

## 4.1 PONATINIB tablet, 15 mg and 45 mg, Iclusig<sup>®</sup>, Specialised Therapeutics.

### 1 Purpose of Application

#### 1.1 Authority Required listing for ponatinib for treatment of adult patients:

- with chronic myeloid leukaemia (CML) who has failed an adequate trial of dasatinib and nilotinib, or where one of nilotinib or dasatinib has failed and who are intolerant of the other drug;
- with CML and T315I mutation in BCR-ABL who have failed first-line therapy with imatinib or dasatinib or nilotinib;
- with relapsed or refractory BCR-ABL positive acute lymphoblastic leukaemia (Ph+ ALL), with or without the T315I mutation.

1.2 Ponatinib was deferred at the November 2014 PBAC meeting. The PBAC requested better alignment of the restrictions to the populations of patients most likely to benefit, adjustments of the economic analyses and financial estimates in line with the considerations of the PBAC, and a significant price reduction of ponatinib to account for the significant cost associated with care of patients with vascular occlusive events induced by ponatinib.

### 2 Requested listing

2.1 An abridged version of the requested listing is presented below.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
PONATINIB 15 mg tablet, 60 45 mg tablet, 30	1 1	5 5	\$ [REDACTED] \$ [REDACTED]	Iclusig	Specialised Therapeutics

#### Authority required (abridged)

##### Chronic myeloid leukaemia:

Initial treatment, as the sole PBS-subsidised therapy, of a patient with chronic myeloid leukaemia in any disease phase who has failed an adequate trial of dasatinib and nilotinib as second-line treatment, or where one of nilotinib or dasatinib has failed and who are intolerant of the other drug.

Continuing treatment, as the sole PBS-subsidised therapy, of a patient who has received initial PBS-subsidised treatment with ponatinib for chronic myeloid leukaemia, and who has demonstrated either a major cytogenetic response, or less than 1% BCR-ABL level in the blood, to ponatinib in the preceding 18 months and thereafter at 12 monthly intervals.

##### Chronic myeloid leukaemia with T315I mutation:

Initial treatment, as the sole PBS-subsidised therapy, of a patient with chronic myeloid leukaemia expressing the T315I mutation, in any disease phase who has failed an adequate trial of imatinib or dasatinib or nilotinib.

Continuing treatment, as the sole PBS-subsidised therapy, of a patient who has received initial PBS-subsidised treatment with ponatinib for chronic myeloid leukaemia, and who has demonstrated either a major cytogenetic response, or less than 1% BCR-ABL level in the blood, to ponatinib in the preceding

18 months and thereafter at 12 monthly intervals.

**Philadelphia chromosome positive acute lymphoblastic leukaemia:**

Initial treatment, as monotherapy, of a patient with acute lymphoblastic leukaemia (ALL) bearing the Philadelphia chromosome or expressing the transcript, BCR-ABL, who has failed treatment with chemotherapy AND imatinib AND dasatinib and where appropriate, allogeneic haemopoietic stem cell transplantation.

OR

Initial treatment, as monotherapy, of a patient with acute lymphoblastic leukaemia (ALL) bearing the Philadelphia chromosome or expressing the transcript, BCR-ABL, and expressing the T315I mutation, who has failed treatment with chemotherapy AND imatinib OR dasatinib and where appropriate, allogeneic haemopoietic stem cell transplantation.

Continuing treatment, as monotherapy, of a patient with acute lymphoblastic leukaemia bearing the Philadelphia chromosome or expressing the transcript, BCR-ABL, where the patient has previously been issued with an authority prescription for ponatinib and does not have progressive disease.

- 2.2 The re-submission provided a cost-minimisation analysis based on clinical evidence presented in Section B(ii), and from which the re-submission concluded that ponatinib was non-inferior in terms of efficacy and inferior in terms of safety to dasatinib and nilotinib when used second line for CML. This was consistent with the PBAC's November 2014 consideration. The cost-minimisation included drug therapy costs and costs associated with the treatment of vascular occlusive events and pleural effusions.
- 2.3 In comparison with the previous submission, the following changes were made to the proposed restriction:
- CML: The proposed restriction was changed to be consistent with the PBAC recommendation to provide treatment for patients where both nilotinib and dasatinib have failed or where one of nilotinib or dasatinib has failed and who are intolerant of the other drug.
  - CML with T315I mutation: There was no change compared with the previous submission. This was consistent with the PBAC recommendation.
  - Ph+ ALL: The PBAC recommended the restriction for patients with relapsed or refractory BCR-ABL positive Ph+ ALL and who have the T315I mutation, as there was limited data available for Ph+ ALL patients without the T315I mutation. The re-submission acknowledged the paucity of data; however, it requested the PBAC to reconsider expanding the listing in Ph+ ALL patients to include patients who are refractory or intolerant of imatinib and dasatinib, but do not have the T315I mutation. The re-submission argued that ponatinib is the only TKI to uniquely inhibit less common mutations such as F317L and E225V. The re-submission provided no further information on patients with these mutations.
- 2.4 The PBAC noted that the CML restriction for dasatinib and nilotinib states 'Nilotinib is not approved for patients in blast crisis'. The PBAC considered that criteria in the ponatinib restriction for CML patients (without the T315I mutation) should include an option 'Patient must not be eligible for PBS-subsidised treatment with nilotinib because the patient has a blast crisis' in addition to 'Patient must have failed an adequate trial of nilotinib; OR Patient must have developed intolerance to nilotinib of a severity necessitating permanent treatment withdrawal'.

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

### 3 Background

- 3.1 TGA status: Ponatinib was TGA registered on 26 November 2014 for the treatment of adult patients with 1) chronic phase, accelerated phase, or blast phase chronic myeloid leukaemia whose disease is resistant to, or who are intolerant of at least two prior TKIs, or where there is a T315I mutation; 2) Ph+ ALL whose disease is resistant to, or who are intolerant of dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate, or where there is a T315I mutation.
- 3.2 The PBAC deferred ponatinib in November 2014.

**Table 1: Summary of the previous submission and current re-submission**

	Ponatinib – November 2014	Current re-submission
Requested PBS listing	<p><b>Authority required</b>  <b>Restriction 1 – CML</b>  <i>Initial treatment:</i>                      The treatment must have failed second-line therapy of dasatinib OR nilotinib.  <i>Continuing treatment:</i>                      Patient must have demonstrated either a major cytogenetic response, or less than 1% BCR-ABL level in the blood, to ponatinib.</p> <p><b>Restriction 2 – CML with T315I mutation</b>                      Patients with the T315I mutation.</p> <p><b>Restriction 3 – ALL (Ph+)</b>  <i>Initial treatment:</i>                      Patients must have failed treatment with chemotherapy                      AND patient must have failed treatment with imatinib                      AND patient must have failed treatment with dasatinib                      AND patient must have failed allogeneic haemopoietic SCT (where appropriate).  <i>Continuing treatment:</i>                      Patient must not have progressive disease.</p> <p><b>PBAC Comment:</b> PBAC recommended the following restrictions: (i) patients with CML 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 who are intolerant of the other drug;                      (iii) patients with relapsed or refractory BCR-ABL positive ALL and whose ALL has the T315I mutation.</p>	<p><b>Authority required</b>  <b>Restriction 1 – CML</b>                      Failed both nilotinib <u>and</u> dasatinib OR failed one and intolerant of the other drug.</p> <p><b>Restriction 2 – CML with T315I mutation</b>                      No change</p> <p><b>Restriction 3 – ALL (Ph+)</b>                      Initial treatment: Patients have failed treatment with chemotherapy and imatinib <u>or</u> dasatinib and where appropriate allogeneic haemopoietic SCT. The re-submission noted the paucity of data in patients without the T315I mutation, but requested listing for patients with Ph+ ALL <u>with or without</u> T315I mutation.</p>
Requested price	DPMQ 15 mg tablet, 60 = \$ [REDACTED] DPMQ 45 mg tablet, 30 = \$ [REDACTED]	15 mg tablet, 60 = \$ [REDACTED] \$ [REDACTED] 45 mg tablet, 30 = \$ [REDACTED] \$ [REDACTED] Due to errors in the cost of treating vascular occlusive events.

