PUBLIC SUMMARY DOCUMENT
Product: Imatinib, tablets, 100 mg and 400 mg (as mesylate), Glivec®
Sponsor: Novartis Pharmaceuticals Australia Pty Ltd
Date of PBAC Consideration: March 2012

1. Purpose of Application

The submission requested an extension to the current Authority Required listing for imatinib for adjuvant treatment of a patient at high risk of recurrence following complete resection of primary gastrointestinal stromal tumour (GIST) to allow a maximum duration of treatment of 3 years.

2. Background

The PBAC has considered submissions requesting PBS listing for imatinib for the adjuvant treatment of GIST on three previous occasions. Submissions to the November 2009 and July 2010 PBAC meetings were rejected on the basis of uncertain clinical benefit and an unacceptably high and uncertain cost-effectiveness ratio.

At its March 2011 meeting, the PBAC recommended listing imatinib on the PBS as an Authority Required benefit for the adjuvant treatment of a patient at high risk of recurrence following complete resection of primary GIST at a dose not exceeding 400 mg per day for a period of 12 months on the basis of an acceptable cost-effectiveness ratio compared with placebo. Listing was effective from 1 September 2011.

A copy of the Public Summary Document from the March 2011 meeting is available at http://www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-imatinib-march11

3. Registration Status

The TGA approved indications for imatinib include the adjuvant treatment of adult patients at high risk of recurrence following complete gross resection of KIT (CD-117)-positive primary GIST. The Dosage and Administration section of the approved Product Information was updated on 30 October 2012 and states:

> "The recommended dose of Glivec is 400 mg/day for the adjuvant treatment of adult patients following resection of GIST. In clinical trials one year of Glivec and three years of Glivec were studied. In the patient population defined in Study SSG XVIII/AIO, three years of Glicec is recommended (see Clinical Trials). The optimal treatment duration with Glivec is not known."

4. Listing Requested and PBAC's View

Authority required

Adjuvant treatment of a patient at high risk of recurrence following complete resection of primary gastrointestinal stromal tumour (GIST) which has been histologically confirmed by the detection of CD117 on immunohistochemical staining, at a dose not exceeding 400 mg per day for a period of 36 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.)

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.

Authority required (grandfathering)
Ongoing treatment of a patient at high risk of recurrence following complete resection of primary gastrointestinal stromal tumour (GIST) who has received adjuvant imatinib mesylate either via the Novartis access program, PBS, or a combination of these supply mechanisms and whose tumour was resected no earlier than [INSERT DATE OF LISTING subtract 39 months]. The patient must meet the PBS eligibility criteria for adjuvant treatment with imatinib mesylate. The patient is eligible to receive sufficient imatinib at a dose of 400 mg per day to complete 36 months of combined PBS-subsidised and non–PBS-subsidised therapy.

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(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.

The PBAC had no objections to the requested restriction wording changes.

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.

Adjuvant treatment with imatinib following complete resection of the primary GIST is a treatment option after surgery. The submission claims that 3 years of treatment is more efficacious in prolonging recurrence-free survival (RFS) and overall survival (OS) than 1 year of treatment.

For PBAC's view, see Recommendation and Reasons

6. Comparator

The submission nominated imatinib treatment for 12 months as the main comparator. The PBAC agreed that this was appropriate. In addition, the submission used placebo as an alternative comparator, for supplementary purposes, as used in previous submissions for imatinib GIST adjuvant therapy.

7. Clinical Trials

The submission presented one open-label randomised trial (SSGXVIII) comparing 3-year with 1-year imatinib adjuvant therapy (400 mg) in patients with resectable GIST. Publication details are in the table below.

Trial ID / First author	Protocol title / Publication title	Publication citation
Direct randomised trial		
SSGXVIII Joensuu H, et al	Twelve versus 36 months of adjuvant imatinib (IM) as treatment of operable GIST with a high risk of recurrence: final results of a randomized trial (SSGXVIII/AIO).	*J Clin Oncol* 2011; 29 (18 Suppl): Abstr LBA1.

