

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

1 Purpose of submission

- 1.1 The Category 1 submission requested a General Schedule Authority Required listing for the treatment of 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). This was the first consideration of asciminib by the PBAC.
- 1.2 PBS listing was requested on the basis of a cost-minimisation approach (CMA) versus nilotinib as the primary comparator, and ponatinib as a supplementary comparator. The key components of the clinical issue addressed by the submission are summarised in Table 1.

Table 1: 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
Intervention	Asciminib 80 mg once daily or 40 mg twice daily
Comparator	Main comparator: Nilotinib Supplementary comparators: ponatinib
Outcomes	MMR, CCyR
Clinical claim	Non-inferior efficacy and superior for safety compared nilotinib Non-inferior efficacy and superior safety compared with ponatinib

Source: Table 1.1-1, p 4 of the submission.

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 The submission was made under the TGA/PBAC Parallel Process. At the time of evaluation for PBAC consideration, the proposed TGA indication was:
- For the treatment of adult patients with Philadelphia chromosome-positive chronic myeloid leukaemia (Ph+ CML) in chronic phase (CP) previously treated with two or more tyrosine kinase inhibitors.*
- 2.2 The Delegate’s Overview became available during the evaluation period. The Delegate stated that “While a decision is yet to be made, at this stage I am inclined to approve the registration of the product.” The Delegate requested advice from the Advisory Committee on Medicines (ACM) regarding:

- Exclusion of patients with the T315I mutation from the indication. The ACM expressed concern around the underdosing of patients with the T315I mutation, given that a higher dose of 200 mg twice daily is required, compared with 80 mg daily for the general CML-CP population. The ACM urged the sponsor to include CML-CP patients with the T315I mutation in the indication, along with specific dosage instructions in the dosage and administration section of the Product Information (PI). The ACM acknowledged that all patients may not be tested for the T315I mutation, but considered that dosage consideration of asciminib is important should the presence of this mutation become known.
- Molecular response assessment. The ACM advised that major molecular response (MMR) is routinely assessed in patients receiving ongoing treatment for CML in Australia. The ACM noted that MMR is the goal of treatment and predicts survival, demonstrates treatment failure, disease progression and resistance. It also determines the need for change or discontinuation of TKIs and/or a need for bone marrow transplant. Treatment may also be discontinued if there is no MMR.
- Subgroup analyses of MMR. The ACM advised that the data regarding the subgroup analysis of MMR would be useful to treating physicians in Australia and should be included within the PI.
- The use of asciminib in patients <18 years. The ACM was of the view that the indication should be amended to exclude patients aged less than 18 years, and preferred the use of “patients 18 years and above” rather than “adults”.
- Overall, the ACM considered this product to have an overall positive benefit-risk profile for the requested indication, with substitution of “patients 18 years and above” for “adults”.

2.3 The pre-PBAC response provided an updated draft PI, which modified the wording of the indication to specifically include T315I mutation patients and added corresponding dosing instructions for this patient group. The updated proposed TGA indication is:

SCEMBLIX 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.*

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

3 Requested listing

3.1 The requested listing is presented below. Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

Public Summary Document – July 2022 PBAC Meeting

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

Initial treatment

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
Episodicity: Chronic
Administrative Advice: Special Pricing Arrangements apply.
Condition: Myeloid leukemia
Indication: Chronic myeloid leukemia
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:
The condition must be expressing the Philadelphia chromosome <i>confirmed through cytogenetic analysis</i> ; OR The condition must have the transcript BCR-ABL tyrosine kinase <i>confirmed through quantitative polymerase chain reaction (PCR)</i>
AND
Clinical criteria:
Patient must have failed an adequate trial of at least two tyrosine kinase inhibitors (imatinib, dasatinib, nilotinib or ponatinib); OR Patient must have developed intolerance to at least two tyrosine kinase inhibitors (imatinib, dasatinib, nilotinib or ponatinib); OR Patient must have failed an adequate trial of at least one tyrosine kinase inhibitor AND developed intolerance to at least another tyrosine kinase inhibitor
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

Public Summary Document – July 2022 PBAC Meeting

<p>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</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>Blast crisis is defined as either:</p> <ol style="list-style-type: none"> 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. <p><i>Administration instruction</i> <i>Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).</i></p>
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First continuing treatment

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction Type: <input checked="" type="checkbox"/> Authority Required – Streamlined
Episodicity: Chronic
Administrative Advice: Special Pricing Arrangements apply.
Condition: Myeloid leukemia
Indication: Chronic myeloid leukemia
Treatment Phase: First continuing treatment
Clinical criteria:
Patient must have received initial PBS subsidised treatment with this drug for this condition
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

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners

Public Summary Document – July 2022 PBAC Meeting

Restriction Type: <input checked="" type="checkbox"/> Authority Required – Streamlined
Episodicity: Chronic
Administrative Advice: Special Pricing Arrangements apply.
Condition: Myeloid leukemia
Indication: Chronic myeloid leukemia
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:
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

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction Type: <input checked="" type="checkbox"/> Authority Required – Streamlined
Episodicity: Chronic
Administrative Advice: Special Pricing Arrangements apply.
Condition: Myeloid leukemia
Indication: Chronic myeloid leukemia
Treatment Phase: Grandfather
Clinical criteria:
Patient must have previously received non-PBS subsidised <i>with this</i> drug for this condition prior to [list date]
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%
Prescriber Instructions:
<i>A Grandfathered patient may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the first continuing treatment criteria.</i>
Prescribing Instructions
<i>This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.</i>

- 3.2 The submission proposed a special pricing arrangement (SPA), where the proposed effective approved ex-manufacturer price (AEMPs) reflects the weighted average cost of treatment of nilotinib (1%) and ponatinib (1%); the basis for this split was not provided. The submission expected approximately 120 patients would be grandfathered if asciminib was PBS listed by 1 December 2022. Subsequent access should then be via the subsequent continuing treatment restriction.
- 3.3 The proposed restriction was consistent with the TGA draft PI provided at the time the submission was lodged. The basis for these restrictions was the key trial (ASCEMBL) population, which only enrolled patients who had failed two or more TKIs before receiving asciminib. ASCEMBL also only enrolled patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2, and excluded patients with T315I-mutated CML; these exclusion criteria were not, however, reflected in the proposed restrictions. The submission stated that T315I-mutated CML patients were excluded from the trial to facilitate the use of bosutinib in the comparator arm, as patients with this mutation would not be expected to respond to bosutinib. The submission claimed asciminib would be effective in patients with a T315I mutation, and the proposed restriction would allow substitution of asciminib for ponatinib in these patients; this issue is further discussed in paragraphs 4.8, 6.22 and 6.31 below.
- 3.4 The Pre-Sub Committee Response (PSCR) noted that ponatinib has two separate PBS restrictions for: 1) patients who demonstrate resistance or intolerance to two prior TKIs (nilotinib or dasatinib); and 2) patients with the T315I mutation who have failed at least one prior TKI (imatinib, nilotinib or dasatinib). The ESC considered that it may be necessary for asciminib to also have 2 restrictions: one for the general population who have failed/are intolerant to prior TKIs (as per the requested restriction), and a separate restriction for patients with the T315I mutation, noting that a higher dose is required for the latter patients (200 mg twice daily, compared with 80 mg once daily or 40 mg twice daily for the non-T315I mutation patients). The ESC noted that patients who harbour the T315I mutation are in a poor prognosis subgroup who require a different dose and specific listing via a separate restriction.
- 3.5 The pre-PBAC response provided an updated draft PI, which modified the wording of the indication to specifically include T315I mutation patients in line with advice from the ACM (paragraph 2.3). The pre-PBAC response stated that the sponsor "... will take advice from the PBAC as to the PBS restriction for asciminib". The PBAC agreed with the ESC that patients with the T315I mutation are a poor prognosis subgroup who should be treated with asciminib and that a separate restriction would be required given the different dosing.
- 3.6 The PBAC noted the comments from the Secretariat that the PBS patient populations for the nominated comparators, nilotinib and ponatinib, differ from the intended population for asciminib as follows: (1) While the requested asciminib restriction for initial treatment specifies that patients must express the Philadelphia chromosome or have the transcript BCR-ABL tyrosine kinase in the clinical criteria, the comparator restrictions for initial treatment in the third-line setting do not specify this (because

patients have already received first-line imatinib or dasatinib, which do specify this clinical criteria in their restrictions for initial treatment, as does first-line nilotinib). (2) While the requested asciminib restriction specifies that patients must have failed or developed an intolerance to at least 2 TKIs (imatinib, dasatinib, nilotinib or ponatinib), or failed one TKI and developed intolerance to another TKI, the nilotinib listing specifically names the prior lines of therapy (i.e. to receive third-line nilotinib, patients must have failed first-line therapy with imatinib and second-line therapy with dasatinib); in contrast, to receive ponatinib, the order of prior therapy is not specified, in that patients must have failed or been intolerant to both dasatinib and nilotinib or they must have failed treatment with one prior TKI and be expressing the T315I mutation. The prior therapies used by patients randomised to the asciminib arm of the ASCEMBL trial were imatinib (82.8%), dasatinib (83.4%), nilotinib (66.2%) and/or ponatinib (14.6%); the trial inclusion criteria also allowed prior therapy with radotinib.

- 3.7 A summary of the restrictions for TKI therapies currently available on the PBS is provided in Table 2. There is a maximum of 18 months of therapy available with dasatinib, imatinib or nilotinib from the date the first application for initial treatment was approved to demonstrate a major cytogenetic response or peripheral blood BCR-ABL level of less than 1% on the international scale.

Table 2: Restrictions of PBS-listed treatments for CML-CP

Component	Description
Imatinib	<p>1L (chronic phase) Initial treatment or Intolerance (not failure to respond) to dasatinib or Intolerance (not failure to respond) to nilotinib</p>
Dasatinib	<p>1L (chronic phase) Initial treatment or Intolerance (not failure to respond) to imatinib or Intolerance (not failure to respond) to nilotinib</p> <p>2L (chronic, blast, accelerated phase) Not failed dasatinib 1L Failed imatinib 1L OR Failed nilotinib 1L OR intolerance (not failure to respond) to 2L nilotinib</p> <p>3L (chronic, blast, accelerated phase) Not failed dasatinib 1L or 2L Failed imatinib 1L Failed nilotinib 2L</p>
Nilotinib	<p>Similar to dasatinib</p> <p>1L (chronic phase) Initial treatment or Intolerance (not failure to respond) to imatinib or Intolerance (not failure to respond) to dasatinib</p> <p>2L (chronic, accelerated phase) Not failed nilotinib 1L Failed imatinib 1L OR Failed dasatinib 1L OR Intolerance to 2L dasatinib</p> <p>3L (chronic, accelerated phase) Not failed nilotinib 1L or 2L Failure of imatinib 1L Failure of dasatinib 2L</p>
Ponatinib	<p>All patients Patients must have failed or developed intolerance to dasatinib AND nilotinib, and must not be eligible for treatment with nilotinib due to a blast crisis.</p> <p>T315I-mutated patients Failure of 1L imatinib OR dasatinib OR nilotinib</p>

Source: Summarised from respective PBS restrictions.

1L = first-line; 2L = second-line; 3L = third-line; CML-CP = chronic myeloid leukaemia in the chronic phase.

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

4 Population and disease

4.1 CML is a myeloproliferative disorder associated with the Philadelphia chromosome t(9;22)(q34;q11) resulting in a BCR-ABL fusion gene. This genetic abnormality results in the formation of a unique gene product (BCR-ABL1), which is a constitutively active

tyrosine kinase, implicated in the development of CML, and a primary target for the treatment of this disease. In Australia in 2017, CML had an annual incidence of 1.3 cases per 100,000 (15-20% of all leukaemias in adults), with a median age of 63 years, and a slight male preponderance¹.

4.2 CML has three disease phases:

- Chronic phase
- Accelerated phase
- Blast crisis.

4.3 The initial, chronic phase is indolent and may last 5-6 years. The disease will progress to a more aggressive disorder (accelerated phase), during which time disease control is more difficult to achieve. In virtually all patients, the disease culminates in an acute leukaemia, termed 'blast crisis'. Prior to the availability of tyrosine kinase inhibitors (TKIs), this phase, which is generally refractory to treatment, occurred approximately three to five years after the diagnosis of CML and 18 months after the onset of the accelerated phase.

4.4 The four TKIs available on the PBS for the treatment of CML-CP are:

- First generation: imatinib
- Second generation: nilotinib and dasatinib
- Third generation: ponatinib.

4.5 With TKI-adherent therapy, patients with CML-CP achieve a life expectancy comparable to the general population.²

4.6 Patients in CML-CP must be monitored for response. There are three categories of response in CML:

- **Hematologic response** is assessed by the white blood cell count, differential, and platelet count. Complete hematologic response (CHR) is defined by a white blood cell count <10,000/microL with no immature granulocytes and <5 percent basophils on differential; platelet count <450,000/microL; and spleen not palpable.
- **Cytogenetic response** is assessed by chromosome banding analysis of marrow cell metaphases. Cytogenetic response is classified according to the percent Philadelphia chromosome positive (Ph+) cells into: no response (>95%), minimal (66-95%), minor (36-65%), major (1-35%), and complete (no Ph+ cells) response. For patients with an inadequate number of metaphases, complete cytogenetic

¹ Australian Institute of Health and Welfare. Cancer data in Australia. Australian Government. 2021.

² Radivoyevitch T, Weaver D, Hobbs B, Maciejewski JP, Hehlmann R, Jiang Q, *et al.* Do persons with chronic myeloid leukaemia have normal or near normal survival? *Leukemia*. 2020 02/01;34(2):333-5.

response (CCyR) can also be documented by fluorescence in situ hybridisation (FISH) of blood interphase cell nuclei demonstrating <1 percent BCR-ABL1-positive nuclei of at least 200 nuclei. Patients may achieve a complete cytogenetic response (no BCR-ABL1 expression), which provides the possibility of therapy discontinuation.

