

## **dasatinib, 20mg, 50 mg, 70 mg tablets (Sprycel®) No. (370/07)** **Bristol-Myers Squibb Pharmaceuticals Ltd**

6 April 2007

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

**ADVICE:** following a full submission

**dasatinib, 20mg, 50mg, 70mg tablets (Sprycel®)** is accepted for restricted use within NHS Scotland for the treatment of adults with chronic myeloid leukaemia (CML) with resistance or intolerance to prior therapy including imatinib mesylate.

It should be restricted to use in patients who are in the chronic phase of the disease. The manufacturer's justification of the treatment's cost in relation to its health benefits for the accelerated or blast phases was not sufficient to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

**Chairman**  
**Scottish Medicines Consortium**

**Indication**

The treatment of adults with chronic, accelerated or blast phase chronic myeloid leukaemia (CML) with resistance or intolerance to prior therapy including imatinib mesylate.

**Dosing information**

70 mg twice daily with the potential for dose escalation (allowed up to 90 mg or 100 mg twice daily in trials) in patients who do not achieve haematological or cytogenetic response, or dose adjustment for undesirable effects.

**Product availability date**

November 2006. Dasatinib is designated an orphan medicinal product for this indication.

**Summary of evidence on comparative efficacy**

Chronic myeloid leukaemia (CML) results in proliferation of abnormal stem cells that compromise normal white blood cell production. It progresses through a chronic phase, which may last several years, an accelerated phase lasting from 6 to 18 months and a blast phase which has a very poor prognosis. Ninety-five percent of people with CML have a chromosomal abnormality resulting in an oncogene called the 'Philadelphia chromosome' or Bcr-Abl. This gene codes for proteins with high tyrosine phosphokinase activity.

Dasatinib is a competitive inhibitor at the binding site for Bcr-Abl (or other protein kinases) and prevents activation or over-expression of pathways responsible for malignant cells. It binds to Bcr-Abl kinase in both active and inactive conformations whereas imatinib binds only in the inactive configuration.

Dasatinib has been studied in five phase II open-label clinical trials involving adult patients in different phases of CML. One comparative study recruited patients with chronic CML who were resistant to imatinib. Imatinib-intolerant patients were excluded. All other studies were single-arm trials that recruited patients resistant to or intolerant of imatinib. Dasatinib was administered at a dose of 70mg twice daily but dose adjustment was allowed for disease progression, lack of response or to manage drug toxicity.

Study outcomes included haematological response (HR), based on numbers or proportions of normal and abnormal cells in the peripheral blood or bone marrow, and classified as complete (CHR), no evidence of leukaemia (NEL), major HR (CHR or NEL), minimum (MiHR) or overall HR (any of the above responses). Cytogenetic response (CyR) was based on the prevalence of Philadelphia-positive metaphases among cells in metaphase on a bone marrow sample and was classified as complete, partial, minor or minimal. Major CyR was defined as complete or partial CyR. Although all of the studies shared entry criteria, such as imatinib resistance, and response criteria, such as haematological response, the definitions for these varied considerably between trials, reflecting the phase of disease under study.

### **Chronic CML**

In the comparative trial, patients were randomised in a 2:1 ratio to dasatinib or high-dose imatinib (400mg twice daily). Patients with a lack of response to study medication, confirmed disease progression or persistent intolerance despite dose reduction could be crossed over to the alternative therapy which was continued until the occurrence of disease progression or intolerable toxicity.

In an interim analysis at 12 weeks, major cytogenetic response (the primary end-point) was achieved by 35/101 (35%) of patients allocated to dasatinib compared with 14/49 (29%) in the imatinib group. The rates for complete CyR were 21% and 8% respectively. Among 35 dasatinib subjects achieving MCyR, one subject lost partial cytogenetic response after a 5-month dosing interruption due to thrombocytopenia. Among 14 imatinib subjects achieving MCyR, one subject had progressed after 5 months.