Public Summary Document – July 2015 PBAC Meeting

	Ponatinib – November 2014	Current re-submission
Main comparator	<p>Dasatinib and nilotinib for all indications.</p> <p><b>PBAC Comment:</b>  <u>For treatment of CML or Ph+ ALL without the T315I mutation:</u>                      Dasatinib and nilotinib reasonable comparators in 3<sup>rd</sup> line;                      Best supportive and SCT most appropriate comparator in 4<sup>th</sup> line  <u>For treatment of CML or Ph+ ALL with T315I mutation:</u>                      BSC or allogeneic SCT are the more appropriate comparators.</p> <p>The PBAC noted that the comparators for ponatinib are complex. Depending on different clinical scenarios they can be dasatinib or nilotinib or other non-TKI therapies, i.e. hydroxyurea, interferon, allogeneic transplantation and salvage chemotherapy. However, 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.</p>	<p>Dasatinib and nilotinib for all indications. No changes from previous submission.</p>
Clinical evidence	<p>Nine single-arm studies. The submission excluded Muller 2009 but this was included during evaluation.</p> <p><b>PBAC Comment:</b> It was not appropriate to exclude Muller 2009 as the study reports results for patients with the T315I mutation.                      No common arm to enable an indirect comparison; high level of heterogeneity between the individual studies.</p>	<p>Updated literature search. 12 single-arm studies, consisting of the nine studies presented in the previous submission, Muller 2009, one new study for ponatinib (Milojkovic 2014), one new study for dasatinib/nilotinib (Lee 2014).</p>
Key effectiveness data	<p><b>PBAC Comment:</b> see below <b>Paragraph 7.5 in November 2014 PBAC Public Summary Document (PSD)</b> .</p>	<p>Results were only updated for chronic phase CML and T315I mutation.</p>
Key safety data	<p>Very limited comparative safety data provided.                      Additional safety information for ponatinib provided on vascular occlusive events.</p> <p><b>PBAC Comment:</b> see below <b>Paragraph 7.5 in November 2014 PBAC PSD</b>.</p>	<p>Submission provided additional safety data on vascular occlusive events and pleural effusions for ponatinib, dasatinib and nilotinib.</p>
Clinical claim	<p>Ponatinib non-inferior in terms of comparative effectiveness to dasatinib and nilotinib.                      No specific claim in terms of comparative safety.</p> <p><b>PBAC Comment: [Paragraph 7.5 in November 2014 PBAC PSD]</b>                      The PBAC considered ponatinib was (1) similar in efficacy in inducing responses in patients with T315I mutant chronic phase CML as other TKIs have been in achieving responses in de novo chronic phase CML; (2) similar in efficacy to dasatinib or nilotinib with respect response rates in 2nd and 3rd line therapy for patients with non-T315I CML; (3) similar in efficacy to dasatinib with respect response rates in dasatinib-naïve patients with blast crisis CML; (4) active at inducing transient responses in Ph+ ALL with the T315I mutation and (5) probably active in non-T315I Ph+ ALL but the paucity of data for non-T315I ALL was insufficient to enable any confidence in the extent of its effectiveness to be drawn.                      The PBAC considered that ponatinib had an inferior toxicity profile to imatinib, dasatinib, and nilotinib, especially with regard to serious vascular occlusive events. Consequently, the PBAC considered that clinical benefit was only likely to exceed clinical harm in patients where use of all other TKIs had or would fail to induce response, or was not appropriate because of significant toxicities or contraindications.</p>	<p>Ponatinib non-inferior in terms of comparative effectiveness and inferior in terms of comparative safety to dasatinib and nilotinib.</p>

Public Summary Document – July 2015 PBAC Meeting

	Ponatinib – November 2014	Current re-submission
Economic evaluation	<p>Cost-minimisation using drug costs only and the following equi-effective dose: ponatinib 30.2 mg daily = dasatinib 111.0 mg daily = nilotinib 792.1 mg daily.</p> <p><b>PBAC Comment:</b> The PBAC considered the equi-effective dose are ponatinib 30.2 mg daily = dasatinib 102 mg daily = nilotinib 797 mg daily. The cost-minimisation analysis may not be accurate as the DPMQ values for ponatinib are higher than the weighted dispensed cost per month. The proposed DPMQ for ponatinib 45 mg per day was almost \$800 per month more than the 30 mg daily dose, yet the higher dose was associated with more adverse events and, according to the submission, no additional efficacy.</p> <p>The PBAC considered the DPMQ should align with the weighted dispensed costs per month. The PBAC also considered that costs of excessive vascular occlusive events seen with ponatinib must be accounted for in determining a benchmarked price that ensured ponatinib use was no more expensive than use of dasatinib or nilotinib in patients who had failed treatment with imatinib.</p>	<p>Cost-minimisation with equi-effective dose: ponatinib 30.2 mg daily = dasatinib 102 mg daily = nilotinib 797 mg daily.</p> <p>While the PBAC only expressed concern regarding vascular occlusive events for ponatinib, the re-submission argued that patients treated with dasatinib had an increased risk of pleural effusions. Therefore, the cost-minimisation analysis included for all three medications the cost of pleural effusions and the cost of vascular occlusive events. This was reasonable.</p>
Number of patients	<ul style="list-style-type: none"> <li>• Less than 10,000 in Year 1 increasing to also less than 10,000 in Year 5.</li> </ul> <p><b>PBAC Comment:</b> The submission underestimated the number of patients treated with TKIs as compared to the February 2014 DUSC review of TKI use.</p>	<p>Similar methodology to previous submission with a number of calculation errors. less than 10,000 in Year 1 increasing to also less than 10,000 in Year 5.</p>
Estimated cost to PBS	<ul style="list-style-type: none"> <li>• Less than \$10 million in Year 1 increasing to less than \$10 million in Year 5 for a total of \$10-20 million over the first 5 years of listing.</li> </ul> <p><b>PBAC Comment:</b> The PBAC considered the financial estimates are inaccurate and required significant revision to reflect:</p> <ol style="list-style-type: none"> <li>1. DUSC's estimates of TKI use by line of therapy and correct calculation of number of patients moving from 1<sup>st</sup> to 2<sup>nd</sup> and subsequent lines per annum;</li> <li>2. Only 15% of patients failing first line TKI therapy will have T315I mutation;</li> <li>3. Although uptake in T315I mutation CML will be &gt;90%, it will not be 100% given the risks in patients with pre-existing cardiovascular disease and the availability of allogeneic SCT;</li> <li>4. Use of ponatinib only after failure of both nilotinib and dasatinib for patients with non-T315I CML, and use only in T315I mutant Ph+ ALL;</li> <li>5. Minimal substitution for nilotinib or dasatinib.</li> </ol>	<p>Similar methodology to previous submission with a number of calculation errors. The re-submission addressed most of the changes recommended by the PBAC but did not use the DUSC's estimates of TKI use.</p> <p>Less than \$10 million in Year 1 increasing to less than \$10 million in Year 5 for a total of \$10-20 million over the first 5 years of listing. Compared with the previous submission, the number of patients treated was lower and the number of packs higher in the re-submission (see Estimated PBS usage).</p>
PBAC decision	Deferred.	-

Source: Compiled during the evaluation

BSC = best supportive care; CML = chronic myeloid leukaemia; DPMQ = dispensed price for maximum quantity; DUSC = Drug utilisation sub committee; PBAC = Pharmaceutical Benefits Advisory Committee; Ph+ ALL = Philadelphia chromosome positive acute lymphoblastic leukaemia; SCT = stem cell transplant; TKI = tyrosine kinase inhibitor.

#### **4 Clinical place for the proposed therapy**

- 4.1 Compared with the previous submission, the re-submission presented separate clinical algorithms for CML and Ph+ ALL. The re-submission proposed the following clinical place for ponatinib:
- Chronic myeloid leukaemia:
    - Second-line therapy in patients with T315I mutation;
    - Third-line therapy in patients intolerant of TKI not used in second-line or with T315I mutation;
    - Fourth-line therapy, after failure of imatinib, dasatinib and nilotinib.
  - Acute lymphoblastic leukaemia:
    - Second-line therapy in patients with T315I mutation;
    - Third-line therapy in patients intolerant of dasatinib.

This was consistent with the proposed restriction.

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

#### **5 Comparator**

- 5.1 The re-submission nominated dasatinib and nilotinib for all requested indications. These were unchanged from the previous submission, and the PBAC considered these acceptable for benchmarking.

