**PUBLIC SUMMARY DOCUMENT**
**Product:** Imatinib, tablet, 100 mg and 400 mg (as mesylate), Glivec®
**Sponsor:** Novartis Pharmaceuticals Australia Pty Ltd
**Date of PBAC Consideration:** November 2009

## 1. Purpose of Application

The submission sought an extension to the current authority required listing for imatinib to include the adjuvant treatment for 12 months of a patient at high risk of recurrence following complete resection of primary gastrointestinal tumour (GIST) who meets certain criteria.

## 2. Background

This drug had not previously been considered by the PBAC for the treatment of GIST in the adjuvant setting following complete resection of the primary tumour.

## 3. Registration Status

The TGA registration for imatinib was extended on 17 June 2009 to include the adjuvant treatment of adult patients following complete gross resection of KIT (CD117)-positive primary GIST.

## 4. Listing Requested and PBAC's View

*Consequential changes to the current restriction for imatinib for metastatic and/or unresectable GIST have been highlighted in bold, italics and strikethrough.*

Authority required
~~Imatinib mesylate is not PBS-subsidised for the treatment of patients with resectable malignant gastrointestinal stromal tumours.~~

Adjuvant treatment of a patient at high risk of recurrence following complete resection of primary gastrointestinal stromal tumour which has been histologically confirmed by the detection of CD117 on immunohistochemical staining, at a dose not exceeding 400 mg/day for a period of 12 months.

Patients would be considered at high risk of recurrence if their primary GIST was either:
>5 cm with a mitotic count of > 5 / 50 high power fields (HPF), or
>10 cm with any mitotic rate, or
Any tumour with a mitotic count of >10 / 50 HPF
(Prognosis definition based on the Australian and New Zealand consensus approach to best practice management, see Zalcberg et al. Asia-Pacific Journal of Clinical Oncology 2008: 4.4: 188-98.)

Adjuvant treatment of a patient who was previously treated with imatinib mesylate under the Compassionate Use Programme and who meets the PBS criteria. The patient is eligible to receive sufficient imatinib at a dose of 400 mg/day to complete 12 months of combined PBS-subsidised and non-PBS-subsidised therapy.

Authority required
Initial PBS-subsidised treatment, for up to 3 months, of adult patients with a metastatic or unresectable malignant gastrointestinal stromal tumour which has been histologically confirmed by the detection of CD117 on immunohistochemical staining.

Patients who have not previously been treated with imatinib mesylate for a metastatic or unresectable malignant gastrointestinal stromal tumour must commence treatment at a dose not exceeding 400 mg per day for at least 3 months. Authority prescriptions for a higher dose will not be approved during this initial 3 month treatment period.

Patients who have previously been treated with non-PBS-subsidised imatinib mesylate for a metastatic or unresectable malignant gastrointestinal stromal tumour are eligible to receive up to 3 months treatment at a dose of up to 600 mg per day.

Applications for authorisation must be in writing and must include:
(1) a completed authority prescription form; and
(2) a completed Imatinib Mesylate (Glivec) PBS Authority Application for Use in the Treatment of Gastrointestinal Stromal Tumour - Supporting Information Form [may be downloaded from the Medicare Australia website (www.medicareaustralia.gov.au)] which includes the following:
(i) a copy of a pathology report from an Approved Pathology Authority supporting the diagnosis of a gastrointestinal stromal tumour and confirming the presence of CD117 on immunohistochemical staining; and
(ii) a copy of the most recent (within 2 months of the application) computed tomography (CT) scan, magnetic resonance imaging (MRI) or ultrasound assessment of the tumour(s), including whether or not there is evidence of metastatic disease; and
(iii) where the application for authority to prescribe is being sought on the basis of an unresectable tumour, written evidence in support of that claim must be provided; and
**(iv)** ***where the application for authority to prescribe is being sought on the basis of adjuvant treatment, a written statement indicating that the date of tumour resection was not more than 3 months prior to the date of this application; and***
***the pathology report must include the size and mitotic rate of the tumour***
(v) for patients who commenced treatment with imatinib mesylate for a metastatic or unresectable malignant gastrointestinal stromal tumour prior to 1 December 2004 the date on which therapy with imatinib mesylate was commenced.