In the dasatinib group, 6 (6%) of patients crossed over to imatinib (3 due to lack of response/progression; 3 for intolerance), compared with 36 (73%) of imatinib patients who crossed over to dasatinib (27 due to lack of response/progression; 9 for intolerance). Among patients for whom data on major CyR were available post-crossover the response rates were 42% for patients crossed over from imatinib to dasatinib (n=19) and 0% for crossover from dasatinib to imatinib (n=4). Complete haematological response rates prior to crossover (with 95% confidence intervals) were 92% (85%, 96%) in the dasatinib group and 82% (68%, 91%) in the imatinib group.

A non-comparative trial provides longer follow-up of patients with imatinib resistant or intolerant chronic phase CML treated with dasatinib. At an interim analysis when patients had been followed up for a median of 8.3 months, the overall response rate for major CyR was 97/186 (52%), with a higher response rate among imatinib-intolerant patients (47/59 [80%]) than among resistant patients (50/127 [39%]). Disease progression had occurred in one imatinib-intolerant and 15 imatinib-resistant patients.

### **Accelerated and blast phase CML**

In three non-comparative open-label studies with a similar design, patients with accelerated phase, myeloid blast phase or lymphoid blast phase CML resistant or intolerant to imatinib were treated with dasatinib. The primary end-points were overall and major haematological response. The results from interim analyses, when patients had been followed up for a median of 8.3 months, are presented below for haematological responses.

**Haematological response rates with  $\geq 8$  months' follow-up in patients with CML resistant or intolerant to imatinib in 3 trials at 3 different phases of CML**

	n	OHR	MaHR	Disease progression*
<b>Accelerated Phase CML</b>				
<b>Number of patients (%)</b>				
Total	107	87 (81%)	69 (64%)	7/69 (10%)
Resistant	99	80 (81%)	64 (65%)	
Intolerant	8	7 (88%)	5 (63%)	
<b>Myeloid Blast phase</b>				
Total	74	39 (53%)	25 (34%)	3/25 (12%)
Resistant	68	36 (53%)	24 (35%)	
Intolerant	6	3 (50%)	1 (17%)	
<b>Lymphoid Blast phase</b>				
Total	42	15 (36%)	13 (31%)	7/13 (54%)
Resistant	37	14 (38%)	12 (32%)	
Intolerant	5	1 (20%)	1 (20%)	

OHR= Overall haematological response MaHR= Major haematological response

\*Disease progression among patients achieving MaHR

### Summary of evidence on comparative safety

The most frequently reported ( $\geq 10\%$ ) non-haematological adverse events (AEs) from the clinical trial programme included gastrointestinal AEs, fluid retention events, headache, musculoskeletal pain, fatigue, asthenia, rash, dyspnoea, and pyrexia. The majority of adverse events were considered to be drug-related. Important identified risks are toxicity affecting the gastrointestinal system and fluid retention. Haemorrhage occurred in 23% of subjects treated with dasatinib.

In the comparative trial involving imatinib resistant patients in the chronic phase of CML (but which excluded imatinib-intolerant patients), gastrointestinal adverse events, fluid retention and muscle spasm were more common with imatinib, while bleeding events and pleural effusion were more common with dasatinib.

### Summary of clinical effectiveness issues

The comparative trial was not designed to test the statistical significance of differences between study groups for any outcome measure. Response rates (haematological and cytogenetic) were estimated along with their 95% exact confidence intervals, however these are not presented in the most recent interim analysis. All other trials are non-comparative.

Although one non-comparative trial in patients with chronic CML provides data from a longer follow-up than from the comparative trial in chronic CML, there are important differences in design between the studies. These include the exclusion of imatinib-intolerant patients from the comparative study but not from the second study, and the potential for crossover from dasatinib to imatinib or vice versa in the comparative trial.

Dose adjustment of dasatinib was permitted during studies and the median daily dose administered was 105mg in the comparative and non-comparative chronic-phase trials respectively, 108mg in the trial involving patients in the accelerated phase and 137-140mg in blast-phase studies.

