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 2012

1. Purpose of Application

The re-submission sought to change the current Authority required listing for the 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

At the March 2012 meeting, the PBAC rejected a submission to increase the maximum duration of treatment from 1 year to 3 years on the basis of uncertainty regarding the magnitude of the survival benefit and unacceptably high cost-effectiveness ratio.

A copy of the Public Summary Document (PSD) from the March 2012 is available at http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2012-03/imatinib

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 Glivec 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 of initial treatment 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.

Applications for continuing treatment may be made by telephone.

5. Clinical Place for the Proposed Therapy

GISTs 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 two 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 claim that 3 years of treatment is more efficacious in prolonging recurrence-free survival (RFS) and overall survival (OS) than 1 year of treatment remains unchanged in the resubmission.

For PBAC's view, see Recommendation and Reasons.

6. Comparator

The re-submission nominated imatinib treatment for 1-year as the main comparator. The PBAC agreed that this was appropriate.

7. Clinical Trials

The scientific basis of comparison with 1-year imatinib is unchanged in the re-submission. Publication details of the SSGXVIII trial have previously been reported in the March 2012 PSD.

The resubmission noted an error in the flow of participants classified as discontinuers: nineteen out of 82 patients in the 3-year arm were incorrectly described as discontinuers in the previous submission; this error was corrected in the submission.

The primary outcome in SSGXVIII was 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. OS was measured in the SSGXVIII trial, as a secondary outcome.

For PBAC's view, see Recommendations and Reasons.

8. Results of Trials

The PBAC recalled its concerns in March 2012 that the trial had an unusual design and was of lower internal validity than is usual for trials in oncology. In particular, there were concerns about the measurement of RFS and that consequently the comparative treatment effect for RFS (i.e. hazard ratio (HR) for RFS) could be over-estimated.

The key primary outcome results of RFS from the SSGXVIII trial for the intention to treat (ITT) population were used for the economic evaluation and are available in the March 2012 PSD.

The PBAC noted an observed difference for RFS between the two treatment arms in favour of the 36-month treatment arm over the 12-month treatment arm (HR 0.46, 95% CI 0.32, 0.65). The PBAC noted that it was unclear exactly how RFS was measured in the trial and also unclear whether there was blinded central review. In the absence of blinded central review, measurement of RFS could be subject to bias. As a result, the HR (RFS) could be an overestimate of the comparative treatment effect for 3-year versus 1-year imatinib.

The key primary outcome results of RFS from the SSGXVIII trial for the efficacy population are presented in the table below.

Results of RFS in SSGXVIII (median follow-up 54 months) – Efficacy population

	Imatinib 400 mg 3-year treatment		**Imatinib 400 mg 1-year treatment**	
	n at risk	**N = 177**	**n at risk**	**N = 181**
Pts with recurrence or death event, n (%)		42 (23.7%)		72 (39.8%)
Censored (alive and recurrence free), n (%)		135		109
Pts censored at baseline, n (%)		1 (0.6)		3 (1.7)
Time to recurrence or death percentiles, months (95%CI)				
25%		48.7 (44.6, 60.8)		24.1 (23.4, 25.3)
50% median		NE		NE
75%		NE		NE
RFS probability estimates, % (95%CI)				
At 6 months	172	98.9 (95.5, 99.7)	166	96.5 (92.4, 98.4)
At 12 months	167	97.1 (93.2, 98.8)	163	95.4 (90.9, 97.7)
At 18 months	164	95.4 (91.0, 97.7)	151	88.9 (83.1, 92.8)
At 24 months	157	91.9 (86.7, 95.1)	126	76.4 (69.2, 82.1)
At 36 months	121	88.1 (82.1, 92.1)	81	62.1 (54.1, 69.1)
At 48 months	71	78.6 (70.4, 84.8)	46	55.2 (46.6, 63.0)
At 60 months	35	67.4 (57.4, 75.6)	25	50.3 (40.7, 59.1)
At 72 months	7	54.1 (35.6, 69.4)	10	50.3 (40.7, 59.1)
Log-rank test p value (two-sided)	**<0.0001**			
3-year vs. 1-year HR (95% CI)	**0.46 (0.31, 0.68)**			

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

The PBAC considered also that the value of RFS as a surrogate for OS had not yet been established in GIST.

The secondary outcome of OS results for the ITT population have previously been reported in the March 2012 PSD. The OS results for the efficacy population are presented in the table below.

