

5.9 PONATINIB tablets; 15 mg and 45 mg; Iclusig®; Specialised Therapeutics Australia Pty Ltd.

1 Purpose of Application

1.1 The submission sought an Authority Required listing for ponatinib for treatment of adult patients:

- with chronic myeloid leukaemia (CML) who are resistant or intolerant to dasatinib or nilotinib, or who have the T315I mutation; or
- with Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia (ALL) who are resistant or intolerant to dasatinib, or who have the T315I mutation.

2 Requested listing

2.1 Abridged versions of the requested restrictions are shown below.

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

Authority Required

Restriction 1 – CML

Chronic Myeloid Leukaemia (CML)

Treatment Phase: Initial treatment

Clinical criteria:

The treatment must be the sole PBS-subsidised therapy for this condition,

AND

The treatment must have failed second line therapy of dasatinib; OR

The treatment must have failed second line therapy of nilotinib.

Chronic Myeloid Leukaemia (CML)

Treatment Phase: Continuing treatment

Clinical criteria:

The treatment must be the sole PBS-subsidised therapy for this condition,

AND

Patient must have received prior PBS-subsidised treatment with ponatinib for chronic myeloid leukaemia (CML),

AND

Patient must have 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.

Restriction 2 – CML with T315I mutation

Chronic Myeloid Leukaemia (CML)

Treatment Phase: Initial treatment

Clinical criteria:

The treatment must be the sole PBS-subsidised therapy for this condition,

AND

Patient must be expressing the T315I mutation,

AND

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.

Chronic Myeloid Leukaemia (CML)

Treatment Phase: Continuing treatment

Clinical criteria:

The treatment must be the sole PBS-subsidised therapy for this condition,

AND

Patient must be expressing the T315I mutation,

AND

Patient must have received prior PBS-subsidised treatment with ponatinib for chronic myeloid leukaemia (CML),

AND

Patient must have 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.

Restriction 3 – ALL (Ph+)

Acute Lymphoblastic Leukaemia (ALL)

Treatment Phase: Initial treatment

Clinical criteria:

The treatment must be as monotherapy,

AND

Patient must bear the Philadelphia chromosome; OR

Patient must express the transcript, BCR-ABL,

AND

Patient 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 stem cell transplantation (where appropriate).

Acute Lymphoblastic Leukaemia (ALL)

Treatment Phase: Continuing treatment

Clinical criteria:

The treatment must be as monotherapy,

AND

Patient must bear the Philadelphia chromosome; OR

Patient must express the transcript, BCR-ABL,

AND

Patient must have received prior PBS-subsidised treatment with ponatinib for acute lymphoblastic leukaemia (ALL),

AND

Patient must not have progressive disease.

- 2.2 Listing is sought on a cost-minimisation basis with ponatinib compared to dasatinib and nilotinib.
- 2.3 The PBAC considered that restrictions that aligned ponatinib use with clinical scenarios where its risk: benefit ratios were most favourable were more appropriate.

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

3 Background

- 3.1 The submission was made under TGA/PBAC Parallel Process. At the time of evaluation, the Sponsor's responses to the TGA's Round I and II clinical evaluation reports (CERs) were available.
- 3.2 The PBAC noted that from the pre-PBAC response that ponatinib had received a positive delegate's recommendation on the 2nd of September 2014, and was considered by the ACPM on the 3rd of October 2014 "...to have an overall positive benefit–risk profile for the amended indication:"

ICLUSIG (ponatinib) is indicated for the treatment of adult patients with:

- Chronic phase, accelerated phase, or blast phase chronic myeloid leukaemia (CML) with intolerance of, or disease resistant to, at least two prior tyrosine kinase inhibitors (TKI's), or where there is a T315I mutation.
- Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) whose disease is resistant to, or who are intolerant of, imatinib and dasatinib, or where there is a T315I mutation

- 3.3 In making this recommendation, the ACPM agreed with the delegate on the proposed conditions of registration and specifically advised on the inclusion of a boxed warning to alert prescribers and patients of the risks of vascular occlusion and cardiac failure.
- 3.4 Ponatinib has not been considered by PBAC previously.

4 Clinical place for the proposed therapy

- 4.1 The submission proposed that patients with CML and Ph+ ALL with the T315I mutation can be treated with ponatinib as a second-line therapy, after failure of imatinib or dasatinib or nilotinib. For CML and Ph+ ALL patients without the T315I mutation, ponatinib is proposed as a third-line therapy. The ESC noted that the proposed algorithm does not make a distinction between CML and Ph+ ALL. Although nilotinib is not PBS listed for Ph+ ALL, the proposed restriction suggested that ponatinib will be used last line.
- 4.2 The PBAC considered that given its toxicity profile, the clinical place for ponatinib therapy would be in patients with BCR-ABL fusion gene positive (BCR-ABL+) CML and ALL where use of all other PBS-listed TKIs had or would fail to induce response, or was not appropriate because of significant toxicities or contraindications.

