NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Ponatinib for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of ponatinib within its licensed indications for treating chronic myeloid leukaemia and acute lymphoblastic leukaemia.

Background

Chronic myeloid leukaemia (CML) is characterised by the excessive production of white cell precursors by the bone marrow. It progresses through 3 phases: the chronic phase, the accelerated phase and the blast crisis phase. The majority of people are diagnosed in the chronic phase, from which they either go through the accelerated phase, or move directly into blast crisis in which the disease transforms into a fatal acute leukaemia. Acute lymphoblastic leukaemia (ALL) is where there is an excess production of immature lymphocyte-precursor cells called lymphoblasts or blast cells, in the bone marrow. This affects the production of normal blood cells and there is a reduction in the numbers of red cells, white cells and platelets in the blood.

CML and ALL are rare diseases. In England in 2013, 624 people were diagnosed with CML[i] and 693 with ALL[ii]. The median age at diagnosis for those with CML is between 50 and 60 years, whereas ALL is most common in children, adolescents and young adults, with 65% of cases diagnosed in people aged under 25 years. A second increase in incidence is however observed in people aged over 60 years. A specific chromosomal abnormality known as the 'Philadelphia chromosome' is present in 95% of people with CML and 20-30% of adults with ALL.

Current treatment for CML

NICE technology appraisal guidance 251 recommends standard-dose imatinib or nilotinib as options for the treatment of adults with untreated chronic phase Philadelphia-chromosome-positive CML. NICE technology appraisal guidance 70 also recommends imatinib for the treatment of people with untreated Philadelphia-chromosome-positive CML who initially present in the accelerated phase or with blast crisis, and for people who present in the chronic phase and then progress to the accelerated phase or blast crisis if they have not received imatinib previously.

NICE technology appraisal guidance 241 recommends nilotinib as second-line treatment for people with chronic or accelerated phase Philadelphia-

chromosome-positive CML who are resistant to treatment with standard-dose imatinib or intolerant of imatinib. NICE technology appraisal guidance 241 does not recommend dasatinib or high dose imatinib[1] for the treatment of chronic, accelerated or blast-crisis phase CML. Dasatinib is not recommended for the treatment of people with chronic, accelerated or blast-crisis phase CML whose disease is resistant to treatment with standard-dose imatinib or who are intolerant of imatinib, however it is used in clinical practice in England through the Cancer Drugs Fund (at the time the draft scope was written) only in people with chronic or accelerated phase CML whose disease is refractory to imatinib or who have significant intolerance to imatinib (Grade 3 or 4 adverse events) and significant intolerance to nilotinib (Grade 3 or 4 adverse events). Dasatinib is currently undergoing appraisal by NICE through the Cancer Drugs Fund reconsideration process [ID1006]. High-dose imatinib is not recommended for the treatment of chronic, accelerated or blast-crisis phase Philadelphia-chromosome-positive CML that is resistant to standard-dose imatinib. NICE technology appraisal guidance 299 does not recommend bosutinib for treating Philadelphia-chromosome-positive CML, but it is used in clinical practice in England through the Cancer Drugs Fund (at the time the draft scope was written) only in people with chronic phase CML with significant intolerance to nilotinib (Grade 3 or 4 events) and significant intolerance to dasatinib (Grade 3 or 4 adverse events) if dasatinib is accessed through its current approved CDF indication. Bosutinib is currently undergoing appraisal by NICE through the Cancer Drugs Fund reconsideration process [ID1004].

People who receive treatment with a first- or second-generation tyrosine kinase inhibitor (such as imatinib, nilotinib, dasatinib or bosutinib) may develop drug resistance through a number of mechanisms, one of which is the T315I mutation that interferes with the inhibition of tyrosine kinase.

Other treatment options in clinical practice can include allogeneic stem cell transplantation (if the treatment is suitable and depending on the availability of a suitable donor), interferon alpha or best supportive care (including hydroxycarbamide).

Current treatment for ALL

There is currently no NICE guidance for treating ALL. Treatment is generally divided into 3 phases; induction, consolidation and maintenance. During these treatment phases, newly diagnosed Philadelphia-chromosome-positive ALL is treated with chemotherapy combinations including tyrosine kinase inhibitor therapy such as imatinib or dasatinib. Resistance to tyrosine kinase inhibitors may develop and therapeutic options following resistance to tyrosine kinase inhibitors are limited. Treatment of relapsed disease includes re-induction

[1] The summary of product characteristics (SPC) for imatinib states that the dose may be increased from 400 mg to 600 mg or 800 mg in patients with chronic phase disease, or from 600 mg to a maximum of 800 mg in patients with accelerated phase or blast crisis (see SPC for full details). High dose imatinib refers to doses of 600 mg or 800 mg in the chronic phase disease or 800 mg in the accelerated phase or blast crisis.

therapy followed by an allogeneic stem cell transplant, where a suitably matched related or unrelated donor is found. Dasatinib was available for the treatment of ALL through the Cancer Drugs Fund until November 2015 when it was removed from the Cancer Drugs Fund list.

