NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Dasatinib, high dose imatinib and nilotinib for the treatment of chronic myeloid leukaemia (part review of Technology Appraisal No. 70)

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of dasatinib, high dose imatinib and nilotinib within their licensed indications for the treatment of people with chronic myeloid leukaemia who are resistant to standard dose imatinib.

Background

Chronic myeloid leukaemia (CML) is characterised by production of an excessive number of white cell precursors by the bone marrow. CML progresses slowly through three identifiable phases: the chronic phase, the accelerated phase and the blast crisis (transformation) phase, with the latter two being grouped together as advanced phase. In some cases categorisation can be difficult and there are various criteria for defining the three phases of CML.

In 95% of cases of CML, people have a specific chromosomal abnormality commonly known as the 'philadelphia chromosome'. This is caused by an exchange of genetic material between two chromosomes (known as reciprocal translocation), between parts of the long arms of chromosome 22 and chromosome 9, and is associated with fusion of the Breakpoint Cluster Region (BCR) and Abelson (ABL) genes and the production of an abnormal tyrosine kinase oncoprotein.

CML is a rare disease with an incidence of approximately 1 case per 100 000 people every year. It accounts for about one in six cases of leukaemia in adults. It has been estimated that there are approximately 600 to 800 new cases of CML diagnosed in England and Wales each year, and 200 registered deaths. It has been estimated that median life expectancy is at least 15 years. The median age at diagnosis is between 50 and 60 years.

Treatment options for people with CML include hydroxycarbamide, imatinib, interferon alfa, stem cell transplantation and acute leukaemia-style chemotherapy. Current NICE technology appraisal guidance 70 recommends imatinib for the first-line treatment for people with philadelphia-chromosome-positive chronic myeloid leukaemia at a dosage of 400 mg/day in the chronic phase and as an option for people who initially present in the accelerated phase or with blast crisis at a dosage of 600 mg/day. In NICE technology appraisal guidance 70, dose escalation of imatinib was recommended only in the context of further clinical study.

The technologies

Dasatinib (Sprycel, Bristol Myers Squibb), imatinib (Glivec, Novartis Pharmaceuticals) and nilotinib (Tasigna, Novartis Pharmaceuticals) are oral tyrosine kinase inhibitors (TKIs). TKIs work by blocking specific signals in cells expressing the BCR-ABL protein, which reduces the uncontrolled proliferation of white blood cells.

Imatinib has a UK marketing authorisation for the treatment of adults and children with newly diagnosed philadelphia chromosome-positive CML where bone marrow transplantation is not considered the first-line treatment and for philadelphia chromosome-positive CML in the chronic phase after failure of interferon alfa (recommended dose 400mg/day), in the accelerated phase or the blast crisis (recommended dose 600mg/day). The marketing authorisation states that dose escalations in 200mg increments up to a maximum of 800mg may be considered in the absence of severe adverse drug reaction and severe non-leukaemia-related neutropenia or thrombocytopenia in the following circumstances: disease progression (at any time; failure to achieve a satisfactory haematological response after at least 3 months of treatment; failure to achieve a cytogenetic response after 12 months of treatment; or loss of a previously achieved haematological and/or cytogenetic response.

Dasatinib has a UK marketing authorisation for the treatment of adults with chronic, accelerated or blast phase chronic myeloid leukaemia with resistance or intolerance to prior therapy including imatinib mesilate.

Nilotinib has a UK marketing authorisation for the treatment of adults with chronic phase and accelerated phase philadelphia chromosome-positive CML) with resistance or intolerance to prior therapy including imatinib.

Interventions	Chronic phase: • Dasatinib • High dose imatinib (600mg/day or 800mg/day) • Nilotinib Accelerated phase: • Dasatinib • High dose imatinib (800mg/day) • Nilotinib Blast crisis: • Dasatinib • High dose imatinib (800mg/day)

Population	Adults with chronic myeloid leukaemia in the chronic, accelerated or blast phase who are resistant to standard dose imatinib (400mg/day in the chronic phase and 600mg/day in the accelerated phase or with blast crisis)
Comparators	Chronic phase: • Allogeneic stem cell transplantation • Hydroxycarbamide • Imatinib 400mg/day • Interferon alfa Accelerated phase: • Acute leukaemia-style chemotherapy • Allogeneic stem cell transplant • Imatinib 600mg/day • Supportive care (which includes hydroxycarbamide) Blast crisis: • Acute leukaemia-style chemotherapy followed by allogeneic stem cell transplant • Best supportive care • Imatinib 600mg/day
Outcomes	• treatment response rates (including molecular, cytogenetic and haematologic responses) • time to and duration of response • overall survival • event free survival • progression-free survival • adverse effects of treatment • health-related quality of life • time to treatment failure

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation for the technologies. If evidence allows, the following subgroups will be considered: • People at different phases of CML • Level of previous response to imatinib If evidence allows, the adoption of an early stopping rule will be considered.
Related NICE recommendations	Related Technology Appraisals: Technology Appraisal No.70, October 2003, 'Guidance on the use of imatinib for chronic myeloid leukaemia'. Technology appraisal in preparation. Dasatinib and nilotinib for the treatment of imatinib-intolerant chronic myeloid leukaemia. Earliest anticipated date of publication: June 2010. Technology appraisal in preparation. Nilotinib within its licensed indication for the first line treatment of chronic myeloid leukaemia. Earliest anticipated date of publication: May 2011. Related Guidelines: Cancer Service Guidance, October 2003, Improving outcomes in haematological cancer. Expected review date: TBC**.**