 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.

[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

Clinical trials

6.4 The submission was based on one head-to-head trial comparing trifluridine/tipiracil with BSC; the RECOURSE trial recruited 800 patients in a 2 (treatment): 1 (placebo) ratio. The ESC considered the trial to be of a reasonable size and appropriate for the requested PBS population.

6.5 A second trial (J003, n=169, recruited 2:1) was excluded from the primary analysis on the assumptions 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 RECOURSE trial to all potentially available options (based on exposure to bevacizumab and EGFR inhibitors). Outcomes from the two trials were pooled in a secondary analysis. While exclusion of this trial might not have been warranted as patients in J003 would still qualify for treatment under the proposed PBS listing, the results of the secondary analysis for OS including J003 are similar to those based on the RECOURSE trial only. The ESC noted the J003 trial did not require patients to have failed all available therapies for inclusion however, may still be relevant for consideration given the proportion of patients who would have met the proposed PBS criteria. The pre-PBAC response (p1) accepted that the J003 trial may be relevant for consideration noting that there is no evidence of a difference in efficacy based on ethnicity.

6.6 An indirect comparison of trifluridine/tipiracil with regorafenib (using placebo as a common reference) was included in the submission on the grounds that in the future a resubmission for regorafenib may be presented to the PBAC. The primary trial for regorafenib is the CORRECT trial (n=760, recruited 2:1). A secondary trial CONCUR (n=204, recruited 2:1) was excluded from the primary indirect comparison for the same reasons that J003 was excluded.

6.7 Details of the trials presented in the submission are provided in Table 1.

Table 1: Trials and associated reports presented in the submission for the main analysis

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trial: Trifluridine/tipiracil versus placebo		
RECOURSE	Randomised, Double-Blind, Phase 3 Study Of TAS-102 plus Best Supportive Care (BSC) Versus Placebo Plus BSC in Patients with Metastatic Colorectal Cancer Refractory to Standard Chemotherapies. (TPU-TAS-102-301 CSR; 20 Nov 2014).	
	Addendum to Clinical Study Report. Randomised, Double-Blind, Phase 3 Study Of TAS-102 plus Best Supportive Care (BSC) Versus Placebo Plus BSC in Patients with Metastatic Colorectal Cancer Refractory to Standard Chemotherapies. Study TPU-TAS-102-301 (referred as RECOURSE). 18 April 2016.	
	Mayer RJ, Van Cutsem E, Falcone A, Yoshino T, Garcia-Carbonero R, et al. (RECOURSE Study Group). Randomized trial of TAS-102 for refractory metastatic colorectal cancer.	N Engl J Med. 2015;372(20):1909-19.
	Mayer RJ, Ohtsu A, Yoshino T, Falcone A, Garcia-Carbonero R, et al. TAS-102 versus placebo plus best supportive care in patients with metastatic colorectal cancer refractory to standard therapies: Final survival results of the Phase III RECOURSE trial.	Abstract 634. 2016 Gastrointestinal Cancers Symposium.J Clin Oncol 2016;34(4 Suppl).
	Falcone A, Garcia-Carbonero R, Tabernero J, Sobrero A, Peeters M, et al. Low rates of hospitalizations with TAS-102 in the European (EU) subregion	Poster 2150. 2015 European Cancer

Trial ID	Protocol title/ Publication title	Publication citation
	of the Phase 3 RECOURSE trial in patients (pts) with metastatic colorectal cancer (mCRC).	Congress. European Journal of Cancer. 2015;51(Suppl3):S383.
	Shinozaki E, Laurent S, Grávalos C, Benavides M, Longo Muñoz F, et al. Timing of adverse events (AEs) in the Phase 3 RECOURSE trial of TAS-102 versus placebo in patients (pts) with metastatic colorectal cancer (mCRC).	Poster 2151. 2015 European Cancer Congress. European Journal of Cancer. 2015;51(Suppl3):S383-384.
	Van Cutsem E, Benedetti FM, Mizuguchi H, Mayer RJ, Ohtsu A. TAS-102 vs placebo (PBO) in patients (pts) ≥65 years (y) with metastatic colorectal cancer (mCRC): An age-based analysis of the RECOURSE trial.	Abstract 3595. 2015 ASCO Annual Meeting. J Clin Oncol 2015;33(15 Suppl).
	Van Cutsem et al. (TAS-102 versus placebo (PBO) in patients (pts) ≥65 years (y) with metastatic colorectal cancer (mCRC): An age-based analysis of the recourse trial.	Abstract 638. 2016 Gastrointestinal Cancers Symposium. J Clin Oncol 2016;34(4 Suppl).
	Ohtsu A, Yoshino T, Wahba MM, Benedetti FM, Mayer RJ et al. (RECOURSE Study Group). Phase 3 RECOURSE trial of TAS-102 versus placebo with best supportive care in patients with metastatic colorectal cancer: Geographic subgroups.	Abstract 3564. 2015 ASCO Annual Meeting. J Clin Oncol 2015;33(15 Suppl).
	Ohtsu A, Yoshino T, Wahba MM, Benedetti FM Mayer RJ et al. (RECOURSE Study Group). Phase 3 RECOURSE trial of TAS-102 versus placebo with best supportive care in patients with metastatic colorectal cancer: Geographic subgroups.	Abstract 646. 2016 Gastrointestinal Cancers Symposium. J Clin Oncol 2016;34(4 Suppl).
	Falcone A, Laurent S, Grávalos C, Benavides M, Longo Muñoz F, et al. Phase 3 RECOURSE trial of TAS-102 versus placebo with best supportive care in patients with metastatic colorectal cancer: European subgroup.	Abstract P-284. ESMO 17th World Congress on Gastrointestinal Cancer. Annals of Oncology 2015;26(Suppl.4):iv84.
	Hochster H, Hager S, Pipas JM, Tebbutt N, Laurent S, et al. KRAS and BRAF gene subgroup analysis in the Phase 3 RECOURSE trial of TAS-102 versus placebo in patients with metastatic colorectal cancer.	Abstract O-010. ESMO 17th World Congress on Gastrointestinal Cancer. Annals of Oncology 2015;26(Suppl.4):iv111.

