PUBLIC SUMMARY DOCUMENT

Product: Dasatinib, tablets, 20 mg, 50 mg and 70 mg, Sprycel®

Sponsor: Bristol-Myers Squibb Pharmaceuticals

Date of PBAC Consideration: March 2007

1. Purpose of Application

To seek Section 100 (Special Authority Program) listing for the treatment of all phases of chronic myeloid leukaemia (CML) in adult patients expressing the Philadelphia chromosome or transcript, bcr-abl tyrosine kinase, who are resistant or intolerant to imatinib mesylate.

2. Background

This drug has not previously been considered by the PBAC.

3. Registration Status

Sprycel was registered by the TGA in January 2007 for:

> Treatment of adults aged 18 years or over with chronic, accelerated or myeloid or lymphoid blast phase chronic myeloid leukaemia with resistance or intolerance to prior therapy including imatinib.
>
> Treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukaemia with resistance or intolerance to prior therapy.

4. Listing Requested and PBAC's View

Section 100 – Authority Required (Special Authority Program)
Treatment of chronic myeloid leukaemia in adult patients expressing the Philadelphia chromosome or transcript, bcr-abl tyrosine kinase, who are resistant or intolerant to imatinib mesylate.

For PBAC's view, see Recommendation and Reasons

5. Clinical Place for the Proposed Therapy

Dasatinib will provide a second-line treatment option for patients who are resistant or intolerant to imatinib mesylate.

6. Comparator

The submission nominated imatinib 800 mg/day for resistant patients and imatinib 300 mg – 400 mg /day for intolerant patients as the comparator. The PBAC accepted that imatinib was the appropriate comparator.

7. Clinical Trials

The scientific basis of comparison was a single randomised trial comparing dasatinib 140 mg/day with imatinib 800 mg/day in chronic phase chronic myeloid leukaemia patients over 12 weeks (32 weeks follow up) (details below). The average doses in the trial were 111 mg/day dasatinib and 798 mg/day imatinib.

In the accelerated and blast phases of CML for resistant and intolerant patients the submission provided a series of phase II, single arm, non-randomised, open label studies with no common comparator.

First author	Publication title	Citation
Kantarjian H et al	Dasatinib or high-dose imatinib for chronic-phase myeloid leukaemia after failure of first-line imatinib: a randomized phase-II trial	Blood (submitted)

8. Results of Trials

The main patient relevant outcome measures were haematological response (major, complete, overall) and cytogenetic response (major, complete, partial). The results of the key trial and supporting studies are summarised in the table below.

Phase	Endpoint	Dasatinib	Imatinib	Comment
Key trial (RCT)				
Chronic Phase imatinib resistant	CCyR	21.8%	8.2%	p=0.04; at 12 weeks
		34.7%	16.3%	p=0.02; follow-up to 1 year
		44.7%	0%	Post-crossover *
	MCyR	35.6%	28.6%	p=0.40; at 12 weeks
		47.5%	32.7%	p=0.09; follow-up to 1 year
		28.9%	0%	Post-crossover *
	CHR	92.1%	81.6%	p=0.06; at 12 weeks and 1 year
Supportive non randomised studies				
Chronic Phase imatinib intolerant	MCyR	64%	60%	Dasatinib trial in TKI failures; 12 wks
	CCyR	42%	41%	Imatinib trial in TKI naïve pts
Accelerated Phase imatinib resistant	MCyR	28%	28%	Dasatinib trial in TKI failures; 12 wks
	CCyR	19%	19%	Imatinib trial in TKI naïve pts
Accelerated Phase imatinib intolerant	MCyR	0%	16%	Dasatinib trial small pt nos (n=8)
	CCyR	0%	10%	Imatinib trial in TKI naïve pts; 12 wks
Blast Phase imatinib resistant	MCyR	28% [a] 49% [b]	16%	Dasatinib trial in TKI failures; 12 wks
	CCyR	21% [a] 41% [b]	7%	Imatinib trial in TKI naïve pts
Blast Phase imatinib intolerant	MCyR	33% [a] 60% [b]	16%	Dasatinib trial in TKI failures; 12 wks
	CCyR	33% [a] 60% [b]	7%	Imatinib trial in TKI naïve pts

MCyR major cytogenetic response, CCyR complete cytogenetic response CHR complete haematological response

* patients were eligible to crossover upon failure; a = CA180-006, b=CA180-015

There was a statistically significant difference in complete cytogenetic response at 12 weeks and one year, favouring dasatinib in the key trial's primary analysis.

