

7.09 RIPRETINIB, Tablet 50 mg, Qinlock[®], Specialised Therapeutics PM Pty Ltd.

1 Purpose

- 1.1 The early re-entry resubmission sought to list ripretinib with a General Schedule Authority Required listing for the treatment of advanced gastrointestinal stromal tumour (GIST) after failure of or intolerance to imatinib and sunitinib.
- 1.2 The resubmission was based on the PBAC advice from March 2021. This resubmission sought to address the issues raised by PBAC at that time; see table below.

Table 1: Summary of key matters to be addressed

Matter of concern	Response	Addressed?
A price reduction to achieve an ICER of approximately \$[REDACTED] ¹ /QALY based on the sensitivity analysis assuming no post progression ripretinib in either treatment arm.	A price reduction to achieve an ICER of approximately \$[REDACTED] ² /QALY assuming no post progression ripretinib in either treatment arm.	Partially – ICER is higher than \$[REDACTED] ¹ /QALY
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.	Approximately 47% of imatinib patients assumed to go onto sunitinib. Financial implications recalculated using the revised ripretinib price.	Y

Source: Paragraph 7.7 and 7.10 of the March 2021 PBAC Public Summary Document (PSD)

The redacted values correspond to the following ranges:

¹ \$75,000 to < \$95,000/QALY gained

² \$95,000 to < \$115,000/QALY gained

2 Background

- 2.1 Ripretinib was TGA registered on 13 July 2020 for the treatment of adult patients with advanced GIST who have received prior treatment with 3 or more kinase inhibitors, including imatinib.
- 2.2 The PICO from the resubmission is presented below.

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Table 2: Key components of the clinical issue addressed by the resubmission (as stated in the resubmission)

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 ($\geq 3L$) 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, p6 of the resubmission. BSC: best supportive care; GIST: gastrointestinal stromal tumours; HRQoL: health-related quality of life; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; TTP: time to progression.

For more detail on PBAC's view, see section 5 PBAC outcome.

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	No. of Rpts	Dispensed price for maximum quantity	Available brands
RIPRETINIB						
ripretinib 50 mg tablet, 90	NEW	1	90	1	Effective price: \$ Published price: \$16,318.90	Qinlock
Category / Program: GENERAL – General Schedule (Code GE)						
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners						
Restriction type:						
<input checked="" type="checkbox"/> Authority Required – non immediate assessment (written only)						
<input checked="" type="checkbox"/> Authority Required – immediate/real-time assessment (telephone/online PBS Authorities system)						
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.						
Indication: Metastatic or unresectable malignant gastrointestinal stromal tumour						
Treatment Phase: Initial treatment						
Clinical criteria						
<i>The condition must not be resectable</i>						
AND						
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						

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Clinical criteria:
Patient must have a WHO performance status of 2 or less
AND
Treatment criteria
<i>Patient must be undergoing treatment with this drug for the first time – retreatment/continuing treatment is not permitted under this listing;</i>
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 PBS Authority Application for Use in the Treatment of Gastrointestinal Stromal Tumour – Supporting Information Form
Prescribing Instructions: <i>State in this authority application the month and year of the last administered dose of each of: (i) imatinib, (ii) sunitinib.</i>
Administrative Advice: 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 7004
Administrative Advice: <i>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).</i>
Administrative Advice: Note Ripretinib is not PBS-subsidised for the treatment of patients with resectable malignant gastrointestinal stromal tumours.
Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction type: <input checked="" type="checkbox"/> Authority Required – immediate/real-time assessment (telephone/online PBS Authorities system)
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.
Indication: Metastatic or unresectable malignant gastrointestinal stromal tumour
Treatment Phase: Continuing treatment
Clinical criteria
<i>The condition must not be resectable</i>
AND
Clinical criteria:
<i>Patient must have received PBS-subsidised treatment with this drug for this condition</i>
AND
Clinical criteria:
The treatment must be as monotherapy
AND
Clinical criteria:
Patient must not have progressive disease while receiving treatment with this drug for this condition.
Patient must not have developed disease progression while receiving treatment with this drug for this condition.
AND

