

PUBLIC SUMMARY DOCUMENT

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

Sponsor: Novartis Pharmaceuticals Australia Pty Ltd

Date of PBAC Consideration: March 2008

1. Purpose of Application

The submission sought to extend the current listing for imatinib to include the treatment of four rare diseases: dermatofibrosarcoma protuberans (DFSP), hypereosinophilic syndrome/chronic eosinophilic leukaemia (HES/CEL), myelodysplastic/myeloproliferative diseases (MDS/MPD) and aggressive systemic mastocytosis (ASM).

2. Background

At the July 2007 meeting, the PBAC rejected a submission for imatinib for these rare diseases based on uncertain clinical benefit and uncertain cost-effectiveness. The PBAC expressed its sympathy for patients with these conditions, acknowledging that effective treatments are limited. The Committee further accepted that because of the rarity of these conditions, any data to support a PBS listing would 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 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.

3. Registration Status

Imatinib is TGA registered for the following indications:

- Patients with chronic myeloid leukaemia (CML).
- 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 (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)
- Patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST). (10 May 2007)
- Adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP). (10 May 2007)

4. Listing Requested and PBAC's View

Dermatofibrosarcoma protuberans:

Section 85 Authority Required

Initial PBS-subsidised treatment, for up to 6 months, of an adult patient with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans.

- 1) Where the application for authority to prescribe is being sought on the basis of unresectable tumour, written evidence in support of that claim must be provided

- 2) Where the application for authority to prescribe is being sought on the basis of metastatic disease, the most recent CT scan, MRI or ultrasound assessment of the tumour must be provided

Continuing PBS-subsidised treatment of an adult patient with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans who has previously been issued with an authority prescription for imatinib and who has demonstrated a response.

Hyper eosinophilic syndrome/ Chronic eosinophilic leukaemia:

Section 85 Authority Required

Initial PBS-subsidised treatment, for up to 6 months, of an adult patient with hyper eosinophilic syndrome and/or chronic eosinophilic leukaemia which has been confirmed by the detection of the FIP1L1-PDGFR fusion gene.

NOTE: Any queries concerning the detection of the FIP1L1- PDGFR fusion gene may be directed to Medicare Australia.

Continuing PBS-subsidised treatment of an adult patient with hyper eosinophilic syndrome and/or chronic eosinophilic leukaemia who has previously been issued with an authority prescription for imatinib and who has demonstrated a response.

Myelodysplastic / myeloproliferative disorders:

Section 85 Authority Required

Initial PBS-subsidised treatment, for up to 6 months, of an adult patient with myelodysplastic syndromes or myeloproliferative disorders

- 1) which has been confirmed by the detection of platelet-derived growth factor receptor (PDGFR) gene re-arrangements by standard karyotyping, or where the karyotyping is not informative for technical reasons, a demonstration of 5q33 abnormalities on FISH, and
- 2) that the patient has previously failed an adequate trial of one or more of the following conventional therapy:
 - cytarabine
 - etoposide
 - hydroxyurea
 - interferon

NOTE: Any queries concerning the FISH detection of 5q33 abnormalities may be directed to Medicare Australia.

Continuing PBS-subsidised treatment of an adult patient with myelodysplastic syndromes or myeloproliferative disorders who has previously been issued with an authority prescription for imatinib and who has demonstrated a response.

Aggressive Systemic Mastocytosis

Section 85 Authority Required

Initial PBS-subsidised treatment, for up to 6 months, of an adult patient with aggressive systemic mastocytosis

- 1) which has been confirmed by the detection of the FIP1L1-PDGFR fusion gene and demonstration of the absence of the D816V c-kit mutation; and
- 2) where the patient has previously failed an adequate trial of one or more of the following conventional therapy:
 - corticosteroids
 - hydroxyurea
 - interferon

NOTE: Any queries concerning the detection of the FIP1L1- PDGFR fusion gene and the demonstration of the absence of the D816V c-kit mutation may be directed to Medicare Australia.

