5.14 RIPRETINIB, Tablet 50 mg, Qinlock®, Specialised Therapeutics PM Pty Ltd.

1 Purpose of Application

1.1 The submission requested a Section 85, Authority Required listing for ripretinib for treatment of advanced gastrointestinal stromal tumour (GIST) after failure of or intolerance to imatinib and sunitinib. This is the first submission for ripretinib in GIST.

1.2 The requested basis for listing is a cost utility analysis against the comparator of best supportive care (BSC) alone.

1.3 Table 1 presents the key components of the clinical issues addressed by the submission.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Patients with advanced unresectable or metastatic GIST who have progressed or are intolerant to imatinib and sunitinib
Intervention	Ripretinib 150mg daily
Comparator	Best Supportive Care
Outcomes	PFS, ORR, OS, TTP, time to best response, duration of response, HRQoL, safety
Clinical claim	In patients with advanced GIST in the three or more line (≥3L) treatment setting following imatinib and sunitinib, ripretinib is an effective treatment option that offers clinically meaningful and durable responses compared with placebo/BSC, along with significant improvements in PFS and prolongation of OS. Ripretinib offers an acceptable safety profile and maintains HRQoL

Source: Table 1.1, p5 of the submission. BSC: best supportive care; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer 30-item; EQ-VAS: EuroQol visual analogue scale; EQ-5D-5L: EuroQol 5 dimensions 5 levels; GIST: gastrointestinal stromal tumours; HRQoL: health-related quality of life; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; TKI: tyrosine kinase inhibitor; TTP: time to progression; 3L: third line; ≥3L: third line or later; ≥4L: fourth line or later

2 Background

Registration status

2.1 Ripretinib was TGA registered on 13 July for 2020 for the following indication:

- the treatment of adult patients with advanced GIST who have received prior treatment with 3 or more kinase inhibitors, including imatinib.

2.2 At the time of evaluation for PBAC consideration, the TGA Delegate's overview and final TGA Delegate's recommendation were available.

3 Requested listing

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

MEDICINAL PRODUCT medicinal product pack	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Dispensed price for maximum quantity**	**Available brands**
RIPRETINIB						
ripretinib 50 mg tablet, 90	NEW	1	90	1	$[redacted] published price $[redacted] effective price	Qinlock
Restriction Summary [new] 4567 / Treatment of Concept: [new] 1234						
	Category / Program: GENERAL – General Schedule (Code GE)					
	Prescriber type: ☒Medical Practitioners					
	Restriction type: ☒Authority Required – non-immediate/delayed assessment by Services Australia (In-writing only via mail/postal service or electronic upload to Hobart)					
	Administrative Advice: *No increase in the maximum quantity or number of units may be authorised.*					
	Administrative Advice: *No increase in the maximum number of repeats may be authorised.*					
	Administrative Advice: *Special Pricing Arrangements apply.*					
	Episodicity: blank					
	Severity: Metastatic or unresectable					
	Condition: Malignant gastrointestinal stromal tumour					
	Indication: Metastatic or unresectable malignant gastrointestinal stromal tumour					
	Treatment Phase: Initial treatment					
	Clinical criteria:					
	The treatment must be as monotherapy					
	AND					
	Clinical criteria:					
	Patient must have previously failed or be intolerant to imatinib mesilate *for this condition*					
	AND					
	Clinical criteria:					
	Patient must have previously failed or be intolerant to sunitinib *for this condition*					
	AND					
	Clinical criteria:					

	Patient must have a WHO performance status of ~~0 to 2~~ *of 2 or less*
	Prescribing Instructions: Patients who progress while on ripretinib will not be eligible to receive further PBS-subsidised treatment with this drug for this condition. Applications for authorisation must be in writing and must include: (1) a completed authority prescription form (2) a completed ripretinib ~~(QINLOCK)~~ PBS Authority Application for Use in the Treatment of Gastrointestinal Stromal Tumour~~s~~ – *Supporting Information Form*~~; and~~ ~~(3) a signed patient acknowledgement indicating they understand and acknowledge that they will not be eligible to receive further PBS-subsidised treatment with this drug for this condition if they progress while on ripretinib.~~
	Administrative Advice: ~~Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).~~ ~~Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au~~ ~~Applications for authority to prescribe should be forwarded to:~~ ~~Department of Human Services~~ ~~Prior Written Approval of Complex Drugs~~ ~~Reply Paid 9826~~ ~~GPO Box 9826~~ ~~HOBART TAS 7001~~ *Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).* *Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au* *Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos* *Or mailed to:* *Services Australia* *Complex Drugs* *Reply Paid 9826* *HOBART TAS 7001*
	Administrative Advice: ***Note*** *Ripretinib is not PBS-subsidised for the treatment of patients with resectable malignant gastrointestinal stromal tumours.*

Restriction Summary [new] 4567 / Treatment of Concept: [new] 1234	
	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒~~Authority Required – Streamlined [new/existing code]~~ ☒Authority Required – immediate/real time assessment by Services Australia (telephone/online) ☒~~Authority Required – non immediate/delayed assessment by Services Australia (In writing only via mail/postal service or electronic upload to Hobart)~~
	Administrative Advice: *No increase in the maximum quantity or number of units may be authorised.*
	Administrative Advice: *No increase in the maximum number of repeats may be authorised.*
	Administrative Advice: *Special Pricing Arrangements apply.*
	Episodicity: blank
	Severity: Metastatic or unresectable
	Condition: Malignant gastrointestinal stromal tumour
	Indication: Metastatic or unresectable malignant gastrointestinal stromal tumour
	Treatment Phase: Continuing treatment
	Clinical criteria:
	~~Patient must have previously received PBS-subsidised therapy with this drug for this condition~~ *Patient must have received PBS-subsidised treatment with this drug for this condition*
	AND

	Clinical criteria:
	The treatment must be as monotherapy
	AND
	Clinical criteria:
	~~Patient must not have had disease progression while receiving treatment with this drug~~ *Patient must not have progressive disease while receiving treatment with this drug for this condition.*
	AND
	Clinical criteria:
	Patient must have a WHO performance status of ~~0 to 2~~ *2 or less*
	~~**Prescribing Instructions:** Patients who progress while on ripretinib will not be eligible to receive further PBS-subsidised treatment with this drug for this condition.~~
	Administrative Advice: ~~Authority applications for continuing treatment may be made by telephone to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).~~ *Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see* www.servicesaustralia.gov.au/HPOS*) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).*
	Administrative Advice: ***Note*** *Ripretinib is not PBS-subsidised for the treatment of patients with resectable malignant gastrointestinal stromal tumours.*

3.2 The submission requested a special pricing arrangement.

3.3 The PBAC noted the requested Authority Required (written) listing for the initial restriction was consistent with that of sunitinib. However, in contrast to the current sunitinib listing, the PBAC considered that an Authority Required (Telephone) listing would be appropriate for a ripretinib continuing restriction.

3.4 The submission acknowledged that the requested restriction deviates from the TGA-approved labelled indication, which is for fourth or later line (≥4L) use following prior treatment with at least three tyrosine kinase inhibitors (TKIs). Comparatively, the proposed restriction requested reimbursement of ripretinib at third line (3L) of treatment following disease progression after second line (2L) sunitinib as there are currently no other active treatment options available to Australian patients in the third or later line (≥3L) setting listed on the PBS (regorafenib is not PBS-listed and salvage imatinib therapy is rarely used). As such, the submission stated that listing for ripretinib in the ≥4L setting would not be considered practical or consistent with clinical practice. The ESC considered that 3L regorafenib was not routinely used in Australia due to cost (as it is not PBS-listed) and toxicity.

3.5 The INVICTUS study required a histologically confirmed diagnosis of GIST with at least 1 measurable lesion based on the mRECIST version 1.1 criteria. The PBAC considered that such requirements would be adequately established during earlier lines of therapy and hence specification in restriction clinical criteria was not required in this instance.

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

4 Population and disease

4.1 GISTs are subset of soft tissue sarcomas (STS) and are the most common mesenchymal (nonepithelial) tumour of the gastrointestinal (GI) tract (Blay 2010; Miettinen 2006a). According to Gamboa 2020, approximately 7% of STS cases are GIST. Common symptoms initially include pain, vomiting of blood, black stools indicating GI bleeding, obstructive symptoms and anaemia. However, up to a third of patients are asymptomatic, with tumours discovered incidentally during other therapeutic procedures.

4.2 The target patient population for ripretinib was patients with metastatic or unresectable GIST who have had disease progression with, or are intolerant to treatment with, first line (1L) imatinib and second line (2L) sunitinib treatment. The ESC considered metastatic or unresectable GIST to be a rare cancer with an unmet need for effective 3L treatment.

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

5 Comparator

5.1 The submission nominated BSC as the main comparator. The main arguments provided in support of this nomination were that regorafenib is not listed on the PBS, and therefore is rarely used following sunitinib and imatinib due to high cost. Likewise, imatinib rechallenge is rarely used post sunitinib. The submission also noted that in the March 2015 Public Summary Document for regorafenib, the PBAC agreed that BSC was the most appropriate comparator in the 3L setting, and there have been no new therapies approved in this line of therapy since. The ESC considered the nomination of BSC as the comparator was reasonable.

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 individuals (98), health care professionals (3) and organisations (4) via the Consumer Comments facility on the PBS website. The comments from individuals described the fear and anxiety associated with not having additional GIST treatment options once progression occurs. Comments noted that the disease is associated with significant morbidity and loss of function, as well as reduced quality of life if not controlled. The comments also highlighted the impact of GIST on families as a result of the typically younger patient population affected by the condition. The Life Raft Group reported 51 years to be the average age at diagnosis for the 2,000 patients included in its registry.