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Clinical criteria:
Patient must have a WHO performance status of 2 or less
Administrative Advice: 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 Consistent with the March 2021 submission the resubmission requested a special pricing arrangement.
- 3.3 In March 2021, the submission acknowledged that the requested restriction deviates from the TGA-approved labelled indication, which is for fourth or later line ($\geq 4L$) 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 ($\geq 3L$) setting listed on the PBS (regorafenib is not PBS-listed and salvage imatinib therapy is rarely used). As such, in March 2021 the submission stated that listing for ripretinib in the $\geq 4L$ setting would not be considered practical or consistent with clinical practice. At that time the ESC considered that 3L regorafenib was not routinely used in Australia due to cost (as it is not PBS-listed) and toxicity (paragraph 3.4, ripretinib Public Summary Document (PSD), March 2021 PBAC Meeting). In March 2021, the PBAC considered that, on balance, it was reasonable to assume that ripretinib effectiveness in the 3L GIST setting would not be less than that observed in the $\geq 4L$ ripretinib group. In addition, the PBAC considered the claim of superior effectiveness compared with BSC [...in 3L treatment of patients with metastatic or unresectable GIST...] was reasonable (paragraph 7.5, ripretinib PSD, March 2021 PBAC Meeting). The PBAC considered the restriction should state the condition must have progressed with all drugs PBS listed specifically for this PBS indication unless the patient has, or is expected to have, an intolerance to a drug PBS listed specifically for this indication. This could be reviewed if further drugs were to become listed for GIST where they are indicated for use after ripretinib.
- 3.4 The PBAC considered the Administrative Advice stating that ripretinib is not PBS subsidised for the treatment of patients with resectable malignant GIST should be included as a clinical criterion.
- 3.5 The PBAC also considered a treatment criterion requiring that the patient be undergoing treatment with ripretinib for the first time be included in the Initial treatment phase to prevent subsidy through that treatment phase on more than one occasion.

- 3.6 The PBAC considered that an Authority Required (telephone/online) listing was appropriate for both initial and continuing treatment based on the low level of complexity of the PBS restrictions.

For more detail on PBAC’s view, see section 5 PBAC outcome.

4 Consideration of the evidence

Sponsor hearing

- 4.1 There was no hearing for this item.

Consumer comments

- 4.2 The PBAC noted and welcomed the input from individuals (3), health care professionals (4) and organisations (2) via the Consumer Comments facility on the PBS website. The comments from individuals as well as those from the GIST Community Patient Submission described the fear and anxiety associated with not having additional GIST treatment options once progression occurs. The comments also highlighted the impact of GIST on families as a result of the typically younger patient population affected by the condition. The comments described a range of benefits of treatment with ripretinib including the ability to control disease progression and maintain quality of life of patients. The PBAC also noted that in March 2021 input was received from 98 individuals, 3 health care professionals and 4 organisations (paragraph 6.2, ripretinib PSD, March 2021 PBAC Meeting).
- 4.3 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.

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

Comparative effectiveness

- 4.4 As per the March 2021 submission, the resubmission was based on a single randomised (2:1) controlled trial (INVICTUS, n=129) comparing ripretinib (+ best supportive care (BSC)) to placebo (+ BSC).
- 4.5 In March 2021, the PBAC noted that the claim of superior comparative effectiveness compared to BSC was based on progression free survival (PFS) and overall survival (OS) from the INVICTUS study. At that time, 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. In March 2021, 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 (paragraph 7.4, ripretinib PSD, March 2021 PBAC meeting).
- 4.6 The resubmission stated that since the March 2021 submission, an updated survival analysis has become available (Table 3, Figure 1). The resubmission noted that, although data are still not mature, an additional 3.1 month improvement in median OS for the ripretinib arm was seen in the most recent data cut, from a median OS of 15.1 months to a median OS of 18.2 months. The resubmission stated that patients treated with ripretinib lived for approximately 12 months longer than those in the placebo arm.