From expert advice received by SMC it appears that mutation analysis may have the potential to guide treatment in patients who are not responding to imatinib by identifying kinase domain mutations which are associated with imatinib resistance. One mutation is also associated with resistance to dasatinib.

The European Public Assessment Report (EPAR) for dasatinib comments that most of the identified risks were manageable, and adds that long-term safety data on the treatment with dasatinib is important missing information. It identifies a risk management plan to address important identified risks (myelosuppression, fluid retention, bleeding related events and QT interval prolongation); important potential risks (severe hepatotoxicities and phototoxicity) and important missing information (patients with moderate to severe hepatic impairment, reproductive and developmental toxicology and carcinogenicity).

## **Summary of comparative health economic evidence**

The manufacturer submitted a cost-utility analysis comparing treatment with imatinib 400mg BD with dasatinib 70mg BD for patients with chronic, accelerated and blast phase CML who were resistant to 400-600mg of imatinib. A Markov model with a lifetime horizon was used and the main clinical data sources were phase II non-comparative studies. The manufacturer estimated that treatment with dasatinib 70mg BD in the chronic phase was dominant i.e. it resulted in more QALYs at a lower cost than treatment with imatinib 400mg BD. The ICERs for patients in the accelerated and blast phases were estimated at £44,456 and £63, 727 respectively.

The model structure did not allow for discontinuation of treatment due to resistance. The clinical data showed a large proportion of patients in the chronic phase were resistant to 400mg BID of imatinib but this was not taken into account in the model as patients were assumed to remain on high dose imatinib even if they were resistant.

In terms of the model inputs, the clinical data were based on phase II non-comparative studies with relatively short-term follow-up. The costs and resource use estimates included in the model for the treatment of adverse events seemed quite high but did not appear to bias the results. However, it should be noted that patients were assumed to only experience adverse events in the initial 3-month treatment period. Resource use estimates were based on one expert opinion and were not included in the one-way sensitivity analysis but SMC clinical experts indicated that the estimates were reasonable. Transition probabilities and the cost of treating adverse events were also not included in the one-way sensitivity analysis.

In summary, for the chronic phase of CML the economic case has been demonstrated. However, for the accelerated and blast phases of CML, the manufacturer's justification of the treatments health benefit in relation to its cost was not favourable enough to gain approval by SMC.

## **Budget impact**

The manufacturer estimated that the net drug budget impact will be £119k in year 1 rising to £122k in year 5.

The net drug budget impact estimates were based on 107 patients receiving dasatinib in year 1 and 109 in year 5. The patient numbers were based on the number of CML patients who are resistant to imatinib – 26% in chronic phase, 45% in accelerated phase and 92% in the blast phase. The manufacturer assumed 100% uptake but also provided data based on a

slower uptake in the first few years after launch. The budget impact will however be less than this due to the restriction to chronic phase applied by SMC.

## Patient and public involvement

Patient Interest Submission: Leukaemia Care

## Comparators

Bone marrow transplant. Imatinib.

## Cost per treatment course and relevant comparators

Although dasatinib is licensed for patients with resistance or intolerance to prior therapy including imatinib, a cost comparison with imatinib at licensed doses is provided below, since continuation of imatinib may be an option for some patients.

Regimen	Cost for 52 weeks' treatment
Dasatinib (Sprycel®) 70 mg to 100 mg twice daily*	£31,627 to £63,254
Imatinib (Glivec®) 400 to 800mg daily	£19,463 to £38,926

\* Doses may be reduced below 70mg in response to intolerance

***Doses are shown for general comparison and do not imply therapeutic equivalence.***

## Additional information

Dasatinib is designated an orphan medicinal product for this indication.

**Advice context:**

*No part of this advice may be used without the whole of the advice being quoted in full.*

*This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.*

*This assessment is based on data submitted by the applicant company up to and including 23 March 2007.*

*Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.*