In the comparison of chronic phase imatinib intolerant patients both dasatinib and imatinib treated subjects showed substantial responses to treatment but a direct comparison of effect was hampered by the non-randomised nature of the studies. Similar results were found in the accelerated and blast phase comparisons.

The adverse events reported were generally mild to moderate toxicities and similar to imatinib – nausea, diarrhoea, fluid retention and skin rash, though cytopenias including

anaemia, neutropenia, leukopenia and thrombocytopenia and infections were higher in dasatinib than imatinib patients.

9. Clinical Claim

The submission claimed dasatinib has significant advantages in effectiveness over imatinib but has more toxicity.

See Recommendations and Reasons for PBAC's view

10. Economic Analysis

A preliminary economic evaluation using a cost-effectiveness approach was presented based on the key trial only (imatinib resistant in chronic phase CML). The resources included were drug costs and costs of treating adverse events (myelosuppression).

Dasatinib was dominant (more effective and less costly) for both complete cytogenic response at 12 weeks and major cytogenic response at 12 weeks.

A modelled economic evaluation was presented based on the key trial (imatinib resistant in chronic phase CML). The choice of the cost-utility approach was considered valid.

The utility weights were derived from Australian subjects (general population). The resources included were drug costs, resources use and costs of treating adverse events.

For both the incremental cost-effectiveness ratios per life year gained and quality adjusted life year gained, the submission claimed dasatinib was dominant.

The PBAC noted that the drug cost is high and that the incremental cost-effectiveness ratio (ICER) is critically sensitive to the dose of the comparator, imatinib.

11. Estimated PBS Usage and Financial Implications

The submission estimated the net cost to the PBS would be < $10 million in Year 4 of listing. The PBAC was advised that this may be an underestimate if uptake in refractory patients is higher than that predicted.

12. Recommendation and Reasons

The PBAC recommended an authority required listing (exact mechanism to be determined) for the treatment of all phases of chronic myeloid leukaemia (CML) in patients not responding to imatinib because of resistance or intolerance, on a cost-effectiveness basis against imatinib. The price of dasatinib should be calculated such that 140 mg of dasatinib is no greater than the price for 670 mg of imatinib.

The Committee agreed that dasatinib has significant advantages in effectiveness over imatinib in imatinib resistant patients with chronic phase CML as determined by the number of patients achieving a complete cytogenetic response (CCyR) even though the difference in the predefined primary outcome major cytogenetic response (MCyR) did not achieve

statistical significance at either the 12 week or one year timepoint. The PBAC was also prepared, by extension, to accept the effectiveness of dasatinib in accelerated and blast phases CML not responding to imatinib, although the comparative efficacy of the drug in this situation could not be determined with any certainty as the evidence in these conditions was much weaker. However PBAC did not feel that restriction to only chronic phase could be logically justified. Although not reasons for rejection, outstanding areas of concern for the Committee were (1) whether or not this array of cytogenetic response outcomes later in the course of the chronic phase of CML result in survival gain and, if so, what is the magnitude of the gain; and (2) the lack of evidence to support the assumption that a cytogenetic response following treatment with dasatinib will be maintained in the same way as in naïve patients treated with imatinib; that is, what is the durability of dasatinib response?

The PBAC noted that the drug cost is high and that the incremental cost-effectiveness ratio (ICER) is critically sensitive to the dose of the comparator, imatinib. The Committee acknowledged that there are no data available, or likely to become available, on the actual dose of imatinib used in imatinib resistant patients. In the absence of such data the PBAC was prepared to recommend listing on the basis that the price of 140 mg of dasatinib be no greater than 670 mg of imatinib.
The PBAC recommended the listing restriction specify that dasatinib is to be the sole PBS-subsidised therapy. The Committee further recommended the restriction does not differentiate CML by phase, but rather allows treatment in all patients with CML who do not respond to imatinib (defined as the failure to achieve or loss of a major cytogenetic response after a minimum of 12 months of imatinib therapy in chronic phase CML); or who have developed accelerated phase or blast crisis CML while being treated with imatinib; or who have developed a Grade 3-4 non-haematological toxicity that is considered to be related to imatinib. The restriction should also allow treatment in a patient in whom the presence of a mutation causing imatinib resistance has been detected. A cytogenetic response should be required for continuing therapy. In circumstances where a demonstration of response to imatinib is required, a patient who has previously failed treatment with imatinib should not be able to recommence it after stopping dasatinib. The detail of the restriction should be finalised by the RWG with input from the sponsor and other stakeholders.

