

nilotinib, 200mg capsules (Tasigna®) (440/08)
Novartis Pharmaceuticals UK Ltd

8 February 2008 (*issued May 2008*)

The Scottish Medicines Consortium 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

nilotinib (Tasigna®) is accepted for restricted use within NHS Scotland for treatment of chronic phase Philadelphia chromosome positive chronic myelogenous leukaemia (CML) in adult patients resistant to or intolerant of at least one prior therapy including imatinib. It should be restricted to use in patients who are in the chronic phase of the disease.

The manufacturer has not made a submission for use in the accelerated phase. As a result we cannot recommend its use within NHSScotland.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

The treatment of chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukaemia (CML) in adult patients resistant to or intolerant of at least one prior therapy including imatinib.

The European Medicines Agency (EMA) suggests that the indication should also include the phrase: Efficacy data in patients with CML in blast crisis are not available.

Dosing information

400mg twice daily.

Date of licensing

19 November 2007

In May 2006 nilotinib was granted orphan drug status in Europe for this indication.

Product availability date

May 2008

Summary of evidence on comparative efficacy

Chronic myelogenous 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' (Ph+) or Bcr-Abl. This gene codes for proteins with high tyrosine phosphokinase activity. Nilotinib is a tyrosine kinase inhibitor (TKI) designed to preferentially target Bcr-Abl and its mutations (32 of the 33 identified imatinib-resistant mutations).

The clinical efficacy of oral nilotinib in chronic phase and accelerated phase imatinib resistant and/or intolerant Ph+ adult CML patients was assessed in a phase II non-comparative, multi-centre, dose escalation study in which nilotinib was given under a continuous daily dosing schedule. This study also assessed the efficacy of nilotinib in other haematological malignancies but the results presented only relate to the treatment arms (chronic and accelerated phase CML) applicable to the current submission. Strict criteria were used to describe imatinib resistance and intolerance. Patients should not have reached blast crisis before starting treatment. Nilotinib was administered as 400mg twice daily until unacceptable toxicity or disease progression occurred, or for as long as the patient was benefiting from treatment. Dose escalation was permitted to 600mg twice daily if the patient showed signs of treatment resistance or disease relapse. The primary efficacy outcome during the chronic phase was the overall rate of major (complete plus partial) cytogenetic response. During the accelerated phase the primary efficacy outcome was haematological response (confirmed after four weeks), defined as complete haematological response, marrow response with no evidence of leukaemia or return to chronic phase. Analysis included the Intention-to-Treat (ITT) population that consisted of patients who received at least one dose of study drug. Data were censored in patients who had discontinued before cytogenetic assessments (chronic phase), or two post-baseline assessments (accelerated phase) unless discontinuation was due to disease progression or death.

The data presented represent the latest analysis (June 2007). Historical duration of Ph+ CML in patients enrolled in the study was 5 to 6 years and patients received a minimum of 6 months of nilotinib treatment at the time of the data cut. In the chronic phase, 71% of patients were resistant to and 29% were intolerant of imatinib, whereas in the accelerated phase 81% of patients were resistant to and 18% were intolerant of imatinib. At the time of the data cut, 59% of patients in the chronic phase and 44% of patients in the accelerated phase remained on nilotinib treatment. The primary reasons for treatment discontinuation were disease progression (in 16% of chronic phase patients and 27% of accelerated phase patients) and adverse events (in 15% and 12% of patients in the chronic and accelerated phases respectively).

Nilotinib induced high haematological and cytogenetic response rates in progressive chronic phase and accelerated phase patients. In the chronic phase, the responses to nilotinib were similar in the imatinib-resistant and intolerant groups. Responses to nilotinib were rapid (of the order of a few months), with haematological response providing symptomatic relief and cytogenetic response providing a reduction/stabilisation of leukaemia burden. The pivotal study demonstrated an estimated survival of 95% (12 months) and 91% (6 months) for chronic phase and accelerated phase patients, respectively.

Table: Haematological and Cytogenetic Response Rates

Outcome	Chronic Phase N=320	Accelerated Phase N=119*
Haematological response	-	44%
Complete haematological response (all patients)	84%	24%
Complete haematological response (patients without CHR at baseline)	76%	-
Major cytogenetic response	56%	29%
Complete cytogenetic response	40%	16%
No evidence of leukaemia	-	7.6%
Return to chronic phase	-	13%

* Efficacy data missing for 8 patients (ITT=127 patients)

*Other data were also assessed but remain commercially confidential.**

Summary of evidence on comparative safety

No comparative safety data are available. In the pivotal study of nilotinib referred to in the efficacy section, both chronic phase and accelerated phase patients reported similar adverse events with the most common being liver function abnormalities, myelosuppression, hyperglycaemia, hypophosphataemia, hypocalcaemia, lipase elevation, skin rash, pruritis, headache, fatigue and gastrointestinal effects (nausea, vomiting, constipation and diarrhoea). The majority of toxicities were mild to moderate in severity. The most common grade 3/4 toxicity was myelosuppression (in the form of thrombocytopenia and neutropenia), which was more common in accelerated phase patients than chronic phase patients. Thrombocytopenia and neutropenia were generally transient with early onset within the first two months of nilotinib treatment. Myelosuppression is a natural effect of progressive Ph+ CML and when this is associated with nilotinib treatment it is indicative of therapeutic effect. Details of the adverse effect profile of nilotinib can be found in the summary of product characteristics.

An analysis of data from the pivotal study found that there was minimal cross-intolerance between nilotinib and imatinib in patients with chronic phase and accelerated phase CML. Cross-intolerance was defined as the occurrence with nilotinib of the same grade 3/4 toxicities, regardless of causality that led to the discontinuation of imatinib treatment.

