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Summary

Lenalidomide is an immunomodulatory drug and a structural analogue of thalidomide which has been developed by Celgene. It is licensed for use in combination with dexamethasone for the treatment of patients with multiple myeloma (MM) who have received at least one prior therapy. For patients to receive lenalidomide in the UK the pharmacy must be registered with Celgene to supply the drug, the patient must sign a consent to confirm their awareness of the risks of treatment and prescribers must complete on a prescription authorisation form on each occasion the drug is supplied to confirm that conditions outlined in associated pregnancy prevention programme have been fulfilled.

NICE recently supported the use of bortezomib as a possible treatment in patients with progressive multiple myeloma whose disease has relapsed for the first time after having one treatment and have either had a bone marrow transplant or are unsuitable for one. Treatment response should be assessed after 4 cycles and only continued in patients who have a partial response or better. NICE do not support the use of bortezomib in any other patient group. This guidance differs from that published by the British Committee for Standards in Haematology in 2006 which suggest that in patients with MM that relapse or progress, management should be determined on an individual basis depending on timing of relapse, age, prior therapy, bone marrow function and other clinical circumstances. It is recommended that thalidomide should be considered (with the addition of dexamethasone or cyclophosphamide if there is no evidence of response after 6-10 weeks) in patients who relapse within 6 months of initial treatment with melphalan and prednisolone, or within 12 months of patients that receive high-dose treatment (HDT) and an autograft. It is felt that bortezomib is appropriate for a 3rd line therapy in patients with reasonable performance status and organ function and reasonable life expectancy. Alternative third line therapies suggested include dexamethasone or weekly cyclophosphamide.

The British Committee for Standards in Haematology has issued a position statement on the use of lenalidomide in multiple myeloma. They recommend the use of lenalidomide (in combination with dexamethasone) in patients at any disease stage where thalidomide treatment is indicated, but is not tolerated because of peripheral neuropathy, somnolence, or any of the other side effects of thalidomide.

Lenalidomide has been evaluated in two phase III clinical studies in patients with relapsed, refractory MM who had received at least one prior therapy (the patients recruited actually received a median of 3 previous therapies). In both studies patients were randomised to receive lenalidomide (25mg daily for 3 weeks every 4 weeks) plus dexamethasone 40mg on days 1-4, 9-12, 17-20 every 4 weeks for 4 months, then 40mg on days 1-4 of each cycle thereafter, or placebo plus dexamethasone. The primary efficacy end-point was time to progression (TTP) which was defined as the time from randomisation to the first occurrence of progressive disease or death from progressive disease. In one study (n= 353) it is reported that the median TTP was 11.1 months in the combination arm compared with 4.7 months in the dexamethasone arm (p< 0.0001). In the other study (n= 351), the median TTP was 11.3 months in the combination arm and 4.7 months in the control arm (p < 0.0001). In one study it is reported that median overall survival (a secondary endpoint) was 29.6 months in the combination arm compared with 20.2 months in control arm, in the other study median overall survival was 20.6 months in the control arm but has not yet been reached in the group that received combination treatment. A combined analysis of the two trials shows a one year survival rate of 82% in patients that received combination treatment compared with 75% in patients that received control treatment. An updated, unpublished analysis of the two trials shows a median overall survival of 35 months in the lenalidomide group compared with 31 months in the control group. However within that report it is stated that 47% of patients crossed over

Summary continued on page 2
Lenalidomide (Revlimid) for relapsed or refractory multiple myeloma

Introduction

Lenalidomide (CC-5013; Revlimid) is an immunomodulatory drug and a structural analogue of thalidomide which has been developed by Celgene (1). It was developed in an attempt to optimise properties such as anti-cancer activity, whilst minimise much of the toxicity associated with thalidomide (2). Potential clinical applications investigated for lenalidomide include CNS cancer, inflammation, malignant melanoma, chronic lymphocytic leukaemia, myelodysplastic syndromes, and multiple myeloma, the latter indication being the subject of this review.

