NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Proposed Health Technology Appraisal

Lenalidomide for the treatment of newly diagnosed multiple myeloma

Draft scope (Pre-referral)

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of lenalidomide within its licensed indications (i) as induction therapy for newly diagnosed multiple myeloma in people for whom autologous stem cell transplant is not appropriate, and (ii) as maintenance therapy for newly diagnosed multiple myeloma in people who have previously received induction chemotherapy and for whom autologous stem cell transplant is not appropriate.

Background

Multiple myeloma is a form of cancer that arises from plasma cells (a type of white blood cell) in the bone marrow. Myeloma cells produce large quantities of an abnormal antibody that does not work properly and is not able to fight infection. Myeloma cells build up in the bone marrow and interfere with the production of normal blood cells, which are responsible for blood clotting, carrying oxygen around the body and fighting infections. They also have the ability to spread throughout the bone marrow and into the hard outer casing of the bone. The term multiple myeloma refers to the presence of more than one site of affected bone at the time of diagnosis. People with multiple myeloma can experience bone pain, bone fractures, tiredness (due to anaemia), infections, hypercalcaemia (too much calcium in the blood) and kidney problems.

About 3900 people were diagnosed with multiple myeloma in England and Wales in 2008. It is most frequently diagnosed in people aged 70–79 and is uncommon in young people (fewer than 2% of diagnoses are in people less than 40 years old). Multiple myeloma is more common in men than in women. Average survival for people with multiple myeloma is between 4 and 6 years, but ranges from a few weeks to more than 20 years.

Multiple myeloma is an incurable disease. The aim of therapy is to achieve as long a period of stable disease as possible, thereby prolonging survival and maximising quality of life. Aggressive initial treatment, in the form of high-dose chemotherapy with stem-cell transplantation, may be possible for people in good general health. However, this approach is too intensive for most people with multiple myeloma (fewer than 20% receive stem-cell transplantation), so alternative first-line treatments are necessary. The most common approach is to give a combination of drugs as induction chemotherapy (that is, treatment that aims to kill as many cancer cells as possible straightaway). Often, the chemotherapeutic regimen will comprise an alkylating agent (such as melphalan or cyclophosphamide), a biological therapy (such as thalidomide or

bortezomib) and a corticosteroid (usually dexamethasone or prednisolone). Two frequently used combinations are cyclophosphamide, thalidomide and dexamethasone (CTD), and melphalan, prednisolone and thalidomide (MPT). When induction chemotherapy is complete, some people receive ongoing (maintenance) treatment, where a regular dose of chemotherapy is given to prevent cancer cells from building up again for as long as possible.

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. Lenalidomide is administered orally.

Lenalidomide does not currently have a UK marketing authorisation for the treatment of newly diagnosed multiple myeloma. It is being studied in clinical trials as induction therapy in combination with several different agents including cyclophosphamide, melphalan, dexamethasone and prednisolone. It is also being studied in clinical trials as maintenance therapy, both on its own (monotherapy) and in combination with corticosteroids.

Lenalidomide has a UK marketing authorisation for the treatment of multiple myeloma in people who have received at least one prior therapy. NICE technology appraisal guidance No. 171 recommends lenalidomide in combination with dexamethasone as a possible treatment for people with multiple myeloma who have received at least two prior therapies.

Intervention(s)	In the induction setting: lenalidomide in combination with an alkylating agent (cyclophosphamide or melphalan) and/or a corticosteroid (dexamethasone or prednisolone) In the maintenance setting: lenalidomide as monotherapy or in combination with a corticosteroid (dexamethasone or prednisolone)
Population(s)	In the induction setting: people with newly diagnosed or previously untreated multiple myeloma which is not suitable for autologous stem cell transplant. In the maintenance setting: people with multiple myeloma which is not suitable for autologous stem cell transplant who have previously undergone induction chemotherapy only.

Comparators	In the induction setting:
	• combination therapy comprising an alkyating agent (cyclophosphamide or melphalan) and a corticosteroid (dexamethasone or prednisolone) either alone or in combination with:
	  ○ thalidomide[1] or
	  ○ bortezomib**Error! Bookmark not defined.**
	• corticosteroid monotherapy
	In the maintenance setting:
	• thalidomide monotherapy
	• corticosteroid monotherapy
	• best supportive care ('watchful waiting')

Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival and/or time to progression • response rates • 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.

[1] subject to ongoing NICE technology appraisal of bortezomib and thalidomide

Other considerations	In the maintenance setting, if the evidence allows, the following subgroups will be considered: • populations according to type of induction therapy received • populations according to response to induction therapy received The costs in the economic model should take into account patient access schemes where relevant. Guidance will only be issued in accordance with the marketing authorisation.
Related NICE recommendations	Related Technology Appraisals: Technology Appraisal No. 129, October 2007, 'Bortezomib monotherapy for relapsed multiple myeloma.' Review date: October 2010. Technology Appraisal No. 171, June 2009, 'Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy.' Review date: October 2010. Technology Appraisal in Preparation, 'Bortezomib and thalidomide for the first-line treatment of multiple myeloma.' Earliest anticipated date of publication TBC. Technology Appraisal in Preparation, 'Denosumab for the treatment of bone metastases from solid tumours and multiple myeloma.' Earliest anticipated date of publication: January 2012. Proposed Technology Appraisal, 'Lenalidomide for the maintenance treatment of multiple myeloma after autologous stem cell transplantation' Publication TBC. Proposed Technology Appraisal, 'Plerixafor for stem cell mobilisation in multiple myeloma' Publication TBC. Related Guidelines: Cancer Service Guidance, October 2003, 'Improving Outcomes in Haematological Cancer.' Related Technology Appraisals:

Questions for consultation

Have the most appropriate comparators for lenalidomide as induction therapy and maintenance therapy for newly diagnosed multiple myeloma in people for whom autologous stem cell transplant is not appropriate been included in the scope? Are the comparators listed routinely used in clinical practice? In particular:

- Is induction with cyclophosphamide–thalidomide–dexamethasone a routine treatment option in the UK?
- Are doxorubicin-based regimens also routinely used as induction therapy in UK clinical practice?
- Is interferon alpha also routinely used as maintenance therapy in UK clinical practice?
- In the maintenance setting, is watchful waiting a reasonable comparator?

Are the subgroups suggested in 'other considerations appropriate? Are there any other 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 appraisal 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).