

**6.08 TRIFLURIDINE with TIPIRACIL,
Tablet containing 15 mg trifluridine with 6.14 mg
tipiracil (as hydrochloride),
Tablet containing 20 mg trifluridine with 8.19 mg
tipiracil (as hydrochloride),
LONSURF[®],
Servier Laboratories (Australia) Pty Ltd.**

1 Purpose of Application

- 1.1 The submission requested an extension to the current Authority Required (STREAMLINED) listing of trifluridine with tipiracil (hereafter referred to as trifluridine/tipiracil), in fixed dose combinations, for the treatment of patients with metastatic gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have been previously treated with, or are not candidates for treatment with, fluoropyrimidine, platinum and either a taxane- or irinotecan-based chemotherapy and, if appropriate, HER2/neu-targeted therapy (i.e., trastuzumab). This was the first application to the PBAC for trifluridine/tipiracil for this indication.
- 1.2 The listing was requested on the basis of a cost-utility analysis compared with placebo plus best supportive care (BSC) alone.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Patients with metastatic gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine, platinum and either a taxane- or irinotecan-based chemotherapy and, if appropriate, HER2/neu-targeted therapy (i.e., trastuzumab)
Intervention	Trifluridine 15 mg + tipiracil 6.14 mg & trifluridine 20 mg + tipiracil 8.19 mg + BSC
Comparator	Placebo (no anticancer therapy) + BSC
Outcomes	Overall survival (OS), progression-free survival (PFS), time to deterioration of performance status, response rate, safety
Clinical claim	In patients with metastatic gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction who have been previously treated with, are intolerant of, or not candidates for standard available anticancer therapies, trifluridine/tipiracil, added to BSC, is associated with improvements in overall survival, progression-free survival, time to deterioration of ECOG-PS, and response rates compared to placebo added to BSC. More adverse events were reported in trifluridine/tipiracil-treated patients than in placebo-treated patients but the majority of reported adverse events were laboratory-based indicators of myelosuppression (i.e., neutropenia and anaemia), which are generally able to be managed by reduction in dosage or by delaying the next dose.

Source: Table 1.1.1, p1 of the submission

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BSC = best supportive care; ECOG-PS = European Cooperative Oncology Group Performance Status

2 Requested listing

2.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
TRIFLURIDINE + TIPIRACIL					
Trifluridine 15 mg + tipiracil 6.14 mg tablet, 20	3	2	\$2,272.44	LONSURF 15/6.14	Servier Laboratories
Trifluridine 20 mg + tipiracil 8.19 mg tablet, 20	4	2	\$3,922.49	LONSURF 20/8.19	
Category / Program	GENERAL – General Schedule (Code GE)				
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives				
Episodicity:	-				
Severity:	<i>Metastatic (Stage IV) [contained within 17773]</i>				
Condition:	<i>adenocarcinoma of the stomach or gastro-oesophageal junction</i>				
PBS Indication:	Metastatic (Stage IV) adenocarcinoma of the stomach or gastro-oesophageal junction [new concept]				
Treatment phase:	Initial treatment				
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined				
Clinical criteria:	Patient must have a WHO performance status of 1 or less [10299; phase out 19462] <hr/> AND Patient must have previously received treatment with fluoropyrimidine, platinum and either a taxane or irinotecan-based chemotherapy and, if appropriate, HER2/neu-targeted therapy (i.e., trastuzumab), OR Patient must not be a candidate for treatment with fluoropyrimidine, platinum and either a taxane or irinotecan-based chemotherapy and, if appropriate, HER2/neu-targeted therapy (i.e., trastuzumab); [new concept] <hr/> AND <i>Patient must have previously received at least two prior lines of chemotherapy that included a fluoropyrimidine, a platinum, either a taxane or irinotecan.</i> <hr/> AND <i>The treatment must be the sole PBS-subsidised therapy for this condition [7890]</i>				

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Administrative Advice Prescriber Instructions:	The patients WHO performance status and body weight must be documented in the patient's medical records at the time the treatment cycle is initiated. [10024]
Administrative Advice	No increase in maximum quantity or number of units may be authorised. [7606]
	No increase in the maximum number of repeats may be authorised. [7607]
	Special Pricing Arrangements apply [7608]

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
TRIFLURIDINE + TIPIRACIL Trifluridine 15 mg + tipiracil 6.14 mg tablet, 20 Trifluridine 20 mg + tipiracil 8.19 mg tablet, 20	3 4	2 2	\$2,272.44 \$3,922.49	LONSURF 15/6.14 LONSURF 20/8.19	Servier Laboratories
Category / Program	GENERAL – General Schedule (Code GE)				
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives				
Episodicity:					
Severity:	Metastatic (<i>Stage IV</i>) [contained within 1773]				
Condition:	Adenocarcinoma of the stomach or gastro-oesophageal junction				
PBS Indication:	Metastatic (<i>Stage IV</i>) adenocarcinoma of the stomach or gastro-oesophageal junction [new concept]				
Treatment phase:	Continuing treatment				
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined				
Clinical criteria:	Patient must have previously been treated with PBS-subsidised treatment with this drug for this condition [21475] <hr/> AND Patient must not develop progressive disease whilst receiving PBS-subsidised treatment with this drug for this condition [21809] <hr/> AND The treatment must be the sole PBS-subsidised therapy for this condition [7890]				
Prescriber Instructions	A patient who has progressive disease when treated with this drug is no longer eligible for PBS-subsidised treatment with this drug. [11473; phase out 20849]				

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Administrative Notes	No increase in maximum quantity or number of units may be authorised [7606]
	No increase in the maximum number of repeats may be authorised [7607]
	Special Pricing Arrangements apply [7608]

- 2.2 The submission requested the same maximum quantity and the dispensed price for maximum quantity (DPMQ) for trifluridine/tipiracil as per the current listing. The ESC noted that no change in the current Special Pricing Arrangement (SPA) was proposed and the same effective price for trifluridine/tipiracil for metastatic colorectal cancer (CRC) was offered for metastatic gastric or gastroesophageal junction (mG/GEJ) adenocarcinoma).
- 2.3 There is potential for trifluridine/tipiracil to be used in second-line therapy, as mentioned in the Therapeutic Goods Administration (TGA) Clinical Evaluation Report (1st round). However, overall the TGA considered the proposed indication represents a third-line setting in most patients.

