PUBLIC SUMMARY DOCUMENT
Product: Nilotinib, capsule, 150 mg, Tasigna®
Sponsor: Novartis Pharmaceuticals Australia Pty Ltd
Date of PBAC Consideration: July 2011

1. Purpose of Application

The submission requested listing of a new strength of nilotinib as an Authority Required benefit for the treatment of patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukaemia (CML) in chronic phase (Ph+ CML-CP).

2. Background

The PBAC had not previously considered an application for first line treatment of CML with nilotinib, nor had this strength of nilotinib been previously considered by the PBAC.

At its March 2008 meeting, the PBAC recommended the listing of nilotinib 200 mg capsules 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 deferred a final decision for nilotinib as a third line treatment. 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.

Following the stakeholder meeting held in May 2008, a submission was lodged to the July 2008 PBAC meeting from the Haematology Society of Australia and New Zealand (HSANZ) requesting changes to the current restriction for the use of nilotinib in CML. The PBAC made recommendations for changes to the restrictions for tyrosine kinase inhibitors which were made effective 1 August 2008.

3. Registration Status

Nilotinib 150 mg capsules were TGA registered on 5 September 2011 for the treatment of adults with newly diagnosed Philadelphia chromosome positive chronic myeloid leukaemia in the chronic phase' at the dose of 300 mg twice daily.

Nilotinib 200 mg capsules are TGA registered 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

The submission based the requested restriction on the current imatinib restriction. An abbreviated version of the requested restriction is below.

<u>Authority Required</u>

Initial treatment of patients in the chronic phase of chronic myeloid leukaemia expressing the Philadelphia chromosome or the transcript, bcr-abl tyrosine kinase, and who have a primary diagnosis of chronic myeloid leukaemia.

Authority Required
Continuing treatment of patients who have received initial treatment with nilotinib as a pharmaceutical benefit for the chronic phase of chronic myeloid leukaemia and who have demonstrated either a major cytogenetic response or less than 1% bcr-abl level in the blood in the preceding 12 months.

The PBAC noted that the availability of nilotinib as first-line therapy for CML would change the current treatment algorithm. The PBAC considered that the PBS listings for TKIs in the second-line setting would need reviewing due to the change in the treatment algorithm. The PBAC noted that further discussion will be needed with the sponsor and stakeholders before finalisation of the restrictions for first and second-line treatment settings.

5. Clinical Place for the Proposed Therapy

The submission proposed that the place in therapy of nilotinib is to provide an alternative first line therapy to imatinib as treatment for newly diagnosed Ph+ CML-CP. The submission claimed that, although nilotinib and imatinib are specific tyrosine kinase inhibitors, they exhibit unique pharmacological profiles and response patterns relative to different patient characteristics and co-morbidities.

The PBAC considered that it was unlikely that imatinib would be used after failure of nilotinib as there is little evidence for this use. The most likely scenario after failure of nilotinib, after dose escalation to 400 mg twice daily, is second-line dasatinib. In future, it will be critical to distinguish between the need to change TKI because of intolerance and because of inadequate response. Second-line therapy after nilotinib should refer to the situation where there has been failure of response and should not include failure due to toxicity. Changes between TKIs should be possible in first–line therapy where there is intolerance to the first initiated TKI.

6. Comparator

The main comparator was imatinib 400 mg once daily (QD), and a supportive comparator (for efficacy only) was dasatinib 100 mg QD. Nominating imatinib at a dose of 400 mg as the main comparator was considered appropriate by the PBAC.

7. Clinical Trials

The submission presented one randomised trial comparing nilotinib 300 mg twice daily (BD) with nilotinib 400 mg BD and imatinib (400 mg QD) in adult patients newly diagnosed with CML in the chronic phase (ENESTnd trial). In addition, for the supportive comparator (dasatinib) the submission included one trial comparing imatinib 400 mg QD with dasatinib 100 mg QD (DASISION trial), and presented an indirect comparison of nilotinib 300 mg BD with dasatinib 100 mg QD using imatinib 400 mg QD as the common reference.

