PUBLIC SUMMARY DOCUMENT
Product: Nilotinib, capsule, 200 mg, Tasigna®
Sponsor: Novartis Pharmaceuticals Australia Pty Limited
Date of PBAC Consideration: March 2008

1. Purpose of Application

The submission sought a Section 85 Authority Required listing for the treatment of chronic phase (CP) and accelerated phase (AP) Philadelphia chromosome positive chronic myeloid leukaemia (CML) in adult patients intolerant of, or resistant to at least one prior therapy including imatinib.

2. Background

This was the first time nilotinib had been considered by the PBAC.

3. Registration Status

Nilotinib was registered by the TGA on 17 January 2008 for the treatment of adults with chronic phase and accelerated phase Philadelphia chromosome positive chronic myeloid leukaemia (CML) resistant to, or intolerant of, prior therapy including imatinib.

4. Listing Requested and PBAC's View

NOTE:

Any queries concerning the arrangements to prescribe nilotinib may be directed to Medicare Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms) is available on the Medicare Australia website at www.medicareaustralia.gov.au. Any queries concerning patients who are enrolled on the Nilotinib Compassionate Program may be directed to Medicare Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

Applications for authority to prescribe nilotinib should be forwarded to:
Medicare Australia
Prior Written Approval of Specialised Drugs
Reply Paid 9826
GPO Box 9826
HOBART TAS 7001

Authority Required

Initial treatment, as the sole PBS-subsidised therapy, of a patient with chronic myeloid leukaemia in chronic or accelerated phase bearing the Philadelphia chromosome or expressing the transcript, *BCR-ABL*, who has active leukaemia (as defined by presence on current pathology assessments of either the Philadelphia chromosome on cytogenetic or FISH analysis, or the presence of the transcript *BCR-ABL* and morphological evidence of leukaemia) and who has failed an adequate trial of imatinib or has failed dasatinib or other second-line therapy (after prior imatinib treatment).

Failure of an adequate trial of imatinib is defined as:
(i) Lack of response to initial imatinib therapy, defined as either:

- failure to achieve a haematological response after a minimum of 3 months therapy with imatinib for patients initially treated in chronic phase; *or*
- failure to achieve any cytogenetic response after a minimum of 6 months therapy with imatinib for patients initially treated in chronic phase as demonstrated on bone marrow biopsy by presence of greater than 95% Philadelphia chromosome positive cells; *or*
- 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
(ii) 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 therapy;
OR

(iii) Development of accelerated phase in a patient previously prescribed imatinib for the chronic phase of chronic myeloid leukaemia.

Accelerated phase is defined by the presence of 1 or more of the following:
(1) Percentage of blasts in the peripheral blood or bone marrow greater than or equal to 15% but less than 30%; *or*
(2) Percentage of blasts plus promyelocytes in the peripheral blood or bone marrow greater than or equal to 30%; *or*
(3) Peripheral basophils greater than or equal to 20%; *or*
(4) Progressive splenomegaly to a size greater than or equal to 10 cm below the left costal margin to be confirmed on 2 occasions at least 4 weeks apart, or a greater than or equal to 50% increase in size below the left costal margin over 4 weeks; *or*
(5) Karyotypic evolution (chromosomal abnormalities in addition to a single Philadelphia chromosome).

OR

(iv) Disease progression (defined as ≥ 50% increase in peripheral white blood cell count, blast count, basophils or platelets) during first-line imatinib therapy in patients with accelerated phase chronic myeloid leukaemia: *or*

(v) Detection of a mutation in *BCR-ABL* (L248V, G250E, Q252H/R, Y253H/F, E255K/V, H396P/R, and D276G) that infers high level imatinib resistance. (Patients with these mutations but without active leukaemia, will not be approved); *or*

(vi) Grade 3 or 4 toxicity that is imatinib related or Grade 2 adverse events related to imatinib therapy that persisted for greater than 1 month or that recurred more than three times despite optimal supportive care.

Failure of dasatinib therapy after imatinib is defined as:
(i) Lack of response to dasatinib therapy, defined as either:

• failure to achieve a haematological response after a minimum of 3 months therapy with dasatinib for patients initially treated in chronic phase; *or*
• failure to achieve any significant cytogenetic response after a minimum of 6 months therapy with dasatinib for patients initially treated in chronic phase *or*

OR

(ii) 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 therapy;

OR

(iii) Development of accelerated phase in a patient previously prescribed dasatinib for the chronic phase of chronic myeloid leukaemia.