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

3 Background

Registration status

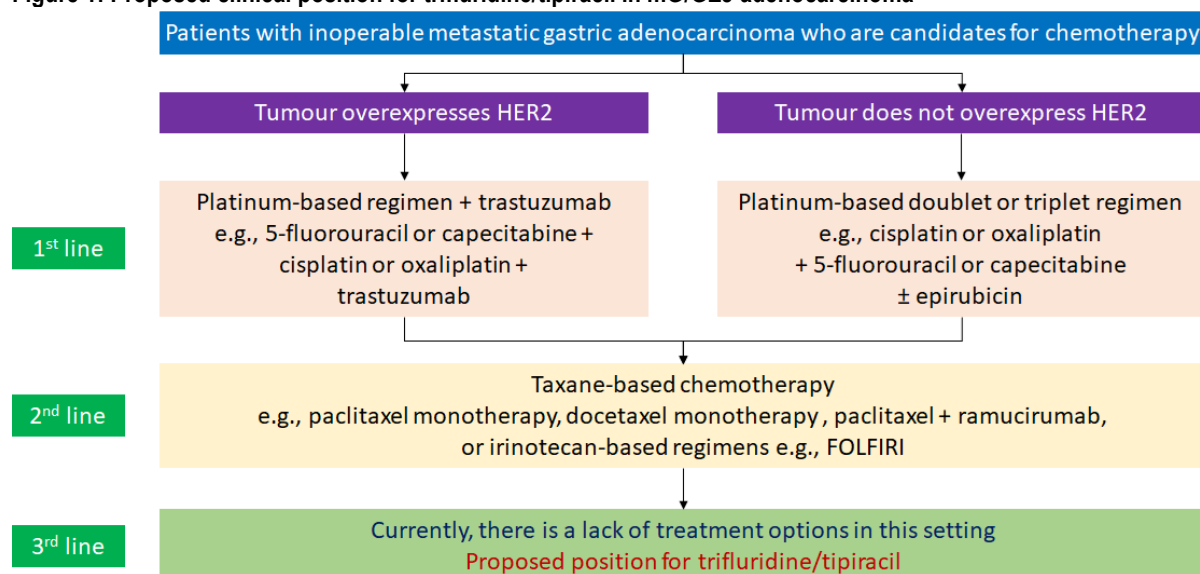
- 3.1 The submission was made under the Therapeutic Goods Administration (TGA)/PBAC parallel process. At the time of PBAC consideration, the TGA Delegate's Overview was available.
- 3.2 The TGA Delegate has proposed the extension of the registration of trifluridine/tipiracil to include the following indication: "treatment of adult patients with metastatic gastric or gastroesophageal junction adenocarcinoma previously treated with at least two prior lines of chemotherapy that included a fluoropyrimidine, a platinum, either a taxane- or irinotecan, and if appropriate, HER2/neu-targeted therapy."
- 3.3 The TGA advised the sponsor that consideration by the Advisory Committee on Medicines is not required, and the registration of the mG/GEJ adenocarcinoma indication is expected by the end of November 2019.

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

4 Population and disease

- 4.1 Metastatic gastric cancer is a malignant tumour arising from cells in the stomach and is a highly aggressive and difficult to treat cancer.
- 4.2 Most of the gastric cancers (> 85%) are classified as adenocarcinomas and a sub-set of patients have tumours at the junction of the oesophagus and stomach defined as gastro-oesophageal junction adenocarcinoma. According to a sponsor-commissioned study, the probability of death within 12 months of diagnosis was 39%, 69% and 91% for patients diagnosed with localised, regionalised and distant spread, respectively.
- 4.3 The submission proposed trifluridine/tipiracil as a new anticancer agent in the third-line (or subsequent) treatment setting. This was appropriate. The proposed PBS population and comparator were largely consistent with the population and line of treatment presented in the clinical evidence in the submission and the recommendation in the European Society Medical Oncology (ESMO) guidelines. However, it differed slightly from the draft product information which did not specify World Health Organisation (WHO) performance status.
- 4.4 The clinical management algorithm was based on the ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of gastric cancer. This is shown in Figure 1. The ESC considered that the proposed clinical management algorithm is consistent with the National Comprehensive Cancer Network guidelines and the proposed restriction for initial and continuing therapy.

Figure 1: Proposed clinical position for trifluridine/tipiracil in mG/GEJ adenocarcinoma



Source: Figure 1-7, p16 of the submission
mG/GEJ = metastatic gastric or gastroesophageal junction adenocarcinoma

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

5 Comparator

- 5.1 The submission nominated placebo in combination with BSC as the main comparator. The evaluation considered that the nominated main comparator may be appropriate given the proposed positioning of trifluridine/tipiracil being a last-line chemotherapy. However, the ESMO clinical guideline suggests some standard treatment options (e.g. taxane or irinotecan or ramucirumab as single agent or in combination with paclitaxel) may be used sequentially in second and third line, but it acknowledged that there is no clear evidence for a benefit beyond second line treatment. Further, in a 2019 National Institute for Clinical Care and Excellence (NICE) scoping document on the same topic, chemotherapy (e.g. docetaxel or paclitaxel as monotherapy or combination therapy) was also nominated as a comparator (1). The ESC agreed that above mentioned treatment options (e.g. irinotecan) may also be used in third line. However, the ESC considered BSC was the appropriate main comparator.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from a health care professional (1) and an organisation (1) via the Consumer Comments facility on the PBS website. The comments from the health care professional noted the benefit of having an oral treatment option for patients with mG/GEJ adenocarcinoma who have limited therapeutic options available to them. The health professional claimed that their experience with the drug in CRC (for which trifluridine/tipiracil is currently PBS listed) is that it is well-tolerated and maintains the patient's quality of life.

6.3 The PBAC noted that the Medical Oncology Group of Australia (MOGA) expressed its support for the trifluridine/tipiracil submission. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for trifluridine/tipiracil, which was limited to 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)¹, based on a comparison with placebo plus BSC.

Clinical trials

6.4 The submission was based on one head-to-head randomised trial (TAGS) comparing trifluridine/tipiracil plus BSC with placebo plus BSC in patients with metastatic gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who had received at least two previous chemotherapy regimens and had experienced radiological disease progression.

6.5 Details of the trial presented in the submission are provided in the table below.

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

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
TAGS	Randomized, double-blind, phase 3 study evaluating TAS-102 plus best supportive care (BSC) versus placebo plus BSC in patients with metastatic gastric cancer refractory to standard treatments.	Clinical Study Report; 30 July 2018
	Shitara K, Doi T, et al. Trifluridine/tipiracil versus placebo in patients with heavily pre-treated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial.	The Lancet Oncology 2018;19(11):1437-1448.
	Ilson DH, Prokharau A, et al. Efficacy and safety of trifluridine/tipiracil (FTD/TPI) in patients (pts) with metastatic gastric cancer (mGC) with or without prior gastrectomy: Results from a phase III study (TAGS).	Journal of Clinical Oncology 2019;37(Suppl.4):3-3 [Abstract: ASCO Gastrointestinal Cancers Symposium, Jan 2019].
	Shitara K, Doi T, et al. Correction: Trifluridine/tipiracil versus placebo in patients with heavily pre-treated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial.	The Lancet Oncology 2018;19(12):e668.
	Shitara K, Tabernero J, et al. Overall survival results from a phase III trial of trifluridine/tipiracil (FTD/TPI) vs. placebo in patients (Pts) with metastatic gastric cancer refractory to standard therapies (TAGS).	Annals of Oncology 2018;29(Suppl.9):ix55. [Abstract 175P: from ESMO Asia Congress, Nov 2018.]
	Tabernero J, Shitara K, et al. Overall survival results from a phase III trial of trifluridine/tipiracil versus placebo in patients with metastatic gastric cancer refractory to standard therapies (TAGS).	Annals of Oncology 2018;29(Suppl.5):v123. [Abstract LBA-002 from ESMO 20th World Congress on Gastrointestinal Cancer, Jun 2018].