The published trials presented in the submission are shown in the table below.

Trial ID / First author	Protocol title / Publication title	Publication citation
Direct randomised trial		
ENESTnd	A phase III multi-center, open-label, randomised study of imatinib versus nilotinib in adult patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukaemia in chronic phase (CML-CP) Clinical efficacy update 23 March 2010 (with 4 months additional follow-up, using data cut-up 2 January 2010) Clinical efficacy update 21 December 2010 (24 month data using data cut-off 20 August 2010)	
Saglio et al.	Nilotinib versus Imatinib for Newly Diagnosed Chronic Myeloid Leukaemia.	*NEJM* 2010, 362 (24):2251-2259
Trial used for indirect comparison: Dasatinib		
DASISION	5-year randomised, open label trial comparing dasatinib (100mg QD) and imatinib (400mg QD)	
Kantarjian et al.	Dasatinib versus imatinib in newly diagnosed chronic-phase myeloid leukaemia.	*NEJM* 2010, 362(24):2260-2270

8. Results of Trials

The primary outcome in ENESTnd was major molecular response (MMR), with the key secondary outcomes being complete cytogenetic response (CCyR), overall survival (OS), event free survival (EFS), progression-free survival (PFS) and safety outcomes. EFS included progression to other disease phases and loss of response compared to PFS which included only progression to other disease phases. The primary outcome for the DASISION trial was confirmed CCyR (cCCyR), with the key secondary outcomes time to CCyR, MMR, OS, EFS and safety outcomes.

Clinical Efficacy

Nilotinib 300 mg BD vs. imatinib 400 mg QD

The table below provides the results for best major cytogenetic response (MCyR), confirmed MCyR, best CCyR and MMR at 12 and 24 months from the ENESTnd trial.

Results of CCyR and MMR at 12 and 24 months from ENESTnd

	Nilotinib 300 mg BD n (%)	Nilotinib 400 mg BD n (%)	Imatinib 400 mg QD n (%)	RD (95% CI) Nilotinib 300 mg BD vs. Imatinib 400 mg
N	**282**	**281**	**283**	
Primary outcome				
MMR – 12 mth	125 (44.3%)[a]	120 (42.7%)	63 (22.3%)	**22.1% (14.5%, 29.6%)**
MMR – 24 mth	174 (61.7%)	166 (59.1%)	106 (37.5%)	**24.2% (16.2%, 32.2%)**
Key Secondary outcome				
CCyR[b] – 12 mth	226 (80.1%)	219 (77.9%)	184 (65%)	**15.1% (7.9%, 22.4%)**
CCyR[b] – 24 mth	245 (86.9%)	238 (84.7%)	218 (77%	**9.8% (3.6%, 16.1%)**
MCyR[b] – 12 mth	238 (84.4%)	227 (80.8%)	219 (77.4%)	**7.0% (0.6%, 13.5%)**
cMCyR–12 mth	195 (69.1%)	193 (68.7%)	183 (64.7%)	4.5% (-3.3%, 12.2%)
MCyR[b] – 24 mth	241 (85.5%)	231 (82.2%)	222 (78.4%)	**7.0% (0.7%, 13.3%)**

MMR = major molecular response; CCyR = cytogenetic response; MCyR = major cytogenetic response; cMCyR = confirmed major cytogenetic response; CI = confidence interval; n.r. = not reported; BD = twice daily; QD = once daily; **Bold** = statistically significant

[a] = Patients without assessment are considered non-responders unless both 9 and 15 mth assessments indicate response. One nilotinib patient was imputed as a response with missing PCR assessment at 12 mths.

[b] = best cytogenetic response and includes patients who achieved a cytogenetic response at or before 12 month time point

The results presented within the submission were based on 12 month and 24 month time points, whereas the proposed PBS restrictions were based on a time point of 18 months.

