

7.09 ASCIMINIB, Tablet 20 mg, Tablet 40 mg, Scemblix[®], Novartis Pharmaceuticals Australia Pty Limited

1 Purpose

- 1.1 The early re-entry resubmission sought to list asciminib with a General Schedule Authority Required listing (Telephone/Online) for the treatment of (i) patients with Philadelphia chromosome-positive chronic myeloid leukaemia (Ph+ CML) in chronic phase (CP), who had been previously treated with two or more tyrosine kinase inhibitors (TKIs); and (ii) patients with Ph+ CML in CP, who had been previously treated with one or more TKIs and harbouring the T315I mutation.
- 1.2 The resubmission responded to the PBAC recommendation from July 2022. The resubmission addressed the issues raised by PBAC (Table 1).

Table 1: Summary of key matters to be addressed

Matter of concern	Response	Addressed?
Requested listing for T315I mutation patients		
<ul style="list-style-type: none"> A separate restriction for patients with the T315I mutation (paragraphs 7.5 and 7.6, July 2022 PSD). <p>The PBAC considered in July 2022 it would be necessary for asciminib to have 2 PBS restrictions: one for the Ph+ CML in CP population who have failed/are intolerant to 2 or more TKIs, and another for Ph+ CML in CP patients with the T315I mutation who have failed/are intolerant to imatinib or dasatinib or nilotinib.</p>	<p>The resubmission:</p> <ul style="list-style-type: none"> Accepted the PBAC's advice to specifically allow access to asciminib for patients previously treated with one or more TKIs and harbouring the T315I mutation via a separate restriction; Proposed restrictions in the T315I mutation population for initial treatment, first and subsequent continuing treatment, and grandfathered patients. 	<p>Yes, noting that patients with the T315I mutation receive a higher dose (400 mg daily) compared with non-T315I-mutation patients (80 mg daily).</p>
Comparator for both T315I and non-315I mutation patients		
<ul style="list-style-type: none"> A clinical comparison against ponatinib for patients with the T315I mutation, and benchmarking against second generation TKIs for the economic evaluation (paragraphs 7.7 and 7.8, July 2022 PSD). <p>The PBAC considered in July 2022 that ponatinib is a relevant comparator for patients with the T315I mutation, however noted that the July 2022 submission did not present any comparative evidence between asciminib and ponatinib in this patient group. The PBAC considered that benchmarking against second generation TKIs was a reasonable basis for establishing a cost-effective price for asciminib.</p>	<p>The resubmission:</p> <ul style="list-style-type: none"> Presented a clinical comparison of asciminib and ponatinib using the T315I mutation cohorts from the X2101 and PACE trials, respectively; Presented an economic evaluation for non-T315I patients involving benchmarking against second generation TKIs. 	<p>Yes, although the resubmission did not specifically redefine the comparator for asciminib.</p>

Matter of concern	Response	Addressed?
Clinical data for T315I mutation patients		
<ul style="list-style-type: none"> • Presentation of clinical data to support asciminib is non-inferior to ponatinib in patients with the T315I mutation (paragraph 7.10, July 2022 PSD). <p>The asciminib evidence from the ASCSEMBL trial was obtained in patients without a T315I mutation. It is likely that almost all current ponatinib use is in patients with this mutation and the PBAC considered in July 2022 that data from patients with the T315I mutation treated with asciminib in the CABL001X2101 trial is relevant.</p>	<p>The resubmission:</p> <ul style="list-style-type: none"> • Presented an unanchored and unadjusted clinical comparison of asciminib and ponatinib using the T315I mutation cohorts from the X2101 and PACE trials, respectively. 	<p>Yes. The resubmission claimed that asciminib has non-inferior efficacy and at least non-inferior safety compared with ponatinib in T315I mutation patients.</p>
Economic model for non-T315I mutation patients, extended to T315I mutation patients		
<ul style="list-style-type: none"> • An economic evaluation in non-T315I mutation patients that reflects benchmarking against the second generation TKIs, nilotinib and dasatinib (paragraph 7.13, July 2022 PSD). <p>The PBAC considered in July 2022 that the CMA of asciminib against nilotinib and dasatinib should be based on the equi-effective doses outlined in paragraph 7.12 of the July PSD, a two year time horizon, and the revised monitoring costs. The PBAC considered there should be no cost offsets for the treatment of AEs associated with nilotinib. The PBAC noted that when benchmarking ponatinib with dasatinib and nilotinib, the relative use of each should inform the overall weighted price.</p>	<p>The resubmission:</p> <ul style="list-style-type: none"> • Presented a revised CMA against nilotinib and dasatinib for non-T315I mutation patients using the equi-effective doses recommended by the PBAC, with revised monitoring costs, and no cost offsets for the treatment of AEs associated with nilotinib. The resubmission proposed a weighted price derived from the relative use of dasatinib and nilotinib shown in the 2022 DUSC Secretariat analysis of 3L use of TKIs. • Proposed that the effective EMP for the non-T315I mutation population (\$█ per pack of 20mg/40mg capsules) should cover all asciminib usage on the PBS, including in any T315I mutation patients who receive PBS treatment. 	<p>Yes. A proposed EMP of \$█ in the resubmission represents a █% reduction in price compared to the July 2022 submission.</p>
Financial estimates for both T315I and non-315I mutation patients		
<ul style="list-style-type: none"> • Recalculation of the financial implications incorporating the advice in paragraph 7.14 July 2022 PSD). <p>The PBAC nominated the following issues to be addressed:</p> <ul style="list-style-type: none"> • The predicted growth in prevalent patients receiving a third TKI; • The predicted distribution of use of TKIs across the prevalent patients; • The uptake of asciminib, including the relative substitution of each of the TKIs. 	<p>The resubmission:</p> <ul style="list-style-type: none"> • Stated that the predicted growth in prevalent patients receiving a third TKI should remain unchanged; • Revised predicted distribution of use of TKIs across the prevalent patients; • Revised the uptake of asciminib; the relative substitution of each of the TKIs was based on the DUSC Secretariat analysis. 	<p>Yes, although the estimates are subject to uncertainty.</p>

Source: Background Section, p7 of the submission; Section 7, asciminib PSD, July 2022 PBAC meeting.

AE = adverse event; CMA = cost minimisation approach; CP = chronic phase; EMP = ex-manufacturer price; 3L = third line; Ph+ CML = Philadelphia chromosome-positive chronic myeloid leukaemia; PSD = Public Summary Document; TKI = tyrosine kinase inhibitor.

1.3 The PICO from the July 2022 submission is presented in Table 2. The updated PICO for the resubmission is added in italics and deletions are crossed out with strikethrough.

Table 2: Key components of the clinical issue addressed by the submission

Component	Description
Population	Adult patients with CML-CP who have failed or are intolerant of at least 2 TKIs; <i>Adult patients with CML-CP and the T315I mutation who have failed or are intolerant to imatinib or dasatinib or nilotinib</i>
Intervention	Asciminib 80 mg once daily or 40 mg twice daily
Comparator	Main comparator: Nilotinib Supplementary comparator: ponatinib
Outcomes	MMR, CCyR
Clinical claim	Non-inferior efficacy and superior safety compared with nilotinib; Non-inferior efficacy and superior <i>at least non-inferior</i> safety compared with ponatinib

Source: Table 1, asciminib PSD, July 2022 PBAC meeting. Italics and strikethrough added by the Secretariat.

CCyR = complete cytogenetic response; CML-CP = chronic phase chronic myeloid leukaemia; MMR = major molecular response; TKI = tyrosine kinase inhibitor.

2 Background

Registration status

2.1 Asciminib was TGA registered on 15 July 2022 for the following indication.

SCSEMBLIX is indicated for the treatment of patients 18 years of age and above with:

- Philadelphia chromosome-positive chronic myeloid leukaemia (Ph+ CML) in chronic phase (CP) previously treated with two or more tyrosine kinase inhibitors.
- Ph+ CML in CP with the T315I mutation.

Previous consideration

2.2 The PBAC considered at the July 2022 meeting that non-inferior efficacy of asciminib against nilotinib is likely supported based on the limited evidence available (paragraph 7.9, asciminib Public Summary Document [PSD], July 2022); however, the PBAC did not support the claim of superior safety to nilotinib (paragraph 7.11, asciminib PSD). The resubmission acknowledged this outcome, but did not re-specify the clinical safety claim for asciminib compared with nilotinib.

2.3 The PBAC considered at the July 2022 meeting that non-inferior efficacy and superior safety of asciminib compared to ponatinib were not supported based on the evidence from the ASCEMBL and PACE trials (paragraphs 7.10 and 7.11, asciminib PSD, July 2022). The indirect treatment comparison (ITC) was vulnerable to differences in baseline characteristics that prognostically favoured asciminib over ponatinib. Further, the PBAC noted that asciminib evidence from the ASCEMBL trial was obtained in patients without a T315I mutation. The PBAC considered that data from patients with the T315I mutation treated with asciminib in the CABL001X2101 (X2101) trial are relevant to this clinical claim.

- 2.4 The PBAC considered the outstanding issues could be resolved in a simple resubmission for asciminib using the early re-entry pathway, including the following changes (paragraph 7.15, asciminib PSD, July 2022):
- A separate restriction for patients with the T315I mutation.
 - Presentation of clinical data to support asciminib is non-inferior to ponatinib in patients with the T315I mutation.
 - An economic evaluation that reflects benchmarking against the second generation TKIs, nilotinib and dasatinib, in patients without the T315I mutation.
 - Recalculation of the financial implications.

For more detail on PBAC's view, see section 6 PBAC outcome.

3 Requested listing

- 3.1 The resubmission accepted the Secretariat's proposed amendments to the restriction for adult patients with CML-CP [without the T315I mutation] who have failed or are intolerant to at least 2 prior TKIs, as presented in the PSD for the July 2022 meeting. The recommended dose for asciminib in this patient group is 80 mg taken orally once daily or 40 mg twice daily. The listing is for asciminib 20 mg and 40 mg tablets, each marketed in a pack containing 60 tablets corresponding to one month's treatment, with a request for five repeats to provide patients with up to six months of treatment. No additional restrictions were presented in the resubmission for this patient population.
- 3.2 The resubmission accepted the PBAC's advice to specifically allow access to asciminib for patients previously treated with one or more TKIs and harbouring the T315I mutation via a separate restriction. The recommended dose for asciminib in this patient group is 200 mg twice daily. A listing is requested for asciminib 40 mg tablets, marketed in a pack containing 60 tablets. Five packs of 60 tablets of asciminib 40 mg corresponds to one month's treatment at the recommended dose, with a request for five repeats to provide patients with up to six months of treatment.
- 3.3 The requested listings for patients previously treated with one or more TKIs and harbouring the T315I mutation are presented below. Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

Public Summary Document – November 2022 PBAC Meeting

Name, manner of administration and form	Max. Qty. (packs)	Max. Qty. (units)	No. of Rpts	Proprietary name and manufacturer
Asciminib 40 mg film coated tablet, 60	5	300	5	Scemblix, Novartis Australia Pty Ltd

Initial treatment (≥1 prior TKI and T315I mutation)

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 (telephone/online application avenues)
Administrative Advice: Special Pricing Arrangements apply
Episodicity: Chronic
Condition: Chronic myeloid leukaemia
Indication: Chronic myeloid leukaemia
Treatment Phase: Initial treatment
Clinical criteria: The treatment must be the sole PBS-subsidised therapy for this condition
AND
Clinical criteria: The condition must be in the chronic phase
AND
Clinical criteria: Patient must be expressing the T315I mutation confirmed through a bone marrow biopsy pathology report
AND
Clinical criteria: Patient must have failed an adequate trial of imatinib, dasatinib or nilotinib <i>confirmed through a pathology report from an Approved Pathology Authority</i>
Prescribing Instructions: Prescribing Instructions: Failure of an adequate trial of a tyrosine kinase inhibitor is defined as: 1. Lack of response defined as either: (i) failure to achieve a haematological response after a minimum of 3 months therapy; or (ii) failure to achieve any cytogenetic response after a minimum of 6 months therapy as demonstrated on bone marrow biopsy by presence of greater than 95% Philadelphia chromosome positive cells; or (iii) failure to achieve or maintain a major cytogenetic response or a peripheral blood BCR-ABL level of less than 1% after a minimum of 12 months therapy; OR 2. Loss of a previously documented major cytogenetic response (demonstrated by the presence of greater than 35% Ph positive cells on bone marrow biopsy), during ongoing tyrosine kinase inhibitor (TKI) therapy; OR 3. Loss of a previously demonstrated molecular response (demonstrated by peripheral blood BCR-ABL levels increasing consecutively in value by at least 5 fold to a level of greater than 0.1% confirmed on a subsequent test), during ongoing tyrosine kinase inhibitor (TKI) therapy; OR 4. Development of accelerated phase or blast crisis in a patient previously prescribed a tyrosine kinase inhibitor for any phase of chronic myeloid leukaemia; OR Accelerated phase is defined by the presence of 1 or more of the following: 1. Percentage of blasts in the peripheral blood or bone marrow greater than or equal to 15% but less than 30%; or

2. Percentage of blasts plus promyelocytes in the peripheral blood or bone marrow greater than or equal to 30%, provided that blast count is less than 30%; or
 3. Peripheral basophils greater than or equal to 20%; or
 4. Progressive splenomegaly to a size greater than or equal to 10 cm below the left costal margin to be confirmed on 2 occasions at least 4 weeks apart, or a greater than or equal to 50% increase in size below the left costal margin over 4 weeks; or
 5. Karyotypic evolution (chromosomal abnormalities in addition to a single Philadelphia chromosome).
- Blast crisis is defined as either:
1. Percentage of blasts in the peripheral blood or bone marrow greater than or equal to 30%; or
 2. Extramedullary involvement other than spleen and liver.