The PBAC recommended the 20 day safety net rule should not apply.

Recommendation
DASATINIB**,** tablets, 20 mg, 50 mg and 70 mg

Restriction:

NOTE:
Any queries concerning the arrangements to prescribe dasatinib may be directed to Medicare Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

Prescribing information (including Authority Application forms) is available on the Medicare Australia website at www.medicareaustralia.gov.au.

Any queries concerning patients who are enrolled on the Dasatinib Compassionate Program may be directed to Medicare Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

Applications for authority to prescribe dasatinib should be forwarded to:

Medicare Australia
Prior Written Approval of Specialised Drugs
Reply Paid 9826
GPO Box 9826
HOBART TAS 7001

Initial treatment

Authority required
Initial treatment, as the sole PBS-subsidised therapy, of a patient with chronic myeloid leukaemia in any disease phase bearing the Philadelphia chromosome or expressing the transcript, *BCR-ABL,* who has active leukaemia (as defined by presence on current pathology assessments of either the Philadelphia chromosome on cytogenetic or FISH analysis, or the presence of the transcript *BCR-ABL* and morphological evidence of leukaemia) and who has failed an adequate trial of imatinib.

Failure of an adequate trial of imatinib is defined as:

(i) Lack of response to initial imatinib therapy, defined as either:

- failure to achieve a haematological response after a minimum of 3 months therapy with imatinib for patients initially treated in chronic phase; *or*
- failure to achieve any cytogenetic response after a minimum of 6 months therapy with imatinib for patients initially treated in chronic phase as demonstrated on bone marrow biopsy by presence of greater than 95% Philadelphia chromosome positive cells; *or*
- failure to achieve a major cytogenetic response or a peripheral blood *BCR-ABL* level of less than 1% after a minimum of 12 months therapy with imatinib; *or*

(ii) Loss of a previously documented major cytogenetic response (demonstrated by the presence of greater than 35% Ph positive cells on bone marrow biopsy), during ongoing imatinib therapy; or

(iii) Development of accelerated phase or blast crisis in a patient previously prescribed imatinib for any phase of chronic myeloid leukaemia.

Accelerated phase is defined by the presence of 1 or more of the following:
(1) Percentage of blasts in the peripheral blood or bone marrow greater than or equal to 15% but less than 30%; or
(2) Percentage of blasts plus promyelocytes in the peripheral blood or bone marrow greater than or equal to 30%; or
(3) Peripheral basophils greater than or equal to 20%; or
(4) Progressive splenomegaly to a size greater than or equal to 10 cm below the left costal margin to be confirmed on 2 occasions at least 4 weeks apart, or a greater than or equal to 50% increase in size below the left costal margin over 4 weeks; or
(5) Karyotypic evolution (chromosomal abnormalities in addition to a single Philadelphia chromosome).

Blast crisis is defined as either:
(1) Percentage of blasts in the peripheral blood or bone marrow greater than or equal to 30%; or
(2) Extramedullary involvement other than spleen and liver.; *or*

(iv) Disease progression (defined as ≥ 50% increase in peripheral white blood cell count, blast count, basophils or platelets) during first-line imatinib therapy in patients with accelerated phase or blast crisis chronic myeloid leukaemia: *or*

(v) Detection of a mutation in *BCR-ABL* (L248V, G250E, Q252H/R, Y253H/F, E255K/V, H396P/R, and D276G) that infers high level imatinib resistance. (Patients with these mutations but without active leukaemia, will not be approved); *or*

(vi) Grade 3 or 4 non-haematological toxicity that is imatinib related.