Continuing PBS-subsidised treatment of an adult patient with aggressive systemic mastocytosis who has previously been issued with an authority prescription for imatinib and who has demonstrated a response.

See Recommendations and Reasons for PBAC's view.

5. Clinical Place for the Proposed Therapy

Imatinib is used in the treatment of a variety of malignancies, such as the four rare diseases above, as the pathogenesis of the disease may involve one or more of the tyrosine kinase enzymes, which is known to be inhibited by the drug.

6. Comparator

The re-submission nominated standard medical management (as detailed below) as the comparator. This was accepted as appropriate by the PBAC.

Dermatofibrosarcoma protuberans:

The submission nominated radiotherapy as the main comparator for patients with unresectable, recurrent and/or metastatic DFSP. In patients who may not be receiving radiotherapy (50%) standard medical management (placebo) may be the comparator.

Hypereosinophilic syndrome / Chronic eosinophilic leukaemia:

The submission nominated standard chemotherapy (alkylating agents, corticosteroids, hydroxyurea and interferon) as the main comparator.

Myelodysplastic / myeloproliferative disorders:

The submission nominated standard medical management/best supportive care as the main comparator. However, an alternative comparator may also be chemotherapy (cytarabine, etoposide, hydroxyurea and interferon).

Aggressive Systemic Mastocytosis:

The submission nominated standard medical management/best supportive care as the main comparator. However, an alternative comparator may also be chemotherapy (corticosteroids, hydroxyurea and interferon).

7. Clinical Trials

No randomised trials were found in an updated literature search, although approximately 15 new case series were found and reported. The re-submission pooled results from case series (from imatinib and non-imatinib case series). The re-submission stated that these case series provided more information on whether patients were carrying particular sensitive molecular targets. The re-submission presented a non-randomised trial, Study B2225, (a case series study of imatinib following failure of standard therapeutic options in patients with DFSP, HES/CEL, MDS/MDP and ASM), which was also included in the previous submission, but this was not used in the economic evaluation.

8. Results of Trials

The key results are summarised in the table below.

Aggregated response rates of the case series

Disease	Imatinib	Comparator
DFSP	11/12 (92%)	85/106 * 20% (16%) ^a
HES/CEL	11/11 (100%)	52/79 (66%)
MDS/MPD (BSC)	15/16 (94%)	0/14 (0%)
MDS/MPD (Chemotherapy)	15/16 (94%)	97/206 * 206/510 (19%) ^b
MDS/MPD (Duration of response for chemotherapy - months)	49.0 (n=10)	10.3 (n=27)
ASM	16/17 (94%)	30/64 (47%)

Notes:

^a This assumption is adopted in calculating the cost-effectiveness of radiotherapy in the economic evaluation.

^b Response rate for all patients weighted by proportion of patients with 5q33 abnormalities, i.e.

47%*206/510=19%

For DFSP the re-submission combined all the response rates (partial, transient, complete and stable disease) for the imatinib case series and the non-imatinib case series. The re-submission stated that the response rate for imatinib is 92%, while the response rate for non-imatinib is 80%. The re-submission argued that only approximately 20% of all the patients represented in this case series would be most representative of patients eligible under the proposed PBS listing.

For the response rates in MDS/MPD the resubmission calculated an overall response by weighting the response rates for chemotherapy (47%) by the proportion of patients who have chromosome 5 or 7 abnormalities (40%).

The PBAC noted the response rates were not defined consistently across studies and could include partial or complete haematological or molecular response. Various case series did not even define a response.

The re-submission stated that, in most cases, there was inadequate reporting in the case series and that any statistical approaches to address potential bias, confounding and pooling of results would not have made up for the lack of robustness in the case series data.