6.3 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the ripretinib submission, categorising it as one of the therapies of "high priority for PBS listing" on the basis of the INVICTUS trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for ripretinib, 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.

Clinical trials

6.4 The submission was based on a single randomised (2:1) controlled trial (INVICTUS, n=129) comparing ripretinib (+ BSC) to placebo (+ BSC). Patients randomised to placebo in INVICTUS were assumed to be representative of BSC patients in the economic evaluation. INVICTUS was double blind up to disease progression, after which patients randomised to ripretinib could continue to be treated with ripretinib and patients randomised to placebo could cross over to receive ripretinib and enter the open label phase.

6.5 As the population of INVICTUS (≥4L) differed from the requested population (3L), a phase 1 non-randomised dose escalation study (NCT02571036) across treatment lines (2L, 3L and 4L) was also presented to support the efficacy of ripretinib in different treatment lines.

6.6 Details of the trials presented in the submission are provided in Table 2.

[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
Pivotal evidence		
INVICTUS	Clinical study report DCC-2618-03-001: A phase 3, interventional, double-blind, placebo-controlled study to assess the safety and efficacy of DCC-2618 in patients with advanced gastrointestinal stromal tumors who have received treatment with prior anticancer therapies (INVICTUS). Clinical Study Report.	13 November 2019.
	Blay JY, Serrano C, Heinrich MC, et al. Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial.	The Lancet Oncology. 2020;21(7):923–34
	Correction to *Lancet Oncol* 2020;21:923–34.	The Lancet Oncology. 21(7) (pp e341),:July 2020
	Serrano C, Heinrich MC, George S, et al. Efficacy and safety of ripretinib as ≥4th-line therapy for patients with gastrointestinal stromal tumor (GIST) following crossover from placebo: Analyses from INVICTUS.	[Presentation] the ESMO World Congress on Gastrointestinal Cancer Virtual Meeting; July 1-4, 2020
	Heinrich MC, George S, Zalcberg JR, et al. Quality of life (QoL) and self-reported function with ripretinib in ≥4th-line therapy for patients with gastrointestinal stromal tumors (GIST): Analyses from INVICTUS	[Poster] 423 ASCO 2020, Virtual Congress May 29-31, 2020]. *JCO*. 2020;38(15_suppl):11535-11535.
	George S, Heinrich MC, Zalcberg JR, et al. Safety profile of ripretinib, including impact of alopecia, and Palmar-Plantar Erythrodysesthesia Syndrome (PPES) on patient-reported outcomes (PROs), in ≥ fourth-line advanced gastrointestinal stromal tumors (GIST): Analyses from INVICTUS	[Poster] 427 ASCO 2020, Virtual Congress May 29-31, 2020]. JCO. 2020;38(15_suppl):11539-11539.
	von Mehren M, Serrano C, Bauer S, et al. INVICTUS: A phase III, interventional, double-blind, placebo-controlled study to assess the safety and efficacy of ripretinib as ≥ 4th-line therapy in patients with advanced gastrointestinal stromal tumors (GIST) who have received treatment with prior anticancer therapies (NCT03353753)	[Presentation] 44th ESMO Congress, Barcelona 2019 Sep 27-Oct 01, 2019]. Annals of Oncology. 2019;30(Supplement 5):v925-v926.
	Zalcberg JR, Heinrich M, George S, et al. Clinical benefit with ripretinib as ≥4th line treatment in patients with advanced gastrointestinal stromal tumors (GIST): Update from the phase III INVICTUS study	[Presentation] at ESMO Virtual Congress 2020 Sep 19-21, 2020. Annals of Oncology. 2020;31(Supplement 4):S973-S974.
	Phase 3 Study of DCC-2618 vs Placebo in Advanced GIST Patients Who Have Been Treated With Prior Anticancer Therapies (INVICTUS)	ClinicalTrials.gov Identifier: NCT03353753
Supporting Evidence		
NCT02571036	Janku F, Abdul Razak AR, Chi P, et al. Switch Control Inhibition of KIT and PDGFRA in Patients With Advanced Gastrointestinal Stromal Tumor: A Phase I Study of Ripretinib.	J Clin Oncol. 2020;38(28):3294-3303.
	Chi P, Janku F, Heinrich M, et al. Updated results of phase 1 study of ripretinib (DCC-2618), a broad-spectrum KIT and PDGFRA inhibitor, in patients with gastrointestinal stromal tumor (GIST) by line of therapy (NCT02571036)	[Abstract] International Conference on Molecular Targets and Cancer Therapeutics; Boston, MA, 2019. Mol Cancer Ther. 2019;18 (12 Supplement):C077-C077

Source: Table 2-2, p40 of the submission, and p40-41 of the submission.

6.7 The key features of the included evidence are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Ripretinib plus BSC versus placebo versus BSC						
INVICTUS	129	R, DB*	Low	GIST 4th line or later	OS, PFS ORR, HRQoL	OS, PFS, HRQoL
Supportive evidence – non randomised dose escalation						
NCT02571036 (GIST sub population)	142	NR, OL	High	GIST, across lines of treatment	ORR	Not used.

Source: pp42-45 and pp83-89 of the submission.
DB=double blind; GIST = gastro intestinal stromal tumour; HRQoL = health related quality of life; MC=multi-centre; OL=open label; ORR = objective response rate; OS=overall survival; PFS=progression-free survival; R=randomised.
*Double blind until progression and open label after. All key endpoints were based on the double blind reporting period except for overall survival, which was based on combined double blind and open label period

6.8 The eligibility criteria of INVICTUS, and consequently the baseline characteristics, were not consistent with the proposed listing because the trial only included patients who failed at least three lines of therapy, while the requested restriction is for patients who have only failed two. The submission noted that 36% of patients in the ripretinib group of INVICTUS had prior treatment with four to seven therapies, representing a more advanced and refractory patient population.

6.9 Most patients enrolled in INVICTUS were ECOG 0 or 1. 7% of patients in the ripretinib arm and 9% of patients in the placebo arm were ECOG 2. The median age was 60 years (range 29-83).

6.10 The pre-specified primary endpoint in INVICTUS was progression free survival (PFS). The pre-specified key secondary endpoint was objective response rate (ORR). Other secondary endpoints included in the hierarchical hypothesis testing approach (used to protect against Type 1 error) were overall survival (OS) and health related quality of life (HRQoL).

Comparative effectiveness

6.11 Table 4 presents a summary of PFS results in the double-blind phase of INVICTUS.

Table 4: Summary of PFS in INVICTUS ITT population, double blind phase

	Ripretinib (n=85)	Placebo (n=44)
PFS event, n (%)	51 (60)	37 (84)
Patients censored, n (%)	34 (40)	7 (16)
Median PFS, months (95% CI)	6.3 (4.6, 6.9)	1.0 (0.9, 1.7)
HR (95% CI)	0.15 (0.09, 0.25)	
P-value	p<0.0001	

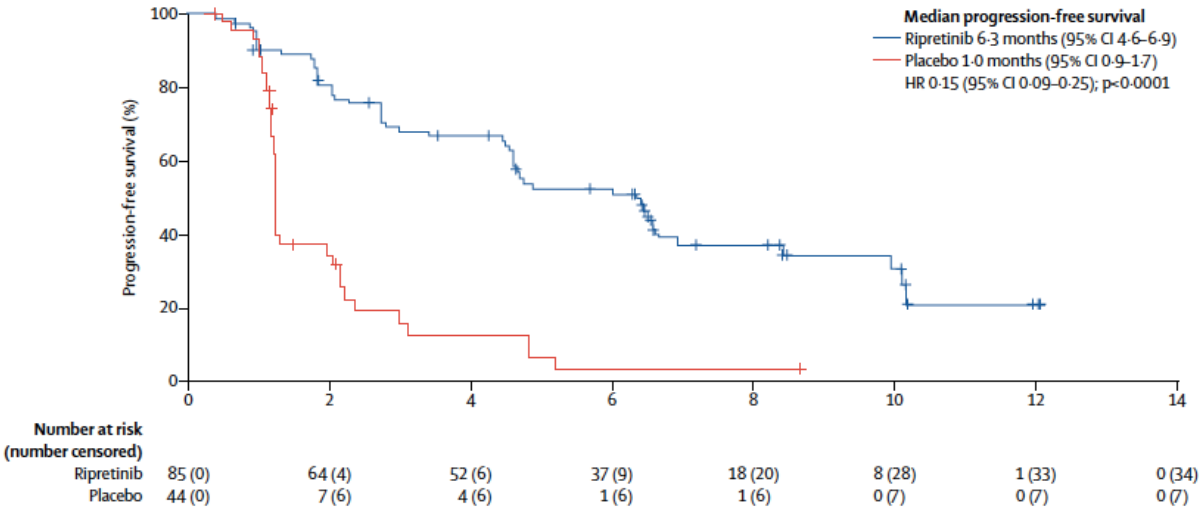
Source: Table 2-12, p66 of the submission.
CI = confidence interval; HR = hazard ratio; PFS = progression free survival

6.12 Median PFS in the ripretinib 150 mg once daily (QD) group was 6.3 months (95% CI 4.6 to 6.9 months) versus 1.0 month (95% CI 0.9 to 1.7 months) in the placebo arm, as assessed by blinded independent central review (BICR).