The mechanisms of action of lenalidomide remain to be fully characterised, however it is thought, like thalidomide, it suppresses the production of tumour necrosis factor alpha (TNF-α), demonstrates anti-angiogenic properties, activates CD4+ and CD8+ cells and increases the cytotoxicity of natural killer cells. It has also been observed that lenalidomide has direct antitumour properties in certain myeloma cell lines (3).

The FDA has approved lenalidomide for use in combination with dexamethasone for the treatment of relapsed or refractory multiple myeloma patients who have received at least one prior therapy (4). The EMEA has approved a similar marketing authorisation request for consideration in Europe through the harmonised procedure and the drug is now fully licensed in the UK for use, in combination with dexamethasone, for the treatment of patients with multiple myeloma (MM) who have received at least one prior therapy (5).

Multiple myeloma

Multiple myeloma (MM) is a plasma-cell neoplasm that is characterised by skeletal destruction, renal failure, anaemia and hypercalcaemia (6). Clinical presentation is varied and might include symptoms of bone disease (typically persistent unexplained backache), impaired renal function, anaemia, hypercalcaemia, recurrent or persistent bacterial infection, hyperviscosity, symptoms suggestive of spinal cord/nerve root compression, features suggestive of amyloidosis (such as nephrotic syndrome or cardiac failure), persistently raised erythrocyte sedimentation rate (ESR) or plasma viscosity as an incidental finding (6.7). The median length of survival after diagnosis is approximately 3 years and despite advances in its treatment multiple myeloma remains incurable (6).

Epidemiology and current treatment

NICE estimate that almost 8000 people have multiple myeloma in the United Kingdom and that around 3000 develop the disease every year – this equates to a prevalence and incidence of around 16 and 6 cases per 100,000 population respectively (8). Myeloma is most common among people over 65 years of age with an incidence of between 25-30 per 100,000 versus approximately 1.5-2.5 per 100,000 in people under 65. However, the prevalence within younger age groups appears to be increasing, with at least 10 to 15 percent of patients now under age 45. Overall, the incidence rates in men are approximately 50 percent higher than in women across all racial/ethnic or validity of the modelling used to establish this estimate of benefit.

There are no studies available that directly compare lenalidomide with either thalidomide or bortezomib in the treatment of relapsed/refractory disease and the ongoing trial programme does not address these questions.

In the two Phase III studies it was reported that 11.4% and 14.7% of patients treated with lenalidomide and dexamethasone developed a Grade 3/4 thromboembolic event compared with 2.3% and 3.5% in the control arm. Thromboprophylaxis (such as low molecular weight heparin or warfarin) is recommended in patients receiving lenalidomide who have additional risks for thrombosis. Other important adverse events associated with the combination included neutropenia (Grade 3/4 occurred in 29.5% vs 2.3% in one study and 41.2% vs 4.6% in the other) and thrombocytopenia (Grade 3/4 11.4% vs 5.7% in one study and 14.7% vs 3.4% in the other). Other significant adverse effects listed in the SPC include fatigue (27.2%), asthenia (17.6%), constipation (23.5%), muscle cramp (20.1%), thrombocytopenia (18.4%), anaemia (17.0%), diarrhoea (14.2%) and rash (10.2%).

To treat a patient with lenalidomide 25mg daily for 21 days for one 28-day cycle costs £4,368 (excluding VAT). Therefore to treat a patient with 11 cycles (median duration of treatment in the two published Phase III studies) could cost up to £48,000 although this may be slightly less if dose reductions are required. No published health economic analyses were identified. An unpublished analysis suggests that it costs an average £56,155 to treat a patient with lenalidomide (compared to £3819 with dexamethasone) and that this produces an incremental gain of 2.53 years (4.53 vs 2 years) and 1.8 QALYs (3.19 vs 1.39 years) in patients treated with one previous line of therapy. It is not possible to assess the validity of the assumptions behind these estimates but if they are valid it suggests that lenalidomide costs £20,648 per life year gained and £28,980 per QALY gained.

