Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

nilotinib 150mg hard capsules (Tasigna®) SMC No. (709/11)
Novartis Pharmaceuticals UK Ltd

08 July 2011

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 Scotland. The advice is summarised as follows:

ADVICE: following a full submission

nilotinib 150mg hard capsules (Tasigna®) is accepted for use within NHS Scotland.

Indication under review: for the treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukaemia (CML) in the chronic phase.

First-line treatment with nilotinib in newly diagnosed patients has resulted in significantly higher molecular and cytogenetic response rates compared to the standard tyrosine kinase inhibitor. Further longer term follow-up data are needed to confirm the duration of this response and assess the impact on disease progression and overall survival.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of nilotinib. This SMC advice is contingent upon the continuing availability of the PAS in NHS Scotland.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

For the treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myelogenous leukaemia (CML) in the chronic phase.

Dosing Information

The recommended dose for patients with newly diagnosed chronic phase CML is 300mg twice daily. Treatment should be continued as long as the patient continues to benefit. Haematological toxicities (neutropenia, thrombocytopenia), not related to the underlying leukaemia, may lead to a need to temporarily withhold and/or dose reduce nilotinib (to 400mg once daily). Therapy should be initiated by a physician experienced in the diagnosis and the treatment of patients with CML.

Product availability date

13 January 2011

In May 2006, nilotinib was designated orphan drug status for this indication.

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). Nilotinib was initially licensed, at a dose of 400mg twice daily, for the treatment of chronic phase and accelerated phase Philadelphia chromosome positive CML in adult patients resistant to or intolerant of at least one prior therapy including imatinib. This submission considers a licence extension to the treatment of newly diagnosed patients in the chronic phase, using a lower dose of 300mg twice daily.

Evidence to support the use of nilotinib as first-line treatment in CML comes from the results of an ongoing, phase III, comparative study with imatinib. Eligible patients were adults who had been diagnosed with Philadelphia chromosome-positive CML in the chronic phase within the previous 6 months. They had adequate organ function and an Eastern Co-operative Oncology Group (ECOG) performance status of ≤2. They had not received previous treatment with a tyrosine kinase inhibitor (except imatinib for ≤2 weeks) or more than 2 weeks of any medical treatment for CML (except hydroxyurea or anagrelide). Patients were randomised, with stratification by Sokal risk score at diagnosis, to receive nilotinib 300mg twice daily (n=282), nilotinib 400mg twice daily (n=281) or imatinib 400mg daily (n=283) and treatment was continued until treatment failure, including disease progression, intolerable side effects or other reasons.

The primary endpoint was the rate of major molecular response (MMR) at 12 months. This was defined as the proportion of patients with BCR-ABL/ABL ratio ≤0.1% on an International Scale using real-time quantitative polymerase-chain-reaction (RQ-PCR) assay on peripheral blood. This corresponds to a ≥3 log reduction in BCR-ABL from standardised baseline. MMR at 12 months was achieved in 44% (125/282) of the nilotinib 300mg twice daily group, 43% (120/281) of the nilotinib 400mg twice daily group and 22% (63/283) of the imatinib 400mg daily group. Both nilotinib groups achieved significantly higher MMR rates than imatinib at 12 months. Rates of MMR were also higher in both nilotinib groups than imatinib at 12 months when analysed by Sokal risk factor.

The key secondary endpoint was a durable MMR at 24 months which was defined as MMR at 12 and 24 months with no documented loss between these time points. This was not available at the time of the key publication, but subsequent abstracts have reported these as 42%, 39% and 21% respectively. In the key publication, the main secondary endpoint was the rate of complete cytogenetic response (CCyR) by 12 months, which was significantly higher in nilotinib than imatinib patients: 80% (226/282) nilotinib 300mg twice daily patients, 78% (219/281) nilotinib 400mg twice daily patients and 65% (184/283) imatinib patients. Further analysis at 24 months, found rates of CCyR of 87%, 85% and 77% respectively. According to Kaplan-Meier, the median time to first MMR was shorter in patients treated with nilotinib (8.6 months with 300mg and 11.0 months with 400mg) compared with imatinib (median not reached in key publication).

At 12 months, complete molecular response (CMR: defined as BCR-ABL transcript level of ≤0.01%) was achieved in 12% (33/282), 8.5% (24/281) and 3.9% (11/283) of nilotinib 300mg, 400mg and imatinib patients respectively and undetectable disease (defined as BCR-ABL transcript level of ≤0.0032%) in 4.3% (12/282), 4.6% (13/281) and 0.4% (1/283) of patients respectively.

Progression to accelerated phase or blast crisis was reported in 0.7% (2/282) nilotinib 300mg twice daily patients, 0.4% (1/281) nilotinib 400mg twice daily patients and 3.9% (11/283) imatinib patients at 12 months. During the study, none of these 14 patients had achieved MMR, and three of the 11 imatinib patients had achieved a CCyR. Kaplan-Meier estimates of overall survival at 12 months were 99.3%, 99.2% and 99.3% for nilotinib 300mg, 400mg and imatinib respectively.