6.13 The ESC noted that patients treated with ripretinib had a statistically significantly reduced hazard rate of disease progression or death by 85% compared with placebo (HR 0.15; 95% CI 0.09 to 0.25; p<0.0001).

6.14 Figure 1 presents the Kaplan-Meier (KM) curve of PFS as assessed by BICR in the double-blind phase, ITT population.

Figure 1: Kaplan-Meier of INVICTUS PFS curve as assessed by BICR (ITT population, double blind phase)



Source: Figure 2-4, p65 of the submission.
BICR: blinded independent central review; CI: confidence interval; HR: hazard ratio; ITT: intent-to-treat; PFS: progression-free survival
Note: crosses denote censoring of data

6.15 ORR was the pre-specified key secondary endpoint. 8/85 (9%) had ORR in the ripretinib arm versus 0/44 (0%) in the placebo arm. The difference was not statistically significant, p=0.05. The Pre-Sub-Committee Response (PSCR) stated that, historically, achieving a high Response Evaluation Criteria in Solid Tumors (RECIST) - confirmed ORR has been challenging in GIST in the post-imatinib setting. The PSCR argued that stable disease was instead considered a more appropriate clinically successful tumour response, and is generally more predictive of PFS and OS benefit in patients with advanced GIST (Blay et al., 2020). The PSCR noted that compared with outcomes seen in the pivotal studies of sunitinib and regorafenib in earlier lines of advanced GIST, high ORR rates were not achieved (7% and 4.5%, respectively) despite significant gains in PFS (Demetri et al., 2013; Demetri et al., 2006). The PSCR argued that although not statistically significant, ripretinib achieved an ORR of 9% in this advanced study population with 7 of the 8 responders obtaining durable responses (median duration of response not yet reached). The ESC agreed with the PSCR that ORR > 10% are historically not achieved in GIST in the post imatinib setting.

6.16 Table 5 presents a summary of the OS results in the double-blind and open-label periods of the INVICTUS trial. A hierarchical hypothesis testing approach was used in the trial to protect against Type 1 error (in this case, the risk of claiming effect when

there is none) in testing multiple outcomes. Consequently, as no statistical difference was observed in the outcome in the hierarchy (ORR) prior to OS, it was not possible to claim statistically significant differences in OS between treatment arms in INVICTUS based on the pre-specified statistical plan.

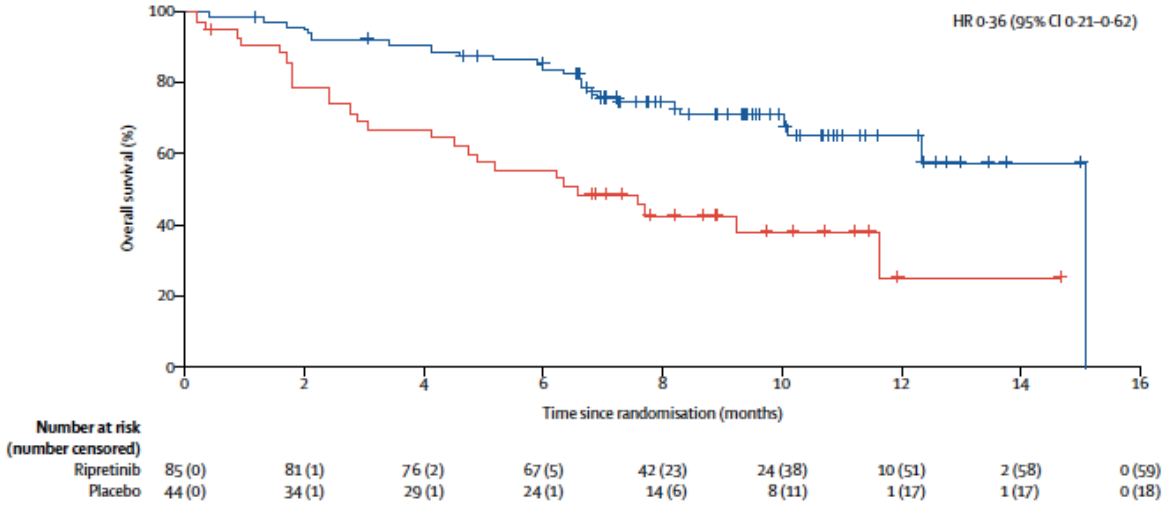
Table 5: Summary of OS results (ITT population double blind and open label period)

	Ripretinib (n=85)	Placebo (n=44)
OS event, n (%)	26 (31)	26 (59)
Patients censored, n (%)	59 (69)	18 (41)
Median OS, months (95% CI)	15.1 (12.3, 15.1)	6.6 (4.1, 11.6)
HR (95% CI)*	0.36 (0.21, 0.62)	
P-value**	p=0.0004	

Source: Table 2-15, p70 of the submission.
BICR: blinded independent central review; CI: confidence interval; HR: hazard ratio; ITT: intent-to-treat; N/A: not applicable; OS: overall survival; PFS: progression-free survival
* Calculated using the Cox regression model, which includes treatment and randomisation stratification factors as fixed factors; 95% CI based on Wald method
** Due to the hierarchal testing procedure of the endpoints, OS could not be formally tested for statistical significance because the objective response was not significant; the nominal p-value displayed is based on 2-sided stratified log-rank test
Note: OS is defined as the time interval between the date of randomisation until the date of death or censored at the date of last follow-up; patient groups are based on the treatment initially assigned.

6.17 Figure 2 presents the KM OS results for the double-blind and open label periods of INVICTUS.

Figure 2: KM Overall survival results in the double blind and open - label periods of INVICTUS



CI: confidence interval; HR: hazard ratio; OS: overall survival
* Owing to the hierarchical testing procedures of the endpoints, OS endpoint could not be formally tested because the objective response rate was not statistically significant.
Source: Figure 2-7, p67 of the submission

6.18 The submission claimed that patients achieved a clinically meaningful survival benefit when treated with ripretinib versus patients on placebo. The median OS was reported as 15.1 months (95% CI 12.3 to 15.1 months) in the ripretinib group and 6.6 months (95% CI 4.1 to 11.6 months) in the placebo group, inclusive of the double-blind and open-label periods. Though the submission reported median survival estimates for the

ripretinib arm, Figure 2 showed that median survival was actually not reached (>50% still assumed alive at end of follow up) and seems to be estimated by drawing a vertical line to 0 from the last point of observation.

6.19 Median survival was not reached in the ripretinib arm in INVICTUS as last follow up occurred before death in censored patients (59/85 (69%) of ripretinib patients were censored). Therefore, while a median OS for ripretinib was estimated by the submission, this estimate was immature and unreliable. The PSCR argued that median survival not being reached in the ripretinib arm reflected the durability of response to treatment. In contrast, the low median OS observed with placebo reflected the aggressive nature of GIST in patients with advanced disease experiencing progression. Together, the PSCR argued that these findings signified the strong trend towards efficacy of ripretinib in extending OS over BSC (placebo). The PSCR stated that no patients were lost to follow-up and given that all still in the trial had been enrolled for more than 16 months, the OS for the ripretinib arm is likely to be longer than 15.1 months, and certainly no worse, when mature. The ESC considered the OS difference to be clinically meaningful in this rare cancer and agreed with the PSCR that the OS difference is unlikely to become less clinically meaningful with longer follow-up.

6.20 The submission stated that no adjustments for crossover were made for OS analyses in the open label phase. The PBAC considered that by not adjusting for crossover OS differences associated with ripretinib may be underestimated.

6.21 The submission considered that as there are no alternative treatment options for patients with advanced unresectable or metastatic GIST in ≥3L setting, the pattern of treatment switching in INVICTUS, wherein patients were able to cross over from placebo to active treatment with ripretinib after disease progression, reflects what would reasonably be expected to occur in clinical practice if ripretinib were listed on the PBS.

6.22 The placebo arm in INVICTUS would not be expected to and is not intended to reflect what may occur in clinical practice after listing of ripretinib because it is the comparator arm. Consequently, the relevant question is whether the placebo arm reflects current practice without listing of ripretinib. It would be unreasonable to assume that 3L treatment with BSC will be followed with 4L ripretinib in a scenario in which ripretinib was not PBS subsidised, noting that lack of PBS listing was the reason why regorafenib was not considered to be a valid comparator.

6.23 For regorafenib, adjustment for crossover had a substantial impact on effect estimates in the GRID trial. Based on the post final analysis cut-off[2], a significant difference in overall survival for regorafenib compared to placebo was not observed (HR 0.91; 95%

[2] Demetri GD, Reichardt P, Kang Y, Blay, JY, Joensuu H, Schaefer K; Casali PG, Kappeler C. Final overall survival analysis with modeling of crossover impact in the phase III GRID trial of regorafenib vs placebo in advanced gastrointestinal stromal tumors. J Clin Oncology. 2016; 34: 156-156.

CI 0.65 to 1.27). However, with adjustment for cross over, the hazard ratio for overall survival was 0.59 (95% CI 0.42 to 0.82).

6.24 The exploratory HRQoL outcomes of European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer 30-item (EORTC QLQ-C30) and EuroQoL Visual Analogue Scale (EQ-VAS) showed significant differences between ripretinib and placebo, favouring ripretinib, in changes from baseline to Cycle 2, Day 1 mean scores. The submission did not present EuroQoL 5 Dimensions 5 Level (EQ-5D-5L) results, which were the basis of the utilities used in the economic evaluation. The PSCR presented the EQ-5D-5L results (see Table 6). The ESC noted the EQ-5D-5L results showed no statistically significant differences between placebo and ripretinib and considered this may due to the instrument not being disease specific and the short duration of follow-up for this outcome (baseline to cycle 2, day 1).

