PUBLIC SUMMARY DOCUMENT
Product: Imatinib, tablet, 100 mg and 400 mg (as mesylate), Glivec®
Sponsor: Novartis Pharmaceuticals Australia Pty Ltd
Date of PBAC Consideration: March 2011

1. Purpose of Application

To seek an Authority Required listing for the adjuvant treatment of an adult patient at high risk of recurrence following complete resection of primary gastrointestinal stromal tumour (GIST) who meets certain criteria.

2. Background

This is the third submission seeking an Authority Required listing for adjuvant treatment of GIST.

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

A copy of the Public Summary Document from that meeting is available from http://www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-Imatinib-nov09

At the July 2010 meeting, the PBAC rejected a resubmission seeking an authority required listing for adjuvant treatment of GIST on the basis of uncertain clinical benefit and an unacceptably high and uncertain cost-effectiveness ratio.

A copy of the Public Summary Document from that meeting is available from

http://www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-Imatinib-july10

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

The requested listing was the same as that in the July 2010 submission.

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

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.

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

6. Comparator

The submission previously nominated placebo as the main comparator, which was considered appropriate by the PBAC.

7. Clinical Trials

The submission did not provide any additional clinical data compared to the July 2010 submission. See July 2010 Public Summary Document (PSD) for details.

8. Summary of Submission

The submission stated that clinical data from the following on-going trials will become available in 2015, which may help address the PBAC's concerns regarding the comparative effect for overall survival:
1) Intergroup Study (EORTC 62024, EudraCT number 2004-001810-16): "Intermediate and high risk localized, completely resected, gastrointestinal stromal tumors (GIST) expressing KIT receptor: a controlled randomized trial on adjuvant Imatinib mesylate (Glivec) versus no further therapy after complete surgery".

2) SSG XVIII/AIO Trial: "Short (12 months) versus long (36 months) duration of adjuvant treatment with imatinib of operable GIST with a high risk for recurrence: a randomized phase III study".

To address the issue of whether imatinib affects the emergence of resistance under imatinib therapy in the metastatic setting, the submission outlined published results of treatment interruption in patients with non-progressive disease after 3 years of imatinib in a randomised trial, *Le Cesne et al (2010)*.

The table below details the published trial presented in the submission.

Trial/First author	Protocol title/Publication title	Publication citation
Le Cesne et al	Discontinuation of imatinib in patients with advanced gastrointestinal stromal tumours after 3 years of treatment: an open -label multicentre randomised phase 3 trial.	The Lancet Oncology 2010 Oct; 11 (10): 942-9.

Although this trial did not directly address the impact of rechallenging with imatinib following use in the adjuvant setting, the submission stated the authors of the study concluded that while treatment interruption after 3 years in metastatic patients resulted in tumour progression in most patients, there was further tumour control in all cases after the reintroduction of imatinib. Importantly the time to secondary resistance to imatinib was similar in the continued treatment group vs interrupted treatment group, which provided

evidence that imatinib interruption neither prevents nor promotes the emergence of imatinib resistance in GIST cells.

9. Economic Analysis

The submission stated that in the absence of substantive clinical data to address the overall survival issue raised by the PBAC, the sponsor proposed to reduce the daily cost of imatinib (400 mg/day) in the adjuvant setting to mitigate the PBAC concerns regarding the high and uncertain cost-effectiveness ratio, and uncertain clinical benefit of imatinib as adjuvant treatment for GIST over a range of estimates of overall survival.

The submission presented a revised modelled economic analysis based on the reduced price.

The incremental cost per QALY was estimated to be in the range of $15,000 - $45,000.

In an attempt to address the PBAC's concerns regarding whether adjuvant treatment using imatinib offers an increase in overall survival (OS) and whether recurrence-free survival (RFS) would be a valid surrogate for OS in GIST patients, the submission presented a series of scenarios to test and demonstrate that imatinib represents a cost-effective option for the adjuvant treatment of GIST.

The base case incremental cost per life year gained was estimated to be in the range of $15,000 - $45,000.

For PBAC's view, see Recommendation and Reasons.

10. Estimated PBS Usage and Financial Implications

The submission presented revised financial implications for imatinib in adjuvant setting in patients at high risk of metastatic GIST recurrence.

The submission estimated lees than 10,000 patients would be eligible for imatinib in year 4 of listing.

The submission estimated the overall net costs to the PBS of imatinib (adjuvant setting) to be less than $10 million in year 4 of listing.

11. Recommendation and Reasons

The PBAC recommended listing imatinib on the PBS as an Authority Required benefit for the adjuvant treatment of GIST following complete resection of the primary tumour on the basis of an acceptable cost-effectiveness ratio compared with placebo.

The PBAC noted that there were no new clinical data, but supportive evidence was provided in relation to imatinib resistance and treatment interruption. A price decrease was offered by the sponsor and a revised modelled economic analysis and financial implications were presented.

The PBAC considered that the evidence provided from La Cesne (2010) addressed concerns regarding treatment interruption in patients with non-progressive disease and the emergence of resistance under imatinib therapy in the metastatic setting and agreed with the authors'

conclusion that "interruption of treatment with imatinib neither prevents nor promotes emergence of imatinib resistance in GIST cells".

The PBAC noted that the revised ICER calculated using the same model and the price decrease was estimated to be in the range of $15,000 - $45,000/QALY compared with $45,000 - $75,000/QALY in the November 2010 submission. The PBAC considered the revised ICER to be acceptable but in the higher range compared with other adjuvant treatments. The PBAC noted that the impact of survival assumptions was calculated as LYG rather than QALYs, to address PBAC's previous concerns about uncertainty in relation to the QALY gains in the model. The PBAC also noted the sensitivity analysis in relation to survival advantage showed that even with a 30% reduction in survival advantage, the incremental cost per LYG was acceptable.

The PBAC agreed that there was a high clinical need for use of imatinib in the adjuvant treatment of GIST, a rare disease, in a small population where patient numbers were low (less than 10,000 per year in year 5), and that the financial cost to the PBS was also relatively low.

The PBAC noted that there was an ongoing trial which will report at a future date on progression free survival versus overall survival for this indication. The PBAC requested that the sponsor provide the PBAC with an update on the results of this trial when available.

The PBAC recommended that imatinib is not suitable for inclusion in the PBS medicines for prescribing by nurse practitioners within collaborative arrangements.

Recommendation:
IMATINIB, tablet, 100 mg and 400 mg (as mesylate), Glivec®

Extend the current restriction to include:

Restriction:

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

Authority required
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.

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 pathology report must include the size and mitotic rate of the tumour, and the date of tumour resection must be documented, which must not be more than 3 months prior to the date of this application.

Max qty: 60 (100 mg), 30 (400 mg)
Repeats: 5

Amend the current listing for imatinib use in metastatic or unresetcable GIST to read as follows as highlighted by italics and strikethrough:

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

Patients 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.

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 *Metastatic or Unresectable* 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.

Authority Required
Continuing PBS-subsidised treatment, at a dose of up to 600 mg per day, of a ~~adult~~ patient~~s~~ 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).

Patients who have failed to respond or are intolerant to imatinib are no longer eligible to receive PBS-subsidised imatinib.
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.)
NOTE:
No applications for increased 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

The sponsor has no comments.