PUBLIC SUMMARY DOCUMENT

Product: Imatinib mesylate, tablet, 100 mg and 400 mg (base), Glivec®

Sponsor: Novartis Pharmaceuticals Australia Pty Ltd

Date of PBAC Consideration: July 2007

1. Purpose of Application

The submission sought to extend the current listing for imatinib to include the treatment of acute lymphoblastic leukaemia (ALL) expressing the Philadelphia chromosome or the transcript, bcr-abl tyrosine kinase, in newly diagnosed patients or patients with relapsed or refractory disease.

2. Background

This drug has not previously been considered by the PBAC for this indication.

3. Registration Status

Imatinib is currently registered for:

- Treatment of patients with chronic myeloid leukaemia.
- Treatment of patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours.
- Adult patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) integrated with chemotherapy
- Adult patients with relapsed or refractory Ph+ ALL as monotherapy
- Adult patients with myelodysplastic/myeloproliferative diseases associated with platelet-derived growth factor receptor gene re-arrangements, where conventional therapies have failed
- Adult patients with aggressive systemic mastocytosis, where conventional therapies have failed
- Adult patients with hypereosinophilic syndrome and/or chronic eosinophilic leukaemia Adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans.

4. Listing Requested and PBAC's View

Authority Required

Treatment in combination with chemotherapy of adult patients with newly diagnosed acute lymphoblastic leukaemia (ALL) expressing the Philadelphia chromosome or the transcript, bcr-abl tyrosine kinase.

Treatment as monotherapy of adult patients with relapsed or refractory acute lymphoblastic leukaemia (ALL) expressing the Philadelphia chromosome or the transcript, bcr-abl tyrosine kinase.

The PBAC recommended listing for newly diagnosed patients only. Following a period of initial treatment, prescriptions for further treatment should be dependent on achievement of a complete response. Imatinib should not be subsidised for use post-stem cell transplant. In patients who did not proceed to stem cell transplant, the total course of treatment should not exceed 2 years.

5. Clinical Place for the Proposed Therapy

Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukaemia (ALL) is an aggressive form of acute leukaemia with extremely poor prognosis.

Current chemotherapy regimens for Ph+ ALL produce disappointing results with median survival of less than one year in adults. Allogeneic stem cell transplantation remains the only curative option so far. However, less than 30% of patients have a matched sibling donor and patients aged 55 years or over, are generally not considered deal candidates for a transplant. Imatinib provides an additional treatment option for some of these patients.

6. Comparator

Appropriately, the submission nominated chemotherapy as the main comparator for patients with newly diagnosed Ph+ ALL and for patients with relapsed/refractory Ph+ ALL.

7. Clinical Trials

Newly diagnosed Ph+ ALL:

The submission presented two single arm studies (imatinib +chemotherapy) versus separate historical controls (chemotherapy alone):

- Lee et al (2005) – younger patients (median age 36, 35 years) who had a stem cell transplant and
- Study AFR09 – older patients (median age 66, 61 years) who did not receive a stem cell transplant.

Relapsed/refractory Ph+ ALL:

The submission presented three single arm studies – two imatinib studies (Study 109 and Study 114) vs one chemotherapy alone study (GIMEMA ALL).

The trials that had been published at the time of submission are as below:

Trial/First author	Protocol title	Publication citation
Lee S et al	The effect of first-line imatinib interim therapy on the outcome of allogeneic stem cell transplantation in adults with newly diagnosed Philadelphia-chromosome positive acute lymphoblastic leukemia.	Blood 2005; 105: 3449-57
Lee S et al	Minimal residual disease-based role of imatinib as a first-line interim therapy prior to allogeneic stem cell transplantation in Philadelphia chromosome-positive acute lymphoblastic leukemia.	Blood 2003; 102: (8): 3068-3070
Study AFR09		
Delannoy A et al	Imatinib and methylprednisolone alternated with chemotherapy improve the outcome of elderly patients with Philadelphia-positive acute lymphoblastic leukemia: results of the GRALL AFR09 study.	Leukemia 2006; 20: 1526-1532
Study 109		
Ottman OG et al	A phase 2 study of imatinib in patients with relapsed or refractory Philadelphia chromosome-positive acute lymphoid leukemias.	Blood 2002; 100: 1965-1971
Study 114 (expansion of Study 109)		
Wassmann B et al	Early prediction of response in patients with relapsed or refractory Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) treated with imatinib.	Blood 2004; 103(4): 1495-1498
GIMEMA ALL		
Camera A et al	GIMEMA ALL - Rescue 97: a salvage strategy for	Haematologica 2004; 89:

Trial/First author	Protocol title	Publication citation
	primary refractory or relapsed adult acute lymphoblastic leukemia.	145-153

8. Results of Trials

Comparative effectiveness

The results of the key studies are summarised below.