Accelerated phase is defined by the presence of 1 or more of the following:
(1) Percentage of blasts in the peripheral blood or bone marrow greater than or equal to 15% but less than 30%; *or*
(2) Percentage of blasts plus promyelocytes in the peripheral blood or bone marrow greater than or equal to 30%; *or*
(3) Peripheral basophils greater than or equal to 20%; *or*
(4) Progressive splenomegaly to a size greater than or equal to 10 cm below the left costal margin to be confirmed on 2 occasions at least 4 weeks apart, or a greater than or equal to 50% increase in size below the left costal margin over 4 weeks; *or*
(5) Karyotypic evolution (chromosomal abnormalities in addition to a single Philadelphia chromosome).

OR

(iv) Disease progression (defined as ≥ 50% increase in peripheral white blood cell count, blast count, basophils or platelets) during dasatinib therapy in patients with accelerated phase chronic myeloid leukaemia: *or*

(vi) Grade 3 or 4 toxicity that is dasatinib related or Grade 2 adverse events related to dasatinib therapy that persisted for >1 month or that recurred more than three times despite optimal supportive care.

Applications for authorisation must be in writing and must include:
(a) a completed authority prescription form; and
(b) a completed Chronic Myeloid Leukaemia Nilotinib PBS Authority Application –Supporting Information Form,
(c) a signed patient acknowledgement

(d) a bone marrow biopsy pathology report demonstrating the patient has active chronic myeloid leukaemia, either manifest as cytogenetic evidence of the Philadelphia chromosome, or morphological evidence of chronic myeloid leukaemia plus qualitative RT-PCR evidence of *BCR-ABL* transcript. (The date of the relevant pathology report needs to be provided); and
(e) 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 or details of prolonged Grade 2, or Grade 3 or 4 imatinib or dasatinib related toxicity.

NOTE:
Nilotinib will only be subsidised for patients with chronic myeloid leukaemia who are not receiving concomitant PBS-subsidised imatinib mesylate, dasatinib or interferon alfa therapy. Patients should be commenced on a dose of nilotinib of 400 mg twice daily. Continuing therapy is dependent on patients demonstrating a major cytogenetic response to nilotinib therapy or a peripheral blood *BCR-ABL* level of less than 1% at 12 monthly intervals, irrespective of the daily nilotinib dose received.

Authority Required
Continuing treatment, as the sole PBS-subsidised therapy, of a patient who has received initial treatment with nilotinib as a pharmaceutical benefit for chronic myeloid leukaemia, and who has demonstrated either a major cytogenetic response, or less than 1% *BCR-ABL* level in the blood, to nilotinib in the preceding 12 months.
Applications for authorisation must be in writing and must include:
(1) a completed authority prescription form; and
(2) a completed Chronic Myeloid Leukaemia Nilotinib Authority Application Form for continuing treatment; and
(3) demonstration of continued response to treatment as evidenced by either:
(a) major cytogenetic response [see Note explaining definitions of response]. Where this has been supplied within the previous 12 months, only the date of the relevant pathology report need be provided; or
(b) a peripheral blood level of *BCR-ABL* of less than 1% on the international scale [see Note explaining definitions of response]. Where this has been supplied within the previous 12 months, only the date of the relevant pathology report need be provided.

NOTE:
Definitions of response.
A major cytogenetic response is defined as less than 35% Philadelphia positive bone marrow cells.
A bone marrow or 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.

Authority approval requirements.
For the purposes of assessing response to PBS-subsidised treatment with nilotinib, 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 as follows:
(i) between 10 and 12 months of the commencement of treatment with nilotinib, 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
(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.

For each authority application where eligibility for continuing PBS-subsidised treatment is to be demonstrated, a copy of the cytogenetic analysis indicating the number of Philadelphia positive [t (9;22)] cells in the bone marrow measured by standard karyotyping, or a copy of the quantitative PCR indicating the relative level of *BCR-ABL* transcript in the peripheral blood using the international scale, must be submitted as described in (i) and (ii) above. For bone marrow analyses, where the standard karyotyping conducted at the time of application is not informative, a copy of a cytogenetic analysis conducted on the bone marrow using FISH with *BCR-ABL* specific probe must be submitted with the authority application. A copy of the non-informative standard karyotype analysis must be included with the authority application. Where a patient has previously received

PBS-subsidised treatment with nilotinib, no approval will be granted for PBS-subsidised re-treatment where that patient has at any time failed to meet the criteria for continuing treatment.

See recommendations and Reasons for PBAC's view.

5. Clinical Place for the Proposed Therapy

Nilotinib will provide a second-line treatment option for patients who are resistant or intolerant to imatinib mesylate.

6. Comparator

The submission nominated the main comparator as dasatinib 70 mg twice a day and high-dose imatinib (600 to 800 mg per day) as the comparator in the imatinib resistant population, as shown below.