The technology

Ponatinib (Iclusig, Incyte) is a multi-targeted tyrosine kinase inhibitor, primarily inhibiting the breakpoint cluster region and Abelson (Bcr-Abl) tyrosine kinase found in some receptors on the surface of leukaemia cells where it is involved in stimulating the cells to divide uncontrollably. By blocking Bcr-Abl, ponatinib helps to control the growth and spread of leukaemia cells. Ponatinib is administered orally.

Ponatinib has a marketing authorisation in the UK for treating adult patients with 'chronic-phase, accelerated-phase, or blast-phase chronic myeloid leukaemia (CML) who are resistant to dasatinib or nilotinib, who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate, or who have the T315I mutation' and 'Philadelphia-chromosome-positive acute lymphoblastic leukaemia (Ph+ ALL) who are resistant to dasatinib, who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate, or who have the T315I mutation'. The marketing authorisation for ponatinib for CML and Philadelphia-chromosome-positive ALL was based on a single-arm open-label international multicentre trial.[iii]

Ponatinib is used in clinical practice in England through the Cancer Drugs Fund (at the time the draft scope was written) only in people with documented T315I mutation (for both chronic, accelerated or blast phase CML and Philadelphia-chromosome-positive ALL).

Intervention(s)	Ponatinib
Population(s)	• Adults with chronic phase, accelerated phase, or blast phase chronic myeloid leukaemia, whose disease is resistant to dasatinib or nilotinib, who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate, or who have the T315I mutation. • Adults with Philadelphia-chromosome-positive acute lymphoblastic leukaemia whose disease is resistant to dasatinib, who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate, or who have the T315I mutation.
Comparators	For people with chronic myeloid leukaemia: • Bosutinib (NICE guidance is in development [ID1004]; funded by the CDF in the interim) • Allogeneic stem cell transplantation (with or without chemotherapy depending on the phase of the disease) • Interferon alpha • Best supportive care (including but not limited to hydroxycarbamide). For people with acute lymphoblastic leukaemia: • Established clinical management without ponatinib (including but not limited to best supportive care).
Outcomes	The outcome measures to be considered include: • overall survival • progression and/or event-free survival • response rates • time to response • duration of response • adverse effects of treatment • health-related quality of life.

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. The availability of any patient access schemes for the intervention or comparator technologies will be taken into account. The availability and cost of biosimilars should be taken into account.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE pathways	Related Technology Appraisals: Technology Appraisal No. 70, October 2003, 'Guidance on the use of imatinib for chronic myeloid leukaemia' (partially updated by NICE technology appraisal guidance 241). Technology Appraisal No. 241, January 2012, 'Dasatinib, high-dose imatinib and nilotinib for the treatment of imatinib-resistant chronic myeloid leukaemia (CML) (part review of NICE technology appraisal guidance 70), and dasatinib and nilotinib for people with CML for whom treatment with imatinib has failed because of intolerance'. Dasatinib subject to ongoing NICE CDF transition review [ID1006], publication date to be confirmed. Technology Appraisal No. 251, April 2012, Dasatinib, nilotinib and standard-dose imatinib for the first-line treatment of chronic myeloid leukaemia. Review Proposal Date September 2014. Dasatinib subject to ongoing NICE CDF transition review [ID1014], publication date to be confirmed. Technology Appraisal No. 299, November 2013, 'Bosutinib for the treatment of chronic myeloid leukaemia'. Subject to ongoing NICE CDF transition

	review [ID1004], expected date of publication October 2016. 'Inotuzumab ozogamicin for treating relapsed or refractory acute lymphoblastic leukaemia' NICE technology appraisals guidance [ID893]. Publication date to be confirmed. 'Blinatumomab for treating Philadelphia-chromosome-positive relapsed or refractory acute lymphoblastic leukaemia' NICE technology appraisals guidance [ID1008]. Publication date to be confirmed. Leukaemia (acute lymphoblastic) – dasatinib (suspended appraisal) NICE Technology Appraisal ID386. Related Guidelines: Cancer Service Guidance (CSGHO), October 2003, 'Improving outcomes in haematological cancers. Guidelines in development: Haematological cancers – improving outcomes (update). Publication expected May 2016. Related NICE Pathways: Blood and bone marrow cancers
Related NHS England Policy	NHS England (2015) National Cancer Drugs Fund List v.6.1: https://www.england.nhs.uk/wp-content/uploads/2016/02/ncdf-list-01-02-16.pdf NHS England (2016) Manual for Prescribed Specialised Services 2016/17 Chapter 29, Blood and marrow transplantation services (all ages). Department of Health (2011) Improving outcomes: a strategy for cancer Department for Health (Modified 2011) Manual for Cancer Services

[i] Cancer Research UK 'Chronic myeloid leukaemia (CML) incidence by sex and UK region'. Accessed May 2016
[ii] Cancer Research UK 'Acute lymphoblastic leukaemia (ALL) incidence by sex and UK region'. Accessed May 2016
[iii] Summary of product characteristcs http://www.medicines.org.uk/emc/medicine/28145. Accessed June 2016