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

5 Comparator

- 5.1 Dasatinib and nilotinib, for all indications (CML with/without T315I mutation and Ph+ ALL with/without T315I mutation); these may not be the appropriate comparators. Imatinib is not considered as a comparator as it is a first-line treatment option generally; patients who develop resistance to therapy can have their leukaemia tested to identify mutations and target treatment.
- 5.2 The ESC considered that for the treatment of CML or Ph+ ALL without the T315I mutation:
- In 3rd line therapy, after imatinib and dasatinib or nilotinib, dasatinib/nilotinib would be reasonable comparators.
 - In 4th line therapy, after imatinib, dasatinib and nilotinib, the most appropriate comparators would be best supportive care (BSC) or allogeneic haematopoietic stem cell transplantation (SCT). The PSCR (p2) argued against BSC and SCT as comparators, on the basis that patients are unlikely to receive BSC before a third TKI, and SCT is a limited treatment option, available only to patients with excellent performance status with an appropriate donor and comes with a risk of transplant related mortality of over 30%.
 - In addition, the ESC considered that for the subgroup of patients with CML or Ph+ ALL with T315I mutation, dasatinib/nilotinib are not as effective as ponatinib and BSC or allogeneic SCT are the more appropriate comparators in this patient population.
- 5.3 The PBAC considered that the treatments most likely to be replaced by ponatinib in patients meeting its proposed restrictions would be non-TKI therapies, including

hydroxyurea, interferon, cytotoxic drugs, allogeneic stem cell transplantation, and supportive care.

- 5.4 This consideration notwithstanding, the PBAC did agree with the sponsor that comparison with the data for dasatinib and nilotinib in patients who had failed or who were intolerant to imatinib would be informative in benchmarking efficacy and toxicity, as well as effectiveness and costs

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 presented clinical case studies and discussed the natural history of the disease and how the drug would be used in practice. The clinician also clarified that mechanism of higher vascular occlusion events induced by ponatinib is still unknown and most patients die from progressive disease rather than from the cardiovascular events directly. The PBAC considered that the hearing was informative as it provided a clinical perspective on treating this disease.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (2) and health care professionals (4) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with ponatinib including a reasonable response rate for patients who have no other therapeutic alternatives and a significant prolongation of life in the small number of patients who would be eligible.

Clinical studies

- 6.3 The submission was based on analysis of ten single-arm studies.
- 6.4 Details of the studies presented in the submission were provided in the following table.

Nonrandomised studies associated reports presented in the submission

Study ID	Protocol title/ Publication title	Publication citation
Ponatinib open-label, nonrandomised studies		
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, et al. A phase II trial of ponatinib in Philadelphia chromosome-positive leukemias.	13 July 2012 New England Journal of Medicine 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, et al. Ponatinib in refractory Philadelphia chromosome-positive leukemias.	14 June 2012 New England Journal of Medicine 2012; 367(22): 2075-2088.
Dasatinib studies		
Muller 2009	Muller MC, Cortes JE, Kim DW, et al. Dasatinib treatment of chronic-phase chronic myeloid leukemia: analysis of responses according to preexisting BCR-ABL mutations.	Blood 2009; 114(24): 4944-4953.
Quintas-Cardama 2007	Quintas-Cardama A, Kantarjian H, Jones D, et al. Dasatinib is active in Philadelphia chromosome-positive chronic myelogenous leukemia after imatinib and nilotinib therapy failure.	Blood 2007; 109(2): 497-499.
Nilotinib studies		
Giles 2010	Giles FJ, Abruzzese E, Rosti G, et al. Nilotinib is active in chronic and accelerated phase chronic myeloid leukemia following failure of imatinib and dasatinib therapy.	Leukemia 2010; 24(7): 1299-1301.
Nicolini 2009 [abstract]	Nicolini FE, Alimena G, Al-Ali HK, et al. 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.	Haematologica 2009; 94: 257.
Dasatinib and nilotinib studies		
Garcia-Gutierrez 2012 [abstract]	Garcia-Gutierrez JV, Maestro B, Casado LF, et al. 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, et al. The use of nilotinib or dasatinib after failure to two prior tyrosine kinase inhibitors: long-term follow up.	Blood 2009; 114(20): 4361-4368.
Ibrahim 2010	Ibrahim AR, Paliompeis C, Bua M, et al. 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.	Blood 2010; 116(25): 5497-5500.
Rossi 2013	Rossi AR, Breccia M, Abruzzese E, et al. Outcome of 82 chronic myeloid leukemia patients treated with nilotinib or dasatinib after failure of two prior tyrosine kinase inhibitors.	Haematologica 2013; 98(3): 399-403.

Source: Table 6, pp50-51 and Table 9, pp53-55 of the submission

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

6.5 The key features of the nonrandomised studies were summarised in the following table.

Key features of the nonrandomised studies

Study	N	Design/ Median follow-up	Risk of bias	Patient population	Outcomes
Ponatinib					
PACE	449	Phase II, MC, OL, SA 9.9 months	High	CP, AP and BC CML and Ph+ ALL: - resistant or intolerant to 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, AP and BC CML, Ph + ALL) and AML.	To determine the recommended dose; safety and efficacy.
Dasatinib					
Quintas-Cardama 2007	23	Observational, SC, SA; 7.8 months	High	CP, AP and BC CML: - 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
Nilotinib					
Giles 2010	60	Phase II, MC, SA, non-comparative; 12 months	High	CP and AP CML: - 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, AP and BC CML: - resistant or intolerant to imatinib and dasatinib.	CHR, MCyR, CCyR
Dasatinib and nilotinib					
Garcia-Gutierrez 2012	31	Analysis of national registry data; 9 months	High	CP CML: - resistant or intolerant to imatinib and a 2 nd generation TKI.	CCyR, CHR
Garg 2009	48	Observational, SC, SA; 13 months	High	CP, AP and BC CML: - switched to 2 nd or 3 rd 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 = nonrandomised; OL = open label; PCyR = partial cytogenetic response; Ph+ = Philadelphia chromosome positive; SA = single arm; SC = single centre; TKI = tyrosine kinase inhibitor

- 6.6 Muller 2009 was excluded by the submission as the proportion of patients with the T315I mutation was deemed too small (n = 21). This may not be appropriate and the results for this subgroup analysis were presented where appropriate in the commentary. In addition, Muller 2009 and PACE are the only studies to report results for patients with the T315I mutation.