First continuing treatment (≥1 prior TKI and T315I mutation)

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction Type: <input checked="" type="checkbox"/> Authority Required – Streamlined
Administrative Advice: Special Pricing Arrangements apply
Episodicity: Chronic
Condition: Chronic myeloid leukaemia
Indication: Chronic myeloid leukaemia
Treatment Phase: First continuing treatment
Clinical criteria: Patient must have previously been issued with an authority prescription for this drug for this condition under the initial treatment restriction
Note there is a contradiction here -AND
Clinical criteria: Patient must have previously demonstrated to be expressing the T315I mutation confirmed through a bone marrow biopsy pathology report
AND
Clinical criteria: The treatment must be the sole PBS-subsidised therapy for this condition
AND
Clinical criteria: Patient must have demonstrated a major cytogenetic response; OR Patient must have demonstrated a peripheral blood level of BCR-ABL of less than 1%

Subsequent continuing treatment (≥1 prior TKI and T315I mutation)

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction Type: <input checked="" type="checkbox"/> Authority Required – Streamlined
Administrative Advice: Special Pricing Arrangements apply
Episodicity: Chronic

Public Summary Document – November 2022 PBAC Meeting

Condition: Chronic myeloid leukaemia
Indication: Chronic myeloid leukaemia
Treatment Phase: Subsequent continuing treatment
Clinical criteria: Patient must have previously received PBS-subsidised treatment with this drug for this condition under the First continuing treatment restriction
AND
Clinical criteria: Patient must have previously demonstrated to be expressing the T315I mutation confirmed through a bone marrow biopsy pathology report
AND
Clinical criteria: The treatment must be the sole PBS-subsidised therapy for this condition
AND
Clinical criteria: Patient must have maintained a major cytogenetic response at 12 month intervals; OR Patient must have maintained a peripheral blood level of BCR-ABL of less than 1% at 12 month intervals

Grandfather patients (≥1 prior TKI and T315I mutation)

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction Type: <input checked="" type="checkbox"/> Authority Required – Streamlined
Administrative Advice: Special Pricing Arrangements apply
Episodicity: Chronic
Condition: Chronic myeloid leukaemia
Indication: Chronic myeloid leukaemia
Treatment Phase: Grandfather
Clinical criteria: Patient must have previously received non-PBS subsidised with this drug for this condition prior to [list date]
AND
Clinical criteria: Patient must have previously demonstrated to be expressing the T315I mutation confirmed through a bone marrow biopsy pathology report
AND
Clinical criteria: The treatment must be the sole PBS-subsidised therapy for this condition
AND
Clinical criteria: The condition must be in the chronic phase
AND
Clinical criteria: Patient must have demonstrated a major cytogenetic response; OR Patient must have demonstrated a peripheral blood level of BCR-ABL of less than 1%

For more detail on PBAC’s view, see section 6 PBAC outcome.

4 Comparator

- 4.1 The July 2022 submission nominated nilotinib as the main comparator; the submission stated this was based on an analysis of a 10% PBS sample of TKI sequences showing that nilotinib was used in the largest number of patients receiving a third TKI. Ponatinib was nominated as a supplementary comparator; the submission stated it was likely to be the most used TKI in patients receiving a fourth TKI.
- 4.2 The PBAC considered at the July 2022 meeting that defining the comparator was complex due to the change in the use of TKIs over the last 24-48 months, whereby the second generation TKIs are increasingly being used first and second line, and imatinib is increasingly the third TKI prescribed (paragraph 7.7, asciminib PSD, July 2022). The PBAC considered the analyses based on the 10% PBS sample which looked at the pattern of use of TKIs were difficult to interpret. The analysis of the individual treatment sequences was limited by the small sample size and lack of applicability to current clinical practice given it relied on patients initiating treatment back to 2016. The analysis of the proportion of patients on a third or later TKI was limited because it used a prevalence approach rather than considering initiating patients and patients are unlikely to switch TKI treatment unless they experience treatment failure or intolerance.
- 4.3 The PBAC considered in July 2022 the treatment replaced or displaced by asciminib would depend on the clinical scenario and could include a second generation TKI (nilotinib or dasatinib), imatinib, ponatinib (primarily for patients with T315I mutation) or a non-TKI therapy including allogeneic transplantation. The PBAC considered that, for some patients, asciminib likely provides a significant improvement in efficacy over imatinib, and as an additional TKI with a different mechanism of action, asciminib likely provides a significant improvement in efficacy and/or reduction in toxicity over standard of care (non-TKI therapy) for patients who have either failed, or are unable to tolerate, both dasatinib and nilotinib. In this context, the PBAC considered that the comparison presented in the July 2022 submission of asciminib versus nilotinib was informative but advised that a resubmission should reflect benchmarking against the second generation TKIs, nilotinib and dasatinib (paragraph 7.7, asciminib PSD, July 2022).
- 4.4 The PBAC considered at the July 2022 meeting that ponatinib is a relevant comparator for patients with the T315I mutation, however noted that the submission did not present any comparative evidence between asciminib and ponatinib in this patient group (paragraph 7.8, asciminib PSD, July 2022).
- 4.5 The resubmission did not specifically re-define the comparator for asciminib; however, it presented clinical data for a comparison in the T315I mutation population of asciminib vs ponatinib, and it presented an economic evaluation in the non-T315I mutation population for both asciminib versus nilotinib and asciminib versus dasatinib.

For more detail on PBAC's view, see section 6 PBAC outcome.

5 Consideration of the evidence

- 5.1 As an early re-entry resubmission, the clinical evidence has not been independently evaluated.

Sponsor hearing

- 5.2 There was no hearing for this item.

Consumer comments

- 5.3 The PBAC noted that no consumer comments were received for this item. The PBAC previously noted and welcomed the input from a health care professional and two organisations (The Leukemia Foundation and Rare Cancers Australia) via the Consumer Comments facility on the PBS website in relation to consideration of asciminib at the July 2022 PBAC meeting (paragraph 6.2, July 2022 PSD).

Clinical trials

- 5.4 The July 2022 consideration of asciminib for patients with CML-CP who have failed or are intolerant of at least 2 prior TKIs was based on one head-to-head trial comparing asciminib to bosutinib (N=233), ASCEMBL. Efficacy and safety data from the asciminib arm of ASCEMBL were used to perform an unadjusted, unanchored indirect treatment comparison (ITC) against two single-arm nilotinib trials, ENACT and Giles et al. (2010), and one single-arm ponatinib trial, PACE. The PBAC considered that non-inferior efficacy of asciminib against nilotinib is likely supported but did not support the claim of superior safety to nilotinib (paragraph 2.2). No additional clinical data were presented in the resubmission for this patient population.
- 5.5 The July 2022 submission did not seek a PBS listing for asciminib in patients with the T315I mutation, although the proposed PBS restrictions did not specifically exclude this patient group. The ASCEMBL trial excluded patients with the T315I-mutation to facilitate the use of bosutinib in the comparator arm, as patients with this mutation would not be expected to respond to bosutinib. The July 2022 submission presented the results of the X2101 trial, as reported in Hughes et al. 2019 (data cut-off: September 2017).
- 5.6 As requested by the PBAC, the resubmission presented an unanchored and unadjusted comparison of asciminib and ponatinib using the T315I mutation cohorts from the X2101 and PACE trials, respectively. Further details are provided for patients with the T315I mutation from the X2101 trial Clinical Study Report (data cut-off: 2 April 2020) as well as a supplementary analysis which was conducted in the T315I mutation analysis set with a later data cut (data cut-off date: 6 January 2021). Table 3 shows details of the trials presented in the submission.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Asciminib trials		
ASCEMBL	ASCEMBL CSR: A Phase III, multi center, open-label, randomised study of oral ABL001 (asciminib) versus bosutinib in patients with chronic myelogenous leukaemia in chronic phase (CML-CP), previously treated with 2 or more tyrosine kinase inhibitors.	- Version date: 20 September 2019 (Week 24 data – primary endpoint analysis) - Version date: 5 March 2021 (supplementary CSR to support 30 day efficacy and safety update)
CABL001X2101 (X2101)	Hughes et al. Asciminib in Chronic Myeloid Leukemia after ABL Kinase Inhibitor Failure.	N Engl J Med 2019; 381, 2315-2326 (data cut-off September 2017)
	X2101 CSR: A phase I, multicenter, open-label study of oral ABL001 in patients with chronic myelogenous leukemia or Philadelphia Chromosome-positive acute lymphoblastic leukemia	- Version date: 20 September 2019 (data cut-off 2 April 2020)
	X2101 CSR: Supplementary analysis in the T315I mutation analysis set	- Version date: 5 March 2021 (data cut-off 6 Jan 2021)
Ponatinib trial		
PACE	Cortes et al. A Phase 2 trial of ponatinib in Philadelphia chromosome-positive leukaemias.	New Eng J Med 2013; 369 (19): 1783-1796.
	Cortes et al. Ponatinib efficacy and safety in Philadelphia chromosome-positive leukaemia: final 5-year results of the phase 2 PACE trial.	Blood 2018; 132 (4): 393-404.

Source: Submission p34 and submission Appendix 4.

5.7 The key eligibility criteria for the X2101 and PACE studies relating to the patients enrolled with the T315I mutation are presented in Table 4. Patients with CML-CP who had developed the T315I mutation were eligible for either clinical trial if the patient had received at least one prior TKI treatment. Both clinical trials enrolled patients with an Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2, adequate renal function, adequate hepatic function, and normal pancreatic status.