The submission also used data from study Z9011, a randomised trial comparing 1-year imatinib adjuvant therapy with placebo, in the economic model. This was the same study used previously to support the current listing of 1-year imatinib therapy for patients with GIST.

The primary outcome in SSGXVIII was recurrence-free survival (RFS), based on physician judgement and subsequent confirmation on a radiology scan. The PBAC has previously considered that improvement in overall survival is the preferred outcome measure for trials in patients in the adjuvant setting. Overall survival (OS) was measured in the SSGXVIII trial, as a secondary outcome.

For PBAC's view, see Recommendations and Reasons

8. Results of Trials

The key primary outcome results from the SSGXVIII trial are presented in the table below.

Results of recurrence-free survival in SSGXVIII for Imatinib 400 mg (final analysis March 2011)

	n at risk	Imatinib 400 mg 36 months N = 198	n at risk	Imatinib 400 mg 12 months N = 199
Pts with recurrence or death event, n (%)		50 (25.3)		84 (42.2)
Censored (alive and recurrence free), n (%)		148 (74.7)		115 (57.8)
Pts censored at baseline, n (%)		1 (0.5)		3 (1.5)
Time to recurrence or death percentiles, months (95%CI)				
25%		48.7 (44.6, 53.1)		24.0 (23.2, 25.2)

	n at risk	Imatinib 400 mg 36 months N = 198	n at risk	Imatinib 400 mg 12 months N = 199
50% median		NE		53.2 (39.1, NE)
75%		NE		NE
RFS probability estimates, % (95%CI)				
At 6 months	189	97.4 (94.0, 98.9)	182	95.8 (91.8, 97.9)
At 12 months	184	95.9 (91.9, 97.9)	177	93.7 (89.2, 96.4)
At 18 months	181	94.3 (90.0, 96.8)	163	86.8 (81.1, 90.9)
At 24 months	173	90.7 (85.6, 94.0)	137	75.4 (68.6, 81.0)
At 36 months	133	86.6 (80.8, 90.8)	88	60.1 (52.5, 66.9)
At 48 months	82	78.3 (70.8, 84.1)	49	52.3 (44.0, 59.8)
At 60 months	39	65.6 (56.1, 73.4)	27	47.9 (39.0, 56.3)
At 72 months	8	54.0 (37.5, 67.9)	10	47.9 (39.0, 56.3)
Log-rank test p value (two-sided)	<0.0001		<0.0001	
36 months vs. 12 months HR (95% CI)	**0.46 (0.32, 0.65)**			

CI = confidence interval; HR = hazard ratio; NE = not estimable; pts = patients; RFS = recurrence-free survival; SD = standard deviation; **bold** = statistically significant

A significant difference in RFS was found between the two treatment arms in favour of the 36-month treatment arm.

The results of secondary outcome (overall survival) from the SSGXVIII trial for imatinib 400 mg are shown in the table below.

Results of overall survival from the SSGXVIII trial for imatinib 400 mg

	n at risk	Imatinib 400 mg 36 months N = 198	n at risk	Imatinib 400 mg 12 months N = 199
Patients with events/censorings, n		12/186		25/174
Overall survival probability estimates, % (95% CI)				
At 6 months	196	100.0 (100.0, 100.0)	190	99.0 (95.9, 99.7)
At 12 months	192	100.0 (100.0, 100.0)	188	99.0 (95.9, 99.7)
At 24 months	184	97.4 (93.8, 98.9)	176	95.8 (91.7, 97.9)
At 36 months	152	96.3 (92.4, 98.2)	140	94.0 (89.5, 96.7)
At 48 months	100	95.6 (91.2, 97.8)	87	87.9 (81.1, 92.3)
At 60 months	56	92.0 (85.3, 95.7)	46	81.7 (73.0, 87.8)
At 72 months	13	87.8 (74.6, 94.4)	20	77.0 (66.0, 84.9)
Log-rank test p value (two-sided)	0.0187			
36 month vs. 12 months HR (95% CI)	**0.45 (0.22, 0.89)**			

CI = confidence interval; HR = hazard ratio; **bold** = statistically significant

The PBAC noted the hazard ratio for OS for the 36-month versus 12-month arm of the SSGXVIII trial was 0.45 (95%CI: 0.22, 0.89). A large proportion of the patients were still alive at 72 months of follow-up (87.8% for 36 months vs. 77.0% for 12 months imatinib treatment).

