

## 6.16 PONATINIB

**Tablet 15 mg (as hydrochloride),  
Tablet 45 mg (as hydrochloride),  
Iclusig<sup>®</sup>, Specialised Therapeutics Australia Pty Ltd.**

### 1 Purpose of Application

- 1.1 The minor submission requested changes to the existing PBS restrictions for ponatinib for the treatment of chronic myeloid leukaemia (CML):
- Removal of the time limitation for bone marrow biopsy pathology report(s) to have been obtained within the six months prior to initiating treatment with ponatinib.
  - The continuing restriction that follows the initial treatment with ponatinib after failure or intolerance to prior dasatinib and nilotinib, as well as the initial treatment with ponatinib after failure of prior therapy of imatinib or dasatinib or nilotinib in patients with T315I mutation into first continuing (Authority Required - written) and subsequent continuing (Authority Required - telephone).
- 1.2 The minor submission detailed the flow on amendments to DHS PBS authority application forms that would be required if the changes to the existing PBS restrictions outlined above were approved. In addition, the minor submission also included requests for amendments to two additional DHS initial PBS authority application forms for ponatinib. PBAC consideration was not required for these proposed amendments.

### 2 Background

- 2.1 Ponatinib was recommended for listing at the July 2015 PBAC meeting for the treatment of:
- CML in (i) Patients who have failed first line therapy with imatinib or dasatinib or nilotinib and whose CML has the T315I mutation; (ii) Patients with CML where both nilotinib and dasatinib have failed or where one of nilotinib or dasatinib has failed and the patient is intolerant of the other drug; and
  - relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) in patients whose ALL has the T315I mutation (paragraph 2.1, ponatinib Public Summary Document (PSD), November 2017).
- 2.2 In November 2017, the PBAC recommended amending the current ponatinib restriction for relapsed or refractory Ph+ ALL to include patients without the T315I mutation who have failed or are intolerant to dasatinib (paragraph 5.1, ponatinib PSD, November 2017). The PBAC reiterated its view that there is a clinical need for

*Public Summary Document – November 2018 PBAC Meeting*

treatments of Ph+ALL patients without the T315I mutation at its April 2018 meeting (paragraph 8.1, ponatinib PSD, November 2017).

- 2.3 The minor submission claimed that the requirement for pathology reports to have been obtained within the 6 months prior to application for initiation of treatment was not present in the recommended listing from the July 2015 recommendation of ponatinib for CML.
- 2.4 The minor submission claimed that the requirement for written authority for applications for ongoing treatment may result in delays for patient access and stated that this issue was previously considered by the PBAC in its July 2016 consideration of dasatinib. At the July 2016 meeting the PBAC recommended the authority requirement type for dasatinib be changed from Authority Required (written) to Authority Required (telephone) for subsequent continuing treatment applications for first-line treatment of CML (paragraph 6.1, dasatinib Public Summary Document, July 2016).

### **3 Requested listing**

- 3.1 The minor submission requested a change to the prescriber instruction pertaining to pathology report timeframes for the two initial treatment listings for CML.
- 3.2 The minor submission also requested the continuing restriction be split into first continuing and subsequent continuing, with the first continuing an Authority Required (written) listing and the subsequent continuing restriction an Authority Required (telephone) listing.
- 3.3 An abridged version of the requested listings is presented. The requested changes to the current listings (PBS items 10520Q and 10530F) are in bold. Secretariat suggested additions are in italics and deletions are in strikethrough.

| <b>Name, Restriction, Manner of administration and form</b> | <b>Max. Qty</b> | <b>No. of Rpts</b> | <b>Dispensed Price for Max. Qty</b> | <b>Proprietary Name and Manufacturer</b>   |
|---|-----------------|--------------------|-------------------------------------|--|
| PONATINIB   |                 |                    |                                     |  |
| 15 mg tablet, 60  | 1               | 5                  | \$5759.65                           | Iclusig                                    |
| 45 mg tablet, 30  | 1               | 5                  | \$6479.09                           | Specialised Therapeutics Australia Pty Ltd |

#### Removal of time limitation on pathology reports

|                           |   |
|---------------------------|---|
| <b>Category / program</b> | General Schedule  |
| <b>Prescriber type</b>    | <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse Practitioners<br><input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives |
| <b>Episodicity:</b>       | Chronic   |
| <b>Condition:</b>         | Myeloid leukaemia   |
| <b>PBS Indication:</b>    | Chronic myeloid leukaemia (CML)   |
| <b>Treatment phase:</b>   | Initial treatment   |