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

#### **6 Consideration of the evidence**

##### ***Sponsor hearing***

- 6.1 The sponsor requested a hearing for this item. The clinician highlighted the unmet clinical need for treatment in patients with CML who were intolerant or resistant to current PBS-subsidised treatments, and addressed other matters in response to the Committee's questions.

##### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from individuals (2), health care professionals (8) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described the clinical need for ponatinib in patients who do not respond to currently available PBS-listed treatments.
- 6.3 The PBAC noted the advice received from the Haematology Society of Australia and New Zealand (HSANZ) which highlighted the clinical need for ponatinib for patients with CML with the T315I mutation. The PBAC specifically noted the advice that the average doses of ponatinib used in practice would likely be lower than those seen in the PACE study.

**Clinical trials**

- 6.4 The re-submission was based on 12 single-arm non-randomised studies. These included nine studies presented in the previous submission, one study for dasatinib excluded in the previous submission but presented in the previous commentary (Muller 2009), one new study for ponatinib (Milojkovic 2014) and one new study for dasatinib/nilotinib (Lee 2014).
- 6.5 Details of the studies presented in the re-submission are provided in Table 2.

**Table 2: Non-randomised studies and associated reports presented in the re-submission**

Study ID/first author	Protocol title/ publication title	Publication citation
<b>Ponatinib open-label, non-randomised studies</b>		
PACE	Phase II open-label, nonrandomised, single-arm study in patients with Ph+ leukaemia (CP-CML, AP-CML, BP-CML and Ph+ ALL) resistant or intolerant to prior dasatinib or nilotinib or have the T315I mutation.  Cortes JE, Kim DW, Pinilla-Ibarz J, <i>et al.</i> A phase II trial of ponatinib in Philadelphia chromosome-positive leukemias.	13 July 2012  <i>N Eng J Med</i> 2013; 369(19): 1783-1796.
Study 101	Phase I open-label, nonrandomised, single-arm dose escalation study, in patients with refractory hematologic malignancies: Ph+ leukaemia (CP-CML, AP-CML, BP-CML and Ph+ ALL), AML, and other hematologic malignancies.  Cortes JE, Kantarjian H, Shah NP, <i>et al.</i> Ponatinib in refractory Philadelphia chromosome-positive leukemias.  Talpaz M, Cortes JE, Deininger MW, <i>et al.</i> Phase I trial of AP24534 in patients with refractory chronic myeloid leukemia and hematologic malignancies.	14 June 2012  <i>N Eng J Med</i> 2012; 367(22): 2075-2088.  <i>Journal of Clinical Oncology</i> 2010;28(15).
Milojkovic 2014	Milojkovic D, de Lavallade H, Mehta P, <i>et al.</i> A national experience of the use of ponatinib in patients failing multiple tyrosine kinase inhibitors confirms efficacy in a heavily pre-treated cohort of patients with Ph+ leukaemias.	<i>Haematologica</i> 2014; 99:333.
<b>Dasatinib studies</b>		
Muller 2009	Muller MC, Cortes JE, Kim DW, <i>et al.</i> Dasatinib treatment of chronic-phase chronic myeloid leukemia: analysis of responses according to preexisting BCR-ABL mutations.	<i>Blood</i> 2009; 114(24): 4944-4953.
Quintas-Cardama 2007	Quintas-Cardama A, Kantarjian H, Jones D, <i>et al.</i> Dasatinib is active in Philadelphia chromosome-positive chronic myelogenous leukemia after imatinib and nilotinib therapy failure.	<i>Blood</i> 2007; 109(2): 497-499.
<b>Nilotinib studies</b>		
Giles 2010	Giles FJ, Abruzzese E, Rosti G, <i>et al.</i> Nilotinib is active in chronic and accelerated phase chronic myeloid leukemia following failure of imatinib and dasatinib therapy.	<i>Leukemia</i> 2010; 24(7): 1299-1301.
Nicolini 2009	Nicolini FE, Alimena G, Al-Ali HK, <i>et al.</i> Expanding nilotinib access in clinical trials (ENACT) study in adult patients with imatinib-resistant or -intolerant chronic myeloid leukemia: subgroup analysis of patients who failed prior dasatinib therapy.	<i>Haematologica</i> 2009; 94: 257.

Public Summary Document – July 2015 PBAC Meeting

Study ID/first author	Protocol title/ publication title	Publication citation
<b>Dasatinib or nilotinib studies</b>		
Garcia-Gutierrez 2012	Garcia-Gutierrez JV, Maestro B, Casado LF, <i>et al.</i> Outcomes of chronic myeloid leukemia patients who stopped second generation tyrosine kinase inhibitors as second-line treatment. Results of the CML Spanish National Registry.	ASH Annual Meeting Abstracts 2012; 120(21): 3764.
Garg 2009	Garg RJ, Kantarjian H, O'Brien S, <i>et al.</i> The use of nilotinib or dasatinib after failure to two prior tyrosine kinase inhibitors: long-term follow up.	<i>Blood</i> 2009; 114(20): 4361-4368.
Ibrahim 2010	Ibrahim AR, Paliompeis C, Bua M, <i>et al.</i> Efficacy of tyrosine kinase inhibitors (TKI) as third-line therapy in patients with chronic myeloid leukemia in chronic phase who have failed 2 prior lines of TKI therapy.	<i>Blood</i> 2010; 116(25): 5497-5500.
Lee 2014	Lee SE, Lee MY, Choi SY, <i>et al.</i> Outcomes of third-line BCR-ABL1 tyrosine kinase inhibitors in the treatment failed chronic phase chronic myeloid Leukemia patients who have received two prior TKIs.	<i>Haematologica</i> 2014; 99:333.
Rossi 2013	Rossi AR, Breccia M, Abruzzese E, <i>et al.</i> Outcome of 82 chronic myeloid leukemia patients treated with nilotinib or dasatinib after failure of two prior tyrosine kinase inhibitors.	<i>Haematologica</i> 2013; 98(3): 399-403.

Source: Table 7, pp55-58 of the re-submission

ALL = acute lymphoblastic leukaemia; AML = acute myeloid leukaemia; AP = accelerated phase; BP = blast phase; CML = chronic myeloid leukaemia; CP = chronic phase; Ph+ = Philadelphia chromosome positive; TKI = tyrosine kinase inhibitor.

Lee (2014) was inappropriately included by the re-submission. The study included patients treated with dasatinib, nilotinib, radotinib, and bosutinib. While major cytogenetic response was reported, the results were not presented by treatment received. This study was not included during evaluation.

6.6 The key features of the non-randomised studies are summarised in Table 3.

Table 3: Key features of the included evidence

Study	N	Design/ duration	Risk of bias	Patient population	Outcomes
<b>Ponatinib</b>					
PACE	449	Phase II, MC, OL, SA 9.9 months	High	CP (n=270), AP (n=85) and BC CML and Ph+ ALL (n=94): - resistant or intolerant of dasatinib or nilotinib; or - who have the T315I mutation.	CP CML: MCyR (CCyR, PCyR) AP and BC CML and Ph+ ALL: MHR (CHR or NEL)
Study 101	81	Phase I, MC, OL, SA; 19.5 months	High	Refractory haematologic malignancies (CP (n=43), AP (n=9) and BC CML (n=8), Ph + ALL (n=5) and AML (n=12) and other malignancies (n=4).	To determine the recommended dose; safety and efficacy.
Milojkovic 2014	51	Observational, SA, 9 months	High	CP CML (n=51) With T315I mutation (6/51)	CCyR, MMR
<b>Dasatinib</b>					
Quintas-Cardama 2007	23	Observational, SC, SA; 7.8 months	High	CP (n=4), AP and BC CML (n=19): - resistant or intolerant to imatinib and nilotinib.	CHR, CCyR, PCyR,
Muller 2009	21	Subgroup analyses of 3 studies; Duration not reported	High	CP CML: - resistant or intolerant to imatinib; or - who have the T315I mutation.	CHR, MCyR, CCyR
<b>Nilotinib</b>					
Giles 2010	60	Phase II, MC, SA, non-comparative; 12 months	High	CP (n=39) and AP CML (n=21): - resistant or intolerant to imatinib and dasatinib.	CP CML: MCyR (CCyR, PCyR) AP CML: MHR (CHR or NEL)
Nicolini 2009	292	Post-hoc sub-group analysis of OL, SA, NR study; Duration not reported	High	CP (n=218), AP (n=34) and BC (n=40) CML: - resistant or intolerant to imatinib and dasatinib.	CHR, MCyR, CCyR
<b>Dasatinib or nilotinib</b>					
Garcia-Gutierrez 2012	31	Analysis of national registry data; 9 months	High	CP CML: - resistant or intolerant to imatinib and a 2 <sup>nd</sup> generation TKI.	CCyR, CHR
Garg 2009	48	Observational, SC, SA; 13 months	High	Dasatinib (n= 34) and nilotinib (n=14) CP, AP and BC CML: - switched to 2 <sup>nd</sup> or 3 <sup>rd</sup> line TKI following treatment failure.	CHR, MCyR (CCyR, PCyR), MMR
Ibrahim 2010	26	Observational, SC, SA; 21.5 months	High	CP CML: - treated with dasatinib or nilotinib after failing imatinib.	MCyR, CCyR, MMR
Rossi 2013	82	Prospective, observational, SA; 14 months	High	CP, AP or BC CML: - Sequentially treated with 3 TKIs.	CCyR, PCyR, mCyR, CHR, MMR

Source: compiled during the evaluation.