- 6.7 As all the studies were nonrandomised single-arm observational studies, there was no common arm to enable an indirect comparison. This limitation, as well as the high levels of heterogeneity between the individual studies made interpretation of the results of the key outcomes difficult.

Comparative effectiveness

- 6.8 The submission compared cytogenetic, molecular and haematological response rates of ponatinib as a second-, third- and fourth-line agent in patients with and without the T315I mutation from the PACE study. Patients were tested for mutations following resistance to therapy. A summary of the major cytogenetic response rates for ponatinib is presented in the following table.

Rates of major cytogenetic response for ponatinib when used second-, third- and fourth-line in patients from the PACE study with and without the T315I mutation.

	2 nd line	3 rd line	4 th line	All patients
Chronic phase CML				
Resistant or intolerant to previous therapy	3/5 (60%)	41/76 (54%)	55/122 (45%)	144/267 (54%)
T315I mutation present	10/11 (91%)	24/31 (77%)	11/21 (52%)	
Accelerated phase CML				
Resistant or intolerant to previous therapy	1/1 (100%)	9/27 (33%)	12/37 (32%)	32/83 (39%)
T315I mutation present	3/3 (100%)	4/6 (67%)	3/9 (33%)	
Blast crisis or Ph+ ALL				
Resistant or intolerant to previous therapy	1/2 (50%)	6/13 (46%)	6/33 (18%)	29/94 (31%)
T315I mutation present	4/7 (57%)	9/24 (38%)	3/15 (20%)	

Source: Table 30, p78; Table 42, p94; Table 54, p105 of the submission

ALL= acute lymphoblastic leukaemia; CML = chronic myeloid leukaemia; Ph+ = Philadelphia chromosome positive

- 6.9 The results suggested that ponatinib may be more effective when used as second- or third-line therapy in patients with the T315I mutation who are in the chronic phase. For patients with accelerated phase CML and blast crisis CML or those with Ph+ ALL ponatinib seems to be as effective in patients with the T315I mutation as in those who are resistant or intolerant to previous therapy. Low patient numbers in a number of the patient categories and the absence of randomisation means that these results may be of limited reliability.
- 6.10 The submission also compared cytogenetic, molecular and haematological response rates between the two ponatinib studies and eight dasatinib or nilotinib studies. The complete cytogenetic response for chronic phase CML and major cytogenetic response for accelerated phase and blast crisis CML or Ph+ ALL results were presented in the following table.

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 (%)
Chronic phase CML – CCyR				
PACE	118/267 (44%)			
Study 101	28/43 (65%)			
Quintas-Cardama 2007		0/4 (0%) ^a		
Giles 2010			9/37 (24%)	
Nicolini 2009			60/218 (28%) ^a	
Garg 2009		5/16 (31%)	1/9 (11%)	
Ibrahim 2010				9/26 (35%)
Rossi 2013				27/82 (33%) ^a
Accelerated phase CML - MCyR				
PACE	32/83 (39%)			
Study 101	2/9 (22%)			
Quintas-Cardama 2007		4/10 (40%) ^b		
Giles 2010			2/17 (12%)	
Nicolini 2009			2/34 (7%)	
Garg 2009		3/8 (38%)	1/2 (50%)	
Blast crisis CML or Ph+ ALL - MCyR				
PACE	29/94 (31%)			
Study 101	5/13 (38%)			
Quintas-Cardama 2007		1/9 (11%) ^b		
Nicolini 2009			6/40 (14%)	
Garg 2009		3/10 (30%)	1/3 (33%)	

^a When best response is reported: CCyR = MMR + CCyR

^b When best response is reported: MCyR = MMR + CCyR + PCyR

Source: Table 18, p69; Table 32, p87; Table 44, p99; of the submission; and individual trial papers

ALL = acute lymphoblastic leukaemia; 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

- 6.11 The rates of complete cytogenetic response or major cytogenetic response did not suggest differences between ponatinib, dasatinib and nilotinib. Due to differences in study design, CML disease phase, time of reporting, heterogeneity within and between the studies and the lack of randomisation, the claim of comparative efficacy may not be valid. Additionally, the response rates for the PACE study included patients with the T315I mutation which may skew the results in favour of ponatinib. It is unclear whether the dasatinib and nilotinib studies included patients with the T315I mutation in their results.
- 6.12 The submission did not present a comparison between ponatinib and dasatinib or nilotinib for those patients who have the T315I mutation. One excluded study (Muller 2009) reported a major cytogenetic response rate of 2/21 (10%) for chronic phase CML patients with the T315I mutation when treated with second-line dasatinib, compared to a response rate of 10/11 (91%) for ponatinib when used second-line in the PACE study.
- 6.13 The ESC considered that the estimate of the comparative effect size is unreliable because:
- Indirect trial evidence with a high risk of bias: ponatinib is based on two single-arm studies (PACE study and Study 101); while the evidence for dasatinib and nilotinib is based on seven studies, most of which were

- observational and single centre studies;
- The populations in the reported studies are highly heterogeneous; and
- There is no common comparator between the ponatinib, dasatinib and nilotinib studies making it difficult to compare effectiveness.
- the treatment effect size is based on a small number of patients for both accelerated phase CML and blast phase or Ph+ ALL in the PACE study.