*Public Summary Document – November 2018 PBAC Meeting*

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|------------------------------------|---|
| <b>Restriction Level / Method:</b> | <input type="checkbox"/> Restricted benefit<br><input checked="" type="checkbox"/> Authority Required - In Writing<br><input type="checkbox"/> Authority Required - Telephone<br><input type="checkbox"/> Authority Required - Emergency<br><input type="checkbox"/> Authority Required - Electronic<br><input type="checkbox"/> Streamlined  |
| <b>Clinical criteria:</b>          | <p>The treatment must be the sole PBS-subsidised therapy for this condition,<br/>         AND<br/>         Patient must be expressing the T315I mutation,<br/>         AND<br/>         Patient must have failed an adequate trial of imatinib; OR<br/>         Patient must have failed an adequate trial of dasatinib; OR<br/>         Patient must have failed an adequate trial of nilotinib.</p>   |
| <b>Prescriber Instructions</b>     | <p>Failure of an adequate trial of imatinib or dasatinib or nilotinib is defined as:</p> <ol style="list-style-type: none"> <li>1. Lack of response to imatinib or dasatinib or nilotinib therapy, defined as either: (i) failure to achieve a haematological response after a minimum of 3 months therapy with imatinib or dasatinib or nilotinib; or (ii) failure to achieve any cytogenetic response after a minimum of 6 months therapy with imatinib or dasatinib or nilotinib as demonstrated on bone marrow biopsy by presence of greater than 95% Philadelphia chromosome positive cells; or (iii) failure to achieve a major cytogenetic response or a peripheral blood BCR-ABL level of less than 1% after a minimum of 12 months therapy with imatinib or dasatinib or nilotinib; OR</li> <li>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 imatinib or dasatinib or nilotinib therapy; OR</li> <li>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 imatinib or dasatinib or nilotinib therapy; OR</li> <li>4. Development of accelerated phase or blast crisis in a patient previously prescribed imatinib or dasatinib or nilotinib for any phase of chronic myeloid leukaemia; OR</li> <li>5. Disease progression (defined as a greater than or equal to 50% increase in peripheral white blood cell count, blast count, basophils or platelets) during imatinib or dasatinib or nilotinib therapy in patients with accelerated phase or blast crisis chronic myeloid leukaemia.</li> </ol> <p>Accelerated phase is defined by the presence of 1 or more of the following:</p> <ol style="list-style-type: none"> <li>1. Percentage of blasts in the peripheral blood or bone marrow greater than or equal to 15% but less than 30%; or</li> <li>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</li> <li>3. Peripheral basophils greater than or equal to 20%; or</li> <li>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</li> <li>5. Karyotypic evolution (chromosomal abnormalities in addition to a single Philadelphia chromosome).</li> </ol> <p>Blast crisis is defined as either:</p> <ol style="list-style-type: none"> <li>1. Percentage of blasts in the peripheral blood or bone marrow greater than or equal to 30%; or</li> <li>2. Extramedullary involvement other than spleen and liver.</li> </ol> <p>The authority application must be made in writing and must include:</p> |

Public Summary Document – November 2018 PBAC Meeting

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|  | <p>1. a completed authority prescription form; and</p> <p>2. a completed Chronic Myeloid Leukaemia - ponatinib Initial PBS authority application form; and</p> <p>3. a signed patient acknowledgement; and</p> <p>4. a bone marrow biopsy pathology report demonstrating the patient has active chronic myeloid leukaemia, either manifest as cytogenetic evidence of the Philadelphia chromosome, or RT-PCR level of BCR-ABL transcript greater than 0.1% on the international scale and evidence of the T315I mutation. (The date of the relevant pathology report(s), <del>which should be within the previous 6 months</del>, need(s) to be provided); and</p> <p>5. where there has been a loss of response to imatinib or dasatinib or nilotinib, a copy of the current confirming pathology report(s) from an Approved Pathology Authority or details of the dates of assessment in the case of progressive splenomegaly or extramedullary involvement.</p> |
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|------------------------------------|---|
| <b>Category / program</b>          | General Schedule  |
| <b>Prescriber type</b>             | <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse Practitioners<br><input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives   |
| <b>Episodicity:</b>                | Chronic   |
| <b>Condition:</b>                  | Myeloid leukaemia   |
| <b>PBS Indication:</b>             | Chronic myeloid leukaemia (CML)   |
| <b>Treatment phase:</b>            | Initial treatment   |
| <b>Restriction Level / Method:</b> | <input type="checkbox"/> Restricted benefit<br><input checked="" type="checkbox"/> Authority Required - In Writing<br><input type="checkbox"/> Authority Required - Telephone<br><input type="checkbox"/> Authority Required - Emergency<br><input type="checkbox"/> Authority Required - Electronic<br><input type="checkbox"/> Streamlined  |
| <b>Clinical criteria:</b>          | <p>The treatment must be the sole PBS-subsidised therapy for this condition,<br/>AND</p> <p>Patient must have failed an adequate trial of dasatinib; OR</p> <p>Patient must have developed intolerance to dasatinib of a severity necessitating permanent treatment withdrawal,<br/>AND</p> <p>Patient must have failed an adequate trial of nilotinib; OR</p> <p>Patient must have developed intolerance to nilotinib of a severity necessitating permanent treatment withdrawal; OR</p> <p>Patient must not be eligible for PBS-subsidised treatment with nilotinib because the patient has a blast crisis.</p>   |
| <b>Prescriber Instructions</b>     | <p>Failure of an adequate trial of dasatinib or nilotinib is defined as:</p> <p>1. Lack of response to dasatinib or nilotinib therapy, defined as either: (i) failure to achieve a haematological response after a minimum of 3 months therapy with dasatinib or nilotinib; or (ii) failure to achieve any cytogenetic response after a minimum of 6 months therapy with dasatinib or nilotinib as demonstrated on bone marrow biopsy by presence of greater than 95% Philadelphia chromosome positive cells; or (iii) failure to achieve a major cytogenetic response or a peripheral blood BCR-ABL level of less than 1% after a minimum of 12 months therapy with dasatinib or nilotinib; OR</p> <p>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 dasatinib or nilotinib therapy; OR</p> <p>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</p> |