- **Molecular response** is assessed by quantitative polymerase chain reaction (Q-PCR) of the peripheral blood and defined according to the level of detection of the assay. The most recent European LeukaemiaNet (ELN) definition of a MMR is when BCR-ABL1 expression is <0.1%.

- 4.7 Whilst TKIs offer effective therapy, there are some patients who are unable to tolerate the side effects of treatment or develop resistance to treatment. Up to 5% of patients treated with a TKI will be unable to tolerate long-term treatment due to side effects.³ Patients who require additional lines of treatment due to resistance to prior TKIs are less likely to respond to subsequent TKI therapy, which correlates with poorer survival.^{4,5} This is reflected in the classification used in Australia, where patients only progress in ‘lines’ of therapy if they demonstrate resistance, not intolerance, to a previous TKI. The PBAC noted that asciminib could be used after 2 prior TKIs, but would be considered the third drug being used in the first line if the patient had been intolerant to both prior TKIs.
- 4.8 Disease mutations may confer resistance to particular TKIs and susceptibility to other treatments. The most clinically relevant is the T315I mutation, which is resistant to all currently listed TKI therapy except ponatinib (paragraphs 3.3 and 3.4). The pivotal ASCEMBL trial excluded patients with the T315I mutation; however, asciminib is active against the T315I mutation and the ACM supported the inclusion of patients with the T315I mutation in the indication. The PBAC previously estimated that 15% of patients who fail first-line TKI therapy will have the T315I mutation (paragraph 6.41, ponatinib Public Summary Document (PSD), November 2014 PBAC meeting).
- 4.9 There are no randomised trials that have directly compared the efficacy of second generation TKIs (nilotinib and dasatinib) in patients with chronic phase CML who experience failure of an initial TKI. Comparisons of TKIs in phase II trials in this population suggest that they have similar efficacy, however second-generation TKIs

³ Negrin, R, Schiffer, C, Atallah, E. UpToDate: Treatment of chronic myeloid leukaemia in chronic phase after failure of initial therapy. Wolters Kluwer, 2022.

⁴ Ibrahim AR, Paliompeis C, Bua M, Milojkovic D, Szydlo R, Khorashad JS, *et al.* Efficacy of tyrosine kinase inhibitors (TKIs) as third-line therapy in patients with chronic myeloid leukemia in chronic phase who have failed 2 prior lines of TKI therapy. *Blood*. 2010 Dec 16;116(25):5497-500.

⁵ Ongoren S, Eskazan AE, Suzan V, Savci S, Erdogan Ozunal I, Berk S, *et al.* Third-line treatment with second-generation tyrosine kinase inhibitors (dasatinib or nilotinib) in patients with chronic myeloid leukemia after two prior TKIs: real-life data on a single center experience along with the review of the literature. *Hematology*. 2018 May;23(4):212-20.

demonstrated significantly deeper and faster responses than imatinib.⁶ Modelling based on clinical trials of imatinib, nilotinib, dasatinib and bosutinib suggest that in patients with newly diagnosed CML-CP, early aggressive treatment with second-generation TKIs, instead of imatinib (see paragraph 5.1 below), may reduce the risk of disease resistance/mutation, halving the proportion of patients who will fail 3 TKIs (6% vs 12% in patients initially treated with imatinib).⁷

- 4.10 The available TKIs have unique safety profiles, which must be considered in the long-term care of patients with CML-CP. The choice of TKI is based on the side effect profiles and comorbid conditions of individual patients, combined with testing for any mutations which may confer treatment resistance.
- 4.11 All the TKIs available on the PBS for CML bind to the ATP receptor site of the BCR-ABL tyrosine kinase. In contrast, asciminib inhibits the kinase activity of the BCR-ABL fusion protein, by specifically targeting the ABL myristoyl pocket. For this reason, asciminib is the first and only medicine to be considered a Specifically Targeting the ABL Myristoyl Pocket (STAMP) inhibitor.
- 4.12 The submission proposed asciminib 80 mg once daily or 40 mg twice daily in patients with CML-CP, who had been previously treated with two or more TKIs. This is consistent with the draft PI, and means asciminib may be prescribed as ‘first line’ (intolerant to two prior TKIs) and up to ‘fourth line’ (resistant to three prior TKIs).

5 Comparator

- 5.1 The submission nominated nilotinib as the main comparator. This was based on drug sequence data from the 10% PBS sample, which suggested that, from 2016 – 2021, nilotinib made up 49.1% of third-line usage. These data are derived from the low number of patients (N=108) who had recorded specific sequential use of three TKIs at any time between 2016–2021, and do not account for recent changes in prescribing trends. The most comprehensive prescription data are provided in the 10% PBS sample describing patient data for nearly 4,000 patients who required TKIs, by line of use, from June 2016–June 2021. These data show that nilotinib was the most-used third TKI in late 2016 (approximately 50% of all third-TKIs prescribed), but since then has declined in use, while imatinib has recently increased in use as the third TKI prescribed, whilst declining as the first TKI used. This trend change is reflective of shifting clinical practice; there is evidence to suggest that CML-CP should be ‘hit hard and hit early’, where use of second-generation TKIs (nilotinib and dasatinib) in the

⁶ Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2020 update on diagnosis, therapy and monitoring. *American Journal of Hematology*. 2020 06/01;95(6):691-709.

⁷ Akard L, Albitar M, Hill CE, Pinilla-Ibarz J. The "hit hard and hit early" approach to the treatment of chronic myeloid leukemia: Implications of the updated national comprehensive cancer network clinical practice guidelines for routine practice. *Clinical Advances in Hematology and Oncology*. 2013 07/01;11:421-32.

first-line (paragraph 4.9) may produce more enduring disease control with less potential for mutation/resistance, compared to using imatinib in the first line.

- 5.2 The evaluation provided a summary of prescription frequencies in third-line therapy, based on the 10% PBS sample between 2016–2021 (Table 3). According to these data, dasatinib, not nilotinib, is the most-used therapy as ‘third TKI’ in Australia. The PSCR argued that the figures presented by the evaluation correspond to the share of medicines used in third or later lines (i.e., a combined total) in the original data set, and that in later lines of treatment there is less certainty that patients are in the chronic phase, as opposed to the accelerated or blast phases. However, the ESC noted that the vast majority of prescriptions are for the chronic phase; if a patient progressed due to an accelerated or blast phase, the goal of treatment is to return them to the chronic phase. If they cannot be returned to chronic phase, then their management is progressed beyond TKI therapy to transplant, and if they are returned to chronic phase, they remain on treatment until disease progression, at which point they may try an alternative TKI. The ESC noted that allogeneic bone marrow transplant would be discussed with a patient as a future option at the third-line stage of treatment.

Table 3: Australian prescription rates and costs of TKI use in treatment of CML

PBS-subsidised TKI	Share of use as third TKI (number of patients, %)		Mean use as third TKI, June 2020 – June 2021 (mean number of patients, %) N=437	DPMQ
	June 2016 N=190	June 2021 N=463		
Imatinib	32 (17%)	116 (25%)	87 (20%)	\$662.61
Dasatinib	74 (39%)	168 (36%)	167 (38%)	\$3,247.11
Nilotinib	84 (44%)	137 (30%)	146 (33%)	\$5,056.76
Ponatinib	0 (0%)	42 (9%)	37 (8%)	\$6,172.87

Source: ‘Total patients on Drugs by line’ tab, 10% PBS sample DUSC Reanalysis.xlsx, PBS listings of DPMQ as of 10/04/2022.
CML = chronic myeloid leukaemia; DPMQ = Dispensed Price for Maximum Quantity; TKI = tyrosine kinase inhibitor.

- 5.3 The PSCR maintained that nilotinib is the appropriate comparator. It stated that asciminib will only replace therapies when patients fail or experience intolerance to their current treatment, and thus provided an updated analysis of treatment sequences to determine which TKI is the most frequently used to initiate treatment after failure or intolerance to a second TKI. The PSCR stated that the analysis presented in the submission, and the PSCR analysis, showed that nilotinib was the most commonly used third TKI in all treatment sequences (49.1% and 54.5% (re-analysis) of patients). The ESC noted that these data only represent 108 patients with specific sequences and the updated data only represent 116 patients, and furthermore considered it to be out of date (data range started at 2016). The pre-PBAC response maintained that nilotinib is the appropriate main comparator, and stated that dasatinib is listed on the PBS for patients in all three CML phases (chronic, accelerated or blast; Table 2), whereas nilotinib has restrictions for only chronic or accelerated phases, and that the proportion of dasatinib use in third or later lines in CML therefore reflects a wider population relative to nilotinib.

- 5.4 The submission stated that asciminib may also be used in later lines of treatment. In the pivotal ASCSEMBL trial, 56.7% of patients in the asciminib arm had been treated with two prior TKIs and 33.8% had been treated with three prior TKIs. For patients who have received three prior TKIs, ponatinib is the only remaining choice of PBS-subsidised therapy. As such, ponatinib was nominated as the supplementary comparator. This is the most appropriate comparator for patients who have failed 3 prior TKIs, however only in patients who do not have the T315I mutation; this represents a minority market share of ponatinib use in Australia. The pre-PBAC response further clarified that ponatinib was not nominated as the supplementary comparator on the basis that it was likely used in patients with the T315I mutation; rather, the claim of non-inferior efficacy of asciminib versus ponatinib was based on the comparison between asciminib and the resistant/intolerant cohort of the PACE trial (with 98% of the patients in this cohort having received at least two prior TKIs).
- 5.5 The PBAC previously estimated that 15% of patients who fail first-line TKI therapy will have the T315I mutation (paragraph 4.8), and ponatinib will be used in >90% of these patients. The PBAC estimation of ponatinib uptake is consistent with the submission's projected ponatinib use in 9-11% of the target population over the next 6 years, assuming the vast majority of this use is in patients with the T315I mutation. The submission did not present any comparative evidence between asciminib and ponatinib in patients with the T315I mutation, but claimed that asciminib is non-inferior to ponatinib in terms of its effectiveness. The ESC noted that there are single arm data available for 45 patients with Ph+ CML in CP with the T315I mutation treated with asciminib in a multi-centre, open-label clinical trial, CABL001X2101; this trial was excluded from the main analysis of the submission as it was a dose-finding study, but presented in an appendix. The evaluation provided a brief analysis of the T315I-mutated patients in the CABL001X2101 (asciminib) and PACE (ponatinib) trials (see paragraph 6.22 below).
- 5.6 In the PBAC consideration of ponatinib in CML (November 2014 and July 2015), the PBAC noted that the comparators for ponatinib were complex. It considered that depending on different clinical scenarios, the comparators could be dasatinib or nilotinib or other non-TKI therapies, e.g. allogeneic transplantation. The PBAC considered that benchmarking against nilotinib and dasatinib in second- and subsequent line therapy in CML was a reasonable basis for establishing a cost-effective price for ponatinib (paragraph 7.7, ponatinib PSD, November 2014 PBAC meeting). The ESC and the PBAC considered that the same principles could apply in the current consideration for asciminib.
- 5.7 In the context of the cost-minimisation approach taken by the submission, a further consideration for PBAC is that, under Section 101(3B) of the National Health Act 1953, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. If the committee is so

satisfied, it must make a statement to this effect. For the requested population, imatinib and dasatinib are less costly than nilotinib and ponatinib, and are possible alternative therapies. The ESC noted that imatinib, as a first generation TKI, is less effective than the second generation TKIs. Specifically, dasatinib was recommended for listing in March 2007 for CML-CP patients not responding to imatinib because of resistance or intolerance, on the basis of significant advantages in effectiveness over imatinib in this patient group. The PBAC was satisfied that asciminib provides, for some patients, a significant improvement in efficacy over imatinib. The PBAC considered that the clinical data presented in the submission did not adequately support that asciminib would provide a significant improvement in efficacy and/or reduction in toxicity over the second generation TKIs. However, the PBAC was satisfied that asciminib, as an additional TKI with a different mechanism of action, may provide a significant improvement in efficacy and/or reduction in toxicity over standard of care (non-TKI therapy) for patients who have either failed, or unable to tolerate, both dasatinib and nilotinib.

5.8 Overall, the ESC and the PBAC considered that:

- Prescription data from 2016 is not likely to be representative of current or future use of TKIs in CML-CP. Prescription data from 2021 reflects increased use of imatinib in the third-line setting, and may also indicate that there is increased use of second generation TKIs (nilotinib and dasatinib) as first-line therapy.
- Second-generation TKIs have demonstrated significantly deeper and faster responses than imatinib.
- A benchmarking approach may be appropriate for asciminib to establish a cost-effective price (consistent with the approach for the listing of ponatinib), given that TKI treatments are used in sequence following failure or intolerance.
- Either dasatinib or both dasatinib and nilotinib may be appropriate comparator/s in patients without the T315I mutation. A comparison of asciminib and dasatinib was not included in the submission, however nilotinib was listed on a cost-minimisation basis versus dasatinib (nilotinib PSD, p11, March 2008). Dasatinib is less costly than nilotinib.
- Ponatinib is the appropriate comparator for patients with the T315I mutation.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from a health care professional (HCP) and

organisations (2; The Leukemia Foundation and Rare Cancers Australia) via the Consumer Comments facility on the PBS website.