Disease and patient setting	Relevant comparator
Chronic Phase CML	
- Imatinib resistant	Dasatinib 70 mg bd and imatinib 800 mg/day
- Imatinib intolerant	Dasatinib 70 mg bd
- Imatinib and dasatinib resistant or intolerant	Placebo (or in reality remaining on previous ineffective therapy i.e. dasatinib)
Accelerated Phase CML	
- Imatinib resistant	Dasatinib 70 mg bd
- Imatinib intolerant	Dasatinib 70 mg bd
- Imatinib and dasatinib resistant or intolerant	Placebo (or in reality remaining on previous ineffective therapy i.e. dasatinib)

This was accepted by the PBAC as appropriate.

7. Clinical Trials

CML-CP:

The comparison of nilotinib and dasatinib was based on data from imatinib resistant patients of one single-arm open-label trial (Study 2101) with 120 days update for nilotinib and one open-label single-arm trial with dasatinib (START C) with a similar median duration and two supplementary single arms of randomised dasatinib trials (START R and the 2 x 2 Study).

The comparison of nilotinib and high-dose imatinib was based on one single-arm open-label trial with nilotinib and high-dose imatinib data collected during imatinib clinical trials and published case series of the use of high-dose imatinib.

The treatment algorithm for nilotinib included use after failure of imatinib 800 mg. In study 2101, 70% of patients enrolled were reported as imatinib resistant but as fewer than 70% of all patients had the maximal imatinib dose the actual proportion of patients in the study with imatinib resistance is unknown.

Characteristics of patients in the nilotinib and dasatinib studies are presented in the table below.

Characteristics of patients in the nilotinib and dasatinib studies

	Total Study 2101-CP Efficacy pop.	Study 2101-CP Imatinib resistant Safety Pop	Study 2101-CP Imatinib intolerant Safety Pop	START-C total[3]	START-C imatinib resistant[3]	START-C imatinib intolerant[3]	START-R[4] (dasatinib patients)	2x2 100 mg qd[5]	2x2 50 mg bd[5]	2x2 140 mg qd[5]	2x270 mg bd[5]
N	280[1]	194	85	186	127	59	101	55	52	56	52
Median age	58.0[1]	58	59	59 (24-79)	59 (24-79)	59 (24-79)	51 (24-85)	NR	NR	NR	NR
Male gender (%)	51.4[1]	56	39	46	47	44	52	NR	NR	NR	NR
Median duration of CML (months)	65.2[1]	NR	NR	64	77	26	64	55	52	56	52
Proportion of imatinib resistance	69.3[1]	NR	NR	68%	100	0	100	74	74	73	75
Prior highest imatinib dose											
> 400 mg	NR	NR	NR	NR	NR	NR	64				
< 600 mg	27.5[1]	NR	NR	48	27	93	NR	64	66	66	66
≥ 600 mg- < 800 mg	32.5[1]	72.1		52	73	7	NR	36	34	33	33
≥ 800 mg	39.6[1]										
missing	0.4[1]	NR	NR	0	0	0	NR	0	0	<1	<1
Prior therapy											
Allogenic or stem cell transplant	8[2]	NR	NR	9	10	7	7	6	8	3	4
Hydroxyurea	83[2]	NR	NR	42	50	25	96				
Cytarabine	25[2]						39	24	31	25	26
Interferon	66[2]			70	77	54	73	52	52	56	49
Baseline CHR yes	33.9[1]			NR	NR	NR	50	NR	NR	NR	NR

NR: not reported

Source: 1: 120 day Efficacy Update of Study 2101, Table 4-1 and 4-2 p25-26., post-text table 3.5-1.9B, 2. Kantarjian publication of Study 2101-CP 3. START-C, Table 1. 4. START-R, Table 1. 5.2x2 presentation at ASCO 2007

CML-AP:
The submission presented one single-arm open-label trial (Study 2101) with 120 days update for nilotinib and one single-arm open-label trial with dasatinib (START-A) and supplementary single arms of one randomised dasatinib trial (Pasquini et al 2007)

Failure of imatinib and dasatinib:
The evidence for nilotinib after imatinib and dasatinib treatment is data from a single arm open-label nilotinib study for both CML-CP and CML-AP patients (Study 2101).

The evidence available for nilotinib and dasatinib is briefly summarised in the table below.

