

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 four rare diseases: dermatofibrosarcoma protuberans, hypereosinophilic syndrome, myelodysplastic/myeloproliferative diseases and aggressive systemic mastocytosis.

2. Background

This drug had not previously been considered by the PBAC for these indications.

3. Registration Status

Imatinib is currently registered for:

- Treatment of patients with chronic myeloid leukaemia (CML).
- Treatment of patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST).
- Adult patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) integrated with chemotherapy (10 May 2007)
- Adult patients with relapsed or refractory Ph+ ALL as monotherapy (10 May 2007)
- Adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements, where conventional therapies have failed (10 May 2007)
- Adult patients with aggressive systemic mastocytosis (ASM), where conventional therapies have failed (10 May 2007)
- Adult patients with hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL) (10 May 2007)
- Adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP) (10 May 2007)

4. Listing Requested and PBAC's View

Section 100 authority required (Special Authority Program)

Treatment of adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP).

Treatment of adult patients with hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL).

Treatment, where conventional therapies have failed, in patients with

- myelodysplastic syndromes/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements; or
- aggressive systemic mastocytosis (SM) without the D816V c-kit mutation or with c-kit mutational status unknown.

The PBAC considered that the restriction requested for each of the uncommon haematological malignancies did not accurately reflect the patient characteristics that predict a response to imatinib.

The PBAC noted that responsiveness to imatinib is predicted by the molecular detection of FIP1L1-PDGFR transcript in HES, 5q33 abnormalities in MDS/MPD with PDGFR gene rearrangement and the presence of the FIP1L1-PDGFR transcript in patients with SM. The PBAC was also concerned about the cost, availability and access to the molecular testing, and the number of patients who will need to be screened.

5. Clinical Place for the Proposed Therapy

Dermatofibrosarcoma protuberans (DFSP):

Dermatofibrosarcoma protuberans is a locally aggressive, highly invasive soft tissue sarcoma with ulceration, bleeding and pain at the lesion sites commonly occurring in the skin of the trunk, proximal extremities, head and neck. As this malignancy is dependent on a genetic rearrangement of the platelet-derived growth factor (PDGF) and Collagen 1A1 genes it may be sensitive to imatinib.

Hypereosinophilic syndrome (HES) / Chronic eosinophilic leukemia (CEL):

Hypereosinophilic syndrome / chronic eosinophilic leukemia is a rare haematological disorder characterised by chronic overproduction of eosinophils, tissue infiltration and organ damage. The disease is thought to have multiple genetic origins with a high frequency of PDGFR rearrangements, and therefore may be highly sensitive to imatinib. Nearly any organ system may be involved. The most common and often serious are the cardiovascular complications which are often life-threatening in patients with HES.

Myelodysplastic (MDS) / myeloproliferative disorders (MPS):

Myelodysplastic / myeloproliferative disorders are a group of myeloid disorders with dysplastic and proliferative characteristics. Three major disorders are identified: chronic myelomonocytic leukemia (CMML), atypical chronic myelogenous leukemia (aCML), and juvenile myelomonocytic leukemia (JMML). A subgroup of these patients exhibit disease that is dependent on genetic rearrangement of PDGFR and therefore may be highly sensitive to imatinib. Patients experience anaemia, thrombocytopenia, and splenomegaly with frequent lymph node, skin and other organ involvements. This disease can progress much like an acute leukaemia with similar complications, morbidity and mortality.

Systemic Mastocytosis (SM):

Systemic mastocytosis involves infiltration of mast cells into multiple organs resulting in many different clinical manifestations in the patient including peptic ulcers, malabsorption deficiency, increased liver enzymes, osteoporosis, anaemia, thrombocytopenia, leukaemia and angina. The disease is commonly dependent on over-activity of KIT and may therefore be sensitive to imatinib. However, it is thought that a majority of cases are dependent on a particular mutant form of KIT (D816V) that is resistant to imatinib and in whom the drug is unlikely to be effective.

6. Comparator

Appropriately, the submission nominated standard medical management as the comparator.

7. Clinical Trials

The submission presented a case series study (B2225) of imatinib following failure of standard therapeutic options in patients with dermatofibrosarcoma protuberans (N=12), hypereosinophilic syndrome / chronic eosinophilic leukemia (N=14), myelodysplastic / myeloproliferative disorders (N=7) and systemic mastocytosis (N=5).

The submission also presented a number of additional case series for each disease with and without imatinib.

The case series trial, B2225, had been published at the time of submission as follows:

Trial/First author	Protocol title/Publication title	Publication citation
McArthur G, Demetri G, van Oosterom A, et al.	Molecular and clinical analysis of locally advanced dermatofibrosarcoma protuberans treated with imatinib: Imatinib Target Exploration Consortium Study B2225.	J Clin Oncol 2005; 23: 866-873
McArthur G, Demetri G, Heinrich M et al.	Molecular and clinical analysis of response to imatinib for locally advanced dermatofibrosarcoma protuberans.	Eur J Cancer 2004 (Supplement); 2(8):13 [abstract 28].
Apperley J, Dimitrijevic S, Browne P et al.	Imatinib (STI571, Glivec) for chronic Ph-negative myeloproliferative disorders associated with eosinophilia.	Br J Haematol 2003; 121(Suppl.1): 41-86 [abstract 213]
Apperley J, Gardembas M, Melo J et al.	Response to imatinib mesylate in patients with chronic myeloproliferative diseases with rearrangements of the platelet-derived growth factor receptor beta.	N Engl J Med 2002; 347: 481-487

8. Results of Trials

Comparative effectiveness

The results of the case series study are summarised in the table below.

