PUBLIC SUMMARY DOCUMENT

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

Sponsor: Bristol-Myers Squibb Pharmaceuticals

Date of PBAC Consideration: July 2007

1. Purpose of Application

The submission sought an authority required listing on the PBS for adults with acute lymphoblastic leukaemia (ALL), expressing the Philadelphia chromosome or the transcript BCR-ABL kinase, who are resistant to or intolerant of, prior therapy.

2. Background

At the March 2007 meeting, the PBAC rejected a submission for this indication because of the inability of the Committee to form a view on the cost-effectiveness of the comparator, imatinib, in the treatment of ALL due to the absence of adequate data. The Committee was therefore unable to determine whether dasatinib treatment was cost-effective.
(See also Public Summary Document for March 2007).

3. Registration Status

Dasatinib was registered by the TGA on 15 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

Authority required

Initial treatment, as monotherapy, of acute lymphoblastic leukaemia in an adult 18 years or over expressing the Philadelphia chromosome or the transcript, bcr-abl tyrosine kinase, who is resistant to, or intolerant of, prior therapy.

Resistance or intolerance is defined 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 Philadelphia Positive Acute Lymphoblastic Leukaemia PBS Authority Application – Supporting Information form [www.medicareaustralia.gov.au], which includes details of all prior therapy(s) and the nature of the resistance or intolerance. If approval is sought on the grounds of resistance to prior therapy, a copy of the pathology report from an Approved Pathology Authority must be provided.
(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 been issued with an authority prescription for dasatinib. Continuing treatment applications may be made by telephone.

The PBAC accepted that many current and essentially all future patients with relapsed or refractory Philadelphia +ve ALL will have received and by definition failed imatinib. Hence, it was most appropriate to consider the application for dasatinib specifically in the situation of leukaemia relapsed or refractory to chemotherapy and imatinib.

5. Clinical Place for the Proposed Therapy

Dasatinib would provide a second-line treatment option for patients with acute lymphoblastic leukaemia who have failed prior therapy.

6. Comparator

There was no change to the comparator nominated previously.

7. Clinical Trials

The submission presented the results for an additional interim analysis of data from the key study, CA180-015, which was presented in the March 2007 submission.

The analysis was specific to all 46 Ph+ ALL patients enrolled and treated – with a minimum follow-up of 8 months (32 weeks; reported at the American Society of Haematology (ASH) conference).

8. Results of Trials

The results for the third interim analysis were broadly comparable to those of the second interim analysis, but included the first estimation of the effect of treatment on overall survival (median 8 months). Fifty four percent of patients achieved a complete cytogenetic response at 32 weeks and 22% of all patients were alive and free of progressive disease at 1 year.

For PBAC's view of these results, see Recommendation and Reasons.

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 view.

10. Economic Analysis

The submission presented a stepped approach economic analysis – firstly a cost consequence analysis using the surrogate endpoints, haematologic response and cytogenetic response, from Key Study CA180-015; and secondly, an incremental cost-effectiveness analysis comparing dasatinib with salvage chemotherapy and imatinib using the endpoints of progression free survival and overall survival.

Overall survival analysis:
The base case analysis of dasatinib versus salvage chemotherapy in Ph+ ALL patients who have failed prior therapy estimated the incremental cost-effectiveness ratio to be in the range $75,000 - $105,000 per additional year of survival.

The base case analysis of dasatinib versus imatinib in Ph+ ALL patients who have failed prior therapy estimated the incremental cost-effectiveness ratio to be between $15,000 - $45,000 per additional year of survival.

Progression free analysis:
The base case analysis of dasatinib versus imatinib in Ph+ ALL patients who have failed prior therapy estimated the incremental cost-effectiveness ratio to be between $45,000 - $75,000 per additional year of progression free survival.

The weighted comparative analysis of dasatinib versus salvage chemotherapy and imatinib in Ph+ ALL patients who have failed prior therapy estimated the incremental cost-effectiveness ratio to be between $75,000 - $105,000 per additional year of survival.

11. Estimated PBS Usage and Financial Implications

The PBAC considered the submission's estimate of the number of patients who would commence dasatinib was underestimated, and it was highly likely all relapsed or refractory patients would receive dasatinib if imatinib has been used first-line. The PBAC requested the Pharmaceutical Benefits Pricing Authority consider entering into a risk sharing arrangement for dasatinib.

12. Recommendation and Reasons

The PBAC recommended the listing of dasatinib on the PBS for the treatment of patients with acute lymphoblastic leukaemia, expressing the Philadelphia chromosome or the transcript bcr-abl kinase, who are resistant to, or whose disease has relapsed on, prior therapy. The PBAC considered that the estimated incremental cost-effectiveness ratio per life year gained for dasatinib versus salvage chemotherapy and imatinib was very high and uncertain. The PBAC noted the incremental cost-effectiveness ratio varied between $45,000 - $75,000 (versus imatinib) to between $75,000 - $105,000 (versus salvage chemotherapy only), though a valid assessment of the true costs and benefits was difficult from the data provided. However, the PBAC considered that the listing of dasatinib in this small patient group was consistent with the intention of its 'Rule of Rescue' guidelines.