The PBAC agreed that the results from the direct comparison of nilotinib 300 mg twice daily (BD) versus imatinib 400 mg daily (QD) (the ENESTnd trial) indicated that patients treated with nilotinib 300 mg BD were statistically significantly more likely to achieve a MMR than patients receiving imatinib 400 mg QD (12 month difference 22.1% (95% CI: 14.5%, 29.6%) and 24 month difference 24.2% (95% CI: 16.2%, 32.2%) and numerically more likely to achieve a MMR compared to nilotinib 400 mg BD. The difference in achieving a CCyR diminished over time (12 month difference 15.1% (95% CI: 7.9%, 22.4%) compared to 24 month difference 9.8%, (95% CI: 3.6%, 16.1%)). The respective 12 and 24 month results for MCyR (CCyR plus partial cytogenetic response) for nilotinib 300 mg BD was 84.4% and 85.5% compared to 77.4% and 78.4% for imatinib 400 mg QD. The 12 month result for the confirmed MCyR (MCyR confirmed by second subsequent test) was 69.1% for nilotinib 300 mg BD and 64.7% for imatinib 400 mg QD (95% CI: 0.6%, 13.5%). The difference in best MCyR was statistically significant at both 12 and 24 months, however, the cMCyR result at 12 months was not statistically significant (RD 4.5%; 95% CI: -3.3%, 12.2%).

Indirect comparison nilotinib 300 mg BD vs. dasatinib 100 mg QD

A supplementary indirect comparison of nilotinib and dasatinib was included in the submission. The PBAC noted that the primary outcome measures differed between the nilotinib (ENESTnd) trial (MMR) and the dasatinib (DASISION) trial (cCCyR).

The table below summarises the main results from the indirect comparison of nilotinib 300 mg BD vs. dasatinib 100 mg QD, using imatinib 400 mg QD as the common reference.

Summary of results of the indirect comparison of MMR and CCyR by 12 months

Trial ID	Trial of Nilotinib 300 mg BD			Trial of Dasatinib 100 mg QD			Indirect OR[c] (95% CI)
	OR[a] (95% CI)	Nilotinib n/N (%)	Imatinib n/N (%)	Imatinib n/N (%)	Dasatinib n/N (%)	OR[b] (95% CI)	
MMR by 12 months – primary outcome ENESTnd, secondary outcome DASISION							
ENESTnd	**3.28 (2.30, 4.66)**	154/282 (54.6%)	76/283 (26.9%)				–
DASISION				73/260 (28%)	118/259 (46%)	**2.18 (1.51, 3.14)**	
Indirect comparison nilotinib 300 mg BD vs. dasatinib 100 mg QD							1.51 (0.91, 2.50)
CCyR by 12 months – secondary outcome ENESTnd, primary outcome DASISION							
ENESTnd	**2.17 (1.48, 3.18)**	226/282 (80.1%)	184/283 (65%)				–
DASISION [d]				172/260 (66%)	199/259 (77%)	**1.70[f] (1.15, 2.50)**	
DASISION [e]				186/260 (72%)	216/259 (83%)	**2.00 (1.30, 3.05)**	
Indirect comparison nilotinib 300 mg BD vs. dasatinib 100 mg QD [d]							1.28 (0.74, 2.20)
Indirect comparison nilotinib 300 mg BD vs. dasatinib 100 mg QD[e]							1.09 (0.61, 1.92)

CI = confidence interval; OR = odds ratio; CCyR = complete cytogenetic response; QD = once daily; BD = twice daily; **Bold** = statistically significant.

[a] nilotinib 300 mg over imatinib

[b] dasatinib over imatinib

[c] inferred as nilotinib 300 mg over dasatinib

[d] confirmed complete cytogenetic response (cCCyR) two recorded complete cytogenetic responses confirmed at least 28 days apart.