Results of secondary outcome OS from the SSGXVIII trial – efficacy population

	Imatinib 400 mg 3-year treatment		Imatinib 400 mg 1-year treatment	
	n at risk	N = 177	n at risk	N = 181
Patients with events, n (%)		8 (4.5%)		20 (11.0%)
Overall survival probability estimates, % (95% CI)				
At 6 months	176	100.0 (100, 100)	173	99.4 (96.0, 99.9)
At 12 months	172	100.0 (100, 100)	171	99.4 (96.0, 99.9)
At 24 months	166	98.2 (94.7, 99.4)	162	97.1 (93.1, 98.8)
At 36 months	138	97.6 (93.8, 99.1)	128	95.8 (91.3, 98.0)
At 48 months	87	96.8 (92.3, 98.7)	77	88.8 (81.4, 93.3)
At 60 months	48	93.9 (86.8, 97.3)	41	81.7 (72.0, 88.3)
At 72 months	12	89.4 (74.5, 95.9)	19	79.1 (67.9, 86.7)
Log-rank test p value (two-sided)	0.0146			
3-year vs. 1-year HR (95% CI)	0.37 (0.16, 0.85)			

CI = confidence interval; HR = hazard ratio; efficacy population = excludes patients without confirmed GIST, with metastatic GIST, and who did not provide consent post-randomisation.

The results for the ITT and efficacy population were similar, with a lower percentage of patients who died reported in the efficacy population. This can be explained by the exclusion of patients with metastatic GIST (3-year: n=11; 1-year: n=13). A large proportion of the patients were still alive at 72 months of follow-up (87.8% for 3-year vs. 77.0% for 1-year imatinib treatment). More than 50% of the patients were censored at 48 months, making the results beyond four years less certain. Median survival rates could not be estimated, as most patients were still alive at the end of the trial.

The PBAC noted that a HR for OS for the high-risk subgroup relevant for the listing was not provided. The data presented did not provide sufficient evidence that 3-year treatment is superior to 1-year treatment for OS, as the number of deaths was low and the mean or median survival could not be calculated. The PBAC noted that the survival benefit in the economic model was largely derived by extrapolation beyond the time horizon of the trial.

The PBAC further noted that it is also unknown whether the extended adjuvant imatinib treatment for GIST modifies the effectiveness of treatment in the metastatic setting. 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 re-submission did not present any new safety information additional to that presented in the previous submission. The incidence of adverse events in the SSGXVIII trial has previously been reported in the March 2012 PSD.

The PBAC recalled its concerns from the previous consideration of 3-year imatinib in the adjuvant setting in March 2012 that the claimed benefits of 3-year treatment versus 1-year treatment may be outweighed by the increased risk of adverse events. The PBAC had noted that up to 40% of patients may never relapse, but may be at risk of significant toxicity.

The PBAC noted that the comparative safety for 3-year imatinib is inferior to 1-year imatinib with more patients experiencing serious adverse events (SAEs) on extended imatinib treatment, but no new types of adverse events were reported. The PBAC noted a more

favourable incidence of SAEs (decreased neutrophil count, increased alanine aminotransferase, decreased white blood cell count, increased aspartate aminotransferase and infections) in the 3-year arm compared with the 1-year arm during the first year of the trial (3.0% vs. 6.7%), although this result was not statistically significant. The PBAC noted that this result is unexpected as both treatment arms were exposed to the same duration and dose intensity of imatinib at that time point, and baseline characteristics were well matched. The PBAC noted that this result was obtained despite the trial not being powered to detect differences in treatment-related SAEs and considered that this may indicate under-reporting for the 3-year arm, possibly due to the open-label nature of the clinical trial. Furthermore, no details on the frequency of unscheduled visits in the first year of the clinical trial were provided, possibly also influencing the reporting of treatment related SAEs.

9. Clinical Claim

The submission described imatinib 3-year treatment as superior in terms of comparative effectiveness and inferior in terms of comparative safety over 1-year imatinib treatment.

10. Economic Analysis

The re-submission presented a modelled economic evaluation based on a superiority claim for comparative benefit and inferiority for comparative harms. The submission presented an incremental cost-effectiveness ratio (ICER) of between $45,000 and $75,000 per quality adjusted life years (QALY) gained based on the RFS outcome from the trial, applied to the PBS population and extrapolated to 10 years duration (from median duration of 54 months in the trial), and applying utility weights from previous PBAC considerations.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

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

12. Recommendation and Reasons

The major re-submission sought to change the current Authority required listing for the 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 (presently 12 months).

The PBAC reaffirmed that imatinib has an established place in the adjuvant treatment of GIST patients at high risk of relapse following surgery, however the optimal duration of therapy is as yet not determined.

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, but was the same as the trial presented in March 2012 to support the initial submission for 3-year adjuvant treatment. The primary outcome was RFS. The PBAC recalled its concerns in March 2012 that the trial had an unusual design and was of lower internal validity than is usual for trials in oncology. In particular, there were concerns about the measurement of RFS and that

consequently the comparative treatment effect for RFS (i.e. HR for RFS) could be over-estimated.

The PBAC noted an observed difference for RFS between the two treatment arms in favour of the 36-month treatment arm over the 12-month treatment arm (HR 0.46, 95% CI 0.32, 0.65). The PBAC noted that it was unclear exactly how RFS was measured in the trial and also unclear whether there was blinded central review. In the absence of blinded central review, measurement of RFS could be subject to bias. As a result, the HR (RFS) could be an overestimate of the comparative treatment effect for 3-year versus 1-year imatinib.