The PBAC noted the submission proposed several diagnostic tests as part of the restriction. The submission obtained preliminary information obtained from the various testing facilities indicate that the costs for each of the tests are approximately

- \$200 (for FISH or RT-PCR testing of FIP1L1-PDGFR)
- \$250 (for FISH testing of 5q33 abnormalities)
- \$2000 (for PCR testing of D816V c-kit mutation analysis)

These costs were used in the economic evaluation.

The re-submission did not present new toxicity data. Toxicity information from Study B2225 was provided in the previous submission. Gastrointestinal disorders, general disorders, skin complaints and oedema at various sites were the most frequently reported adverse events.

9. Clinical Claim

The re-submission suggested that imatinib produced good response rates in all four diseases.

The PBAC accepted the clinical claims of effectiveness in these rare disease subsets with respect to high response rates. The PBAC noted that the quality of reported responses with

imatinib is substantially superior to those with standard care and considered that the case report data clearly reflect a clinically important benefit to patients who respond to imatinib.

10. Economic Analysis

An economic evaluation was presented. The cost-effectiveness analysis was based on non-randomised case series and no modelling was further conducted. The resources included were drug costs and the costs of testing patients with PDGFR gene-rearrangements (in patients with MDS/MPD) and patients without D816V c-kit mutation (in patients with ASM). The incremental costs per extra responder are summarised in the table below.

Incremental cost per responder for all diseases

	ICER
Incremental cost/extra responder for DFSP	\$15,000 - \$45,000
Incremental cost/extra responder for HES/CEL	\$45,000 - \$75,000
Incremental cost/extra responder for MDS/MPD (BSC)	\$45,000 - \$75,000
Incremental cost/extra responder for MDS/MPD (Chemotherapy)	\$45,000 - \$75,000
Incremental cost/extra month for MDS/MPD (Chemotherapy)	<\$15,000
Incremental cost/extra responder for ASM	\$45,000 - \$75,000

The PBAC noted that the results of the cost-effectiveness analysis were subject to significant uncertainty.

11. Estimated PBS Usage and Financial Implications

The estimated likely number of patients per year who would be eligible for imatinib under the PBS for each disease was considerably less than 10,000 in Year 5.

The financial cost per year to the PBS was estimated to be less than \$10 million in Year 5.

The re-submission requested a rule of rescue for MDS/MPD and ASM. The requested restriction positions imatinib after the failure of conventional therapy for these diseases. Left untreated, the prognosis of these patients is often poor. Imatinib is designated an orphan drug for the treatment of MDS/MPD and ASM.

See Recommendations and Reasons for PBAC's view.

12. Recommendation and Reasons

The PBAC recommended the listing of imatinib on the PBS for dermatofibrosarcoma protuberans (DFSP), hypereosinophilic syndrome/chronic eosinophilic leukaemia (HES/CEL), myelodysplastic/myeloproliferative diseases (MDS/MPD) and aggressive systemic mastocytosis (ASM) based on acceptable clinical benefit and acceptable but high cost-effectiveness compared with standard medical management.

The PBAC accepted the clinical claims of effectiveness in these rare disease subsets with respect to high response rates despite the small numbers of patients and the absence of high quality trial data. The PBAC noted that the quality of reported responses with imatinib is substantially superior to those with standard care and considered that the case report data clearly reflect a clinically important benefit to patients who respond to imatinib.

The PBAC agreed that the results of the cost-effectiveness analysis are subject to significant uncertainty, and without more information, it is more appropriate to assume that the non-

imatinib therapy would be of a similar efficacy to imatinib in sub-groups of the population. The PBAC noted there is the risk of ongoing use in patients who are not benefiting or in whom benefit is only equivalent to cheaper therapies (i.e. incomplete responses).

The PBAC recommended that the restrictions be administered through the Tasmanian Specialised Drugs Program similar to the other listings for imatinib, to enable data collection, that applications for initial authorisations be in writing and that, to be eligible for continuing therapy, patients HES/CEL, MDS/MPD and ASM must achieve a complete response confirmed by a blood test, or, in the case of DFSP, a demonstrated response but the disease remains unresectable.