6.14 Within the constraints imposed by the poor quality of the comparative data, and recalling data reviewed in previous applications for imatinib, dasatinib and nilotinib, PBAC considered that ponatinib was:

- (i) 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, with a high rate of sustained major cytogenetic response at 12 months, but that the overall survival of the ponatinib-treated population was less than seen with other TKI therapy in chronic phase CML;
- (ii) similar in efficacy to dasatinib or nilotinib with respect response rates in second and third line therapy for patients with non-T315I CML, but that relative durability of responses could not be compared;
- (iii) similar in efficacy to dasatinib with respect response rates in dasatinib-naïve patients with blast crisis CML, but that the relative durability of responses could not be compared between the two drugs;
- (iv) active at inducing transient responses in Ph+ ALL with the T315I mutation, and may have activity against non-T315I Ph+ ALL, but that the paucity of data for non-T315I ALL was insufficient to enable any confidence in determining the extent of its effectiveness.

Comparative harms

6.15 The submission provided very limited comparative safety data for ponatinib, dasatinib and nilotinib. The incidence of adverse events was presented in the following table.

A summary of the adverse events reported across the nonrandomised studies

	Ponatinib; n/N (%)		Dasatinib; n/N (%)			Nilotinib; n/N (%)			
	PACE 13 July 2012	Study 101 14 June 2012	Quintas- Cardama 2007	Garg 2009	Rossi 2013	Giles 2010	Garg 2009	Nicolini 2009	Rossi 2013
N	449	81	23	34	34	60	14	292	48
Any TE AE	446/449 (99%)	81/81 (100%)	-	-	-	-	-	285/292 (98%)	-
Discontinued: AE	50/449 (11%)	61/81 (75%)	1/23 (4%)	7/34 (21%)	14/34 (41%)	10/60 (17%)	0/14 (0%)	33/292 (11%)	24/48 (50%)
Discontinued: lack of effect	-	-	8/23 (35%)	3/34 (9%)	-	19/60 (32%)	2/14 (14%)	68/292 (23%)	-
Discontinued: death	18/449 (4%)	-	7/23 (30%)	4/34 (12%)	-	2/60 (3%)	1/14 (7%)	-	-

Source: Table 56, p111; Table 57, p112 of the submission

AE = adverse event; TE = treatment emergent; Italics = extracted during evaluation

Due to the lack of adverse event reporting in the dasatinib and nilotinib studies, the heterogeneity across the studies and the absence of a head to head comparison, it was difficult to compare meaningfully the safety of ponatinib, dasatinib and nilotinib.

The most common adverse events reported in the ponatinib studies were decreased platelets (27-40%), decreased neutrophils (12-23%), rash (33-36%) and arthralgia (17-25%). The rate of pancreatitis should also be noted: 6% in the PACE study and 14% in Study 101.

- 6.16 Neither the PACE study nor Study 101, identified arterial or venous occlusion as an adverse event in their respective clinical study reports. Additional analysis of the PACE study data to 3 September 2013 was provided in the submission and is shown in the table below.

A summary of vascular occlusion events in the PACE study (data to 3 September 2013; median 16 months follow-up)

	Treatment emergent events (all causality); n/N (%)		Treatment related events; n/N (%)	
	All events	Serious events	All related events	Serious related events
Vascular occlusion events (arterial and venous)	91/449 (20.3%)	62/449 (13.8%)	42/449 (9.4%)	26/449 (5.8%)
Cardiovascular	41/449 (9.1%)	28/449 (6.2%)	16/449 (3.6%)	13/449 (2.9%)
Cerebrovascular	26/449 (5.8%)	18/449 (4.0%)	9/449 (2.0%)	6/449 (1.3%)
Peripheral vascular	28/449 (6.2%)	16/449 (3.6%)	14/449 (3.1%)	4/449 (0.9%)
Venous	23/449 (5.1%)	13/449 (2.9%)	10/449 (2.2%)	6/449 (1.3%)

Source: Table 62, p122 of the submission

- 6.17 In the PACE study after 16 months of follow-up, the overall percentage of patients with vascular occlusion was 20.3% and serious vascular occlusion event was 13.8%. The risk of an arterial thrombotic event increases substantially with an increase in risk factors (0 risk factors: risk = 6.4% vs. ≥ 2 risk factors: risk = 26.1%). Hypertension, diabetes and hypercholesterolemia were the major individual risk factors that resulted in an increased risk of an arterial thrombotic event, and the risk of a serious event with any individual risk factor was high. A history of ischaemic cardiac disease resulted in a 37% increased risk of developing an arterial thrombotic event. The PACE study excluded patients who had significant or active cardiovascular disease.

