NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Proposed Health Technology Appraisal

Lenalidomide for the treatment of myelodysplastic syndromes associated with deletion 5q cytogenetic abnormality

Draft scope (Pre-referral)

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of lenalidomide within its licensed indication for the treatment of myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality in people with red blood cell transfusion dependence.

Background

The myelodysplastic syndromes (MDS) are a diverse group of haematological disorders in which the bone marrow functions abnormally and insufficient numbers of mature blood cells are produced. Red blood cells, white blood cells and platelets may all be affected by MDS, resulting in life threatening disease, with anaemia and increased risk of bleeding and infections. MDS affect patients' quality of life due to debilitating symptoms such as fatigue and dyspnoea, treatment regimens involving hospitalisation with intravenous drug infusions and blood transfusions, and complications such as severe infections.

MDS are caused by a cumulative acquisition of genetic errors in the bone marrow and common abnormalities include chromosomal deletions in 5q, 7, 20q, Y and trisomy 8. Other risk factors include previous cancer therapy including radiotherapy, and environmental toxins. MDS are associated with an increased risk of transformation to acute myeloid leukaemia (AML). AML is a rapidly growing cancer of the blood and bone marrow, with poor prognosis if left untreated. Around 30% of patients with MDS will progress to AML.

MDS are subdivided using the International Prognostic Scoring System (IPSS), and the French-American-British (FAB) and World Health Organisation (WHO) classification systems. Based on the proportion of leukaemic cells (or 'blasts'), bone marrow cytogenetic findings, and the presence of blood cytopenia, the IPSS classifies outcome as either low-risk, intermediate-I risk, intermediate-II risk or high-risk. Low risk and intermediate-1 risk MDS together form approximately 70% of all MDS.

The annual incidence of MDS is estimated at 4 per 100,000, but incidence increases with age and is 30 per 100,000 per year in people over 70 years of age. Many cases remain undiagnosed. There were 1993 people newly diagnosed with MDS in England in 2004, with over 90% of patients aged over 60 at the time of diagnosis. Deletion of chromosome 5q is one of the most common cytogenetic abnormalities in MDS, occurring in between 16% to 28%

of patients. Median survival with low risk and intermediate-I risk MDS is 5.7 years and 3.5 years respectively. It can be less than 6 months for people with high risk MDS.

The mainstay of treatment for MDS is best supportive care (transfusions, growth factors, antibiotics) to control the symptoms of bone marrow failure, low-dose standard chemotherapy or immunosuppressive therapies are used for some patients. For people with low risk MDS, often a preferred approach is one of no active treatment or 'watchful waiting' and for some people, stem cell transplantation is a potentially curative treatment option. Many patients become red blood cell transfusion dependent, particularly those with low or intermediate-1 risk MDS. A major goal of treatment is then to achieve transfusion independence and a number of treatments can be used to reduce or eliminate the transfusion need for MDS patients.

The technology

Lenalidomide (Revlimid, Celgene) is a structural analogue of thalidomide. Its mechanism of action includes anti-neoplastic, anti-angiogenic, pro-erythropoeitic, and immunomodulatory properties. Lenalidomide inhibits proliferation of certain haematopoietic tumour cells, enhances T cell- and Natural Killer (NK) cell-mediated immunity, increases foetal haemoglobin production by CD34+ haematopoietic stem cells and inhibits production of pro-inflammatory cytokines. It is administered orally.

Lenalidomide does not currently have UK marketing authorisation for the treatment of MDS. It has been studied in clinical trials as monotherapy compared with placebo in adults who have low risk or intermediate-1 risk MDS associated with a deletion 5q cytogenetic abnormality and who are red blood cell transfusion dependent.

Intervention(s)	Lenalidomide
Population(s)	Adults with myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality and who are red blood cell transfusion dependent
Comparators	• low-dose chemotherapy (such as cytarabine and anthracyclines) • immunosuppression (such as combination treatment with prednisolone and ciclosporin) • best supportive care (including blood transfusions, growth factors, antibiotics)

Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival (including time to transformation to AML or death) • response rates, including haematologic response and improvement • frequency of blood-transfusions (including blood-transfusion independence) • serious infections • 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.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation.
Related NICE recommendations	Related Technology Appraisals: Technology Appraisal in Preparation, 'Azacitidine for the treatment of myelodysplastic syndrome, chronic myelomonocytic leukaemia and acute myeloid leukaemia' Earliest anticipated date of publication TBC. Related Guidelines: Guidance on Cancer Services, Oct 2003, 'Improving outcomes in haemato-oncology cancer'.

Questions for consultation

Have the most appropriate comparators for lenalidomide for the treatment of myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality in people who are red blood cell transfusion dependent been included in the scope?

- Should stem-cell transplantation be included?
- Are there any other chemotherapy agents that are routinely used?
- Should treatments that reduce blood-transfusion dependence be included? If so which treatments are routinely used?

Is best supportive care an appropriate comparator? If so, is best supportive care defined appropriately?

Are there any subgroups of people in whom the technology is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Please consider whether in the remit or the scope there are any issues relevant to equality. Please pay particular attention to whether changes need to be made to the remit or scope in order to promote equality, eliminate unlawful discrimination, or foster good relations between people who share a characteristic protected by the equalities legislation and those who do not share it, or if there is information that could be collected during the assessment process which would enable NICE to take account of equalities issues when developing guidance.

Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technology_appraisal_process_guides.jsp)