Source: Table 2.2.1, p27 of the submission

- 6.6 The key trial eligibility criteria was patients with confirmed metastatic gastric adenocarcinoma and ECOG performance status of 0 or 1 at time of randomization, who received at least two prior regimens (at least one cycle per regimen), which must have included a fluoropyrimidine, platinum, and either a taxane- and/or irinotecan-containing regimen; patients whose tumours were HER2+ must have received prior anti-HER2+ therapy if available and who were refractory to or unable to tolerate their most recent prior therapy. The ESC considered that the TAGS trial was relevant to the proposed PBS population in clinical practice.
- 6.7 The evaluation considered that the trial participants were generally well balanced between treatment arms in terms of baseline demographics, disease severity and pre-study treatment.
- 6.8 The key features of the direct randomised trial are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Trifluridine/tipiracil + BSC vs. Placebo + BSC						
TAGS	507	R, MC, DB 24 mths	Low	Failed 2 nd -line treatment	OS, PFS, HRQoL & Safety	OS, PFS, HRQoL & Safety

Source: Compiled during the evaluation based on p32-38 of the submission

BSC = best supportive care; DB=double blind; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HRQOL = health-related quality of life; MC=multi-centre; ORR = objective response rate; OL=open label; OS=overall survival; PFS=progression-free survival; R=randomised.

- 6.9 Overall, the evaluation considered that the risk of bias in the TAGS trial was low. However, the median PFS estimates were potentially confounded by the timing of the first on-treatment tumour assessment, which took place approximately 8 weeks (1.9 months) after treatment initiation. The ESC considered that the predictable and substantial toxicity of trifluridine/tipiracil may have adversely affected masking by investigators and participants, with a risk of bias for PFS (which was investigator-assessed) and HRQoL respectively, both in favour of trifluridine/tipiracil.

Comparative effectiveness

Primary outcome: OS

- 6.10 Table 4 summarises the OS results from the TAGS trial for the ITT population.

Table 4: Results of overall survival in TAGS trial (ITT population)

Outcome	Trifluridine/tipiracil (N = 337)	Placebo (N = 170)	Treatment difference
Number of deaths, n (%)	244 (72.4)	140 (82.4)	-
Median overall survival, in months (95% CI)	5.72 (4.8, 6.2)	3.57 (3.1, 4.1)	2.15
Mean ^a overall survival, in months (95% CI)	8.21 (7.1, 9.6)	5.82 (5.1, 7.0)	2.39
Log-rank p-value (2-sided) ^b	0.0006		-
Hazard ratio (95% CI)	0.69 (0.56, 0.85)		-

Source: Table 2.5.1, p38 in the submission & Table 21, p80 in the TGS CSR

CI = confidence interval; ITT = intention to treat; **Bold** = statistically significant;

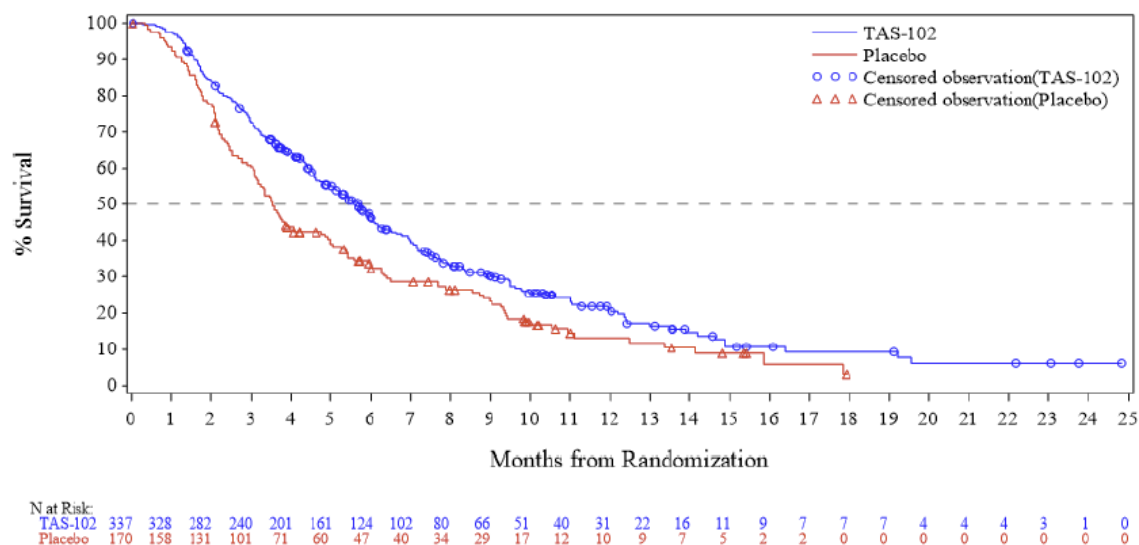
^a Mean OS in each of the arms of the TAGS is derived by measuring the area under the Kaplan-Meier overall survival curves using patient-level data.

^b Stratified log-rank test (stratification factors: region, ECOG status at baseline, prior treatment with ramucirumab)

- 6.11 Median OS was 5.7 months (95% CI: 4.8, 6.2) for the trifluridine/tipiracil group versus 3.6 months (95% CI: 3.1, 4.1) for the placebo group. The submission stated this demonstrated that the addition of trifluridine/tipiracil to BSC resulted in a statistically significant improvement in OS compared to placebo plus BSC with an HR of 0.69 (95% CI: 0.56, 0.85), corresponding to a 31% reduction in the hazard of death. The Kaplan-Meier curves for OS showed that at approximately month 15 the curves converged. At this time point, the number of patients at risk was very small, complicating the interpretation of any OS difference after that point. The ESC noted that the magnitude of clinical benefit for OS according to the ESMO Magnitude of Clinical Benefit Scale

version 1.1 was only modest (i.e. grade 3 out of 5, where grades 4 and 5 represent the grades with substantial improvement)².

Figure 2: Kaplan-Meier plot of overall survival in TAGS trial (ITT population)



Source: Figure 2.2, p39 of the submission
ITT = intention to treat; TAS-102 = trifluridine/tipiracil

6.12 The submission also reported the mean OS from individual patient data of the TAGS trial. Mean OS in the trifluridine/tipiracil arm was 8.2 months (95% CI: 7.1, 9.6) and 5.8 months (95% CI: 5.1, 7.0) in the placebo arm.

Secondary outcome: PFS

6.13 Table 5 summarises the PFS results from the TAGS trial for the ITT population.

Table 5: Results of progression-free survival in TAGS trial (ITT population)

Outcome	Trifluridine/tipiracil (N = 337)	Placebo (N = 170)	Treatment difference
Number of PFS Events, n (%)	287 (85.2)	156 (91.8)	-
Median progression-free survival, in months (95% CI)	1.97 (1.9, 2.3)	1.81 (1.7, 1.9)	0.16
Mean ^a progression-free survival, in months (95% CI)	3.60 (3.2, 4.0)	2.41 (2.0, 3.2)	1.19
Log-rank p-value (2-sided) ^b	<0.0001		-
Hazard ratio (95% CI)	0.57 (0.47, 0.70)		-