ALL = acute lymphoblastic leukaemia; AML = acute myeloid leukaemia; AP = accelerated phase; BC = blast crisis; CCyR = complete cytogenetic response; CHR = complete haematological response; CML = chronic myeloid leukaemia; CP = chronic phase; MC = multi-centre; MCyR = major cytogenetic response; mCyR = minor cytogenetic response; MHR = major haematological response; MMR = major molecular response; NEL = no evidence of leukaemia; NR = non-randomised; OL = open-label; PCyR = partial cytogenetic response; Ph+ = Philadelphia chromosome positive; SA = single-arm; SC = single centre; TKI = tyrosine kinase inhibitor.

### Comparative effectiveness

- 6.7 The new studies included in the re-submission included patients in chronic phase CML only. Therefore, efficacy results were only updated for chronic phase CML. The complete cytogenetic response for chronic phase CML and major cytogenetic response for accelerated phase and blast crisis CML or Ph+ ALL results are presented in Table 4.

**Table 4: Complete cytogenetic or major cytogenetic response results across the nonrandomised studies**

Study	Ponatinib; n/N (%)	Dasatinib; n/N (%)	Nilotinib; n/N (%)	Dasatinib or nilotinib; n/N (%)
<b>Chronic phase CML – CCyR</b>				
PACE <sup>a</sup>	118/267 (44%)			
Study 101	28/43 (65%)			
Milojkovic 2014 <sup>b</sup>	12/36 (33%)			
Quintas-Cardama 2007		0/4 (0%) <sup>c</sup>		
Giles 2010 <sup>d</sup>			9/37 (24%)	
Nicolini 2009			60/218 (28%) <sup>c</sup>	
Garcia-Gutierrez 2012				< 20% <sup>c</sup>
Garg 2009 <sup>e</sup>		5/16 (31%)	1/9 (11%)	
Ibrahim 2010				9/26 (35%)
Rossi 2013				27/82 (33%) <sup>c</sup>
<b>Accelerated phase CML – MCyR</b>				
PACE <sup>a</sup>	32/83 (39%)			
Study 101	2/9 (22%)			
Quintas-Cardama 2007		4/10 (40%) <sup>f</sup>		
Giles 2010 <sup>d</sup>			2/17 (12%)	
Nicolini 2009			2/34 (7%)	
Garg 2009 <sup>e</sup>		3/8 (38%)	1/2 (50%)	
<b>Blast crisis CML or Ph+ ALL – MCyR</b>				
PACE	29/94 (31%)			
Study 101	5/13 (38%)			
Quintas-Cardama 2007		1/9 (11%) <sup>d</sup>		
Nicolini 2009			6/40 (14%)	
Garg 2009 <sup>e</sup>		3/10 (30%)	1/3 (33%)	

Source: Table 19, p78; Table 33, p97; Table 45, p109; of the re-submission; Table B(ii).6.2, p5.9.COM37 of November 2014 commentary, and individual trial papers.

ALL = acute lymphoblastic leukaemia; AP = accelerated phase; BC = blast crisis; CP = chronic phase; CCyR = complete cytogenetic response; CML = chronic myeloid leukaemia; MCyR = major cytogenetic response; MMR = major molecular response; PCyR = partial cytogenetic response; Ph+ = Philadelphia chromosome positive; Italics = extracted during evaluation

<sup>a</sup> In the PACE study, 267/270 patients in CP-CML and 83/85 patients in AP-CML were evaluated for efficacy.

<sup>b</sup> In the Milojkovic study, 48 patients were evaluated but 6 patients commenced treatment in CCyR. Results are presented for 42 patients, including 6 patients with T315I mutation.

<sup>c</sup> When best response is reported: CCyR = MMR + CCyR

<sup>d</sup> In the Giles study, 37/39 patients in CP-CML and 17/21 patients in AP-CML were included in the efficacy analysis.

<sup>e</sup> In the Garg study, in the 34 patients who received dasatinib, 16/34 were in CP-CML, 8/34 were in AP-CML and 10/34 were in BC-CML or Ph+ALL. In the 14 patients who received nilotinib, 9/14 were in CP-CML, 2/14 were in AP-CML and 3/14 were in BC-CML or Ph+ALL

<sup>f</sup> When best response is reported: MCyR = MMR + CCyR + PCyR

- 6.8 The rates of complete cytogenetic response or major cytogenetic response did not suggest differences in ponatinib, dasatinib or nilotinib. There were significant differences in study design, CML disease phase, time of reporting, heterogeneity within and between the studies.

**Table 5: Response rates for patients with the T315I mutation in chronic phase CML**

	Ponatinib – 2 <sup>nd</sup> , 3 <sup>rd</sup> and 4 <sup>th</sup> line			Dasatinib – 2 <sup>nd</sup> line
	PACE	Study 101	Milojkovic 2014	Muller 2009
CCyR	42/64 (66%)	10/12 (83%)	3/6 (50%)	0/21 (0%)
MCyR	45/64 (70%)	11/12 (92%)	3/6 (50%)	2/21 (10%)
CHR	58/64 (91%)	12/12 (100%)	-	6/21 (29%)
MMR	32/64 (50%)	8/12 (67%)	-	-

Source: Table 30, p86 of the submission.

CCyR = complete cytogenetic response; CHR = complete haematological response; CML = acute myeloid leukaemia; MCyR = major cytogenetic response; MMR = major molecular response.

- 6.9 For chronic phase CML patients with the T315I mutation, the response rates were higher for ponatinib than for dasatinib. There was no data for dasatinib or nilotinib to allow a comparison in patients with accelerated phase CML or blast crisis CML/Ph+ ALL with the T315I mutation. Therefore, it is unknown whether ponatinib has similar efficacy in these situations.

### **Comparative harms**

- 6.10 The new studies identified in the re-submission from the systematic literature review did not provide safety outcomes. The previous submission provided very limited comparative safety data for ponatinib, dasatinib, and nilotinib. Based on FDA information and data from the PACE study, Study 101, and the EPIC trial, the PBAC considered that ponatinib had an inferior toxicity profile to imatinib, dasatinib, and nilotinib.
- 6.11 The re-submission provided additional data on potential safety concerns beyond those identified in the non-randomised studies. The re-submission estimated an average rate of pleural effusions and vascular occlusive events for ponatinib, dasatinib, and nilotinib based on studies reviewed in the literature. While the PBAC considered that ponatinib was associated with a higher frequency of vascular occlusive events than nilotinib and dasatinib; the re-submission argued that patients treated with dasatinib had an increased risk of pleural effusions and patients treated with nilotinib had a high risk of Grade 3 or 4 cardiovascular events. The submission only provided safety data for pleural effusions, which was reasonable in the context of the submission.

**Table 6: Rates of pleural effusions and vascular occlusive events used in Section D(i).**

Type of event		Ponatinib	Dasatinib	Nilotinib
<b>Vascular occlusive event</b>				
All grades	Re-sub	17.1%	2.9%	11.5%
	<i>Com</i>	22.5%	3.0%	4.9%
Grade 3 or 4	Re-sub	11.7%	2.0%	7.9%
	<i>Com</i>	16.0%	2.1%	3.5%
<b>Pleural effusions</b>				
All grades	Re-sub	8.1%	24.0%	1.7%
	<i>Com</i>	7.6%	23.8%	1.7%
Grade 3 or 4	Re-sub	1.7%	2.7%	0.4%
	<i>Com</i>	1.4%	0.6%	0.4%

Source: Compiled during evaluation.