Three supportive, single-arm, open-label, non-randomised studies also assessed the efficacy of nilotinib in the first-line treatment of CML in the chronic phase. Only one study used the licensed dose of 300mg twice daily.

No cases of the tyrosine kinase inhibitor multi-resistant mutation (T315I) have been observed to date.

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

Summary of evidence on comparative safety

Use of nilotinib in the first-line treatment of CML did not suggest any new or unexpected major safety concerns. The safety of nilotinib 300mg twice daily was generally better than 400mg twice daily. During the first 12 months of the pivotal study described above, adverse events were reported in 98% (274/279) nilotinib 300mg twice daily patients, 99% (273/277) nilotinib 400mg twice daily patients and 98% (275/280) imatinib patients.

The majority of adverse events were of grade 1 or 2 severity. The most frequently reported study-related adverse events with higher incidences with nilotinib than imatinib were rash (31%, 36% and 11% respectively), increased alanine aminotransferase (20%, 24% and 4.6% respectively), headache (14%, 21% and 8.2% respectively), alopecia (7.9%, 13% and 3.9% respectively), pruritus (15%, 13% and 5.4% respectively) and hyperbilirubinaemia (14%, 13% and 1.8% respectively). The most frequently reported study-related adverse events with lower incidences with nilotinib than imatinib were nausea (12%, 20% and 31% respectively), muscle spasms (7.2%, 6.1% and 24% respectively), diarrhoea (7.9%, 6.5% and 21% respectively), neutropenia (14%, 10% and 20% respectively), leukopenia (7.9%, 7.6% and 15% respectively), vomiting (4.7%, 8.7% and 14% respectively), anaemia (6.1%, 8.3% and 14% respectively) and oedema-related events (6.5%, 10% and 47% respectively).

There were no cases of prolongation of the QTc>500msec in any group at the time of the 12 month analysis. In patients receiving nilotinib 300mg twice daily the change from baseline in mean time-averaged QTcF interval at steady state was 6msec. The Summary of Product Characteristics warns that QT prolongation may occur if nilotinib is co-administered with strong CYP-3A4 inhibitors or drugs or food known to prolong the QT interval. No cases of sudden death or Torsade de pointes were reported during the pivotal study.

Summary of clinical effectiveness issues

Nilotinib, like the other two tyrosine kinase inhibitors, imatinib and dasatinib, has been designated an orphan drug for the treatment of CML. The key evidence to support the first-line use of nilotinib in newly diagnosed patients comes from the pivotal study comparing with imatinib, the current standard first-line therapy. This used the primary surrogate endpoint of MMR at 12 months which was described by the European Medicines Agency (EMA) as relevant. The results to date demonstrate a significantly higher MMR compared to imatinib and although this appeared to be maintained to 24 months, longer term follow-up of duration of response and clinical endpoints, including disease progression to accelerated or blast phase and overall survival, are needed. Guidance from the EMA recommends follow-up of over five years on duration of response and resistance development and data for the pivotal imatinib study now extend to 84 months.

The main limitation of the study is its open-label design. However use of objectively measured endpoints, i.e. molecular and cytogenetic responses, should minimise bias.

Nilotinib offers an alternative first-line option for newly diagnosed patients with CML. However if nilotinib was used first-line, there are no licensed options for use in the second-line setting should intolerance or failure occur.

Recently updated National Comprehensive Cancer Network (NCCN) guidelines include nilotinib and dasatinib as treatment options to imatinib for the primary treatment of chronic phase adult CML. They recommend that patients with failure to a first-line tyrosine kinase inhibitor should be treated with an alternative tyrosine kinase inhibitor in the second-line setting.

Nilotinib requires twice daily dosing, unlike imatinib and dasatinib which can be administered once daily and if this increased dosing affects compliance, it may result in suboptimal responses. In addition, the bioavailability of nilotinib is increased by food, and capsules must not be taken with food. It is recommended that no food is consumed for two hours before the dose is taken and for at least one hour after.

Nilotinib is only licensed for treatment of adult patients whereas imatinib is also licensed for paediatric patients.

There are no direct comparative data against the other tyrosine kinase inhibitor, dasatinib, which has also recently been licensed for first-line use.

Summary of comparative health economic evidence

The submitting company provided a cost-utility analysis comparing nilotinib with imatinib for first-line treatment of adult patients with newly diagnosed Ph+ CML in the chronic phase. Clinical data from the nilotinib pivotal study relating to time to discontinuation (TTD) were used to model the effectiveness of first-line treatments. A number of different data sources were used to model the effectiveness of subsequent lines of therapy. A Markov model was used to model the treatment pathway over a lifetime horizon and a Weibull function was selected to extrapolate the TTD data beyond the end of the study. In the base case analysis patients in the imatinib arm were assumed to receive nilotinib second-line, whereas no tyrosine kinase inhibitor treatment was included in the nilotinib arm on the basis that none of the tyrosine kinase inhibitors are specifically licensed for use following failure of first-line nilotinib. However, this assumption was tested in various scenario analyses.