Source: Table 2.5.2, p41 in the submission & Table 25, p89 in the TGS CSR

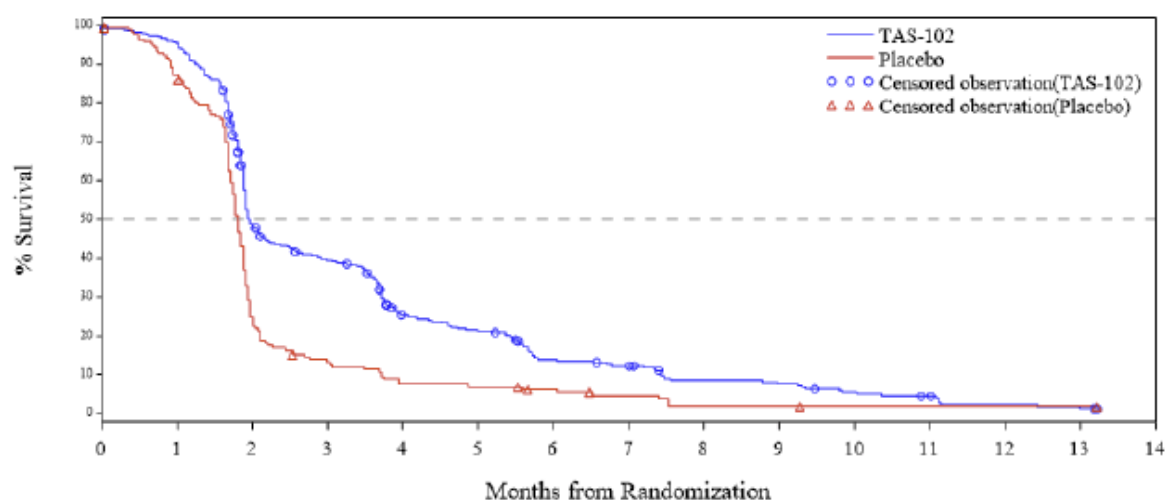
CI = confidence interval; ITT = intention to treat; PFS = progression-free survival; **Bold** = statistically significant

^a Mean PFS in each of the arms of the TAGS is derived by measuring the area under the Kaplan- Meier progression free survival curves using patient-level data.

^b Stratified log-rank test (stratification factors: region, ECOG status at baseline, prior treatment with ramucirumab)

² Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 28:2340-2366, 2017]

Figure 3: Kaplan-Meier plot of progression-free survival in TAGS trial (ITT population)



N at Risk:		0	1	2	3	4	5	6	7	8	9	10	11	12	13
TAS-102	337	314	154	122	72	60	37	32	20	18	12	9	4	2	
Placebo	170	145	41	21	12	11	8	5	2	2	1	1	1	1	

Source: Figure 2.3, p41 in the submission
 ITT = intention to treat; TAS-102 = trifluridine/tipiracil

- 6.14 The median PFS was approximately 2.0 months for the trifluridine/tipiracil group versus 1.8 months for the placebo group, resulting in a 43% reduction in the hazard of disease progression (HR 0.57, 95% CI: 0.47, 0.70). However, the difference in median PFS was approximately 5 days (1.97 months vs. 1.81 months). The evaluation considered that while this difference was statistically significant, it seemed of little clinical relevance. The ESC agreed with the evaluation that the difference in median PFS was not clinically relevant, and noted that the majority (>50%) of participants in the trifluridine/tipiracil arm had progressed within the first two months following randomisation. The submission argued that had the radiologic assessments been performed at 4 weekly increments (instead of 8 weekly), there would be a greater difference in median PFS. However, the ESC considered that the largest plausible difference in the median PFS for this scenario would be <1.5 months (i.e. correlating to a low grade on the ESMO Magnitude of Clinical Benefits Scale version 1.1) and would remain not clinically relevant.
- 6.15 The mean PFS reported in the submission in the trifluridine/tipiracil arm was 3.6 months (95% CI: 3.2, 4.0) and 2.4 months (95% CI: 2.0, 3.2) in the placebo arm.
- 6.16 The submission argued that mean survival was more appropriate outcome than improvement in median survival because the mean survival reflects the overall improvement in survival rather than the difference in survival at a single point (when 50% of patients have died or progressed). In the previous consideration of trifluridine/tipiracil for mCRC, the PBAC agreed “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, trifluridine/tipiracil Public Summary Document (PSD), November 2016 PBAC meeting). As a result, the PBAC accepted the use of the mean OS and mean PFS in the economic evaluation for trifluridine/tipiracil for mCRC.

Secondary outcome: HRQoL

- 6.17 The detailed HRQoL results were not reported in the submission. HRQoL was measured using European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLC-C30). It was balanced between the groups at baseline and remained stable in both treatment groups with no clinically relevant changes from baseline. The ESC noted that there was no evidence that trifluridine/tipiracil improved HRQoL, as assessed by the EORTC QLQ-C30.
- 6.18 The Pre-Sub-Committee Response (PSCR) acknowledged that trifluridine/tipiracil did not improve quality of life for patients with mG/GEJ adenocarcinoma in equivalent health states. The objective of treatment with trifluridine/tipiracil was to improve quality-adjusted survival (i.e. improve both mean PFS and mean OS without causing substantial reduction in QoL). However, the ESC was concerned that the detrimental effect of toxicity of trifluridine/tipiracil on HRQoL may have been underestimated, given that the EORTC QLQ-C30 was administered prior to dose administration on Day 1 in each of the 28 day cycle of study treatment, and relates to HRQoL over the previous week (i.e. Days 21-28 of the previous cycle when the drug is not administered, whereas trifluridine/tipiracil is administered on Days 1-5 and 8-12 of each cycle).
- 6.19 The Clinical Study Report (CSR) for the TAGS trial reported an overall compliance rate of 84% for the QLQ-C30 questionnaire. However, the TGA Clinical Evaluation Report raised concerns over the meaningfulness of the assessment of the comparative quality of life and noted that “Compliance is difficult to assess for subsequent cycles as the CSR reports only the proportion that completed the questionnaire of the whole population rather than as a proportion of those that remained on treatment (who were eligible for the questionnaire)”. Approximately 16% non-response rate at each measurement point raised concerns on the validity of the quality of life data, as patients who responded to the HRQoL questionnaire may not be representative of all patients in the trial and may represent a healthier cohort of the patients.

Secondary outcome: Response rate

- 6.20 The ESC noted that the objective tumour response rate was similar between patients receiving trifluridine/tipiracil and those receiving placebo (4% vs. 2%), but the disease control rate (i.e. proportion of patients with a best overall response of complete/partial response, or stabilised disease) was significantly higher in the trifluridine/tipiracil treatment group, compared with placebo (44% vs.14%).

Comparative harms

6.21 A summary of the adverse events (AEs) reported in the TAGS trial are presented below. The ESC noted that the incidence of ‘any adverse event’ was almost universal in both treatment groups, but that grade 3 or worse AEs and treatment-emergent AEs (TEAEs) leading to dose modifications were substantially more frequent with trifluridine/tipiracil than placebo (BSC). Table 6 summarises the key AEs reported in the TAGS trial.