Public Summary Document – November 2018 PBAC Meeting

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|--|---|
|  | <p>greater than 0.1% confirmed on a subsequent test), during ongoing dasatinib or nilotinib therapy; OR</p> <p>4. Development of accelerated phase or blast crisis in a patient previously prescribed dasatinib or nilotinib for any phase of chronic myeloid leukaemia; OR</p> <p>5. Disease progression (defined as a greater than or equal to 50% increase in peripheral white blood cell count, blast count, basophils or platelets) during dasatinib or nilotinib therapy in patients with accelerated phase or blast crisis chronic myeloid leukaemia.</p> <p>Accelerated phase is defined by the presence of 1 or more of the following:</p> <ol style="list-style-type: none"> <li>1. Percentage of blasts in the peripheral blood or bone marrow greater than or equal to 15% but less than 30%; or</li> <li>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</li> <li>3. Peripheral basophils greater than or equal to 20%; or</li> <li>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</li> <li>5. Karyotypic evolution (chromosomal abnormalities in addition to a single Philadelphia chromosome).</li> </ol> <p>Blast crisis is defined as either:</p> <ol style="list-style-type: none"> <li>1. Percentage of blasts in the peripheral blood or bone marrow greater than or equal to 30%; or</li> <li>2. Extramedullary involvement other than spleen and liver.</li> </ol> <p>The authority application must be made in writing and must include:</p> <ol style="list-style-type: none"> <li>1. a completed authority prescription form;</li> <li>2. a completed Chronic Myeloid Leukaemia - ponatinib Initial PBS authority application form;</li> <li>3. a signed patient acknowledgement;</li> <li>4. a bone marrow biopsy pathology report demonstrating the patient has active chronic myeloid leukaemia, either manifest as cytogenetic evidence of the Philadelphia chromosome, or RT-PCR level of BCR-ABL transcript greater than 0.1% on the international scale. (The date of the relevant pathology report, <b>which should be within the previous 6 months</b>, needs to be provided); and</li> <li>5. where there has been a loss of response to dasatinib or nilotinib, a copy of the current confirming pathology report(s) from an Approved Pathology Authority or details of the dates of assessment in the case of progressive splenomegaly or extramedullary involvement.</li> </ol> |
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Continuing restriction split into first and subsequent continuing treatment

Existing benefit:

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|---------------------------|---|
| <b>Category / program</b> | General Schedule  |
| <b>Prescriber type</b>    | <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse Practitioners<br><input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives |
| <b>Episodicity:</b>       | Chronic   |
| <b>Condition:</b>         | Myeloid leukaemia   |
| <b>PBS Indication:</b>    | Chronic myeloid leukaemia (CML)   |
| <b>Treatment phase:</b>   | <b>First continuing treatment</b>   |

Public Summary Document – November 2018 PBAC Meeting

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|------------------------------------|--|
| <b>Restriction Level / Method:</b> | <input type="checkbox"/> Restricted benefit<br><input checked="" type="checkbox"/> Authority Required - In Writing<br><input type="checkbox"/> Authority Required - Telephone<br><input type="checkbox"/> Authority Required - Emergency<br><input type="checkbox"/> Authority Required - Electronic<br><input type="checkbox"/> Streamlined   |
| <b>Clinical criteria:</b>          | <p><i>The condition must be in the chronic phase,</i><br/> <b>AND</b><br/>         Patient must have previously been issued with an authority prescription for this drug for this condition,<br/> <b>AND</b><br/>         The treatment must be the sole PBS-subsidised therapy for this condition,<br/> <b>AND</b><br/>         Patient must have demonstrated either a major cytogenetic response, or less than 1% BCR-ABL level in the blood, to ponatinib within 18 months of commencement and at no greater than 12 month intervals thereafter.</p>   |
| <b>Prescriber Instructions</b>     | <p><i>First continuing</i> Applications for authorisation must be in writing and must include:</p> <ol style="list-style-type: none"> <li>1. a completed authority prescription form; and</li> <li>2. a completed Chronic Myeloid Leukaemia Continuing PBS authority application Supporting information form; and</li> <li>3. demonstration of continued response to treatment as evidenced by either:             <ol style="list-style-type: none"> <li>(a) major cytogenetic response [see Note explaining definitions of response]. Where this has been supplied within the previous 12 months (or 18 months for the initial supply), only the date of the relevant pathology report needs to be provided; or</li> <li>(b) a peripheral blood level of BCR-ABL of less than 1% on the international scale [see Note explaining definitions of response]. Where this has been supplied within the previous 12 months (or 18 months for the initial supply), only the date of the relevant pathology report needs to be provided.</li> </ol> </li> </ol> |

New benefit:

|                                    |  |
|------------------------------------|--|
| <b>Category / program</b>          | General Schedule   |
| <b>Prescriber type</b>             | <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse Practitioners<br><input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives  |
| <b>Episodicity:</b>                | Chronic  |
| <b>Condition:</b>                  | Myeloid leukaemia  |
| <b>PBS Indication:</b>             | Chronic myeloid leukaemia (CML)  |
| <b>Treatment phase:</b>            | Subsequent continuing treatment  |
| <b>Restriction Level / Method:</b> | <input type="checkbox"/> Restricted benefit<br><input type="checkbox"/> Authority Required - In Writing<br><input checked="" type="checkbox"/> Authority Required - Telephone<br><input type="checkbox"/> Authority Required - Emergency<br><input type="checkbox"/> Authority Required - Electronic<br><input type="checkbox"/> Streamlined |

Public Summary Document – November 2018 PBAC Meeting

|                           |   |
|---------------------------|---|
| <b>Clinical criteria:</b> | The condition must be in the chronic phase,<br>AND<br>Patient must have received the First continuing PBS-subsidised treatment with this drug<br><i>for this condition</i> ,<br>AND<br>Patient must have maintained a major cytogenetic response, OR<br>Patient must have maintained a peripheral blood level of BCR-ABL of less than 1%,<br>AND<br>The treatment must be the sole PBS-subsidised therapy for this condition. |
|---------------------------|---|