6.18 FDA information

On 31 October 2013, the FDA suspended the marketing and sale of ponatinib due to a steady increase in the number of serious vascular events. It was observed that the proportion of patients on ponatinib experiencing vascular occlusion events was significantly greater than the proportion reported at the time of approval. The FDA conducted an independent data analysis of the vascular and arterial events and released a 'Drug Safety Communication' for ponatinib advising that:

- It is unlikely that underlying cardiovascular risk factors were responsible for these events as they occurred in patients with and without risk factors and in all age ranges;
- Although the cumulative number of vascular events was shown to increase with longer use of ponatinib, there was no safe duration for ponatinib use, with events occurring within 2 weeks of starting the drug;
- Ponatinib can also cause recurrent or multi-site vascular occlusions; Events can occur in patients treated at dose levels as low as 15 mg per day, suggesting that the optimal dose of ponatinib has not yet been identified.

Following the introduction of several new safety measures, the FDA, in December 2013, allowed restricted access to ponatinib (FDA 2013). The required safety measures included:

- A new indication limiting use to adult patients:
 - with T315I-positive CML (chronic, accelerated or blast phase) or Ph+ ALL; and
 - with CML (chronic, accelerated or blast phase) or Ph+ ALL for whom no other TKI therapy is indicated.
- The revision of the Warnings and Precautions in the label to describe the vascular occlusion events, including a description of the observed arterial and venous thrombosis and occlusion that have occurred in at least 27% of patients (it should be noted that the FDA did not provide the sponsor with details of their incidence calculations – the most current data from the Sponsor cites a vascular occlusion rate of 20% in the PACE study and 35% in Study 101); and
- The revision of the Dosage and Administration recommendations to state that the optimal dose of ponatinib has not been identified. The recommended starting dose remained at 45 mg once daily, however additional information regarding dose decreases and discontinuations was included.

6.19 EPIC trial

Additional safety data provided by the Sponsor to the TGA included information from the EPIC trial. The EPIC trial was a phase III, randomised, open-label study which compared imatinib with ponatinib in newly diagnosed CML patients. Although this trial was terminated prematurely due to the concerns regarding vascular adverse events with ponatinib, it is the only available trial that provides comparative safety data against an approved agent.

The trial, at the time of discontinuation, had a total of 307 randomised subjects. Demographic and baseline disease characteristics were comparable for the two arms.

The incidence of adverse events in the EPIC trial are summarised in the table below.

	Ponatinib (n=153)	Imatinib (n=150)
Median duration of exposure	114 days	140 days
Any AE	94%	93%
Treatment related AE	90%	87%
Grade ≥ 3 AE	59%	27%
SAE	30%	9%
Treatment related SAE	22%	3%
Death	1	2
Discontinued: AE	10%	2%

Source: Table 79, p147 of the Office of Medicines Authorisation clinical evaluation report for ponatinib (TGA)

AE = adverse event; SAE = serious adverse event; Italics = extracted during evaluation

The data suggests that ponatinib has an inferior safety profile compared to imatinib when used in first-line treatment of CML, with a higher incidence of Grade 3 to 5 adverse events (59% vs. 27%), serious adverse events (30% vs. 9%) and discontinuations due to adverse events (10% vs. 2%).

Ponatinib was associated with a higher incidence of dermatological toxicity (rash, dry skin, alopecia and pruritus), hypertension, headache, thrombocytopenia and

abnormal liver function tests than imatinib. Imatinib had a higher rate of oedema, nausea, vomiting, diarrhoea and muscle spasms.

Serious adverse events that occurred in at least two patients are listed in the table below.

Serious adverse events occurring in ≥ 2 patients in the EPIC trial

	Ponatinib; n/N (%)	Imatinib; n/N (%)
Pancreatitis	5/153 (3.3%)	0/150 (0%)
Atrial fibrillation	3/153 (2.0%)	0/150 (0%)
Thrombocytopenia	3/153 (2.0%)	0/150 (0%)
Acute myocardial infarction	2/153 (1.3%)	0/150 (0%)
Cardiac failure	2/153 (1.3%)	0/150 (0%)

Source: Table 81, p150 of the Office of Medicines Authorisation clinical evaluation report for ponatinib (TGA)

Italics = extracted during evaluation

Notably, there were five cases of pancreatitis in the ponatinib arm.

6.20 The PBAC noted the submission claimed that the cardiovascular effects seen with ponatinib are class effects, citing QT interval prolongation with nilotinib as a particular concern. The Product Information for both dasatinib and nilotinib contain a warning stating that they should be used with caution in patients who have or who are at significant risk of developing prolongation of QT interval. However, various publications indicate that while nilotinib is associated with QT interval prolongation, the incidence of prolongation above 500 milliseconds is uncommon (less than 1%) (Brave 2008, Breccia 2013, and Kim 2012). One study of 233 patients receiving nilotinib as first- or second-line therapy found five cases (2%) of severe peripheral artery occlusive disease (Quintas-Cardama 2012). This rate is lower than that seen with ponatinib. Long-term experience for dasatinib and nilotinib in first- and second-line treatment has not indicated a high risk of vascular occlusive events.

6.21 The PBAC considered that ponatinib had an inferior toxicity profile to imatinib, dasatinib, and nilotinib, especially with regard to serious vascular occlusive events.

Benefits/harms

6.22 A summary of the comparative benefits and harms for ponatinib versus dasatinib and nilotinib was presented in the following table.