Source: Table 2.1 p 44 of the submission.
Citations and references for the JOO3, CORRECT and CONCUR trials are provided in the Commentary, and Table 2.1 of the submission

6.8 The key features of the randomised trials are summarised in Tables 2 and 3.

Table 2: Key features of the included evidence

Trial	N	Design	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Trifluridine/tipiracil versus placebo						
RECOURSE	800	R, DB in a 2:1 ratio of treatment:placebo	Low	Refractory mCRC	OS, PFS, time to deterioration ECOG-PS $\leq$ 2 Safety and tolerability	OS, time to deterioration ECOG-PS $\leq$ 2 and adverse events used.

J003	169	R, DB in a 2:1 ratio of treatment:placebo	Low	Refractory mCRC	OS, PFS, safety and tolerability.	Not used.
Meta-analysis	969	Included RECOURSE and J003; assessed OS				Survival gain included in modelled evaluation as a sensitivity analysis.

DB=double blind; MC=multi-centre; OS=overall survival; PFS=progression-free survival; R=randomised.
Source: compiled during the evaluation

Table 3: Key features of the included evidence – indirect comparison

Trial	N	Design	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Regorafenib vs. placebo						
CORRECT	760	R, DB in a 2:1 ratio of treatment:placebo	Low	Previously treated mCRC	OS, PFS, EORTC QLQ-C30, EQ-5D and safety tolerability	Not used

DB=double blind; OS=overall survival; PFS=progression-free survival; R=randomised. EORTC QLQ C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D = EuroQol-5 dimension.
Source: compiled during the evaluation

Comparative effectiveness

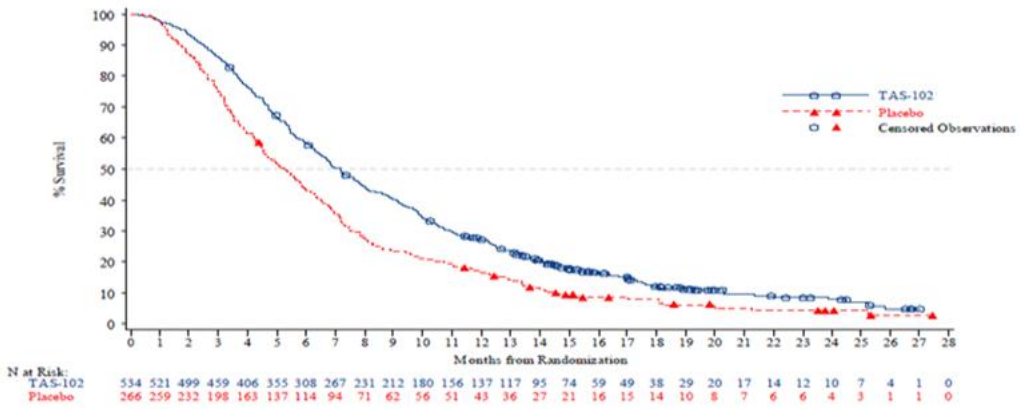
6.9 The key results from the clinical trials are summarised in Tables 4 to 6, and Figures 1 and 2. The original RECOURSE trial report dated August 2014 described the study design, dose regimens, investigational plan and baseline characteristics. Efficacy and safety results were presented with a cut-off date of 24 January 2014 for OS and 31 January 2014 for clinical non-survival outcomes. A further report dated April 2016 was based on an updated cut-off date of 08 October 2014 and included an additional 138 deaths over the previous analysis. Results presented in this document are based on the updated cut-off time unless otherwise stated. The ESC and PBAC noted that quality of life was not measured in the RECOURSE study.

Table 4: Results of overall survival in the RECOURSE trial

Parameter	Trifluridine/tipiracil (N=534)	Placebo (N=266)*
Number (%) of patients by censoring status • not censored (dead) • censored	 463 (86.7%) 71 (13.3%)	 249 (93.6%) 17 (6.4%)
KM estimates of survival (in months) 95% CI • median	 7.2 (6.6, 7.8)	 5.2 (4.6, 5.9)
Hazard ratio (95% CI) p-value	0.69 (0.59, 0.81) < 0.0001	

Source: Table 2-9, page 62 of submission, . updated cut-off date of 08 October 2014.

Figure 1: Overall survival in the RECOURSE trial



TAS-102 = trifluridine/tipiracil.
Source: Figure 2-2, page 63 of submission, updated cut-off date of 08 October 2014.