- 6.3 The comments from a HCP described a range of benefits of treatment with asciminib, including effectiveness where other TKIs have failed and a lower level of toxicity than all the currently available TKIs. The HCP considered asciminib to be an essential medication for a small number of patients with CML who have no other options.
- 6.4 The PBAC noted that The Leukaemia Foundation received feedback from Australian clinicians using asciminib via the ASCEND-CML trial (in combination with imatinib) and the sponsor's Compassionate Access Scheme, as well as from a patient being treated with the second generation TKIs nilotinib and dasatinib. The clinicians noted that the tolerability of asciminib compares favourably with imatinib (with respect to gastrointestinal side effects) or dasatinib (with respect to pleural effusions), and considered it to be efficacious in reducing leukemia load rapidly. The clinicians noted the achievement of deeper molecular responses than with previously prescribed TKIs. They noted that responses to asciminib have been variable (as expected in the resistant setting) but can be excellent in some patients, and day-to-day side effects are non-existent for the majority of patients. The clinicians stated that some patients who could not tolerate any other TKI have shown good tolerance to asciminib and that the only alternative would have been an allograft. The patient being treated with second generation TKIs nilotinib and dasatinib described the serious toxicity associated with these agents and associated hospitalisations for recovery. The patient stated that the side effects of the drugs have significantly reduced their quality of life. Overall, the Leukemia Foundation stated that asciminib has been shown in the ASCEMBL trial to be comparatively effective and well tolerated, and urged the PBAC to recommend listing for eligible patients who have already undergone treatment with TKIs.
- 6.5 Rare Cancers Australia have previously supported a number of patients with CML and state that they would welcome the listing of asciminib on the PBS as it is well tolerated and does not have the same side-effect profile as other treatments for this population.
- 6.6 In general, the PBAC noted that the advice was supportive of the evidence provided in the submission.

Clinical trials

- 6.7 The submission presented one head-to-head trial comparing asciminib to bosutinib (N=233), ASCEMBL. As bosutinib is not PBS-listed in Australia, 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 outcome measures compared were MMR and CCyR, which have previously been accepted by the PBAC (Nilotinib PSD July 2011; Ponatinib PSD July 2015).

6.8 Details of the trials presented in the submission are provided in Table 4. Whilst the ENACT and Giles et al. (2010) trials also enrolled patients in accelerated phase and blast crisis, these groups were excluded from the comparison.

Table 4: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Asciminib trial		
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. Réa et al. A Phase 3, Open-Label, Randomised Study of Asciminib, a STAMP Inhibitor, vs Bosutinib in CML After ≥ 2 Prior TKIs.	- 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) Blood 2021; 138(21): 2031-2041.
Nilotinib trials		
ENACT	An open-label, multicenter, expanded access study of oral AMN 107 in adult patients with Imatinib (Glivec®/Gleevec®) - resistant or - intolerant chronic myeloid leukaemia in blast crisis, accelerated phase or chronic phase. Nicolini et al. Expanding Nilotinib Access in Clinical Trials (ENACT). An Open-Label, Multicenter Study of Oral Nilotinib in Adult Patients With Imatinib-Resistant or Imatinib-Intolerant Philadelphia Chromosome-Positive Chronic Myeloid Leukaemia in the Chronic Phase. Nicolini et al. Expanding nilotinib access in clinical trials (ENACT) study in adult patients (PTS) with imatinib-resistant or -intolerant chronic myeloid leukaemia (CML): subgroup analysis of patients who failed prior dasatinib therapy.	15 September 2009. Cancer 2012; 118 (1): 118-126. Blood 2009; 94 (S2): p 257
Giles, Abruzzese ¹	Giles et al. (2010). Nilotinib is active in chronic and accelerated phase chronic myeloid leukaemia following failure of imatinib and dasatinib therapy.	Leukaemia 2010; 24 (7): 1299-1301.
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: Table 2.2-1, p 38 and Table 2(a).2-1, p 116 of the submission.

6.9 The key features of the evidence informing the unadjusted, unanchored ITC are summarised in Table 5. ASCEMBL excluded patients with the T315I mutation, while the nilotinib trials did not; 8% of patients in Giles et al. (2010) had this mutation, and it was not tested for in ENACT. Nilotinib is ineffective in patients with this mutation, and this may have biased the efficacy results against nilotinib. The risk of bias in individual studies was found to be low, however the risk of bias in the ITC are considered to be high, due to the combination of transitivity issues, bias in ASCEMBL safety data reporting with fewer AEs considered treatment-related for asciminib versus bosutinib, and mismatched patient exposure/follow-up between the asciminib arm of ASCEMBL and the PACE trial population.

Table 5: Key features of the included evidence – indirect comparison

Trial	N	Design/ duration	Risk of bias	Patient population	Key outcomes
asciminib vs bosutinib					
ASCEMBL	233	R, MC, OL 22.3 mths ^a	Low	Failed at least 2 prior TKIs	MMR and CCyR
Nilotinib Trials					
ENACT	1,422	SA, MC, OL 7.4 mths	Low	Prior imatinib failure; subgroup (n=218) failed 2 prior TKIs	MMR and CCyR
Giles et al. (2010)	39	SA, MC, OL 12 mths	Low	Failed 2 prior TKIs	MMR and CCyR
Ponatinib trial					
PACE	270	SA, MC, OL 15 mths ^b	Low	Failed at least 2 prior TKIs	MMR and CCyR

Source: Table 2(a).3-4, p 126 of the submission and Appendix 12 to the submission.

CCyR = complete cytogenetic response; DB = double blind; MC = multi-centre; MMR = major molecular response; OL = open label; OS = overall survival; PFS = progression-free survival; R = randomised; SA = single arm; TKI = tyrosine kinase inhibitor.

^a Updated analysis

^b Primary analysis; the updated analysis provided 56.8 months of follow-up.

6.10 Table 6 shows the median duration of treatment and dose across the asciminib, nilotinib and ponatinib trials.

Table 6: Median duration of treatment between studies

Trial ID	Duration of treatment Median (range) (weeks)	Duration of follow-up Median (range) (months)	Mean / median dose intensity per day
Asciminib (Primary and secondary analyses)			
ASCEMBL (DCO 25 May 2020; Wk 24)	43.36 (0.1-129.9)	14.9 (5.7-30.3)	74.2 mg / 80.0 mg
ASCEMBL (DCO 6 Jan 2021; Wk 48)	67.14 (0.1-162.1)	22.3 (13.1-37.7)	71.1 mg / 79.8 mg
ASCEMBL (DCO 6 Oct 2021; Wk 96) ^c	103.1 (0.1-201.1)	NR	NR / NR
Nilotinib			
ENACT	All CML-CP: 37.9 (0.1-115.0) 2 prior TKIs: 32.2 (0.6-108.0)	All CML-CP: 7.4 (0.03- 26.5) 2 prior TKIs: NR	All CML-CP: NR / 782.5 mg 2 prior TKIs: NR / NR
Giles, Abruzzese ¹	47.7 (< 4.3-126.5)	12	NR / NR
Ponatinib			
PACE primary analysis	55.5 (0.1 – 107.5) ^a	All CML-CP: 15 (< 1-25) Resistant/intolerant cohort: 16 (0.1-25)	NR / 30 mg
PACE end of study analysis	139.1 (0.4-316.3) ^b	All CML-CP: 56.8 (0.1- 73.1)	NR / 27.2 mg

Source: Table 2.6-7, p 95 and Table 2(a).4-1, p 131 of the submission, Table 12-02, p 98 of the ASCEMBL CSR.

CML-CP = chronic myeloid leukaemia-chronic phase; DCO = data cut-off; NR = not reported; Wk = week

^a Reported for entire PACE population (including patients with CML-CP, AP, BP and Ph+ ALL)

^b Reported in the total CML-CP population

^c The pre-PBAC response presented additional data from ASCEMBL trial (data cutoff of Oct 2021, compared to Jan 2021 in the ESC ADV).

Asciminib versus nilotinib

- 6.11 Age, gender and race were reasonably similar between patients enrolled in the ASCEMBL and ENACT trials. ASCEMBL enrolled fitter patients, reflected in the better ECOG PS (ECOG PS = 0 in 80% of patients, compared to the ENACT and Giles *et al.* (2010) rates of vs 73.3% and 64%, respectively), and patients in the ASCEMBL trial had a substantially shorter time since initial diagnosis, compared with the nilotinib trials (3.8 years vs 6.7 and 7.4 years, respectively). The proportion of patients with resistance to the prior TKI differed substantially between the ASCEMBL (60.5%) and Giles *et al.* (2010) (31%) trials, a difference which may bias the results in favour of nilotinib. Patients in ASCEMBL had higher rates of baseline MCyR compared to the nilotinib trials, which recorded MCyR as ‘best response to prior TKI’ (28-36% vs 14.2% [2 prior TKI subgroup of ENACT] and 21% in Giles *et al.* [2010]), which may bias the results in favour of asciminib. The PSCR noted (p2) that the outcome of CCyR in ASCEMBL is measured in the CCyR analysis set (defined as the patients who were not in CCyR at baseline), but is measured in all patients in ENACT, which is likely to bias the indirect comparison of CCyR against asciminib; however, this highlights the difficulty of the comparison, as ENACT listed the ‘best response to second-line TKI’, where ASCEMBL listed baseline MCyR rates. It is unknown how many patients in the ENACT trial had a baseline CCyR.
- 6.12 Patients in ASCEMBL had more prior TKIs (approximately 57% had 2 prior, and 43% had ≥ 3 prior) compared to those in ENACT (1 prior TKI, apart from a subgroup of 218 patients who had 2 prior) and Giles *et al.* (2010) (2 prior TKIs). This difference may bias the results in favour of nilotinib in the ITC. ASCEMBL only reported the discontinuation reason for the last TKI (61% resistance, 38% intolerance). According to the Australian definition, the patient populations in these trials represent an unknown mixture of first-line (all prior TKIs failed due to intolerance), second-line (one prior TKI failed due to intolerance), third- and fourth-line (two and three prior therapies failed due to resistance) therapies.

Asciminib versus ponatinib

- 6.13 Comparing the asciminib arm of the ASCEMBL trial vs ponatinib in the PACE trial, ponatinib patients were older (52 vs 60 years), not as fit (ECOG PS of 0 in 80.3% vs 70%), had fewer patients with a baseline MCyR (28-36% vs 20%), had more prior TKIs (≥ 3 prior TKIs 43% vs 56%), and more failure of prior TKI due to lack of efficacy (61% vs 84%). All of these differences suggested a poor prognosis in patients in the PACE trial and thus biased the results in favour of asciminib over ponatinib in the unanchored comparison. The difference in lack of efficacy of prior TKIs may be influenced by the inclusion of the T315I mutation subgroup in PACE (24% of the study population), which renders CML-CP resistant to other TKIs (imatinib, dasatinib, nilotinib). These differences prognostically favour patients in the asciminib arm of ASCEMBL compared to PACE. The PACE trial excluded patients who had a baseline CCyR, whilst ASCEMBL did not, which may bias efficacy results in favour of asciminib. The asciminib arm also had substantially fewer prior TKIs compared to the

resistant/intolerant (R/I) cohort of PACE (≥ 3 prior TKIs 43.3% vs 66.5%); these two populations are the most comparable (no T315I mutations).

- 6.14 The patients in the ASCEMBL trial were approximately 10 years younger compared with the age of patients newly diagnosed with CML in Australia (mean 51 vs 61.1; median 52 vs 63 respectively), according to AIHW data from 2017.⁸ Median time since diagnosis ranged from 3.8 years (ASCSEMBL) to 7.0 years (PACE), meaning the target Australian population may have a median age of approximately 67 - 70 years by the time they require a third TKI, which represents an applicability issue for the efficacy and safety data from ASCSEMBL.
- 6.15 In response to the above mentioned concerns, the PSCR provided a matching adjusted indirect comparison (MAIC) between the ASCSEMBL (asciminib) and PACE (ponatinib) trials, adjusting for sex, median age, race, PCyR at baseline, prior TKIs, resistance/intolerance to prior TKIs, mutation status and ECOG performance status.

Comparative effectiveness

- 6.16 An unadjusted, unanchored ITC was performed in the submission, comparing MMR and CCyR between asciminib and nilotinib or ponatinib treatment, to justify the clinical claim that asciminib demonstrated non-inferior efficacy. Data were analysed for the ITC at Weeks 24 and 48, where available. The pre-PBAC response provided a Week 96 update, however data from this update have not been formally evaluated.

Asciminib versus nilotinib

- 6.17 The outcome of MMR was only provided in the French subgroup of ENACT (n/N = 168/1,422), as described in Table 7. This represents a potential source of bias, as the baseline demographic and disease characteristics are unknown for this French subgroup. The PSCR stated that although the full-text publication (Nicolini et al., 2012) did not report the baseline demographic and disease characteristics of the 168 French patients, an earlier conference abstract reported that the median age of patients was 57 years, 56% were imatinib-resistant and 43% were imatinib-intolerant (Nicolini et al., 2009). This compares to a median age of 52 years in the asciminib arm of ASCSEMBL, of whom 60.5% discontinued their last TKI due to lack of efficacy and 37.6% due to intolerance. The PSCR noted that as response rates decrease with increasing prior TKI use, especially if a patient was resistant to the prior TKI, the naïve (indirect) comparison may be biased against asciminib. Notwithstanding, the abstract has not listed comprehensive baseline characteristics, such as best response to prior TKI, time since initial diagnosis, or their ECOG PS.

⁸ Australian Institute of Health and Welfare. Cancer incidence by age visualization. Link: <https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/cancer-incidence-by-age-visualisation>

6.18 The submission did not perform an ITC with Giles et al. (2010) because they did not report the specific timepoint of analysis. The submission did not propose any non-inferiority margins.