Table 4: Key eligibility criteria

X2101 trial ^a	PACE trial ^a
Inclusion criteria	
Male or female patients ≥ 18 years of age who presented the following: Patients with CML in the CP or AP who exhibited relapsed disease associated with the presence of the T315I “gatekeeper mutation” after at least one TKI were also eligible provided that no other effective therapy exists (criteria introduced with protocol amendment 4).	Patients ≥ 18 years must have CML in any phase (CP, AP or BP of any phenotype) or Ph+ ALL. All patients must have screening bone marrow cytogenetics with conventional banding performed within 42 days prior to initiating treatment. Examination of at least 20 metaphases is required. If less than 20 metaphases are examined, the bone marrow aspirate should be repeated
	Develop the T315I mutation after any TKI therapy. Patients with T315I mutation after any TKI need not have been treated with dasatinib or nilotinib. Patients with T315I in CP must have less than a CCyR (> 0% Ph+). Patients with any history of T315I mutation will be eligible for study participation. However, only those patients who

X2101 trial ^a	PACE trial ^a
	carry a T315I mutation that is detected by direct sequencing in a pre-treatment blood sample using the study's central laboratory will be analysed in the T315I subset.
ECOG PS of 0 to 2	ECOG PS of ≤ 2
	<p>Adequate renal function defined as serum creatinine $< 1.5 \times$ ULN.</p> <p>Adequate hepatic function defined as:</p> <ul style="list-style-type: none"> • Total bilirubin $< 1.5 \times$ ULN, • ALT and AST $< 2.5 \times$ ULN ($< 5 \times$ ULN if liver involvement with leukemia)
	<p>Normal pancreatic status defined as:</p> <ul style="list-style-type: none"> • Lipase $\leq 1.5 \times$ ULN for institution • Amylase $\leq 1.5 \times$ ULN for institution • Prothrombin time $< 1.5 \times$ ULN. <p>Normal QTcF interval on screening ECG evaluation, defined as QTcF of ≤ 450 ms in males or ≤ 470 ms in females.</p>
Exclusion criteria	
<p>The following clinical laboratory results within 3 days before the first dose of study treatment:</p> <ul style="list-style-type: none"> • For CML-CP and AP patients: <ul style="list-style-type: none"> ○ Absolute neutrophil count (ANC) $\leq 0.5 \times 10^9/L$ ○ Haemoglobin ≤ 9.0 g/dL ○ Platelets $\leq 50 \times 10^9/L$ • Total bilirubin > 1.5 times the ULN, except for patients with Gilbert's syndrome, who were excluded if total bilirubin is > 3 times the ULN or if direct bilirubin is > 1.5 times the ULN • AST or ALT > 3 times the ULN • Alkaline phosphatase > 2.5 times the ULN unless considered to be not of hepatic origin • Creatinine > 1.5 ULN • Amylase values above the institutional ULN • Lipase values above the institutional ULN. 	

Source: Resubmission Table 2-1; Appendix 4: X2101 CSR, Section 9.3, p123-126, Appendix 5: Cortes et al. (2013).

ALL = acute lymphoblastic leukemia; ALT = alanine aminotransferase; AP = acute phase; AST = aspartate aminotransferase; CCyR = complete cytogenetic response; CP = chronic phase; CML = chronic myeloid leukaemia; ECOG PS = Eastern Cooperative Oncology Group performance status; Ph+ = Philadelphia chromosome positive; TKI = tyrosine kinase inhibitor; ULN = upper limit of the normal range.

^a Only eligibility criteria pertaining to patients with T315I mutations is presented.

5.8 In the X2101 trial, 48 CML-CP patients harbouring the T315I mutation were treated with asciminib 200 mg twice daily. Of these patients, 77.1% were male and 22.9% female. The patients were White (58.3%), Asian (25.0%), and Black or African American (2.1%), and unreported or unknown (14.6%). The Eastern Cooperative Oncology Group performance status (ECOG) performance status was 0 in 75.0% of patients and 1 in 25.0% of patients.

5.9 Table 5 presents the comparable baseline characteristics of the patients with the T315I mutation in the X2101 and PACE trials. The median age of patients was 56.2 years in X2101 compared with 52 years in PACE. Patients in the X2101 trial were more likely to have received a greater number of TKIs, with 25/48 patients (52.0%) receiving ≥ 3 prior TKIs compared 26/64 (41%) in PACE.

Table 5: Comparable baseline characteristics in X2101 and PACE

	X2101 T315I mutation cohort (N = 48)	PACE T315I mutation cohort (N = 64)
Age (years), median (range)	56.5 (26-86)	52 (18-87)
Number of prior TKIs		
1	8 (16.7)	-
2	15 (31.3)	-
3	17 (35.4)	-
4	7 (14.6)	-
≥ 5	1 (2.1)	-
Prior TKIs,		
Median number, n	-	2.0
2, n (%)	-	27 (42)
≥ 3 , n (%)	-	26 (41)

TKI = tyrosine kinase inhibitor.

Source: Resubmission Table 2-2; Appendix 4: X2101 CSR, Table 10-24, p179; Table 10-36, p191; Appendix 5: Cortes et al. (2013), Table S5, p46.

Comparative effectiveness

X2101 trial (asciminib)

5.10 The primary objective of the Phase 1 study X2101 was to determine the maximum tolerated dose and/or recommended dose for expansion. The asciminib 200 mg twice daily dose was selected for patients with CML-CP and harbouring the T315I mutation. The secondary objective of X2101 was to assess preliminary anti-CML activity associated with asciminib. Major molecular response (MMR) rate by 24 weeks of treatment was the main efficacy outcome.

5.11 Table 6 presents a summary of the MMR rate and cumulative MMR rate for the T315I mutation analysis set at the data cut of 6 January 2021. There were 45 patients in the T315I mutation analysis set, defined as CML-CP patients with centrally confirmed T315I mutation (Sanger sequencing), treated with asciminib 200 mg twice daily, with evaluable real time quantitative polymerase chain reaction (RQ-PCR) data (IS) who were not in MMR at baseline. Of these 45 patients, 19 patients were ponatinib naïve at baseline and 26 patients had previously received treatment with ponatinib.

Table 6: MMR and cumulative MMR in the X2101 study

Response, n (%)	Asciminib 200 twice daily, n (%)		
	T315I mutation set N = 45	Ponatinib-naive N = 19	Ponatinib pre-treated N = 26
MMR rate at specific timepoints			
Week 24	N = 45; 17 (37.8)	N = 19; 10 (52.6)	N = 26; 7 (26.9)
Week 48	N = 45; 16 (35.6)	N = 19; 9 (47.4)	N = 26; 7 (26.9)
Week 72	N = 44; 15 (34.1)	N = 19; 9 (47.4)	N = 25; 6 (24.0)
Week 96	N = 37; 13 (35.1)	N = 16; 10 (62.5)	N = 21; 3 (14.3)
Cumulative MMR rate by specific timepoints			
Week 24	N = 45; 19 (42.2)	N = 19; 11 (57.9)	N = 26; 8 (30.8)
Week 48	N = 45; 20 (44.4)	N = 19; 11 (57.9)	N = 26; 9 (34.6)
Week 72	N = 45; 21 (46.7)	N = 19; 12 (63.2)	N = 26; 9 (34.6)
Week 96	N = 45; 22 (48.9)	N = 19; 13 (68.4)	N = 26; 9 (34.6)

Source: Resubmission Table 2-3; Appendix 3: PI, p16, Appendix 4: X2101 Supplement 1, Table 14.2-2.4, p60-61; Table 14.2-2.5, p65-67; Table 14.2-2.6, p77-80; Table 14.2-4.4, p111-112; Table 14.2-4.5, p116-118; Table 14.2-4.6, p128-131.

MMR = major molecular response.

- 5.12 The MMR rate includes only patients who are in MMR at a specific timepoint. The MMR rates at Week 24, Week 48, Week 72 and Week 96 were 37.8%, 35.6%, 34.1%, and 35.1% respectively. The majority of responses were observed within the first 24 weeks of treatment.
- 5.13 The cumulative MMR rate includes patients who achieved MMR up to the time of measurement even if they might have subsequently lost response (i.e., by later timepoints). The cumulative incidence of MMR kept increasing steadily over time. MMR was achieved by 24 weeks in 42% of patients and in 49% patients by Week 96.
- 5.14 The MMR rate was numerically higher amongst ponatinib-naïve patients at Week 24 (52.6%) compared with patients previously treated with ponatinib (26.9%). Similarly, the cumulative MMR rate was higher amongst ponatinib-naïve patients at Week 24 (57.9%) compared with patients previously treated with ponatinib (30.8%). A higher MMR and cumulative MMR was observed at all time points for ponatinib-naïve patients compared with ponatinib pre-treated patients.
- 5.15 With respect to cytogenetic response, of the 48 patients with CML-CP harbouring the T315I mutation and treated with asciminib 200 mg twice daily, 9 patients were in complete cytogenetic response (CCyR) at screening and hence were not considered in the analysis of CCyR. A further 7 patients did not have a bone marrow sample to assess cytogenetic response at study entry and were also excluded from the analysis of CCyR. A total of 32 patients were not in CCyR at baseline and had a valid bone marrow sample to assess cytogenetic response at baseline.
- 5.16 Table 7 presents the cytogenetic responses to asciminib for these 32 patients at the data cut-off of 2 April 2020, which was the most recent analysis of CCyR. Bone marrow samples were not collected for all patients at all time points and were not collected at any time post-screening for 9 patients. Therefore, the proportions of patients who achieved a CCyR at each time point were also recalculated as a proportion of patients

with non-missing data and presented in Table 7. By Week 24, 10 patients of the 23 (47.6%) evaluable patients with at least one valid assessment after screening had achieved a CCyR and this increased to 13 patients (56.5%) by Week 96.

Table 7: Cumulative CCyR in the X2101 study

	Asciminib 200 mg twice daily cohort			
	Week 24 (N = 32) ^a	Week 48 (N = 32) ^a	Week 72 (N = 32) ^a	Week 96 (N = 32) ^a
MCyR	17 (53.1)	17 (53.1)	17 (53.1)	18 (56.3)
CCyR	10 (31.3)	12 (37.5)	12 (37.5)	13 (40.6)
PCyR	7 (21.9)	5 (15.6)	5 (15.6)	5 (15.6)
Minor cytogenetic response	0	0	0	0
Minimal cytogenetic response	1 (3.1)	1 (3.1)	2 (6.3)	2 (6.3)
No cytogenetic response	3 (9.4)	3 (9.4)	3 (9.4)	3 (9.4)
Missing	11 (34.4)	11 (34.4)	10 (31.3)	9 (28.1)
CCyR as a proportion of patients with non-missing data	n = 21 10 (47.6)	n = 21 12 (57.1)	n = 22 12 (54.5)	n = 23 13 (56.5)

Source: Resubmission Table 2-4; Appendix 4: X2101 CSR, p17, p216, Table 14.2-7.4, p1197-1203.

CCyR = complete cytogenetic response; MCyR = major cytogenetic response; PCyR = partial cytogenetic response.

PACE trial (ponatinib)

5.17 The results of the PACE trial were presented in full in the July 2022 submission. The July 2022 submission focused on the resistant/intolerant cohort of PACE because 98% patients received at least two prior TKIs, which aligns with the population proposed in that submission (non-T315I mutation). The clinical evaluation in the resubmission focused on the T315I mutation cohort of the PACE trial.

5.18 The cumulative MMR was a secondary efficacy outcome in the PACE trial and the results are presented for the T315I cohort in Table 8. At the primary analysis, 56% patients harbouring a T315I mutation had achieved an MMR by 12 months. This proportion increased to 58% patients at the 5-year analysis.

Table 8: Cumulative MMR rates in the PACE trial

Proportion of patients	T315I cohort N = 64 n (%)
By 6 months	26 (40.6) ^a
By 12 months (primary analysis)	36 (56)
By 5-years	37 (58)

Source: Resubmission Table 2-5; Appendix 1: July 2022 submission, Appendix 16, Table 1, p3; main body Table 5(a).5-2, p140; Appendix 5: Cortes et al. (2013) Figure 1A p 1789; Cortes et al. (2013) supplement Table S3 pdf p 43; Cortes et al. (2018) Figure 1A p 396, Supplement, Figure S1C, p9.

MMR = major molecular response.

^a Estimated from Cortes et al. (2018) Figure S1C.

5.19 Patients in the CML-CP T315I cohort of the PACE trial were required to have less than a CCyR at baseline (Table 4) to be eligible for the clinical trial. Hence, all patients (N = 64) were considered in the analysis of CCyR and the results are presented in

Table 9. The cumulative CCyR rate increased from 62.5% by 6 months to 70% by 5 years.