Com = commentary; Re-sub = resubmission; *italics* = estimated during evaluation.

Note: In the list of studies reviewed by the re-submission, only studies with follow-up similar to the PACE study (27 months) were included during evaluation (follow-up from 24 to 36 months). Rates for pleural effusions and vascular occlusive events are presented in *italic*.

- 6.12 When identifying studies in the literature, the re-submission did not provide the search strategies, and selected studies with different follow-up lengths and potentially with different baseline cardiac risk. This was not appropriate. For the rates calculated during evaluation, only studies with similar follow-up periods were selected. Using this approach, ponatinib was associated with more vascular occlusive events (all grades and Grade 3 or 4) and pleural effusions (Grade 3 or 4) compared with dasatinib or nilotinib. Ponatinib was associated with fewer all grades pleural effusions than dasatinib. The PSCR disagreed with the exclusion of some of the trials and inclusion of Giles et al. (2013), Larson et al. (2012), and Castagnetti et al. (2014) in the evaluation's analyses of estimation of the incidence of vascular occlusive events, and argues that inclusion of these significantly underestimate the incidence of vascular occlusive events in nilotinib treated patients.

### **Benefits/harms**

- 6.13 A summary of the comparative benefits and harms for ponatinib versus dasatinib and nilotinib is presented in Table 7.

Table 7: Summary of comparative benefits and harms for ponatinib versus dasatinib and nilotinib

Study	Ponatinib	Dasatinib	Nilotinib	Event rate/100 patients		
				Ponatinib	Dasatinib	Nilotinib
<b>BENEFITS</b>						
<b>Chronic phase CML – McyR</b>						
PACE	144/267	-	-	54	-	-
Study 101	31/43	-	-	72	-	-
Milojkovic 2014	3/36	-	-	8	-	-
Quintas-Cardama 2007	-	1/4	-	-	25	-
Giles 2010	-	-	16/37	-	-	43
Nicolini	-	-	89/218	-	-	41
Garg 2009	-	6/16	2/9	-	38	22
Ibrahim 2010	-	-	13/26	-	-	50
Rossi 2013	-	-	39/82	-	-	48
<b>Chronic phase CML – MCyR for patients with the T315I mutation – second-line TKI</b>						
PACE	10/11	-	-	91	-	-
Milojkovic 2014	3/6	-	-	50	-	-
Muller 2009	-	2/21	-	-	10	-
<b>HARMS</b>						
<b>Vascular occlusion – 2-3 year follow-up, evaluation estimate</b>						
<i>All</i>				23	3	5
<i>Grade 3 or 4</i>				16	2	4
<b>Pleural effusion – 2-3 year follow-up, evaluation estimate</b>						
<i>All</i>				8	24	2
<i>Grade 3 or 4</i>				1	0	0

Source: Compiled during the evaluation

CML = chronic myeloid leukaemia; MCyR = major cytogenetic response; TKI = tyrosine kinase inhibitor; *italics* = performed during evaluation

- 6.14 From the available evidence, it was unclear whether ponatinib would be more or less effective than nilotinib and dasatinib in patients with CML or Ph+ ALL, in the absence of the T315I mutation. Ponatinib appears more effective in patients with the T315I mutation. The efficacy of ponatinib in second or third line in patients with T315I mutant CML appears similar to that of dasatinib and nilotinib as later line therapy of the non-T315I CML.
- 6.15 Based on single-arm non-comparative evidence, for every 100 patients treated with ponatinib in comparison with dasatinib over a duration of follow-up of approximately 2 to 3 years:
- approximately 14 additional patients would have a Grade 3 or 4 vascular occlusive event;
  - approximately 16 fewer patients would have pleural effusions (all grades);
  - approximately one additional patient would have a Grade 3 or 4 pleural effusion.
- 6.16 Based on single-arm non-comparative evidence, for every 100 patients treated with ponatinib in comparison with nilotinib over a duration of follow-up of approximately 2 to 3 years:
- approximately 12 additional patients would have a Grade 3 or 4 vascular occlusive event;
  - approximately 6 additional patients would have pleural effusions (all grades);

- approximately one additional patient would have a Grade 3 or 4 pleural effusion.

### **Clinical claim**

- 6.17 The re-submission described ponatinib as non-inferior in terms of comparative effectiveness and inferior in terms of comparative safety over dasatinib and nilotinib. In the previous submission, the re-submission made the same claim in terms of comparative effectiveness and no claim in terms of comparative safety. The clinical claim in the re-submission was consistent with the PBAC recommendation.
- 6.18 The evaluation noted that the indirect evidence to support the comparative effectiveness and safety of ponatinib compared with dasatinib and nilotinib remained uncertain because:
- the evidence for ponatinib was based on three single-arm studies (PACE study, Study 101, and Milojkovic 2014); while the evidence for dasatinib and nilotinib was based on nine studies, most of which were observational and single centre studies;
  - there was no common comparator between the ponatinib, dasatinib and nilotinib studies making it difficult to compare effectiveness; and
  - the populations in the reported studies were highly heterogeneous.

### **Economic analysis**

- 6.19 The re-submission presented a cost-minimisation analysis for ponatinib. This was similar to the previous submission. The re-submission updated the equi-effective dose compared with the previous submission to reflect the PBAC recommendation.
- 6.20 The equi-effective doses were estimated as:
- Ponatinib 30.2 mg daily = Dasatinib 102 mg daily = Nilotinib 797 mg daily
- These were consistent with the previous PBAC consideration.
- 6.21 The re-submission included drug costs and the cost of treating Grade 1/2 and Grade 3/4 pleural effusions and vascular occlusive events as presented in Table 8. The re-submission acknowledged the higher risk of serious vascular occlusive events associated with ponatinib. However, the re-submission argued that patients treated with dasatinib had an increased risk of pleural effusions; this was consistent with the product information for dasatinib and was mentioned in the public summary document for dasatinib (July 2011). Therefore, the re-submission included the cost of treating pleural effusions and vascular occlusive events for dasatinib, nilotinib and ponatinib. The proportion of the cost of treatment assigned for dasatinib, nilotinib, and ponatinib was not reasonable.
- 6.22 In deriving treatment costs for vascular occlusive events, the re-submission assumed that patients with a Grade 1 or 2 vascular occlusive event would require hospitalisation and patients with a Grade 3 or 4 vascular occlusive event would require surgery. The re-submission assumed that 68.4% of patients who had a vascular occlusive event following any treatment, would require surgery (i.e. be a Grade 3 or 4 event). The proportion of patients requiring surgery was not justified, but

higher than the estimates from the survey of Australian haematologists who estimated that 32.5% (mean, [min 15.0%, max 100%]) of patients with a VOE would require surgery. The re-submission estimated the cost of treatment for vascular occlusive events based on the weighted average cost of treatment of four AR-DRG codes. Each cost was weighted by the number of separations. To estimate the cost of treating Grade 1 or 2 vascular occlusive event, the re-submission incorrectly subtracted the cost of operating theatre from the number of separations rather than the average cost per DRG. The re-submission also incorrectly applied the cost of surgery to the proportion of patients with vascular occlusive event not requiring surgery. These were corrected during evaluation and are presented in table below. In deriving treatment costs for pleural effusions, the re-submission assumed that patients with a Grade 1 or 2 pleural effusion would be treated with prednisolone 25 mg and frusemide 20 mg while patients with a Grade 3 or 4 pleural effusion would require drainage. The cost of drainage was based on the AR-DRG code E73C (pleural effusion without complication). These assumptions were poorly justified, but could be reasonable.