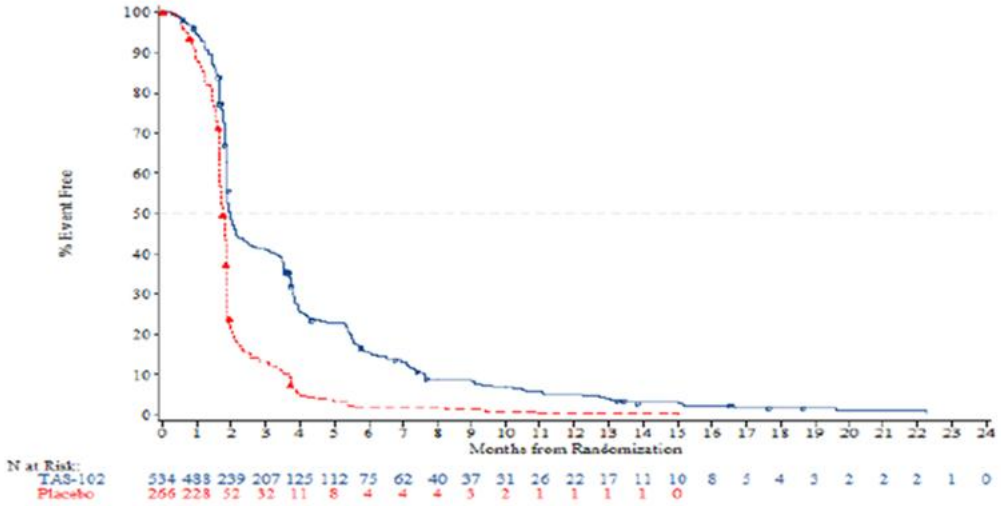
6.10 The submission calculated mean OS from individual patient data from the first cut-off date of 24 January 2014 of the RECOURSE trial. Mean OS was 9.7 months (95% CI: 9.2, 10.3) in the trifluridine/tipiracil arm and 7.2 months (95% CI: 6.6, 7.9) in the placebo arm. The PSCR (p2) stated that the difference in mean OS (i.e. the difference in the area under the survival curves) was more relevant to determining the magnitude of benefit associated with trifluridine/tipiracil than the median difference in OS (i.e. the difference in the survival curves at the point where 50% of the population have died), and that this was particularly the case given that the slope of the survival curves was not constant. The ESC noted that the economic evaluation was based on the difference in mean survival.

Table 5: Results of progression free survival in the RECOURSE trial

Parameter	Trifluridine/tipiracil (N=534)	Placebo (N=266)
Number (%) of patients by censoring status • not censored (progressed or dead) • censored	 496 (92.9%) 38 (7.1%)	 254 (95.5%) 12 (4.5%)
KM estimates of radiologic PFS (in months) 95% CI • Median	 2.0 (1.9, 2.1)	 1.7 (1.7, 1.8)
Hazard ratio (95% CI) p-value	0.49 (0.42, 0.58) < 0.0001	

Source: Table 2-10, page 66 of submission, updated cut-off date of 08 October 2014.

Figure 2: Radiologic progression-free survival in the RECOURSE trial



TAS-102 = trifluridine/tipiracil
Source: Figure 2-5, page 66 of submission, updated cut-off date of 08 October 2016.

6.11 The median radiologic PFS in the trifluridine/tipiracil arm was 0.3 months longer than in the placebo group. The submission argued that PFS was not an accurate measure of benefit because a substantial period of time elapsed in the RECOURSE trial (8 weeks) prior to the assessment of radiologic PFS. It argued that had the assessments been performed at 4 weekly intervals, there would be a greater difference in median PFS. The PFS outcome was not used in the economic evaluation. The ESC noted the majority of patients in both treatment arms progressed quickly (i.e. 53% of patients in the trifluridine/tipiracil treatment arm and 79% of patients in the BSC arm had progressed by week 8, and hence the difference in the median PFS was small).

6.12 The submission proposed that the pre-specified secondary outcome in the RECOURSE trial of time to deterioration in ECOG-PS from the baseline of 0-1 to ≥2, is a better measure of benefit in this patient group. This was supported by input from a survey of 13 medical oncologists, who had accessed trifluridine/tipiracil through the TGA special access scheme for the patient group proposed for listing. The survey was conducted on a clinician-by-clinician basis and the process for forming a consensus view is unclear. Moreover, the representativeness of the clinicians cannot be discerned as no information was provided as to whether they came from multiple centres within the same city, and it excluded centres from Queensland. Further, the questions in the survey asked whether radiologic assessment or ECOG status would be better indicators of patients' quality of life, not the validity of using the ECOG to infer patients' quality of life.

Table 6: Results of Time to deterioration of ECOG-PS to ≥ 2 in the RECOURSE trial

Parameter	Trifluridine/tipiracil (N=534)	Placebo (N=266)
Number (%) of patients by censoring status • not censored (ECOG ≥ 2) • censored	 470 (88.0%) 64 (12.0%)	 251 (94.4%) 15 (5.6%)
KM estimates of time to deterioration of ECOG to ≥ 2 (in months) 95% CI • median • mean[a]	 6.2 (5.6, 6.8) 6.5 (6.1, 6.9)	 4.4 (3.6, 5.1) 4.8 (4.3, 5.3)
Hazard ratio (95% CI) p-value	0.74 (0.64, 0.87) 0.0002	

[a] individual patient data from the original data cut-off. All other results are from the updated cut-off date of 08 October 2014.
Source: Table 2-11, page 67 of submission.