The PBAC considered also that the value of RFS as a surrogate for OS had not yet been established in GIST. The PBAC noted that a HR for OS for the high-risk subgroup relevant for the listing was not provided. The data presented do not provide sufficient evidence that 3-year treatment is superior to 1-year treatment for OS, as the number of deaths was low and the mean or median survival could not be calculated. The PBAC noted that the survival benefit in the economic model was largely derived by extrapolation beyond the time horizon of the trial.

The PBAC recalled its concerns from the previous consideration of 3-year imatinib in the adjuvant setting in March 2012 that the claimed benefits of 3-year treatment versus 1-year treatment may be outweighed by the increased risk of adverse events. The PBAC had noted that up to 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. 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 that the comparative safety for 3-year imatinib is inferior to 1-year imatinib with more patients experiencing serious adverse events (SAEs) on extended imatinib treatment, but no new types of adverse events were reported. The PBAC noted a more favourable incidence of SAEs (decreased neutrophil count, increased alanine aminotransferase, decreased white blood cell count, increased aspartate aminotransferase and infections) in the 3-year arm compared with the 1-year arm during the first year of the trial (3.0% vs. 6.7%), although this result was not statistically significant. The PBAC noted that this result is unexpected as both treatment arms were exposed to the same duration and dose intensity of imatinib at that time point, and baseline characteristics were well matched. The PBAC noted that this result was obtained despite the trial not being powered to detect differences in treatment-related SAEs and considered that this may indicate under-reporting for the 3-year arm, possibly due to the open-label nature of the clinical trial. Furthermore, no details on the frequency of unscheduled visits in the first year of the clinical trial were provided, possibly also influencing the reporting of treatment related SAEs.

The PBAC noted updates to some key assumptions in the economic model comparing three years of adjuvant imatinib treatment with one year of adjuvant imatinib treatment;

- the convergence of RFS by 10 years,
- including disutility from imatinib treatment,
- a reduced price,
- a reduction of the time horizon from 30 years to 10 years and
- a reduced utility value in the adjuvant health state from 1.0 to 0.95.

The PBAC recalled concerns previously expressed in March 2012 about the optimistic assumption that the use of a constant annual probability of recurrence, suggesting continued efficacy over time and non-convergence of the treatment arms beyond the trial period, was implausible. The PBAC therefore considered these amended inputs to the model to be appropriate.

The PBAC noted that the base case ICER presented by the submission, taking into account revised assumptions, was still between $45,000 and $75,000. The PBAC considered this ICER high for treatment in the adjuvant setting and noted some residual uncertainty. The PBAC noted that the ICER was most sensitive to changes in model duration, time to RFS convergence and RFS efficacy; a sensitivity analysis assuming identical cost and efficacy of 1-year vs. 3-year treatment resulted in an increased ICER per QALY gained, still remaining between $45,000 and $75,000, which the PBAC considered plausible. The PBAC recalled that when it recommended the treatment of adjuvant GIST for 1 year the ICER was between $15,000 and $45,000 per QALY gained.

The PBAC recommended the extension to listing, contingent on a price reduction to bring the ICER down from between $45,000 and $75,000 to between $15,000 and $45,000. With this further lower price and the changes to the assumptions in the model the PBAC considered that the concerns it had previously had been addressed.

Recommendation:
Amend the current duration of treatment from 12 months to 36 months as follows:

Restriction:

Authority required
Gastrointestinal stromal tumour

- The treatment must be adjuvant to complete surgical resection of primary gastrointestinal stromal tumour (GIST);
- Patient must be at high risk of recurrence following complete surgical resection of primary GIST;
- The condition must be histologically confirmed by the detection of CD117 on immunohistochemical staining; and
- The treatment must not exceed a dose of 400 mg per day for a period of ~~12~~ *36* months

Prescriber instructions:

- Applications for authorisation of initial treatment 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 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.

- Applications for continuing therapy may be made by telephone.
- 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.

Notes:

- Any queries concerning the arrangements to prescribe imatinib mesylate may be directed to the Department of Human Services (Medicare) on 1800 700 270
- Any queries concerning patients who are enrolled on the Imatinib Compassionate Program may be directed to the Department of Human Services (Medicare) on 1800 700 270.

Applications for authority to prescribe imatinib should be forwarded to:
Department of Human Services
Prior Written Approval of Specialised Drugs
Reply Paid 9826
GPO Box 9826
HOBART TAS 7001

For the following diseases, written approval is needed at initiation and for continuation:
Chronic myeloid leukaemia (chronic phase)
Dermatofibrosarcoma protuberans
Hypereosinopilic syndrome
Chronic eosinophilic leukaemia
Myelodysplastic or myeloproliferative disorder
Aggressive systemic mastocytosis with eosinophilia.

Max Qty:	60 (100 mg) 30 (400 mg)
Rpts:	5

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 did not provide further comment.