**Table 8: Summary of the cost per adverse event for nilotinib, dasatinib and ponatinib per 100 patients**

Type of event	Cost/event	Dasatinib		Nilotinib		Ponatinib	
		Rate <sup>a</sup>	Cost	Rate <sup>a</sup>	Cost	Rate <sup>a</sup>	Cost
<b>Calculations in submission</b>							
Vascular occlusive event							
Grade 1 or 2	\$3,572.98	0.9%	\$33.23	3.6%	\$130.21	5.4%	\$193.56
Grade 3 or 4	\$3,855.05	2.0%	\$77.53	7.9%	\$303.75	11.7%	\$451.54
Pleural effusion							
Grade 1 or 2	\$18.97	21.4%	\$4.05	1.3%	\$0.25	6.4%	\$1.22
Grade 3 or 4	\$3,838.00	2.7%	\$102.13	0.4%	\$15.15	1.7%	\$65.17
<b>Cost for adverse event/year</b>			<b>\$216.94</b>		<b>\$449.36</b>		<b>\$711.49</b>
<b>Calculations during evaluation with updated event rates</b>							
Vascular occlusive event							
Grade 1 or 2	\$3,572.98	0.9%	\$32.16	1.4%	\$50.02	6.5%	\$232.24
Grade 3 or 4	\$3,855.05	2.1%	\$80.96	3.5%	\$134.93	16.0%	\$616.81
Pleural effusion							
Grade 1 or 2	\$18.97	23.2%	\$4.40	1.3%	\$0.25	6.3%	\$1.20
Grade 3 or 4	\$3,838.00	0.6%	\$23.03	0.4%	\$15.35	1.4%	\$53.73
<b>Cost for adverse event/year</b>			<b>\$140.54</b>		<b>\$200.55</b>		<b>\$903.98</b>

Source: Ponatinib\_PBAC\_March2015\_SectionD.xlsx

<sup>a</sup> This represents the rate of patients who would require the specific treatment. These were presented in Table 6 above.

- 6.23 The cost minimisation analysis is presented in Table 9. The re-submission assumed a weighted use of 53.4% and 46.6% for dasatinib and nilotinib respectively. Weighting is based on Medicare services for 2<sup>nd</sup> line treatment of chronic CML for dasatinib and nilotinib; and 2<sup>nd</sup> line treatment of ALL for dasatinib. The PBAC considered that the weighting and the cost-mimisation analysis should be based only on the use in CML, given the source of the estimates. The PBAC noted the values proposed in the submission are based on CML use.

**Table 9: The cost-minimisation analysis for ponatinib, dasatinib and nilotinib (prices based on DPMQ)**

Medicinal Product	mg/day	mg/month	Dispensed price/mg	Dispensed price/month	Cost of AEs (per year)	Total cost/year
Dasatinib	102	3060	\$1.65	\$5,045.87	\$216.94	\$60,767.41
Nilotinib	797	23,910	\$0.24	\$5,850.46	\$449.36	\$70,654.86
<b>Weighted average price (DAS/NIL)</b>						\$65,372.44
<b>Ponatinib</b>	30.2	906	\$ [REDACTED] <sup>a</sup>	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
15 mg – 70%			\$ [REDACTED]	\$ [REDACTED]		
45 mg – 30%			\$ [REDACTED]	\$ [REDACTED]		

Source: Table 80, p195 of the submission and Excel spreadsheet

AE = adverse event; DAS = dasatinib; DPMQ = dispensed price, maximum quantity; NIL = nilotinib; *italics = correction made to the errors made by the re-submission on the cost of treating occlusive events.*

<sup>a</sup> Weighted price per mg across strengths

- 6.24 The cost-minimisation analysis might not be accurate as the DPMQ values for ponatinib were higher than the weighted dispensed cost per month. The proposed DPMQ for ponatinib 45 mg per day was more than \$ [REDACTED] per month higher than for the 30 mg daily dose, yet the higher dose was associated with more adverse events and, according to the submission, no additional efficacy. The PSCR disagreed that the resubmission stated there was no additional efficacy with the higher dose and that in the resubmission “a multivariate analysis of the PACE trial showed a significant relationship between dose intensity and probability of MCyR in CP-CML patients”.
- 6.25 The cost of treating pleural effusions and vascular occlusive events were included in the cost-minimisation analysis. However, the re-submission incorrectly estimated the cost of treating vascular occlusive events. Correcting these errors resulted in a DPMQ of \$ [REDACTED] for 15 mg ponatinib and \$ [REDACTED] for 45 mg ponatinib.
- 6.26 During evaluation, the rates for pleural effusions and vascular occlusive events were updated by using only studies with follow-up similar to the PACE study. When using the updated adverse event rates, the cost of ponatinib per year was \$ [REDACTED]. The PSCR disagreed with the exclusion and inclusion of some of the trials (see ‘Comparative Harms’ section) but noted that the discrepancies in the analyses had little impact on the overall cost of treatment (\$ [REDACTED] per year in the re-submission compared with \$ [REDACTED] in the Commentary). The ESC suggested that it may be possible to include all the studies but adjust for the differences in follow-up, noting however that this was not a major issue as it would likely have only a minor impact on the total cost.

**Table 10: Sensitivity analyses performed during evaluation**

	DPMQ Ponatinib		Cost of AE (per year)	Total cost per year
	15mg	45mg		
Re-submission base case	\$ [REDACTED]	\$ [REDACTED]	\$688.81	\$ [REDACTED]
Errors corrected in the base case	\$ [REDACTED]	\$ [REDACTED]	\$711.49	\$ [REDACTED]
Updated rates for adverse events	\$ [REDACTED]	\$ [REDACTED]	\$903.98	\$ [REDACTED]

Source: Ponatinib\_PBAC\_March2015\_SectionD.xlsx, calculated during evaluation.

AE = adverse event; DPMQ = dispensed price, maximum quantity; *italics = correction made during evaluation.*

- 6.27 The PBAC considered it reasonable to include pleural effusions as well as vascular occlusions in the economic model. However, the PBAC noted the following issues:

- the costs of treatments for major toxicities and the distributions of these costs across different grades of toxicity, were not well justified by the resubmission and were therefore uncertain. The PBAC noted that the percentage distribution of vascular occlusion events for patients receiving dasatinib and nilotinib was the same as observed for ponatinib, which is an unsupported assumption. This could favour ponatinib.
  - the resubmission selected and compared studies with different follow-up lengths to estimate the average rate of pleural effusions and vascular occlusive events for ponatinib, dasatinib and nilotinib. The PBAC considered that the percentage of patients experiencing a severe adverse event is time dependent and it cannot be assumed that adverse events, even of similar nature, will occur at the same rate.
- 6.28 In the absence of independently verified estimates of rates of serious adverse events of interest (i.e. vascular occlusions and pleural effusions) per unit time, the PBAC considered the approach of the evaluation ('Updated rates for adverse events' in the table above) was more appropriate than that proposed in the submission. While noting that the evaluation approach did not result in a major change in the price of drug based on cost-minimisation, it did appropriately reflect the anticipated difference in costs for adverse events between the drugs.

**Drug cost/patient/month: \$ [REDACTED].**

- 6.29 The drug cost per patient per month was \$ [REDACTED], assuming:
- the adverse event rates were updated using studies with follow-up duration similar to the PACE study,
  - a ponatinib price per mg of \$ [REDACTED],
  - a higher price per mg for 15 mg (60 tablets) compared with 45 mg (30 tablets),
  - a 70:30 split for ponatinib 15 mg (60 tablets) and 45 mg (30 tablets), and
  - an equi-effective dose of 30.2 mg per day (see Table 9).

For CML patients the treatment is continuous, provided that the patient has a continued major cytogenetic response. For patients with ALL treatment continues until disease progression.

- 6.30 The PBAC considered these assumptions to be appropriate, but noted that the drug cost per month would be lower, using the calculation method preferred by the PBAC.

**Estimated PBS usage & financial implications**

- 6.31 This re-submission was not considered by DUSC. Similar to the previous submission, the re-submission used a market share approach to estimate the utilisation and cost of ponatinib over a five-year time horizon. The re-submission addressed most of the PBAC concerns, except it did not use the DUSC's estimates of TKI use. Further, the re-submission assumed an uptake rate of [REDACTED]% in patients resistant or intolerant to imatinib plus either nilotinib plus dasatinib and a rate of [REDACTED]% in patients resistant or intolerant to imatinib plus nilotinib and dasatinib.
- 6.32 Compared with the previous submission, the number of patients treated was lower and the number of packs higher in the re-submission. These were due to updated

assumptions on the estimation of use and corrections on the number of scripts for ponatinib.