6.13 Examination of the individual patient data used to calculate the time to deterioration of ECOG-PS revealed that the result for this outcome was the same as for OS for a large number of patients (n=404; 140/266 placebo and 264/534 trifluridine/tipiracil patients), and longer than OS for some patients. The PSCR (p3) stated it was likely that the schedule of assessments in the RECOURSE trial, which had ECOG-PS being assessed at approximately 4-weekly intervals, did not capture the actual date of decline of ECOG-PS to ≥ 2 as it may have occurred in the period between the prior assessment and the date of death. It was further stated that it is not uncommon for patients with advanced mCRC to experience a rapid acceleration in rate of deterioration in health status close to death. The ESC noted the reference provided to support this statement was not specific to CRC. The ESC also noted that this does not explain the cases where the time to deterioration to ECOG-PS ≥ 2 was longer than OS. The pre-PBAC response (p3) explained that this was due to 7 alive patients being censored at the time of primary analysis on the 24 January 2014, while censoring did not apply for the time to ECOG-PS ≥ 2 analysis and therefore events occurring from 24 to 29 January 2014 were included.

Summary of supplementary evidence: J003 trial

6.14 The hazard ratio for death in the J003 trial was numerically lower than in the RECOURSE trial: HR = 0.56 (95% CI: 0.39, 0.81; p = 0.0011) for J003 compared with HR = 0.69 (95% CI: 0.59, 0.81; p< 0.0001) in RECOURSE. A random-effects meta-analysis combining the OS outcome produced a result consistent with that of RECOURSE alone; HR = 0.67 (95% CI: 0.57, 0.78). The median OS gain in J003 was 2.4 months with a pooled median OS advantage of 2.04 months.

6.15 The analysis of radiologic PFS in the J003 trial showed a statistically significant improvement in the trifluridine/tipiracil group compared to placebo: HR = 0.41 (95% CI = 0.28, 0.59; p < 0.0001), which was similar to the HR observed in the RECOURSE trial. The median PFS in the trifluridine/tipiracil group (2.0 months) was 1.0 month longer than in the placebo group. The difference in median PFS was longer in J003 (1 month) than in RECOURSE (0.3 months). This was potentially due to the difference in the schedule of radiological assessments in J003, being 4 weekly.

6.16 Time to deterioration of ECOG-PS to ≥ 2 was not assessed in the J003 trial.

Summary of primary evidence for indirect comparison: regorafenib versus placebo

6.17 The results of the indirect comparison of trifluridine/tipiracil with regorafenib showed that there was no statistically significant difference in the HR for death between the two treatments (HR = 0.90; 95% CI: 0.70, 1.15). At the November 2014 meeting, the PBAC concluded that regorafenib was not cost-effective for the treatment of patients with mCRC. This was 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"[2].

Comparative harms

6.18 Adverse events (AEs) of Grade ≥3 occurred more frequently in the trifluridine/tipiracil group than in the placebo group (in 69% vs 52% of the patients). Myelosuppression was the main AE caused by trifluridine/tipiracil; 38% of patients had neutropenia of Grade ≥ 3, and 4% had febrile neutropenia of Grade ≥ 3.

6.19 The incidence of anaemia Grade ≥ 3 (18% vs 3%), and thrombocytopenia Grade ≥ 3 (5% vs <1%) was greater in the trifluridine/tipiracil group than in the placebo group. Other commonly reported AEs included nausea, vomiting, decreased appetite, fatigue and diarrhoea. There was one treatment-related death resulting from septic shock reported for trifluridine/tipiracil.

6.20 The safety profile of trifluridine/tipiracil appeared to differ from that of regorafenib. In the CORRECT trial, the most common AEs of Grade ≥3 were hand-foot skin reaction, fatigue, diarrhoea, hypertension and rash or desquamation hand-foot skin reaction, whereas myelosuppression events were the most common AEs of Grade ≥3 reported for trifluridine/tipiracil e.g. neutropenia. An indirect comparison provided an odds ratio for Grade ≥ 3 AEs of 0.58 (95%: 0.37, 0.89) for trifluridine/tipiracil compared with regorafenib. During its review of the November 2014 regorafenib submission, the PBAC had noted from the trial evidence that for every 100 patients treated with regorafenib compared with BSC, one patient would die from a treatment related adverse event.

Benefits/harms

6.21 A summary of the comparative benefits and harms for trifluridine/tipiracil versus placebo is presented in Table 7.

[2] Regorafenib submission Public Summary Document – July 2014 PBAC Meeting. Available from http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2014-07/regorafenib-psd-07-2014.pdf. Accessed 12 September 2016.

Table 7: Summary of comparative benefits and harms for trifluridine/tipiracil and placebo

Overall Survival: RECOURSE				
	Trifluridine/ tipiracil	**Placebo**	**Absolute Difference**	**HR (95% CI)**
# dead	463/534	249/266	-	0.69 (0.59, 0.81)
Median (mths)	7.2 (6.6, 7.8)	5.2 (4.6, 5.9)	2	-
Progression Free Survival: RECOURSE				
	Trifluridine/ tipiracil	**Placebo**	**Absolute Difference**	**HR (95% CI)**
# Progressed	496/534	254/266	-	0.49 (0.42, 0.58)
Median (mths)	2.0 (1.9, 2.1)	1.7 (1.7, 1.8)	0.3	-
Time to ECOG-PS ≥ 2: RECOURSE				
	Trifluridine/ tipiracil	**Placebo**	**Absolute Difference**	**HR (95% CI)**
# ECOG-PS ≥ 2`	470/534	251/266	-	0.74 (0.64, 0.87)
Median (mths)	6.2 (5.6, 6.8)	4.4 (3.6, 5.1)	1.8	-