In total, there were 25 deaths in the 12-month arm and 12 deaths in the 36-month arm.

In the SSGXVIII trial, adverse events (AEs) occurred in almost 100% of patients taking imatinib. A significant proportion (32.8%) of patients receiving 36-month treatment and 20.1% in the 12-month arm experienced at least one grade 3 or 4 event (RR 1.63, 95%CI:

1.16-2.30). The most frequent grade 3 or 4 AEs were decreased neutrophil count, increased alanine aminotransferase, decreased white blood cell count, increased aspartate aminotransferase and infections.

There were no reported deaths due to treatment. AEs led to 14% of patients discontinuing, 27% treatment interruptions and 10% dose reduction. AEs resulting in discontinuations were relatively high (but not statistically significantly) in the 36-month arm than the 12-month arm (RR 1.75, 95%CI: 0.96, 3.18) as were treatment interruptions (RR 1.81, 95%CI: 1.20, 2.71*).* No deaths related to the study medication were reported. A total of 37 deaths occurred during the study, two of which occurred while on treatment; 21 deaths were classified as GIST-related and 16 were due to other reasons.

For PBAC's view, see Recommendations and Reasons

9. Clinical Claim

The submission described imatinib 3-year treatment as superior in terms of comparative effectiveness and did not make a claim in terms of comparative safety over 1-year imatinib treatment.

The claim of superior comparative effectiveness was not accepted by the PBAC.

For PBAC's view, see Recommendations and Reasons

10. Economic Analysis

A stepped economic evaluation was presented. The structure of the model compared three strategies: 1-year imatinib, 3-year imatinib and no treatment (best supportive care) or placebo. The submission presented a Markov cohort model with 6-month cycles and seven health states.

The model relied on data from 5 years follow-up in the SSGXVIII trial and extrapolated beyond 5 years.

The base case incremental cost per QALY was between $45,000 and $75,000. When the lower and upper 95% confidence limits of clinical efficacy of 3-year imatinib were applied (hazard ratio), the ICER ranges from between $15,000 and $45,000 to between $105,000 and $200,000.

For PBAC's view, see Recommendations and Reasons

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated in the submission to be less than 10,000 in Year 5, at an estimated net cost per year to the PBS of less than $10 million Year 5.

12. Recommendation and Reasons

The PBAC noted the submission is being evaluated under the TGA/PBAC parallel process and that at the time of PBAC consideration no Clinical Evaluator Report had been received.

The PBAC agreed that there is a clinical need for treatment in the adjuvant setting as there is a high risk of recurrence after surgery for patients with high risk GIST and treatment in the

metastatic setting is not curative. However, treatment in the metastatic setting does improve both PFS and OS.

The PBAC agreed that imatinib treatment for 12 months is the appropriate comparator.

The PBAC noted that the key clinical trial (SSGXVIII) in the submission is a different trial to that used to support the current listing of 1-year imatinib therapy for GIST. The selected primary outcome was recurrence-free survival (RFS) and recurrence was based on physician judgement with subsequent confirmation on a radiology scan. The PBAC noted that since the study began in December 2003, the protocol has changed four times which made it difficult to map the flow of patients throughout the clinical trial. This also impacted on the reliability of the survival estimates used to inform the economic evaluation. In addition, the trial patients did not always reflect the requested PBS population as the trial included patients who did not have high risk of recurrence of disease as well as patients with intra-abdominal overt metastases removed by surgery.