Table 6: EQ-5D-5L Index (Utility) Score and Change from Baseline to Cycle 2 Day 1 in Double-Blind Treatment Period (Intention-to-Treat Population)

Statistic	Placebo (N=44)	Ripretinib (N=85)
Baseline (n, SD)	0.7547 (42, 0.2521)	0.7606 (74, 0.2085)
Cycle 2, day 1 (n, SD)	0.7545 (33, 0.2201)	0.7762 (78, 0.1680)
Mean change (n, SD)	0.0596 (32, 0.1954)	0.0058 (70, 0.1399)
Treatment difference (95% CI)	0.05 (-0.02, 0.12))	

Source: Table 1, p5 of PSCR.

6.25 The submission did not anticipate the Australian patient population being in an earlier treatment setting would result in poorer efficacy or safety outcomes to those seen in the INVICTUS trial. The submission cited findings from Phase 1 study, NCT02571036, to demonstrate a comparable efficacy and safety profile in the 3L setting to that observed in INVICTUS.

6.26 In NCT02571036, patients with advanced GIST treated with 3L ripretinib at a 150 mg daily dose was well tolerated. The submission acknowledged that the 3L GIST cohort included only a small number of patients (n=28) and cross-trial comparisons with INVICTUS cannot be drawn directly. However the submission suggested that as PFS and ORR outcomes in the NCT02571036, 3L GIST cohort (PFS = 8.3 months, ORR = 14.3%) exceeded those in the ≥4L ripretinib group in INVICTUS (median PFS: 6.3 months; ORR = 9.4%), ripretinib may have greater efficacy in proposed PBS population than in the INVICTUS population. The submission noted the steady decline in PFS and ORR across the 2L to ≥4L GIST cohorts in the phase 1 study (2L, n=31, PFS = 10.7 months, ORR = 19.4%; 3L, n=28, PFS = 8.3 months, ORR=14.3%; 4L, n=83, PFS = 5.5 months, ORR = 7.2%). The PSCR stated that the steady decline in PFS and ORR across the 2L to ≥4L GIST cohorts in NCT02571036 was consistent with the variation in efficacy with subsequent lines of treatment seen with other therapeutic agents used in the treatment of GIST.

6.27 Comparatively, the PFS for ≥4L in NCT02571036 was 5.5 months (95% CI 3.6, 6.2), which was shorter than the PFS reported in INVICTUS (6.3 months, 95% CI 4.6, 6.9). This may suggest that the PFS benefit observed in INVICTUS may be uncertain, though noting that it might also be reflective of the small patient numbers enrolled in both INVICTUS and NCT02571036. Also, PFS is difficult to interpret in a single-arm study.

6.28 The ESC considered that while the results of the small phase 1 non-randomised dose escalation study (NCT02571036) should be interpreted with caution they suggest ripretinib efficacy in the 3L setting. Furthermore, while acknowledging the uncertainty, the ESC considered that clinically it was reasonable to assume that effectiveness in the 3L GIST setting would not be less than that observed in the ≥4L ripretinib group in INVICTUS.

6.29 A second line randomised study is underway of ripretinib versus sunitinib (NCT03673501). The sample size is 213 in each arm. The ESC noted the primary completion date of the INTRIGUE trial was June 2021 and considered it likely that the results of the trial would not be available until at least late 2021. The PBAC would welcome consideration of ripretinib in the 2L setting versus sunitinib following presentation of the INTRIGUE trial results.

Comparative harms

6.30 The submission stated that safety analyses were conducted for the safety population during the double-blind period. The safety population was defined as all patients who received at least one dose of study drug, and included all 85 patients randomised to ripretinib 150 mg QD and 43 out of the 44 patients randomised to placebo (128 in total). The submission considered that ripretinib was generally well tolerated and associated with an acceptable safety profile in INVICTUS.

6.31 Table 7 presents a summary of the treatment emergent adverse events in the double-blind phase of INVICTUS.

Table 7: Summary of TEAEs in the double-blind phase (safety population)

Categories	Ripretinib (n=85) n (%)	Placebo (n=43)* n (%)	Risk difference % (95%CI) ***
Any TEAE	84 (98.8)	42 (97.7)	1.0 (-0.4, 11)
Any grade 3/4 TEAE	42 (49.4)	19 (44.2)	0.5 (-13, 23)
Any treatment-emergent SAE	26 (30.6)	19 (44.2)	-14 (-31, 4)
Any treatment-related TEAE	72 (84.7)	26 (60.5)	**24 (8, 41)**
Any grade 3/4 treatment-related TEAE	21 (24.7)	7 (16.3)	8 (-7, 22)
Any treatment-related treatment-emergent SAE	8 (9.4)	3 (7.0)	2 (-10, 12)
Any TEAE leading to dose reduction	6 (7.1)	1 (2.3)	5 (-6, 13)
Any TEAE leading to dose interruption	20 (23.5)	9 (20.9)	3 (-14, 17)
Any TEAE leading to treatment discontinuation	7 (8.2)	5 (11.6)	-3 (-17, 7)
Any TEAE leading to death	5 (5.9)	10 (23.3)	**-17 (-33, -5)**
Any treatment-related TEAE leading to dose reduction	5 (5.9)	1 (2.3)	4 (-7, 11)
Any treatment-related TEAE leading to dose interruption	12 (14.1)	3 (7.0)	7 (-6, 18)
Any treatment-related TEAE leading to treatment discontinuation	4 (4.7)	1 (2.3)	2 (-8, 10)
Any treatment-related TEAE leading to death	1 (1.2)	1 (2.3)	-1 (-11, 4)
Death	1 (1.2)	0	1 (-7, 6)
Pulmonary oedema	0	1 (2.3)**	-2 (-12, 2)
Septic shock	0	1 (2.3)**	-2 (-12, 2)

Source: Table 2-17, pp77-78 of the submission.

SAE: serious adverse event; QD: once a day; TEAE: treatment-emergent adverse event

* 44 patients randomised to placebo yet one did not receive treatment

** Pulmonary oedema and septic shock were reported in the same patient

*** calculated during evaluation using StatsDirect v3.3.4

Text in bold indicates statistically significant differences

Note: One treatment-emergent "FEVER" which misses severity grade is summarised as grade 3 ("severe"). TEAEs occurring during the double-blind treatment period are summarised by treatment arms. Incidences are based on the number of patients who initially received placebo or ripretinib 150 mg QD.

6.32 A summary of specific adverse events is presented in Table 8.

Table 8: TEAEs in >10% of patients in the ripretinib group vs placebo – double-blind period (safety population)

TEAE, n (%)	Ripretinib 150 mg QD any grade (n=85)	Placebo any grade (n=43)*	Risk difference % (95%CI) ***	Ripretinib 150 mg QD grade 3/4 (n=85)†	Placebo grade 3/4 (n=43)*†	Risk difference % (95%CI) ***
Any TEAE or grade 3/4 TEAE**	84 (98.8)	42 (97.7%)	1.1 (-4.4, 11)	42 (49.4%)	19 (44.2%)	5.3 (-13.0, 22.9)
Alopecia	44 (51.8)	2 (4.7)	**47.1 (33, 58.6)**	0	0	0 (-8.3, 4.4)
Fatigue	36 (42.4)	10 (23.3)	**19.1 (1.5, 34.3)**	3 (3.5)	1 (2.3)	1.2 (-8.9, 8.0)
Nausea	33 (38.8)	5 (11.6)	**27.2 (11.4, 40.3)**	3 (3.5)	0	3.5 (-4.8, 9.9)
Myalgia	27 (31.8)	5 (11.6)	**20.1 (4.7, 33.1)**	1 (1.2)	0	1.2 (-7.1, 6.4)
PPES	18 (21.2)	0	**21.2 (12.4, 31.1)**	0	0	0 (-8.3, 4.4)
Vomiting	18 (21.2)	3 (7.0)	**14.2 (0.7, 25.6)**	3 (3.5)	0	3.5 (-4.8, 9.9)
Headache	16 (18.8)	2 (4.7)	**14.2 (1.7, 24.8)**	0	0	0 (-8.3, 4.4)
Weight decreased	16 (18.8)	5 (11.6)	7.2 (-7.4, 19.3)	0	0	0 (-8.3, 4.4)
Arthralgia	15 (17.6)	2 (4.7)	**13.0 (0.6, 23.5)**	0	0	0 (-8.3, 4.4)
Blood bilirubin increased	14 (16.5)	0	**16.5 (7.8, 25.8)**	1 (1.2)	0	1.2 (-7.1, 6.4)
Dyspnoea	11 (12.9)	0	**12.9 (4.3, 21.7)**	0	0	0 (-8.3, 4.4)
Hypophosphataemia	9 (10.6)	0	**10.6 (2.0, 19.0)**	4 (4.7)	0	4.7 (-3.7, 11.5)
Lipase increased	9 (10.6)	0	**10.6 (2.0, 19.0)**	4 (4.7)	0	4.7 (-3.7, 11.5)
Stomatitis	9 (10.6)	0	**10.6 (2.0, 19.0)**	0	0	0 (-8.3, 4.4)

Source: Table 2-18, p79 of the submission.
PPES: palmar-plantar erythrodysaesthesia syndrome; QD: once a day; TEAE: treatment-emergent adverse event
* 44 patients were randomised to placebo, but 1 did not receive treatment
** Regardless of causality
*** calculated during evaluation using StatsDirect v3.3.4
Text in bold indicate statistically significant differences
† Corresponding grade 3/4 TEAEs to TEAEs in >10% of patients receiving ripretinib

6.33 There were no statistically significant differences in specific Grade 3 or 4 adverse events. Considering the small sample size, this was expected. Nevertheless, ripretinib was associated with higher rates of any grade treatment-emergent adverse events (TEAEs), grade 3/4 treatment related TEAEs, fatigue, nausea, grade 3/4 nausea, constipation, myalgia, diarrhoea, PPES, vomiting, headache, arthralgia, peripheral oedema, muscle spasms dyspnoea, hypophosphatemia, pruritus and stomatitis.