Harms						
	Trifluridine/ tipiracil	**Placebo**	**RR (95% CI)**	**Event rate/100 patients**		**RD (95% CI)**
				Trifluridine/ tipiracil	**Placebo**	
Adverse event – Neutropenia (RECOURSE)						
Any grade	353/528	2/263	87.9 (22.1, 350.1)	66.9	0.8	66.1 (61.9, 70.2)
Grade ≥ 3	200/528	0/263	NC	38	0	38 (24,42)
Adverse event – Leukopenia (RECOURSE)						
Any grade	407/528	12/263	16.9 (9.7, 29.4)	77.1	4.6	72.5 (68.1, 76.9)
Grade ≥ 3	113/528	0/263	NC	21	0	21 (18, 25)
Adverse event – Anaemia (RECOURSE)						
Any grade	404/528	87/263	2.3 (1.9, 2.8)	76.5	33.0	43.4 (36.9, 50.1)
Grade ≥ 3	96/528	8/263	6.0 (3.0, 12)	18	3	15 (11,19)

Abbreviations: NC = not calculable; PBO = placebo; RD = risk difference; RR = risk ratio
Source: Compiled during the evaluation

6.22 On the basis of direct trial evidence presented in the submission, there would be a difference in median OS of approximately 2 months in the group of patients treated with trifluridine/tipiracil compared with placebo. For every 100 patients treated with trifluridine/tipiracil compared with placebo over a mean duration of follow-up of 28 months, approximately:

- 38 additional patients would have grade 3 or 4 neutropenia;
- 21 additional patients would have grade 3 or 4 leukopenia; and
- 15 additional patients would have grade 3 or 4 anaemia.

Clinical Claim

6.23 The submission claimed that trifluridine/tipiracil is superior in terms of efficacy to placebo in patients with refractory mCRC. The submission also claimed that trifluridine/tipiracil is inferior to placebo in terms of safety, but that the associated AEs were mainly attributable to myelosuppression which is manageable by dose modification or prolongation of the treatment interval. The ESC agreed with the submission that trifluridine/tipiracil is superior in terms of efficacy and inferior in terms

of safety to placebo. However, noted the clinical significance of the OS and PFS gains may be uncertain.

6.24 The PBAC considered the submission's claim of superior comparative effectiveness of trifluridine/tipiracil over placebo was adequately supported, however, considered that the benefit was modest, and that the benefit realised in clinical practice may be smaller. The PBAC considered that the submission's claim of inferior safety of trifluridine/tipiracil compared to placebo was reasonable.

6.25 The submission claimed that trifluridine/tipiracil is no worse, in terms of efficacy, than regorafenib as a treatment for patients with mCRC, and that the safety profile of trifluridine/tipiracil is different to that for regorafenib. The PBAC considered the efficacy of trifluridine/tipiracil to be similar to that for regorafenib, but noted that trifluridine/tipiracil appears to be better tolerated.

Economic analysis

6.26 The submission presented a trial-based economic evaluation, summarised in Table 8.

Table 8: Summary of model structure and rationale

Component	Summary
Time horizon	Trial based analysis; data was derived directly from the RECOURSE trial
Outcomes	Life-years and Quality-adjusted life-years
Methods used to generate results	Partitioned survival analysis.
Health states	ECOG-PS<1, ECOG-PS ≥2, dead.
Cycle length	One month.
Transition probabilities	Estimated from the IPD from the RECOURSE trial.

Abbreviations: IPD = individual patient data
Source: table 3-1, page 80 of submission.

6.27 During the evaluation, the use of a within-trial analysis was considered appropriate. The model relied on health states defined by deterioration in ECOG status. This was a departure from models presented previously to the PBAC for oncology drugs which focused on the presence/absence of disease progression. The PSCR (p3) maintained that the use of ECOG-PS to define health states is more appropriate than radiologic progression and noted the results from the survey of Australian medical oncologists supported a correlation between ECOG-PS and quality of life. The ESC noted that the sponsor's trifluridine/tipiracil submission to NICE defined health states based on progression and included utilities sourced from the CORRECT trial (previously presented to the PBAC for regorafenib) for progression-free and post-progression health states. The ESC considered that a model based on progression would be more informative, in part because utility values are available for progression-free and post-progression for mCRC patients.

6.28 The ESC noted that discounting of health outcomes and costs was not applied in the second year of economic analysis however, considered this would have a minimal impact given the small proportion of patients alive in the second year.

6.29 The key drivers of the model are summarised in Table 9.

Table 9: Key drivers of the model

Description	Method/Value	Impact
Overall survival data	Mean overall survival from RECOURSE trial	Low
Patient performance status defined by ECOG-PS	Mean time to ECOG-PS $\geq$ 2 as an alternate to RECIST defined PFS	Low
Utility values	Values applied are transformed from ECOG-PS scores and are higher than PBAC has previously reviewed for mCRC	Moderate, favours trifluridine/tipiracil.

Source: compiled during the evaluation

6.30 Utility values applied in the model were higher than the published[3] utility values that were used in the submission previously considered by PBAC for regorafenib.