Applications for authorisation must be in writing and must include:

(a) a completed authority prescription form; and

(b) a completed Chronic Myeloid Leukaemia Dasatinib PBS Authority Application – Supporting Information Form,

(c) a signed patient acknowledgement

(d) a bone marrow biopsy pathology report demonstrating the patient has active chronic myeloid leukaemia, either manifest as cytogenetic evidence of the Philadelphia chromosome, or morphological evidence of chronic myeloid leukaemia plus qualitative RT-PCR evidence of *BCR-ABL* transcript. (The date of the relevant pathology report needs to be provided); and

(e) a copy of the current confirming pathology report(s) from an Approved Pathology Authority or details of the dates of assessment in the case of progressive splenomegaly or extramedullary involvement or details of Grade 3 or 4 non-haematological toxicity.

NOTE:
Dasatinib will only be subsidised for patients with chronic myeloid leukaemia who are not receiving concomitant PBS-subsidised imatinib mesylate or interferon alfa therapy.

Patients should be commenced on a dose of dasatinib of at least 100mg (base) daily. Continuing therapy is dependent on patients demonstrating a major cytogenetic response to dasatinib therapy or a peripheral blood *BCR-ABL* level of less than 1% at 12 monthly intervals, irrespective of the daily dasatinib dose received.

Continuing treatment
Continuing treatment, as the sole PBS-subsidised therapy, of a patient who has received initial treatment with dasatinib as a pharmaceutical benefit for chronic myeloid leukaemia, and who has demonstrated either a major cytogenetic response, or less than 1% *BCR-ABL* level in the blood, to dasatinib in the preceding 12 months

Applications for authorisation must be in writing and must include:
(1) a completed authority prescription form; and
(2) a completed Chronic Myeloid leukaemia Dasatinib Authority Application Form for continuing treatment; and
(3) demonstration of continued response to treatment as evidenced by either:
(a) major cytogenetic response [see Note explaining definitions of response]. Where this has been supplied within the previous 12 months, only the date of the relevant pathology report need be provided; or
(b) a peripheral blood level of *BCR-ABL* of less than 1% on the international scale [see Note explaining definitions of response]. Where this has been supplied within the previous 12 months, only the date of the relevant pathology report need be provided.

NOTE:
Definitions of response.
A major cytogenetic response is defined as less than 35% Philadelphia positive bone marrow cells.
A bone marrow or peripheral blood *BCR-ABL* level of less than 1% on the international scale (Blood 108: 28-37, 2006) also indicates a response, at least the biological equivalent of a major cytogenetic response.

Authority approval requirements.
For the purposes of assessing response to PBS-subsidised treatment with dasatinib, either cytogenetic analysis indicating the number of Philadelphia positive [t (9;22)] cells in the bone marrow measured by standard karyotyping, or quantitative PCR indicating the relative level of *BCR-ABL* transcript in the peripheral blood using the international scale, must be submitted. For bone marrow analyses, where the standard karyotyping is not informative for technical reasons, a cytogenetic analysis performed on the bone marrow by the use of fluorescence in situ hybridisation (FISH) with *BCR-ABL* specific probe must be submitted.
The cytogenetic or peripheral blood quantitative PCR analyses must be submitted as follows:
(i) between 10 and 12 months of the commencement of treatment with dasatinib, at which time patients in whom a major cytogenetic response or peripheral blood *BCR-ABL* level of less than 1% has been demonstrated may receive authorisation for a further 12 months of treatment; and

(ii) at no greater than 12 month intervals thereafter, to demonstrate that the major cytogenetic response or peripheral blood *BCR-ABL* level of less than 1% has been sustained.
For each authority application where eligibility for continuing PBS-subsidised treatment is to be demonstrated, a copy of the cytogenetic analysis indicating the number of Philadelphia positive [t (9;22)] cells in the bone marrow measured by standard karyotyping, or a copy of the quantitative PCR indicating the relative level of *BCR-ABL* transcript in the peripheral blood using the international scale, must be submitted as described in (i) and (ii) above. For bone marrow analyses, where the standard karyotyping conducted at the time of application is not informative, a copy of a cytogenetic analysis conducted on the bone marrow using FISH with *BCR-ABL* specific probe must be submitted with the authority application. A copy of the non-informative standard karyotype analysis must be included with the authority application.
Where a patient has previously received PBS-subsidised treatment with dasatinib, no approval will be granted for PBS-subsidised re-treatment where that patient has at any time failed to meet the criteria for continuing treatment.

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 chose not to make a comment.