Summary of comparative benefits and harms for ponatinib versus dasatinib and nilotinib

Study	Ponatinib	Dasatinib	Nilotinib	Event rate/100 patients		
				Ponatinib	Dasatinib	Nilotinib
BENEFITS						
Chronic phase CML – MCyR						
PACE	144/267	-	-	54	-	-
Study 101	31/43	-	-	72	-	-
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	
Chronic phase CML – MCyR for patients with the T315I mutation – second-line TKI						
PACE	10/11	-	-	91	-	-
Muller 2009	-	2/21	-	-	10	-
HARMS						
Vascular occlusion						
PACE	91/449	-	-	20	-	-
Study 101	28/81	-	-	35	-	-

Source: Compiled during the evaluation

CML = chronic myeloid leukaemia; MCyR = major cytogenetic response; TKI = tyrosine kinase inhibitor

6.23 Based on single-arm non-comparative evidence presented in the submission, it is not clear whether ponatinib is better or worse than dasatinib or nilotinib in the treatment of chronic phase chronic myeloid leukaemia. Additionally, the ponatinib studies included patients with or without the T315I mutation and after failure of one to three TKIs, while mutation status in the dasatinib and nilotinib studies was unclear (and likely to be lower as ponatinib trial preferentially included patients with the mutation) and after failure of two or more TKIs.

- For chronic phase chronic myeloid leukaemia, the outcome assessed was major cytogenetic response.
- Based on single-arm non-comparative evidence presented in the submission, and supportive mechanistic evidence, ponatinib has efficacy as second-line treatment of chronic phase chronic myeloid leukaemia in patients with the T315I mutation. In contrast, dasatinib and nilotinib are now not considered appropriate treatments for chronic phase chronic myeloid leukaemia with the T315I mutation.

6.24 Based on single-arm evidence from ponatinib studies and long-term experience with dasatinib and nilotinib for the treatment of patients with chronic myeloid leukaemia, ponatinib is associated with a higher frequency of vascular occlusive events than nilotinib and dasatinib in the treatment of chronic myeloid leukaemia and Philadelphia chromosome positive acute lymphoblastic leukaemia in patients with and without the T315I mutation. Long-term experience for dasatinib and nilotinib in first- and second-line treatment has not indicated a high risk of vascular occlusive events.

Clinical claim

6.25 The submission described ponatinib as non-inferior in terms of comparative effectiveness to dasatinib and nilotinib. The submission did not make a claim in terms of the comparative safety of ponatinib to dasatinib and nilotinib, however it stated that

the adverse cardiovascular issues appear to be a class effect (particularly with nilotinib), which require ongoing monitoring and management of patients.

- 6.26 This claim is not adequately supported because:
- There is no direct evidence available for the comparative efficacy and safety of ponatinib versus dasatinib or nilotinib.
 - Dasatinib and nilotinib may not be suitable comparators for ponatinib. Stem cell transplantation or best supportive care may have been more appropriate comparators, particularly in 4th line therapy and in patients with the T315I mutation.
- 6.27 The submission did not provide a comparative claim for safety. The submission mentioned that the adverse cardiovascular events may be a class effect and that the precaution in the proposed Product Information will minimise the use of ponatinib in high risk patients. This may not be reasonable as dasatinib and nilotinib have not been associated with vascular occlusive events to the same extent as ponatinib, but rather with cardiac arrhythmias secondary to long QT syndrome. Furthermore, as noted in the FDA Risk Evaluation and Mitigation Strategy, vascular occlusive events were observed with ponatinib even in patients without vascular risk factors in the phase II trial (16% in those without vascular risk factors vs 33% in those with vascular risk factors) (<http://www.fda.gov/downloads/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm379551.pdf>). The ESC noted that cardiac events included vascular occlusion, QT prolongation and arrhythmia. The ESC considered that ponatinib is likely to have a higher risk of vascular occlusive events than dasatinib and nilotinib.
- 6.28 The PBAC considered that ponatinib is active in T315I mutant CML whereas dasatinib and nilotinib are not, that ponatinib has apparently similar efficacy in patients with CML who have failed (including intolerance) both dasatinib and nilotinib as observed for dasatinib and nilotinib in patients who had failed imatinib, and induces responses in patients with relapsed or refractory T315I Ph+ ALL. The PBAC considered that these comparative benefits over dasatinib and nilotinib for the select group of patients relevant to this application need to be weighed against the inferior safety profile of ponatinib compared to dasatinib and nilotinib.

Economic analysis

- 6.29 The submission presented a cost minimisation analysis for ponatinib. The ESC considered that the clinical evidence did not adequately support such an economic evaluation because:
- the clinical place of therapy may not support the choice of comparator
 - the clinical evidence does not support the claim that ponatinib is non-inferior to dasatinib and nilotinib for efficacy
 - ponatinib appears to be inferior to dasatinib and nilotinib for safety regarding vascular occlusive events;
- 6.30 The PBAC considered that a cost minimisation analysis was problematic given the expected clinical place of ponatinib and the treatments most likely to be replaced. Nevertheless, it 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, given the similarities between introduction of ponatinib in 2014/5 and the applications for dasatinib and nilotinib for patients with imatinib failure in 2007 and 2008. However, the PBAC also considered that it was essential to account for the costs of excessive vascular occlusive events seen with ponatinib 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.

- 6.31 The equi-effective doses were estimated by the sponsor as:

Ponatinib 30.2 mg daily = Dasatinib 111.0 mg daily = Nilotinib 792.1 mg daily

Due to the lack of comparative data, mean daily doses of dasatinib and nilotinib were obtained from the Therapeutic Relativity Sheets for second-line treatment. The mean daily dose from the PACE study was used as the likely equivalent dose of ponatinib. However, though the dose estimates for dasatinib and nilotinib may be reasonable, they may not be reasonable in the context described in the submission. The equi-effective dose of ponatinib may not be reasonable as it is not based on any comparative data.