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Table 3. Summary of OS results (ITT population double blind and open label period)

	Ripretinib (n=85)	Placebo (n=44)
July 2021 resubmission (August 2020 data cut)		
OS event, n (%)	46 (54%)	36 (82%)
Patients censored, n (%)	39 (46%)	8 (18%)
Median OS, months (95% CI)	18.2 (13.1, 30.7)	6.3 (4.1, 10.0)
HR (95% CI)*	0.41 (0.26, 0.65)	
P-value	0.0002	
March 2021 submission (March 2020 data cut)		
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	

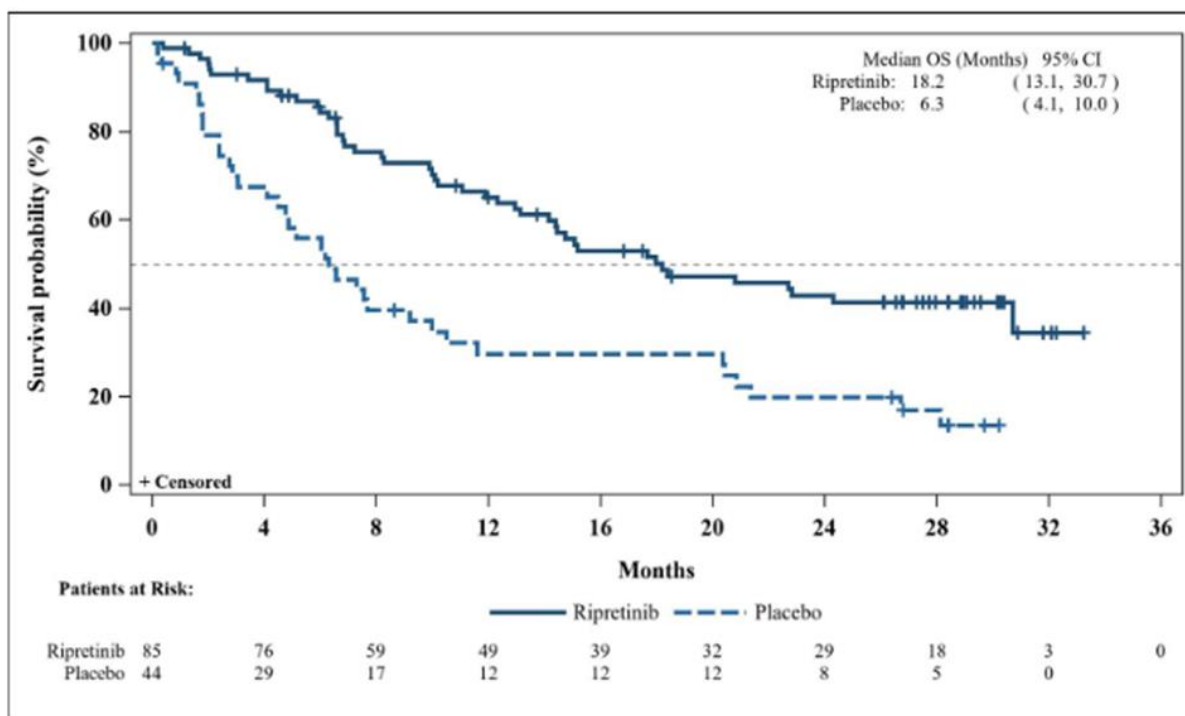
Source: Table 2.16, p70 of the resubmission, Table 5, p10 ripretinib Public Summary Document (PSD), March 2021 PBAC meeting
 CI: confidence interval; HR: hazard ratio; ITT: intent-to-treat; OS: overall survival

* 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 hierarchical 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 and the date of death or censored at the date of last follow-up; patient groups are based on the treatment initially assigned.

