Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy with bortezomib (partial review of TA171)

Patient/Carer Organisation Statement from Myeloma UK

[redacted]

Sources for evidence for inclusion in this statement

The patient perspective included in this submission is gathered from the day-to-day contact that Myeloma UK has with patients across the UK. We have also conducted our own comprehensive review of relevant published literature and have interpreted this very much from the perspective of patients.

We also work closely with a broad range of healthcare professionals involved in the treatment and care of myeloma patients, nationally and internationally, informally and more formally, via a number of advisory boards and committees. We have sought input and opinions from these professionals in relation to this appraisal.

In addition, we have been able to draw on over six years of clinical experience of using lenalidomide and have solicited feedback from clinicians and patients in a variety of ways. We have reflected this in our submission.

About myeloma

Myeloma is an incurable, complex and debilitating cancer of the plasma cells. Complications of myeloma include severe bone destruction, bone fractures, fatigue, frequent infection and kidney failure. The complexity and range of co-morbidities of myeloma set it aside from almost every other cancer.

Across the UK there are around 4,700 people diagnosed with myeloma each year, with around 19,000 myeloma patients at any one time. Myeloma occurs mostly in older people, with around 70% of patients over the age of 65.

Whilst survival rates for myeloma have historically been poor, the introduction of 'novel' drugs such as thalidomide, bortezomib and lenalidomide have transformed the treatment of myeloma and improved both the survival and quality of life.

Recent statistics show that the ten-year survival rates for myeloma have increased from just 5% in 1970 to over 17% in 2011.[1] The Office for National Statistics (ONS) in 2010 also showed that five year survival rates in myeloma are increasing at one of the fastest paces among all cancer types in the UK with over one-third of myeloma patients surviving for at least five years.[2]

Due to the complex, relapsing and remitting nature of myeloma, patients require a range of treatment options and doctors need a degree of flexibility to pick the best and most appropriate treatment. This applies to all stages of myeloma.

Appraisal technology treatment setting

Current practice

In the newly diagnosed or 'upfront' setting, myeloma patients who are not eligible for high-dose therapy and stem cell transplantation typically receive thalidomide in combination with a corticosteroid (usually dexamethasone or prednisolone) and chemotherapy (usually melphalan or cyclophosphamide). This is in line with NICE guidance TA228.

If patients are intolerant or contraindicated to thalidomide they can then receive bortezomib on the NHS, again in combination with a corticosteroid and chemotherapy. In the revised scope, this is only

---

[1] **Cancer Research UK (2011)** http://www.cancerresearchuk.org/cancer-info/news/archive/pressrelease/2010-07-12-deadly-cancer-survival-doubles

[2] **Office for National Statistics** - Five-year age-standardised relative survival (%) for adults (15-99 years) diagnosed during 2003-2007 and followed up to 2008: England, 21 common cancers, by sex, 16 April 2010

referred to as 'contraindicated' which needs to be updated to include 'intolerant' as these are two different concepts. Approximately 20% of myeloma patients who go down the 'non-intensive pathway' (i.e. that are not eligible for high-dose therapy and stem cell transplantation) receive bortezomib in this setting. It is therefore only a small cohort of myeloma patients that would apply under this guidance.

In the first relapse setting (the appraisal setting), as per NICE TA129, myeloma patients currently receive bortezomib in combination with dexamethasone. This is regardless of the initial treatment they have received in the newly diagnosed setting.

However, if you are one of the 20% of patients who receive bortezomib (i.e. those who are contraindicated or intolerant to thalidomide) and have had a poor response to bortezomib (defined as less than 25% reduction in paraprotein, stable disease or progression) it is not clinically appropriate for a patient to receive repeat bortezomib in the first relapse setting.

For this group of patients, lenalidomide is currently approved on the Cancer Drugs Fund in England but prior to this (as is the situation currently in Wales) there is no routinely available clinical alternative. Myeloma UK therefore welcomes the commitment of the NICE Appraisal Committee to look at lenalidomide in this setting.

Consensus of expert opinion

The latest version of the British Committee for Standards in Haematology (BCSH) Guidelines on the Diagnosis and Management of Multiple Myeloma make the following recommendations:

- The most appropriate management should be determined on an individual basis depending on the timing of relapse, age, prior therapy, BM function and co-morbidities, and patient preference (Grade A1)
- Extensive trial data support the use of thalidomide, bortezomib and lenalidomide-based regimens as treatment modalities at first and subsequent relapse (Grade A1)[3]

The guidelines also go on to recommend that 'patients at second and subsequent relapse, or patients at first relapse intolerant of thalidomide or bortezomib should be considered for lenalidomide[4]'.

These recommendations taken into account with the positive approval of lenalidomide in the first relapse setting by the Cancer Drugs Fund in England highlight that the consensus of expert opinion is overwhelmingly in favour of having lenalidomide available in the setting covered by the appraisal and expanding the range of treatment options routinely available to clinicians and their patients.

Literature review

Lenalidomide in combination with dexamethasone is licensed for use in myeloma patients who have received at least one prior therapy. Clinical trial data has therefore highlighted that lenalidomide is safe and effective in myeloma patients in the setting covered by the appraisal.

Both the MM009 AND MM010 studies assessed lenalidomide plus dexamethasone vs. dexamethasone in placebo in 704 relapsed/refractory myeloma patients (in all relapse stages) and found that it improved patient outcomes in terms of progression-free survival and overall survival.