6.31 The summary of costs and outcomes in the economic analysis is presented in Table 10. The redacted table below shows that the incremental cost of trifluridine/tipiracil vs BSC was $45,000 - $75,000 per LY gained, while the incremental cost of trifluridine/tipiracil vs BSC was $75,000 - $105,000 per LY gained.

Table 10: Results of the trial based economic evaluation

	Trifluridine/ tipiracil arm	Placebo arm	Increment
Costs			
Average total drug costs	$[redacted]	$0.00	$[redacted]
Average cost per patient to manage AEs	$317.21	$0.00	$317.21
Clinician visits	$807.85	$543.60	$264.25
Monitoring costs	$74.97	$0.00	$74.97
Total costs:	**$[redacted]**	**$543.60**	**$[redacted]**
Outcomes			
Mean time (in years) with ECOG = 0 or 1	0.54	0.40	0.14
Mean overall survival (in years)	**0.81**	**0.60**	**0.21**
Mean QALYs	**0.63**	**0.46**	**0.16**
Incremental cost of trifluridine/tipiracil vs BSC per LY gained:			**$[redacted]**
Incremental cost of trifluridine/tipiracil vs placebo per QALY gained:			**$[redacted]**

Source: Table 3-3, page 91 of submission.

6.32 The use of ECOG-PS to define the health states within the model resulted in a number of areas of uncertainty:

- Previous models submitted to the PBAC for mCRC have used disease progression (not-progressed, progressed) to define health states, and to reflect proposed PBS criteria. These are primarily based on radiological assessments of disease and therefore are less subjective than assessments of deterioration in ECOG status.
- Although it can be assumed that there is a relationship between ECOG-PS and quality of life, the applicability of the utility values from Teckle et al., 2011 publication is questionable. The publication relates to a study where only 57

[3] Grothey A, Van Cutsem E, Sobrero A, Siena S, Falcone A et al. (CORRECT Study Group). Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, Phase 3 trial. Lancet. 2013;381(9863):303-12.

(31%) patients had CRC, of which 48% had stage 4 disease. Moreover, the reported relationship had not been stratified for underlying cancer type or stage. The ESC agreed that the use of ECOG-PS in the model introduced a level of uncertainty as the utility values from the Teckle et al., 2011 publication were not specific to mCRC and limited in the distribution across ECOG-PS status.

- It was not consistent with the continuation criteria in the proposed PBS listing which relied on the absence of disease progression (which may or may not correspond with deterioration in ECOG status). The ESC considered criteria based on the ECOG-PS were not appropriate for continuing treatment given assessment of ECOG-PS is subjective.

6.33 The pre-PBAC response included a revised economic analysis with a base case ICER of $45,000 - $75,000 per QALY gained. The following revisions were made to the model:

- Increase of the mean OS gain from 2.5 months to 3.2 months based on extrapolation of the pooled OS data from the RECOURSE and J003 trials;
- Replacement of ECOG-PS based health states with radiologic time to progression based health states. The pre-PBAC response provided a pooled analysis of PFS from RECOURSE and J003 with time to progression in the trifluridine/tipiracil arm of 3.7 months and time to progression in the placebo arm of 1.9 months;
- Utility values from the CORRECT trial (0.73 for not progressed disease in both groups and 0.59 for progressed disease in both groups) are applied.

6.34 The pre-PBAC response (p1) stated that the above model input values had been accepted by NICE. The PBAC noted that the revised model included in the Pre-PBAC response, which included a revised efficacy estimate, had not been evaluated.

6.35 The results of the key sensitivity analyses for the model presented in the submission are presented in Table 11. The redacted table below shows that, in the sensitivity analysis, the ICER was in the range of $75,000 - $105,000 per QALY.

Table 11: Results of the univariate sensitivity analysis

Analysis	Incremental costs	Incremental discounted life-years	ICER
Base-case (mean OS from RECOURSE)	$[redacted]	0.16	$[redacted]
Utility values – This is based on utility values of 0.73 for pre-progressed disease and 0.59 for progressed disease, from the CORRECT trial. This analysis assumes that an ECOG-PS score of 0-1 represents pre-progression and a score of ≥ 2 represents progression.	$[redacted]	0.14	$[redacted]

Source: conducted during the evaluation.

6.36 The analyses showed that the model results were sensitive to variations in the utility values used (substituting the values used in the submission for those the PBAC considered previously for regorafenib).

Drug cost/patient/course: $[redacted]

6.37 The average drug cost per patient per cycle (one month) is $[redacted]. This was based on an average dose of 60 mg, and represents the cost of 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

6.38 This submission was not considered by DUSC.

6.39 The submission adopted a market share approach based on utilisation of first and second line treatments in mCRC, and a projected rate of uptake of the new drug as a last-line option in these patients.

6.40 An analysis of 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, was undertaken to inform an estimation of the likely number of patients to be treated. A uniform/linear rate of growth in the likely number of patients being treated for mCRC from 2017 to 2022 based on 2011-2015 data was then applied. This approach appeared reasonable and broadly correlated with the Australian Institute of Health and Welfare (AIHW) cancer incidence projections 2011 to 2020[4]. However, the approach did not take into account patients who are not candidates for first and second line treatments but may still receive trifluridine/tipiracil. Including these patients would increase the patient estimates.