	Nilotinib	**Dasatinib (March 2007)**
Chronic phase	A phase II, single arm, open-label study with no comparator.	A phase II, single arm, open-label study with no comparator. One randomised trial comparing dasatinib 140mg/day with imatinib 800mg/day over 12 weeks (32 weeks follow up) in imatinib resistant.
Accelerated phase	A phase II, single arm, open-label study with no comparator.	A series of phase II, single-arm, open-label studies with no common comparator.
Blast Crisis	Not TGA approved.	A series of phase II, single-arm, open-label studies with no common comparator.
Third-line	A single arm, open label study with nilotinib in CML-CP and CML-AP patients.	

It was requested that the sponsor provide the PBAC with updates on the key trial data as it becomes available.

The following table lists the published studies presented in the submission.

Trial/First author	**Protocol title/Publication title**	**Publication citation**
Nilotinib		
Chronic phase – Non-randomised studies		
Study 2101-CP Kantarjian HM	Nilotinib (formerly AMN107), a highly selective Bcr-Abl tyrosine kinase inhibitor, is effective in patients with Philadelphia chromosome-positive chronic myelogenous leukemia in chronic phase following imatinib resistance and intolerance.	*Blood 2007 110:3540-46.*
Accelerated phase – Non-randomised studies		
Study 2101-AP Le Coutre P	Nilotinib (formerly AMN107), a highly selective BCR-ABL tyrosine kinase inhibitor, is active in patients with imatinib-resistant or -intolerant accelerated phase chronic myelogenous leukemia.	*Blood 2007, epubl ahead of print.*

Dasatanib		
Chronic phase – Single arms of randomised trials		
START-R Kantarjian HP (Dasatinib arm)	Dasatinib or high-dose imatinib for chronic-phase chronic myeloid leukemia after failure of first-line imatinib: A randomized phase 2 trial.	*Blood 2007 Jun 15;109(12):1543-1550.*
Chronic phase – Non-ransomised studies		
START-C Hochhaus A	Dasatinib induces notable hematologic and cytogenetic responses in chronic phase chronic myeloid leukemia after failure of imatinib therapy.	*Blood 2007;109(6):2303-9.*
Accelerated phase – Non-randomised studies		
START-A Guilhot F	Dasatinib induces significant hematologic and cytogenetic responses in patients with imatinib-resistant or -intolerant chronic myeloid leukemia in accelerated phase.	*Blood 2007;109(10):4143-50.*
Imatinib dose escalation up to 800 mg		
Chronic phase – Single arms of randomised trials		
START-R Kantarjian HP (High dose imatinib arm)	Dasatinib or high-dose imatinib for chronic-phase chronic myeloid leukemia after failure of first-line imatinib: A randomized phase 2 trial.	*Blood 2007 Jun 15;109(12):1543-1550.*
Chronic phase – Non-randomised studies		
Kantarjian et al Cortes J	Dose escalation of imatinib mesylate can overcome resistance to standard-dose therapy in patients with chronic myelogenous leukemia. An update to these data was contained in: Dose escalation of imatinib may improve responses in patients with CML who fail standard dose-dose imatinib.	*Blood 2003 Jan 15;101(2):473-5.* *Blood 2003 Oct 1;102(7):2703*
Chronic phase – Case Reports		
Marin et al	Transient benefit only from increasing the imatinib dose in CML patients who do not achieve complete cytogenetic remissions on conventional doses.	*Blood 2003 Oct1;102(7): 2702-3.*
Sohn et al	Efficacy of dose escalation of imatinib mesylate in patients with cytogenetic or hematologic resistance.	*Leukemia and Lymphoma2007; 48(8):1659-61.*
Zonder et al	The Effect of Dose Increase of Imatinib Mesylate in Patients with Chronic or Accelerated Phase Chronic Myelogenous Leukemia with Inadequate Hematologic or Cytogenetic Response to Initial Treatment.	*Clin Cancer Res 2003 Jun 1;9(6):2092-7.*

8. Results of Trials

CML – Chronic Phase

The submission stated that the most appropriate comparison is between the 120 day update to Study 2101-CP and the publication of START-C for imatinib resistant patients, because this group is most comparable and the treatment duration was similar (8.6 and 8.3 months, respectively). The imatinib resistant patients in Study 2101-CP achieved a rate of major cytogenetic response (MCR) of 50% (95% CI 38.8-60.1%); and the similar patient group from START-C achieved a MCR rate of 39% (95% CI 30.8-48.4%). Different definitions of imatinib intolerance were used in the nilotinib and dasatinib studies preventing any comparison between studies in this patient group. The PBAC noted the values reported in the publication of Study 2101 were lower than the values reported in the Study 2101 Clinical Study Report. The submission explained this difference by stating that in the publication patients with a MCR at baseline were excluded from analysis. The dasatinib arm of the START-R study reported data from a longer median treatment duration (14 months) and the rate of MCR was 52% for imatinib resistant patients (95%CI 42.3-62.5%). The rate of MCR was not calculated for the conventional ITT populations for imatinib resistant and imatinib intolerant patients in the 180 day update report to Study 2101, however, the MCR rate in the entire patient cohort was 56% after a median of 10 months nilotinib treatment.