Treatment effectiveness:

Outcome	DFSP (N=12)	HES (N=14)	MDS/MPD (N=7)	SM (N=5)
Complete response	1 (8%)	–	3 (43%)	–
Partial response	8 (67%)	4 (29%)	1 (14%)	1 (20%)
Stable disease	–	2 (14%)	–	1 (20%)
Progressive disease	–	2 (14%)	1 (14%)	–
Unknown ^a	3 (25%)	6 (43%)	2 (29%)	3 (60%)
Overall response rate	9/12 (75%)	4/14 (29%)	4/7 (57%)^b	1/5 (20%)
Duration response (median), days	112; n=9	266; n=4	400; n=4	127; n=1

a Only confirmed responses were included, all unconfirmed PR or SD or patients who are ongoing at the time of cut-off date and have only the baseline assessment at the time of cut-off or patients with assessments not done are listed as unknown.

b Of the four patients with PDGFR gene-rearrangements, 2 had CR and 1 had PR for an overall response rate in this subgroup of 75%

Flow of participants through the case series study

Study B2225 Disease types	DFSP (N=12)	HES (N=14)	MDS/MPD (N=7)	SM (N=5)
Completed	1 (8%)	3 (21%)	3 (43%)	1 (20%)
Discontinued	8 (67%)	9 (64%)	3 (43%)	4 (80%)
- Unsatisfactory therapeutic effect	2 (17%)	8 (57%)	1 (14%)	1 (20%)
- Adverse events	2 (17%)	-	2 (29%)	1 (20%)

- No longer require imatinib	4 (33%)	-	-	1 (20%)
- Withdrew consent	-	1 (7%)	-	-
- Death	-	-	-	1 (20%)
Ongoing at cut-off date	3 (25%)	2 (14%)	1 (14%)	-

See Recommendation and Reasons for PBAC's view.

Comparative toxicity

Gastrointestinal disorders, general disorders, skin complaints and oedema at various sites were the most frequently reported adverse events in study B2225. No patients died during the study.

9. Clinical Claim

The submission suggested that imatinib produced good response rates with an acceptable safety profile. The submission also argued that patients with these rare diseases who have failed conventional therapies face a poor prognosis, with unmet clinical need.

The PBAC acknowledged that effective treatments are limited and that because of the rarity of these conditions, any data to support a PBS listing will have limitations. However, the Committee considered that there was only very weak evidence of greater efficacy of imatinib over standard care, particularly with regards durable benefit.

The PBAC also considered there was uncertainty regarding the dose, the duration of response and the appropriate duration of treatment in all the rare diseases in the submission.

10. Economic Analysis

The PBAC noted that the submission stated that the trial based economic evaluation presented was a cost-consequence analysis. However, there was only one outcome and no comparator, hence there was no incremental cost or benefit, nor was there a comparison across outcomes. The data provided were the average cost per treatment response. The PBAC was therefore unable to form a judgement based on an average cost per treatment response estimate about the true cost-effectiveness of this drug for these chronic conditions.

11. Estimated PBS Usage and Financial Implications

The financial cost/year to the PBS (excluding co-payments) was estimated by the submission to be less than \$10 million in Year 5.

12. Recommendation and Reasons

The PBAC expressed its sympathy for patients with these rare conditions acknowledging that effective treatments are limited. The PBAC further accepted that because of the rarity of these conditions, any data to support a PBS listing will have limitations.

However, the PBAC considered that there was only very weak evidence of greater efficacy of imatinib over standard care, particularly with regards durable benefit. The data were limited to response rates in case series, with and without imatinib, and with no controlled data, and very minimal long term follow up. The data were very sparse with considerable residual statistical uncertainty and the PBAC considered that the effects of imatinib appeared moderate, at best. The clinical benefits of observed responses were also uncertain because of a lack of follow up data.

The PBAC noted that in study B2225, there was a low level of response in dermatofibrosarcoma protuberans with a complete response observed in 1 out of 12 patients. In myelodysplastic / myeloproliferative, 3 out of 7 patients had a complete response of which 2 had the platelet derived growth factor receptor (PDGFR) gene re-arrangements specified in the proposed restriction. In patients with myelodysplastic / myeloproliferative with PDGFR rearrangement, the PBAC noted that the detection of 5q33 abnormalities would allow diagnosis with a high degree of confidence and also target those patients more likely to respond to imatinib.

The PBAC considered that the data on efficacy in all patients with hypereosinophilic syndrome / chronic eosinophilic leukemia were modest and associated with considerable uncertainty. However, there was a high level of efficacy in a genotypically defined subset in the series reporting outcomes according to FIP1L1-PDGFR status. The PBAC noted that the restriction proposed by the submission does not limit treatment to patients with this transcript. There was also uncertainty about the magnitude of the long term clinical benefits.

The PBAC considered that the case series for SM were informative and indicated that responsiveness to imatinib was predicted by the presence of FIP1L1-PDGFR, with 13/13 patients having this gene rearrangement achieving an apparently durable complete response (CR). It was noted that the presence of D816V predicted no or minimal response; and that lack of D816V was not predictive of a response in the absence of FIP1L1-PDGFR. Furthermore, there was uncertainty regarding the dose, the duration of response and the appropriate duration of treatment in all the rare diseases in the submission.

The PBAC was unable on the basis of the data provided to form a judgement based on an average cost per treatment response estimate about the true cost-effectiveness of this drug for these chronic conditions.

The PBAC was concerned about the cost, availability and access to the molecular testing, and the number of patients who will need to be screened.

The PBAC therefore rejected the submission on the basis of uncertain clinical benefit and uncertain cost-effectiveness.

Recommendation

Reject

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 intends to provide further data to demonstrate the value of imatinib in patients with either of these rare diseases.