Table 7: Unadjusted, unanchored comparison: Cumulative MMR rates, ASCSEMBL ITT primary analysis vs nilotinib (ENACT French subgroup)

Outcomes/ Timepoint	Asciminib N n (%)	Nilotinib N n (%)	Unadjusted OR (95% CI) ^a P-value	Unadjusted RR (95% CI) ^a P-value	Unadjusted RD (95% CI) ^a P-value
Asciminib (≥ 2 prior TKIs) vs French CML-CP ENACT (≥ 1 prior TKI)					
By 24 weeks (6 months)	N = 157 43 (27.4)	N = 168 42 (25.0)	1.13 (0.69, 1.86) P = 0.62	1.10 (0.76, 1.58) P = 0.62	0.02 (-0.07, 0.12) P = 0.62
By 48 weeks (12 months)	N = 157 55 (35.0)	N = 168 62 (36.9)	0.92 (0.59, 1.45) P = 0.73	0.95 (0.71, 1.27) P = 0.73	-0.02 (-0.12, 0.09) P = 0.73
Asciminib (2 prior TKIs) vs French CML-CP ENACT (≥ 1 prior TKI)					
By 24 weeks (6 months)	N = 89 29 (32.6)	N = 168 42 (25.0)	1.45 (0.82, 2.55) P = 0.20	1.30 (0.88, 1.94) P = 0.19	0.08 (-0.04, 0.19) P = 0.21
By 48 weeks (12 months)	N = 89 36 (40.5)	N = 168 62 (36.9)	1.16 (0.69, 1.97) P = 0.58	1.10 (0.80, 1.51) P = 0.57	0.04 (-0.09, 0.16) P = 0.58

Source: Table 2.6-5, p 92 of the submission.

CI = confidence interval; ITT = intention-to-treat; MMR = major molecular response; OR = odds ratio; RD = risk difference; RR = relative risk

^a Calculated using RevMan v5.3 by the submission

6.19 The outcome of CCyR rates were available for the ITT population of ENACT, and was compared to the asciminib arm of ASCSEMBL in Table 8. ENACT did not report CCyR at 12 months.

Table 8: Unadjusted, unanchored comparison: Cumulative CCyR rates, ASCSEMBL CCyR primary analysis set^b vs nilotinib (ENACT ITT)

Timepoint	Asciminib N n (%)	Nilotinib N n (%)	Unadjusted OR (95% CI) ^a P-value	Unadjusted RR (95% CI) ^a P-value	Unadjusted RD (95% CI) ^a P-value
Asciminib (≥ 2 prior TKIs) vs CML-CP ENACT (≥ 1 prior TKI)					
24 weeks (6 months)	N = 103 42 (40.8)	N = 1422 381 (26.8)	1.88 (1.25, 2.84); p = 0.003	1.52 (1.19, 1.95); p = 0.0009	0.14 (0.04, 0.24); p = 0.005

Source: Table 2.6-6, p 94 of the submission.

CCyR = complete cytogenetic response; CI = confidence interval; ITT = intention-to-treat; OR = odds ratio; RD = risk difference; RR = relative risk

^a Calculated using RevMan v5.3 by the submission

^b Based on patients who were not in CCyR at baseline.

Bold indicates statistically significant differences.

Asciminib versus ponatinib

6.20 The asciminib vs ponatinib comparison is provided in Table 9, and produced no significant differences. The efficacy data were based on the ASCSEMBL updated analysis, so exposure to treatment between asciminib and ponatinib was 67 vs 56 weeks (Table 6). The ‘total CML-CP population’ of PACE included 64/267 patients with the T315I mutation.

Table 9: Unadjusted, unanchored comparison: Cumulative MMR and CCyR rates, ASCSEMBL secondary analysis vs ponatinib (PACE primary analysis)

	Asciminib N n (%)	Ponatinib N n (%)	Unadjusted RR (95% CI)^a P-value	Unadjusted RD (95% CI)^a P-value
Cumulative MMR rates				
Number of responders by 24 weeks (6 months)				
Asciminib (total population) vs ponatinib (total CML-CP population)	N = 157 43 (27.4)	N = 267 65 (24.3)	1.13 (0.81, 1.57) P = 0.49	0.03 (-0.06, 0.12) P = 0.49
Asciminib (total population) vs ponatinib (resistant/intolerant cohort)	N = 157 43 (27.4)	N = 203 39 (19.2)	1.43 (0.97, 2.08) P = 0.07	0.08 (-0.01, 0.17) P = 0.07
Number of responders by 48 weeks (12 months)				
Asciminib (total population) vs ponatinib (total CML-CP population)	N = 157 55 (35.0)	N = 267 91 (34.1)	1.03 (0.78, 1.35) P = 0.84	0.01 (-0.08, 0.10) P = 0.84
Asciminib (total population) vs ponatinib (resistant/intolerant cohort)	N = 157 55 (35.0)	N = 203 55 (27.1)	1.29 (0.95, 1.76) P = 0.10	0.08 (-0.02, 0.18) P = 0.11
Cumulative CCyR rates				
Number of responders by 24 weeks (6 months)				
Asciminib (total population) vs ponatinib (resistant/intolerant cohort)	N = 103 42 (40.8)	N = 203 69 (34.0) [^]	1.20 (0.89, 1.62) P = 0.24	0.07 (-0.05, 0.18) P = 0.25
Asciminib (total population) vs ponatinib (total CML-CP population)	N = 103 42 (40.8)	N = 267 109 (40.8) [^]	1.00 (0.76, 1.31) P = 0.99	-0.00 (-0.11, 0.11) P = 0.99
Number of responders by 48 weeks (12 months)				
Asciminib (total population) vs ponatinib (total CML-CP population)	N = 103 47 (45.6)	N = 267 124 (46.4)	0.98 (0.77, 1.26) P = 0.89	-0.01 (-0.12, 0.11) P = 0.89
Asciminib (total population) vs ponatinib (resistant/intolerant cohort)	N = 103 47 (45.6)	N = 203 82 (40.4)	1.13 (0.86, 1.48) P = 0.37	0.05 (-0.07, 0.17) P = 0.38

Source: Table 2(a).6-2, p 153 of the submission.

CCyR = complete cytogenetic response; CI = confidence interval; CML-CP = chronic phase chronic myeloid leukaemia; MMR = major molecular response; OR = odds ratio; RD = risk difference; RR = relative risk

^a Calculated using RevMan v5.3 by the submission

Note: The submission did not define the caret symbol (^) placed over the 6-month CCyR rates; these figures appear to be estimated based on Figure S1 (B), p 8 of the Cortes 2018 supplement.

6.21 The PSCR stated that a MAIC analysis for the ASCSEMBL and PACE trials (paragraph 6.15) showed that after adjustment for baseline characteristics, there was a statistically significant difference in favour of asciminib compared with ponatinib for MMR but not for CCyR. The PSCR stated that the results support a claim of at least non-inferior efficacy for asciminib versus ponatinib. However, this additional MAIC involves a number of assumptions and selections of non-stratified subgroups from the PACE trial, which would require a formal evaluation. Thus, the interpretation of this new evidence remains uncertain.

6.22 The submission did not present any comparative evidence for efficacy between asciminib and ponatinib in patients with the T315I mutation, however it included an

unmatched comparison between the asciminib arm of ASCEMBL and the T315I-mutated subgroup of PACE, which showed ponatinib was statistically significantly superior to asciminib in terms of MMR and CCyR, except for MMR at 6 months (RR 0.67, 95% CI 0.46, 1.00, $p = 0.05$). The sponsor also provided efficacy data from a Phase 1 clinical trial, CABL001X2101 (Appendix 7 of the submission); updated results from this study⁹ show that MMR was achieved in 19/45 (42%) of patients with a T315I mutation by 6 months, compared to MMR in 56.3% of patients at 12 months in the T315I subgroup of the PACE study. Another Phase I trial¹⁰ treated 21 ponatinib-naïve, T315I patients with asciminib 400 mg/day, and demonstrated MMR in 57.1% at 12 months.

Comparative harms

Asciminib versus bosutinib

- 6.23 Safety data are provided from the primary analysis of ASCEMBL comparing asciminib with bosutinib (data cut-off: 25 May 2020; Week 24), which represent the only randomised safety comparison of asciminib and a second-generation TKI presented by the submission (Table 10). As the trial was open-label, investigator determination of treatment-related adverse events (AEs), and subjective patient-reported AEs (such as nausea and headache), may be vulnerable to bias.

⁹<https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-asciminib-philadelphia-chromosome-positive-chronic-myeloid-leukemia>

¹⁰ Cortes JE, Hughes TP, Mauro MJ, Hochhaus A, Rea D, Goh YT, *et al.* Asciminib, a First-in-Class STAMP Inhibitor, Provides Durable Molecular Response in Patients (pts) with Chronic Myeloid Leukaemia (CML) Harboring the T315I Mutation: Primary Efficacy and Safety Results from a Phase 1 Trial. *Blood*. 2020;136(Supplement 1):47-50.

Table 10: Adverse events, ASCEMBL safety population, primary analysis

Proportion of patients,	Asciminib N = 156 n (%)	Bosutinib N = 76 n (%)	RR (95% CI) ^a p-value	RD (95% CI) ^a p-value
Primary analysis DCO (25 May 2020)^b				
Any grade				
AEs	140 (89.7)	73 (96.1)	0.93 (0.87, 1.00); p = 0.06	-0.06 (-0.13, 0.00); p = 0.06
Treatment-related	99 (63.5)	67 (88.2)	0.72 (0.62, 0.83); p < 0.0001	-0.25 (-0.35, -0.14); p < 0.0001
SAEs	21 (13.5)	14 (18.4)	0.73 (0.39, 1.36); p = 0.32	-0.05 (-0.15, 0.05); p = 0.34
Treatment-related	4 (2.6)	7 (9.2)	0.28 (0.08, 0.92); p = 0.04	-0.07 (-0.14, 0.00); p = 0.06
Fatal SAEs	2 (1.3)	1 (1.3)	0.97 (0.09, 10.58); p = 0.98	-0.00 (-0.03, 0.03); p = 0.98
AEs leading to discontinuation	9 (5.8)	16 (21.1)	0.27 (0.13, 0.59); p = 0.001	-0.15 (-0.25, -0.05); p = 0.002
Treatment-related	7 (4.5)	14 (18.4)	0.24 (0.10, 0.58); p = 0.001	-0.14 (-0.23, -0.05); p = 0.003
Grade ≥3				
AEs	79 (50.6)	46 (60.5)	0.84 (0.66, 1.06); p = 0.14	-0.10 (-0.23, 0.04); p = 0.15
Treatment-related	46 (29.5)	38 (50.0)	0.59 (0.42, 0.82); p = 0.002	-0.21 (-0.34, -0.07); p = 0.003
SAEs	16 (10.3)	12 (15.8)	0.65 (0.32, 1.30); p = 0.22	-0.06 (-0.15, 0.04); p = 0.25
Treatment-related	3 (1.9)	5 (6.6)	0.29 (0.07, 1.19); p = 0.09	-0.05 (-0.11, 0.01); p = 0.13
AEs leading to discontinuation	8 (5.1)	12 (15.8)	0.32 (0.14, 0.76); p = 0.01	-0.11 (-0.20, -0.02); p = 0.02
Treatment-related	6 (3.8)	10 (13.2)	0.29 (0.11, 0.77); p = 0.01	-0.09 (-0.17, -0.01); p = 0.03
AEs leading to dose adjustment/ interruption	53 (34.0)	37 (48.7)	0.70 (0.51, 0.96); p = 0.03	-0.15 (-0.28, -0.01); p = 0.03

Source: Table 2.5-13, pp 79-80.

AE = adverse event; CI = confidence interval; RD = risk difference; RR = relative risk; SAE = serious adverse event

^a Calculated using RevMan v5.3 by the submission

^b the median duration of treatment at the primary analysis DCO was 43.4 weeks for asciminib and 29.2 weeks for bosutinib; the median duration of treatment at the updated analysis DCO was 67.1 weeks for asciminib and 29.7 weeks for bosutinib.

Bold indicates statistically significant differences.

6.24 The ‘any grade’, ‘grade ≥3’ AEs and SAEs were not statistically significantly different between arms, until the adjustment for ‘treatment-related’ was made. The asciminib arm had substantially more AEs discounted as not being ‘treatment-related’ compared to the bosutinib arm, summarised in Table 11. This is an unusual finding between randomised treatment arms, where treatment-unrelated AEs are expected to be similar. The difference may be due a combination of bias in this open label trial, and the novelty of asciminib, which has only been used in 840 patients and healthy subjects. This novelty means clinicians may not be adept at identifying which AEs are likely to be drug related.

Table 11: Comparison of AEs and Grade ≥3 AEs unrelated to study treatment, ASCEMBL safety population primary analysis

	Asciminib N = 156	Bosutinib N = 76	RR (95% CI) p-value	RD (95% CI) p-value
Treatment unrelated AEs/ all AEs n/N (%)	41/140 (29.3)	6/73 (8.2)	3.56 (1.59, 8.00); p = 0.002	0.21 (0.11, 0.31); p = < 0.001
Treatment unrelated Grade ≥3 AEs/all Grade ≥3 AEs, n/N (%)	33/79 (41.8)	8/46 (17.4)	2.40 (1.22, 4.75); p = 0.01	0.24 (0.09, 0.40); p = 0.002

Source: Calculations performed in RevMan 5.4, based on data from ASCEMBL CSR Table 12-4 p 101.

AE = adverse event; CI = confidence interval; RD = risk difference; RR = relative risk.

Bold indicates nominally statistically significant differences.

Asciminib versus nilotinib

6.25 Asciminib safety data are compared to nilotinib (from the ENACT trial) in Table 12. Asciminib was associated with statistically significantly fewer AEs, and Grade 3-4 AEs, compared to nilotinib. There were no statistically significant differences in the most common grade ≥3 AEs, however their rates were consistently lower with asciminib treatment compared to nilotinib. The asymmetrically large number of patients in ENACT generated substantial power to detect differences, such that differences in AEs which would not generate statistical significance between the two arms of the ASCEMBL trial, were able to generate strongly statistically significant comparisons for even relatively minor differences, such as ‘Any AE’ (89.7% vs 96.5%: a difference of only 6.8%). However, given that the comparison is unadjusted and unanchored – with multiple transitivity issues outlined above – the statistical analysis is not appropriate or meaningful, as differences may be entirely due to imbalances in confounding factors between the non-randomised and non-adjusted populations. Further, the potential bias in classification of ‘treatment-related’ AEs in the open-label asciminib arm of ASCEMBL carried over to the ITC: for example, only 58% (46/79) of the Grade ≥3 AEs in the asciminib arm were considered to be ‘treatment-related’, compared to 83% (720/872) of Grade ≥3 AEs in the nilotinib arm of ENACT. There were statistically significantly fewer AEs leading to discontinuation reported in the asciminib arm compared to nilotinib (4.5% vs 18%), however the ASCEMBL trial recorded discontinuation reasons due to ‘physician decision’ separately to AEs, while ENACT did not record a ‘physician decision’ category. ‘Physician decision’ and ‘adverse event’ combined made up 14.7% of the reasons for discontinuation in the asciminib arm, which was not statistically significantly different to nilotinib in terms of unadjusted relative risk (RR).