The results are presented in the table below.

Major cytogenetic response (MCR) in the nilotinib, dasatinib and imatinib studies in CML-Chronic Phase

Study	Median time on drug	MCR (% and 95% CI)		
		Entire cohort	Imatinib resistant	Imatinib intolerant
Nilotinib				
Study 2101-CP	8.6 months (0 – 16.5)	52 (46-58)	50 (39-60)	49 (33-65)
	reported in publication	48 (42-54)[a]	47 (36-58)	48 (41-56)
	10.4 months (0-20.5)[b]	56.3 (50.6-61.8)	NR[c]	NR[c]
Dasatinib				
START-C	8.3 months (0.03-11.0)	52 (44.7 – 59.5)	39 (30.8 – 48.4)	80 (67.2 – 89.0)
START-R (dasatinib arm)	13.7 months (0.2 – 19.3)	NA	52 (42.3- 62.5)	NA
High-dose imatinib				
Total high-dose imatinib			35.0 % (69/197)	

Notes: NR, not reported; MCR, major cytogenetic response

[a] note the results of the MCR reported in the paper differ from that reported in the Study report as the Kantarjian analysis excluded patients who already had a response at baseline, a true ITT analysis should have included these patients in the calculation of the rate of response

[b] values extracted from 180 day update report to Study 2101 for EMEA

[c] The conventional ITT values for imatinib resistant and imatinib intolerant populations was not presented in the 180 day update report to Study 2101

CML – Accelerated Phase

The rate of MCR was similar in nilotinib and dasatinib treated CML-AP patients; 30% in nilotinib treated CML-AP patients, and 31-41% in patients treated with dasatinib in the various studies. More patients treated with dasatinib achieved a complete cytogenetic response than patients treated with nilotinib for a similar amount of time (22% in START-A patients at 6 months compared to 16% in nilotinib treated patients in Study 2101-AP).

The results are presented in the table below.

Cytogenetic response rates in the nilotinib and dasatinib studies in CML-Accelerated Phase

	Study 2101-AP N=96 Nilotinib		**START-A N=107 Dasatanib**	
	120 day update	**180 day update**	**6 months**	**8months**
	n (%)	n (%)	n (%)	n (%)
Major response (complete + partial)	29 (30.2)	35 (29)	33 (31)	35 (33)
95% CI	21.3-40.4	21-39	NR	NR
Complete	15 (15.6)	19 (16)	23 (22)	26 (24)
Partial	14 (14.6)	16 (13)	10 (9)	9 (8)
Minor	12 (12.5)	16 (13)	6 (6)	6 (6)
Minimal	20 (20.8)	28 (24)	19 (18)	20 (19)
None	16 (16.7)	19 (16)	37 (35)	33 (31)
Undetermined	NR	NR	12 (11)	13 (12)

NR: not reported

The submission stated that patients who have failed both imatinib and dasatinib treatment are still able to show a response with nilotinib treatment.The PBAC noted that weak evidence was presented for third-line treatment with nilotinib, after failure of both imatinib and dasatinib.

With regard to adverse events (AEs), in CML-CP patients, the submission stated that almost every adverse event noted occurred at a greater frequency in dasatinib treated patients than patients receiving nilotinib.

Results are presented in the table below.

Adverse events suspected to be related to nilotinib and dasatinib at 8 months

	Study 2101-CP (n = 318) Nilotinib		**START-C (n = 186) Dasatinib**	
	All grades	Grade 3-4 (%)	All Grades† (%)	Grade 3-4† (%)
Headache	18	2	34	1
Diarrhoea	10	2	30	2
Fatigue	20	1	28	1
Dyspnoea	4	1	27	3
Rash	28	2	22	0.5
Pruritus	24	1	NR	NR
Asthenia	6	0	20	2

Nausea	22	1	19	1
Pleural Effusion	1	0	19	3
Peripheral oedema	5	0	18	0
Constipation	11	0	NR	NR
Vomiting	10	1	NR	NR
Pancreatitis	1	0	NR	NR
Cytopenias				
Leukocytopenia	3	2	NR	25
Neutropenia	14	13	NR	49
Febrile neutropenia	1	1	NR	NR
Thrombocytopenia	26	19	NR	47
Anaemia	12	4	NR	22
Serum Chemistry				
Elevated bilirubin	6	2	14	0
Elevated ALAT	9	2	52	2
Elevated ASAT	4	0	60	2
Elevated lipase	12	7	NR	NR

† investigator judged as related to study treatment
NR – not reported

In CML-AP patients, the submission stated that the rates of adverse events reported with dasatinib were consistently higher than those reported for nilotinib with the exception of rash and pruritus which occurred at a higher frequency in nilotinib treated patients.