Authority required
Continuing PBS-subsidised treatment, at a dose of up to 600 mg per day, of adult patients with a metastatic or unresectable malignant gastrointestinal stromal tumour who have previously been issued with an authority prescription for this drug.

Applications for continuing treatment may be made by telephone (1800 700 270, hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

NOTE:
Patients ***with metastatic/unresectable disease*** who achieve a response to treatment at an imatinib dose of 400 mg per day should be continued at this dose and assessed for response at regular intervals. Patients who fail to achieve a response to 400 mg per day may have their dose increased to 600 mg per day. Authority applications for doses higher than 600 mg per day will not be approved.
A response to treatment is defined as a decrease from baseline in the sum of the products of the perpendicular diameters of all measurable lesions of 50% or greater. (Response definition based on the Southwest Oncology Group standard criteria, see Demetri et al. N Engl J Med 2002; 347: 472-80.)

*For PBAC's view, see Recommendation and Reasons.*

## 5. Clinical Place for the Proposed Therapy

Gastrointestinal stromal tumours (GIST) are rare and occur in the muscular layer of the digestive tract. Surgery has been the sole treatment for primary localised GIST and most patients after surgery are observed ('watchful waiting'). However, surgery alone is not curative for the majority of patients and over 50% of patients will have disease recurrence within 2 years.

Current guidelines recommend adjuvant imatinib as a possible treatment option in patients with an intermediate to high risk of tumour recurrence.

## 6. Comparator

Appropriately, the submission nominated placebo (watchful waiting) as the main comparator.

## 7. Clinical Trials

The submission presented one randomised trial comparing imatinib 400 mg/day with placebo (watchful waiting) as an adjuvant treatment for GIST following surgery (Z9001 trial).

The trial publications at the time of submission are shown in the table below:

| Trial ID/First author | Protocol title / Publication title | Publication citation |
|---|---|---|
| DeMatteo, et al (2009). | Adjuvant imatinib mesylate after resection of localized, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. | The Lancet 373 (9669) 1097-104. |
| DeMatteo R, et al (2007). | Adjuvant imatinib mesylate increases recurrence free survival (RFS) in patients with completely resected localized primary gastrointestinal stromal tumour (GIST): North American Intergroup phase III trial ACOSOG Z9001 | [Abstract] Journal of Clinical Oncology 25 (Suppl 18): A-10079 |
| ACOSOG Z9001 (2004). | A phase III randomized double-blind study of adjuvant imatinib mesylate versus placebo in patients following the resection of primary gastrointestinal stromal tumour. | [Abstract] Clinical Advances in Hematology and Oncology 2 (5): 310 |

## 8. Results of Trials

The following table summarises the key results (interim recurrence free survival, final recurrence free survival and final overall survival) from the Z9001 trial

**Key results of the Z9001 trial**

| Variable | Imatinib | Placebo | Hazard ratio | p-value |
|---|---|---|---|---|
| **Recurrence-free survival (interim ITT population) (January 2007)** | | | | |
| Number of patients with events (%) | 21/325 (6.5) | 62/319 (19.4) | | |
| Time (months) to recurrence or death[a] - 25th percentile (95% CI) | 37.9 (30.1, NE) | 19.6 (13.2, NE) | 0.325 (0.198, 0.534) | <0.0001 |
| **Recurrence-free survival (final ITT population) (April 2007)** | | | | |
| Number of patients with events (%) | 30/359 (8.4) | 70/354 (19.8) | | |
| Time (months) to recurrence or death[a] - 25th percentile (95% CI) | 37.9 (30.1, NE) | 19.6 (13.7, NE) | 0.398 (0.259, 0.610) | <0.0001 |
| **Overall survival (final ITT population) (April 2007)** | | | | |
| Number of patients with events (%) | 5/359 (1.4) | 8/354 (2.3) | | |
| Time (months) to death - 25th percentile (95% CI) | NE | NE | 0.663 (0.217, 2.028) | 0.4683 |