Table 9: Cumulative CCyR rate in the PACE trial

Proportion of patients, n (%)	T315I cohort N = 64
By 6 months	40 (62.5) ^a
By 12 months	42 (65.6)
By 5-years	45 (70)

Source: Resubmission Table 2-6; Appendix 1: July 2022 submission, Appendix 16, Table 1, p3; main body Table 5(a).5-2, p140; Appendix 5: Cortes et al. (2013) Figure 1A p 1789; Cortes et al. (2013) supplement Table S3 pdf p 43; Cortes et al. (2018) Figure 1A p 396, Supplement, Figure S1B, p9.

CCyR = complete cytogenetic response.

^a Estimated from Cortes et al, 2018 Figure S1B.

Indirect comparison of efficacy: X2101 (asciminib) vs PACE (ponatinib)

5.20 The results of the unanchored and unadjusted indirect comparison of cumulative MMR in CML-CP patients harbouring the T315I mutation are presented in Table 10. The comparisons were conducted using the T315I mutation analysis set from X2101, which comprises both ponatinib-naïve and ponatinib pre-treated patients, as well as the subgroup of ponatinib-naïve patients. Patients in the T315I mutation analysis set are those patients that align with the proposed PBS criteria (i.e., at least one prior TKI and harbour the T315I mutation). Patients in the ponatinib-naïve subgroup of X2101 most closely align with those in PACE with respect to being ponatinib-naïve at baseline. There was no statistically significant difference between asciminib and ponatinib in any of the comparisons of cumulative MMR.

Table 10: Indirect comparison of cumulative MMR in patients with T315I mutation*

Outcomes/ Timepoint	Asciminib 200 mg twice daily n (%)	Ponatinib 45 mg once daily n (%)	OR (95% CI) P value	RR (95% CI) P value	RD (95% CI) P value
Asciminib (T315I mutation analysis set)					
By 24 weeks / 6 months	N = 45 19 (42.2)	N = 64 26 (40.6)	1.07 (0.49, 2.32) P = 0.87	1.04 (0.66, 1.63) P = 0.87	0.02 (-0.17, 0.20) P = 0.87
By 48 weeks / 12 months	N = 45 20 (44.4)	N = 64 36 (56)	0.62 (0.29, 1.34) P = 0.23	0.79 (0.53, 1.17) P = 0.24	-0.12 (-0.31, 0.07) P = 0.22
Asciminib (ponatinib-naïve patients)					
By 24 weeks / 6 months	N = 19 11 (57.9)	N = 64 26 (40.6)	2.01 (0.71, 5.68) P = 0.19	1.43 (0.88, 2.31) P = 0.15	0.17 (-0.08, 0.43) P = 0.18
By 48 weeks / 12 months	N = 19 11 (57.9)	N = 64 36 (56)	1.07 (0.38, 3.01) P = 0.90	1.03 (0.66, 1.60) P = 0.90	0.02 (-0.24, 0.27) P = 0.90

Source: Resubmission Table 2-7

MMR = major molecular response; OR = odds ratio; RD = risk difference; RR = relative risk.

*Note: The results presented in Table 10 are derived from an unanchored and unadjusted indirect comparison specifically for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

5.21 The results of the unanchored and unadjusted indirect comparison of cumulative CCyR in CML-CP patients harbouring the T315I mutation are presented in Table 11. The proportions of patients from X2101 were calculated based on the patients who were not in CCyR at baseline and who had bone marrow samples to determine response at both baseline and the relevant time point. There was no statistically significant difference between asciminib and ponatinib at either time point for the comparison of cumulative CCyR.

Table 11: Indirect comparison of cumulative CCyR in patients with T315I mutation*

Outcomes/ Timepoint	Asciminib 200 mg twice daily n (%)	Ponatinib 45 mg once daily n (%)	OR (95% CI) P value	RR (95% CI) P value	RD (95% CI) P value
By 24 weeks / 6 months	N = 21 10 (47.6)	N = 64 40 (62.5)	0.55 (0.20, 1.47) P = 0.23	0.76 (0.47, 1.24) P = 0.27	-0.15 (-0.39, 0.10) P = 0.23
By 48 weeks / 12 months	N = 21 12 (57.1)	N = 64 42 (65.6)	0.70 (0.26, 1.91) P = 0.48	0.87 (0.58, 1.31) P = 0.51	-0.08 (-0.33, 0.16) P = 0.49

Source: Resubmission Table 2-8

CCyR = complete cytogenetic response; OR = odds ratio; RD = risk difference; RR = relative risk.

*Note: The results presented in Table 11 are derived from an unanchored and unadjusted indirect comparison specifically for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

Comparative harms

X2101 trial (asciminib)

5.22 At the data cut-off of 6 January 2021, the mean duration of exposure to asciminib 200 mg twice daily in patients with a confirmed T315I mutation at screening (n = 48) was 103.0 weeks (SD: 61.90). The median duration of exposure was 108.2 weeks (range 2-215). The mean dose per day was 370.8 mg (SD: 52.54) (and the median dose was 398.3 mg (range 179-400)). An overview of adverse events (AEs) in patients with the T315I mutation who received asciminib 200 mg twice daily is presented in Table 12.

Table 12: Overview of adverse events in the T315I safety population (6 January 2021)

	T315I safety population (N = 48) n (%)
Adverse events	48 (100)
Treatment-related	41 (85.4)
AEs with grade ≥ 3	29 (60.4)
Treatment-related	18 (37.5)
SAEs	11 (22.9)
Treatment-related	2 (4.2)
Fatal SAEs	2 (4.2)
AEs leading to discontinuation	5 (10.4)
Treatment-related	2 (4.2)

Source: Resubmission Table 2-9; Appendix 4: X2101 CSR Supplement 1, Table 14.3.1-20.1, p817.

AEs = adverse events; SAEs = serious adverse events.

5.23 The treatment-related AEs experienced by CML-CP patients harbouring the T315I mutation and treated with asciminib 200 mg twice daily at the data cut-off of 6 January 2021 are presented in Table 13.

Table 13: Treatment-related AEs in greater than 5% population (any AE) or greater than 2% (grade ≥3): X2101 trial

	T315I safety population (N = 48)	
	Any grade n (%)	Grade ≥3 n (%)
Total treatment-related AEs	41 (85.4)	18 (37.5)
Nausea	9 (18.8)	0
Arthralgia	6 (12.5)	0
Lipase increased	11 (22.9)	8 (16.7)
Fatigue	6 (12.5)	1 (2.1)
Myalgia	4 (8.3)	0
Rash	3 (6.3)	0
Diarrhoea	6 (12.5)	0
Pruritus	5 (10.4)	0
Headache	5 (10.4)	0
Thrombocytopenia	6 (12.5)	5 (10.4)
Alanine aminotransferase increased	4 (8.3)	1 (2.1)
Neutropenia	4 (8.3)	3 (6.3)
Vomiting	5 (10.4)	0
Amylase increased	5 (10.4)	1 (2.1)
Hyperuricaemia	4 (8.3)	0
Anaemia	3 (6.3)	1 (2.1)
Aspartate aminotransferase increased	3 (6.3)	0
Gamma-glutamyltransferase increased	2 (4.2)	1 (2.1)
Musculoskeletal pain	4 (8.3)	0
Neutrophil count decreased	2 (4.2)	2 (4.2)
Abdominal pain	2 (4.2)	0
Hypertension	1 (2.1)	1 (2.1)
Rash maculo-papular	3 (6.3)	0
Oedema peripheral	1 (2.1)	1 (2.1)
Platelet count decreased	1 (2.1)	1 (2.1)
Coronary artery disease	1 (2.1)	1 (2.1)
Hyperkalaemia	1 (2.1)	1 (2.1)
Hyperlipasaemia	1 (2.1)	1 (2.1)
Illrd nerve paralysis	1 (2.1)	1 (2.1)
Non-cardiac chest pain	1 (2.1)	1 (2.1)
Pancytopenia	1 (2.1)	1 (2.1)
Weight decreased	1 (2.1)	1 (2.1)

Source: Resubmission Table 2-10; Appendix 4: X2101 CSR Supplement 1, Table 14.3.1-4.1.4, p597-616.

AEs = adverse events.

PACE trial (ponatinib)

- 5.24 The July 2022 submission presented safety outcomes at the primary analysis (12 months) for the PACE trial. The median duration of treatment for the whole PACE population (including CML-CP, AP, BP and Ph+ ALL patients) was 12.8 months (range 0.03 to >24.8). This was not reported for the total CML-CP population (Cortes et al. (2013), p1791).
- 5.25 The safety outcomes in the July 2022 submission focussed on the CML-CP population of PACE (N = 267), which comprised the resistant/intolerant cohort (N = 203) and T315I mutation cohort (N = 64). Although all patients in the CML-CP population received ponatinib 45 mg once daily and the safety outcomes were generally similar across both cohorts, there were numerical differences for some outcomes. For instance, 37% patients in the resistant/intolerant cohort and 17% patients in the T315I mutation cohort experienced Grade 3 or 4 thrombocytopenia. This may be the result of patients in the resistant/intolerant cohort having additional prior TKIs compared with the T315I cohort, as well as differences in the median age of patients between the two cohorts (61 years versus 52 years, respectively), and differences in the median time since diagnosis (7.8 years versus 4.8 years, respectively).
- 5.26 The PACE trial publications only reported treatment-related AEs. The treatment-related AEs at the 12-month follow-up in the T315I mutation cohort are presented in Table 14.

Table 14: Treatment-related AEs by 12-month follow-up: PACE trial

	T315I mutation cohort (N = 64)	
	Any grade %	Grade 3 or 4 %
Non-haematological AEs		
Rash	48	6
Dry skin	41	2
Abdominal pain	22	5
Headache	19	2
Increased lipase	14	6
Fatigue	22	0
Constipation	14	2
Myalgia	25	2
Arthralgia	14	3
Nausea	16	0
Increased ALT	9	0
Pancreatitis	8	8
Hypertension	9	3
Increased AST	8	0
Increased blood amylase	2	0
Increased GGT	2	0
Dyspnoea	5	0
Cardiac failure	3	2
Haematological AEs		
Thrombocytopenia	23	17
Neutropenia	5	5
Anaemia	3	2
Decreased WCC	0	0
Pancytopenia	0	0
Febrile neutropenia	0	0

Source: Resubmission Table 2-11; Appendix 1: July 2022 submission, Table 2(a).5-5, p144; Cortes et al. (2013) Table 4 p 1792; Cortes et al. (2013) supplement Table S10 pdf p 51

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CML-CP = chronic phase chronic myeloid leukemia; GGT = gamma glutamyl aminotransferase; WCC = white cell count.

5.27 The unanchored and unadjusted indirect comparisons of grade ≥ 3 treatment-related AEs for asciminib 200 mg twice daily compared with ponatinib 45 mg once daily in CML-CP patients with the T315I mutation are presented in Table 15. The median duration of exposure to asciminib 200 mg twice daily in these patients from X2101 was 108.2 weeks (range 2-215). In contrast, the median duration of ponatinib 45 mg once daily in the overall PACE population was 12.8 months (range 0.03 to >24.8). The resubmission stated that, as patients are only at risk of treatment-related AEs while on study drug, the comparisons are biased against asciminib, which has a median duration of exposure which is almost twice as long as for ponatinib. Nevertheless, there were no statistically significant differences in grade ≥ 3 treatment-related AEs between the treatments except for pancreatitis. There were no patients treated with

asciminib 200 mg twice daily who experienced treatment-related grade ≥ 3 pancreatitis, whereas 5 patients (8%) of patients treated with ponatinib 45 mg once daily did experience events, which reached statistical significance in terms of risk difference (-0.08, 95% CI: -0.15, -0.00, P = 0.04) but not in terms of odds ratio or relative risk (Table 15).