There was limited safety data on high-dose imatinib. From START-R the most commonly reported AEs were superficial oedema (42%), nausea (33%), diarrhoea (29%) and fatigue (22%). These events were similar to what was reported in patients on the standard imatinib dose of 400 mg/day. The data from the IRIS dose escalation report that GI bleeding was more prevalent when the dose of imatinib was escalated (3% compared to 1% on the standard dose); otherwise the safety of higher doses of imatinib was similar to that seen with imatinib 400 mg/day.

The submission stated that the pattern of adverse events in the sub-group of patients who have failed both imatinib and dasatinib therapy appears generally similar to the adverse events reported in CML-CP and CML-AP patients in Study 2101 who have only failed imatinib.

Overall, the PBAC considered nilotinib to have a different safety profile to both high dose imatinib and dasatinib.

9. Clinical Claim

Chronic phase

Versus dasatinib

The submission described nilotinib as non-inferior in terms of comparative effectiveness and superior in terms of comparative safety over dasatinib.

Versus high-dose imatinib

The submission described nilotinib as superior in terms of comparative effectiveness and non-inferior in terms of comparative safety over imatinib.

With respect to effectiveness in the chronic phase, the PBAC considered that both nilotinib and dasatinib are highly active against truly imatinib-resistant disease with approximately

30% complete cytogenetic response rate at 6-8 months. However, as the trials forming the basis of the comparison included a mix of imatinib resistant and imatinib intolerant patients and used different definitions of intolerance it was considered that current data do not indicate whether one is superior to the other.

Accelerated phase

The submission described nilotinib as non-inferior in terms of comparative effectiveness and superior in terms of comparative safety over dasatinib.

The PBAC considered that while nilotinib is active against imatinib failure, the data provided are insufficient to conclude that it is non-inferior to dasatinib in this setting. It was considered that the significant uncertainty around this issue would be best addressed with a randomised study, but might be informed by longer follow-up of Study 2101-AP.

After imatinib and dasatinib failure

The submission described that some patients treated with nilotinib who have failed imatinib and dasatinib treatment are able to achieve a response and the safety profile in this patient population is similar to the other nilotinib patient groups.

The PBAC considered that insufficient data had been provided to determine what the true rate of response was to nilotinib as a third-line agent.

See also Recommendations and Reasons.

10. Economic Analysis

The submission presented a cost analysis. The equi-effective doses were estimated as nilotinib 697.5 mg per day over 8.3 months (based on trial data) and dasatinib 128.5 mg per day (based on market data). For pricing the submission used the recommended doses for nilotinib and dasatinib as the equi-effective dose, i.e. nilotinib 800 mg to dasatinib 140 mg.

The variables used in the economic evaluation are the costs of drug treatment and the cost of treating adverse events.

The PBAC did not accept the submission's claim that the equi-effective doses are nilotinib 687.3 mg per day and dasatinib 128.5mg per day.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated to be less than 10,000 in Year 5. The PBAC considered this to be an underestimate. The estimated net cost per year of nilotinib on the PBS was less than $10 million. This was also considered to be an underestimate by the PBAC.

12. Recommendation and Reasons

The PBAC recommended the listing of nilotinib on the PBS for the treatment of chronic and accelerated phase Philadelphia positive chronic myeloid leukaemia in patients who have failed imatinib and meet certain criteria on a cost-minimisation basis compared with dasatinib.

The PBAC considered that the average doses from the nilotinib trial (687.3 mg) and from the pivotal randomised dasatinib trial in imatinib resistant patients CA180-017 (START-R) would be more appropriate for determining the equi-effective doses at the time of listing. However, the PBAC noted that the average daily dose of dasatinib from this trial was not available as the START-R study report provides only the median dose (111 mg) and that this is not known to the nilotinib sponsor (the publication of the START-R trial cites a median dose of 103 mg/day). Thus, the equi-effective doses should be nilotinib 792.1mg (the median dose from trial 2101 – 180 day update) and dasatinib 111 mg.

With respect to effectiveness in the chronic phase, the PBAC considered that both nilotinib and dasatinib are highly active against truly imatinib-resistant disease with approximately 30% complete cytogenetic response rate at 6-8 months. However, as the trials forming the basis of the comparison included a mix of imatinib resistant and imatinib intolerant patients and used different definitions of intolerance it was considered that current data do not indicate whether one is superior to the other.