3.4 The pre-PBAC response noted the existing CML continuing treatment restrictions for dasatinib, imatinib and nilotinib that include a criterion regarding the need for the condition to be in the chronic phase, only apply to continuing treatment in the first-line setting. The nilotinib and dasatinib restrictions for continuing treatment in subsequent lines of therapy do not include a criterion for the condition to be in chronic phase. The pre-PBAC response argued that ponatinib is generally used as the last-line treatment option for CML patients and should be available to patients in all phases. The PBAC noted that the existing continuing restriction for ponatinib does not include a clinical criterion for the condition to be in the chronic phase and considered that that it followed that this was not required for the proposed subsequent continuing restriction.

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

## 4 Current situation

4.1 The minor submission presented PBS usage data for ponatinib indicating that uptake was lower than estimated in the 2015 submission (Table 1).

Table 1: Ponatinib PBS services per year

|   | Year 0<br>(2015) | Year 1<br>(2016) | Year 2<br>(2017) | Year 3<br>(2018) | Year 4<br>(2019) | Year 5<br>(2020) |
|---|------------------|------------------|------------------|------------------|------------------|------------------|
| <b>Estimated PBS services for ponatinib<sup>a</sup></b> |                  |                  |                  |                  |                  |                  |
| Packs of ponatinib 15 mg                                | ■                | ■                | ■                | ■                | ■                | ■                |
| Packs of ponatinib 45 mg                                | ■                | ■                | ■                | ■                | ■                | ■                |
| <b>Annual PBS services for ponatinib<sup>b</sup></b>    |                  |                  |                  |                  |                  |                  |
| <b>Packs of ponatinib 15 mg</b>                         |                  |                  |                  |                  |                  |                  |
| - Patients with CML                                     | ■                | ■                | ■                | ■                |                  |                  |
| - Patients with AML                                     |                  |                  |                  |                  |                  |                  |
| <b>Packs of ponatinib 45 mg</b>                         |                  |                  |                  |                  |                  |                  |
| - Patients with CML                                     | ■                | ■                | ■                | ■                |                  |                  |
| - Patients with AML                                     |                  |                  |                  |                  |                  |                  |

<sup>a</sup>Utilisation and cost model spreadsheet agreed with Finance 14/08/2015

<sup>b</sup>PBS usage data accessed 10/08/2018

<sup>c</sup>Annualised

Source: Table 4 minor submission

- 4.2 The minor submission claimed there would be no foreseeable financial implications to the PBS as a consequence of changing the authority requirement method for subsequent continuing treatment of CML from written to telephone.

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

## **5 Consideration of the evidence**

### ***Sponsor hearing***

- 5.1 There was no hearing for this item as it was a minor submission.

### ***Consumer comments***

- 5.2 The PBAC noted that no consumer comments were received for this item.

### ***Clinical trials***

- 5.3 As a minor submission, no clinical trials were presented in the submission.

## **6 PBAC Outcome**

- 6.1 The PBAC recommended an amendment to the existing PBS initial treatment restrictions for ponatinib for chronic myeloid leukaemia (CML), to remove reference to the six month timeframe between the bone marrow biopsy pathology report(s) and the application for initiation of treatment. The PBAC noted this amendment aligns with the current requirements for other tyrosine kinase inhibitors used in second- and third-line treatment of CML.
- 6.2 The PBAC also recommended an amendment to the existing PBS continuing treatment restriction for ponatinib for CML, to enable telephone authority for subsequent continuing treatment. The PBAC noted that a new restriction for the subsequent continuing treatment phase would need to be added to the existing prescribing rule to implement this change.
- 6.3 The PBAC noted that the addition of a new subsequent continuing treatment restriction required changes to the wording of the existing continuing restriction and the administrative advice applicable to the listing of ponatinib in CML. However, the PBAC considered that the recommendations are consistent with the intent of the existing listings for ponatinib for CML.
- 6.4 The PBAC agreed with the minor submission that the requested amendments to the existing restrictions for ponatinib for treatment of CML should not have any financial implication to the PBS.
- 6.5 The PBAC noted the submission's proposed amendments to the DHS application forms would be referred to the DHS for consideration.

Public Summary Document – November 2018 PBAC Meeting

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

**Outcome:**

Recommended

## 7 Recommended listing

7.1 Amend the Prescribing Instructions and Administrative Advice under the Initial restrictions for PBS items 10520Q (15 mg) and 10530F (45 mg) as follows:

| Name, Restriction,<br>Manner of administration and form | Max.<br>Qty | No. of<br>Rpts | Proprietary Name and Manufacturer                  |
|---|-------------|----------------|--|
| PONATINIB   |             |                |  |
| 15 mg tablet, 60  | 1           | 5              | Iclusig Specialised Therapeutics Australia Pty Ltd |
| 45 mg tablet, 30  | 1           | 5              |  |