Table 15: Safety outcomes of grade ≥ 3 treatment-related adverse events*

	Asciminib 200 mg twice daily (N = 48) n (%)	Ponatinib 45 mg once daily (N = 64) n (%)	OR (95% CI) P value	RR (95% CI) P value	RD (95% CI) P value
Non-haematological AEs					
Rash ^a	0	4 (6.3)	0.14 (0.01, 2.64) P = 0.19	0.15 (0.1, 2.67) P = 0.20	-0.06 (-0.13, 0.01)) P = 0.07
Dry skin	0	1 (1.6)	0.44 (0.02, 10.95) P = 0.61	0.44 (0.02, 10.62) P = 0.61	-0.02 (-0.06, 0.03) P = 0.51
Abdominal pain	0	3 (4.7)	0.18 (0.01, 3.59) P = 0.26	0.19 (0.01, 3.58) P = 0.27	-0.05 (-0.11, 0.01) P = 0.14
Headache	0	1 (1.6)	0.44 (0.02, 10.95) P = 0.61	0.44 (0.02, 10.62) P = 0.61	-0.02 (-0.06, 0.03) P = 0.51
Hyperlipasaemia / increased lipase	1 (2.1)	4 (6.3)	0.32 (0.03, 2.95) P = 0.31	0.33 (0.04, 2.89) P = 0.32	-0.04 (-0.11, 0.03) P = 0.26
Fatigue	1 (2.1)	0	4.07 (0.16, 102.21) P = 0.39	3.98 (0.17, 95.61) P = 0.39	0.02 (-0.03, 0.07) P = 0.44
Constipation	0	1 (1.6)	0.44 (0.02, 10.95) P = 0.61	0.44 (0.02, 10.62) P = 0.61	-0.02 (-0.06, 0.03) P = 0.51
Myalgia	0	1 (1.6)	0.44 (0.02, 10.95) P = 0.61	0.44 (0.02, 10.62) P = 0.61	-0.02 (-0.06, 0.03) P = 0.51
Arthralgia	0	2 (3.1)	0.26 (0.01, 5.49) P = 0.39	0.27 (0.01, 5.40) P = 0.39	-0.03 (-0.09, 0.02) P = 0.26
Nausea	0	0	NE	NE	0.00 (-0.04, 0.04) P = 1.00
Increased ALT	1 (2.1)	0	4.07 (0.16, 102.21) P = 0.39	3.98 (0.17, 95.61) P = 0.39	0.02 (-0.03, 0.07) P = 0.44
Pancreatitis	0	5 (7.8)	0.11 (0.01, 2.07) P = 0.14	0.12 (0.01, 2.13) P = 0.15	-0.08 (-0.15, -0.00) P = 0.04
Hypertension	1 (2.1)	2 (3.1)	0.66 (0.06, 7.49) P = 0.74	0.67 (0.06, 7.14) P = 0.74	-0.01 (-0.07, 0.05) P = 0.73
Increased AST	0	0	NE	NE	0.00 (-0.04, 0.04) P = 1.00
Increased (blood) amylase	1 (2.1)	0	4.07 (0.16, 102.21) P = 0.39	3.98 (0.17, 95.61) P = 0.39	0.02 (-0.03, 0.07) P = 0.44
Increased GGT	1 (2.1)	0	4.07 (0.16, 102.21) P = 0.39	3.98 (0.17, 95.61) P = 0.39	0.02 (-0.03, 0.07) P = 0.44
Dyspnoea	0	0	NE	NE	0.00 (-0.04, 0.04) P = 1.00

	Asciminib 200 mg twice daily (N = 48) n (%)	Ponatinib 45 mg once daily (N = 64) n (%)	OR (95% CI) P value	RR (95% CI) P value	RD (95% CI) P value
Cardiac failure	0 ^b	1 (1.6)	0.44 (0.02, 10.95) P = 0.61	0.44 (0.02, 10.62) P = 0.61	-0.02 (-0.06, 0.03) P = 0.51
Haematological AEs					
Thrombocytopenia	5 (10.4)	11 (17.2)	0.56 (0.18, 1.74) P = 0.32	0.61 (0.23, 1.63) P = 0.32	-0.07 (-0.19, 0.06) P = 0.29
Neutropenia	3 (6.3)	3 (4.7)	1.36 (0.26, 7.03) P = 0.72	1.33 (0.28, 6.32) P = 0.72	0.02 (-0.07, 0.10) P = 0.72
Anaemia	1 (2.1)	1 (1.6)	1.34 (0.08, 21.99) P = 0.84	1.33 (0.09, 20.78) P = 0.84	0.01 (-0.05, 0.06) P = 0.84
Decreased neutrophil count/ white cell count	2 (4.2)	0	6.94 (0.33, 147.87) P = 0.21	6.63 (0.33, 135.05) P = 0.22	0.04 (-0.02, 0.11) P = 0.21
Pancytopenia	1 (2.1)	0	4.07 (0.16, 102.21) P = 0.39	3.98 (0.17, 95.61) P = 0.39	0.02 (-0.03, 0.07) P = 0.44
Febrile neutropenia	0 ^b	0	NE	NE	0.00 (-0.04, 0.04) P = 1.00

Source: Resubmission Table 2-12.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma glutamyl aminotransferase; NE = not estimable; OR = odds ratio; RD = risk difference; RR = relative risk.

a For asciminib this combines the terms rash and rash maculo-papular; for ponatinib this combines the terms erythematous and papular rash.

b Assumed to be 0 as no patients reported this outcome.

Note: Grade ≥ 3 oedema peripheral, platelet count decreased, coronary artery disease, hyperkalaemia, Illrd nerve paralysis, weight decreased, and non-cardiac chest pain was reported in one patient from X2101 in each category. However, these outcomes were not reported in the PACE publication which only reported treatment-related AEs in $\geq 10\%$ in the total study population (N = 449) or those with incidence of $> 1\%$ for grade 3/4.

*Note: The results presented in Table 15 are derived from an unanchored and unadjusted indirect comparison specifically for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

Clinical claim

5.28 The clinical claim for asciminib (200 mg twice daily) versus ponatinib (45 mg once daily) in patients with CML-CP who have received at least one prior TKI and harbour the T315I mutation was:

- Non-inferior efficacy. The assessment of efficacy was based on a comparison of MMR and CCyR in the T315I mutation populations of the X2101 and PACE trials. The Sponsor stated that these outcomes are important treatment goals (NCCN, 2022) and have previously been accepted by the PBAC in their consideration in the treatment of CML (Nilotinib PSD July 2011; Ponatinib PSD July 2015).
- At least non-inferior safety. The assessment of safety was based on a comparison of grade ≥ 3 treatment-related adverse events in the T315I mutation populations of the X2101 and PACE trials.

- 5.29 The PBAC considered that the claim of non-inferior comparative effectiveness was not unreasonable, despite the caveats associated with an unanchored and unadjusted comparison, given that there was no material difference between asciminib and ponatinib in any of the comparisons of cumulative MMR or CCyR.
- 5.30 The PBAC considered that the claim of non-inferior comparative safety was not unreasonable, noting that there were no material differences in grade ≥ 3 treatment-related AEs between the treatments except for pancreatitis (5 patients (8%) of patients treated with ponatinib experienced treatment-related grade ≥ 3 pancreatitis compared to no patients treated with asciminib). The PBAC noted that the median duration of exposure to asciminib in the X2101 trial (108.2 weeks) was almost twice as long compared to that for ponatinib in the PACE trial (12.8 months).

Economic analysis

- 5.31 As an early re-entry resubmission, the economic analysis has not been independently evaluated.
- 5.32 The July 2022 submission presented separate analyses of asciminib versus nilotinib and asciminib versus ponatinib using the cost minimisation approach (CMA). Although the PBAC considered that benchmarking against second generation TKIs was a reasonable basis for establishing a cost-effective price for asciminib in patients without the T315I mutation, it requested that this benchmarking be performed against nilotinib and dasatinib (paragraphs 7.13 and 7.15, asciminib PSD, July 2022). Consistent with this advice, separate updated CMAs of asciminib versus nilotinib and asciminib versus dasatinib were presented in the resubmission.

Asciminib vs nilotinib (non-T315I mutation)

- 5.33 Although the PBAC noted that the CMA of asciminib versus nilotinib was informative at the July 2022 meeting, it considered that the equi-effective doses for patients without the T315I mutation should be based on the median doses in the ASCEMBL (79.8 mg/day) and ENACT (782.5 mg/day) trials (paragraph 7.12, asciminib PSD, July 2022). The Committee further considered that there should be no cost offsets for the treatment of AEs and that the monitoring cost be revised to align with that calculated during the evaluation (paragraph 7.13, asciminib PSD, July 2022).
- 5.34 The resubmission stated that in addition to the PBAC's requested revisions, the CMA has been updated to consider the current (August 2022) approved ex-manufacturer prices (AEMPs) for nilotinib and fees for relevant MBS items. The result of the revised CMA over a two-year time horizon is presented in Table 16.

Table 16: Cost minimisation approach for asciminib versus nilotinib (non-T315I mutation)

	Asciminib			Nilotinib			Increment
	60 x 40 mg	60 x 20 mg	Source	120 x 200 mg	120 x 150 mg	Source	
Medicines							
A	Days of treatment	730.5	2 years	730.5	2 years		-
B	Tabs/caps per day	2	40 mg: 80 mg/day / strength 20 mg: 40 mg/day / strength	4	150 mg: 600 mg/day / strength 200 mg: 800 mg/day / strength		
C	Days per pack	30	60 caps / B	30	120 caps / B		-
D	Packs / 2 years	24.35	A / C	24.35	A / C		-
E	Usage by strength	█%	█%	91.25%	8.75%	Equi-effective dose: (800*91.25+600*8.75)/100 = 782.5 mg/day	-
F	Scripts / 2 years	█ ¹	█ ¹	D * E	22.22	2.13	D * E
G	Effective AEMP per script	\$█	\$█	40 mg: H / F 20 mg = 40 mg	\$4,895.54	\$3,694.89	PBS items 1309X and 9171Q
H	Total medicines	\$█	\$█	H * E	\$108,775.84	\$7,872.43	F * G
		\$█	M - L	\$116,648.26	Total		\$█
Monitoring							
I	QT prolongation	\$0.00	-	\$33.05	MBS 11704 100% (\$33.05)		-\$33.05
J	Full blood count	\$457.65	MBS 65070 (\$16.95) 100% * 27	\$440.70	MBS 65070 (\$16.95) 100% * 26		\$16.95
K	Blood tests	\$283.60	MBS items 100% * 24 ^a	\$387.90	MBS items 100% * 24 ^a		-\$104.30
L	Total monitoring	\$741.25	I + J + K	\$861.65	I + J + K		-\$120.40
Total cost of treatment over 2 years							
M	Total cost	\$█	Asciminib = nilotinib	\$117,509.91	H + L		\$█

Source: Resubmission Table 3-1; Asciminib vs Nilotinib – CMA – Aug 22.xls

AEMP = approved ex-manufacturer price; MBS = Medicare Benefits Schedule.

^a Despite asciminib and nilotinib having the same number of blood tests over 2 years (24), the costs may vary because the blood test differs depending on how many individual measurements of the following: lipids, glucose, uric acid, ALT, AST, bilirubin, lipase, amylase. With nilotinib there are more tests, in particular for serum lipase and hepatic function.

The redacted values correspond to the following ranges:

¹ < 500

- 5.35 The equi-effective doses for asciminib and nilotinib are reflected in the split between the strengths in the CMA (Step E in Table 16). The resubmission calculated the proposed effective EMP for the asciminib 40 mg strength (\$) using a weighting of % for the 80 mg/day dose to satisfy the equi-effective dose of 79.8 mg/day. However, the Sponsor proposed the same EMP (\$) for both the asciminib 20 mg and 40 mg strengths. The potential usage split between the asciminib 40 mg and 20 mg strengths (and the associated dose of 80 mg/day or 40 mg/day, respectively, for non-T315I mutation patients) in Australian practice is unknown. In contrast to the resubmission's pricing proposal, nilotinib, dasatinib and ponatinib all have strength-based pricing on the PBS. The PBAC noted the 20 mg strength should be priced such that it does not lead to an increase in cost versus the cost for nilotinib.