Table 12: ASCEMBL (primary analysis) vs ENACT, treatment-related safety outcomes, safety population

Outcomes	Asciminib N = 156 n (%)	Nilotinib N = 1422 n (%)	Unadjusted RR (95% CI) ^a p-value	Unadjusted RD (95% CI) ^a p-value
AEs	140 (89.7)	1372 (96.5)	0.93 (0.88, 0.98); p = 0.009	-0.07 (-0.12, -0.02); p = 0.007
Treatment-related	99 (63.5)	1249 (87.8)	0.72 (0.64, 0.82); p < 0.0001	-0.24 (-0.32, -0.17); p < 0.0001
Grade 3 or 4 AEs	79 (50.6)	872 (61.3)	0.83 (0.70, 0.97); p = 0.02	-0.11 (-0.19, -0.02); p = 0.01
Treatment-related	46 (29.5)	720 (50.6)	0.58 (0.45, 0.75); p < 0.0001	-0.21 (-0.29, -0.14); p < 0.0001
AEs leading to discontinuation	7 (4.5)	256 (18.0)	0.25 (0.12, 0.52); p = 0.0002	-0.14 (-0.17, -0.10); p < 0.0001
Treatment-related Grade ≥3				
Thrombocytopenia	24 (15.4)	285 (20.0)	0.77 (0.52, 1.13); p = 0.18	-0.05 (-0.11, 0.01); p = 0.13
Neutropenia	20 (12.8)	188 (13.2)	0.97 (0.63, 1.49); p = 0.89	-0.00 (-0.06, 0.05); p = 0.89
Headache	1 (0.6)	27 (1.9)	0.34 (0.05, 2.47); p = 0.28	-0.01 (-0.03, 0.00); p = 0.09
Anaemia	1 (0.6)	44 (3.1)	0.21 (0.03, 1.49); p = 0.12	-0.02 (-0.04, -0.01); p = 0.002
ALT increased	0	30 (2.1)	0.15 (0.01, 2.42); p = 0.18	-0.02 (-0.03, -0.01); p = 0.0004

Source: Table 2.6-8, p 97 of the submission.

AE = adverse event; ALT = alanine aminotransferase; CI = confidence interval; RD = risk difference; RR = relative risk

^a Calculated using RevMan v5.3 by the submission

Bold indicates statistically significant differences.

6.26 The submission also compared asciminib treatment-related safety data to Giles *et al.* (2010), which was a single arm study of 39 patients with CML-CP who had failed 2 prior TKIs. ASCEMBL enrolled more fit patients, reflected in the better ECOG PS compared to the Giles *et al.* (2010) (ECOG PS = 0 in 80% [asciminib] vs 64% [nilotinib]). The numbers in the nilotinib arm of Giles *et al.* (2010) were low, making it difficult to conduct a meaningful comparison. Any-grade rash was significantly higher in the nilotinib arm, as was Grade ≥3 alanine aminotransferase (ALT) increase (0 vs 30 cases), and asciminib was associated with numerically fewer treatment-related AEs in all other categories. This comparison was also vulnerable to the bias in classification of ‘treatment-related’ AEs in the asciminib arm of ASCEMBL.

Asciminib versus ponatinib

6.27 The submission used safety data from the primary analyses of the ASCEMBL and PACE trials, which reflected approximately 12 weeks (3 months) more treatment exposure in the ponatinib arm (43.4 weeks [asciminib] vs 55.5 weeks [ponatinib]). This is not reasonable, as the submission used efficacy data from the updated analysis of the ASCEMBL trial (median treatment of 67.14 weeks in the asciminib arm). Comparison of safety data should reflect the median treatment duration used to establish non-inferior efficacy, particularly as the submission characterised this as an unadjusted, unanchored comparison, yet it has attempted to match treatment durations for the safety comparison.

6.28 As discussed above (paragraph 6.13), the asciminib population were younger, fitter and had less time since initial diagnosis compared to the CML-CP ponatinib patients in PACE, which may bias safety outcomes against ponatinib. This comparison was also

vulnerable to the bias in classification of ‘treatment-related’ AEs in the asciminib arm of the ASCEMBL trial, and the safety data from the ponatinib cohort included 64 patients who had the T315I mutation; these patients were excluded from ASCEMBL.

Table 13: Unadjusted, unanchored comparison of treatment-related safety outcomes, ASCEMBL asciminib and PACE CML-CP safety populations (primary analysis)

Safety outcomes, n (%)	Asciminib N = 156 n (%)	Ponatinib N = 270 n (%)	Unadjusted RR (95% CI) ^a P-value	Unadjusted RD (95% CI) ^a P-value
Grade ≥3 TRAEs				
Haematological AEs				
Thrombocytopenia	24 (15.4)	86 (31.9)	0.48 (0.32, 0.73); P = 0.0005	-0.16 (-0.24, -0.09); P < 0.0001
Neutropenia	20 (12.8)	38 (14.1)	0.91 (0.55, 1.51); P = 0.72	-0.01 (-0.08, 0.05); P = 0.71
Anaemia	1 (0.6)	15 (5.6)	0.12 (0.02, 0.87); P = 0.04	-0.05 (-0.08, -0.02); P = 0.001
Pancytopenia	0	2 (0.7)	0.35 (0.02, 7.15); P = 0.49	-0.01 (-0.02, 0.01); P = 0.31
Febrile neutropenia	0	1 (0.4)	0.58 (0.02, 14.04); P = 0.73	-0.00 (-0.02, 0.01); P = 0.56
Non-haematological AEs				
Increased amylase	14 (9.0)	4 (1.5)	6.06 (2.03, 18.08); P = 0.001	0.07 (0.03, 0.12); P = 0.002
Increased lipase	4 (2.6)	27 (10.0)	0.26 (0.09, 0.72); P = 0.010	-0.07 (-0.12, -0.03); P = 0.0008
Hypertension	3 (1.9)	6 (2.2)	0.87 (0.22, 3.41); P = 0.84	-0.00 (-0.03, 0.02); P = 0.83
Headache	1 (0.6)	5 (1.9)	0.35 (0.04, 2.94); P = 0.33	-0.01 (-0.03, 0.01); P = 0.24
Abdominal pain	0	20 (7.4)	0.04 (0.00, 0.69); P = 0.03	-0.07 (-0.11, -0.04); P < 0.0001
Rash	0	10 (3.7)	0.08 (0.00, 1.39); P = 0.08	-0.04 (-0.06, -0.01); P = 0.003
Increased ALT	0	9 (3.3)	0.09 (0.01, 1.55); P = 0.10	-0.03 (-0.06, -0.01); P = 0.006
Arthralgia	0	6 (2.2)	0.13 (0.01, 2.34); P = 0.17	-0.02 (-0.04, -0.00); P = 0.03

Source: Table 2(a).6-1, pp 157-158 of the submission.

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = confidence interval; RD = risk difference; RR = relative risk; TRAE = treatment-related adverse event

^a Calculated using RevMan v5.3 by the submission

Bold indicates statistically significant differences.

Note: Median treatment exposure 43.36 weeks for asciminib, 55.5 weeks for ponatinib.

6.29 The submission presented comparative safety data regarding arterial occlusive events (AOEs), for which ponatinib has a black box warning. The asciminib safety data were based on the primary analysis (median duration of treatment 43.4 weeks, median follow-up 14.9 months), whilst the ponatinib data was based on the end of study analysis (median treatment duration 139 weeks, median follow-up 56.8 months). The ‘Any AOE’ rate was lower in asciminib vs ponatinib (3.2% vs 31%), and serious events such as myocardial infarction, acute coronary syndrome, ischaemic stroke/cerebral infarction were lower in asciminib compared to ponatinib (0.6 – 1.3% vs 3 – 4%). These data are difficult to interpret due to the widely disparate exposure and follow-up, which is most important when measuring serious but rare AEs.

Clinical claim

6.30 The submission described asciminib as non-inferior in terms of effectiveness compared to nilotinib and ponatinib. The evaluation considered this claim to be uncertain given the transitivity issues, methodological flaws and absence of a non-

inferiority margin in the unanchored, unadjusted indirect comparison used as the evidence base:

- In the ITC with nilotinib, MMR rates were compared against a French subgroup of the ENACT trial which was not pre-specified, for which baseline characteristics are unknown, and the 95% CIs of odds ratios had lower limits below 0.7 and 0.6. The comparison of CCyR rates was only performed at a 6-month timepoint, which statistically significantly favoured asciminib. While the PSCR provided limited patient characteristics for age and resistance/intolerance to prior treatment with imatinib, comprehensive baseline characteristics such as best response to prior TKI, time since initial diagnosis, or performance status are not available (paragraph 6.17).
- The ITC with ponatinib was vulnerable to differences in baseline characteristics which prognostically favoured asciminib over ponatinib, and the ITC between the asciminib arm of ASCEMBL and the T315I subgroup of PACE demonstrated MMR and CCyR rates which statistically significantly favoured ponatinib. While the PSCR provided a MAIC analysis (adjusting for sex, median age, race, PCyR at baseline, prior TKIs, resistance/intolerance to prior TKIs, mutation status and ECOG performance status) that may support a claim of non-inferior efficacy for asciminib versus ponatinib, the analysis involves a number of assumptions and selections of non-stratified subgroups from the PACE trial that would require a formal evaluation (paragraph 6.21).

- 6.31 The asciminib evidence from the ASCEMBL trial was only obtained in patients without a T315I mutation. The submission highlighted the fact that the imatinib, dasatinib and nilotinib PBS restrictions do not specifically exclude use in patients with a T315I mutation. This is correct, however many of the clinical trials that established efficacy for these treatments did not exclude patients with a T315I mutation, including the ENACT trial used in this ITC, and clinicians know that first- and second-generation TKIs are not effective in patients with a T315I mutation. The submission claimed that asciminib is effective in patients with a T315I mutation and stated, without qualification, that asciminib is non-inferior in terms of effectiveness compared to ponatinib in the treatment of CML-CP. The proposed PBS restriction for asciminib would allow substitution of asciminib for ponatinib in patients with a T315I mutation. The PBAC previously estimated that 15% of patients who fail first-line TKI therapy will have the T315I mutation (paragraph 6.41, ponatinib PSD, November 2014), and it is likely that almost all current ponatinib use is in patients with this mutation. The ESC noted that there are single arm data available for 45 patients with Ph+ CML in CP with the T315I mutation treated with asciminib in a multi-centre, open-label clinical trial, CABL001X2101 (paragraph 6.22).
- 6.32 The ESC considered that the efficacy claim of non-inferiority compared to nilotinib and ponatinib was uncertain due to the transitivity issues between the trials, analysis interpretations, absence of a non-inferiority margin and different timepoints of

analysis to compare treatments. The PBAC agreed with the evaluation and the ESC that the issues associated with the ITCs of asciminib against nilotinib and ponatinib make the clinical claim of non-inferiority uncertain. However, it considered that in light of the available evidence in the CML-CP therapeutic area, non-inferior efficacy of asciminib against nilotinib is likely supported. The PBAC did not accept the clinical claim of non-inferiority against ponatinib based on the comparison between the ASCEMBL and PACE trials, but noted that asciminib data from patients with the T315I mutation from the CABL001X2101 study is relevant to the consideration.

6.33 The submission described asciminib as superior in terms of safety compared to nilotinib and ponatinib. The ESC agreed with the evaluation that this claim was not adequately supported by the evidence, as follows.

- All-cause AEs in the ASCEMBL trial represent the only randomised safety comparison of asciminib and a second-generation TKI (bosutinib) presented by the submission. This trial failed to demonstrate a statistically significant difference between asciminib and bosutinib in any-grade AEs, SAEs, fatal SAEs or Grade ≥ 3 AEs. There was a significant difference in AEs leading to discontinuation which favoured asciminib. The asciminib arm of ASCEMBL was biased in the recording of treatment-related AEs, which demonstrated statistically significant differences between asciminib and bosutinib, and carried into the indirect safety comparisons.
- The transitivity assumption for the comparisons may not hold, as patients in the asciminib arm of the ASCMEBL trial were younger, with a lower ECOG PS, compared to patients in the nilotinib and ponatinib trials. The asymmetrically large number of patients in the ENACT trial generated substantial statistical power to detect differences, but this power needs to be qualified by the inherent uncertainties of an unanchored, unadjusted ITC.
- Differences in asciminib exposure and follow-up, compared to ponatinib, made interpretation of the safety comparison difficult.
- Finally, patients in the asciminib arm of ASCEMBL were 14-18 years younger than the target Australian population (median age 52 vs 67-70 years), which poses an applicability issue for these safety data. Combined, these factors introduce substantial uncertainty into the indirect safety comparison of asciminib vs nilotinib and ponatinib, and the submission's claim that asciminib is superior in terms of safety.

6.34 The ESC considered that the safety claim would be better described as non-inferior compared to nilotinib and ponatinib. The pre-PBAC response noted that the PBAC had previously considered the safety profile of ponatinib to be inferior to nilotinib (paragraph 7.6, ponatinib PSD, November 2014). The pre-PBAC response claimed that as asciminib is superior to nilotinib in terms of safety, it is reasonable to consider that it is also has superior safety to ponatinib. The PBAC did not accept this reasoning, noting that superior safety of asciminib to nilotinib cannot be assessed in the context

of an unanchored, unadjusted ITC. The PBAC considered that the available data do not support the claim of superior safety to either nilotinib or ponatinib.