The MM009 study found that in 351 patients the time to progression was significantly longer in the patients who received lenalidomide plus dexamethasone plus dexamethasone (11.3months vs.4.7months). A complete or partial response occurred in 106 patients (60.2%) in the lenalidomide group and in 42 patients (24%) with a complete response in 15.9% and 3.4% of patients, respectively. Overall survival was significantly improved in the lenalidomide group[5].

The MM010 study assigned 177 patients to the lenalidomide and dexamethasone group and 176 to the placebo and dexamethasone group. It found that complete, near complete or partial responses

---

[3] **BCSH 2013** Guidelines for the Diagnosis and Management of Multiple Myeloma
http://www.bcshguidelines.com/documents/MYELOMA_GUIDELINE_updated_29_aug_RG_jzw_(3).pdf
[4] **BCSH 2013** Guidelines for the Diagnosis and Management of Multiple Myeloma
http://www.bcshguidelines.com/documents/MYELOMA_GUIDELINE_updated_29_aug_RG_jzw_(3).pdf
[5] **Dimopoulos et al (2007)** Lenalidomide plus dexamethasone for relapsed or refractory myeloma, NEJM 357:2123-2132

occurred in 108 patients in the lenalidomide group (61%) and in 35 patients (19.9% in the placebo group. The median time to progression was 11.1months in the lenalidomide group and 4.7months in the placebo group[6].

These findings were also confirmed in the long-term follow up of the overall survival of patients who had taken part in the MM009 and MM010 studies[7]. The BCSH Guidelines on the Diagnosis and Management of Multiple Myeloma also point out 'Further analysis of these phase III trial results suggests that higher response rates and improved TTP is achieved in patients treated at first relapse, compared to those treated at subsequent relapse (65% versus 58% and 71 weeks versus 41 weeks respectively), although the outcomes for patients treated later in their disease course were still significantly higher in the lenalidomide/dexamethasone arms (Stadtmauer et al, 2009)[8].

Potential advantages and disadvantages

Taking the published evidence, together with knowledge derived from consulting with our clinical experts and a wide range of patients, the following provides a strong case for the approval of lenalidomide in the first relapse setting. Below you will find our opinion on the potential advantages and disadvantages of lenalidomide for patients at first relapse

(a) Potential advantages

Importance of receiving the most efficacious treatment

It is important that myeloma patients are able to access treatments that their clinician thinks are the best option for them in terms of prolonging progression-free and overall survival and in terms of improving quality of life.

Patients who receive bortezomib in the initial setting may not be eligible or most suitable to receive bortezomib again immediately after this.

In such cases, as lenalidomide is not routinely available patient would either have to receive a treatment that is less efficacious than other novel treatments in myeloma or having to receive bortezomib again in line with NICE guidance which would either led to a below par response or serve as an avenue to access the second relapse guidance on the NHS.

Approving lenalidomide in this setting would allow clinicians and patients the option to access the treatment, rather than having the treatment options dictated by what is available on the NHS. As mentioned previously, this is something that has improved since the establishment of the Cancer Drugs Fund.

Lenalidomide is an oral treatment

As lenalidomide in combination with dexamethasone is an oral treatment, myeloma patients at first relapse would be able to take the treatment at home rather than having to travel to hospital on a regular basis to receive intravenous or subcutaneous bortezomib. This would allow the patients to get on with normal day to day activities and improve their quality of life and would also lead to savings on the NHS in terms of outpatient visits and staff time.

We know from a recent Myeloma UK survey that some patients would prefer to have a treatment that they could receive at home (preferably in tablet form) due to ease, convenience, the fact it reduces hospital visits and allows patients to avoid invasive procedures such as infusions[9].

However, in the same survey, some patients reported that they preferred treatments which allow them regular visits to the hospital as it gives them confidence in the quality of care and means that there is medical support available when they are receiving their treatment. Some patients also reported problems with committing to oral dosing schedules.

---

[6] **Weber et al (2007)** Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America, NEJM Nov 22;357:2133-42
[7] **Dimopoulous et al (2009)** Long-term follow-up on overall survival from the MM009 and MM010 phase III trials of lenalidomide plus dexamethasone in patients with relapsed and refractory multiple myeloma' Leukaemia, 23,2147-2152
[8] **BCSH 2013** Guidelines for the Diagnosis and Management of Multiple Myeloma http://www.bcshguidelines.com/documents/MYELOMA_GUIDELINE_updated_29_aug_RG_jzw_(3).pdf
[9] Myeloma UK Survey 2012

(b) Potential disadvantages

Lenalidomide is an immunomodulatory drug (IMiD)

In line with the scope of the appraisal, patients who would need to access lenalidomide in the first relapse setting would have already received bortezomib in the newly diagnosed setting. This means that the patients would have already demonstrated that they are intolerant or contraindicated to thalidomide which, like lenalidomide, is an IMID. Patients who have demonstrated a major intolerance to thalidomide or have not responded to lenalidomide might have a similar response/reaction to lenalidomide.

However, once lenalidomide is available in this setting clinicians would be able to use their clinical discretion as to whether their patient would be suitable for lenalidomide and in addition to this, as the side-effect profile of lenalidomide is better than thalidomide (in particular in terms of peripheral neuropathy) patients may benefit from lenalidomide where they didn't from thalidomide.

Summary

Myeloma UK believes there is a very strong case to support the approval of lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy with bortezomib.

The data is compelling and the potential advantages to patients significantly outweigh any disadvantages.

The approval of lenalidomide in this setting would represent a step forward in the treatment pathway for myeloma in the UK and would secure access to lenalidomide in this setting in the long-term (rather than through the Cancer Drugs Fund).