Table 6: Summary of key adverse events in the TAGS trial

TAGS trial	Trifluridine/tipiracil (n = 335)	Placebo (n = 168)	RD (95% CI)
Any AE, n (%)	326 (97)	157 (93)	0.04 (0, 0.08)
AE of Grade \geq 3, n (%)	267 (80)	97 (58)	0.22 (0.13,0.31)
TEAEs leading to discontinuation, n (%)	43 (13)	28 (17)	-0.04 (-0.11, 0.03)
TEAEs leading to dose modification, n (%)	195 (58)	37 (22)	0.36 (0.28, 0.44)
AE-related deaths, n (%)	45 (13)	19 (11)	-0.03 (-0.07, 0.02)

Source: Table 2.5.6, p45 in the submission and Table 14.3.1.1 in the TAGS CSR Section 14 tables

AE = adverse event; CI = confidence interval; n = number of participants reporting data; RD = risk difference; TEAEs = treatment-emergent adverse events; **Bold** = statistically significant

6.22 There were noteworthy differences in the adverse-event profile between the treatments. Myelosuppression was the main toxicity experienced by the patients receiving trifluridine/tipiracil in the TAGS trial, with the most frequently reported grade 3 or worse AEs being neutropenia (34% versus 0% in placebo group), anaemia (19% versus 8% in placebo group), and leukopenia (9% versus 0% in placebo group).

6.23 In the PSCR, the sponsor argued that the majority of reported Grade \geq 3 AEs were laboratory-based indicators of myelosuppression (i.e. neutropenia and anaemia) rather than clinically evident events which are generally able to be managed by reduction in dosage or by delaying the next dose. The incremental proportion of trifluridine/tipiracil patients experiencing serious neutropenia and serious anaemia was 1.2% and 1.5%, respectively.

6.24 However, the ESC considered that myelosuppressive events may have been clinically significant, noting that supportive products for anaemia (e.g. blood products and /or erythropoietin) were used by 18% of patients receiving trifluridine/tipiracil, but only 5% of patients receiving placebo (Clinical Study Report, table 14.1.9.1). The ESC were also concerned that AEs may be more commonly experienced in the PBS population compared with the trial population, because the TAGS trial excluded patients with cardiovascular disease and poorly controlled diabetes, as noted in the TGA Clinical

Evaluation Report (1st round) (p51). The pre-PBAC response argued that the exclusion of patients with significant comorbidities is standard in most clinical trials.

Benefits/harms

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

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

Benefits: ITT population					
	Trifluridine/tipiracil	Placebo	Absolute difference		HR (95% CI) ^b
Dead n/N (%)	244/337 (72.4)	140/170 (82.4)	-10%		0.69 (0.56, 0.85)
OS median (months) ^a	5.72 (4.8, 6.2)	3.57 (3.1, 4.1)	2.15		-
KM estimates ^c of percentage of patients surviving at:					
3 months	72.4 (67.3, 76.9)	60.3 (52.4, 67.2)	12.1%		
6 months	46.7 (41.1, 52.2)	33.1 (25.9, 40.3)	13.6%		
9 months	30.3 (24.9, 35.8)	23.3 (16.8, 30.3)	7.0%		
12 months	21.2 (16.1, 26.7)	13.0 (7.7, 19.8)	8.2%		
Progressed n/N (%)	287 (85.2)	156 (91.8)	-6.6%		0.57 (0.47, 0.70)
PFS median (months)	1.97 (1.9, 2.3)	1.81 (1.7, 1.9)	0.16		-
KM estimates ^c of percentage of patients free of progression at:					
2 months	49.7 (44.1, 55.1)	25.3 (18.9, 32.1)	24.4%		
4 months	26.8 (21.9, 31.9)	7.7 (4.2, 12.5)	19.1%		
6 months	14.6 (10.7, 19.0)	6.4 (3.2, 10.9)	8.2%		
8 months	9.4 (6.2, 13.3)	2.8 (0.8, 6.8)	6.6%		
Harms: Safety population					
	Trifluridine/tipiracil n/N	Placebo n/N	Event rate/100 patients ^a		RD (95% CI)
			Trifluridine/tipiracil	placebo	
Patients with any Grade ≥ 3 AEs	267/335	97/168	80	58	0.22 (0.13, 0.31)
Grade ≥ 3 Neutropenia	114/335	0/168	34	0	0.34 (0.29, 0.39)
Grade ≥ 3 Anaemia	64/335	13/168	19	08	0.11 (0.06, 0.17)

Source: Table 2.5.1, p38, Table 2.5.6, p45 in the submission

CI = confidence interval; HR = hazard ratio; ITT = intention to treat; OS = overall survival; PFS = progression-free survival; RD = risk difference; RR = risk ratio

^a Median duration of follow-up: trifluridine/tipiracil 10.6 months; placebo 10.7 months

^b Stratification factors: region, ECOG status at baseline, prior treatment with ramucirumab

^c Calculated using log-log transformation methodology of Kalbfleisch and Prentice

6.26 There was some observed benefit at the expense of an increased risk of toxicity. On the basis of the head to head trial presented in the submission, for patients with metastatic gastric cancer who had progressed after at least two-lines of chemotherapy, the comparison of trifluridine/tipiracil to placebo resulted in:

- Approximately 2.2 months benefit in median overall survival with an additional 8 in 100 patients surviving at 12 months; and
 - Approximately 0.2 months benefit in median progression free survival with an additional 8 in 100 patients without progression at 6 months.
- 6.27 For every 100 patients who had trifluridine/tipiracil therapy compared with placebo and over the median duration of follow-up of 11 months:
- 22 additional patients experienced a grade \geq 3 AE;
 - 34 additional patients experienced grade \geq 3 neutropenia; and
 - 11 additional patients experienced grade \geq 3 anaemia.

Clinical claim

- 6.28 The submission claimed trifluridine/tipiracil plus BSC as superior in terms of effectiveness and inferior in terms of safety compared with BSC in patients with mG/GEJ adenocarcinoma who have failed, are intolerant of or not candidates for, standard available anticancer therapies.
- 6.29 The claim of superior effectiveness was based on the clinical evidence from the TAGS trial showing 2.1 months gain in median OS (mean 2.4 months) for trifluridine/tipiracil compared with placebo which corresponded to a HR of 0.69 (95% CI: 0.56, 0.85) of death. Noting the potential confounding by the timing of the first on-treatment tumour assessment (approximately 8 weeks after treatment initiation), a median PFS gain of 0.16 of a month (mean 1.2 months) was reported with a corresponding HR of 0.57 (95% CI: 0.47, 0.70). Although statistically significant, the clinical meaningfulness of the OS and PFS gains to patients with mG/GEJ adenocarcinoma, who were refractory to standard available anticancer therapies, was uncertain. The PSCR, argued that when recommending the PBS listing of ramucirumab in March 2018 (March 2018 PSD), the PBAC considered that a gain in median OS of 2.3 months, as observed in ramucirumab-treated patients, was modest, but sufficient to support a claim of superior efficacy. In addition, the PSCR referred to the sponsor's submission requesting PBS listing of trifluridine/tipiracil for mCRC in July 2018 (paragraph 5.3, July 2018 PSD), where the PBAC considered that in the context of limited treatment options, the modest treatment benefit of trifluridine/tipiracil (i.e. the median gain in overall OS of 2.0 months (HR 0.69; CI: 0.59, 0.81) in the RECURSE trial) may be meaningful for some patients.
- 6.30 The ESC considered that the improvement in overall survival was modest, and there was no clinically meaningful improvement in PFS. Further, there was no evidence to suggest an improvement in HRQoL and the ESC was concerned that the detrimental

effect of toxicity of trifluridine/tipiracil on HRQoL may have been underestimated as assessed by the EORTC QLQ-C30 in the TAGS trial (see paragraph 6.17).