Economic analysis

6.35 The submission presented an analysis using a CMA based on the submission's therapeutic conclusions that asciminib is non-inferior in terms of efficacy, and superior in terms of safety, to nilotinib and ponatinib in patients who are resistant to or intolerant of at least two prior TKIs. As discussed above, there are uncertainties regarding the claim of non-inferior efficacy in patients without the T315I mutation, and the claim of superior safety is uncertain due to a combination of transitivity issues, bias in the ASCEMBL safety data, and mismatched patient exposure/follow-up between the asciminib arm of ASCEMBL, and the PACE trial population.

Equi-effective doses

6.36 The recommended dose for asciminib is 80 mg/day, nilotinib 800 mg/day and ponatinib 45 mg/day. The submission used the mean dose intensity for asciminib from the secondary analysis of ASCEMBL, and the therapeutic relativity sheet to determine the equi-effective doses for nilotinib and ponatinib, consistent with paragraph 6.32, ponatinib PSD November 2014:

Asciminib 71.1 mg daily \equiv Nilotinib 797 mg daily \equiv Ponatinib 30.2 mg daily.

6.37 The submission did not attempt to establish an equi-effective dose of asciminib with the median dose intensities reported for nilotinib and ponatinib in the ENACT (782.5 mg/day) and PACE (30.0 mg/day) trials, respectively (mean doses not reported). The PSCR noted that in the absence of mean or median dose for nilotinib in the proposed population, the approach was aligned with the PBAC's previous consideration of ponatinib whereby the mean and median dose of the ponatinib and nilotinib studies were used to determine the equi-effective doses, respectively (paragraph 6.32 ponatinib PSD states "the PBAC considered the equi-effective dose are Ponatinib 30.2 mg daily = Dasatinib 102 mg daily = Nilotinib 797 mg daily"). The PSCR stated that patients in ENACT received at least one prior TKI, so the nilotinib dose is likely to be slightly higher than 782.5 mg in those who failed two prior TKIs, and therefore argued for the nilotinib dose to be 797 mg daily. Notwithstanding, the ESC considered that the submission's estimated equi-effective doses underestimate the relative dose of asciminib to the comparators, as they are not drawn from consistent sources and are not based on the clinical trial doses used to claim non-inferiority.

6.38 The evaluation considered that the equi-effective asciminib dose should reflect the median dose in the ASCEMBL trial (79.8 mg) from the 6 January 2021 data cut-off (Table 6), rather than the mean dose (71.1 mg), for consistency with the median trial-based doses for nilotinib and ponatinib.

6.39 The evaluation and the ESC considered that the equi-effective doses should be:

Asciminib 79.8 mg daily \equiv Nilotinib 782.5 mg daily \equiv Ponatinib 30.0 mg daily.

- 6.40 The ESC noted that if equi-effective doses are calculated based on the trial dosing, the cost-minimised price of asciminib would be lower than the submission's proposed price.
- 6.41 The PBAC agreed with the evaluation and the ESC that, since there was no mean dose of nilotinib reported in the ENACT trial, the equi-effective doses for asciminib and nilotinib in patients without the T315I mutation should be based on median doses from the ASCEMBL and ENACT trials (Asciminib 79.8 mg daily \equiv Nilotinib 782.5 mg daily). The PBAC considered that the equi-effective doses for asciminib and ponatinib in patients with the T315I mutation could not be established from the analyses presented in the submission.

Adverse events

- 6.42 For the CMA with nilotinib, the submission used comparative safety data between ASCEMBL and Giles et al. (2010), which showed a statistically significant difference in treatment-related Grade ≥ 3 ALT increase (0/156 vs 3/39). The evaluation considered the safety data from Giles et al. (2010) are small and vulnerable to imbalances in confounders, as well as transitivity issues as outlined in 'comparative harms' above. Further, the difference in Grade ≥ 3 ALT increase was not statistically significant in the comparison of safety data between ASCEMBL and ENACT (Grade ≥ 3 ALT increase in 30/1,422 [2.1%]), which had a lot more power. This comparison was dismissed by the submission because ENACT also enrolled patients who had only failed 1 prior TKI, although this is more likely to affect comparative efficacy than comparative safety. Cross reactivity of hepatic injury is uncommon between TKIs, so the differences in line of therapy are unlikely to affect this safety outcome¹¹. The PSCR acknowledged that it may be reasonable to exclude the cost offset associated with the management of ALT increase grade ≥ 3 from the CMA.
- 6.43 For the CMA with ponatinib, the submission used comparative safety data from ASCEMBL and PACE. This found five Grade ≥ 3 treatment-related AEs (TRAEs) were significantly less common in those receiving asciminib than ponatinib (thrombocytopenia, anaemia, increased lipase, abdominal pain and angina) and one Grade ≥ 3 TRAE was more common with asciminib than ponatinib (increase amylase). As discussed under 'comparative harms' above, a combination of transitivity issues, bias in the ASCEMBL safety data, and mismatched patient exposure/follow-up between the asciminib arm of ASCEMBL and the PACE trial population may have biased the safety comparison in favour of asciminib. The of risks of uncertainty in costs associated with safety profiles are further discussed in paragraph 6.51 below.
- 6.44 The PSCR stated that Grade ≥ 3 TRAEs are clinically complex and are likely to require hospitalisation; however, Grade 3 laboratory abnormalities, such as elevated

¹¹ National Institute of Diabetes and Digestive and Kidney Diseases. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. Bethesda (MD); Updated 2020 May 10. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK548443/>.

lipase/amylase, anaemia and thrombocytopenia, are frequently treated in the outpatient setting. Furthermore, the ESC noted that the submission's claim of superior safety of asciminib versus nilotinib and ponatinib is poorly supported by non-comparative evidence. The resultant additional costs of treatment for adverse events associated with nilotinib and ponatinib inflated the total cost of the comparators, and consequently the sponsor requested a higher price for asciminib.

Monitoring

- 6.45 The submission identified the nilotinib PI recommended one additional electrocardiogram (ECG) compared to the draft asciminib PI. The submission incorrectly costed \$236.25 for MBS item 55129, which is for a transthoracic echocardiogram and stress test. The appropriate MBS item is 11704, which represents a standard twelve-lead ECG and report, costing \$32.55. The PSCR agreed with the evaluation that this proposed revision to the CMA is reasonable. In regard to the ECG monitoring requirements for ponatinib, the submission incorrectly assumed that when the ponatinib PI stated "monitor cardiac function and monitor patients for signs and symptoms consistent with heart failure", this meant an ECG must be performed every 6 months whilst on therapy. This is not the case: the PI only recommends measurement of one ECG prior to commencing ponatinib therapy, to establish a baseline QT interval. Cardiac function monitoring is primarily performed clinically, through history taking and physical examination.
- 6.46 The ponatinib PI recommends patients are monitored for evidence of thromboembolism and vascular occlusion; the submission interpreted this as requiring duplex ultrasounds and retinal angiography every 6 months. These tests represent a substantial expense (\$1,326.80 over 2 years, and \$3,648.70 over the 5.06-year time horizon) with a low yield, as these rare events (peripheral vascular disorder occurred in 1%, venous thromboembolism in 6%, and ocular occlusion in < 1% of patients in PACE). Comparatively, the risk of a cerebrovascular occlusive event is much higher (13% of patients in PACE), however it would be inappropriate to screen for these events with 6-monthly magnetic resonance imaging scans. As these are acute, usually symptomatic events, they can be monitored through patient education and regular physician visits.

Time horizon

- 6.47 The submission elected a time horizon of two years, which under-represents the chronicity of CML-CP, and is substantially less than the durations outlined in the most recent DUSC review: 'third or later line' treatments were continued for a mean of 5.06 years (without excluding breaks), and first-line treatments had a mean of 8.49 years (Table 10, p 15 of the public release document, October 2019 DUSC meeting). Asciminib may be used as a first-, second- or third -line treatment under the proposed PBS restriction. The cost-minimised price of asciminib became lower if the time horizon was extended beyond two years, as the one-off costs of investigations associated with commencement made up a smaller proportion of total differences the

longer treatment is continued, and the differences in costs of monitoring/AEs, multiplied over more years, created a larger incremental gap. The pre-PBAC response stated that the cost minimisation for ponatinib (July 2015 PBAC meeting) was performed over a time horizon of one year, and that increasing the time horizon to two years for asciminib is a conservative approach, since reducing the time horizon would increase the proposed AEMP. The PBAC considered the two-year time horizon to be a reasonable basis for the analysis.

Cost minimisation approach

6.48 The results of the CMA are presented in Table 14 and Table 15 against nilotinib and ponatinib, respectively. The submission adjusted the AEMP to correspond to prior 5% and 10% F1 anniversary price reductions for nilotinib (April 2016 and 2019), the 5% F1 anniversary price reduction for ponatinib (April 2021). The submission proposed an effective price on the basis of Clause 5.7 of the Strategic Agreement between Medicines Australia and the Commonwealth (the Strategic Agreement) that, until expiration of the agreement 30 June 2022, asciminib can be listed with a price equivalent to that of the other TKI drugs prior to the application of any F1 statutory cuts. The PBAC has previously considered that the application of Clause 5.7 of the Strategic Agreement is determined by the Minister (or Delegate), and is not a matter for PBAC (paragraph 6.41, levonorgestrel PSD, March 2019 Meeting). The prices shown in Table 14 and Table 15 have been adjusted to remove the application of Clause 5.7.

Table 14: Economic evaluation of asciminib vs nilotinib

	Asciminib 60 x 40 mg	Asciminib 60 x 20 mg	Nilotinib 120 x 150 mg	Nilotinib 120 x 200 mg	Increment
Medicines					
Days of treatment	730.50		730.50		-
Prescriptions			0.37	23.98	-
Prescriptions revised			2.12	22.23	-
AEMP revised ^a no C5.7 ^b	\$	\$	\$3,694.89	\$4,895.54	-
Cost of medicines revised ^a no C5.7 ^b	\$	\$	\$7,827.44	\$108,835.44	\$
Total medicines revised ^a no C5.7 ^b	\$	\$	\$116,662.88		\$
Monitoring					
QT prolongation	\$0.00		\$236.25 Revised: \$32.55		-\$236.25 -\$32.55
Full blood count	\$457.65		\$440.70		\$16.95
Blood tests	\$283.60		\$387.90		-\$104.30
Total monitoring	\$741.25		\$1,064.85 Revised: \$861.15		-\$323.60 -\$119.90
AE grade ≥3					
Increased ALT	\$0.00		\$651.95 Revised: \$373.34		-\$651.95 -\$373.34
Total AEs	\$0.00		\$651.95 Revised: \$373.34		-\$651.95 -\$373.34
Total cost of treatment over 2 years					
Total cost revised ^a no C5.7 ^b	\$	\$	\$117,898.37		\$

Source: Table 3.4-6, p 182 of the submission.

AEMP = Approved ex-manufacturer price; AE = adverse event; C5.7 = Clause 5.7

^a Revised by the evaluation so that the equi-effective doses are consistent with the doses used in the studies, and adjustment of the ECG and liver hospitalisation costs.

^b The submission proposed AEMP corresponded to prior 5% and 10% F1 anniversary price reductions for nilotinib (application of Clause 5.7). "No C5.7" in the table refers to AEMP without Clause 5.7 applied.

6.49 The submission's economic costings were revised during the evaluation so that the dosing is consistent with the doses used in the studies (asciminib 79.8 mg/day, nilotinib 782.5 mg/day). Also, the ECG and liver hospitalisation costs are updated, and application of Clause 5.7 has been removed. With these revised inputs, the submission's model back-calculates an AEMP of \$ per asciminib pack is required for cost-minimisation against nilotinib. The pre-PBAC response acknowledged the difference in the incidence of ALT increase grade ≥3 was not statistically significant and hence it would be appropriate for the cost offset to be excluded from the CMA and as a result, the CMA of asciminib versus nilotinib would not include cost (offsets) due to differences in AEs grade ≥3. The PBAC considered that cost offsets for adverse events should not be included in the CMA and this was consistent with its view that the claim of superior safety was not adequately supported.

Table 15: Economic evaluation of asciminib vs ponatinib

	Asciminib 60 x 40 mg	Asciminib 60 x 20 mg	Ponatinib 60 x 15 mg	Ponatinib 30 x 45 mg	Increment
Medicines					
Days of treatment	730.50		730.50		-
Prescriptions			24.03	0.32	-
Prescriptions revised			24.28	0.07	
AEMP revised ^a no C5.7 ^b	\$	\$	\$5,328.18	\$6,011.65	
Cost of medicines revised ^a no C5.7 ^b	\$	\$	\$129,351.96	\$439.15	\$
Total medicines revised ^a no C5.7 ^b	\$	\$	\$129,791.11		\$
Monitoring					
Blood tests	\$283.60		\$424.80		-\$141.20
Hypersensitivity	\$0.00		\$0.00		\$0.00
TE & VO	\$0.00		\$694.40		-\$694.40
Ocular occlusion	\$0.00		\$632.40		-\$632.40
Cardiac function	\$0.00 Revised \$130.20		\$945.00 \$130.20		-\$945.00 \$0.00
Total monitoring	\$283.60 Revised \$413.80		\$2,696.60 \$1,881.80		-\$2,413.00 -\$1,468.00
TRAE grade ≥3 and occlusive events					
Thrombocytopenia	\$1,325.61		\$2,441.86		-\$1,116.25
Anaemia	\$32.05		\$247.13		-\$215.08
Increased lipase	\$209.92 Revised \$120.53		\$728.42 \$418.25		-\$518.50 -\$297.71
Increased amylase	\$734.73 Revised \$421.87		\$107.91 \$61.96		\$626.82 \$359.91
Abdominal pain	\$0.00		\$211.27		-\$211.27
Angina	\$39.65		\$448.38		-\$408.73
Total TRAE & OE	\$2,341.96 Revised: \$1,939.71		\$4,184.98 \$3,828.85		-\$1,843.02 -\$1,889.14
Total cost of treatment over 2 years					
Total cost revised ^a no C5.7 ^b	\$	\$	\$135,501.76		\$

Source: Table 3(a).4-4, p 194 of the submission.