[e] Best complete cytogenetic response (CCyR) estimated during evaluation

[f] OR within submission appears misreported, the correct OR appears to be used for indirect comparison within submission

For the indirect comparison, the PBAC noted there was no statistically significant difference for nilotinib 300 mg BD compared to dasatinib 100 mg QD (MMR OR 1.51, 95% CI: 0.91, 2.5; CCyR OR 1.28, 95% CI: 0.74, 2.2), using imatinib as the common reference.

Clinical safety

Nilotinib 300 mg BD vs. imatinib 400 mg QD

The table below presents a summary of drug related adverse effects (AEs) reported in the ENESTnd trial.

Summary of selected drug related adverse events: 12 months

ENESTnd	Nilotinib		Imatinib 400 mg QD n (%)	RR (95% CI) Nilotinib 300 vs. Imatinib
	300 mg BD n (%)	400 mg BD n (%)[d]		
N	279	277	280	
All AEs (any grade)	249 (89%)	262 (95%)	256 (91%)	0.97 (0.92, 1.03)
All AEs (Grade 3/4)	103 (37%)	120 (43%)	94 (34%)	1.10 (0.87, 1.37)
Grade 3/4 AEs				

ENESTnd	Nilotinib		Imatinib	RR (95% CI)
	300 mg BD n (%)	400 mg BD n (%)[d]	400 mg QD n (%)	Nilotinib 300 vs. Imatinib
Thrombocytopenia	28 (10%)	31 (11%)	22 (8%)	1.28 (0.75, 2.18)
Hyperbilirubinaemia	7 (3%)	9 (3%)	0	15 (0.86, 261.39)[ab]
Neutropenia	33 (12%)	23 (8%)	37 (13%)	0.90 (0.58, 1.39)
Anaemia	5 (1.8%)	7 (3%)	11 (3.9%)	0.46 (0.16, 1.30)
Lipase increase	18 (6%)	10 (4%)	7 (3%)	**2.58 (1.09, 6.08)**
Number died [c]	2 (0.7%)	1 (.4%)	0	5.02 (0.24, 104.1)[a]

AE = adverse event; RR = relative risk; BD = twice daily; QD = once daily; **Bold** = statistically significant

[a] imputing 0.5 case for both arms

[b] statistically significant using risk difference (RD)

[c] died within 28 days of treatment

[d] added during the evaluation from the clinical study report

Overall, nilotinib 300 mg BD was associated with a statistically significant increase in the incidence of grade 3/4 lipase increase and any grade hyperbilirubinaemia (using RD) compared to imatinib 400 mg QD, while imatinib 400 mg QD appeared to be associated with a numerical (but non-statistically significant) increase in AEs of any grade. There were a statistically significant higher proportion of patients with any grade adverse events for nilotinib 400 mg BD dose versus 300 mg BD, although the difference in grade 3/4 adverse events was not statistically significant.

Overall, the PBAC agreed that nilotinib has a different safety profile compared with imatinib.

Indirect comparison nilotinib 300 mg BD vs. dasatinib 100 mg QD

The submission did not present the safety outcomes from the DASISION trial.

For the indirect comparison, the PBAC considered that nilotinib and dasatinib have different safety profiles, with more pleural effusions and diarrhoea due to dasatinib and more rashes due to nilotinib.

The DASISION trial reported that dasatinib 100 mg QD is associated with statistically significantly more pleural effusion compared to imatinib 400 mg QD treatment. During evaluation an indirect comparison of the comparative safety profiles of nilotinib 300 mg BD and dasatinib 100 mg QD, using imatinib 400 mg QD as common reference, was performed. The indirect comparison indicated that nilotinib 300 mg BD was associated with statistically significantly less any grade pleural effusion and any grade diarrhoea, compared to dasatinib 100 mg QD and a statistically significant increase in the incidence of any grade rash. There was no statistically significant difference in the incidence of Grade 3/4 haematological AEs between nilotinib 300 mg BD and dasatinib 100 mg QD, using imatinib 400 mg BD as the common reference.