Initial treatment benefits:

|                                    |  |
|------------------------------------|--|
| <b>Category / program</b>          | General Schedule   |
| <b>Prescriber type</b>             | <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse Practitioners<br><input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives  |
| <b>Episodicity:</b>                | Chronic  |
| <b>Condition:</b>                  | Myeloid leukaemia  |
| <b>PBS Indication:</b>             | Chronic myeloid leukaemia (CML)  |
| <b>Treatment phase:</b>            | Initial treatment  |
| <b>Restriction Level / Method:</b> | <input type="checkbox"/> Restricted benefit<br><input checked="" type="checkbox"/> Authority Required - In Writing<br><input type="checkbox"/> Authority Required - Telephone<br><input type="checkbox"/> Authority Required - Emergency<br><input type="checkbox"/> Authority Required - Electronic<br><input type="checkbox"/> Streamlined   |
| <b>Clinical criteria:</b>          | The treatment must be the sole PBS-subsidised therapy for this condition,<br>AND<br>Patient must be expressing the T315I mutation,<br>AND<br>Patient must have failed an adequate trial of imatinib; OR<br>Patient must have failed an adequate trial of dasatinib; OR<br>Patient must have failed an adequate trial of nilotinib.   |
| <b>Prescriber Instructions</b>     | Failure of an adequate trial of imatinib or dasatinib or nilotinib is defined as:<br>1. Lack of response to imatinib or dasatinib or nilotinib therapy, defined as either: (i) failure to achieve a haematological response after a minimum of 3 months therapy with imatinib or dasatinib or nilotinib; or (ii) failure to achieve any cytogenetic response after a minimum of 6 months therapy with imatinib or dasatinib or nilotinib as demonstrated on bone marrow biopsy by presence of greater than 95% Philadelphia chromosome positive cells; or (iii) failure to achieve a major cytogenetic response or a peripheral blood BCR-ABL level of less than 1% after a minimum of 12 months therapy with imatinib or dasatinib or nilotinib; OR<br>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 |

Public Summary Document – November 2018 PBAC Meeting

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|                                     | <p>imatinib or dasatinib or nilotinib therapy; OR</p> <p>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 imatinib or dasatinib or nilotinib therapy; OR</p> <p>4. Development of accelerated phase or blast crisis in a patient previously prescribed imatinib or dasatinib or nilotinib for any phase of chronic myeloid leukaemia; OR</p> <p>5. Disease progression (defined as a greater than or equal to 50% increase in peripheral white blood cell count, blast count, basophils or platelets) during imatinib or dasatinib or nilotinib therapy in patients with accelerated phase or blast crisis chronic myeloid leukaemia.</p> <p>Accelerated phase is defined by the presence of 1 or more of the following:</p> <ol style="list-style-type: none"> <li>1. Percentage of blasts in the peripheral blood or bone marrow greater than or equal to 15% but less than 30%; or</li> <li>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</li> <li>3. Peripheral basophils greater than or equal to 20%; or</li> <li>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</li> <li>5. Karyotypic evolution (chromosomal abnormalities in addition to a single Philadelphia chromosome).</li> </ol> <p>Blast crisis is defined as either:</p> <ol style="list-style-type: none"> <li>1. Percentage of blasts in the peripheral blood or bone marrow greater than or equal to 30%; or</li> <li>2. Extramedullary involvement other than spleen and liver.</li> </ol> <p>The authority application must be made in writing and must include:</p> <ol style="list-style-type: none"> <li>1. a completed authority prescription form; and</li> <li>2. a completed Chronic Myeloid Leukaemia - ponatinib Initial PBS authority application form; and</li> <li>3. a signed patient acknowledgement; and</li> <li>4. a bone marrow biopsy pathology report demonstrating the patient has active chronic myeloid leukaemia, either manifest as cytogenetic evidence of the Philadelphia chromosome, or RT-PCR level of BCR-ABL transcript greater than 0.1% on the international scale and evidence of the T315I mutation. (The date of the relevant pathology report(s), <del>which should be within the previous 6 months</del>, need(s) to be provided); and</li> <li>5. where there has been a loss of response to imatinib or dasatinib or nilotinib, a copy of the current confirming pathology report(s) from an Approved Pathology Authority or details of the dates of assessment in the case of progressive splenomegaly or extramedullary involvement.</li> </ol> |
| <p><b>Administrative Advice</b></p> | <p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at <a href="http://www.humanservices.gov.au">www.humanservices.gov.au</a></p> <p>Applications for authority to prescribe should be forwarded to:</p> <p>Department of Human Services<br/>         Prior Written Approval of Complex Drugs<br/>         Reply Paid 9826</p>   |

Public Summary Document – November 2018 PBAC Meeting

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|  | <p>GPO Box 9826<br/>HOBART TAS 7001</p> <p>Patients are eligible for PBS-subsidised treatment with only one of imatinib, dasatinib, nilotinib or ponatinib at any one time and must not be receiving concomitant interferon alfa therapy.</p> <p>1. Continuing treatment<br/><b>First continuing applications are to be written, at which time patients in whom a major cytogenetic response or peripheral blood BCR-ABL level of less than 1% has been demonstrated may receive authorisation for a further 12 months of treatment.</b><br/><b>Subsequent authority applications for continuing therapy may be made by telephoning the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</b></p> <p>2. Authority approval requirements.<br/>Response criteria to <del>initial</del> treatment with ponatinib:<br/>For the purposes of assessing response to PBS-subsidised treatment with ponatinib, either cytogenetic analysis indicating the number of Philadelphia positive [t (9;22)] cells in the bone marrow measured by standard karyotyping, or quantitative PCR indicating the relative level of BCR-ABL transcript in the peripheral blood using the international scale, must be submitted. For bone marrow analyses, where the standard karyotyping is not informative for technical reasons, a cytogenetic analysis performed on the bone marrow by the use of fluorescence in situ hybridisation (FISH) with BCR-ABL specific probe must be submitted. The cytogenetic or peripheral blood quantitative PCR analyses must be submitted within 18 months of the commencement of treatment with <del>dasatinib, nilotinib or</del> ponatinib (patients in whom a major cytogenetic response or peripheral blood BCR-ABL level of less than 1% is demonstrable by 18 months are eligible to receive <b>first</b> continuing treatment with <del>that agent this drug</del>).<br/><b>Thereafter, at no greater than 12 month intervals a major cytogenetic response or a peripheral blood BCR-ABL level of less than 1% must be sustained to receive subsequent continuing treatments with this drug.</b></p> <p>3. Definitions of response.<br/>A major cytogenetic response is defined as less than 35% Philadelphia positive bone marrow cells.<br/>A peripheral blood BCR-ABL level of less than 1% on the international scale (Blood 108: 28-37, 2006) also indicates a response, at least the biological equivalent of a major cytogenetic response.</p> <p>4. Definitions of loss of response.<br/>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 therapy.<br/>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 therapy.</p> |
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| <b>Category / program</b> | General Schedule  |
| <b>Prescriber type</b>    | <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse Practitioners<br><input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives |
| <b>Episodicity:</b>       | Chronic   |