- 6.31 The ESC considered that the claim of inferior safety was adequately supported by the evidence presented in the submission. There was an increased risk of AEs of Grade \geq 3 and TEAEs leading to dose modification for trifluridine/tipiracil. The submission claimed that the AEs associated with treatment with trifluridine/tipiracil were mainly attributable to myelosuppression which was manageable by dose modification or dose delay. However, the ESC considered that myelosuppressive events may have been clinically significant noting an increased use in supportive products for anaemia by patients receiving trifluridine/tipiracil (see paragraph 6.24). The ESC was also concerned that the risk of TAEs would be higher in the PBS population compared with the trial population which excluded patients with comorbidities such as cardiovascular disease and poorly controlled diabetes. The pre-PBAC response argued that the exclusion of patients with significant comorbidities is standard in most clinical trials.
- 6.32 Overall, the ESC considered that the main concern was whether the modest observed benefit associated with treatment with trifluridine/tipiracil plus BSC, compared with placebo plus BSC, would be realised in clinical practice and was clinically meaningful to patients in the context of the substantial increase in toxicity. The pre-PBAC response stated that the decision about whether the expected OS gains are meaningful enough to outweigh the risks of AEs should fundamentally lie with individual patients, their families and their clinicians as the meaningfulness of the potential OS gain will depend on the individual patient's circumstances.
- 6.33 The PBAC considered that the claim of superior comparative effectiveness was reasonable and adequately supported by the data but noted that the magnitude of benefit was modest.
- 6.34 The PBAC considered that the claim of inferior comparative safety was reasonable.

Economic analysis

- 6.35 The submission presented a trial-based cost-utility analysis based on the TAGS trial. The use of a within trial analysis was appropriate given the extent of follow-up in the TAGS trial was such that most patients had died at the end of follow-up.
- 6.36 The key components and assumptions of the cost-utility analysis are presented in Table 8.

Table 8: Summary of model structure and rationale

Component	Summary
Outcomes	Quality-adjusted life years and life years
Time horizon	Lifetime, to the extent this was assessed directly in the TAGS trial
Methods used to generate results	Partitioned survival model
Health states	Progression-free, progressing disease, dead
Utilities	EORTC QLQ-C30 from the TAGS trial mapped to utility with Australian weights (QLU-C10D).

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Component	Summary
	Progression-free = 0.695, Progressing disease = 0.603
Cycle length	1 month
Transition probabilities	Patient-level data from the TAGS trial

Source: Table 3.1.1, p51 of the submission.

- 6.37 The submission derived the utility values for the health states from EORTC QLQ-C30 from the TAGS trial using a preference-based multi-attribute utility instrument, the EORTC QLU-C10D, applying Australian value sets. In the base case, the submission assumed that utility weights varied broadly by health state, but not specifically by treatment arm, thus the mean utilities averaged across all patients for the same health state (e.g. progression-free and progressing disease) were applied in the model. The ESC considered that this was not appropriate given quality of life, from which utilities were derived, may be directly affected by the substantially different safety profiles of the treatments compared. The ESC noted that this was also not consistent with the PBAC Guidelines (Version 5.0, section 3A.5.1) which indicates that pooling results across treatment arms may not be appropriate in circumstances where treatment (rather than disease or condition) directly affects quality of life. Further, the simple averaged utility values for the same health-state was not considered a robust approach to capture longitudinal nature of data. The PSCR stated that the base-case economic analysis applied the same utility weights for patients in equivalent health states on the grounds that the differences in mean utilities in the trifluridine/tipiracil and placebo-treated groups were small. The mean utility weight at baseline (i.e., prior to initiation of treatment) for patients in the trifluridine/tipiracil group was 0.011 lower than that in the placebo group. The utility weight for patients in the progression-free health state during treatment with trifluridine/tipiracil was 0.022 lower than those for patients in the placebo-treated group. When adjusted for the difference in utility at baseline, the difference was reduced to 0.011. The ESC acknowledged that the incremental cost-effectiveness ratio (ICER) was not sensitive to this inappropriate assumption. Applying differential utilities by health state and by treatment increased the ICER per QALY gained by less than \$15,000.
- 6.38 The ESC considered that the progressing disease health state utility may have been overestimated, as it was obtained at a single time point immediately after disease progression and utility was likely to continue to decrease over time. Further, given the concerns over the compliance for the quality-of-life questionnaire, EORTC QLQ-C30 (see paragraph 6.19), the validity of the utilities derived from the EORTC QLQ-C30 were questionable. The PSCR argued that the assessment of utilities was not conducted immediately after progression as the precise time point of progression is largely unknown because tumour measurements (by CT scan) were only conducted

every 8 weeks during study treatment so significant time could have elapsed between actual progression of disease and assessment of quality of life.

- 6.39 The ESC considered that the utility value in the pre-progression health state in the trifluridine/tipiracil arm may be overestimated as disutility associated with AEs was not considered. During a sensitivity analysis attempting to incorporate disutility, the submission estimated pre-progression utility for the trifluridine/tipiracil arm by adjusting for baseline placebo values. This led to only minimal utility adjustment and may not be an appropriate measure of disutility due to AEs. Further, the EORTC QLQ-C30 may not accurately reflect patient experience of the significantly increased risk of Grade ≥ 3 TEAEs associated with trifluridine/tipiracil due to the time point of data collection. Therefore, concern remained on whether the economic model has adequately captured the disutility expected to be associated with the safety differences. The PSCR argued that the majority of reported Grade ≥ 3 AEs were laboratory-based indicators of myelosuppression (i.e., neutropenia and anaemia) rather than clinically evident events which are generally able to be managed by reduction in dosage or by delaying the next dose. However, the ESC considered that myelosuppressive events may have been clinically significant, and was concerned that the incidence of adverse events may be higher in the PBS population compared to the trial population (see paragraph 6.31).
- 6.40 The submission appropriately calculated the unit cost for a trifluridine/tipiracil course of treatment using the mean dispensed amount directly from the TAGS trial. This ensured incorporation of the drug wastage in the treatment cost. However, it was unknown whether the proposed resources applied for the treatment of AEs, or their rates of usage (e.g. a single episode of hospitalisation or a single dose of pegfilgrastim for the treatment of febrile neutropenia) would reflect Australian clinical practice. The submission may have also underestimated the costs of hospitalisation due to increased grade 3 or worse AEs with trifluridine/tipiracil compared with placebo and costs of disease monitoring in the economic model. However, the ESC noted that these issues appeared to have only moderate impact on ICER.
- 6.41 The key drivers of the model are summarised in the table below.