AEMP: Approved ex-manufacturer price; C5.7 = Clause 5.7; TRAE = treatment-related adverse event; TE = thromboembolism; VO = vascular occlusion; OE = occlusive events.

^a Revised by the evaluation so that the equi-effective doses are consistent with the doses used in the studies, and adjustment of the increased lipase/amylase hospital cost estimate, and no incremental cost for ECG.

^b The submission proposed AEMP corresponded to prior 5% F1 anniversary price reductions for ponatinib (application of Clause 5.7). "No C5.7" in the table refers to AEMP without Clause 5.7 applied.

6.50 The submission's economic costings have been revised during the evaluation so that the dosing is consistent with the doses used in the studies (asciminib 79.8 mg/day, ponatinib 30.0 mg/day). Also, the ECG and increased lipase/amylase hospitalisation costs are updated, and application of Clause 5.7 has been removed. With these revised inputs, the submission's model back-calculates an AEMP of \$1 per asciminib pack is required for cost-minimisation against ponatinib.

6.51 As discussed previously, the equi-effective doses proposed by the submission are not based on the evidence, and the evaluation revised the equi-effective doses and prescription requirements to match the median doses used in the studies. In addition, the AE hospitalisation costs are likely to be an overestimate and an adjustment has only been made to the increased lipase/amylase hospital cost estimate. Also, as

asciminib and ponatinib require one baseline ECG only, there should be no incremental cost of this investigation. The PSCR agreed with the evaluation that this proposed revision to the CMA is reasonable.

- 6.52 The PBAC considered the economic evaluation of asciminib versus ponatinib was not informative as it was not based on the circumstance of use for patients with the T315I mutation.
- 6.53 The proposed effective AEMP was calculated as the weighted average of the AEMPs for asciminib that resulted in an identical cost of treatment over two years from the cost-minimisation analyses versus nilotinib and ponatinib, where the relative substitution from nilotinib (1%) and ponatinib (1%) served as the weights. It was unclear how the submission determined these weightings.
- 6.54 Table 16 summarises the pricing of asciminib without the application of Clause 5.7 of the Strategic Agreement (paragraph 6.48), using the weighting for the relative substitution of nilotinib and ponatinib (1% and 1%, respectively) applied in the submission. The calculations are summarised for both the submission base case and the revisions performed during the evaluation.

Table 16: Asciminib pricing summary without the application of Clause 5.7 of the Strategic Agreement^a

	Asciminib EMP 40 mg and 20 mg	Asciminib EMP 40 mg and 20 mg weighted ^b	Asciminib DPMQ 40 mg and 20 mg weighted ^b
Submission			
Asciminib vs nilotinib	\$		
Asciminib vs ponatinib	\$		
Weighted		\$	\$
Revised by evaluation			
Asciminib vs nilotinib ^c	\$		
Asciminib vs ponatinib ^d	\$		
Weighted		\$	\$

EMP = Ex-manufacturer price; DPMQ = dispensed price for maximum quantity.

^a The Strategic Agreement specifies that, until expiration of the agreement 30 June 2022, asciminib can be listed with a price equivalent to that of the other TKI drugs prior to the application of any F1 statutory cuts.

^b Weighted according to the relative substitution of nilotinib and ponatinib (1% and 1%, respectively) applied in the submission.

^c Revised by the evaluation so that the equi-effective doses are consistent with the doses used in the studies, and adjustment of the ECG and liver hospitalisation costs.

^d Revised by the evaluation so that the equi-effective doses are consistent with the doses used in the studies, and adjustment of the increased lipase/amylase hospital cost estimate, and no incremental cost for ECG.

Asciminib cost/patient/year

- 6.55 The expected cost of asciminib is \$| per patient per year. The cost is calculated using the asciminib price revised by the evaluation and without Clause 5.7 applied. It assumes a DPMQ of \$| (Table 16), which is weighted between nilotinib (1%) and ponatinib (1%) as requested by the submission, and 12.2 prescriptions per year (Table 14 and Table 15).

Estimated PBS usage & financial implications

- 6.56 This submission was considered by DUSC.

6.57 The submission used an epidemiological approach to predict the likely use and financial impact of listing of asciminib on the PBS/RPBS. The key inputs for the financial estimates are summarised in Table 17. The mean doses and distributions by strength are consistent with those used by the submission in the economics section and respective relativity sheets. The sponsor requested a SPA for asciminib such that the proposed published AEMP for 1 pack containing 60 x 20 mg or 60 x 40 mg tablets is \$1. The financial estimates were based on the proposed effective (weighted average) AEMP of \$1. The prices applied to the financial estimates in the submission were inappropriately derived by applying Clause 5.7 to the prices for nilotinib/ponatinib; this has been rectified below (see paragraph 6.58).

Table 17: Key inputs for financial estimates

Parameter	Value applied				Source/Comment	
Prevalent patients receiving treatment with their third TKI	<u>Patients</u>				Linear trend analysis of a 6-month moving average, based on the 10% PBS sample data from 2018 – 2021. This is a reasonable linear fit to the available data, however may be an overestimate given data from 2018 – 2021 suggests that the growth in third-line treatment may not be sustained in a linear fashion. AIHW data show that the incidence of all CML has demonstrated little growth, from 306 cases in 2008 to 362 in 2017 (actual data) and 376 in 2021 (projected). DUSC considered the 10% PBS sample data is likely not representative for this population (e.g. analysis appears to be based on 53 people) and thus considered the estimated growth is not accurate. DUSC also noted the method for identifying the third line utilisation was not defined.	
	2022:	528				
	2023:	599				
	2024:	671				
	2025:	742				
	2026:	814				
Distribution of patients by third TKI		<u>Nil.</u>	<u>Pon.</u>	<u>Das.</u>	<u>Ima.</u>	Linear trend analysis of a 12-month moving average using the distribution of treatments from 2018 – 2021. This likely overestimates nilotinib and underestimates imatinib proportions. The 12-month moving average masks the changes in prescribing trends observed in the final year of data, where there was a decline in the share of nilotinib in the third line, and an increase in third line imatinib: in this one year, the nilotinib share dropped by 10% (from 40% to 30%) whilst imatinib share increased by 10% (from 15% to 25%). The submission's model predicts nilotinib use will jump back up to 33% in 2022, then resume its decline and take 5 years to drop 4%, whilst imatinib use will drop back down to 20%, then take 5 years to increase by 3%.
	2022:	33%	9%	38%	20%	
	2023:	32%	10%	38%	21%	
	2024:	31%	10%	37%	22%	
	2025:	30%	11%	37%	22%	
	2026:	29%	11%	37%	23%	
Uptake (%) of asciminib	<u>Uptake</u>				Sponsor assumed. This is likely an underestimate, as explained in the row below.	
	2022:	35.0%				
	2023:	40.0%				
	2024:	45.0%				
	2025:	47.5%				
	2026:	48.5%				
2027:	49.5%					

Public Summary Document – July 2022 PBAC Meeting

Parameter	Value applied	Source/Comment
Distribution (%) of substitution from nilotinib, ponatinib, dasatinib and imatinib	<p style="text-align: center;"><u>Distribution</u></p> Nilotinib: 49.1% Ponatinib: 10.2% Dasatinib: 20.4% Imatinib: 20.4%	Analysis of 10% PBS sample data treatment sequences since 2016. This is an inappropriate source of data to predict the substitutions; the addition of asciminib to the PBS would alter the later-line treatment landscape in Australia. Currently, if a TKI is given after failure of two prior TKIs, 75-80% of patients will fail ¹² . Asciminib represents a novel mechanism of action, which is preferable in these pre-treated patients, and is why UpToDate guidelines recommend asciminib, rather than a third TKI, in patients who have failed ≥ 2 prior TKIs ¹³ . It is unlikely that clinicians will continue to prescribe nilotinib in 51%, and dasatinib/imatinib in 80% of patients if asciminib were available. This is particularly true if the submission's claim of superior safety of asciminib is accepted. DUSC considered the distribution highly uncertain, given the significant changes in first line and the 2016 market being significantly different from the current market in 2021. DUSC noted polynomial functions may be more appropriate to model the trend.
Grandfathered patients	2022: ██████ ¹ patients	Novartis MAP.
Persistence grandfathered patients	88% per annum	Persistence of nilotinib over the period 12 to 36 months since initiating treatment from 10% PBS sample data. DUSC noted this step may not be necessary.
Asciminib	Published AEMP: 20 mg x 60: \$ ██████ 40 mg x 60: \$ ██████ Effective AEMP: 20 mg x 60: \$ ██████ 40 mg x 60: \$ ██████ Revised effective AEMP: 20 mg x 60: \$ ██████ 40 mg x 60: \$ ██████ Revised effective AEMP no C5.7: 20 mg x 60: \$ ██████ 40 mg x 60: \$ ██████	Novartis proposed Revised AEMP based on revised equi-effective doses, as described in the economic analysis above, and removal of Clause 5.7.
Nilotinib	Effective AEMP: 150 mg x 120: \$3,694.89 200 mg x 120: \$4,895.54	Schedule of Pharmaceutical Benefits, items 1309X & 9171Q (February 2022)
Ponatinib	Effective AEMP: 15 mg x 60: \$5,328.18 45 mg x 30: \$6,011.65	Schedule of Pharmaceutical Benefits, items 10520Q & 10530F (February 2022)
Dasatinib	Effective AEMP: 70 mg x 60: \$3,820.54 100mg x 30: \$3,085.89	Schedule of Pharmaceutical Benefits, items 1415L & 1416M (February 2022)

¹² Akard L, Albitar M, Hill CE, Pinilla-Ibarz J. The "hit hard and hit early" approach to the treatment of chronic myeloid leukaemia: Implications of the updated national comprehensive cancer network clinical practice guidelines for routine practice. *Clinical Advances in Hematology and Oncology*. 2013 07/01;11:421-32.

¹³ Negrin, R, Schiffer, C, Atallah, E. UpToDate: Treatment of chronic myeloid leukaemia in chronic phase after failure of initial therapy. Wolters Kluwer, 2022.

Public Summary Document – July 2022 PBAC Meeting

Parameter	Value applied	Source/Comment
Imatinib	Effective AEMP: 100 mg x 60: \$290.33 400 mg x 30: \$580.65	Schedule of Pharmaceutical Benefits, various items

Source: Table 4.1-1, pp 197-198 of the submission.

C5.7 = Clause 5.7; Nil. = nilotinib; Pon. = ponatinib; Das. = dasatinib; Ima. = imatinib; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; DPMQ = Dispensed Price for Maximum Quantity; AEMP = approved ex-manufacturer price; MAP = managed access program

The redacted values correspond to the following ranges:

¹ < 500

- 6.58 The estimated net financial implications for the proposed listing of asciminib for CML-CP after failure of 2 prior TKIs over the first 6 years are summarised in Table 18. The submission proposed that there would be additional MBS savings associated with asciminib use, but did not estimate what this difference may be, due to differences in monitoring requirements and difficult in capturing time-dependent aspects of Grade ≥ 3 AEs. For the calculation of cost offsets, the submission used the published DPMQ for the comparators, which included the anniversary price reductions and reduction for dasatinib moving to the F2 formulary. In the submission, the cost of asciminib was minimised against the price of nilotinib/ponatinib prior to anniversary price reductions, but the analysis was adjusted by the evaluation to remove the application of Clause 5.7 (paragraph 6.48). The financial impact has been recalculated from that presented in the submission to remove the application of this clause.
- 6.59 The submission added < 500 grandfathered patients to the predicted number of prevalent patients treated in Year 1, and assumed 88% of patients remained on treatment for each subsequent year. The PBAC noted as the grandfathered patients are accounted for separately, they are not included in the uptake rates. The uptake rates including grandfathered patients have been added to Table 18.

Table 18: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Total eligible population	528	599	671	742	814	885
Eligible prevalent pts	35%	40%	45%	47.5%	48.5%	49.5%
Treated GF patients	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Total treated population	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ²
Uptake including GF patients	58%	58%	59%	59%	57%	57%
Total asciminib R/PBS scripts	█ ²	█ ²	█ ²	█ ⁶	█ ⁶	█ ⁶
Estimated financial implications of asciminib (effective price)						
Revised ^{a,b} total R/PBS DPMQ	\$█ ³	\$█ ⁵	\$█ ⁵	\$█ ⁵	\$█ ⁵	\$█ ⁷
Revised ^{a,b} total R/PBS copayments	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴
Revised ^{a,b} cost to R/PBS less copayments	\$█	\$█ ⁵	\$█ ⁵	\$█ ⁵	\$█ ⁵	\$█ ⁷
Estimated financial implications for nilotinib, imatinib, dasatinib and ponatinib						
Cost to PBS/RPBS	\$█ ³	\$█ ³	\$█ ³	\$█ ⁵	\$█ ⁵	\$█ ⁵
Copayments	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴
Cost to PBS/RPBS less copayments	\$█ ³	\$█ ³	\$█ ³	\$█ ⁵	\$█ ⁵	\$█ ⁵
Net financial implications (effective price)						
Revised ^{a,b} net effective cost to R/PBS no C5.7 ^b	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴

Source: Table 4.2-3, p 205; Table 4.2-6, p 207; Table 4.3-4, p 209; of the submission.

asciminib = asciminib; pop. = population; GF = grandfathered.

^a Re-calculated using revised EMP for asciminib based on revised equi-effective doses in the economic analysis.

^b Re-calculated using the revised equi-effective doses and without the application of Clause 5.7.