With respect to the accelerated phase, the PBAC considered that while nilotinib is active against imatinib failure, the data provided are insufficient to conclude that it is non-inferior to dasatinib in this setting. It was considered that the significant uncertainty around this issue would be best addressed with a randomised study, but might be informed by longer follow up of Study 2101-AP.

The PBAC also noted that whilst nilotinib has a different safety profile to both high dose imatinib and dasatinib, there is considerable uncertainty around the claims that nilotinib has significant activity after failure of both imatinib and dasatinib and that nilotinib has a superior safety profile to dasatinib.

Furthermore, the Committee, while recognising the clinical need of patients who have failed both imatinib and dasatinib, considered that there are insufficient data to provide any certainty about the clinical benefit of either nilotinib (or dasatinib) as third-line tyrosine kinase inhibitor (TKI) therapy and that nilotinib should be restricted to use in patients who are resistant to imatinib only i.e. second-line use after imatinib failure and not after imatinib and dasatinib failure as requested in the submission. The PBAC recommended the restriction include a NOTE stating that nilotinib is not PBS-listed for third-line therapy. The PBAC noted that this recommendation also means that dasatinib-intolerant but sensitive patients would not have access to nilotinib via the PBS. However, the PBAC considered it likely that such patients would continue to be picked up by the Novartis compassionate access program.

The PBAC deferred a final decision for nilotinib for the treatment of chronic and accelerated phase Philadelphia chromosome positive chronic myeloid leukaemia (CML) for patients who are intolerant of at least one prior therapy including imatinib. The PBAC considered that a Stakeholder meeting was necessary prior to further consideration of this matter to discuss issues such as the intolerance to imatinib rules in the current restrictions; the use of bone marrow biopsy as the marker for loss of major cytogenetic response and imatinib resistance, rather than rising BCR-ABL transcript levels in blood; and to discuss ground rules for assessment of tyrosine kinase inhibitors in third-line management of CML.

Recommendation
NILOTINIB, capsule, 200 mg

Restriction: NILOTINIB

NOTE:
Any queries concerning the arrangements to prescribe nilotinib may be directed to Medicare Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms) is available on the Medicare Australia website at www.medicareaustralia.gov.au.

Any queries concerning patients who are enrolled on the Nilotinib Compassionate Program may be directed to Medicare Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

Applications for authority to prescribe nilotinib should be forwarded to:
Medicare Australia
Prior Written Approval of Specialised Drugs
Reply Paid 9826
GPO Box 9826
HOBART TAS 7001

Authority Required
Initial treatment, as the sole PBS-subsidised therapy, of a patient with chronic myeloid leukaemia in chronic or accelerated phase bearing the Philadelphia chromosome or expressing the transcript, *BCR-ABL,* who has active leukaemia (as defined by presence on current pathology assessments of either the Philadelphia chromosome on cytogenetic or FISH analysis, or the presence of the transcript *BCR-ABL* and morphological evidence of leukaemia in sites other than peripheral blood) and who has failed an adequate trial of imatinib.

Failure of an adequate trial of imatinib is defined as:
(i) Lack of response to initial imatinib therapy, defined as either:
- failure to achieve a haematological response after a minimum of 3 months therapy with imatinib for patients initially treated in chronic phase; *or*
- failure to achieve any cytogenetic response after a minimum of 6 months therapy with imatinib for patients initially treated in chronic phase as demonstrated on bone marrow biopsy by presence of greater than 95% Philadelphia chromosome positive cells; *or*
- 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*

(ii) 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 therapy (Note: a *BCR/ABL* qPCR >1% alone is not evidence of loss of response); *or*

(iii) Development of accelerated phase in a patient previously prescribed imatinib for the chronic phase of chronic myeloid leukaemia.

Accelerated phase is defined by the presence of 1 or more of the following:
(1) Percentage of blasts in the peripheral blood or bone marrow greater than or equal to 15% but less than 30%; or
(2) Percentage of blasts plus promyelocytes in the peripheral blood or bone marrow greater than or equal to 30%, provided that blast count is less than 30%; or
(3) Peripheral basophils greater than or equal to 20%; or
(4) Progressive splenomegaly to a size greater than or equal to 10 cm below the left costal margin to be confirmed on 2 occasions at least 4 weeks apart, or a greater than or equal to 50% increase in size below the left costal margin over 4 weeks; or
(5) Karyotypic evolution (chromosomal abnormalities in addition to a single Philadelphia chromosome); *or*