*Other data were also assessed but remain commercially confidential.**

Summary of clinical effectiveness issues

The efficacy and safety evidence is limited to one non-comparative study. The submitting company stated that it was not possible to identify an appropriate and recognised control arm for the pivotal study because at the time of designing the study there was no standard treatment recommended for patients failing imatinib. Hence, high-dose imatinib and dasatinib, which has been available in the UK since November 2006, were not considered.

The surrogate marker, rate of cytogenetic response, has been used as the primary efficacy outcome for chronic phase patients in the pivotal study. Cytogenetic response has previously been shown to be a good surrogate marker for survival in CML patients treated with imatinib. No data correlating cytogenetic response and survival have been demonstrated yet for nilotinib due to the relatively short follow-up period.

In the pivotal study the dose of nilotinib could be increased to 600mg twice daily, whereas the proposed licensed dose is 400mg twice daily.

No data on quality of life of patients receiving nilotinib were submitted.

Summary of comparative health economic evidence

The manufacturer presented a cost- utility analysis of nilotinib relative to high dose imatinib for the treatment of patients in the chronic phase of CML. Dasatinib was not considered as a comparator on the basis that it is not considered to be a standard treatment at present. No direct comparison between nilotinib and imatinib was available. The key data inputs were the 18 month mortality rates. For nilotinib this was drawn from the main clinical trial. For imatinib this was drawn from data on file with the manufacturer. These mortality rates were converted to monthly mortality risks relative to best supportive care. A 5-year survival curve for best supportive care from the literature was then used in conjunction with the relative mortality risks to model the five year survival curves for nilotinib and imatinib. These modelled 5-year survival curves were then extrapolated to 50 years using a Weibull extrapolation.

Coupled with data as to the probable duration of the accelerated phase and the blast phase of CML, these 50-year survival curves were used to estimate the quarterly transition probabilities of moving from the chronic phase to the accelerated phase, from the accelerated phase to the blast phase and from the blast phase to CML related death. Only the quarterly probability of moving from the chronic phase to the accelerated phase was differentiated by treatment, this being 0.0098 for nilotinib while quarterly progression under high dose imatinib was estimated to be roughly twice as fast at 0.0184. These quarterly transition probabilities were then used to model the lifetime experience under nilotinib and under high dose imatinib, with the additional qualification of age-standardised mortality rates being applied. Quality of life values were drawn from the literature. Adverse events were included in the first 6 months of treatment only.

As a result of the modelling, the manufacturer estimated that the lifetime costs for the nilotinib arm would be £216k as compared to £235k for imatinib: a saving of £19k. An additional 2.1 QALYs were anticipated, leading to the conclusion that nilotinib dominated high dose imatinib. However, the base case modelling assumed a constant quarterly proportion of patients coming off treatment regardless of their disease state. Revision of the model to make this a constant proportion of those remaining in the chronic phase coming off treatment resulted in the previous cost savings of £19k becoming an additional cost of £5k from nilotinib use, and a cost effectiveness estimate of £11,365 per QALY.

No health economic case for the use of nilotinib in accelerated phase CML was provided.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

National Institute for Health and Clinical Excellence (NICE) guidance on the use of imatinib for chronic myeloid leukaemia (Technology Appraisal TA70, October 2003).

The July 2007 British Society of Haematology recommendations for the management of Bcr-Abl-positive chronic myeloid leukaemia suggest that dose escalation of imatinib or switching to a second generation TKI should be considered for patients failing first-line imatinib treatment in the chronic phase of CML and that a second generation TKI should be considered for patients progressing to the accelerated phase.

Additional information: previous SMC advice

After review of a full submission the Scottish Medicines Consortium (SMC) issued advice on 8th March 2002 that imatinib (Glivec®) is approved for restricted use in NHS Scotland for the treatment of CML under the overall supervision of haematologists / oncologists, within the context of the guidelines on this medicine issued by the British Society of Haematology in November 2001. Following the extension to imatinib's licence to include first-line treatment of newly diagnosed CML in both adults and children, the SMC issued further advice in January 2003: 'this license extension was granted on the basis of interim analyses that show superiority of imatinib over interferon combination therapy in terms of cytogenetic and haematological response. There should be a formal process of audit and monitoring with a central registry of all patients receiving it and / or entry into a clinical trial.'

After review of a full submission SMC issued advice on 7th May 2007 that dasatinib 20mg, 50mg, 70mg tablets (Sprycel®) is accepted for restricted use within NHS Scotland for the treatment of adults with CML with resistance or intolerance to prior therapy including imatinib mesilate. 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.

Additional information: comparators

Imatinib, which is licensed for use in adult and paediatric patients with newly diagnosed Ph+ CML and dasatinib, which is licensed for use in adults with chronic, accelerated or blast phase CML with resistance or intolerance to prior therapy including imatinib mesilate are comparator products.

Cost of relevant comparators

Drug	Dose regimen	Cost per year (£)
nilotinib	400mg twice daily	£31,627 ¹
imatinib	400mg once daily to 400mg twice daily (chronic phase)	£19,463 to £38,926 ²
	600mg once daily to 400mg twice daily (accelerated phase)	£29,199 to £38,926 ²
dasatinib	100mg to 140mg once daily (chronic phase)	£31,627 ³
	70mg to 100mg twice daily (accelerated phase)	£31,627 to £63,254 ³

Doses are for general comparison and do not imply therapeutic equivalence. 1) The cost of nilotinib was confirmed by the manufacturer on 13th December 2007 as £2432.85 for 28 days supply. 2) Cost taken from Novartis price list on 8th October 2007. 3) Cost taken from MIMs on 8th October 2007.

Additional information: budget impact

*Other data were also assessed but remain commercially confidential.**

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 24 January 2008.

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.

** Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: <http://www.scottishmedicines.org.uk/>*