The redacted values correspond to the following ranges:

¹ < 500

² 500 to < 5000

³ \$10 million to < \$20 million

⁴ \$0 to < \$10 million

⁵ \$20 million to < \$30 million

⁶ 5,000 to < 10,000

⁷ \$30 million to < \$40 million

6.60 The total cost to the PBS/RPBS of listing asciminib was estimated by the submission to be \$10 million to < \$20 million in Year 6, and a total of \$60 million to < \$70 million in the first 6 years of listing, based on the effective price (data not shown). This additional cost was primarily due to asciminib replacing dasatinib and imatinib, which are cheaper than nilotinib and ponatinib (see Table 3), and therefore only offset a portion of the proposed asciminib price. Further, the submission used an inflated asciminib price, which was revised by the evaluation to include modifications to the equi-effective doses and remove application of Clause 5.7 to the comparator prices. With these revisions, the total cost to the PBS/RPBS of listing asciminib was reduced to \$0 to < \$10 million in Year 6, and a total of \$30 million to < \$40 million in the first 6 years of listing (Table 18). The submission stated that asciminib represented savings on monitoring requirements and management of Grade ≥3 AEs, which it could not

estimate in its prevalence-based approach, but proposed that listing asciminib may result in a reduction in the cost to State and Territory health budgets.

6.61 The DUSC consideration of asciminib found the estimates presented in the submission to be underestimated. The main issues are:

- The representativeness of the 10% PBS sample for the requested population is uncertain and modelled trends may not be accurate. The 10% PBS sample was used to estimate the number of prevalent patients, the distribution of use of TKIs across the prevalent patients, and the distribution of substitution of PBS-listed TKIs with asciminib.
- The submission estimated the eligible patient population for asciminib treatment in Year 1 to be 528 patients, increasing to 885 patients in Year 6. Triangulation with the 2019 DUSC review which noted between 2 and 24% of CML patients are intolerant and discontinue therapy suggests the submission's first year estimate (528 patients, equivalent to 12%) is within this range, but the eligible patient numbers could go up to 24% of the total CML patients.
- It is uncertain which PBS-listed third line TKIs asciminib will substitute for. Based on the current trends, increased substitution from imatinib and ponatinib may be likely, however, this would be best estimated from a full PBS sample, rather than the 10% PBS sample. This has implications for accuracy of the projected drug cost and cost offsets.
- The submission likely underestimated the uptake rate of asciminib due to the different mechanism of action of asciminib compared to the other available TKIs.

6.62 A sensitivity analysis was included in the Commentary using different substitution patterns (equal for nilotinib, dasatinib and imatinib, lower for ponatinib) and increased uptake rates in later years (30%-70%); the overall impact was an increase in the financial estimates. During the evaluation it was noted that these uptake rates are high for a new drug, however the differing mechanism of action offered by asciminib means it has the potential to transform the later-line treatment landscape, and could become the preferred choice of therapy within its first 6 years of listing; the DUSC noted that UpToDate already recommends asciminib in patients who have failed ≥ 2 prior TKIs¹⁴.

¹⁴ Negrin, R, Schiffer, C, Atallah, E. UpToDate: Treatment of chronic myeloid leukaemia in chronic phase after failure of initial therapy. Wolters Kluwer, 2022.

Quality Use of Medicines

- 6.63 The asciminib draft PI proposed additional monitoring in Australia, to quickly identify new safety information.

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend the listing of asciminib for the treatment of 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).
- 7.2 The PBAC considered that the claim of non-inferior effectiveness of asciminib compared with nilotinib (based on the ASCEMBL and ENACT trials) is likely supported, despite the uncertainty associated with the unanchored, unadjusted indirect treatment comparison (ITC). However, it considered that the claim of non-inferior effectiveness of asciminib compared with ponatinib was not supported based on the comparison between the ASCEMBL and PACE trials. Further, it considered that the available data do not support the claim of superior safety to either nilotinib or ponatinib.
- 7.3 The PBAC noted the clinical place of asciminib in patients with Ph+ CML in CP and its clinical need. Asciminib is the first STAMP inhibitor in CML (Specifically Targeting the ABL Myristoyl Pocket) and is recommended in international guidelines for treatment of CML-CP. The PBAC noted that the consumer comments consistently described asciminib as effective and well tolerated compared to the currently available TKIs, and that it is an essential medication for a small number of patients with CML who have no remaining options with respect to TKI therapy and for whom the only alternative treatment would be allogeneic transplantation. The PBAC noted that internationally there appears to be high uptake of asciminib due to a relatively favourable toxicity profile and the increased use of second generation TKIs in the front line.
- 7.4 The PBAC noted the complexity of the asciminib restrictions in terms of accurately reflecting its intended use among the currently listed TKIs, in terms of the order of prior TKI treatment received by patients before receiving asciminib, and whether the prior treatment was ceased due to failure or intolerance. The PBAC considered that further review may be required regarding how prior therapy with TKIs should be described in the restrictions, and if flow on changes to TKI listings for the third-line treatment of CML-CP would be required.
- 7.5 The PBAC noted that the PBS restriction initially proposed did not specifically exclude patients with Ph+ CML in CP who harbour the T315I mutation, even though these patients were excluded from the key trial (ASCSEMBL). The rationale for excluding these patients from ASCSEMBL (asciminib versus bosutinib) was that bosutinib is inactive against the T315I mutation. The PBAC acknowledged, as per the ACM advice

to the TGA Delegate, that underdosing of patients with the T315I mutation may occur without specific dosage instructions in the PI. The PBAC noted that all Ph+ CML in CP patients may not be tested for the T315I mutation, but agreed with the ACM that dosage consideration of asciminib is important should the presence of this mutation become known. The PBAC considered it would be necessary for asciminib to have 2 PBS restrictions that reflect the updated indication provided with the pre-PBAC response: 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.

- 7.6 The PBAC advised that asciminib should have a separate restriction for patients with the T315I mutation in the context of it being active against this mutation: it has similar efficacy in patients with the T315I mutation as it does in the non-T315I population, noting that a higher dose is required in the former group. The PBAC noted that the single arm trial CABL001X2101 evaluated asciminib in CML patients with the T315I mutation, and that the ACM supported the inclusion of patients with the T315I mutation in the asciminib indication. The PBAC considered that asciminib could be accessible to these patients via a separate restriction on the PBS, should it be recommended in the future, noting the clinical need in this poor prognosis subgroup. The PBAC also considered that, before gaining access to asciminib, patients with the T315I mutation would be required to have failed an adequate trial of imatinib or dasatinib or nilotinib, in line with both the restriction for ponatinib and the inclusion criteria of the CABL001X2101 trial (patients with relapsed disease who have the T315I mutation must have received treatment with at least one prior TKI).
- 7.7 The PBAC considered defining the comparator to be 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. 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. Overall, the PBAC considered 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 unable to tolerate, both dasatinib and nilotinib. Therefore, the PBAC considered that benchmarking against second

generation TKIs was a reasonable basis for establishing a cost-effective price for asciminib, and noted that this approach was consistent with that used to determine the cost-effective price for ponatinib. In this context, the PBAC considered that the comparison presented of asciminib versus nilotinib to be informative.

- 7.8 The PBAC considered 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.
- 7.9 The PBAC noted the uncertainties associated with the clinical claim of non-inferior efficacy of asciminib compared to nilotinib based on the evidence from the ASCEMBL and ENACT trials. The ITC involved a French subgroup of the ENACT trial that was not pre-specified and had unknown baseline characteristics, although partial patient characteristics were subsequently provided. Despite the limitations of the evidence, the PBAC considered that non-inferior efficacy of asciminib against nilotinib is likely supported.
- 7.10 The PBAC did not accept the claim of non-inferior efficacy of asciminib compared to ponatinib based on the evidence from the ASCEMBL and PACE trials. The 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, but it is likely that almost all current ponatinib use is in patients with this mutation. The PBAC considered that data from patients with the T315I mutation treated with asciminib in the CABL001X2101 trial (paragraph 7.6) is relevant to this clinical claim.
- 7.11 The PBAC did not accept the claim of superior safety of asciminib compared to nilotinib and ponatinib. The PBAC noted that the randomised ASCEMBL trial comparing asciminib to a second-generation TKI (bosutinib) failed to show statistically significant differences between arms in any-grade AEs, SAEs, fatal SAEs or Grade ≥ 3 AEs. Further, the PBAC noted that the transitivity assumption for the ITCs may not hold, as patients in the asciminib arm of the ASCMEBL trial were younger, with a lower ECOG PS, compared to patients in the ENACT (nilotinib) and PACE (ponatinib) trials. The PBAC considered that superior safety of asciminib to nilotinib cannot be assessed in the context of an unanchored, unadjusted ITC. The PBAC considered that the available data do not support the claim of superior safety to either nilotinib or ponatinib.
- 7.12 The PBAC considered that the equi-effective doses for asciminib and nilotinib in patients without the T315I mutation should be based on median doses in the ASCEMBL (79.8 mg/day) and ENACT (782.5 mg/day) trials, respectively. The PBAC acknowledged that the appropriate statistic is the mean daily dose however, as this was not available for nilotinib and as the proposed equi-effective dose in the submission for nilotinib was also a median dose (797 mg/day; paragraph 6.32, ponatinib PSD, November 2014 PBAC meeting), the PBAC considered the median doses should be used for both asciminib and nilotinib. The PBAC considered it would

be reasonable to determine the equi-effective doses for asciminib and dasatinib using the previously established equi-effective doses for dasatinib and nilotinib (792.1 mg/day nilotinib and 111 mg/day dasatinib, which are also median doses (p12, nilotinib PSD, March 2008 PBAC meeting)).

- 7.13 The PBAC noted that the submission included separate cost minimisation calculations of asciminib versus nilotinib and asciminib versus ponatinib, assuming an identical cost of treatment over two years, and including the costs of medicines, monitoring and treatment of adverse events. The PBAC considered that a reasonable basis for establishing a cost effective price for asciminib, for the reasons discussed in paragraph 7.7, would be to benchmark against the second generation TKIs. In this context, the PBAC considered that the economic evaluation presented for asciminib versus nilotinib to be informative. The PBAC considered the CMA of asciminib and nilotinib should be based on the equi-effective doses outlined in paragraph 7.12, a two year time horizon, and the revised monitoring costs as calculated during the evaluation. Consistent with its view that the claim of superior safety has not been supported, the Committee considered there should be no cost offsets for the treatment of adverse events associated with nilotinib. The PBAC noted when benchmarking ponatinib with dasatinib and nilotinib that the relative use of each informed the overall weighted price and considered that a similar approach may be reasonable in a future submission for asciminib.
- 7.14 The PBAC considered the financial estimates to be unreliable, mainly because changes in the relative use of the TKIs over the last 12-18 months were not appropriately accounted for. In terms of the inputs informing the financial estimates the PBAC noted:
- The number of prevalent patients receiving a third TKI was estimated from an analysis of the 10% PBS sample, and although the estimate in Year 1 (528 patients) was consistent with the estimates from the 2019 DUSC review, the assumption of linear growth resulted in a substantial increase in the number of patients by year 6 (885, 67% increase versus Year 1). The PBAC considered the growth in the number of prevalent patients to have been overestimated.
 - The distribution of use of TKIs across the prevalent patients was extrapolated based on data from 2018-2021, and in 2027 the assumed distribution was 29% nilotinib, 37% dasatinib, 23% imatinib and 11% ponatinib. The PBAC considered the relative use of imatinib to have been underestimated, and that the use of ponatinib should reflect use primarily in patients with the T315I mutation.
 - The uptake, including the relative substitution from each of the TKIs, was poorly supported and difficult to interpret. The submission assumed uptake of 35% of the prevalent patients in Year 1 increasing to 49.5% in Year 6. The PBAC noted that these percentages did not account for the grandfathered patients and the uptake including these patients was 57-59% across the 6 years. The PBAC considered the uptake in the initial years to be overestimated as patients are unlikely to switch TKI treatment unless

they experience treatment failure or intolerance. The PBAC considered the uptake in the later years may be underestimated given asciminib is likely to be the preferred choice of therapy when switching treatments. The PBAC considered the assumed uptake rates in the sensitivity analysis undertaken by the evaluators (30% in Year 1 increasing to 70% in Years 5 and 6) to be reasonable, although noted the grandfathered patients should be included in this uptake. In terms of the relative substitution from each of the TKIs, the PBAC considered the submission's estimates (49.1% from nilotinib, 10.2% from ponatinib, 20.4% from dasatinib and 20.4% from imatinib), which were based on an analysis of the 10% PBS sample from 2016, do not reflect current or expected future substitution. The PBAC considered substantially higher substitution from nilotinib relative to dasatinib was unlikely, and substitution for imatinib would be expected to increase consistent with the increasing use of imatinib as the third TKI. The PBAC noted the sensitivity analysis undertaken by the evaluators assumed equal substitution from nilotinib and dasatinib which seemed more plausible.

7.15 The PBAC considered the outstanding issues could be easily resolved in a simple resubmission for asciminib using the early re-entry pathway. If the sponsor accepts this pathway, the following changes may address these outstanding issues without requiring further re-evaluation.

- A separate restriction for patients with the T315I mutation (paragraphs 7.5 and 7.6).
- Presentation of clinical data to support asciminib is non-inferior to ponatinib in patients with the T315I mutation (paragraph 7.10).
- An economic evaluation that reflects benchmarking against the second generation TKIs, nilotinib and dasatinib (paragraph 7.13).
- Recalculation of the financial implications incorporating the advice in paragraph 7.14.

The early re-entry resubmission must be lodged by week 7 of the current PBAC cycle or the next cycle. If the issues cannot be addressed by the sponsor in a simple resubmission and the early re-entry timing is not acceptable, a standard re-entry pathway is available.

7.16 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Not recommended

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

Novartis are committed to working with the PBAC to achieve sustainable PBS listing conditions and timely Scemblix® (asciminib) access for chronic myeloid leukaemia patients.