Asciminib versus dasatinib (non-T315I mutation)

- 5.36 The resubmission stated that in accordance with the PBAC's advice, the equi-effective doses that were used to inform the CMA were based on the median dose of asciminib in the ASCEMBL trial (79.8 mg/day) and the median dose of dasatinib (111 mg/day) that had previously been used to establish the equi-effective doses of dasatinib and nilotinib (paragraph 7.12, asciminib PSD, July 2022). The resubmission may not have correctly interpreted the PBAC's advice; the equi-effective doses for nilotinib and dasatinib are nilotinib 792.1 mg/day and dasatinib 111 mg/day (Section 12, nilotinib PSD, March 2008 meeting), translating into equi-effective doses of asciminib (79.8 mg/day) \equiv nilotinib (782.5 mg/day) \equiv dasatinib (109.7 mg/day). The Pre-PBAC Response accepted this approach.
- 5.37 Consistent with the approach to the CMA of asciminib versus nilotinib, the median dose of asciminib (79.8 mg/day) was obtained by assuming that % of patients would be treated with asciminib 80 mg/day and the remainder with 40 mg/day. For dasatinib (median dose 111 mg/day), it was assumed that 27.5% of patients would be treated with 140 mg/day and 72.5% with 100 mg/day. The PBAC noted that an adjustment in the CMA for a median dasatinib dose of 109.7 mg/day would be required.
- 5.38 A review of the TGA approved Product Information for asciminib and dasatinib identified differences in monitoring requirements that are appropriate for inclusion into the CMA. Specifically, the asciminib TGA approved PI describes that an ECG should be performed prior to initiating treatment whereas this is not mentioned in the TGA approved PI for dasatinib. Further, while the requirement to undertake full blood counts is described in the TGA approved PI for both asciminib and dasatinib, this test must be performed monthly after the first three months of treatment with asciminib, whereas this is every three months after the first three months of treatment with dasatinib. Finally, patients treated with asciminib require blood tests for lipase, amylase, potassium, and magnesium on or prior to initiation followed by monthly monitoring of lipase and amylase thereafter. Those treated with dasatinib on the

other hand only require potassium and magnesium measurements on treatment initiation.

- 5.39 The result of the CMA based on an equi-effective doses of asciminib 79.8 mg/day and dasatinib 111 mg/day and the identified additional costs for asciminib over a two-year time horizon is presented in Table 17. Similar to the nilotinib comparison, the Sponsor has proposed the same EMP for both the asciminib 20 mg and 40 mg strengths. The PBAC noted the 20 mg strength should be priced such that it does not lead to an increase in cost versus the cost for dasatinib.

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Table 17: Cost minimisation approach for asciminib versus dasatinib (non-T315I mutation)

		Asciminib			Dasatinib			Increment
		60 x 40 mg	60 x 20 mg	Source	30 x 100 mg ^a	60 x 70 mg ^a	Source	
Medicines								
A	Days of treatment	730.5		2 years	730.5		2 years	-
B	Tabs/caps per day	2		40 mg: 80 mg/day / strength 20 mg: 40 mg/day / strength	1	2	100 mg: 100 mg/day / strength 70 mg: 140 mg/day / strength	
C	Days per pack	30		60 caps / B	30		100 mg: 30 tabs / B 70 mg: 60 tabs / B	-
D	Packs / 2 years	24.35		A / C	24.35		A / C	-
E	Usage by strength	%	%	Equi-effective dose: (80*99.5+40*0.5)/100 = 79.8 mg/day	72.5%	27.5%	Equi-effective dose: (100*72.5+140*27.5)/100 = 111 mg/day	-
F	Scripts / 2 years	1	1	D * E	17.65	6.70	D * E	
G	Effective AEMP per script	\$	\$	40 mg: H / F 20 mg = 40 mg	\$3,085.89	\$3,820.54	100 mg: PBS items 12902C,12842X 70 mg: PBS items 12886F,12866E	-
H	Total medicines	\$	\$	H * E	\$54,477.53	\$25,583.29	F * G	-
		\$		M - L	\$80,060.82		Total	-\$
Monitoring								
I	QT prolongation	\$33.05		MBS 11704 100% (\$33.05)	\$0.00		-	\$33.05
J	Full blood count	\$457.65		MBS 65070 (\$16.95) 100% * 27	\$220.35		MBS 65070 (\$16.95) 100% * 13	\$237.30
K	Blood tests	\$283.60		MBS item 66509 100% * 24	\$11.65		MBS item 66503 (\$11.65) 100%	\$271.95
L	Total monitoring	\$774.30		I + J + K	\$232.00		I + J + K	\$542.30
Total cost of treatment over 2 years								
M	Total cost	\$		Asciminib = dasatinib	\$80,292.82		H + L	\$

Source: Resubmission Table 3-2; Asciminib vs Dasatinib – CMA – Aug 22.xls

a Some table columns in the resubmission's Word document and Excel file had the 100 mg and 70 mg column headings incorrectly switched. It did not change the results of the CMA. This has been rectified for this overview.

AEMP = approved ex-manufacturer price; MBS = Medicare Benefits Schedule.

The redacted values correspond to the following ranges:

¹ < 500

Weighted average cost-effective price (non-T315I mutation)

5.40 Although benchmarking asciminib against nilotinib and dasatinib results in different cost-effective prices, the PBAC noted that it would be reasonable to estimate an overall weighted cost-effective price for asciminib by considering the relative use of dasatinib and nilotinib (paragraph 7.13, asciminib PSD, July 2022). To assist with the determination of the relative use, the DUSC Secretariat analysed the 100% PBS data and showed that █% and █% of patients received dasatinib and nilotinib, respectively, as their third TKI, noting that the asciminib is for patients resistant to or intolerant of at least two prior TKIs (i.e., third TKI). Based on these data, the proposed weighted EMP for asciminib is \$█ (Table 18).

Table 18: Weighted average cost-effective proposed EMP for asciminib (non-T315I mutation)

	Effective EMP/pack	Strength (mg)	Tablets/pack	DUSC Secretariat		Effective weighted EMP
				Patients ^a	% use	
vs. dasatinib	\$█	20 / 40	60	█ [†]	█%	\$█
vs. nilotinib	\$█	20 / 40	60	█ [†]	█%	

Source: Resubmission Table 3-3; Asciminib AEMP estimation – Aug 22.xls

DUSC = Drug Utilisation Sub-Committee; EMP = ex-manufacturer price.

^a Total number of prevalent patients by drug in third-line in the 2021-22 financial year.

The redacted values correspond to the following ranges:

[†] < 500

5.41 The submission in July 2022 requested an EMP of \$█ (weighted according to the relative substitution of nilotinib and ponatinib and revised by the evaluation [Table 16, asciminib PBAC PSD, July 2022]). An EMP of \$█ (weighted according to the relative substitution of nilotinib and dasatinib) in the resubmission represents a █% reduction in price compared to the July 2022 submission.

Price proposal for asciminib in the T315I population

5.42 The resubmission stated that, consistent with the approach previously taken with regards to very small subgroups within a broader patient pool (e.g., ranibizumab use in patients with rare choroidal neovascularisation), a pragmatic approach was proposed with respect to the price of asciminib for patients with T315I mutation, of whom there are likely to be ~2 per year. The Sponsor proposed that the effective EMP for the non-T315I mutation population (\$█ per pack of 20mg/40mg capsules) should cover all asciminib usage on the PBS, including in any T315I mutation patients who receive PBS treatment.

Drug cost/patient/year

5.43 The expected cost of asciminib is \$█ per patient per year for the non-T315I mutation patients. The cost is calculated assuming an asciminib effective dispensed price for maximum quantity (DPMQ) of \$█ (maximum quantity of 1) and < 500 prescriptions per year (Table 16 and Table 17). This compares to a cost of \$█ per patient per year for the July 2022 submission.

Estimated PBS utilisation and financial implications

- 5.44 As an early re-entry resubmission, the estimated utilisation and financial implications have not been independently evaluated.
- 5.45 The resubmission stated that the PBAC considered the financial estimates presented in the July 2022 submission to be unreliable, mainly because changes in the relative use of the TKIs over the last 12-18 months were not appropriately accounted for (paragraph 7.14, asciminib PSD, July 2022). As such the Committee requested that the resubmission address several assumptions. Table 19 presents a summary of the specific issue to be addressed, the findings of the analyses of the 100% PBS data by the DUSC Secretariat, as well as the resulting changes to the estimation of the predicted use and financial implications.

Table 19: Revisions to the predicted use

	July 2022 consideration	DUSC 100% PBS data	Changes in resubmission
Growth in prevalent patients	The linear extrapolation increased the number of prevalent patients by year 6 by 67%.	The DUSC Secretariat analysis showed that the prevalent patients receiving a third TKI increased by 11.3% per year. The DUSC analysis showed that the prevalent patients receiving a first TKI increased by 2.5%.	Considering that the PBAC noted that the estimated [redacted] ¹ patients in Year 1 was consistent with the estimates from the 2019 DUSC Secretariat review, the number of patients in Year 1 remains unchanged. The DUSC Secretariat analysis showed that the prevalent patients receiving a third TKI increased by 11.3% per year which, when applied to [redacted] ¹ patients in Year 1, results in a total prevalent population greater than estimated in the July 2022 submission. The analysis was revised to conservatively assume an annual increase of 2.5% to reflect the growth in the prevalent patients receiving a first TKI.
Distribution of use of TKI across prevalent patients	Relative use of imatinib (23%) over the analysis period 2022 to 2027 was underestimated.	The DUSC Secretariat analysis showed that while the use of imatinib in patients receiving a third TKI has increased somewhat (i.e., 21% in 2017-18 to 24% in 2021-22), this change is not substantial. Further, compared to 2020-21, the use of imatinib has declined from 26% to 24% .	Relative use of TKIs was revised to that reported in the DUSC Secretariat analysis for the period 2021-22 (nilotinib: 45.7%, ponatinib: 9.0%, dasatinib: 21.2%, imatinib: 24.1%).
	Use of ponatinib should reflect use primarily in patient with T315I mutation.	The DUSC Secretariat analysis showed that only 7.2% of patients receiving ponatinib have the T315I mutation.	Unchanged, but use of ponatinib and associated substitution has been revised to separately consider patients with and without the T315I mutation.
Uptake and substitution rates	Uptake of 35% in Year 1 increasing to 49.5% in Year 6. The uptake in the initial years was overestimated but were underestimated in Year 6.	N/A	Revised in accordance with sensitivity analysis undertaken during the evaluation (i.e., Year 1 30% increasing by 10% every year until 70% in Year 5 and 6). Note that grandfathered patients are included in the prevalent population.
	Relative substitution from the 10% PBS sample data do not reflect current or expected future substitution.	N/A	Unchanged, asciminib will substitute all other TKIs based on their relative use. However, the relative use of the other TKIs is based on the DUSC Secretariat analysis (nilotinib: 45.7%, ponatinib: 9.0%, dasatinib: 21.2%, imatinib: 24.1%).

Source: Resubmission Table 4-1.

DUSC = Drug Utilisation Sub-Committee; TKI = tyrosine kinase inhibitor.

The redacted values correspond to the following range:

¹ 500 to < 5,000

5.46 The impact of these revisions to the financial implications are presented in Table 20. Overall, a PBS listing for asciminib based on the proposed resubmission price (effective DPMQ \$) is expected to result in an incremental cost to the R/PBS of \$0 to < \$10 million in Year 1, and an incremental cost to the R/PBS of \$30 million to < \$40 million

over the first 6 years of listing. The compares to an estimated net financial impact of \$30 million to < \$40 million (evaluation corrected) over 6 years for the July 2022 submission.

Table 20: Estimated extent of use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Predicted use						
Eligible pop.	1	1	1	1	1	1
Asciminib no T315I	2	2	2	2	2	2
Asciminib T315I	2	2	2	2	2	2
Total asciminib pts	2	2	2	2	2	2
Financial implications						
R/PBS Asciminib	3	4	4	5	5	5
R/PBS TKIs	6	6	6	6	6	6
Cost to R/PBS	3	3	3	3	3	3
Revised^a R/PBS	3	3	3	3	3	3
July 2022 submission						
Cost to R/PBS	3	3	3	3	3	3

Source: Resubmission Table 4-2 and modified by the Secretariat; worksheet 5. Impact - net

Abbreviations: Pop. = population; TKI = tyrosine kinase inhibitor; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; SPA = special pricing arrangement; fin. = financial; impl. = implications.