Figure 1. KM Overall survival results in the double blind and open - label periods of INVICTUS (August 2020 data cut)



CI: confidence interval; 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 2-8, p71 of the resubmission

Economic analysis

- 4.7 In the key trial (INVICTUS), 65.9% (29/44) of patients in the BSC arm crossed over to receive ripretinib after progression. At the March 2021 meeting the PBAC noted the cost-utility analysis presented assumed that these patients would receive treatment with ripretinib post progression. 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, in March 2021 the PBAC considered the base case ICER to be substantially underestimated (paragraph 7.7, ripretinib PSD, March 2021 PBAC meeting).
- 4.8 The March 2021 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. At that time the PBAC acknowledged the sensitivity analysis as presented in paragraph 4.7 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. In March 2021, 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 (paragraph 7.8, ripretinib PSD, March 2021 PBAC meeting).
- 4.9 The resubmission offered a price reduction from the \$ [REDACTED] per pack (90 tablets) requested in the March 2021 submission to \$ [REDACTED] per pack (a [REDACTED] % reduction). However, the resubmission stated they were unable to meet the PBAC's preferred target of \$75,000 to < \$95,000/QALY in the base case of the model that excludes the costs of post-progression ripretinib.
- 4.10 Table 4 presents total costs, LYs, QALYs and incremental cost per QALY gained for ripretinib versus BSC. In the base case analysis, ripretinib generates 0.86 incremental QALYs and \$75,000 to < \$95,000 incremental costs over a seven year time horizon compared with BSC, resulting in an ICER of \$95,000 to < \$115,000/QALY gained.

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Table 4: Results of the economic evaluation

Component	Ripretinib	BSC	Increment
Costs	\$ [REDACTED]	\$13,879	\$ [REDACTED] ¹
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 preparation of the submission overview

Source: Table 3-25 of the resubmission, QINLOCK_Cost_Effectiveness_Model_April2021.xlsm.

The redacted values correspond to the following ranges:

¹ \$75,000 to < \$95,000/QALY gained

² \$95,000 to < \$115,000/QALY gained

4.11 The resubmission, and subsequently the pre-PBAC response, argued that the model was not updated to reflect the almost 3.1 month additional improvement in median OS seen in the August 2020 data cut (Table 3) compared to the March 2020 data cut and therefore may underestimate the true treatment benefit of ripretinib.

Drug cost/patient/course

4.12 The estimated drug cost/patient per course of ripretinib based on the mean 49.82 weeks of treatment used in the model was \$ [REDACTED].

Estimated PBS usage & financial implications

4.13 The March 2021 submission took an epidemiological approach as well as a market share approach to support to the epidemiological estimates (paragraph 6.62, ripretinib PSD, March 2021 PBAC meeting).

4.14 The evaluation of the March 2021 submission considered the 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 evaluation of the March 2021 submission considered this miscalculation underestimated total number of scripts per patient, and consequently, total costs to the PBS by approximately 8% (paragraph 6.64, ripretinib PSD, March 2021 PBAC meeting).

4.15 During the March 2021 evaluation, it was determined that the MBS costs presented in the submission only included costs associated with specialist attendances (at an MBS rebate of 80%). MBS estimates were amended during the March 2021 evaluation to include CT scan costs and blood test costs in line with the economic evaluation (paragraph 6.65, ripretinib PSD, March 2021 PBAC meeting).

4.16 At its March 2021 meeting, 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

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patients go onto sunitinib in clinical practice than the 90% assumed in the submission. As a result, in March 2021 the PBAC considered the proposed number of patients treated with ripretinib was likely overestimated (paragraph 7.9, ripretinib PSD, March 2021 PBAC meeting).

4.17 The resubmission provided revised financial estimates which:

- Adjusted the number of days per month on treatment in the estimation of scripts per treatment as per the March 2021 evaluation (see paragraph 4.11).
- Included CT scan costs and blood test costs in MBS estimates in line with the economic evaluation (see paragraph 4.12).
- Revised the assumption of the proportion of imatinib patients who go onto sunitinib from 90% to 46.85% (see paragraph 4.13).
- Recalculated the financial implications using the revised ripretinib price (see paragraph 4.6).