(iv) Disease progression (defined as ≥ 50% increase in peripheral white blood cell count, blast count, basophils or platelets) during first-line imatinib therapy in patients with accelerated phase chronic myeloid leukaemia, provided that blast crisis has been excluded on bone marrow biopsy: *or*

(v) Detection of a mutation in *BCR-ABL* (L248V, G250E, Q252H/R, Y253H/F, E255K/V, H396P/R, and D276G) that infers high level imatinib resistance. (Patients with these mutations but without active leukaemia, will not be approved); *or*

(vi) Grade 3 or 4 non-haematological toxicity that is imatinib related

Applications for authorisation must be in writing and must include:
(a) a completed authority prescription form; and
(b) a completed Chronic Myeloid Leukaemia Nilotinib PBS Authority Application –Supporting Information Form,
(c) a signed patient acknowledgement
(d) a bone marrow biopsy pathology report demonstrating the patient has active chronic myeloid leukaemia, either manifest as cytogenetic evidence of the Philadelphia chromosome, or morphological evidence of chronic myeloid leukaemia in bone marrow plus qualitative RT-PCR evidence of *BCR-ABL* transcript. (The date of the relevant pathology report needs to be provided); and

(e) details of Grade 3 or 4 non-haematological imatinib related toxicity.

NOTE:
Nilotinib will only be subsidised for patients with chronic myeloid leukaemia who are not receiving concomitant PBS-subsidised imatinib mesylate, dasatinib or interferon alfa therapy. Patients should be commenced on a dose of nilotinib of 400 mg twice daily. Continuing therapy is dependent on patients demonstrating a major cytogenetic response to nilotinib therapy or a peripheral blood *BCR-ABL* level of less than 1% at 12 monthly intervals, irrespective of the daily nilotinib dose received.

Nilotinib is not PBS-subsidised for patients with CML that is resistant to dasatinib.
Nilotinib is not TGA-registered and not PBS-subsidised for patients with CML in blast crisis.
Requests for doses of greater than nilotinib 400mg twice daily will not be approved.

Authority Required
Continuing treatment, as the sole PBS-subsidised therapy, of a patient who has received initial treatment with nilotinib as a pharmaceutical benefit for chronic myeloid leukaemia, and who has demonstrated either a major cytogenetic response, or less than 1% *BCR-ABL* level in the blood, to nilotinib in the preceding 12 months.
Applications for authorisation must be in writing and must include:
(1) a completed authority prescription form; and
(2) a completed Chronic Myeloid Leukaemia Nilotinib Authority Application Form for continuing treatment; and
(3) demonstration of continued response to treatment as evidenced by either:
(a) major cytogenetic response [see Note explaining definitions of response]. Where this has been supplied within the previous 12 months, only the date of the relevant pathology report need be provided; or
(b) a peripheral blood level of *BCR-ABL* of less than 1% on the international scale [see Note explaining definitions of response]. Where this has been supplied within the previous 12 months, only the date of the relevant pathology report need be provided.

NOTE:
Definitions of response.
A major cytogenetic response is defined as less than 35% Philadelphia positive bone marrow cells.
A bone marrow or 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.

Authority approval requirements.
For the purposes of assessing response to PBS-subsidised treatment with nilotinib, 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 as follows:
(i) between 10 and 12 months of the commencement of treatment with nilotinib, 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
(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.

For each authority application where eligibility for continuing PBS-subsidised treatment is to be demonstrated, a copy of the cytogenetic analysis indicating the number of Philadelphia positive [t (9;22)] cells in the bone marrow measured by standard karyotyping, or a copy of the quantitative PCR indicating the relative level of *BCR-ABL* transcript in the peripheral blood using the international scale, must be submitted as described in (i) and (ii) above. For bone marrow analyses, where the standard karyotyping conducted at the time of application is not informative, a copy of a cytogenetic analysis conducted on the bone marrow using FISH with *BCR-ABL* specific probe must be submitted with the authority application. A copy of the non-informative standard karyotype analysis must be included with the authority application. Where a patient has previously received PBS-subsidised treatment with nilotinib, no approval will be granted for PBS-subsidised re-treatment where that patient has at any time failed to meet the criteria for continuing treatment.

Maximum quantity: 112
Repeats: 5

13. 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.

14. Sponsor's Comment

Novartis Pharmaceuticals Australia thank the PBAC for recommending the use of nilotinib in patients who are intolerant of, or resistant to imatinib. We look forward to working with the PBAC and other Stakeholders to further streamline the listing of the Tyrosine Kinase Inhibitors and to permit patients who have failed both imatinib and dasatinib access to nilotinib on the PBS.