The ESC considered that based on the evidence available, the calculation of the equi-effective dose may be reasonable. The ESC noted that nilotinib and dasatinib also have a first line listing, which usually has better outcomes than later line treatment. Therefore, it may not be reasonable to extrapolate the price for these agents, generated from their benefit in earlier lines of treatment, to ponatinib in later lines of treatment, when benefit is likely to be smaller.

- 6.32 The PBAC recalled that the estimated equi-effective doses of dasatinib and nilotinib for second line use after imatinib were considered to be dasatinib 101 - 103mg and nilotinib 797mg, based on the median daily dose of the drugs in the key clinical trials [see Nilotinib listing in 2008]. The utilisation data for these two drugs since listing on PBS are reasonably consistent with the trial-based data, and so the latter can be considered justified for use in a pragmatic estimation of equi-effectiveness among the three TKIs. The mean daily dose on the PACE trial (30.2mg) is the appropriate input for ponatinib to this estimate. Therefore, the PBAC considered the equi-effective dose are Ponatinib 30.2 mg daily = Dasatinib 102 mg daily = Nilotinib 797mg daily.
- 6.33 The cost minimisation analysis was presented in the following table. The submission used drug costs only as they assumed the cardiovascular issues associated with ponatinib are a class effect. This assumption may not be valid. As the incidence of vascular occlusive events are higher in the ponatinib studies compared to dasatinib and nilotinib, it may have been appropriate to include the costs of these adverse events in the analysis.

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

	DPMQ	Price per mg	% use	Weighted price per mg	Average dose per day (mg)	Weighted price per month	DAS/NIL use 2 nd /3 rd line (%)	Weighted price per month
Dasatinib tablets; strength (pack size)								
20 mg (60)	\$3,095.79	\$2.58	4%	\$1.65	111.0	\$5,491.10	53.4%	\$5,641.71
50 mg (60)	\$5,004.14	\$1.67	25%					
70 mg (60)	\$6,160.53	\$1.47	28%					
100 mg (30)	\$5,004.14	\$1.67	43%					
Nilotinib capsules; strength (pack size)								
200 mg (120)	\$5,872.48	\$0.24	100%	\$0.24	792.1	\$5,814.49	46.6%	
Ponatinib tablets; strength (pack size)								
15 mg (60)					30.2	-		
45 mg (30)								

Source: Excel workbook: Ponatinib – Section D.

DAS = dasatinib; DPMQ = dispensed price, maximum quantity; NIL = nilotinib

- 6.34 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 is almost \$800 per month more than for the 30 mg daily dose, yet the higher dose is associated with more adverse events and, according to the submission, no additional efficacy.
- 6.35 The PBAC considered that costs for the major vascular occlusive events must be accounted for in any costing exercise, and that the DPMQ should align with the weighted dispensed costs per month.

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

Drug cost/patient/month: [REDACTED]

- 6.36 The drug cost per patient per month is [REDACTED], compared to \$5,641.71 for dasatinib and nilotinib. This value is based on the assumption that 70% of the patients will receive the 15 mg (60 tablets) strength and the remainder the higher 45 mg (30 tablets) strength, resulting in an average daily dose of 34.5 mg, compared to the proposed equi-effective dose of 30.2 mg per day. The submission did not provide information on the duration of treatment, but the treatment is likely to be ongoing.
- 6.37 The PBAC considered that a significant reduction in price would be required to account for the significant costs associated with care of patients with vascular occlusive events.

Estimated PBS usage & financial implications

- 6.38 This submission was not considered by DUSC.
- 6.39 The submission used a market share approach to estimate the utilisation and cost of ponatinib over a five year time horizon. This was presented in the following table.

Estimated use and financial implications of ponatinib listing on the PBS

	Year 1 2015	Year 2 2016	Year 3 2017	Year 4 2018	Year 5 2019
Estimated extent of use					
Number treated					
2 nd line (T315I mutation) ^a	█	█	█	█	█
3 rd line ^b					
4 th line ^c					
Total	█	█	█	█	█
Market share					
2 nd line (T315I mutation)	█	█	█	█	█
3 rd line ^b					
4 th line					
Scripts ^d – 15 mg (60) 45 mg (30)	█	█	█	█	█
Estimated net cost to PBS/RPBS/MBS					
Net cost to PBS/RPBS	█	█	█	█	█
Net saving to the PBS/RPBS ^e	█	█	█	█	█
Estimated total net cost					
Net cost to PBS/RPBS/MBS	█	█	█	█	█
Sensitivity analysis					
T315I mutation is subset of patients who fail treatment and 12 months of treatment per patient per year	█	█	█	█	█

^a Submission assumes a ponatinib uptake rate of █ for patients with the T315I mutation

^b Submission assumes a ponatinib uptake rate of █ for patients with the T315I mutation and █ for those without the mutation but requiring a 3rd line treatment

^c Submission assumes a ponatinib uptake rate of █ for patients with the T315I mutation and for those patients without the mutation but requiring a 4th line treatment

^d Assuming one script per year for patients receiving ponatinib 15 mg/day or 45 mg/day dose and two scripts per year for patients receiving 30 mg/day, as estimated by the submission.