The PBAC did not consider that the rule of rescue requested for MDS/MPD and ASM was appropriate as other therapies with some efficacy, although inadequate, are available and the clinical data proving a rescue are insufficient.

Recommendation

IMATINIB MESYLATE, tablets, 100 mg (base) and 400 mg (base)

Restriction:

NOTE:

Any queries concerning the arrangements to prescribe imatinib 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.

Applications for authority to prescribe imatinib should be forwarded to:

Medicare Australia
Prior Written Approval of Specialised Drugs
Reply Paid 9826
GPO Box 9826
HOBART TAS 7001

For each disease, written authority is required at initiation and for continuation.

Dermatofibrosarcoma protuberans:

Authority Required

Initial PBS-subsidised treatment of a patient with unresectable, locally recurrent or metastatic dermatofibrosarcoma protuberans.

Maximum dose: 800mg/day

- (1) Where the application for authority to prescribe is being sought on the basis of unresectable tumour, written evidence in support of that claim must be provided; and
- (2) Where the application for authority to prescribe is being sought on the basis of locally recurrent disease, the site of the local recurrence must be specified; and
- (3) Where the application for authority to prescribe is being sought on the basis of metastatic disease, the site(s) of metastatic disease must be provided .

Applications for authorisation for initial treatment must be made in writing and must include:

- (a) a completed authority prescription form; and
- (b) a completed Rare Diseases Imatinib PBS Authority Application – Supporting Information Form; and

(c) a signed patient acknowledgement.

Authority Required

Continuing PBS-subsidised treatment of a patient with unresectable, locally recurrent or metastatic dermatofibrosarcoma protuberans who has previously been issued with an authority prescription for imatinib and who has demonstrated a response, but whose disease remains unresectable.

Maximum dose: 800 mg/day

Applications for authorisation must be made in writing and must include:

- (a) a completed authority prescription form; and
- (b) a completed Rare Diseases Imatinib PBS Authority Application – Supporting Information Form; and
- (c) a statement that the disease has not progressed on imatinib therapy

Quantity: 60 (100 mg), 30 (400 mg)

Repeats: 2

No increase in maximum repeats will be authorised

Hypereosinophilic syndrome or Chronic eosinophilic leukaemia:

Authority Required

Initial PBS-subsidised treatment of a patient with hypereosinophilic syndrome or chronic eosinophilic leukaemia requiring treatment and confirmed to carry the FIP1L1-PDGFR fusion gene

Maximum dose: 400 mg/day

Applications for authorisation for initial treatment must be made in writing and must include:

- (a) a completed authority prescription form; and
- (b) a completed Rare Diseases Imatinib PBS Authority Application – Supporting Information Form; and
- (c) a copy of the pathology report confirming the presence of the FIP1L1-PDGFR fusion gene; and
- (d) a copy of the full blood examination report confirming the presence of hypereosinophilic syndrome or chronic eosinophilic leukaemia; and
- (e) details of organ involvement requiring treatment, including a copy of the radiology, nuclear medicine, respiratory function or anatomical pathology reports as appropriate; and
- (f) a signed patient acknowledgement.

Authority Required

Continuing PBS-subsidised treatment of a patient with hypereosinophilic syndrome or chronic eosinophilic leukaemia who has previously been issued with an authority prescription for imatinib and who has achieved and maintained a complete haematological response.

Applications for authorisation must be made in writing and must include:

- (a) a completed authority prescription form; and
- (b) a completed Rare Diseases Imatinib PBS Authority Application – Supporting Information Form; and
- (c) a copy of the full blood examination report which demonstrates a complete haematological response, with a normal eosinophil count; and
- (d) a statement that the disease has not progressed on imatinib therapy.

Maximum dose: 400 mg/day

Quantity: 60 (100mg), 30 (400 mg)

Repeats: 2

NOTE:

No increase in maximum repeats will be authorised.