6.41 The ESC considered that use of the PBS data to ascertain the number of patients treated for mCRC was appropriate but noted that the estimates could not be verified because details of the analysis using the 10% PBS sample were not provided. For example, it was not clear which drugs were included in the analysis, whether the analysis counted incident or prevalent patients, and whether an apparent decline in patients receiving first-line therapy from mid-2013 to 2015 was real or an artefact of the method. Based on triangulation with epidemiological data (assuming 50% of incident colorectal cancer patients develop metastatic disease, and 31.6% of mCRC patients received no active therapy (data from ACCORD), and noting that patients must have a WHO performance status of 1 or less, the ESC considered that the number of patients likely to be treated with trifluridine/tipiracil was overestimated.

6.42 The pre-PBAC response (p3) maintained that the estimates of uptake were unlikely to be overestimated. The pre-PBAC response claimed that based on the triangulation approach taken by ESC (assuming 50% of incident CRC patients develop metastatic disease, and 31.6% of mCRC patients received no active therapy), then accounting for the fact that patients must have a WHO performance status of 1 or less to be eligible for treatment (86% as per Table 6 in the ACCORD report), it is estimated that 4,400 patients received first-line treatment for mCRC in 2012. The pre-PBAC response argued that as the submission's estimate (4,963 mCRC patients in 2012) is within 11% of the estimate calculated using the approach advised by the ESC, it is a reasonable estimate.

[4] Australian Institute of Health and Welfare 2012. Cancer incidence projections: Australia, 2011 to 2020. Cancer Series no. 66. Cat. No. CAN 62. Canberra: AIHW.

6.43 The estimated uptake of trifluridine/tipiracil was [redacted]% in year 1 in patients who have received first and second line treatments for mCRC, followed by [redacted]% each year thereafter. Uptake was estimated based on a survey of 13 medical oncologists that accessed trifluridine/tipiracil through the TGA special access scheme (SAS) for this patient group. The estimates did not include patients who were not candidates for current standard treatment. The ESC considered that clinicians seeking last-line treatment options via the SAS may not represent all prescribers and may overestimate the uptake of trifluridine/tipiracil. The pre-PBAC response (p3) argued that the Australian year 1 estimate is [redacted]% below the actual year 1 uptake (adjusted to Australia by ratio of incidence) in Japan (7,061) and [redacted]% above the actual year 1 uptake (adjusted to Australia by ratio of incidence) in the USA (5,935). The PBAC agreed with the ESC that the uptake was likely to have been overestimated, and it is unclear if uptake in Japan and the USA is likely to reflect that in Australia.

6.44 The projected financial implications for the PBS budget associated with listing of trifluridine/tipiracil are shown in Table 12. The redacted table below shows that at year 5 the estimated number of patients was less than 10,000 and the net cost to the government would be $30 - $60 million per year.

Table 12: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Total number of patients on PBS-subsidised first-line regimens for mCRC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Uptake of trifluridine/tipiracil	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Likely number of patients to be prescribed trifluridine/tipiracil	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net financial implications for PBS budget	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Source: Tables 4-1 and 4-3, pages 96 and 98 respectively of submission.

6.45 The estimates provided in the submission excluded any costs to the PBS, MBS and hospitals for the treatment of AEs. Based on data from the RECOURSE trial, 9.4% of patients would require treatment for neutropenia which would incur additional hospital based costs. Costs to the MBS as a result of physician visits (MBS item 116) and full blood count determination (MBS item 65070) had an incremental value of $339 in the economic model. This equated to an additional cost of less than $10 million in year 1 rising to less than $10 million by year 6 in the financial estimates. Overall, it was estimated that the costs of managing AEs associated with trifluridine/tipiracil would be much lower than the costs of the drug itself if the rate of AEs from the clinical trial were reflected in ongoing clinical practice.

6.46 The results of sensitivity analyses on the financial estimates are shown in Table 13. The redacted table below shows that the net cost to the PBS at year 5 when applying the lower confidence limit around estimated uptake would be $20 - $30 million the upper confidence limit would be $30 - $60 million and when applying full treatment cycles dispensed on each occasion, would be $30 - $60 million. The estimates were most sensitive to variations in the uptake rate.

Table 13: Sensitivity analysis on estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Base-case						
Net financial implications for PBS budget	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Applying lower confidence limit around estimated uptake ([redacted]% in Year 1, [redacted]% thereafter)						
Net financial implications for PBS budget	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Applying upper confidence limit around estimated uptake (40% in Year 1, 46% thereafter)						
Net financial implications for PBS budget	$[redacted]	$[redacted]3	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Applying full treatment cycles dispensed on each occasion (average number of cycles dispensed increased to 4)						
Net financial implications for PBS budget	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Source: Table 4-5, page 99-100 of submission, and developed.

Quality Use of Medicines

6.47 The submission noted that the sponsor is currently considering the development of additional aides and educational materials for prescribers, pharmacists, patients and their carers to ensure quality use of the product. The submission stated that the unique dosing regimen will receive particular attention in these materials.

Financial Management – Risk Sharing Arrangements

6.48 The submission noted that the sponsor expects that a risk sharing arrangement (RSA) to minimise the financial risk to government will be required for greater than expected use of trifluridine/tipiracil. It did not propose what form that RSA might take.

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

7 PBAC Outcome

7.1 The PBAC did not recommend the listing of trifluridine with tipiracil on the PBS for the treatment of patients with metastatic colorectal cancer (mCRC) who have been previously treated with, or are not considered suitable for, currently available therapies. This decision was made 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.