6.34 8% of patients in the ripretinib arm discontinued treatment due to an adverse event.

6.35 The ESC considered that the safety profile of ripretinib would be unlikely to be different in the 3L versus the 4L setting.

Benefits/harms

6.36 A summary of the comparative benefits and harms for ripretinib plus BSC versus BSC alone (placebo + BSC) is presented in the table below.

Table 9: Summary of comparative benefits and harms for Ripretinib plus BSC versus Placebo plus BSC

Benefits				
Time to event (PFS and OS) in INVICTUS trial*				
	Ripretinib	**Placebo**	**Absolute difference**	**HR (95% CI)**
PFS event, n/N (%)	51/85 (60)	37/44 (84)	14%	0.15 (0.09, 0.25), p<0.0001
Median PFS, months (95% CI)	6.3 (4.6, 6.9)	1.0 (0.9, 1.7)	5.3	-
OS event, n/N (%)	26/85 (31)	26/44 (59)	Not appropriate: because of the hierarchical hypothesis testing in INVICTUS, a comparison of overall survival was not possible due to the absence of a statistically significant result in ORR.	
Median OS, months (95% CI)	15.1 (12.3, 15.1)	6.6 (4.1, 11.6)		

Harms in INVICTUS trial						
	Ripretinib n/N	**Placebo n/N**	**RR (95% CI)****	**Event rate/100 patients***		**RD (95% CI)****
				Ripretinib	**Placebo**	
Alopecia	44/85	2/43	**11.13 (3.3,40.8)**	51.8	4.7	**47.1 (33, 58.6)**
Fatigue	36/85	10/43	**1.82 (1.04, 3.37)**	42.4	23.3	**19.1 (1.5, 34.3)**
Nausea	33/85	5/43	**3.31 (1.50, 7.94)**	38.8	11.6	**27.2 (11.4, 40.3)**
Myalgia	27/85	5/43	**2.73 (1.21, 6.58)**	31.8	11.6	**20.1 (4.7, 33.1)**
PPE	18/85	0/43	**18.9 (1.2, NE)**	21.2	0	**21.2 (12.4, 31.1**)
Vomiting	18/85	3/43	**3.04 (1.04, 9.38)**	21.2	7.0	**14.2 (0.7, 25.6)**
Headache	16/85	2/43	**4.05 (1.13, 15.48)**	17.1	11.6	**14.2 (1.7, 24.8)**
Arthralgia	15/85	2/43	**3.79 (1.05, 14.58)**	17.6	4.7	**13.0 (0.6, 23.5)**
Blood bilirubin increased	14/85	0/43	**14.84 (1.98, NE)**	16.5	0	**16.5 (7.8, 25.8)**
Dyspnoea	11/85	0/43	**11.77 (1.55, NE)**	12.9	0	**12.9 (4.3, 21.7)**
Hypophosphataemia	9/85	0/43	**9.72 (1.26, NE)**	10.6	0	**10.6 (2.0, 19.0)**
Lipase increased	9/85	0/43	**9.72 (1.26, NE)**	10.6	0	**10.6 (2.0, 19.0)**
Stomatitis	9/85	0/43	**9.72 (1.26, NE)**	10.6	0	**10.6 (2.0, 19.0)**

* Median duration of follow-up in INVICTUS: Ripretinib arm (double blind period) = 6.3 months; Placebo (double blind period) =1.6 months; BSC = best supportive care; HR = hazard ratio; PPE = palmar-plantar erythrodysaesthesia syndrome; RD = risk difference; RR = risk ratio, NE = not estimable

** Indicate values calculated during evaluation with StatsDirect v3.3.4.

Text in bold indicate statistically significant differences.

Source: Table 2-12, p66, Table 2-15, p70 and Table 2-18, p79 of the submission.

6.37 On the basis of the INVICTUS trial, for every 100 patients treated with ripretinib plus best supportive care (BSC) in comparison to BSC alone, and over a median duration of treatment of 24 weeks for ripretinib and 6 weeks for BSC:

- Approximately 14 more patients remained progression-free over a median duration of follow-up of 6.3 months for ripretinib and 1.6 months for placebo; however, no difference in overall survival can be formally claimed;
- Approximately 47 additional patients would experience alopecia;
- Approximately 19 additional patients would experience fatigue;
- Approximately 27 additional patients would experience nausea;
- Approximately 20 additional patients would experience myalgia;
- Approximately 21 additional patients would experience palmar-plantar erythron-dysaesthesia syndrome;
- Approximately 14 additional patients would experience vomiting;
- Approximately 14 additional patients would experience headache;
- Approximately 13 additional patients would experience arthralgia;

- Approximately 17 additional patients would experience blood bilirubin increase;
- Approximately 13 additional patients would experience dyspnoea;
- Approximately 11 additional patients would experience hypoposphataemia;
- Approximately 11 additional patients would experience lipase increase; and
- Approximately 11 additional patients would experience stomatitis

Clinical claim

6.38 The submission described maintenance therapy with ripretinib plus BSC at a dose of 150 mg daily in 28 day cycles until disease progression as superior in terms of efficacy compared with placebo/BSC and non-inferior in terms of safety compared to placebo/BSC in 3L treatment of patients with metastatic or unresectable GIST.

6.39 The evaluation considered that the therapeutic conclusions presented in the submission were not adequately supported by the evidence presented in the submission for the following reasons.

- The INVICTUS trial represented later line therapy compared to the requested restriction. Though the submission included supportive evidence from NCT02571036 to support the assertion that the efficacy of ripretinib was similar across treatment lines, NCT02571036 was a single arm, open-label study with a small sample size (n=28 for 3L treatment). The PSCR argued that the steady decline in PFS and ORR across the second line to ≥4L GIST cohorts in NCT02571036 was consistent with the variation in efficacy with subsequent lines of treatment seen with other therapeutic agents used in the treatment of GIST. The ESC considered that while the results of NCT02571036 should be interpreted with caution they suggest ripretinib efficacy in the 3L setting.

- INVICTUS did not show a statistically significant effect in ORR. As a result, though there was a numerical increase in OS survival for ripretinib compared to placebo, the hierarchical testing procedure of INVICTUS did not allow for a statistical comparison of OS outcomes, in order to minimise type 1 error from testing multiple outcomes.

- Median OS was not reached in the ripretinib arm in INVICTUS. 69% (59/85) of patients in the ripretinib arm were censored due to end of follow-up. This indicates that OS results from INVICTUS were immature. The PSCR argued that median survival not being reached in the ripretinib arm together with the low median OS observed with placebo signified the strong trend towards efficacy of ripretinib in extending OS over BSC (placebo). The ESC considered the OS difference to be clinically meaningful in this rare cancer.

- With regard to safety, while the submission claimed non-inferiority on the basis of its similar rate of TEAEs compared with placebo and lower rate of TEAEs leading to death and treatment discontinuation, the ripretinib arm of INVICTUS was

associated with statistically significantly higher rates of several specific adverse events such as fatigue, nausea, myalgia, PPES, vomiting, headache and arthralgia. The Risk Management Plan also notes identified risks including hypertension and cardiac dysfunction.

The ESC acknowledged the uncertainty associated with using the INVICTUS results to estimate effectiveness in the 3L setting. However, the ESC considered that clinically it was reasonable to assume that effectiveness in the 3L GIST setting would not be less than that observed in the ≥4L ripretinib group. The ESC considered the claim of superior efficacy compared with placebo/BSC was uncertain but reasonable in the context of metastatic or unresectable GIST being a rare cancer with an unmet need for effective 3L treatment. In addition, the ESC considered the evidence presented indicated ripretinib had an acceptable safety profile.

6.40 The PBAC considered that the claim of superior comparative effectiveness was reasonable.

6.41 The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data but agreed with ESC that ripretinib had an acceptable safety profile.

Economic analysis

6.42 The submission presented a partitioned survival model (PSM) to model the costs and health outcomes for patients receiving ripretinib or BSC over a 7 year time horizon using a cost-utility analysis (CUA).

6.43 Key components of the economic evaluation are presented in Table 10.

Table 10: Key components of the economic evaluation

Component	Description
Type of analysis	Cost utility analysis
Outcomes	Incremental cost/ QALY
Time horizon	7 years in the model base case vs. median follow up of 6.3 months in ripretinib arm of INVICTUS.
Methods used to generate results	Partitioned survival model
Health states	Progression free, progressed disease, death
Cycle length	4 weeks
Transition probabilities	Transition probabilities from survival analysis fitted to survival data from INVICTUS and extrapolated over full time horizon
Subsequent treatment costs	Given ripretinib will not be reimbursed beyond treatment progression it was assumed TTD=PFS pre-progression; TTD post progression for ripretinib in BSC arm modelled, but not presented
Software package	Excel

Source: Table 3-1, p97 of the submission. PFS = Progression free survival, QALY = quality adjusted life year, TTD = time to treatment discontinuation

6.44 The model included three health states: progression-free (PF), progressed disease (PD), and death. The distribution of patients between the PF and PD health states over

time are informed by the OS and PFS curves from INVICTUS. The area under the curve approach is then used to estimate the time patients spend in the PF and PD states and QALY calculated based on this information.

