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 acute lymphoblastic leukaemia (ALL) in adult patients expressing the Philadelphia chromosome or transcript, bcr-abl tyrosine kinase, who are resistant or intolerant to prior therapy.

2. Background

Dasatinib 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)
Initial treatment of acute lymphoblastic leukaemia in adult patients expressing the Philadelphia chromosome or the transcript, bcr-abl tyrosine kinase, who are resistant or intolerant to prior therapy.

Resistance to prior therapy may be manifested as progression or lack of response to therapy.

Applications for authorisation must be in writing and must include:

1) a completed authority prescription form; and
2) a completed dasatinib (Sprycel) PBS Authority Application for Use in the Treatment of Adult Philadelphia Positive Acute Lymphoblastic Leukaemia (Ph+ ALL) – Supporting Information form, which includes a statement asserting whether a patient is resistant or intolerant to prior therapy and a definition of prior therapy. In addition, a copy of the confirmatory pathology report from an Approved Pathology Authority must be provided in the case of resistance. For intolerance, details of the nature of the intolerance must be provided; and
3) a pathology cytogenetic report conducted on peripheral blood or bone marrow supporting the diagnosis of Ph+ ALL to confirm eligibility for treatment, or a qualitative PCR report documenting the presence of the bcr-abl transcript in either peripheral blood or bone marrow.

Continuing treatment of adult patients with acute lymphoblastic leukaemia expressing the Philadelphia chromosome or the transcript, bcr-abl, where the patient has previously received PBS-subsidised treatment with dasatinib.

For the 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 have failed chemotherapy for prior therapy.

6. Comparator

The submission nominated imatinib as the comparator.

Although the Committee acknowledged that imatinib is used in this condition and is an appropriate comparator according to the 2006 PBAC Guidelines as the therapy likely to be replaced in practice, it is not subsidised by the PBS for this use, nor are there any data on the dose and cost-effectiveness of imatinib in ALL, and thus no basis upon which to determine if dasatinib is a cost-effective treatment.

7. Clinical Trials

The submission presented two phase II, single arm, open label, non randomised studies: 140 mg/day dasatinib in imatinib resistant or intolerant Ph+ ALL patients (follow up for 32 weeks) and imatinib (400 mg/day or 600 mg/day to 800 mg/day) in relapsed or refractory Ph+ ALL patients over 12 weeks.

The studies forming the basis of the submissions are tabulated below.

Trials	Study/Citation
Dasatinib	Bristol-Myers Squibb CA180-015 A phase II study of dasatinib in subjects with Lymphoid Blast phase Chronic Myeloid Leukaemia or Philadelphia Chromosome Positive Acute Lymphoblastic Leukaemia resistant to or intolerant of imatinib mesylate 2005 (12 week interim analysis) and 2006 (32 weeks safety update).
Imatinib	Ottman OG, Druker BJ, et al. (2002). A phase 2 study of imatinib in patients with relapsed or refractory Philadelphia chromosome-positive acute lymphoid leukaemia. Blood; 100 (6): 1965-1971

8. Results of Trials

The following table shows the effectiveness results from the studies.

Outcomes	CA180-015 *(N=36)*		Ottmann (2002) (N=48)	
	12 weeks	32 weeks	All responses [a]	Sustained responses [b]
Major Haematological Response (MaHR) [c]	41.7% (15/36)	41.7% (15/36)	-	6%
Complete Haematological Response (CHR)	30.6% (11/36)	33.3% (12/36)	19% (9/48)	6% (3/48)
Major Cytogenetic Response (MCyR)	58.3% (21/36)	58.3% (21/36)	-	-
Complete Cytogenetic Response (CCyR)	44% (16/36)	58.3% (21/36)	17% (8/48)	NR
No evidence of Leukaemia	11.1% (4/36)	8.3% (3/36) [d]	-	0%
Progression free survival (95%CI) [e]	-	3.3 (1.1, 7.2) mo	-	2.2 (1.8, 2.8) mo
No response/not evaluable	-	55.6%	39.6% (19/48)	72.9% (35/48)

a represents best response at any time during therapy
b footnote noted in table but not defined.

c "Only" 5/15 subjects who achieved a MaHR progressed with most of them in excess of 6 months: a progression free survival >8 months in >20% of subjects.
d reported as 4.8% in 'sustained' response in submission.
e This outcome could be time to progression as the submission states that "the imatinib group were also quicker to progress".
Definitions:
Haematological response (HR): § major (MHR), complete (CHR), overall (OHR)
• White Blood Cells = institutional ULN (upper limit of normal)
• Platelets <450,000/mm^3
• No blasts of promyelocytes in peripheral blood
• <5% myelocytes plus metamyelocytes in peripheral blood
• Basophils <20% in peripheral blood
• No extramedullary involvement (including no hepatomegaly or splenomegaly)
• Maintained at least 4 weeks after the first documented at =day 14
Cytogenetic response (CyR): Defined as prevalence of Ph+ metaphases on a bone marrow biopsy/aspirate. Major (MCyR) is defined as having =35% Ph+ cells - divided into two components: 1) a complete cytogenetic response (CCyR) which is the complete elimination of Ph+ cells (or 0% Ph+ cells), and 2) a partial cytogenetic response (PCyR [1% to 35% Ph+ cells]).
§ This definition is for complete HR .