^a Revised in the pre-PBAC response to reflect (i) revised EMP for asciminib of \$█ using a dasatinib equi-effective dose of 109.7 mg/day; and (ii) correction of an error in the estimation of the cost of asciminib for patients who harbour the T315I mutation.

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² < 500

³ \$0 to < \$10 million

⁴ \$10 million to < \$20 million

⁵ \$20 million to < \$30 million

⁶ net cost saving

- 5.47 The Pre-PBAC response provided updated financial estimates to reflect (i) the accepted dasatinib equi-effective dose of 109.7 mg/day; and (ii) correction of an error in the estimation of the cost of asciminib for patients who harbour the T315I mutation. The listing of asciminib is expected to result in a revised incremental cost to the R/PBS of \$10 million to < \$20 million over the first 6 years of listing.
- 5.48 As the reasons for the additional cost to government were unclear in the resubmission, the Pre-PBAC Response provided a breakdown of the additional spend for the revised financial estimates in terms of replaced therapies (Table 21). The Pre-PBAC response stated (p1) that the revised uptake rates and removal of the grandfathered population (included in the prevalent population in the resubmission) had the most significant impact on the overall cost to the R/PBS. Since the changes in the number of prescriptions for asciminib and substituted TKIs are consistent with the change in the total number of patients, the incremental cost to the R/PBS is predominantly due to differences in cost of substituted therapies.

Table 21: Source of incremental cost to the R/PBS

Replaced therapies	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Nilotinib	1	1	1	1	1	1
Ponatinib	2	2	2	2	2	2
Dasatinib	2	2	2	2	2	2
Imatinib	2	2	2	2	2	2
Total	2	2	2	2	2	2

Source: Pre-PBAC Response, Asciminib - UCM - Aug 2022 - Corrected.xlsx, worksheet 3c. Impact – proposed (eff)

The redacted values correspond to the following ranges:

¹ net cost saving

² \$0 to < \$10 million

For more detail on PBAC’s view, see section 6 PBAC outcome.

6 PBAC Outcome

6.1 The PBAC recommended the Authority Required listing of asciminib for the treatment of (i) patients with Philadelphia chromosome-positive chronic myeloid leukaemia (Ph+ CML) in chronic phase (CP) or accelerated phase (AP), who had been previously treated with two or more tyrosine kinase inhibitors (TKIs); and (ii) patients with Ph+ CML in CP or AP, who had been previously treated with one or more TKIs and harbouring the T315I mutation.

6.2 The PBAC considered that the resubmission had addressed the outstanding issues identified at the July 2022 PBAC meeting. The resubmission proposed a separate restriction for patients with the T315I mutation; provided clinical data to support non-inferiority of asciminib to ponatinib in patients with the T315I mutation; provided an economic evaluation reflecting benchmarking against the second generation TKIs nilotinib and dasatinib in patients without the T315I mutation; and recalculated the financial implications. Overall, the PBAC considered that the concerns raised at the July 2022 meeting had been sufficiently addressed.

6.3 The doses used to inform the cost minimisation were based on the median dose of asciminib in the ASCEMBL trial (79.8 mg/day) and the median dose of dasatinib (111 mg/day) that had previously been used to establish the equi-effective doses of dasatinib against nilotinib (792.1 mg/day) (Section 12, nilotinib PSD, March 2008 meeting). Given that the PBAC accepted equi-effective doses for asciminib and nilotinib based on median doses in the ASCEMBL (79.8 mg/day) and ENACT (782.5 mg/day) trials, respectively (paragraph 7.12, asciminib PSD, July 2022), the equi-effective doses of the three agents can be represented by:

$$\text{asciminib (79.8 mg/day)} \equiv \text{nilotinib (782.5 mg/day)} \equiv \text{dasatinib (109.7 mg/day)}.$$

The Sponsor accepted these equi-effective doses in their pre-PBAC response and the PBAC considered this to be appropriate.

6.4 The PBAC has previously noted the clinical place of asciminib in patients with Ph+ CML in CP and its clinical need in patients with CML who have no remaining options with TKI therapy and for whom the only alternative treatment would be allogeneic transplantation (paragraph 7.3, asciminib PSD, July 2022).

- 6.5 The PBAC noted that the resubmission accepted the Secretariat’s proposed amendments to the restriction for CML patients without the T315I mutation, as presented in the PSD for the July 2022 meeting, and did not present additional restrictions for this patient population. The recommended asciminib dose in non-T315I mutation patients is 80 mg daily, requiring a maximum quantity of 1 pack.
- 6.6 Consistent with the PBAC’s recommendation in July 2022, the resubmission requested a separate Authority Required restriction for patients with the T315I mutation, in line with the separate restriction for ponatinib in T315I patients. While the submission requested telephone/online immediate assessment for initial treatment, the PBAC considered that due to the documentation required to demonstrate expression of the T315I mutation (a bone marrow biopsy pathology report), and the higher dosage required for these patients (200 mg twice daily) with the associated increase in the maximum quantity of packs (5), a written Authority would be required for initial treatment.
- 6.7 While the PBAC noted asciminib does not have a registered indication for the rare subgroup in accelerated phase, the PBAC acknowledged the high clinical need in this small number of patients. The PBAC suggested that the clinical criterion in the requested restriction wording “must be in the chronic phase” be amended to “must not be in the blast phase”.
- 6.8 The PBAC recalled from the July 2022 meeting that the comparator was considered to be complex due to the change in the use of TKIs over the last 24-48 months. The PBAC considered in July 2022 that, for some patients, asciminib likely provides a significant improvement in efficacy over imatinib, and as an additional TKI with a different mechanism of action, it likely provides a significant improvement in efficacy and/or reduction in toxicity over standard of care (non-TKI therapy) for patients who have either failed, or are unable to tolerate, both dasatinib and nilotinib. The PBAC advised that a resubmission should reflect benchmarking against the second generation TKIs, nilotinib and dasatinib (paragraph 7.7, asciminib PSD, July 2022). The PBAC also considered at the July 2022 meeting that ponatinib is a relevant comparator for patients with the T315I mutation (paragraph 7.8, asciminib PSD, July 2022).
- 6.9 The resubmission did not specifically re-define the comparator for asciminib; however, consistent with the PBAC’s recommendation in July 2022, it presented clinical data for a comparison in the T315I mutation population of asciminib versus ponatinib, and it presented an economic evaluation in the non-T315I mutation population for both asciminib versus nilotinib and asciminib versus dasatinib.
- 6.10 The PBAC recalled from the July 2022 consideration that, for the clinical comparison of asciminib versus nilotinib in the non-T315I mutation population, non-inferior efficacy is likely supported despite the limitations of the evidence from the ASCSEMBL and ENACT trials (paragraph 7.9, asciminib PSD, July 2022). The PBAC also recalled that the available data do not support the claim of superior safety compared with nilotinib

[or ponatinib] in the non-T315I mutation population (paragraph 7.11, asciminib PSD, July 2022).

- 6.11 Consistent with the PBAC's request in July 2022 (paragraph 7.15, asciminib PSD), the resubmission presented clinical data to support asciminib being non-inferior to ponatinib in patients with the T315I mutation. While the PBAC acknowledged the inherent uncertainties associated with an unanchored and unadjusted indirect comparison, it considered that there was no signal of a difference between asciminib and ponatinib with respect to clinical efficacy or safety and noted that the small numbers of patients in the evidence base reflected the low prevalence of the patient population.
- 6.12 Consistent with the PBAC's request in July 2022 (paragraph 7.15, asciminib PSD), the resubmission presented an economic evaluation that reflects benchmarking against the second generation TKIs, nilotinib and dasatinib, in patients without the T315I mutation. The PBAC considered that the revised cost minimisations were appropriate, noting that the monitoring costs in the CMAs were required to be calculated over a 2-year time horizon, along with an adjustment to the equi-effective dose for dasatinib (paragraph 6.3). The PBAC noted that the Sponsor proposed the same EMP for both the asciminib 20 mg and 40 mg strengths and that the 20 mg strength should be priced such that it does not lead to an increase in cost versus the cost for nilotinib or dasatinib. The PBAC noted that the weighted average price of asciminib was calculated according to the relative use of dasatinib (%) and nilotinib (%) as reported in a DUSC Secretariat analysis of usage of a third TKI, and considered this to be appropriate. The PBAC noted the Sponsor's price proposal for non-T315I mutation patients was extended to the T315I population and considered that while the cost-effectiveness of asciminib in the T315I population is uncertain at the proposed price, it is acceptable in the context of very few patients (approximately 6 per year) having this mutation.
- 6.13 Consistent with the PBAC's request in July 2022 (paragraph 7.15, asciminib PSD), the resubmission recalculated the financial implications. The revised financial estimates in the Pre-PBAC Response used an asciminib price reflecting an updated dasatinib equi-effective dose of 109.7 mg/day (paragraph 6.3). The estimated net financial impact to the PBS/RPBS for the listing of asciminib was \$10 million to < \$20 million over six years, predominantly due to differences in cost of substituted therapies.
- 6.14 The PBAC recommended that asciminib should not be treated as interchangeable with any other drugs.
- 6.15 The PBAC advised that asciminib is not suitable for prescribing by nurse practitioners. The PBAC noted that existing TKI therapies are not available for nurse prescribing.
- 6.16 The PBAC recommended that the Early Supply Rule should apply to asciminib. The PBAC noted that the Early Supply Rule applies to existing TKI therapy.
- 6.17 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because asciminib is not expected to provide a substantial and clinically

relevant improvement in efficacy, or reduction of toxicity, over existing TKI therapy, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.

- 6.18 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

7 Recommended listing

- 7.1 Add new medicinal product as follows:

Patients who have received at least 2 prior TKIs

Initial Treatment and Grandfather

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
ASCIMINIB					
asciminib 20 mg tablet, 60	NEW	1	60	5	scemblix
asciminib 40 mg tablet, 60	NEW	1	60	5	scemblix

Restriction Summary [new] / Treatment of Concept: [new]

	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction type: <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)
Prescri bing	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: Chronic
	Severity: [blank]
	Condition: myeloid leukaemia
	Indication: Chronic myeloid leukaemia
	Treatment Phase: Initial PBS-subsidised treatment for patients without T315I mutation
	Clinical criteria
	The treatment must be the sole PBS-subsidised therapy for this condition
	AND
	Clinical criteria:
	The condition must not be in the blast phase
	AND
	Clinical criteria:
	The treatment must not exceed a total maximum of 18 months of therapy with PBS-subsidised treatment with a tyrosine kinase inhibitor for this condition under this restriction.
	AND
	Clinical criteria:
	The condition must be expressing the Philadelphia chromosome confirmed through cytogenetic analysis; or

