# Scottish Medicines Consortium

## dasatinib, 20mg, 50mg, 70mg tablets (Sprycel®) No. (371/07)

### 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 (Sprycel®)** is not recommended for use within NHS Scotland for the treatment of adults with Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia with resistance or intolerance to prior therapy.

It has been associated with haematological and cytogenetic responses in patients resistant or intolerant to existing treatment. However, the economic case was not sufficiently robust and the manufacturer's justification of the treatment's cost in relation to its health benefits 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 Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia with resistance or intolerance to prior therapy.

## 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 as an orphan medicinal product for this indication.

## Summary of evidence on comparative efficacy

Acute lymphoblastic leukaemia (ALL) results from the uncontrolled proliferation and expansion of immature lymphoid cells in the bone marrow, blood and other organs. This disrupts the production of normal blood cells. About 25% of adults with ALL are Ph+, with 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 one phase II non-comparative open-label clinical trial involving adult patients with Ph+ ALL and which also recruited patients with Ph+ lymphoid blast phase chronic myeloid leukaemia (CML). All patients were resistant or intolerant to imatinib. Dasatinib was administered at a dose of 70mg/day 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 Ph+-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.

The trial recruited 36 patients with Ph+ ALL resistant or intolerant to imatinib. Results for overall and major HR (the primary end-points) in those patients are presented below.

**Haematological response rates with ≥8 months' follow-up in patients with Ph+ ALL resistant or intolerant to imatinib**

| | n | OHR | MaHR | Disease progression* |
|---|---|---|---|---|
| **Ph + ALL** | | **Number of patients (%)** | | |
| Total | 36 | 18 (50%) | 15 (42%) | 5/15 (33%) |
| Resistant | 34 | 16 (47%) | 13 (38%) | |
| Intolerant | 2 | 2 (100%) | 2 (100%) | |

Ph+ ALL= Philadelphia chromosome positive acute lymphocytic leukaemia
OHR= Overall haematological response MaHR= Major haematological response
*Disease progression among patients achieving MaHR

## Summary of evidence on comparative safety

The most frequently reported non-haematological adverse events (AEs) from the clinical trial programme (including trials involving patients with Ph+ CML) 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.

## Summary of clinical effectiveness issues

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

No formal economic analysis was provided for patients with Ph+ALL. The manufacturer assumed that Ph+ALL patients were similar to blast phase CML patients and estimated a cost/QALY of £63,727.

The assumption that patients with Ph+ALL were similar to patients with blast phase CML seemed unrealistic as these diseases differ both in terms of the course of the disease and the patient populations affected. Due to the lack of information and the high cost per QALY estimate the economic case has not been demonstrated.

## Budget impact

No budget impact estimate was provided by the manufacturer.

## Patient and public involvement

Patient Interest Group Submission: Leukaemia Care

## Comparators

Bone marrow transplant. Imatinib.

## Cost per treatment course and relevant comparators

| Regimen | Cost for 52 weeks' treatment |
|---|---|
| **Dasatinib (Sprycel®) 70 mg to 100 mg twice daily*** | **£31,627 to £63,254** |
| Imatinib (Glivec®) 600mg daily | £29,194 |

* 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 as 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.*