The submission asserted that the patients treated with dasatinib showed a greater response than those treated with imatinib. The PBAC was advised that direct comparison of results from the respective studies was not possible as this is a comparison of phase II, single arm, open label, non randomised studies with no common comparator and dissimilar patient populations.

The toxicity results at 12 weeks are shown in the following table.

Results, % (n/N)	**CA180-015 (N=36)**	**Ottmann (2002) (N=56)**
SAE's (>Grade 2 nonhaematological toxicity)	**78% (28/36)**	**-**
Pyrexia	22% (8/36)	-
Pleural Effusion	14% (5/36)	-
Febrile Neutropenia	14% (5/36)	8% (4/56)
Nausea, Vomiting	-	4% (2/56) 77%, 63% [a]
Elevated liver aminotransferases	-	2% (1/56)
Fever, Headache	-	4% (2/56)
Cerebral Oedema	-	2% (1/56)
Anorexia	-	2% (1/56)
Cachexia	-	2% (1/56)
Generalised Rash	-	2% (1/56)
Lower limb oedema [a]	-	29%
Periorbital oedema [a]	-	27%
Face oedema [a]	-	11%
Muscle cramps [a]	-	14%
Diarrhoea [a]	-	11%
Skin rash [a]	-	11%
Myelosuppression (Grade 3-4)		
Leukopenia	64% (23/36)	68% (38/56)
Neutropenia	74% (26/36)	66% (37/56)
Anaemia [b]	44% (16/36)	38% (21/56)
Thrombocytopenia	75% (27/36)	48% (27/56)
Deaths	***42% (15/36)***	***NR***
Within 30 days of treatment	86.7% (13/15)	
Disease progression	26.7% (4/15)	

Results, % (n/N)	CA180-015 (N=36)	Ottmann (2002) (N=56)
Infection	46.7% (7/15)	
Other [c]	13.3% (2/15)	
>30 days after treatment	13.3% (2/15)	
Disease Progression	100% (2/2)	

a Treatment related adverse events with >10% frequency and >grade 2 toxicity reported only in the text on p200 of the submission (nausea 77%, vomiting 66%)
b anaemia of any grade
c respiratory failure/damaged general status)
SAE = serious adverse events; NR = not reported

Both treatments showed considerable toxicity including myelosuppression. Thrombocytopenia occurred more often with dasatinib patients than imatinib patients.

9. Clinical Claim

The submission claimed that dasatinib had significant clinical advantages over imatinib but had more toxicity.

See Recommendation and Reasons for PBAC's views

10. Economic Analysis

A preliminary economic evaluation was not presented.

A modelled economic evaluation was not presented.

The drug costs/patient/year were estimated to be between $75,000 – $105,000 for 140 mg/day for dasatinib and were estimated to be between $ 45,000 – $75,000 for imatinib 400 mg/day and between $75,000 - $105,000 for 600mg to 800mg/day.

11. Estimated PBS Usage and Financial Implications

The cost was estimated to be < $10 million per year.

12. Recommendation and Reasons

The PBAC is sympathetic to the needs of people with Philadelphia chromosome positive acute lymphoblastic leukaemia (ALL) and acknowledged that, with some caveats as described below, treatment with dasatinib may result in clinically meaningful benefits in this rare condition. However, the Committee rejected the application on the basis of uncertain cost-effectiveness against the comparator, imatinib. Although the Committee acknowledges that imatinib is used in this condition and is an appropriate comparator according to the 2006 PBAC Guidelines as the therapy likely to be replaced in practice, it is not subsidised by the PBS for this use, nor are there any data on the dose and cost-effectiveness of imatinib in ALL, and thus no basis upon which to determine if dasatinib is a cost-effective treatment.

The Committee was unable to confidently conclude that dasatinib is more effective than imatinib in the treatment of adult patients with Philadelphia chromosome positive ALL, who are resistant to, or intolerant of, prior therapy, although the submitted data show this may be the case. A conclusion of superior effectiveness was hampered by the submission's use of an indirect comparison of two phase II, single arm, open label, non randomised studies (dasatinib: CA1890-015; imatinib: Ottmann et al, 2002). Although the Committee generally

accepted the Pre-PBAC Response arguments that the groups in the two studies are adequately comparable in the context of this disease, residual uncertainty about the comparative clinical effectiveness of the two agents remained because of the lack of a common reference.

Although the validity of the primary outcome in the dasatinib trial, major haematological response, as a surrogate for progression of disease is unknown, and the submission did not attempt to quantify the deferred time to progression of disease, which is the aim of therapy – the proportion of patients remaining on treatment at 32 weeks was high, which tends to support the clinical relevance of the surrogate outcomes.

The PBAC considered that the rule of rescue cannot apply to the use of dasatinib in ALL as there are a number of other treatment options available including bone marrow transplant, and salvage chemotherapy, as well as imatinib.

The PBAC considered that the dose of dasatinib was unlikely to exceed 140 mg/day in the majority of patients as the use of higher doses is limited by toxicity.

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 is continuing to work with the PBAC to achieve a suitable listing.