**Table 11: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5
<b>Estimated extent of use</b>					
Number treated					
Number treated - Nov 2014					
Packs					
15 mg packs					
45 mg packs					
Packs - Nov 2014					
15 mg packs					
45 mg packs					
<b>Estimated net cost to PBS/MBS</b>					
Net cost to PBS	\$	\$	\$	\$	\$
Net cost to PBS Nov 2014	\$	\$	\$	\$	\$
Net saving to PBS	-\$	-\$	-\$	-\$	-\$
Net saving to PBS Nov 2014	-\$	-\$	-\$	-\$	-\$
<b>Estimated total net cost</b>					
<b>Net cost PBS/MBS</b>	\$	\$	\$	\$	\$
Net cost PBS/MBS Nov 2014	\$	\$	\$	\$	\$

Source: Compiled during the evaluation

PBS = Pharmaceutical Benefits Scheme; MBS = Medicare Benefits Schedule.

Values in italics for this re-submission were corrections for errors in the Excel spreadsheet. Values for the November 2014 submission were extracted from the 5-9 Commentary 10-2014.

*The redacted table above shows the estimated patients to receive treatment with ponatinib to be less than 10,000 per year and the estimated net cost to the PBS/MBS to be less than \$10 million per year.*

- 6.33 The re-submission did not include the cost of genetic testing and noted that genetic testing is a routine part of current practice when patients no longer respond to their current therapy. Therefore, the re-submission argued that the listing of ponatinib is unlikely to significantly impact on the number of tests required.
- 6.34 The accuracy of the financial estimates was uncertain. The main factors contributing to this uncertainty were:
- The re-submission incorrectly estimated and potentially underestimated the number of patients treated with TKIs (imatinib, dasatinib, and nilotinib) compared with the February 2014 DUSC review of TKIs use (less than 10,000 patients treated in 2015 according to the re-submission compared with 2,500 patients treated in 2012/2013). The PSCR claims that the re-submission estimated less than 10,000 patients would be treated with a TKI in 2015 ( in first line and in at least second-line).
  - The re-submission made the following calculation errors:
    - the number of patients who became resistant or intolerant in third-line therapy;
    - the number of scripts per year for ponatinib;
    - the change in the number of scripts for dasatinib and nilotinib in second-line therapy; and
    - the co-payment was applied per script.
  - The re-submission did not consider the cost of adverse events due to ponatinib.

- 6.35 The ESC noted that calculation errors were corrected during the evaluation.
- 6.36 The PBAC recognised that the financial estimates revised during the evaluation (including net costs to PBS/MBS of less than \$10 million in Year 5) could be an under or overestimated, because:
- the estimated number of patients seeking treatment, though appropriately lower than presented in the previous submission, were uncertain and included Ph+ ALL patients without the T315 mutation
  - it was based on inexact assumptions of the distribution of use between CML and ALL indications the duration of use.
  - the cost of adverse events due to ponatinib were not included in the estimates.

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

## **7 PBAC Outcome**

- 7.1 The PBAC recommended the PBS-listing of ponatinib as an Authority Required benefit for
- the treatment of chronic myeloid leukemia (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
  - the treatment of relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) in patients whose ALL has the T315I mutation. The PBAC considered that the cost-effectiveness of ponatinib would be acceptable when benchmarked against the costs of dasatinib and nilotinib, with adjustments required to account for the toxicity of the treatments. The equi-effective doses were considered to be ponatinib 30.2 mg daily, dasatinib 102 mg daily and nilotinib 797 mg daily.
- 7.2 The PBAC considered that there was a clinical need for treatments of Ph+ ALL patients without the T315 mutation (including patients with less common mutations such as F317L and E225V). However, in the absence of additional evidence, the PBAC could not recommend approval for ponatinib in Ph+ ALL without the T315 mutation. The PBAC did not alter its view from November 2014 in recommending the use of ponatinib in clinical scenarios where its risk:benefit ratios were most favourable. The PBAC would welcome additional quality evidence of the benefit of ponatinib in Ph+ ALL patients without the T315 mutation to facilitate any future reconsideration.
- 7.3 The PBAC recalled its view from November 2014, that the comparators for ponatinib are complex, and depending on different clinical scenarios, they can be dasatinib or nilotinib or other non-TKI therapies, i.e. hydroxyurea, interferon, allogeneic transplantation and salvage chemotherapy. The PBAC reiterated 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.
- 7.4 The PBAC reaffirmed its previous conclusion that ponatinib is the most active TKI for

CML patients who carry the T315I mutation, and that response rates to ponatinib in CML patients with the T315I mutant CML are similar to those seen in CML patients without this mutation treated with dasatinib or nilotinib in second line.

- 7.5 The PBAC reaffirmed its view that ponatinib has an inferior toxicity profile to imatinib, dasatinib and nilotinib, especially with regard to serious vascular occlusive events.
- 7.6 The PBAC noted the cost-mimimisation based on the appropriate equi-effective doses of ponatinib 30.2 mg daily, dasatinib 102 mg daily and nilotinib 797 mg daily. The PBAC considered the cost-mimimisation analysis should be based on the use of the treatments in CML. The PBAC considered it reasonable to include pleural effusions as well as vascular occlusions in the economic model and the methodology (updated in the evaluation) was consistent with the previous view of the PBAC.
- 7.7 The PBAC noted the discrepancy between the weighted price and DPMQ was a consequence of the estimate that 15% of patients would only receive 15 mg per day rather than 30 mg (i.e. 15 mg twice per day) or 45 mg per day. Advice received from HSANZ supported the general contention that average doses used in practice will be lower than those used in the PACE study.
- 7.8 The PBAC noted the modification to the patient and financial estimates compared to the previous submission but considered that the patient numbers and estimated cost to Government may be an under or over estimate. Overall, the PBAC considered that the revised estimates presented in the evaluation would likely reflect the very upper bound of net costs to government, with the listing of ponatinib in line with recommended indications.
- 7.9 The PBAC specified under Section 101 (3BA) of the *National Health Act 1953* that ponatinib should not be treated as interchangeable on an individual patient basis with any other drug.
- 7.10 The PBAC advised that ponatinib is not suitable for prescribing by nurse practitioners.
- 7.11 The PBAC recommended that the Safety Net 20 Day Rule should apply.
- 7.12 The PBAC noted that this submission is not eligible for an Independent Review, as it received a positive recommendation.

**Outcome:**

Recommended

**8 Recommended listing**

- 8.1 Add new item:

Public Summary Document – July 2015 PBAC Meeting

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
PONATINIB ponatinib 15 mg tablet, 60	1	5	Iclusig	Specialised Therapeutics Australia
ponatinib 45 mg tablet, 30	1	5		

**CML (without T315I mutation)**

<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Episodicity:</b>	Chronic
<b>Severity:</b>	-
<b>Condition:</b>	Myeloid leukaemia
<b>PBS Indication:</b>	Chronic myeloid leukaemia
<b>Treatment phase:</b>	Initial
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	The treatment must be the sole PBS-subsidised therapy for this condition  AND  Patient must have failed an adequate trial of dasatinib; OR Patient must have developed intolerance to dasatinib of a severity necessitating permanent treatment withdrawal  AND  Patient must have failed an adequate trial of nilotinib; OR Patient must have developed intolerance to nilotinib of a severity necessitating permanent treatment withdrawal; OR Patient must not be eligible for PBS-subsidised treatment with nilotinib because the patient has a blast crisis.