Newly diagnosed Ph+ ALL

Lee S et al (2005) with SCT	Imatinib + chemotherapy (N=29)	Chemotherapy (N=33)	p- value
After consolidation therapy • Sustained CR1 • Relapse	 22/23 (95.7%) 1/23 (4.3%)	 16/27 (59.3%) 11/27 (40.7%)	0.003
Pre-transplantation status • CR1 • CR2 • Refractory	 25/29 (86.2%) 0/29 (0%) 4/29 (13.8%)	 17/33 (51.5%) 9/33 (27.3%) 7/33 (212%)	0.004
Survival			
Disease-free survival	78.1% ± 11.6%	38.7% ± 8.8%	<0.01
Overall survival	78.1% ± 11.6%	38.7% ± 8.8%	<0.001
Study AFR09 without SCT	**(N=30)**	**(N=21)**	**p-value**
Induction therapy CR at completion (95% CI) Salvage therapy CR at completion (95% CI)	21/29, 72% (53%, 87%) Imatinib + steroids 27/29, 90% (73%, 98%)	6/21, 29% (11%, 52%) Additional chemotherapy 10/21, 48% (26%, 70%)	0.003 0.001
Survival			
1-yr overall survival (95% CI) Median overall survival	66% (49%, 83%) 23.2 months	43% (24%, 62%) 11.2 months	0.004
Median relapse-free survival	20.1 months	4.2 months	0.0003

CR1 = first complete remission; CR2 = second complete remission; SCT = stem cell transplant

Survival curves for DFS and OS

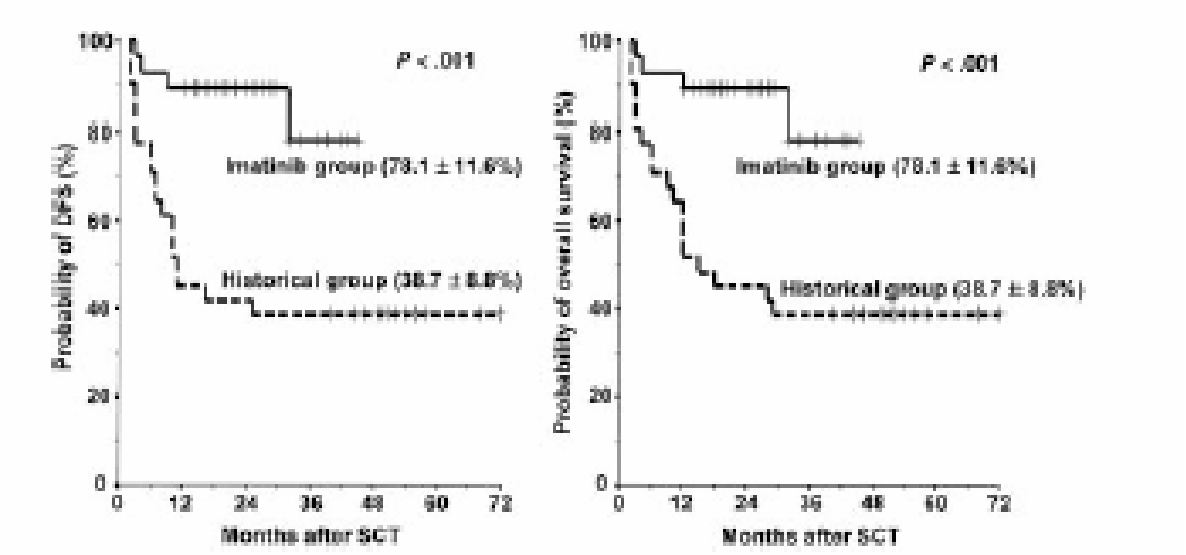

Figure 4. Probabilities of disease-free survival and overall survival in the imatinib group versus the historical group. Solid line indicates imatinib group; dotted line, historical group.

Relapsed /refractory Ph+ ALL

Outcome	Imatinib group			Chemotherapy group
	Study 109 (N=48)	Study 114 (N=353)	Wassmann et al (2004) (N=68) §	GIMEMA ALL (N=135) †
Marrow CR rate	10%	NR	29%	12/22 (54.6%)
Median OS	4.9 months	8.9 months	6.2 months	6.4 months

§ Analysis based on 14 patients from Study 109 and 54 patients from Study 114

† n=22 Ph+ ALL patients; CR complete remission; OS overall survival; NR not reported

Lee S et al (2005) reported no detrimental effects of imatinib on engraftment, graft-versus-host disease or transplant-related organ toxicity, compared to historical data but no tabulation of comparative toxicity was provided.

The PBAC noted that there seems to be little additional toxicity of imatinib in addition to the adverse events caused by chemotherapy regimens.

For PBAC's view of these results, see Recommendations and Reasons.

9. Clinical Claim

Newly diagnosed Ph+ ALL

The submission claimed that imatinib when used in combination with chemotherapy is significantly more effective than, and has similar toxicity to, chemotherapy alone. The PBAC accepted this claim.