6.45 Patients accrued costs associated with their treatment arm (drug costs and adverse event management costs) as well as health state costs. Patients in the ripretinib arm were assumed to remain on treatment until progression, and then stop. However, 65.9% of patients in the placebo arm were inappropriately assumed to cross over to ripretinib after progression (see paragraphs 6.47 and 6.48). An end of life cost was also applied as a transition cost when patients die (transition to dead health state).

6.46 Table 11 presents key drivers of the model.

Table 11: Key drivers of the model

Description	Method/Value	Impact
Extrapolation OS	Exponential extrapolation for both BSC and ripretinib OS curves over 7 year time horizon	High, favours ripretinib
Extrapolation PFS	Log-logistic extrapolation of PFS curves for both BSC and ripretinib over 7 year time horizon	Moderate, favours BSC, compared to other extrapolations in terms of ICER (see Table 12)
Post progression ripretinib in BSC arm	Model assumes a majority (65.9%) of patients in BSC arm will receive ripretinib drug costs post progression. No patients in ripretinib arm are assumed to receive ripretinib post progression	High, favours ripretinib
Post progression ripretinib in ripretinib arm	In the model, no patients in the ripretinib arm were assumed to receive ripretinib post progression. In INVICTUS, 42/85 (49.4%) patients who were randomised to ripretinib continued treatment post progression, (31/85 36.5%) doubled their dose frequency	High, favours ripretinib
Treatment switching	No adjustment of OS was undertaken for the high uptake of ripretinib post progression in the BSC arm	Favours BSC

Source: QinLock Cost-effectiveness model _november 2020 (version 1).xlsx
BSC = best supportive care. OS = overall survival; PFS =progression free survival

6.47 In the INVICTUS trial, 29/44 (65.9%) patients who were randomised to placebo (i.e. BSC) in the double-blind period crossed over to receive ripretinib after progression. The submission accounted for this high proportion of crossover by assigning ripretinib costs to this proportion of patients in the post progression state in BSC. These patients who crossed over were assumed to continue ripretinib treatment until second progression (based on second progression [PFS-2] in the INVICTUS trial), with a log-normal curve selected based on the lowest AIC values.

6.48 This approach was inconsistent with the requested population as patients in the BSC arm would not be expected to receive ripretinib post progression in a scenario where ripretinib is not PBS subsidised (which is what the BSC comparator arm is supposed to demonstrate). This unreasonable assumption strongly favoured ripretinib. The PSCR disagreed that the approach taken was unreasonable but suggested the sponsor was willing to discuss an appropriate methodology for accounting for cross over patients. The ESC agreed with the evaluation that the assumption that patients in the BSC arm

would receive post progression ripretinib was unreasonable and strongly favoured ripretinib. The ESC noted that the PBAC guidelines (version 5) provides methodological guidance on adjustments for treatment switching.

6.49 Moreover, the submission was inconsistent in applying post progression ripretinib costs from INVICTUS, as no post progression ripretinib was assumed in the ripretinib arm of the model. In INVICTUS, 42/85 (49.4%) patients who were randomised to ripretinib continued treatment post progression, and 31/85 (36.5%) patients actually doubled their dose frequency. The ESC agreed with the evaluation that the omission of post progression ripretinib in the ripretinib arm also strongly favoured ripretinib. The pre-PBAC response stated that the model excluded post-progression ripretinib costs as the proposed restriction precludes the use of ripretinib following progression. In addition, the pre-PBAC response argued that the mean [SD] treatment duration for the ripretinib arm was 24.44 [13.94] weeks, which is consistent with the median PFS in the study. As such, the pre-PBAC response argued that there was limited ripretinib use post progression in the ripretinib arm.

6.50 As outlined in paragraph 6.19 the ESC considered the OS difference observed in the INVICTUS trial be clinically meaningful. However, the ESC considered that, as it was not possible to demonstrate statistically significant superiority in OS and the INVICTUS trial was undertaken in a later line treatment setting, the extrapolation of survival gains was subject to considerable uncertainty. The ESC noted that the model was highly sensitive to choice of OS extrapolation. The ESC considered that the least conservative (exponential) extrapolation model was selected for extrapolating OS (see Table 13). The ESC also noted that flexible parametric models were reported, but the visual fit of these models was not presented.

6.51 Review of the landmark PFS-BICR rates indicates that the submission's selected parametric curves for the base case PFS extrapolation produced the longest estimates of PFS, but this favoured BSC (see Table 13). This was because:

- Patients are assumed to continue ripretinib treatment until progression and then stop. A shorter PFS gain in the ripretinib arm means shorter time on treatment therefore lower costs; and
- The utility difference between PF and PD is negligible. Without any corresponding change in OS, there was no tangible difference in QALY.

The ICER was sensitive to choice of PFS extrapolation. Using the Weibull function for PFS extrapolation in the ripretinib arm, the ICER decreases by 32%.

6.52 Table 12 presents the results of the submissions' economic evaluation.

Table 12: Results of the economic evaluation

Component	Ripretinib	BSC	Increment
Costs	$[redacted]	$[redacted]	$[redacted]
LY	2.036	0.889	1.146
QALYs	1.512	0.656	0.856
Incremental cost/extra LY gained			**$[redacted]*,1**
Incremental cost/extra QALY gained			**$[redacted]2**

LY = life years, QALY = quality adjusted life-year
*Indicates values calculated during evaluation
Source: Table 3-26 of the submission, QINLOCK_Cost_Effectiveness_Model_Nov2020.xlsm.
The redacted values correspond to the following ranges:
[1] *$55,000 to < $75,000*
[2] *$75,000 to < $95,000*

6.53 The incremental treatment cost and therefore the ICER was substantially underestimated due to the inappropriate assumption of post progression ripretinib use in the BSC arm.

6.54 The submission stated that deterministic one-way analyses were presented as well as probabilistic sensitivity analyses. The presented one-way sensitivity analyses were poorly described and did not present incremental costs or incremental QALYs.

6.55 During the evaluation, one-way sensitivity analyses were conducted on key inputs. These are presented in Table 13.

Table 13: Results of key sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER	%Δ from base case
Base case	**$** [redacted]	**0.856**	**$** [redacted][1]	**NA**
Assuming no BSC patients cross over to receive ripretinib*	$ [redacted]	0.856	$ [redacted][2]	+136.1%
Assuming no BSC patients cross over to receive ripretinib and that costs for post progression use of ripretinib are accrued, consistent with INVICTUS trial**	$ [redacted]	0.856	$ [redacted][3]	+434.1%
Time horizon (base case 7 years)***				
5 years	$ [redacted]	0.779	$ [redacted][1]	+4.5%
3 years	$ [redacted]	0.580	$ [redacted][4]	+28.2%
OS ripretinib and BSC extrapolation (base case exponential)***				
Weibull	$ [redacted]	0.442	$ [redacted][5]	+77.7%
Gompertz	$ [redacted]	0.132	$ [redacted][6]	+451.3%
Log-logistic	$ [redacted]	0.567	$ [redacted][7]	+46.5%
Log-normal	$ [redacted]	0.758	$ [redacted][1]	+11.4%
Flexible – Hazards (K=0)	$ [redacted]	0.442	$ [redacted][5]	+77.7%
Flexible – Hazards (K=1)	$ [redacted]	0.325	$ [redacted][2]	+137.0%
Flexible – Odds (K=0)	$ [redacted]	0.567	$ [redacted][7]	+46.5%
Flexible – Odds (K=1)	$ [redacted]	0.423	$ [redacted][2]	+93.9%
Assume switching to extrapolation of OS at cycle 6 for both arms (base case cycle 17 for ripretinib and 16 for BSC)***	$ [redacted]	0.851	$ [redacted][1]	+0.51%
PFS ripretinib and BSC extrapolation (base case log-logistic)***				
Exponential	$ [redacted]	0.853	$ [redacted][8]	-26.9%
Weibull	$ [redacted]	0.853	$ [redacted][8]	-32.1%
Gompertz	$ [redacted]	0.853	$ [redacted][8]	-28.0%
Flexible – Hazards (K=0)	$ [redacted]	0.853	$ [redacted][8]	-32.1%
Flexible – Hazards (K=1)	$ [redacted]	0.853	$ [redacted][8]	-21.6%
Flexible -Normal (k=1)	$ [redacted]	0.855	$ [redacted][1]	-11.5%

Source: Tables 3-30 and 3-31, pp160-161 of the submission and QinLock Cost-effectiveness model _november 2020 (version 1).xlsx

*The submission did not incorporate functionality for removing ripretinib costs of cross over patients. During the evaluation, this was tested by setting cells J1623:J2141 in Datastore worksheet of the economic model to equal 0.