Public Summary Document – November 2018 PBAC Meeting

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| <b>Condition:</b>                  | Myeloid leukaemia  |
| <b>PBS Indication:</b>             | Chronic myeloid leukaemia (CML)  |
| <b>Treatment phase:</b>            | Initial treatment  |
| <b>Restriction Level / Method:</b> | <input type="checkbox"/> Restricted benefit<br><input checked="" type="checkbox"/> Authority Required - In Writing<br><input type="checkbox"/> Authority Required - Telephone<br><input type="checkbox"/> Authority Required - Emergency<br><input type="checkbox"/> Authority Required - Electronic<br><input type="checkbox"/> Streamlined   |
| <b>Clinical criteria:</b>          | <p>The treatment must be the sole PBS-subsidised therapy for this condition,<br/>AND<br/>           Patient must have failed an adequate trial of dasatinib; OR<br/>           Patient must have developed intolerance to dasatinib of a severity necessitating permanent treatment withdrawal,<br/>AND<br/>           Patient must have failed an adequate trial of nilotinib; OR<br/>           Patient must have developed intolerance to nilotinib of a severity necessitating permanent treatment withdrawal; OR<br/>           Patient must not be eligible for PBS-subsidised treatment with nilotinib because the patient has a blast crisis.</p>  |
| <b>Prescriber Instructions</b>     | <p>Failure of an adequate trial of dasatinib or nilotinib is defined as:</p> <ol style="list-style-type: none"> <li>1. Lack of response to dasatinib or nilotinib therapy, defined as either: (i) failure to achieve a haematological response after a minimum of 3 months therapy with dasatinib or nilotinib; or (ii) failure to achieve any cytogenetic response after a minimum of 6 months therapy with dasatinib or nilotinib as demonstrated on bone marrow biopsy by presence of greater than 95% Philadelphia chromosome positive cells; or (iii) failure to achieve a major cytogenetic response or a peripheral blood BCR-ABL level of less than 1% after a minimum of 12 months therapy with dasatinib or nilotinib; OR</li> <li>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 dasatinib or nilotinib therapy; OR</li> <li>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 dasatinib or nilotinib therapy; OR</li> <li>4. Development of accelerated phase or blast crisis in a patient previously prescribed dasatinib or nilotinib for any phase of chronic myeloid leukaemia; OR</li> <li>5. Disease progression (defined as a greater than or equal to 50% increase in peripheral white blood cell count, blast count, basophils or platelets) during dasatinib or nilotinib therapy in patients with accelerated phase or blast crisis chronic myeloid leukaemia.</li> </ol> <p>Accelerated phase is defined by the presence of 1 or more of the following:</p> <ol style="list-style-type: none"> <li>1. Percentage of blasts in the peripheral blood or bone marrow greater than or equal to 15% but less than 30%; or</li> <li>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</li> <li>3. Peripheral basophils greater than or equal to 20%; or</li> <li>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</li> <li>5. Karyotypic evolution (chromosomal abnormalities in addition to a single Philadelphia chromosome).</li> </ol> <p>Blast crisis is defined as either:</p> |