Abbreviations: CI, confidence interval; ITT, intention-to-treat; NE, not estimable.
Note: Differences in the patient numbers included in the interim and final analyses were due to the ongoing recruitment of patients as well as the availability of 'cleaned' patient data
[a] Median recurrence-free survival was not reached during the follow-up period of the Z9001 trial. Analyses were based on the time until 25% of patients experienced recurrence or death.

Recurrence-free survival was significantly increased with imatinib treatment compared to placebo in both the interim and final analyses of results (38 months vs. 20 months). There was no significant difference in overall survival between treatment groups.

The submission also presented post-hoc subgroup analyses of recurrence-free survival based on both the NIH and AFIP risk classification systems. These analyses are yet to be published.

The PBAC noted that post-hoc subgroup analyses of recurrence-free survival suggest that patients with either a high risk of recurrence according to the NIH criteria or a moderate to high risk of recurrence according to the AFIP criteria may gain the most benefit from imatinib treatment. The subgroup analyses also showed dependency of hazard ratio and 24 month recurrence-free survival (RFS) rates on risk criteria system. Based on these analyses the submission proposed limiting adjuvant imatinib treatment on the PBS to NIH high risk patients. However, the PBAC considered that this may not be appropriate as it will exclude an unknown proportion of AFIP moderate to high risk patients.

Adjuvant imatinib treatment was associated with a higher frequency of serious adverse events compared to placebo, notably abdominal pain, diarrhoea, nausea, vomiting, exfoliative rash, fatigue and laboratory value abnormalities (i.e. ALT levels, AST levels and neutrophil counts). More patients treated with imatinib required dose reductions and/or discontinued therapy due to adverse events compared to placebo.

## 9. Clinical Claim

The submission described imatinib as superior in terms of comparative efficacy over placebo.

The PBAC considered the claim that imatinib is superior in terms of comparative efficacy over placebo appeared reasonable, and is based on recurrence-free survival which was significantly increased with imatinib treatment compared to placebo (38 months vs. 20 months).

*For full details see Recommendation and Reasons.*

## 10. Economic Analysis

The submission presented a stepped economic evaluation based on a 30-year single cohort Markov model with seven health states encompassing both the adjuvant and metastatic settings. The outcomes generated by the modelled economic evaluation were the incremental cost per recurrence-free year, incremental cost per life year gained and incremental cost per QALY gained.

The PBAC noted that the main driver of the economic model was the assumption that most of the increase in recurrence-free survival with adjuvant imatinib treatment would be maintained as an overall survival gain. Both treatment groups received similar imatinib therapy in the metastatic setting and it was assumed that treatment in the adjuvant setting did not affect treatment outcomes in the metastatic setting. The model also assumed that no dose escalation to 800 mg would occur and that no use of imatinib beyond disease progression would occur.

Based on the structure and assumptions used in the submission's model, adjuvant imatinib treatment of GIST was associated with an incremental cost per life year gained in the range of $45,000 – $75,000 and an incremental cost per QALY gained in the range of $45,000 – $75,000 compared with placebo. The decrease from cost/life year gained to cost/QALY gained in the base case was due in part to the higher utility applied in the adjuvant setting. The PBAC considered that a utility of 1.0 in the adjuvant setting may not be appropriate as side effects are a significant issue when treating people, some of whom may not have disease.

*For PBAC's comments, see Recommendation and Reasons.*

## 11. Estimated PBS Usage and Financial Implications

The financial cost per year to the PBS was estimated to be less than $10 million per year in the fifth year of listing.