Table 9: Key drivers of the model

Description	Method/Value	Impact
Overall survival	Mean overall survival from TAGS trial	High, favours trifluridine/tipiracil
Progressing disease utility values	Assumed same utility value for both trifluridine/tipiracil and placebo	Low, favours trifluridine/tipiracil
Drug acquisition cost	The cost of treatment is based on mean time to treatment discontinuation rather than mean treatment cycles in TAGS trial	Moderate, favours trifluridine/tipiracil

Source: Compiled during evaluation

6.42 The results of the economic evaluation are summarised in the table below.

Table 10: Results of the economic evaluation

Component	Trifluridine/tipiracil	Placebo	Increment
Costs	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	0.440	0.311	0.129
LYs	0.684	0.201	0.199
Incremental cost/extra QALY gained			\$ [REDACTED]
Incremental cost/extra LY gained			\$ [REDACTED]

Source: Compiled during evaluation

LY = life years; QALY = quality adjusted life year

6.43 The results of key sensitivity analyses are summarised in the table below.

Table 11: Results of key sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER
Base case	\$ [REDACTED]	0.129	\$ [REDACTED]
Apply 95% lower confidence bound around mean progression-free and overall survival estimates in each arm of the TAGS trial	\$ [REDACTED]	0.108	\$ [REDACTED]
Apply lower 95% confidence limits around mean OS and PFS for trifluridine/tipiracil from the TAGS trial	\$ [REDACTED]	0.069	\$ [REDACTED]
Apply drug costs for treatment until progression ^a	\$ [REDACTED]	0.129	\$ [REDACTED]
Use mean treatment cycles (3.3) to calculate drug cost	\$ [REDACTED]	0.129	\$ [REDACTED]
Incorporating management cost of Grade \geq 3 neutropenia and anaemia ^b	\$ [REDACTED]	0.129	\$ [REDACTED]

Source: Table 3.9.2, p63 of the submission.

EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life years; QLU-C10D = Quality of Life Utility Measure-Core 10 dimensions; OS = overall survival; PFS = progression free survival

^a Mean PFS used instead of time on treatment

^b Based on incremental 34% and 11% incidence of neutropenia and anaemia from table 2.5.6, p45 in the submission, and \$1,740 (DRG Q60B NHCCD) and \$376 (DRG Q61C NHCCD) per hospitalisation for neutropenia and anaemia respectively.

6.44 Based on the sensitivity analyses, the results of the base-case analysis appeared to be sensitive to the survival benefits that would be gained from trifluridine/tipiracil but otherwise remained generally robust. The ESC noted that when applying lower 95% confidence limits of mean OS and PFS for trifluridine/tipiracil from TAGS, the ICER increased from \$15,000 - \$45,000 per QALY gained in the base case to \$75,000 - \$105,000 per QALY gained. The pre-PBAC response argued it was inappropriate to only present outcomes for sensitivity analyses that focus on the worst possible scenario for trifluridine/tipiracil.

6.45 The PSCR acknowledged that the results of the economic analysis are sensitive to estimates of survival gains however, survival gains in trifluridine/tipiracil-treated patients could be considered relatively certain given that the vast majority of patients were followed through to death in the TAGS trial. The ESC considered that it was uncertain whether the modest observed benefit associated with treatment with trifluridine/tipiracil plus BSC, compared with placebo plus BSC would be realised in clinical practice and was clinically meaningful to patients in the context of the substantial increase in toxicity, which may not have been captured within the

economic analysis by the utilities derived from the quality-of-life questionnaire, EORTC QLQ-C30.

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

6.46 Based on the effective DPMQ, the submission estimated the cost per course of treatment with trifluridine/tipiracil to be \$ [REDACTED]. As shown in the table below, the submission’s approach to calculating drug cost was different in the economic model compared with the financial estimates. In the economic model, treatment duration was applied while in the financial estimates, the mean treatment cycles (3.0) from the TAGS trial was applied and the drug cost per patient per course would be \$ [REDACTED]. The ESC considered that these differences were not meaningful.

Table 12: Drug cost per patient for trifluridine/tipiracil

	Trifluridine/tipiracil		
	Trial dose and duration	Economic model	Financial estimates
Mean total treatment cycles	3.3	-	3.0
Mean time to discontinuation	2.98 months	2.98 months	-
Cost/patient/cycle	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Cost/patient/course	\$ [REDACTED] ^a	\$ [REDACTED] ^a	\$ [REDACTED] ^b

Source: Compiled during evaluation

^a cost of course of treatment per patient calculated based on mean time to treatment discontinuation

^b cost of course of treatment per patient calculated based on mean treatment cycles.

Estimated PBS usage & financial implications

6.47 This submission was not considered by DUSC. The submission used an epidemiological approach to estimate the use and financial impact of listing trifluridine/tipiracil on the PBS.

6.48 The submission estimated eligible patients using the Australian Bureau of Statistics projections, Australian Institute of Health and Welfare Stomach cancer 2018, sponsor-commissioned studies based on New South Wales Registry data from 2010-2015 and a survey of oncologists. The ESC agreed with the evaluation that the validity of the estimates derived from the sponsor-commissioned studies was poor given the

uncertain representativeness of the study populations (both the patients in the New South Wales Registry and clinicians in the survey) to the target populations.

6.49 Table 13 provides the submission’s estimates of use and financial implications of PBS listing trifluridine/tipiracil.

Table 13: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	■	■	■	■	■	■
Number of scripts dispensed	■	■	■	■	■	■
Estimated financial implications of trifluridine/tipiracil						
Cost to PBS/RPBS	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■
Copayments	-\$ ■	-\$ ■	-\$ ■	-\$ ■	-\$ ■	-\$ ■
Cost to PBS/RPBS less copayments	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■
Estimated financial implications for GCSF						
Cost to PBS/RPBS	■	■	■	■	■	■
Net financial implications						
Net cost to PBS/RPBS	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■
Net cost to MBS	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■

Source: Table 4.2.4, p70 of the submission

GCSF = granulocyte colony stimulating factor; PBS = pharmaceutical benefits scheme; RPBS = repatriation pharmaceutical benefits scheme

6.50 At year 6, the estimated number of treated patients was less than 10,000 and the net cost to the PBS would be less than \$10 million.

6.51 The ESC considered that the financial estimates to the PBS/RPBS may be uncertain due to an underestimate of the number of patients with mG/GEJ adenocarcinoma, and an overestimate of the number of eligible patients who would uptake trifluridine/tipiracil given its toxicity profile. The results from the key sensitivity analyses are presented in Table 14.

Table 14: Results of key sensitivity analyses on estimated financial implications for PBS

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Base case ^a	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■
Proportion patients with metastasis at diagnosis (base case = 37.6%)						
60%	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■
Proportion of eligible incident patients (base case = 26.1%)						
Using 14% eligibility based on Davidson et al 2018 (2)	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■
Lower uptake of trifluridine/tipiracil (base case = 74% – 90%)						
50% - 75% uptake	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■	\$ ■

Source: Compiled during the evaluation.