Public Summary Document – November 2018 PBAC Meeting

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|                                     | <p>1. Percentage of blasts in the peripheral blood or bone marrow greater than or equal to 30%; or<br/>                 2. Extramedullary involvement other than spleen and liver.</p> <p>The authority application must be made in writing and must include:</p> <ol style="list-style-type: none"> <li>1. a completed authority prescription form;</li> <li>2. a completed Chronic Myeloid Leukaemia - ponatinib Initial PBS authority application form;</li> <li>3. a signed patient acknowledgement;</li> <li>4. a bone marrow biopsy pathology report demonstrating the patient has active chronic myeloid leukaemia, either manifest as cytogenetic evidence of the Philadelphia chromosome, or RT-PCR level of BCR-ABL transcript greater than 0.1% on the international scale. (The date of the relevant pathology report, <b>which should be within the previous 6 months</b>, needs to be provided); and</li> <li>5. where there has been a loss of response to dasatinib or nilotinib, a copy of the current confirming pathology report(s) from an Approved Pathology Authority or details of the dates of assessment in the case of progressive splenomegaly or extramedullary involvement.</li> </ol>  |
| <p><b>Administrative Advice</b></p> | <p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).<br/>                 Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at <a href="http://www.humanservices.gov.au">www.humanservices.gov.au</a><br/>                 Applications for authority to prescribe should be forwarded to:</p> <p>Department of Human Services<br/>                 Prior Written Approval of Complex Drugs<br/>                 Reply Paid 9826<br/>                 GPO Box 9826<br/>                 HOBART TAS 7001</p> <p>Patients are eligible for PBS-subsidised treatment with only one of imatinib, dasatinib, nilotinib or ponatinib at any one time and must not be receiving concomitant interferon alfa therapy.</p> <p>1. Continuing treatment<br/> <b>First continuing applications are to be written, at which time patients in whom a major cytogenetic response or peripheral blood BCR-ABL level of less than 1% has been demonstrated may receive authorisation for a further 12 months of treatment.</b><br/> <b>Subsequent authority applications for continuing therapy may be made by telephoning the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</b></p> <p>2. Authority approval requirements.<br/>                 Response criteria to <b>initial</b> treatment with ponatinib:<br/>                 For the purposes of assessing response to PBS-subsidised treatment with ponatinib, either cytogenetic analysis indicating the number of Philadelphia positive [t (9;22)] cells in the bone marrow measured by standard karyotyping, or quantitative PCR indicating the relative level of BCR-ABL transcript in the peripheral blood using the international scale, must be submitted. For bone marrow analyses, where the standard karyotyping is not informative for technical reasons, a cytogenetic analysis performed on the bone</p> |

Public Summary Document – November 2018 PBAC Meeting

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|  | <p>marrow by the use of fluorescence in situ hybridisation (FISH) with BCR-ABL specific probe must be submitted. The cytogenetic or peripheral blood quantitative PCR analyses must be submitted within 18 months of the commencement of treatment with <del>dasatinib, nilotinib or</del> ponatinib (patients in whom a major cytogenetic response or peripheral blood BCR-ABL level of less than 1% is demonstrable by 18 months are eligible to receive <b>first</b> continuing treatment with <del>that agent this drug</del>).</p> <p><b>Thereafter, at no greater than 12 month intervals a major cytogenetic response or a peripheral blood BCR-ABL level of less than 1% must be sustained to receive subsequent continuing treatments with this drug.</b></p> <p>3. Definitions of response.<br/>A major cytogenetic response is defined as less than 35% Philadelphia positive bone marrow cells.<br/>A peripheral blood BCR-ABL level of less than 1% on the international scale (Blood 108: 28-37, 2006) also indicates a response, at least the biological equivalent of a major cytogenetic response.</p> <p>4. Definitions of loss of response.<br/>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 therapy.<br/>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 therapy.</p> |
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7.2 Amend the Clinical Criteria, Prescribing Instructions and Administrative Advice under the Continuing restrictions for PBS items 10520Q (15 mg) and 10530F (45 mg) as follows:

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| <b>Category / program</b>          | General Schedule   |
| <b>Prescriber type</b>             | <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse Practitioners<br><input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives  |
| <b>Episodicity:</b>                | Chronic  |
| <b>Condition:</b>                  | Myeloid leukaemia  |
| <b>PBS Indication:</b>             | Chronic myeloid leukaemia (CML)  |
| <b>Treatment phase:</b>            | <b>First continuing treatment</b>  |
| <b>Restriction Level / Method:</b> | <input type="checkbox"/> Restricted benefit<br><input checked="" type="checkbox"/> Authority Required - In Writing<br><input type="checkbox"/> Authority Required - Telephone<br><input type="checkbox"/> Authority Required - Emergency<br><input type="checkbox"/> Authority Required - Electronic<br><input type="checkbox"/> Streamlined   |
| <b>Clinical criteria:</b>          | <b>Patient must have received initial PBS subsidised treatment with this drug for this condition,</b><br><b>AND</b><br>The treatment must be the sole PBS-subsidised therapy for this condition,<br><b>AND</b><br><b>Patient must have demonstrated a major cytogenetic response, OR</b><br><b>Patient must have demonstrated a peripheral blood level of BCR-ABL of less than 1%.</b> |
| <b>Prescriber Instructions</b>     | <b>First continuing</b> applications for authorisation must be in writing and must include:<br>1. a completed authority prescription form; and   |