Utility values for the chronic phase and accelerated/blast phase of the model were selected from a literature study where quality of life was estimated using EQ-5D in newly diagnosed CML patients who were receiving imatinib treatment. Resource use associated with routine monitoring, stem cell transplant and end of life care were included in the model and were largely based on expert opinion.

A patient access scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. The PAS offered a simple discount on the list price of nilotinib. Without the PAS, the manufacturer estimated that imatinib would be the dominant treatment as nilotinib treatment is estimated to result in an incremental cost (£17,938) but is also estimated to be less effective than imatinib (QALY loss of 0.4). Therefore imatinib would be the preferred treatment. With the inclusion of the PAS, nilotinib is estimated to be less costly (savings of £39,793) but also less effective (QALY loss of 0.4).

The main limitations of the analysis were:

- The base case analysis without the PAS indicates that imatinib would be the preferred treatment. However, the base case treatment pathway may not be appropriate as patients may be likely to receive another tyrosine kinase inhibitor second-line.
- A scenario analysis was provided where both arms received dasatinib second-line, which clinical experts have indicated broadly reflects current practice in Scotland. In this analysis the cost per QALY was estimated to be £155,550 without the PAS (incremental cost of £46,375 and QALY gain of 0.3). With the inclusion of the PAS nilotinib was estimated to be the dominant treatment (savings of £11,355 and a QALY gain of 0.3).
- A Weibull function was selected to extrapolate the TTD data in the model but no goodness of fit statistics were presented to support this assumption. However, sufficient justification was subsequently provided to support the choice of extrapolation method.
- The use of TTD data instead of modelling response rates is unusual, but this approach is unlikely to have introduced any bias. The manufacturer justified this approach on the basis that it avoids some of the assumptions that would be required if a response model was used.

Given the acceptance of the patient access scheme by PASAG, the economic case has been demonstrated.

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

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

Published guidelines generally recommend the use of imatinib as first-line therapy in patients with chronic phase CML as they predate the publication of pivotal studies and subsequent licensing of first-line use of nilotinib and dasatinib. The only exception is the National Comprehensive Cancer Network (NCCN) guideline as detailed below.

The British Committee for Standards in Haematology published "Recommendation for the management of BCR-ABL-positive chronic myeloid leukaemia" in 2007. These recommended initial treatment with imatinib 400mg daily for patients presenting with the chronic phase of the disease.

The European LeukemiaNet published "CML: an update of concepts and management recommendations of European LeukemiaNet" in December 2009. This recommended imatinib 400mg daily as standard treatment for patients who present with chronic phase CML.

The European Society for Medical Oncology (ESMO) published "CML – ESMO clinical practice guidelines for diagnosis, treatment and follow-up" in 2010. This recommended imatinib 400mg daily as standard first-line treatment for all patients with chronic phase CML.

The NCCN produced updated clinical practice guidelines on CML in 2011. These include nilotinib and dasatinib as treatment options to imatinib for the primary treatment of chronic phase adult CML. They recommend that patients with failure to a first-line tyrosine kinase inhibitor should be treated with an alternative tyrosine kinase inhibitor in the second-line setting.

Additional information: comparators

The main comparator in clinical practice is imatinib. The license for dasatinib has also recently been extended to include treatment of newly diagnosed patients. However this has yet to be reviewed by SMC.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Nilotinib	**300mg twice daily**	**31,627**
Imatinib	400mg daily	20,923
Dasatinib	100mg daily	30,394

Doses are for general comparison and do not imply therapeutic equivalence. Cost for imatinib is from eVadis on 5 May 2011. Costs for nilotinib and dasatinib are from MIMs April 2011.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 39 newly diagnosed patients per year, to which an assumption was made regarding market share for nilotinib. The impact on the medicines budget without the PAS was estimated at £30k in year 1 and £323k in year 5 assuming displacement of imatinib.

With the PAS the company estimated the impact on the medicines budget would be savings of £12k in year 1 rising to £40k in year 5

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

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

Saglio G, Kim DW, Issaragrisil S et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med 2010;362:2251-9.

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Rosti G, Palandri F, Castagnetti F, Breccia M, Levato L, Gugliotta G, et al. Nilotinib for the frontline treatment of Ph(+) chronic myeloid leukemia. Blood 2009;114(24):4933-8.

The European Medicines Agency (EMA). European Public Assessment Report for nilotinib (Tasigna®), www.ema.europa.eu Procedure No : EMEA/H/C/000798/X/0028

Longer term phase III data show Novartis Corporation (NVS) drug Tasigna continues to surpass Gleevec. Biospace news report 6 December 2010.

The European Medicines Agency (EMA). Appendix 2 to the guidelines on the evaluation of anticancer medicinal products in man on confirmatory studies on haematological malignancies. www.ema.europa.eu

Signorovitch JE, Wu EQ, Betts KA et al. Comparative efficacy of nilotinib and dasatinib in newly diagnosed chronic myeloid leukaemia: a matching-adjusted indirect comparison of randomised trials. Curr Med Research Opin 2011;27:1263-71.

This assessment is based on data submitted by the applicant company up to and including 01 July 2011.

**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/About_SMC/Policy_Statements/Policy_Statements

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. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards.

These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

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.