4.18 Table 5 presents the estimated use and financial implications.

Table 5: Estimated use and financial implications (effective price)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Number of scripts dispensed ^a	█ ¹	█ ²	█ ²	█ ²	█ ²	█ ²
Estimated financial implications of ripretinib						
Cost to PBS	\$ █ ³	\$ █ ³	\$ █ ³	\$ █ ³	\$ █ ³	\$ █ ³
Estimated financial implications for additional BSC due to longer estimated survival						
Cost to PBS	\$ █ ³	\$ █ ³	\$ █ ³	\$ █ ³	\$ █ ³	\$ █ ³
Net financial implications						
Net cost to PBS	\$ █ ³	\$ █ ³	\$ █ ³	\$ █ ³	\$ █ ³	\$ █ ³
Net cost to MBS	\$ █ ³	\$ █ ³	\$ █ ³	\$ █ ³	\$ █ ³	\$ █ ³
Net cost to PBS/MBS	\$ █ ³	\$ █ ³	\$ █ ³	\$ █ ³	\$ █ ³	\$ █ ³
Previous submission March 2021						
Net cost to PBS with adjusted volumes	\$ █ ³	\$ █ ³	\$ █ ³	\$ █ ³	\$ █ ³	\$ █ ³
Net cost to health budget after PBS adjustment and MBS correction	\$ █ ³	\$ █ ³	\$ █ ³	\$ █ ³	\$ █ ³	\$ █ ³

^a assuming 2.03 scripts per initiating patients, and 9.01 scripts per continuing patients, for a total of 11.04 scripts

Source: Tables 4-4 and 4-6 to 4-10 of the resubmission. Table 16, p27 ripretinib Public Summary Document (PSD), March 2021 PBAC meeting

BSC = best supportive care; MBS = Medicare Benefits Scheme; PBS = Pharmaceutical Benefits Scheme

The redacted values correspond to the following ranges:

¹ < 500

² 500 to < 5,000

³ \$0 to < \$10 million

⁴ \$10 million to < \$20 million

- 4.19 The resubmission estimated a net cost to the PBS of \$0 to < \$10 million in Year 6 of listing, with a total net cost to the PBS of \$20 million to < \$30 million over the first 6 years of listing.

For more detail on PBAC's view, see section 5 PBAC outcome.

5 PBAC Outcome

- 5.1 The PBAC recommended the Authority Required (immediate/real-time assessment) listing of ripretinib for treatment of advanced gastrointestinal stromal tumour (GIST). The resubmission provided a revised price and financial estimates in response to previous concerns raised by the PBAC. In addition, the resubmission included updated survival data from the key clinical trial. The PBAC considered the revised incremental cost-effectiveness ratio (ICER) was high but likely overestimated due to the survival benefit being underestimated as a result of using the less favourable earlier data cut and the control group crossing over to receive treatment with ripretinib. The PBAC considered the ICER was acceptable in the context of advanced GIST being a rare cancer with an unmet need for effective third line treatment. In addition, the PBAC considered the revised financial estimates addressed previous concerns.
- 5.2 The PBAC is satisfied that ripretinib provides, for some patients, a significant improvement in efficacy over best supportive care (BSC). The PBAC's recommendation for listing was based on, among other matters, its assessment, as described above, that the cost-effectiveness of ripretinib would be acceptable at the price proposed in the resubmission.
- 5.3 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 (see paragraph 4.3).
- 5.4 The PBAC recalled that in its March 2021 consideration of ripretinib it had previously considered the claim of superior effectiveness compared with BSC was reasonable (paragraph 7.5, ripretinib PSD, March 2021 PBAC meeting). The PBAC also recalled that it had considered that the claim of non-inferior comparative safety was not adequately supported by the data presented in March 2021 but that ripretinib had an acceptable safety profile (paragraph 7.6, ripretinib PSD, March 2021 PBAC meeting).
- 5.5 The PBAC noted the resubmission provided updated survival data reporting an additional 3.1 month improvement in median overall survival (OS) for the ripretinib arm in the August 2020 data cut, from a median OS of 15.1 months in the ripretinib arm to a median OS of 18.2 months in the ripretinib arm.
- 5.6 The PBAC noted the resubmission provided a price reduction resulting in an ICER of \$95,000 to < \$115,000/QALY using the base case of the model that excluded the costs