Public Summary Document – November 2018 PBAC Meeting

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|                                     | <p>2. a completed Chronic Myeloid Leukaemia Continuing PBS authority application Supporting information form; and</p> <p>3. demonstration of continued response to treatment as evidenced by either:</p> <p>(a) major cytogenetic response [see Note explaining definitions of response]. Where this has been supplied within the previous <del>12 months (or 18 months for the initial supply)</del> of the initial treatment, only the date of the relevant pathology report needs to be provided; or</p> <p>(b) a peripheral blood level of BCR-ABL of less than 1% on the international scale [see Note explaining definitions of response]. Where this has been supplied within the previous <del>12 months (or 18 months for the initial supply)</del> the initial treatment, only the date of the relevant pathology report needs to be provided.</p>   |
| <p><b>Administrative Advice</b></p> | <p>Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at <a href="http://www.humanservices.gov.au">www.humanservices.gov.au</a></p> <p>Applications for authority to prescribe should be forwarded to:</p> <p>Department of Human Services<br/>         Prior Written Approval of Complex Drugs<br/>         Reply Paid 9826<br/>         GPO Box 9826<br/>         HOBART TAS 7001</p> <p>Patients are eligible for PBS-subsidised treatment with only one of imatinib, dasatinib, nilotinib or ponatinib at any one time and must not be receiving concomitant interferon alfa therapy.</p> <p>1. Continuing treatment<br/> <b>First continuing applications are to be written, at which time patients in whom a major cytogenetic response or peripheral blood BCR-ABL level of less than 1% has been demonstrated may receive authorisation for a further 12 months of treatment.</b><br/> <b>Subsequent authority applications for continuing therapy may be made by telephoning the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</b></p> <p>2. Authority approval requirements.<br/>         Response criteria to <del>initial</del> treatment with ponatinib:<br/>         For the purposes of assessing response to PBS-subsidised treatment with ponatinib, either cytogenetic analysis indicating the number of Philadelphia positive [t (9;22)] cells in the bone marrow measured by standard karyotyping, or quantitative PCR indicating the relative level of BCR-ABL transcript in the peripheral blood using the international scale, must be submitted. For bone marrow analyses, where the standard karyotyping is not informative for technical reasons, a cytogenetic analysis performed on the bone marrow by the use of fluorescence in situ hybridisation (FISH) with BCR-ABL specific probe must be submitted. The cytogenetic or peripheral blood quantitative PCR analyses must be submitted within 18 months of the commencement of treatment with <del>dasatinib, nilotinib or</del> ponatinib (patients in whom a major cytogenetic response or peripheral blood BCR-ABL level of less than 1% is demonstrable by 18 months are eligible to receive <b>first</b> continuing treatment with <del>that agent this drug</del>).<br/> <b>Thereafter, at no greater than 12 month intervals a major cytogenetic response or a peripheral blood BCR-ABL level of less than 1% must be sustained to receive subsequent continuing treatments with this drug.</b></p> |

Public Summary Document – November 2018 PBAC Meeting

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|  | <p>3. Definitions of response.<br/>A major cytogenetic response is defined as less than 35% Philadelphia positive bone marrow cells.<br/>A peripheral blood BCR-ABL level of less than 1% on the international scale (Blood 108: 28-37, 2006) also indicates a response, at least the biological equivalent of a major cytogenetic response.</p> <p>4. Definitions of loss of response.<br/>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 therapy.<br/>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 therapy.</p> |
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7.3 Add new restriction:

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| <b>Category / program</b>          | General Schedule  |
| <b>Prescriber type</b>             | <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse Practitioners<br><input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives   |
| <b>Episodicity:</b>                | Chronic   |
| <b>Condition:</b>                  | Myeloid leukaemia   |
| <b>PBS Indication:</b>             | Chronic myeloid leukaemia (CML)   |
| <b>Treatment phase:</b>            | Subsequent continuing treatment   |
| <b>Restriction Level / Method:</b> | <input type="checkbox"/> Restricted benefit<br><input type="checkbox"/> Authority Required - In Writing<br><input checked="" type="checkbox"/> Authority Required - Telephone<br><input type="checkbox"/> Authority Required - Emergency<br><input type="checkbox"/> Authority Required - Electronic<br><input type="checkbox"/> Streamlined  |
| <b>Clinical criteria:</b>          | Patient must have received the First continuing PBS subsidised treatment with this drug for this condition,<br>AND<br>The treatment must be the sole PBS-subsidised therapy for this condition,<br>AND<br>Patient must have maintained a major cytogenetic response; OR<br>Patient must have maintained a peripheral blood level of BCR-ABL of less than 1%.  |
| <b>Administrative Advice</b>       | Subsequent authority applications for continuing therapy may be made by telephoning the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).<br><br>Patients are eligible for PBS-subsidised treatment with only one of imatinib, dasatinib, nilotinib or ponatinib at any one time and must not be receiving concomitant interferon alfa therapy.<br><br>1. Continuing treatment<br>First continuing applications are to be written, at which time patients in whom a major cytogenetic response or peripheral blood BCR-ABL level of less than 1% has been demonstrated may receive authorisation for a further 12 months of treatment. |

*Public Summary Document – November 2018 PBAC Meeting*

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|  | <p>Subsequent authority applications for continuing therapy may be made by telephoning the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</p> <p>2. Authority approval requirements.<br/>Response criteria to treatment with ponatinib:<br/>For the purposes of assessing response to PBS-subsidised treatment with ponatinib, either cytogenetic analysis indicating the number of Philadelphia positive [t (9;22)] cells in the bone marrow measured by standard karyotyping, or quantitative PCR indicating the relative level of BCR-ABL transcript in the peripheral blood using the international scale, must be submitted. For bone marrow analyses, where the standard karyotyping is not informative for technical reasons, a cytogenetic analysis performed on the bone marrow by the use of fluorescence in situ hybridisation (FISH) with BCR-ABL specific probe must be submitted. The cytogenetic or peripheral blood quantitative PCR analyses must be submitted within 18 months of the commencement of treatment with ponatinib (patients in whom a major cytogenetic response or peripheral blood BCR-ABL level of less than 1% is demonstrable by 18 months are eligible to receive first continuing treatment with this drug).<br/>Thereafter, at no greater than 12 month intervals a major cytogenetic response or a peripheral blood BCR-ABL level of less than 1% must be sustained to receive subsequent continuing treatments with this drug.</p> <p>3. Definitions of response.<br/>A major cytogenetic response is defined as less than 35% Philadelphia positive bone marrow cells.<br/>A peripheral blood BCR-ABL level of less than 1% on the international scale (Blood 108: 28-37, 2006) also indicates a response, at least the biological equivalent of a major cytogenetic response.</p> <p>4. Definitions of loss of response.<br/>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 therapy.<br/>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 therapy.</p> |
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## **8 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

## **9 Sponsor's Comment**

The sponsor had no comment.