<p><b>Prescriber Instructions</b></p>	<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:             <ol style="list-style-type: none"> <li>(i) failure to achieve a haematological response after a minimum of 3 months therapy with dasatinib or nilotinib; or</li> <li>(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</li> <li>(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> </ol> </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> <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><b>Administrative Advice</b></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; and</li> <li>2. a completed [To be confirmed] - Supporting Information 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. (The date of the relevant pathology report 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</li> </ol>

	<p>splenomegaly or extramedullary involvement.</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: Department of Human Services Prior Written Approval of Complex Drugs Reply Paid 9826 GPO Box 9826 HOBART TAS 7001</p> <p>Patients are eligible for PBS-subsidised treatment with only one of dasatinib, nilotinib or ponatinib at any one time and must not be receiving concomitant interferon alfa therapy.</p> <p>1. Continuing treatment</p> <p>All continuing applications are to be written and must include a pathology report demonstrating the patient has responded to PBS-subsidised treatment as follows:</p> <p>(i) within 18 months of the commencement of treatment, 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; and</p> <p>(ii) at no greater than 12 month intervals thereafter, to demonstrate that the major cytogenetic response or peripheral blood BCR-ABL level of less than 1% has been sustained.</p> <p>2. Authority approval requirements.</p> <p>Response criteria to initial treatment with ponatinib:</p> <p>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 dasatinib, nilotinib or 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 continuing treatment with that agent).</p> <p>3. Definitions of response.</p>
--	--

Public Summary Document – July 2015 PBAC Meeting

	<p>A major cytogenetic response is defined as less than 35% Philadelphia positive bone marrow cells.</p> <p>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.</p> <p>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.</p> <p>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>
--	---

***CML (with T315I mutation)***

<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Episodicity:</b>	Chronic
<b>Severity:</b>	-
<b>Condition:</b>	Myeloid leukaemia
<b>PBS Indication:</b>	Chronic myeloid leukaemia
<b>Treatment phase:</b>	Initial
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	<p>The treatment must be the sole PBS-subsidised therapy for this condition</p> <p>AND</p> <p>Patient must be expressing the T315I mutation</p> <p>AND</p> <p>Patient must have failed an adequate trial of imatinib; OR Patient must have failed an adequate trial of dasatinib; OR Patient must have failed an adequate trial of nilotinib.</p>

<p><b>Prescriber Instructions</b></p>	<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:             <ol style="list-style-type: none"> <li>(i) failure to achieve a haematological response after a minimum of 3 months therapy with imatinib or dasatinib or nilotinib; or</li> <li>(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</li> <li>(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> </ol> </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><b>Administrative Advice</b></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; and</li> <li>2. a completed [To be confirmed] - Supporting Information 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 needs to be provided); and</li> <li>5. where there has been a loss of response to imatinib or dasatinib or nilotinib,</li> </ol>

	<p>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> <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: Department of Human Services Prior Written Approval of Complex Drugs Reply Paid 9826 GPO Box 9826 HOBART TAS 7001</p> <p>Patients are eligible for PBS-subsidised treatment with only one of dasatinib, nilotinib or ponatinib at any one time and must not be receiving concomitant interferon alfa therapy.</p> <p>1. Continuing treatment</p> <p>All continuing applications are to be written and must include a pathology report demonstrating the patient has responded to PBS-subsidised treatment as follows:</p> <p>(i) within 18 months of the commencement of treatment, 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; and</p> <p>(ii) at no greater than 12 month intervals thereafter, to demonstrate that the major cytogenetic response or peripheral blood BCR-ABL level of less than 1% has been sustained.</p> <p>2. Authority approval requirements.</p> <p>Response criteria to initial treatment with ponatinib:</p> <p>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 dasatinib, nilotinib or 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 continuing treatment with that agent).</p>
--	--

Public Summary Document – July 2015 PBAC Meeting

	<p>3. Definitions of response.</p> <p>A major cytogenetic response is defined as less than 35% Philadelphia positive bone marrow cells.</p> <p>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.</p> <p>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.</p> <p>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>
--	--

**CML (continuing restriction)**

<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Episodicity:</b>	Chronic
<b>Severity:</b>	-
<b>Condition:</b>	Myeloid leukaemia
<b>PBS Indication:</b>	Chronic myeloid leukaemia
<b>Treatment phase:</b>	Continuing
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	<p>Patient must have previously been issued with an authority prescription for this drug for this condition</p> <p>AND</p> <p>The treatment must be the sole PBS-subsidised therapy for this condition</p> <p>AND</p> <p>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>Administrative Advice</b>	<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 [To be confirmed– Continuing] PBS authority application - Supporting Information Form; and</li> <li>3. demonstration of continued response to treatment as evidenced by either:</li> </ol>

	<p>(i) 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</p> <p>(ii) 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</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 Prior Written Approval of Complex Drugs Reply Paid 9826 GPO Box 9826 HOBART TAS 7001</p> <p>Patients are eligible for PBS-subsidised treatment with only one of dasatinib, nilotinib or ponatinib at any one time and must not be receiving concomitant interferon alfa therapy.</p> <p>1. Continuing treatment</p> <p>All continuing applications are to be written and must include a pathology report demonstrating the patient has responded to PBS-subsidised treatment as follows:</p> <p>(i) within 18 months of the commencement of treatment, 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; and</p> <p>(ii) at no greater than 12 month intervals thereafter, to demonstrate that the major cytogenetic response or peripheral blood BCR-ABL level of less than 1% has been sustained.</p> <p>2. Authority approval requirements.</p> <p>Response criteria to initial treatment with ponatinib:</p> <p>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</p>
--	--

Public Summary Document – July 2015 PBAC Meeting

	<p>treatment with dasatinib, nilotinib or 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 continuing treatment with that agent).</p> <p>3. Definitions of response.</p> <p>A major cytogenetic response is defined as less than 35% Philadelphia positive bone marrow cells.</p> <p>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.</p> <p>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.</p> <p>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>
--	---

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
PONATINIB ponatinib 15 mg tablet, 60	1	2	Iclusig	Specialised Therapeutics Australia
ponatinib 45 mg tablet, 30	1	2		

**Ph+ ALL (with T315I mutation)**

<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Episodicity:</b>	Acute
<b>Severity:</b>	-
<b>Condition:</b>	Lymphoblastic leukaemia
<b>PBS Indication:</b>	Acute lymphoblastic leukaemia
<b>Treatment phase:</b>	Initial
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined

Public Summary Document – July 2015 PBAC Meeting

<p><b>Clinical criteria:</b></p>	<p>The treatment must be the sole PBS-subsidised therapy for this condition</p> <p>AND</p> <p>Patient must be expressing the T315I mutation</p> <p>AND</p> <p>Patient must have failed treatment with chemotherapy,</p> <p>AND</p> <p>Patient must have failed treatment with PBS-subsidised imatinib for this condition,</p> <p>AND</p> <p>Patient must have failed allogeneic haemopoietic stem cell transplantation (where appropriate).</p>
<p><b>Prescriber Instructions</b></p>	<p>Failure of treatment is defined as either:</p> <ol style="list-style-type: none"> <li>1. Failure to achieve a complete morphological and cytogenetic remission after a minimum of 2 months treatment with intensive chemotherapy and imatinib OR dasatinib;</li> <li>2. Morphological or cytogenetic relapse of leukaemia after achieving a complete remission induced by chemotherapy and imatinib OR dasatinib;</li> <li>3. Morphological or cytogenetic relapse or persistence of leukaemia after allogeneic haemopoietic stem cell transplantation.</li> </ol> <p>Patients must have active leukaemia, as defined by presence on current pathology assessments of either morphological infiltration of the bone marrow (greater than 5% lymphoblasts) or cerebrospinal fluid or other sites; OR the presence of cells bearing the Philadelphia chromosome on cytogenetic or FISH analysis in the bone marrow of patients in morphological remission.</p>

Public Summary Document – July 2015 PBAC Meeting

<b>Administrative Advice</b>	<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 [To be confirmed] PBS Authority Application - Supporting Information Form; and</li> <li>3. a signed patient acknowledgement; and</li> <li>4. a pathology report demonstrating that the patient has active acute lymphoblastic leukaemia, either manifest as cytogenetic evidence of the Philadelphia chromosome, or morphological evidence of acute lymphoblastic leukaemia plus qualitative RT-PCR evidence of BCR-ABL transcript.; and evidence of the T315I mutation. The date of the relevant pathology report(s) need(s) to be provided</li> </ol> <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          Prior Written Approval of Complex Drugs          Reply Paid 9826          GPO Box 9826          HOBART TAS 7001</p>
------------------------------	--

**Ph+ ALL (continuing)**

<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Episodicity:</b>	Acute
<b>Severity:</b>	-
<b>Condition:</b>	Lymphoblastic leukaemia
<b>PBS Indication:</b>	Acute lymphoblastic leukaemia
<b>Treatment phase:</b>	Continuing
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	<p>Patient must have previously been issued with an authority prescription for this drug for this condition</p> <p>AND</p> <p>The treatment must be the sole PBS-subsidised therapy for this condition</p> <p>AND</p> <p>Patient must not have progressive disease.</p>

<b>Administrative Advice</b>	<p>Authority applications for continuing treatment may be made by telephone to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</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: Department of Human Services Prior Written Approval of Complex Drugs Reply Paid 9826 GPO Box 9826 HOBART TAS 7001</p>
------------------------------	---

## **9 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.

## **10 Sponsor's Comment**

The sponsor had no comment.