**this was done during the during the development of the ESC advice by making the above change as well as changing Cell N9 (with corresponding changes to all cells in the column) of Trace (ripretinib)
to =I9*((0.13*Intervention_compliance*Intervention_RDI*(Intervention_trt_cost_X+admin_Intervention_cost_X))+(0.37*Intervention_compliance*Intervention_RDI*2*(Intervention_trt_cost_X+admin_Intervention_cost_X))+
(0.5*Comparator1_compliance*Comparator1_RDI*(Comparator1_trt_cost_X+admin_Comparator1_cost_X)))*1/(1+dr_cost)^$C9

*** Analyses undertaken during the evaluation

The redacted values correspond to the following ranges:

[1] *$75,000 to < $95,000*
[2] *$155,000 to < $255,000*
[3] *$355,000 to < $455,000*
[4] *$95,000 to < $115,000*
[5] *$135,000 to < $155,000*
[6] *$455,000 to < $555,000*
[7] *$115,000 to < $135,000*
[8] *$55,000 to < $75,000*

6.56 The economic model presented by the submission did not have the operability to remove post progression ripretinib costs for BSC. Instead, the proportion of patients who received post progression ripretinib were set to be zero throughout the model during the evaluation meaning only the costs were adjusted. This resulted in an ICER

of $155,000 to < $255,000/QALY, 136% higher than the base case proposed by the submission.

6.57 The ESC considered the submission's base case was among the most favourable in regards to OS extrapolations of the modelled options. Given that the INVICTUS trial failed to demonstrate statistically significant superiority in OS, the ESC advised the modelled survival gains could be considered unreasonably favourable to ripretinib. In addition, the ESC considered that the assumptions used to manage post progression ripretinib costs strongly favoured ripretinib (see paragraphs 6.48 and 6.49). As such, the ESC recommended the following amendments to the economic analysis:

- Exclude post progression ripretinib costs in BSC arm
- Include post progression ripretinib costs in ripretinib arm
- Adjust OS for cross over in the BSC arm.

The ESC noted that amending post progression ripretinib costs in both arms of the economic model increased the ICER to $355,000 to < $455,000/QALY. The ESC noted that adjustments for cross over were not made in the submission for OS analyses. However, the ESC advised that if such analyses were not forthcoming, non-adjustment for treatment switching would be considered conservative.

6.58 The pre-PBAC response suggested a way forward could be based on the sensitivity analysis that removed post progression ripretinib costs for BSC resulting in an ICER of $155,000 to < $255,000/QALY (see paragraph 6.56). The pre-PBAC response proposed a modified version of the sensitivity analysis in paragraph 6.56 which assumed a 50% reduction in QALYs in the BSC arm. The pre-PBAC response advised that the sponsor would be open to a price reduction that takes into account a modified version of this sensitivity analysis that adjusts for post progression cross over treatment effect in the BSC arm. The PBAC did not accept the approach taken in the pre-PBAC response to modify the sensitivity analysis in paragraph 6.56. Instead, the PBAC considered that the sensitivity analysis outlined in paragraph 6.56, would be an appropriate basis for a price reduction.

Drug cost/patient/course: $[redacted]

6.59 The submission did not calculate intervention cost per course in the economic evaluation. However the submission referred to the economic evaluation in its estimation of cost per course in the financial estimates for duration of treatment. The estimate of 49.82 weeks used in the financial estimates could not be verified in the economic evaluation, though the differences between the evaluation calculations and the 49.82 weeks were small.

6.60 The cost per course of ripretinib based on the mean 49.82 weeks of treatment used in the model (area under the curve of and the $[redacted] price per four week cycle) was

$[redacted] ($[redacted]/30*28/4 × 49.82). In patients who remained progression-free in the ripretinib arm, an additional cost per cycle for BSC of $[redacted] was also applied.

6.61 The cost per course of BSC, based on an equivalent 49.82 weeks of treatment and a per cycle cost of an average cost of a basket of treatments of $[redacted] per four-week cycle was $[redacted] ($[redacted]/4 × 49.82). This cost was applied to all patients who were progression-free in the BSC arm and also to all patients who had progressed disease in the ripretinib arm.

Table 14: Drug cost per patient for proposed and comparator drugs

	Ripretinib Trial dose and duration	Ripretinib Model	Ripretinib financial estimates
Price	$[redacted] (50mg tablets, 90 tablets)		
Mean dose	150mg/day		
Duration of treatment	23.86 weeks	49.82 weeks	11.50 months (49.82/52x12)
Adjustment: Dose density	-	-	11.50* 96.5%=11.09
Cost/patient/course	$[redacted]	$[redacted] ($[redacted]/30*28/4 × 49.82)	$[redacted] ($[redacted] * 11.09 months of treatment)

Source: QINLOCK_Cost_effectiveness_modelNov 2020.xlsx and QINLOCK_utilisation_and_cost_modelnov2020.xlsx
NA = not applicable

Estimated PBS usage & financial implications

6.62 This submission was not considered by DUSC. The submission took an epidemiological approach as well as a market share approach to support to the epidemiological estimates.

6.63 Table 15 presents key inputs in the financial estimates.

Table 15: Data sources and parameter values applied in the utilisation and financial estimates

Data	Value	Source	Comment
Eligible population			
Number of imatinib patients	Year: Patients 2022: [redacted]1 2023: [redacted]1 2024: [redacted]1 2025: [redacted]1 2026: [redacted]1 2027: [redacted]1	DUSC 2017 Review The submission used imatinib patients from 2014 and applied the annual growth rate of the Australian population (1.6%)	The evaluation considered this was reasonable.
Proportion of imatinib patients who go onto sunitinib	90%	Clinical expert advice	The PBAC considered the assumption regarding the proportion of imatinib patients who go onto sunitinib was overestimated based on PBS prescription data for sunitinib provided by the DUSC Secretariat (see paragraph 6.69).
Proportion of sunitinib patients who would receive 3L therapy	90%		
Treatment utilisation			

Data	Value	Source	Comment
Patients electing treatment	80% in year 1, 100% in year 2 onwards	Assumption	
Scripts per treatment (initial and continuing)	10.16 in "3.a scripts proposed" worksheet (sum of cells Q117 and Q118) 11.09 in "1.Overview" worksheet (cell I406)	11.50 (49.82 weeks from mean time to discontinuation from economic evaluation converted to months) x 96.5% and a 97.74% compliance for the continuing treatment (100% compliance assumed during 2 months initiation).	Mean treatment duration of ripretinib in the INVICTUS double blind phase was 24.44 weeks. While the PFS data was not fully mature and mean treatment time could be expected to increase, 49.82 weeks may be an overestimate. Additionally, during the evaluation, the estimate of 49.82 could not be verified in the economic evaluation, though the differences between the evaluation calculations and the 49.82 were small. The submission's approach to calculating doses and scripts per patient was overly complicated and poorly explained. It appeared to assume that there would only be 28 days of treatment per month on treatment. See discussion below.
Additional survival for accruing BSC and MBS costs	8.5 months	INVICTUS	Though patients treated with ripretinib lived for an additional 8.5 months (median OS 15.1 months versus 6.6 months in the placebo/BSC group), the median survival in ripretinib was not reached due to extensive censoring, and there was no formal statistical improvement in survival. Given the issues with overall survival outcomes discussed, this may overestimate additional BSC costs associated with listing of ripretinib.
Market share approach:			
PBS statistics for imatinib and sunitinib	-	Medicare data. PBS Item reports.	-
Proportion of sunitinib patients who would receive 3L therapy	90%	Clinical advice	See above.
Annual growth rate	1.60%	2017 DUSC review of imatinib	This may not be up to date, but would not be expected to vary greatly.
Costs			
Proposed medicine	$[redacted] (published) $[redacted] (effective)	Requested price	-
BSC costs	Average cost of a basket of treatments	PBS published prices and INVICTUS	See above.
Patient co-payment	-	Not estimated	This will lead to slight overestimation of PBS costs
MBS costs	$45.00 8.5 services/pt/yr	MBS item 105 – specialist attendance	These costs were not actually applied in the financial estimates file, and the estimates presented in the submission could not be verified.
	$87.25 2.83 services/pt/yr	MBS item 56507 - CT scan	
	$16.95 8.5 services/pt/yr	MBS item 65070 – Blood test	

Source: {QunLOCK_Utilisation_and_cost_model_Nov2020.xlsx

3L = third line; BSC = Best supportive care; DUSC = drug utilisation sub-committee; GIST = gastrointestinal stromal tumours; MBS = Medicare Benefits Scheme; PBS = Pharmaceutical Benefits Scheme; PSD = Public Summary Document;

The redacted values correspond to the following ranges:

[1] *< 500*

6.64 The submission's approach to calculating doses and scripts per patient was overly complicated and poorly explained and appeared to assume that there would only be 28 days of treatment per month on treatment. This had the effect of underestimating the number of scripts per patient based on 11.50 months of treatment. After adjusting the calculations during the evaluation, the estimated total ripretinib scripts per treatment increased from 10.16 to 11.04. The submission's miscalculation underestimated total number of scripts per patient, and consequently, total costs to the PBS by approximately 8%.

6.65 During the evaluation, it was determined that the MBS costs presented in the submission only included costs specialist attendances (at an MBS rebate of 80%). MBS estimates were amended during the evaluation to include CT scan costs and blood test costs in line with the economic evaluation.