7.2 The PBAC noted and welcomed the consumer comments received relating to this submission, including from Bowel Cancer Australia and the Medical Oncology Group of Australia, via the Consumer Comments facility on the PBS website. The PBAC acknowledged the unmet need for additional effective and well-tolerated therapies for patients with mCRC who have failed or are unsuitable for the currently available therapies.

7.3 The PBAC noted that the submission was made under the TGA/PBAC parallel process and that neither a final (second round) TGA Clinical Evaluation Report or a TGA Delegate's Overview were available at the time of PBAC consideration.

7.4 The PBAC considered best supportive care to be the appropriate comparator.

7.5 The PBAC noted the submission was based on one key trial (RECOURSE) and one supportive trial (J003). Both trials were double-blind and patients were randomised to ether trifluridine/tipiracil or placebo. The median increase in PFS in the RECOURSE trial was small (0.3 months) and the PBAC noted that this reflected that the majority of patients in both treatment arms had progressed prior to the first assessment at 8 weeks, however the PBAC considered that a proportion of patients did benefit from treatment with trifluridine/tipiracil. The median increase in OS was 2.0 months (HR 0.69; CI: 0.59, 0.81). The PBAC agreed with the PSCR 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. The mean gain in OS was 2.5 months. The PBAC noted the results of the J003 trial were similar to those for the RECOURSE trial. The PBAC considered the claim of superior efficacy of trifluridine/tipiracil over best supportive care to be adequately supported by the data, although considered the magnitude of the benefit to be modest.

7.6 The PBAC considered the submission's claim of inferior safety of trifluridine/tipiracil compared to placebo to be reasonable. The PBAC noted the toxicity associated with trifluridine/tipiracil was predictable, with myelosupression being the key adverse event.

7.7 The PBAC noted the efficacy of trifluridine/tipiracil appears to be similar to that for regorafenib, but that trifluridine/tipiracil appears to be better tolerated.

7.8 The PBAC raised the following issues relating to the applicability of the trial data to Australian clinical practice, and noted that the magnitude of the benefit as observed in the trials may not be realised in clinical practice. Firstly, patients in clinical trials are generally healthier on average than patients treated in clinical practice, and specifically in the trifluridine/tipiracil trials the majority of patients (approximately 63% in RECOURSE and 57% in J003) had an ECOG performance status of 0. A higher proportion of patients with an ECOG performance status of 1 may be treated in clinical practice. Secondly, 9.4% of patients in RECOURSE received granulocyte colony stimulating factors (GCSF) for neutropenia. It was 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.

7.9 The PBAC noted the ICER presented in the submission was $75,000 - $105,000 per QALY gained, and that this was based on an unconventional model that defined health states on the basis of ECOG performance status. The PBAC noted and agreed with ESC's advice that a model which defined health states based on progression would be more informative, in part because such a model could be populated using utility values specific for mCRC patients. It was further noted that when a sensitivity analysis was undertaken using the utility values from the regorafenib mCRC trial, the ICER increased to $75,000 - $105,000. The PBAC noted the arguments in the pre-PBAC response that the utility values from the regorafenib

trial may not be appropriate given the differences in toxicity for trifluridine/tipiracil compared with regorafenib, however, considered these values most appropriate in the absence of quality of life data from the trifluridine/tipiracil trials.

7.10 A revised economic model was presented in the pre-PBAC response that incorporated health states based on radiological progression and the utility values from the regorafenib trial. The PBAC noted the decreased ICER with this model ($45,000 - $75,000 per QALY gained) was inconsistent with the sensitivity analysis above where the ICER increased. The PBAC noted that this probably reflected the additional changes incorporated into the model, including:

- Using pooled clinical data from the RECOURSE and J003 trials rather than data from the RECOURSE trial only. The PBAC noted the RECOURSE trial was presented in the submission as key and considered it reasonable to present an economic model based on this trial only.
- Extrapolating the OS data beyond the trial duration. The PBAC noted the incremental gain in OS in the model presented in the submission was 2.5 months and that this increased to 3.2 months in the model presented in the pre-PBAC response. The PBAC considered, given the survival data from the trial were almost complete, the model presented in the submission which did not extrapolate the OS data to be more appropriate. The PBAC noted using the trial based estimates of OS from RECOURCE and J003 in the revised model increased the ICER from $45,000 - $75,000 to $75,000 - $105,000 per QALY gained.

7.11 The PBAC considered the results from the revised economic model presented in the pre-PBAC response to be uncertain because substantive changes were made to the model and the changes had not been evaluated. Notwithstanding this, the PBAC considered that the base case ICER was unacceptably high at the requested price, and likely to be underestimated given the applicability issues noted in paragraph 7.8.

7.12 The PBAC agreed with the ESC that the submission's estimate of the number of patients to be treated and the associated financial impact is 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.

7.13 As advised by the ESC, 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. The PBAC considered that the base case ICER for this scenario should not exceed a specifc target ICER in the range $45,000 - $75,000per QALY gained. The PBAC stated the resubmission would need to be in the form of a major submission if substantive changes are made to the model evaluated as part of the current submission.

7.14 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

Although Servier was disappointed that its submission requesting PBS-listing of LONSURF was rejected, Servier is appreciative of the constructive feedback provided by the PBAC. Servier believes that the provision of clear advice from the PBAC has helped Servier assemble a minor resubmission that will have a higher chance of success than might otherwise have been the case had the advice from PBAC not been so clear.