The submission stated that no new safety concerns for nilotinib were identified within the periodic safety update report beyond what have been labelled or included in the risk management plan.

9. Clinical Claim

Nilotinib 300 mg BD vs. Imatinib 400 mg QD

The submission described nilotinib 300 mg BD as superior in terms of comparative effectiveness (MMR) and having a similar safety profile compared with imatinib 400 mg QD for the treatment of patients with newly diagnosed Philadelphia (Ph)+ CML in the chronic phase.

The PBAC agreed that nilotinib 300 mg BD is superior in terms of comparative effectiveness for the surrogate outcome MMR with imatinib 400 mg QD, but that there is no statistically significant difference in OS. The PBAC agreed that nilotinib has a different safety profile compared with imatinib.

Indirect comparison: nilotinib 300 mg BD vs. Dasatinib 100 mg QD

The submission described nilotinib 300 mg BD as non-inferior to dasatinib 100 mg QD in terms of comparative effectiveness and made no claim as to the comparative safety profiles of nilotinib 300 mg BD compared with dasatinib 100 mg QD.

The PBAC noted that the primary outcome measures differed between the nilotinib (ENESTnd) trial (MMR) and the dasatinib (DASISION) trial (cCCyR). For the indirect comparison, the PBAC agreed that nilotinib 300 mg BD is non-inferior to dasatinib 100 mg QD in terms of comparative effectiveness. However, the PBAC considered that nilotinib and dasatinib have different safety profiles, with more pleural effusions and diarrhoea due to dasatinib and more rashes due to nilotinib.

10. Economic Analysis

While the submission claimed superior efficacy for nilotinib based on MMR results, it presented a cost-minimisation analysis. The rationale for this was that at this stage, nilotinib does not result in a significant difference in OS compared to imatinib treatment. This was considered appropriate given no statistically significant differences were demonstrated within the ENESTnd trial for confirmed MCyR at 12 months between nilotinib and imatinib for the first-line treatment of CP CML.

The equi-effective doses used in the analysis were nilotinib 553.9 mg and imatinib 423.0 mg. The PBAC noted that the equi-effective dose of imatinib was derived from the ENESTnd Trial (24 month data), where the mean dose for imatinib was 423 mg in patients who commenced at 400 mg per day and whose dose could escalate depending on response. This reflects reasonable practice in Australia in 2011, and equates to 11.51% of imatinib patients receiving 600 mg of imatinib. The PBAC considered this approach reasonable.

The cost minimisation analysis was based on the price to pharmacist using the cost of imatinib 400 mg tablets, using the in-trial estimated mean dose of imatinib. The mean dose for nilotinib was based from the mean intensity dose from the trial.

The PBAC noted that the costs of monitoring liver function tests and electrocardiogram monitoring, (which is recommended prior to commencement of treatment with nilotinib and after seven days of treatment), were not included in the cost-minimisation analysis. The PBAC considered that these costs should be included. The PBAC noted that dose escalation to nilotinib 400 mg BD was also not included in the analysis and that as this was likely to happen in clinical practice and would increase costs of treatment with nilotinib.

The submission did not include costs for the treatment of AEs. The PBAC considered that as the AE profile was different for nilotinib and imatinib, it would have been appropriate to include those costs in the cost-minimisation analysis.

11. Estimated PBS Usage and Financial Implications

The submission estimated the likely number of patients treated with nilotinib be less than 10,000 in year 5.

The submission estimated a total net cost saving to the PBS of less than $10 million in year 5. The financial implications were still to be further verified by the Department.

12. Recommendation and Reasons

The PBAC recommended listing nilotinib on the PBS as an Authority Required benefit for first-line treatment of chronic phase Philadelphia positive chronic myeloid leukaemia on a cost-minimisation basis compared with imatinib 400 mg. The PBAC considered that the equi-effective doses are nilotinib 553.9 mg and imatinib 423 mg.