^a accounting for the costs of granulocyte colony stimulating factor use

- 6.52 The ESC considered that the net cost to the MBS presented in the submission was likely to be underestimated given costs of hospitalisation for managing severe AEs (febrile neutropenia and anaemia) and radiological monitoring of disease progression (every 8 weeks) while undergoing trifluridine/tipiracil treatment were not included.
- 6.53 The ESC noted that the sponsor did not propose any risk sharing arrangements (RSA). The sponsor confirmed in its pre-PBAC response confirmed that it was not proposing an RSA given the low number of patients that would be eligible for third-line treatment leading to a low budget impact.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the Authority Required (STREAMLINED) listing of trifluridine/tipiracil for third (or subsequent) line treatment of patients with metastatic gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction previously treated with at least two prior lines of chemotherapy that included a fluoropyrimidine, a platinum, and either a taxane- or irinotecan.
- 7.2 The PBAC considered it was not necessary to specify in the restriction that patients must have previously been treated with, if appropriate, "HER2/neu-targeted therapy" in the restriction, as per the request in the submission. Rather, the PBAC considered that the use of a HER2/neu-targeted therapy in appropriate patients could be left to the judgement of the treating clinician without resulting in use outside the intended population.
- 7.3 The PBAC acknowledged that there is a high and unmet clinical need for additional therapies for patients with refractory mG/GEJ adenocarcinoma and good performance status. The PBAC was satisfied that trifluridine/tipiracil, for some patients, provides a small improvement in overall survival over BSC. The PBAC's recommendation for listing was based on, among other matters, its assessment, as described above, that the cost-effectiveness of trifluridine/tipiracil would be acceptable at the price proposed in the submission.
- 7.4 The PBAC considered that the proposed trifluridine/tipiracil place as a third line treatment in the clinical management algorithm was appropriate and consistent with the National Comprehensive Cancer Network guidelines and the proposed restriction for initial and continuing therapy.
- 7.5 The PBAC considered that BSC alone was the appropriate comparator.
- 7.6 The PBAC noted that the submission was based on a head-to-head randomised trial (TAGS) comparing trifluridine/tipiracil plus BSC to placebo plus BSC. The PBAC considered that the TAGS trial was well balanced between treatment arms in terms of baseline demographics, disease severity and pre-study treatment, and relevant to the

proposed PBS population in the clinical practice. The PBAC noted that the risk of bias in the trial was low.

- 7.7 The PBAC noted the submission's claim of superior effectiveness was based on the clinical evidence from the TAGS trial showing 2.1 months gain in median OS (mean 2.4 months) for trifluridine/tipiracil compared with placebo with a HR of 0.69 (95% CI: 0.56, 0.85), corresponding to a 31% reduction in the hazard of death. The PBAC noted that the magnitude of the clinical benefit for OS according to the ESMO-MCBS version 1.1 was small (i.e. grade 3 out of 5, where grades 4 and 5 represent the grades with substantial improvement). The PBAC considered that in the context of limited treatment options, the small benefit of trifluridine/tipiracil may be meaningful for some patients.
- 7.8 The PBAC noted that the gain in median PFS was approximately 0.16 months (mean 1.2 months), corresponding to a 43% reduction in the hazard of disease progression or death (HR 0.57, 95% CI: 0.47, 0.70). The PBAC noted that the difference in the median PFS was approximately 5 days (1.97 months vs. 1.81 months). As such, the PBAC agreed with the evaluation that, while this difference was statistically significant, the gain in PFS observed in the trial was unlikely to be clinically meaningful to patients.
- 7.9 The PBAC noted the ESC's concerns regarding whether the small observed benefit associated with treatment with trifluridine/tipiracil would be realised in clinical practice, and was clinically meaningful to patients in the context of the substantial increase in toxicity. The PBAC considered 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. However the PBAC were concerned that the impact of such toxicity on patients with metastatic gastric cancer receiving third-line systemic therapy may be more significant than in patients with other malignancies who may be less heavily pre-treated. The PBAC considered although the toxicity associated with trifluridine/tipiracil may be significant in the context of a small benefit, the appropriateness of treatment with trifluridine/tipiracil could be left up to the treating clinician.
- 7.10 The PBAC noted that the submission presented a cost-utility analysis based on the TAGS trial, with a base-case ICER of \$15,000 - \$45,000 per QALY gained. The PBAC noted that the results of the economic analysis were sensitive to the survival benefit associated with trifluridine/tipiracil. However, the PBAC considered the small survival gain was moderately certain given that the vast majority of patients were followed through to death in the TAGS trial. Accordingly, on this basis, the PBAC considered that the trifluridine/tipiracil was acceptably cost effective in the context of limited treatment options for patients with mG/GEJ adenocarcinoma who have failed or are intolerant to earlier line therapies.
- 7.11 The PBAC noted that there were uncertainties in the estimates number of patients likely to be treated with trifluridine/tipiracil due to several estimates from sponsor-

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commissioned studies having uncertain validity. Further to this, the PBAC noted that costs to the PBS and hospitals for the treatment of adverse events were not included in the submission, as well as the MBS costs related to radiological monitoring of disease progression. However, the PBAC considered that given the small patient population, very short life expectancy of patients with mG/GEJ adenocarcinoma, and the expected low uptake of trifluridine/tipiracil due to its toxicity profile, the financial implications for the PBS were likely to be modest.

- 7.12 The PBAC advised that trifluridine/tipiracil should not be treated as interchangeable on an individual patient basis with any other drugs under Section 101 (3BA) of the *National Health Act 1953*.
- 7.13 The PBAC recommended that the Early Supply Rule should apply to trifluridine/tipiracil.
- 7.14 The PBAC advised that trifluridine/tipiracil is not suitable for prescribing by nurse practitioners.
- 7.15 The PBAC noted that this submission would not meet the criteria for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Amend existing/recommended listing as follows:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer
TRIFLURIDINE + TIPIRACIL			
Trifluridine 15 mg + tipiracil 6.14 mg tablet, 20	3	2	LONSURF 15/6.14
Trifluridine 20 mg + tipiracil 8.19 mg tablet, 20	4	2	LONSURF 20/8.19 Servier Laboratories
Category / Program	GENERAL – General Schedule (Code GE)		
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives		
Episodicity:	-		
Severity:	Metastatic (Stage IV) [contained within 17773]		
Condition:	adenocarcinoma of the stomach or gastro-oesophageal junction		
PBS Indication:	Metastatic (Stage IV) adenocarcinoma of the stomach or gastro-oesophageal junction [new concept]		
Treatment phase:	Initial treatment		

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Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria:	Patient must have a WHO performance status of 1 or less [10299; phase out 19462] AND Patient must have previously received at least two prior lines of chemotherapy that included a fluoropyrimidine, a platinum and either a taxane or irinotecan. AND The treatment must be the sole PBS-subsidised therapy for this condition [7890]
Prescriber Instructions:	The patients WHO performance status and body weight must be documented in the patient's medical records at the time the treatment cycle is initiated. [10024]
Administrative Advice	No increase in maximum quantity or number of units may be authorised. [7606] No increase in the maximum number of repeats may be authorised. [7607] Special Pricing Arrangements apply [7608]

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
TRIFLURIDINE + TIPIRACIL Trifluridine 15 mg + tipiracil 6.14 mg tablet, 20 Trifluridine 20 mg + tipiracil 8.19 mg tablet, 20	3 4	2 2	LONSURF 15/6.14 LONSURF 20/8.19 Servier Laboratories
Category / Program	GENERAL – General Schedule (Code GE)		
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives		
Episodicity:	-		
Severity:	Metastatic (Stage IV) [contained within 1773]		
Condition:	Adenocarcinoma of the stomach or gastro-oesophageal junction		
PBS Indication:	Metastatic (Stage IV) adenocarcinoma of the stomach or gastro-oesophageal junction [new concept]		
Treatment phase:	Continuing treatment		
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined		

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Clinical criteria:	Patient must have previously been treated with PBS-subsidised treatment with this drug for this condition [21475]
	AND Patient must not develop progressive disease whilst receiving PBS-subsidised treatment with this drug for this condition [21809]
	AND The treatment must be the sole PBS-subsidised therapy for this condition [7890]
Administrative Notes	No increase in maximum quantity or number of units may be authorised [7606]
	No increase in the maximum number of repeats may be authorised [7607]
	Special Pricing Arrangements apply [7608]

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor had no comment.