^e The submission applies the number of patients receiving 4th line treatment, rather than 3rd line treatment, uses an incorrect weighting and uses the incorrect cost of nilotinib for Year 2 to 5. These are the corrected values.

Source: Table E(cma).2..2 – E(cma).4.1 of the commentary

MBS = Medical Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

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.

6.40 The accuracy of the financial estimates is uncertain. The main factors contributing to this uncertainty are:

- The submission underestimated the number of patients treated with TKIs (imatinib, dasatinib and nilotinib) as compared to the February 2014 DUSC review of TKI use (2013 TKI patients in the submission = 1,937 vs. approximately 2,500 in the DUSC review); The ESC noted that in the PSCR (p3), the sponsor accepted that the estimates in the DUSC review are more likely to be more accurate.
- The submission overestimated the number of patients with the T315I mutation. For example, to estimate the number of patients on second-line therapy with the T315I mutation, the proportion of patients with the mutation is multiplied by all patients on first-line treatment. The correct method is to multiply this proportion by all patients failing first-line treatment.

- The uptake of ponatinib was overestimated as the submission assumed 100% of patients with T315I mutation will receive ponatinib. This assumption did not consider that the serious adverse effects of ponatinib and the availability of allogeneic stem cell therapy will reduce the uptake of ponatinib.
- The lack of consideration given to the cost of adverse effects due to ponatinib (underestimation). The ESC noted costs not considered in the submission (such as treatment of additional vascular occlusive events and testing for T315I mutation) have an increased but unknown financial effect.
- The submission assumed that ponatinib treated patients on 15 mg per day will receive two months' supply and those on 30 mg or 45 mg per day will receive one month supply per year. For dasatinib and nilotinib, the submission assumed that patients will receive one month supply per year. This is an underestimate as treatment is expected to continue for as long as a patient continues to receive benefits, until disease progression or development of intolerance. The PSCR (p4) acknowledged the error in the calculation of the number of scripts per patient.
- The ESC noted that the savings resulted in change of use dasatinib and nilotinib are unclear as patients are likely to trial all agents, especially if they do not have the T315I mutation.

6.41 The PBAC considered that the financial estimates are inaccurate and required significant revision to reflect:

- i) DUSC's estimates of TKI use by line of therapy and correct calculation of number of patients moving from first to second and subsequent lines per annum;
- (ii) that only 15% of patients failing first line TKI therapy will have T315I;
- (iii) that although uptake in T315I mutation CML will be >90%, it will not be 100% given the risks in patients with pre-existing cardiovascular disease and the availability of allogeneic SCT;
- (iv) 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;
- (v) minimal substitution for nilotinib or dasatinib.

7 PBAC Outcome

7.1 The PBAC deferred the submission to request 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 costs associated with care of patients with vascular occlusive events induced by ponatinib.

7.2 The PBAC considered that restrictions that aligned ponatinib use with clinical scenarios where its risk:benefit ratios were most favourable were more appropriate than those originally proposed by the sponsor. The PBAC recommended the following restrictions: (i) Patients with CML who have failed [standard definition as per dasatinib and nilotinib] 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 [standard definition as above]; or where one of nilotinib or dasatinib has failed and who are intolerant of the other drug; (iii) Patients with relapsed or refractory [standard definition] BCR-ABL positive acute lymphoblastic leukaemia and whose ALL has the T315I mutation.

- 7.3 The PBAC considered the clinical place of ponatinib will be determined by (1) presence or absence of T315I mutation in patients who had failed to respond to current TKI therapy or who had progressed during current TKI therapy after achieving an initial response; (2) the response to, and tolerability of, current TKIs in patients who are beyond first line therapy; and (3) co-morbid conditions given the differing toxicity profiles of the TKIs. The PBAC noted the considered restrictions have reflected these determinants.
- 7.4 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.
- 7.5 Based on the comparative data presented in the submission and recalling data reviewed in previous applications for imatinib, dasatinib and nilotinib, 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+ve ALL with the T315I mutation and (5) probably active in non-T315I Ph+ve 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.
- 7.6 According to the FDA information and trial data (PACE study, Study 101 and EPIC trial), 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.
- 7.7 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, because of the similarities between the submission for ponatinib and the applications for dasatinib and nilotinib for patients with imatinib failure in 2007 and 2008. However, the PBAC considered that it was essential to account for the costs of excessive vascular occlusive events seen with ponatinib 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.
- 7.8 The PBAC recalled that the estimated equi-effective doses of dasatinib and nilotinib for second line use after imatinib were considered to be dasatinib 101 - 103mg and nilotinib 797mg, based on the median daily dose of the drugs in the key clinical trials [see Nilotinib listing in 2008]. The utilisation data for these two drugs since listing on PBS are reasonably consistent with the trial-based data, and so the latter can be considered justified for use in a pragmatic estimation of equi-effectiveness among the three TKIs. The mean daily dose on the PACE trial (30.2mg) is the appropriate input for ponatinib to this estimate. Therefore, the PBAC considered the equi-effective dose are Ponatinib 30.2 mg daily = Dasatinib 102 mg daily = Nilotinib 797mg daily.

- 7.9 The PBAC considered the financial estimates are inaccurate as the realistic patient numbers are likely overestimated.

Outcome:

Deferred

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

Given the urgent life saving need for an active therapy to treat patients with CML who are refractory to previous TKI therapies, Specialised Therapeutics looks forward to meeting and working with the PBAC to find a rapid and commercially feasible solution to achieve equitable access to Iclusig for all Australians.