PUBLIC SUMMARY DOCUMENT
Product: IMATINIB, tablets, 100 mg and 400 mg (as mesylate), Glivec®
Sponsor: Novartis Pharmaceuticals Australia Pty Ltd.
Date of PBAC Consideration: July 2010

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

At the November 2009 meeting, the PBAC rejected a submission for an authority required listing for adjuvant treatment of GIST on the basis of uncertain clinical benefit and a high and highly uncertain cost-effectiveness ratio.

Full details in the November 2009 Public Summary Document.

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

Changes to the current restriction for imatinib for metastatic and/or unresectable GIST have been highlighted in italics and strikethrough.

Authority required

Adjuvant treatment of an adult 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.

High risk of recurrence is defined as:
Primary GIST greater than 5 cm with a mitotic count of greater than 5/50 high power fields (HPF); or
Primary GIST greater than 10 cm with any mitotic rate; or
Primary GIST with a mitotic count of greater than 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.)

Authority required (grandfathering)

Initial treatment of a patient who was receiving adjuvant imatinib mesylate for GIST prior to {list date} and who meets the above 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.

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 Adjuvant 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) a written statement indicating that the date of tumour resection was not more than 3 months prior to the date of this application; and
(iv) a copy of the pathology report must include the size and mitotic rate of the tumour

Change the NOTE in the current continuing treatment restriction for metastatic GIST as follows:
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.

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.

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. Recurrence can occur as a result of tumour rupture during surgery or after "complete" resection due to unsuspected microscopic tumour dissemination.

It is proposed that adjuvant treatment with imatinib following complete resection of the primary GIST would provide a treatment option after surgery and may prevent disease recurrence in those patients classified as being at high risk of metastatic disease recurrence.

For PBAC's view, see Recommendation and Reasons.

6. Comparator

The submission nominated placebo as the main comparator.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials

No changes were made to the trial data which were presented in the November 2009 submission. The trials have been previously reported in the November 2009 Public Summary Document.

8. Results of Trials

The key results of Trial Z9001 have been previously reported in the November 2009 Public Summary Document.

9. Clinical Claim

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

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The re-submission presented an updated stepped economic evaluation based on a single cohort Markov model and included seven health states. 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. Compared to the model used in the November 2009 submission, the re-submission included the use of sunitinib treatment for patients with progressive disease in the metastatic setting.

Based on the structure and assumptions used in the re-submission's model, adjuvant imatinib treatment of GIST is associated with both an incremental cost per life year gained and an incremental cost per QALY gained of between $45,000 and $75,000 compared with placebo and could be more than $100,000 per QALY if no survival gain is assumed. These were higher, but within the same range than the ICER's generated in the previous submission.

The PBAC noted the results of the sensitivity analyses indicated that the model was most sensitive to; the trial-based treatment effect (hazard ratio for recurrence-free survival), 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 metastatic imatinib in patients with prior adjuvant exposure.

Although the re-submission had incorporated sunitinib into the economic analysis and updated the supportive evidence, the PBAC considered that many of the uncertainties identified with the economic analysis in the November 2009 submission remained in the re-submission.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The re-submission estimated the likely number of patients per year to be less than 10,000 in Year 5, at a cost per year to the PBS of less than $10 million in Year 5, lower than in the previous submission.

If cost offsets are not included in the estimates, the financial cost to the PBS in Year 5 of listing is higher, though still less than $10 million.

12. Recommendation and Reasons

The PBAC noted that no new clinical data were provided and the comparator and the clinical claim were the same as for the November 2009 submission, both of which were previously accepted by the PBAC. The revised treatment algorithm included sunitinib as second line treatment in the metastatic setting which was not available on the PBS at the time of lodging the November 2009 submission.

The PBAC accepted it was reasonable to limit the eligible population to patients at high-risk of recurrence according to the NIH criteria as a pragmatic way forward.

However, the PBAC agreed that that the following issues remain unresolved.

The PBAC considered that there was insufficient evidence to determine whether adjuvant therapy prevents or delays disease recurrence as the follow up of Study Z9001 was too short. The PBAC noted that a minimum 3 year follow-up post imatinib data will be available in 2011 for Study Z9001.

The PBAC acknowledged there was a clinical need for adjuvant treatment and an improvement in overall survival is the desired outcome for patients in the adjuvant setting. The PBAC noted that clinical trial demonstrated significantly increased recurrence-free survival (RFS) with imatinib compared with placebo (all risk groups combined) (38 months versus 20 months). However, the PBAC considered that whilst recurrence-free survival may be a useful surrogate outcome in particular cancers (breast cancer, colorectal cancer) which have a substantial body of evidence supporting the use of surrogate measures in the adjuvant setting, this did not mean that recurrence-free survival would necessarily be a valid surrogate for overall survival in GIST patients. The PBAC agreed that until definitive data become available in 2015, considerable uncertainty will remain around the estimate of the comparative treatment effect for overall survival.

The PBAC noted that although the restriction limits treatment to 12 months based on the duration of treatment in Trial Z9001, the appropriate length of treatment is still unknown. The PBAC noted that clinical trials were currently testing the following treatment durations: 0 versus 1 year (Z9001), 0 versus 2 year (EORTC) and 1 versus 3 year (SSG), and comparative data with RFS as endpoint will be available in 2013.

The PBAC noted that the economic model did not incorporate the costs and disutility associated with adverse events. However, adjuvant imatinib treatment is associated with a higher frequency of serious adverse events and dose reduction and/or discontinued therapy due to adverse events compared to placebo. The model also assumed that adjuvant imatinib treatment did not affect the effectiveness of imatinib in the metastatic setting (i.e. there is no imatinib resistance). However, there was uncertainty regarding whether use in the adjuvant

setting modifies the treatment effect of imatinib in the metastatic setting. The PBAC noted that the clinical trials indicated that imatinib is effective in previously exposed patients, but there was uncertainty about whether the effect is equivalent to that seen in naïve patients. The PBAC agreed that the model is highly sensitive to estimated efficacy of imatinib in the metastatic setting.

The PBAC noted that the economic model assumed that the delay in disease recurrence translated directly into an increase in survival despite no trial data to support an overall survival benefit with adjuvant imatinib, nor data to support recurrence-free survival as a valid surrogate for overall survival in the adjuvant setting in GIST. The PBAC agreed that the main gains in quality-adjusted life years (QALYs) in the model are related to gains in life years not gains in quality of life, despite no validated evidence demonstrating a survival benefit.

Based on the structure and assumptions used in the re-submission's model, adjuvant imatinib treatment of GIST is associated with an incremental cost per life year gained and an incremental cost per QALY gained of between $45,000 and $75,000 compared with placebo (correcting for errors in the calculation of costs for sunitinib and non-drug costs in the adjuvant setting) and could be more than $100,000 per QALY if no survival gain is assumed. The PBAC noted that the cost-effectiveness ratios are disproportionally higher than cost-effectiveness ratios accepted in other adjuvant settings such colorectal and breast cancer.

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

The PBAC noted that whilst the Managed Entry proposal might address the clinical uncertainty, the ICER remains unacceptably high at the price proposed by the sponsor. The PBAC also noted that the earliest starting date of any Managed Entry Scheme is 1 January 2011 as agreed with Medicines Australia in the Memorandum of Understanding.

The PBAC noted that the submission meets the criteria for an independent review.

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

Novartis Pharmaceuticals Australia welcomes the PBAC's acknowledgement of the clinical need for Glivec® for adjuvant treatment of GIST and will continue to work with the PBAC to make Glivec® available under the PBS for this patient group.