The PBAC noted that the equi-effective dose of imatinib was derived from the ENESTnd Trial (24 month data), where the mean dose for imatinib was 423 mg in patients who commenced at 400 mg per day and whose dose could escalate depending on response. This reflects reasonable practice in Australia in 2011, and equates to 11.51% of imatinib patients receiving 600 mg of imatinib. The PBAC considered this approach reasonable.

The PBAC noted that the availability of nilotinib as first-line therapy for CML would change the current treatment algorithm. The PBAC considered that it was unlikely that imatinib would be used after failure of nilotinib as there is little evidence for this use. The most likely scenario after failure of nilotinib, after dose escalation to 400 mg twice daily, is second-line dasatinib. The PBAC therefore considered that the PBS listings for TKIs in the second-line setting would also need reviewing due to the change in the treatment algorithm. In future, it will be critical to distinguish between the need to change TKI because of intolerance and because of inadequate response. Second-line therapy after nilotinib should refer to the situation where there has been failure of response and should not include failure due to toxicity. Changes between TKIs should be possible in first–line therapy where there is intolerance to the first initiated TKI. The PBAC noted that further discussion will be needed with the sponsor and stakeholders before finalisation of the restrictions for first and second-line treatment settings.

The PBAC agreed that the results from the direct comparison of nilotinib 300 mg BD versus imatinib 400 mg daily (QD) (the ENESTnd trial) indicate that patients treated with nilotinib 300 mg BD were statistically significantly more likely to achieve a MMR than patients receiving imatinib 400 mg QD (12 month difference 22.1% (95% CI: 14.5%, 29.6%) and 24 month difference 24.2% (95% CI: 16.2%, 32.2%) and numerically more likely to achieve a MMR compared to nilotinib 400 mg BD.

For the indirect comparison, the DASISION trial, the PBAC noted there is no statistically significant difference for nilotinib 300 mg BD compared to dasatinib 100 mg QD (MMR OR 1.51, 95% CI: 0.91, 2.5; CCyR OR 1.28, 95% CI: 0.74, 2.2), using imatinib as the common reference. The PBAC noted that the primary outcome measures differed between the ENESTnd trial (MMR) and the DASISION trial (CCyR).

The PBAC agreed that nilotinib 300 mg BD is superior in terms of comparative effectiveness for the surrogate outcome MMR with imatinib 400 mg QD, but that there is no statistically significant difference in OS. Nilotinib has a different safety profile compared with imatinib. The PBAC noted that the costs of monitoring liver function tests and electrocardiogram monitoring, (which is recommended prior to commencement of treatment with nilotinib and after seven days of treatment), were not included in the cost-minimisation analysis. The PBAC considered that these costs should be included. The PBAC noted that dose escalation to nilotinib 400 mg BD was also not included in the analysis and that as this was likely to happen in clinical practice and would increase costs of treatment with nilotinib, it should be addressed by means of a risk share.

For the indirect comparison, the PBAC agreed that nilotinib 300 mg BD is non-inferior to dasatinib 100 mg QD in terms of comparative effectiveness. However, the PBAC considered that nilotinib and dasatinib have different safety profiles, with more pleural effusions and diarrhoea due to dasatinib and more rashes due to nilotinib.

The PBAC acknowledged and noted the consumer comments received in its consideration of nilotinib.

Nilotinib is not included on the PBS medicines for prescribing by nurse practitioners.

Recommendation:
NILOTINIB, capsule, 150 mg (as hydrochloride)

Restriction: **To be finalised**

Maximum quantity: 120
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 will work with the PBAC to finalise the restriction wording to make nilotinib available on the PBS to patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukaemia.

Novartis recommends the use of nilotinib in newly diagnosed patients with CML according the TGA approved Product Information which can be found by following the link:
http://www.novartis.com.au/healthcare_professionals.html