Relapsed/refractory disease

The submission claimed that imatinib monotherapy is significantly more effective than, and has similar toxicity to, standard chemotherapy. The PBAC did not accept this claim.

See also Recommendation and Reasons.

10. Economic Analysis

The submission presented a preliminary economic evaluation. The resources included were cost of drug treatment, chemotherapy and stem cell transplants (and septicaemia in newly diagnosed patients with no stem cell transplant).

The trial-based incremental cost per extra complete responder was estimated to be in the range $45,000 - $75,000 for newly diagnosed patients who either go on to have a stem cell transplant or do not go on to have a stem cell transplant, and greater than $200,000 for relapsed/refractory patients.

The submission presented a modelled economic evaluation. The choice of the cost-effectiveness approach was considered valid. The resources included were cost of drug treatment, chemotherapy and stem cell transplants (and septicaemia in newly diagnosed patients with no stem cell transplant). A stem cell transplant rate of 30% was assumed.

The base case modelled incremental cost/extra discounted life year gained was estimated to be <$15,000 for newly diagnosed patients who go on to have a stem cell transplant; between $15,000 - $45,000 for newly diagnosed patients who do not go on to a stem cell transplant; and between $15,000 - $45,000 for relapsed/refractory patients. In the relapsed/refractory

patients, the sensitivity analysis for the incremental cost per extra complete responder was as high as $100,000 to $200,000. The incremental cost/extra discounted life year gained was as high as $100,000 in the sensitivity analysis.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The submission estimated the likely number of patients/year to be <10,000 in Year 4 at an estimated financial cost/year to the PBS (excluding co-payments) of less than $10 million.

12. Recommendation and Reasons

The PBAC recommended the listing of imatinib for the treatment of acute lymphoblastic leukaemia (ALL) expressing the Philadelphia chromosome or transcript, bcr-abl tyrosine kinase (Ph +ve) in newly diagnosed patients in combination with chemotherapy on the basis of an acceptable cost-effectiveness ratio compared to chemotherapy alone.

The PBAC considered the studies in newly diagnosed Ph +ve ALL patients who go on to have a stem cell transplant, demonstrated that imatinib in combination with chemotherapy had significant advantages in effectiveness over chemotherapy alone, and was of similar, or less toxicity. The PBAC noted that, in some patients, these benefits translated into a major survival benefit post stem cell transplant. The PBAC noted there was some uncertainty associated with the benefits in patients who did not proceed to a stem cell transplant as the active and comparator studies were not completely comparable.

The PBAC agreed the incremental costs per life-year gained in these patient groups were acceptable overall, though in the case of those patients who do not progress to a stem cell transplant, the incremental cost effectiveness ratio was noted to be high. While the economic evaluation did not model quality adjusted life years gained, the PBAC accepted that significant utility improvements would be achieved in patients who responded.

The PBAC noted that the optimum duration of treatment with imatinib in both patient groups is unknown, and that without some limitations, the use of imatinib would not remain cost-effective. The Committee took account of the data as well as opinions about current clinical practice provided by the sponsor to determine this aspect of its recommendation. The PBAC requested the Pharmaceutical Benefits Pricing Authority consider entering into a risk sharing arrangement taking account of imatinib use in this patient group.

The PBAC rejected the application for use of imatinib as monotherapy in relapsed or refractory patients who are resistant or intolerant to prior the therapy, on the basis of an unacceptably high and uncertain cost-effectiveness ratio.

The PBAC was of the view that many current patients and the great majority of all future patients with relapsed or refractory Ph+ve ALL will have received and hence failed imatinib, either alone or in combination with chemotherapy. As no data were provided in the submission to demonstrate efficacy in this clinical situation, the Committee could not support its use in patients previously treated with imatinib.

The PBAC noted the data provided related to imatinib-naïve patients, and demonstrated modest clinical efficacy, with significant uncertainty about the durability of responses.

Significant uncertainty also existed about the incremental cost effectiveness ratio because of the low quality of the clinical data, the uncertainty of durability of clinical responses and the lack of an appropriate Ph+ve control group for the chemotherapy comparator. In the face of an incremental cost effectiveness ratio potentially as high as $105,000 - $200,000, which is outside the usual range that the committee considers acceptable, the "rule of rescue" could not be considered appropriate as another treatment, dasatinib, is available for this situation.

Recommendation
IMATINIB MESYLATE, tablet, 100 mg and 400 mg (base)
To be finalised

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
The sponsor welcomes the decision by the PBAC to recommend listing of imatinib in newly diagnosed Ph+ ALL patients.

Further data will be submitted to the PBAC to support the clinical benefits of continued treatment with imatinib for more than 2 years in newly diagnosed Ph+ ALL patients without a stem cell transplant as well as for treatment in post-stem cell transplant patients.