## 12. Recommendation and Reasons

The PBAC considered that there were a number of uncertainties with regards to the requested restriction and treatment population. While tumour size and mitotic index are recognised as prognostic factors neither has been prospectively validated. Additionally, assessments of mitotic index have not been standardised in practice and the reproducibility of measurements between pathologists has not been proven. The risk classification systems are subject to considerable uncertainty due to limitations of the epidemiological data as GIST has only been recently recognised as a disease. The PBAC noted that post-hoc subgroup analyses of recurrence-free survival suggest that patients with either a high risk of recurrence according to the NIH criteria or a moderate to high risk of recurrence according to the AFIP criteria may gain the most benefit from imatinib treatment. The subgroup analyses also showed dependency of HR and 24 month recurrence-free survival (RFS) rates on risk criteria system. Based on these analyses the submission proposed limiting adjuvant imatinib treatment on the PBS to NIH high risk patients. However, the PBAC considered that this may not be appropriate as it will exclude an unknown proportion of AFIP moderate to high risk patients.

The PBAC considered the claim that imatinib is superior in terms of comparative efficacy over placebo appeared reasonable, and is based on recurrence-free survival which was significantly increased with imatinib treatment compared to placebo (38 months vs. 20 months). However, the trial data did not show any statistically significant overall survival benefit with adjuvant imatinib treatment. The trial design limited its capacity to assess overall survival advantage as patients in the placebo arm were allowed to switch to imatinib on recurrence. The PBAC considered that due to limited longer-term patient follow-up data, adjuvant imatinib treatment may delay rather than prevent disease recurrence, as similar proportions of patients in both treatment arms had experienced disease recurrence after 36-42 months.

The PBAC noted that adjuvant imatinib treatment was associated with a higher frequency of serious adverse events and laboratory value abnormalities compared to placebo. More patients treated with imatinib also required dose reductions and/or discontinued therapy due to adverse events compared to placebo. Therefore, the PBAC considered that a utility of 1.0 in the adjuvant setting may not be appropriate as side effects are a significant issue when treating people, some of whom may not have disease.

The PBAC noted that the results of the sensitivity analyses indicated that the model is most sensitive to adherence rates in the adjuvant setting, utility scores in the adjuvant health state, disutility associated with adjuvant imatinib, baseline risk of recurrence in different patient populations and the estimated efficacy of imatinib use in metastatic disease in patients with prior adjuvant exposure. The PBAC noted that the base case incremental cost-effectiveness ratio was in the range of $45,000 – $75,000 per QALY gained is estimated using the most optimistic value of multiple inputs. Patients are assumed to cease therapy after 12 months. However, in clinical practice imatinib treatment may continue for longer. If 10% and 50% of patients remain on the drug for 2 years the ICER increases to in the range of $45,000 – $75,000/QALY and $75,000 – $105,000/QALY respectively. The PBAC noted that the

duration of treatment in the adjuvant setting is undergoing further evaluation with two ongoing randomised control trials (NCT00116935, NCT00103168) evaluating the continued use of imatinib beyond the maximum treatment period of one year.

The PBAC considered that there was uncertainty about the extrapolation of the treatment effect beyond the 12-month trial period. After 30 months the model assumes no treatment benefit with imatinib. The submission did not request listing for the ITT population, however if the treatment effect is derived from the ITT population the ICER is in the range of $75,000 – $105,000/QALY. If the moderate risk NIH were included in the analyses they would probably gain from treatment in the adjuvant setting, but the ICER would likely be higher than the base-case calculated by the submission.

The PBAC concluded that the main of areas of uncertainties were the clinical benefit in the overall treatment of GIST, the value of delaying recurrence without any changing survival and the cost effectiveness, which in multivariate sensitivity analysis could be greater than $45,000 – $75,000/QALY.

Therefore, the PBAC rejected the submission on the basis uncertain clinical benefit and a high and highly uncertain cost-effectiveness ratio.

***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 Sponsors will continue to work with PBAC to resolve the issues raised in this submission.