6.66 Table 16 presents the estimated use and financial implications.

Table 16: 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	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of scripts dispensed*	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Adjusted Total volumes**	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Estimated financial implications of ripretinib						
Cost to the PBS (Published Price)	[redacted][3]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
Cost to the PBS (Effective Price)	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Effective price with adjusted volumes* **	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Estimated financial implications for additional BSC due to longer estimated survival						
Cost to PBS	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]
Net financial implications						
Net cost to PBS (published price)	[redacted][3]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
Net cost to PBS (effective price)	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Net cost to PBS with adjusted volumes***	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Net cost to MBS	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]
Corrected MBS costs****	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][5]
Total cost to Government (published price)	[redacted][3]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
Total cost to Government (effective price)	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Net cost to health budget after PBS adjustment and MBS correction* **	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]

Source: Tables 4-4 and 4-6 to 4-10 of the submission. BSC = best supportive care; MBS = Medicare Benefits Scheme; PBS = Pharmaceutical Benefits Scheme

*assuming [redacted][1] scripts per initiating patients, and [redacted][1] scripts per continuing patients, for a total of [redacted][1] scripts

** The submission's approach to calculating doses and scripts per patient appeared to assume that there would only be 28 days of treatment per month on treatment. This had the effect of underestimating the number of scripts per patient based on 11.4 months of treatment. Adjusting cells P117 and P118 of worksheet 3.a scripts proposed to = 3*365/12 rather than 3*28. The estimated total scripts per treatment increases from [redacted][1] to [redacted][1]. This miscalculation underestimates total number of scripts per patient, and consequently, total costs to the PBS by approximately 8%. Assuming [redacted][1] scripts per initiating patients, and [redacted][1] scripts per continuing patients, for a total of [redacted][1] scripts

*** Indicates values calculated during the evaluation.

*** During the evaluation, it was determined that the MBS costs presented in the submission only included costs specialist attendances (at an MBS rebate of 80%). MBS estimates were amended during the evaluation to include CT scan costs and blood test costs in line with the economic evaluation.

Note: the submission's financial estimates model included initiating patients as non-whole numbers. For example, in Year 1, the model estimated that [redacted][1] patients would initiate. Though this was inappropriate it would not be expected to affect the model results substantially. This also explains why downstream calculations using the numbers in the tables do not match exactly.

The redacted values correspond to the following ranges:

[1] < 500

[2] 500 to < 5,000

[3] $10 million to < $20 million

[4] $20 million to < $30 million

[5] $0 to < $10 million

6.67 The submission estimated a total cost to government of $80 million to < $90 million over the first six years of listing, ranging from $10 million to < $20 million in year one and increasing to $$10 million to < $20 million by year six.

6.68 Errors in the estimation of ripretinib scripts per patient and costs to the MBS led to an underestimation of costs to Government by approximately $0 to < $10 million over the first six years of listing ($90 million to < $100 million without corrections versus $100 million to < $200 million with corrections). The PSCR acknowledged the errors in the estimation of script numbers and agreed with the corrected estimation of cost to government presented in the evaluation.

6.69 The PBAC noted PBS prescription data provided by the DUSC Secretariat which indicated between < 500 and <500 patients initiated treatment with sunitinib for GIST between 2015 and 2020 (2015: < 500 patients, 2016: < 500 patients, 2017: < 500 patients, 2018: < 500 patients, 2019: < 500 patients, 2020: < 500 patients). The PBAC recalled that sunitinib is continued until disease progression with the median time to tumour progression reported as 26.6 weeks (95% CI 16.0 to 32.1) in the A618-1004 trial (Sunitinib Public Summary Document (PSD), July 2009 PBAC Meeting). The PBAC considered these data indicate a lower proportion of imatinib patients go onto sunitinib in clinical practice than the 90% assumed in the submission. As a result, the PBAC considered the proposed number of patients treated with ripretinib was likely overestimated.

Quality Use of Medicines

6.70 The submission provided a copy of European Risk Management Plan for ripretinib and the Australian Specific Annex.

6.71 No further details of Quality use of medicines were presented.

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

7 PBAC Outcome

7.1 The PBAC did not recommend ripretinib for treatment of advanced gastrointestinal stromal tumour (GIST). The PBAC considered the claim of superior efficacy compared to best supportive care (BSC) was reasonable based on improvements in progression free survival (PFS) with the magnitude of gain in overall survival (OS) uncertain but clinically meaningful in the context of metastatic or unresectable GIST being a rare cancer with an unmet need for effective third line treatment. In addition, the PBAC considered the evidence presented indicated ripretinib had an acceptable safety profile. However, the PBAC considered the incremental cost-effectiveness ratio (ICER) was very high and uncertain at the proposed price. Furthermore, the PBAC considered

the proposed number of patients to be treated with ripretinib was likely overestimated.

7.2 The PBAC noted the input from individuals, health care professionals and organisations which highlighted the high clinical need for treatment options post imatinib and sunitinib. In addition, the PBAC noted the Medical Oncology Group of Australia's strong support for the submission.

7.3 The PBAC considered BSC to be an appropriate comparator.

7.4 The PBAC noted that the claim of superior comparative effectiveness compared to BSC was based on PFS and OS from the INVICTUS study (n = 129). The PBAC noted the significant improvement in the primary outcome of PFS for patients receiving ripretinib compared with BSC (HR 0.15; 95% CI 0.09 to 0.25; p<0.0001) with a gain in median PFS of 5.3 months. The PBAC noted that based on the pre-specified hierarchical testing plan, the submission was unable to claim a statistically significant difference for OS (HR 0.36; 95% CI 0.21 to 0.62). While acknowledging the OS data was immature (69% of ripretinib patients were censored), the PBAC agreed with the ESC that the OS difference was clinically meaningful in this rare cancer and unlikely to become less clinically meaningful with longer follow-up.

7.5 The PBAC noted that the INVICTUS trial enrolled patients from later lines of therapy (four or more lines of therapy; ≥4L) compared to the requested restriction (third line (3L) setting). The submission cited findings from a small phase 1 non-randomised dose escalation study (NCT02571036) to support the claim of comparable efficacy in the 3L setting to that observed in INVICTUS. Acknowledging the limitations of NCT02571036 the PBAC noted PFS and objective response rate (ORR) outcomes in the 3L GIST cohort (PFS = 8.3 months, ORR = 14.3%) exceeded those in the ≥4L ripretinib group in INVICTUS (median PFS: 6.3 months; ORR = 9.4%). On balance, the PBAC agreed with the ESC that clinically it was reasonable to assume that effectiveness in the 3L GIST setting would not be less than that observed in the ≥4L ripretinib group. The PBAC considered the claim of superior effectiveness compared with BSC was reasonable.

7.6 The PBAC noted that while the ripretinib arm of INVICTUS was associated with statistically significantly higher rates of several specific adverse events (see paragraph 6.33) only 8% of patients in that arm discontinued treatment due to an adverse event. The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data but agreed with ESC that ripretinib had an acceptable safety profile.

7.7 In the INVICTUS trial, 65.9% (29/44) of patients in the BSC arm crossed over to receive ripretinib after progression. The PBAC noted the cost-utility analysis presented assumed that these patients would receive treatment with ripretinib post progression (see paragraph 6.47). The PBAC agreed with the ESC that the assumption that patients in the BSC arm would receive post progression ripretinib was incorrect and strongly favoured ripretinib. Assuming no post progression ripretinib in either treatment arm,

the PBAC noted the ICER increased from $75,000 to < $95,000/QALY to $155,000 to < $255,000/QALY. As such, the PBAC considered the base case ICER to be substantially underestimated.

7.8 The pre-PBAC response indicated a willingness to reduce the price of ripretinib with the extent of the reduction considered acceptable to the sponsor not quantified. The PBAC acknowledged the sensitivity analysis as presented in paragraph 7.7 potentially underestimated the benefit of ripretinib due to use of the ITT OS results without adjustment for the 65.9% (29/44) of patients in the BSC arm receiving ripretinib. The PBAC considered given the high clinical need and noting that the benefit was potentially underestimated, that an ICER of approximately $75,000 to < $95,000/QALY would be required for the sensitivity analysis for ripretinib to be considered cost-effective. This took into account the fact that the small sample size in the control group (n=44, 29 of who received ripretinib on progression) would mean that any adjustment to the OS data for switching would be prone to statistical imprecision and subject to much uncertainty, such that it may not be helpful for decision-making.

7.9 The PBAC noted PBS prescription data provided by the DUSC Secretariat which indicated < 500 patients initiated treatment with sunitinib for GIST in 2020. The PBAC considered these data indicate a lower proportion of imatinib patients go onto sunitinib in clinical practice than the 90% assumed in the submission. As a result, the PBAC considered the proposed number of patients treated with ripretinib was likely overestimated.

7.10 The PBAC considered the outstanding issues may be addressed in a simple resubmission for ripretinib if the following changes were made, without any additional amendments to the economic evaluation or financial implications:

- A price reduction to achieve an ICER of approximately $75,000 to < $95,000/QALY based on the scenario outlined in paragraph 7.7.
- Revision of the assumption that 90% of imatinib patients go onto sunitinib in the financial estimates and recalculation of the financial implications using the revised ripretinib price.

7.11 The PBAC considered an early re-entry pathway would be acceptable if the resubmission addressed each of the points in the above paragraph with no further adjustment. The resubmission must be lodged by week 7 of the current PBAC cycle or the next cycle. If any of these terms are not acceptable to the sponsor, a standard re-entry pathway is available.

7.12 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 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.

9 Sponsor's Comment

Specialised Therapeutics (ST) are committed to working with the PBAC to make Qinlock available for refractory GIST patients via the Early Re-Entry pathway. If this subsequent application is unsuccessful, ST will make Qinlock available as a private prescription.