The PBAC noted that there was a significant difference in RFS between the two treatment arms in favour of the 36-month treatment arm HR 0.46 (95% CI 0.32, 0.65). Also, the proportion of patients with either recurrence or death as an event is greater in the 12-month arm (42.2%) compared to the 36-month arm (25.3%). However, in both trial arms, extensive censoring occurred and a greater proportion of patients were censored in the 36-month arm. The PBAC noted that by the end of the study, 33% of patients in the 12-month arm and 47% in the 36-month arm either discontinued treatment, withdrew prior to treatment, had unknown status or should have been excluded at entry (no confirmed GIST/overtly metastatic). The PBAC also considered that the efficacy results in the primary analyses are uncertain and potentially biased due to the presence of a large proportion of patients with unknown outcomes.

Therefore, the PBAC did not accept with the clinical claim that imatinib 3-year treatment is superior in terms of comparative effectiveness. The PBAC considered that the main reasons not to support the claim are the extensive censoring which occurred, the open-label trial with a subjective primary outcome – RFS, and the high discontinuations or out-of-protocol status of the trial participants. In addition, the claimed benefits of 3-year imatinib versus 1-year of imatinib may be outweighed by the increased risk of adverse events. The PBAC noted that 40% of patients may never relapse, but may be at risk of significant toxicity. It is also unknown whether the extended adjuvant imatinib treatment for GIST modifies the effectiveness of treatment in the metastatic setting, an issue which remains unresolved. The PBAC noted that there is an ongoing EORTC trial that will examine RFS after cessation of imatinib therapy and that this may provide information regarding the effect of adjuvant treatment on recurrence.

The PBAC noted the submission made no claim in terms of comparative safety over 1-year imatinib treatment. The PBAC considered that a more appropriate description for comparative safety is that 3-year imatinib is inferior to 1-year imatinib with more patients experiencing serious adverse events on extended imatinib treatment, but noted that there are no new types of adverse events than those already established.

The PBAC noted that the economic model compares three years of adjuvant imatinib treatment with one year of adjuvant imatinib treatment (main comparator) using data from

five years' follow-up of the SSGXVIII trial with the transition probabilities derived from this trial. The economic model uses a constant annual probability of recurrence beyond 5 years in both treatment arms (36-month and 12-month imatinib treatment) which suggests continued efficacy over time and non-convergence of the treatment arms beyond the trial period. The PBAC considered that there is inconsistency in the interpretation and use of constant probabilities of recurrence beyond the clinical trial and that the use of constant probabilities is an optimistic assumption that is not well justified.

In addition, the PBAC considered that the utility value of 1.0 applied in the adjuvant setting is unrealistic, as it implies that patients experiencing adverse events do not experience a utility decrement. It therefore leads to an overestimate of the incremental QALYs gained. There is also no consideration of adverse event rates in the economic model and this favours the 36-month imatinib treatment arm because a greater number of grade 3-4 adverse events were observed in this arm of the SSGXVIII trial.

The PBAC considered that the SSGXVIII study results did not provide sufficient evidence that there is a survival advantage in the 36-month arm because few deaths occurred and consequently, median or mean survival gains were not directly observed. The PBAC considered that the claim of life-years gained for the three years versus one year of imatinib, derived from modelling over 30 years was very uncertain as it is based mainly on modelling assumptions about the unobserved (and unknown) treatment effect beyond the timeframe of the trial. The PBAC noted that the extrapolation from 5 years to a lifetime model reduced the incremental cost per life years gained considerably. The PBAC also noted that the base case ICER of between $45,000 and $75,000 per QALY gained is based on the extrapolation to 30 years. When the lower and upper 95% confidence limits of the clinical efficacy of 3-year imatinib are applied (hazard ratio), the ICER ranges from between $15,000 and $45,000 to between $105,000 and $200,000 per QALY gained.

The PBAC therefore rejected the submission on the basis of uncertainty regarding the magnitude of the survival benefit and unacceptably high 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 sponsor has no comments.