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	The condition must have the transcript BCR-ABL tyrosine kinase confirmed through quantitative polymerase chain reaction (PCR)
	AND
	Clinical criteria:
	Patient must have failed an adequate trial of at least two tyrosine kinase inhibitors; OR
	Patient must have experienced intolerance, not failure to respond, to at least two tyrosine kinase inhibitors; OR
	Patient must have failed an adequate trial of at least one tyrosine kinase inhibitor with intolerance to at least another tyrosine kinase inhibitor.
	Administrative Advice: Tyrosine Kinase Inhibitors (TKI) are defined as either (i) imatinib, (ii) dasatinib, (iii) nilotinib
	Prescribing Instructions:
	<p>Failure of an adequate trial of a tyrosine kinase inhibitor is defined as:</p> <ol style="list-style-type: none"> Lack of response defined as either: <ol style="list-style-type: none"> failure to achieve a haematological response after a minimum of 3 months therapy; or failure to achieve any cytogenetic response after a minimum of 6 months therapy as demonstrated on bone marrow biopsy by presence of greater than 95% Philadelphia chromosome positive (Ph+) cells; or failure to achieve or maintain a major cytogenetic response or a peripheral blood BCR-ABL level of less than 1% after a minimum of 12 months therapy; OR Loss of a previously documented major cytogenetic response (demonstrated by the presence of greater than 35% Ph+ cells on bone marrow biopsy), during ongoing tyrosine kinase inhibitor (TKI) therapy; OR Loss of a previously demonstrated molecular response (demonstrated by peripheral blood BCR-ABL levels increasing consecutively in value by at least 5 fold to a level of greater than 0.1% confirmed on a subsequent test), during ongoing TKI therapy; OR Development of accelerated phase in a patient previously prescribed a TKI for any phase of chronic myeloid leukaemia; OR Disease progression (defined as a greater than or equal to 50% increase in peripheral white blood cell count, blast count, basophils or platelets) during TKI therapy in patients with accelerated phase chronic myeloid leukaemia. <p>Accelerated phase is defined by the presence of 1 or more of the following:</p> <ol style="list-style-type: none"> Percentage of blasts in the peripheral blood or bone marrow greater than or equal to 15% but less than 30%; or Percentage of blasts plus promyelocytes in the peripheral blood or bone marrow greater than or equal to 30%, provided that blast count is less than 30%; or Peripheral basophils greater than or equal to 20%; or Progressive splenomegaly to a size greater than or equal to 10 cm below the left costal margin to be confirmed on 2 occasions at least 4 weeks apart, or a greater than or equal to 50% increase in size below the left costal margin over 4 weeks; or Karyotypic evolution (chromosomal abnormalities in addition to a single Philadelphia chromosome).
	<p>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. Monday to Friday).</p>
	Administrative Advice:

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	Patients are eligible for PBS-subsidised treatment with only one TKI agent at any one time and must not be receiving concomitant interferon alfa therapy. Eligible patients may only swap between TKI agents if they have not failed prior PBS-subsidised treatment with that agent.
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Continuing Treatment

Restriction Summary [new] / Treatment of Concept: [new]	
	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction type: <input checked="" type="checkbox"/> Authority Required (streamlined) [new/existing code]
Prescribing rule level	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: Chronic
	Severity: [blank]
	Condition: myeloid leukaemia
	Indication: Chronic myeloid leukaemia
	Treatment Phase: Continuing treatment for patients without T315I mutation
	Clinical criteria:
	The treatment must be the sole PBS-subsidised therapy for this condition
	AND
	Clinical criteria:
	Patient must have received initial PBS-subsidised treatment with this drug for this condition;
	AND
	Clinical criteria:
	Patient must be undergoing first continuing treatment with this drug, demonstrating either (i) a major cytogenetic response (ii) a peripheral blood level of BCR-ABL of less than 1%; or
	Patient must be undergoing subsequent continuing treatment with this drug, demonstrating a 12-month response of either (i) a major cytogenetic response (ii) a peripheral blood level of BCR-ABL of less than 1%;
	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. Monday to Friday).
	Prescribing instruction:
	A major cytogenetic response [see Note explaining requirements] or a peripheral blood level of BCR-ABL of less than 1% on the international scale [see Note explaining requirements] must be documented in the patient's medical records.

Patients who have received at least 1 prior TKI and harbour the T315I mutation

Initial Treatment and Grandfather

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
ASCIMINIB asciminib 40 mg tablet, 60	NEW	5	300	5	scemblix

Restriction Summary [new] / Treatment of Concept: [new]	
	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction type: <input checked="" type="checkbox"/> Authority Required – (in writing only via mail/postal service or electronic upload to Hobart)

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Prescribing rule level	Administrative Advice: Special Pricing Arrangements apply.
	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.
	Episodicity: Chronic
	Severity: [blank]
	Condition: myeloid leukaemia
	Indication: Chronic myeloid leukaemia
	Treatment Phase: Initial PBS-subsidised treatment for patients with T315I mutation
	Clinical criteria:
	The condition must not be in the blast phase
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised therapy for this condition,
	AND
	Clinical criteria:
	The condition must be expressing the T315I mutation confirmed through a bone marrow biopsy pathology report
	AND
	Clinical criteria:
	The condition must be expressing the Philadelphia chromosome confirmed through cytogenetic analysis; or
	The condition must have the transcript BCR-ABL tyrosine kinase confirmed through quantitative polymerase chain reaction (PCR)
	AND
	Clinical criteria:
	Patient must have failed an adequate trial of at least one tyrosine kinase inhibitor as confirmed through a pathology report from an Approved Pathology Authority; OR
	Patient must have experienced intolerance, not failure to respond, to at least one tyrosine kinase inhibitor as confirmed through a pathology report from an Approved Pathology Authority.
	Administrative Advice: Tyrosine Kinase Inhibitors (TKI) are defined as either (i) imatinib, (ii) dasatinib, (iii) nilotinib, (iv) ponatinib
	Prescribing Instructions:
	<p>Failure of an adequate trial of a tyrosine kinase inhibitor is defined as:</p> <ol style="list-style-type: none"> Lack of response defined as either: <ul style="list-style-type: none"> (i) failure to achieve a haematological response after a minimum of 3 months therapy; or (ii) failure to achieve any cytogenetic response after a minimum of 6 months therapy as demonstrated on bone marrow biopsy by presence of greater than 95% Philadelphia chromosome positive (Ph+) cells; or (iii) failure to achieve or maintain a major cytogenetic response or a peripheral blood BCR-ABL level of less than 1% after a minimum of 12 months therapy; OR Loss of a previously documented major cytogenetic response (demonstrated by the presence of greater than 35% Ph+ cells on bone marrow biopsy), during ongoing tyrosine kinase inhibitor (TKI) therapy; OR Loss of a previously demonstrated molecular response (demonstrated by peripheral blood BCR-ABL levels increasing consecutively in value by at least 5 fold to a level of greater than 0.1% confirmed on a subsequent test), during ongoing tyrosine kinase inhibitor (TKI) therapy; OR Development of accelerated phase in a patient previously prescribed a TKI inhibitor for any phase of chronic myeloid leukaemia; OR

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	<p>5. Disease progression (defined as a greater than or equal to 50% increase in peripheral white blood cell count, blast count, basophils or platelets) during TKI therapy in patients with accelerated phase chronic myeloid leukaemia.</p> <p>Accelerated phase is defined by the presence of 1 or more of the following:</p> <ol style="list-style-type: none"> 1. Percentage of blasts in the peripheral blood or bone marrow greater than or equal to 15% but less than 30%; or 2. Percentage of blasts plus promyelocytes in the peripheral blood or bone marrow greater than or equal to 30%, provided that blast count is less than 30%; or 3. Peripheral basophils greater than or equal to 20%; or 4. Progressive splenomegaly to a size greater than or equal to 10 cm below the left costal margin to be confirmed on 2 occasions at least 4 weeks apart, or a greater than or equal to 50% increase in size below the left costal margin over 4 weeks; or 5. Karyotypic evolution (chromosomal abnormalities in addition to a single Philadelphia chromosome).
	<p>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. Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au</p> <p>Applications for authorisation under this restriction should be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/hpos)</p> <p>Alternatively, applications for authority to prescribe can be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos</p> <p>Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001</p>
	<p>Prescribing Instruction: Finalised</p> <p>The authority application must be made via the Online PBS Authorities System (real time assessment), or in writing via HPOS form upload or mail and must include:</p> <ol style="list-style-type: none"> (i) details (date, unique identifying number/code or provider number) of a bone marrow biopsy pathology report demonstrating the patient has active chronic myeloid leukaemia, either manifest as cytogenetic evidence of the Philadelphia chromosome; or (ii) details (date, unique identifying number/code or provider number) of a bone marrow biopsy/peripheral blood pathology report demonstrating RT-PCR level of BCR-ABL transcript greater than 0.1% on the international scale; and (iii) details (date, unique identifying number/code or provider number) of a bone marrow biopsy pathology report demonstrating evidence of the T315I mutation; and (iv) where there has been a loss of response to imatinib or dasatinib or nilotinib, details (date, unique identifying number/code or provider number) of the confirming pathology report(s) from an Approved Pathology Authority or details of the dates of assessment in the case of progressive splenomegaly or extramedullary involvement. <p>All reports must be documented in the patient's medical records.</p>
	<p>Prescribing Instruction:</p>

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	<p>Finalised</p> <p>If the application is submitted through HPOS form upload or mail, it must include:</p> <p>(i) A completed authority prescription form; and</p> <p>(ii) A completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).</p>
	<p>Prescribing Instruction: Patients are eligible for PBS-subsidised treatment with only one of imatinib, dasatinib, nilotinib ponatinib; or asciminib at any one time and must not be receiving concomitant interferon alfa therapy.</p>
	<p>Prescribing Instruction: Up to a maximum of 18 months of treatment may be authorised under this initial restriction.</p>

Continuing Treatment

Restriction Summary [new] / Treatment of Concept: [new]	
	<p>Category / Program: GENERAL – General Schedule (Code GE)</p>
	<p>Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners</p>
	<p>Restriction type:</p> <p><input checked="" type="checkbox"/> Authority Required (in writing only via mail/postal service or electronic upload to Hobart)</p>
Prescribing rule level	<p>Administrative Advice: Special Pricing Arrangements apply.</p> <p>Administrative Advice: No increase in the maximum quantity or number of units may be authorised.</p> <p>Administrative Advice: No increase in the maximum number of repeats may be authorised.</p>
	<p>Episodicity: Chronic</p>
	<p>Severity: [blank]</p>
	<p>Condition: myeloid leukaemia</p>
	<p>Indication: Chronic myeloid leukaemia</p>
	<p>Treatment Phase: Continuing Treatment for patients with T315I mutation</p>
	<p>Clinical criteria:</p>
	<p>Patient must have received initial PBS-subsidised treatment with this drug for this condition</p>
	<p>AND</p>
	<p>Clinical criteria:</p>
	<p>The treatment must be the sole PBS-subsidised therapy for this condition</p>
	<p>AND</p>
	<p>Clinical criteria:</p>
	<p>Patient must be undergoing first continuing treatment with this drug, demonstrating either (i) a major cytogenetic response (ii) a peripheral blood level of BCR-ABL of less than 1%; OR</p>
	<p>Patient must be undergoing subsequent continuing treatment with this drug, demonstrating a 12-month response of either (i) a major cytogenetic response (ii) a peripheral blood level of BCR-ABL of less than 1%.</p>
	<p>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. Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au</p> <p>Applications for authorisation under this restriction should be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/hpos)</p> <p>Alternatively, applications for authority to prescribe can be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos</p> <p>Or mailed to: Services Australia</p>

	Complex Drugs Reply Paid 9826 HOBART TAS 7001
	Prescribing instruction:
	A major cytogenetic response [see Note explaining requirements] or a peripheral blood level of BCR-ABL of less than 1% on the international scale [see Note explaining requirements] must be documented in the patient's medical records.
	<p>Prescribing Instruction: The continuing application for authorisation must be made via the Online PBS Authorities System (real time assessment), or in writing via HPOS form upload or mail and must include:</p> <p>(i) details (date, unique identifying number/code or provider number) of the pathology report from an Approved Pathology Authority demonstrating a major cytogenetic response [see Note explaining definitions of response]; or</p> <p>(ii) details (date, unique identifying number/code or provider number) of the pathology report from an Approved Pathology Authority demonstrating a peripheral blood level of BCR-ABL of less than 1% on the international scale [see Note explaining definitions of response].</p> <p>All reports must be documented in the patient's medical records.</p>
	<p>Prescribing Instruction: Finalised If the application is submitted through HPOS form upload or mail, it must include:</p> <p>(i) A completed authority prescription form; and</p> <p>(ii) A completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).</p>
	Prescribing Instruction: Patients are eligible for PBS-subsidised treatment with only one of imatinib, dasatinib, nilotinib; ponatinib or asciminib at any one time and must not be receiving concomitant interferon alfa therapy.

There may be flow-on changes to restrictions for imatinib, dasatinib, nilotinib and ponatinib.

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

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

The sponsor had no comment.