The PBAC noted the prognosis of patients with overt leukaemia who have failed chemotherapy and imatinib is extremely poor (< 4 month median survival), as no effective anti-leukaemia therapies exist. The updated data from Study CA180-015 specifically addressed the efficacy of dasatinib in this clinical scenario and convincingly demonstrated evidence of rescue in a significant minority of patients. Specifically, that 54% of patients achieved a complete cytogenetic response at 32 weeks and 22% of all patients were alive and free of progressive disease at 1 year clearly indicated both rescue from a near death situation and durable benefit.

Recommendation

DASATINIB, tablet, 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

Section 85 Authority required
Initial treatment, as monotherapy, of a patient with acute lymphoblastic leukaemia (ALL) bearing the Philadelphia chromosome or expressing the transcript, *BCR-ABL*, who has failed treatment with chemotherapy AND imatinib and where appropriate, allogeneic haemopoietic stem cell transplantation.

Failure of treatment is defined as either:

(i) Failure to achieve a complete morphological and cytogenetic remission after a minimum of two months treatment with intensive chemotherapy and imatinib;
(ii) Morphological or cytogenetic relapse of leukaemia after achieving a complete remission induced by chemotherapy and imatinib;
(iii) Morphological or cytogenetic relapse or persistence of leukaemia after allogeneic haemopoietic stem cell transplantation.

Patients must have active leukaemia, as defined by presence on current pathology assessments of either morphological infiltration of the bone marrow (>5% lymphoblasts) or cerebrospinal fluid or other sites; OR the presence of cells bearing the Philadelphia chromosome on cytogenetic or FISH analysis in the bone marrow of patients in morphological remission.

The first authority application must be made in writing and must include:
(a) a completed authority prescription form; and
(b) a completed Acute Lymphoblastic Leukaemia Dasatinib PBS Authority Application – Supporting Information Form; and
(c) a signed patient acknowledgement; and
(d) a pathology report demonstrating that the patient has active acute lymphoblastic leukaemia, either manifest as cytogenetic evidence of the Philadelphia chromosome, or morphological evidence of acute lymphoblastic leukaemia plus qualitative RT-PCR evidence of *BCR-ABL* transcript. The date of the relevant pathology report(s) need(s) to be provided.

Maximum quantity: 60 (20mg, 50 mg, 70 mg)
Repeats: 2

No applications for increased maximum repeats will be authorised.

Section 85 Authority required
Continuing treatment, as monotherapy, of a patient with acute lymphoblastic leukaemia bearing the Philadelphia chromosome or expressing the transcript, *BCR-ABL*, where the patient has previously been issued with an authority prescription for dasatinib and does not have progressive disease.

Authority applications for continuing treatment may be made by telephone on 1800 700 270 (hours of operation 8 a.m. to 5p.m. EST Monday to Friday).

Note:
Dasatinib will only be subsidised for patients with acute lymphoblastic leukaemia who are not receiving concomitant PBS-subsidised imatinib mesylate and who are not appropriate for an allogeneic haemopoietic stem cell transplant.

Maximum quantity: 60 (20mg, 50 mg, 70 mg)
Repeats: 2

No applications for increased maximum repeats will be authorised.

GRANDFATHER
Section 85 Authority required
Initial treatment, as monotherapy, of a patient with acute lymphoblastic leukaemia bearing the Philadelphia chromosome or expressing the transcript, *BCR-ABL*, who has been treated **prior to LISTING DATE 2007** and has failed treatment with chemotherapy and where appropriate, allogeneic haemopoietic stem cell transplantation.

Patients must have active leukaemia, as defined by presence on current pathology assessments of either morphological infiltration of the bone marrow (>5% lymphoblasts) or cerebrospinal fluid or other sites; OR the presence of cells bearing the Philadelphia chromosome on cytogenetic or FISH analysis in the bone marrow of patients in morphological remission.

The first authority application must be made in writing and must include:
(a) a completed authority prescription form; and
(b) a completed Acute Lymphoblastic Leukaemia Dasatinib PBS Authority Application – Supporting Information Form; and
(c) a signed patient acknowledgement; and
(d) a pathology report demonstrating that the patient has active acute lymphoblastic leukaemia, either manifest as cytogenetic evidence of the Philadelphia chromosome, or morphological evidence of acute lymphoblastic leukaemia plus qualitative RT-PCR evidence of *BCR-ABL* transcript. The date of the relevant pathology report(s) need(s) to be provided.

Maximum quantity: 60 (20mg, 50 mg, 70 mg)
Repeats: 2

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 comment.