of post-progression ripretinib. The PBAC recalled that in March 2021 the Committee had considered a price reduction to achieve an ICER of approximately \$75,000 to < \$95,000/QALY would be appropriate (see Table 1). The PBAC noted the base case provided in the resubmission had no adjustment for crossover (see paragraph 4.7) and was not updated to reflect the improvement in OS seen in the August 2020 data cut. As such, the PBAC considered the model underestimated the treatment benefit of ripretinib and hence the revised ICER was high but likely overestimated. Overall, the PBAC considered the revised ICER was acceptable in the context of advanced GIST being a rare cancer with an unmet need for effective third line treatment.

- 5.7 The PBAC noted the resubmission provided financial estimates which revised the number of scripts per patient, included MBS costs, amended the proportion of imatinib patients who go onto sunitinib and recalculated the financial implications using the ripretinib price proposed in the resubmission (see paragraph 4.17). The PBAC considered the revised financial estimates addressed the concerns raised by the Committee in March 2021.
- 5.8 The PBAC recommended that ripretinib should not be treated as interchangeable with any drugs.
- 5.9 The PBAC advised that ripretinib is not suitable for prescribing by nurse practitioners.
- 5.10 The PBAC recommended that the Early Supply Rule should apply.
- 5.11 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for ripretinib:
 - a) The treatment is expected to provide a substantial and clinically relevant improvement in efficacy over alternative therapies.
 - b) The treatment is not expected to address a high and urgent unmet clinical need due to availability of earlier line of treatment options of imatinib and sunitinib.
 - c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.
- 5.12 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

6 Recommended listing

6.1 Add new medicinal product as follows:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
RIPRETINIB ripretinib 50 mg tablet, 90	NEW	1	90	1	Qinlock
Restriction Summary [New 1] / Treatment of Concept: [New 2]					
	Category / Program: GENERAL – General Schedule (Code GE)				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
	Restriction type: <input checked="" type="checkbox"/> Authority Required – immediate/real-time assessment (telephone/online PBS Authorities system)				
	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.				
	Indication: Metastatic or unresectable malignant gastrointestinal stromal tumour				
	Treatment Phase: Initial treatment				
	Clinical criteria				
	The condition must not be resectable				
	AND				
	Clinical criteria:				
	The treatment must be as monotherapy				
	AND				
	Clinical criteria:				
	The condition must have progressed despite treatment with all drugs PBS-listed specifically for this PBS-indication; or				
	The condition must have progressed despite each of: (i) treatment with a drug PBS-listed specifically listed for this PBS-indication, (ii) an intolerance/expected intolerance to all other drugs PBS-listed for this specific PBS-indication.				
	AND				
	Clinical criteria:				
	Patient must have a WHO performance status of 2 or less				
	AND				
	Treatment criteria				
	Patient must be undergoing treatment with this drug for the first time – retreatment/continuing treatment is not permitted under this listing;				
	Administrative Advice: 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: Currently PBS-listed drugs with the indication of: 'metastatic or unresectable malignant gastrointestinal stromal tumour' are: imatinib and sunitinib				

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Restriction Summary [New 3] / Treatment of Concept: [New 4]	
	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction type: <input checked="" type="checkbox"/> Authority Required – immediate/real-time assessment by Services Australia
	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.
	Indication: Metastatic or unresectable malignant gastrointestinal stromal tumour
	Treatment Phase: Continuing treatment
	Clinical criteria
	The condition must not be resectable
	AND
	Clinical criteria:
	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 developed disease progression while receiving treatment with this drug for this condition.
	Administrative Advice: 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).

This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

7 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.

8 Sponsor’s Comment

The sponsor had no comment.