PDGFRB fusion gene-positive Myelodysplastic or myeloproliferative disorder:

Authority Required

Initial PBS-subsidised treatment of a patient with a myelodysplastic or myeloproliferative disorder where

- 3) there is confirmed evidence of a platelet-derived growth factor receptor (PDGFR) gene re-arrangement either by standard karyotyping, or FISH, or *PDGFRB* fusion gene transcript; and
- 4) the patient has previously failed an adequate trial of one or more of the following conventional therapy:
 - cytarabine
 - etoposide
 - hydroxyurea

Maximum dose: 400 mg/day

Applications for authorisation for initial treatment must be made in writing and must include:

- (a) a completed authority prescription form; and
- (b) a completed Rare Diseases Imatinib PBS Authority Application – Supporting Information Form; and
- (c) a copy of the pathology report confirming the platelet-derived growth factor receptor (PDGFR) gene re-arrangement; and
- (c) a copy of the bone marrow biopsy report which demonstrates the presence of a myelodysplastic or myeloproliferative disorder; and
- (d) details of the prior therapy trialled and the response; and
- (e) a signed patient acknowledgement.

Authority Required

Continuing PBS-subsidised treatment of a patient with a *PDGFRB* fusion gene-positive myelodysplastic or myeloproliferative disorder who has previously been issued with an authority prescription for imatinib and who has demonstrated a clinically significant response.

Maximum dose: 400 mg/day

Applications for authorisation must be made in writing and must include:

- (a) a completed authority prescription form; and
- (b) a completed Rare Diseases Imatinib PBS Authority Application – Supporting Information Form; and
- (c) a statement that the disease has not progressed on imatinib therapy

Quantity: 60 (100mg), 30 (400 mg)

Repeats: 2

NOTE:

No increase in maximum repeats will be authorised.

Aggressive Systemic Mastocytosis with Eosinophilia

Authority Required

Initial PBS-subsidised treatment of a patient with aggressive systemic mastocytosis with eosinophilia where

- 3) there is confirmed evidence of the *FIP1L1-PDGFR*A fusion gene; and

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- 4) the patient has previously failed an adequate trial of one or more of the following conventional therapy:
- corticosteroids
 - hydroxyurea

Maximum dose: 400 mg/day

Applications for authorisation for initial treatment must be made in writing and must include:

- (a) a completed authority prescription form; and
- (b) a completed Rare Diseases Imatinib PBS Authority Application – Supporting Information Form; and
- (c) a copy of the pathology report confirming the presence of the FIP1L1-PDGFR fusion gene; and
- (d) a copy of the bone marrow biopsy report and/or other tissue biopsy report confirming the diagnosis of aggressive systemic mastocytosis and a copy of the full blood examination report demonstrating eosinophilia; and
- (e) details of symptomatic organ involvement requiring treatment, including a copy of the radiology, nuclear medicine, respiratory function or anatomical pathology reports as appropriate; and
- (f) details of prior treatment trialled and the response; and
- (g) a signed patient acknowledgement.

Authority Required

Continuing PBS-subsidised treatment of a patient with aggressive systemic mastocytosis confirmed to carry the *FIP1L1-PDGFR* fusion gene, who has previously been issued with an authority prescription for imatinib and who has demonstrated a clinically significant response.

Maximum dose: 400 mg/day

Applications for authorisation must be made in writing and must include:

- (a) a completed authority prescription form; and
- (b) a completed Rare Diseases Imatinib PBS Authority Application – Supporting Information Form; and
- (c) a statement that the disease has not progressed on imatinib therapy.

Quantity: 60 (100mg), 30 (400 mg)

Repeats: 2

NOTE:

No increase in maximum repeats will be authorised.

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 welcomes the positive recommendation of the PBAC and looks forward to finalising the listing of imatinib on the PBS for the treatment of these rare diseases affecting a small number of patients.