NICE estimate that there are about 2000 patients in England currently eligible for bortezomib and 785 new patients that would be eligible each year equating to a prevalence of around 4 cases per 100,000 population and an incidence of around 1.6 cases per 100,000 population, this is probably similar to the population that might then go on to receive lenalidomide. Alternatively, data from Cancer Research UK estimate that the mortality incidence from multiple myeloma is 2.8 people per 100,000 population – again it could be assumed that is the population that might be offered lenalidomide as a salvage therapy. So if we assume that between 1.6 and 2.8 patients per 100,000 population could receive lenalidomide every year for an average 11 cycles this could increase costs by between £76,800 and £134,400 per 100,000 population (excluding VAT).
Lenalidomide (Revlimid) for relapsed or refractory multiple myeloma

There is a higher incidence in African-Caribbean ethnic groups than in Caucasians (9). For people with asymptomatic (or smouldering) myeloma no treatment other than monitoring is normally given. Patients with asymptomatic myeloma who show signs of bone disease may be given a bisphosphonate. Myeloma can remain asymptomatic for many years although the median time from diagnosis to the progression to symptomatic disease is two to three years (6). The British Committee for Standards in Haematology state that treatment should be deferred until there is evidence of disease progression or organ impairment (7).

Once there is disease progression the aim of treatment should aim to control disease, maximise quality of life and prolong survival. The regimen chosen should reflect whether high-dose treatment (HDT) is planned or not. If HDT is planned then VAD (vincristine, doxorubicin, dexmethasone) or a VAD-type regimen should be administered as an initial therapy. For older patients in whom HDT is not planned either melphalan or cyclophosphamide should be used (with or without the addition of prednisolone). HDT plus autologous stem-cell transplantation (ASCT) should be considered in newly diagnosed patients up to the age of 65 years with adequate performance status and organ function and in older patients with good organ function (7).

NICE recently supported the use of bortezomib as a possible treatment in patients with progressive multiple myeloma whose disease has relapsed for the first time after having one treatment and have either had a bone marrow transplant or are unsuitable for one. Treatment response should be assessed after 4 cycles and only continued in patients who have a partial response or better. NICE do not support the use of bortezomib in any other patient group (8). This guidance differs from that published by the British Committee for Standards in Haematology in terms of suggested role for bortezomib (7). These guidelines suggest that in patients with MM that relapse or progress, management should be determined on an individual basis depending on timing of relapse, age, prior therapy, bone marrow function and other clinical circumstances. It is recommended that thalidomide should be considered (with the addition of dexamethasone or cyclophosphamide if there is no evidence of response after 6-10 weeks) in patients who relapse within 6 months of initial treatment with melphalan and prednisolone, or within 12 months of patients that receive high-dose treatment (HDT) and an autograft. It is felt that bortezomib is appropriate for a 3rd line therapy in patients with reasonable performance status and organ function and reasonable life expectancy. Alternative third line therapies suggested include dexamethasone or weekly cyclophosphamide.

In a Position Statement on the use of lenalidomide in multiple myeloma the British Committee for Standards in Haematology reiterate the opinion that there can be no standard approach recommended for the treatment at relapse (10). Factors which may influence the choice of regimen may include:

- Prior treatment history influences the choice of therapy, short remission duration with a given treatment being a strong indicator to change to an alternative approach
- Relapsed/ refractory myeloma is a well-defined state, which has by definition, a very poor outcome and is rapidly fatal

Therapies will also be required to achieve pain control and treat hypercalcaemia and bone disease, anaemia, renal failure and infections (7).

Efficacy

Lenalidomide has been studied in both the relapsed, refractory MM setting and in patients with newly diagnosed MM, but at present lenalidomide is only licensed for use in the relapsed/ refractory setting and that is the focus of this review.

Lenalidomide has been evaluated in two phase III clinical studies in patients with relapsed, refractory MM (MM-009, n=354 and MM-010, n=351). Both of these studies are now fully published (11, 12).

In both studies patients were randomised to receive lenalidomide (25mg daily for 3 weeks every 4 weeks) plus dexamethasone 40mg on days 1-4, 9-12, 17-20 every 4 weeks for 4 months, then 40mg on days 1-4 of each cycle thereafter, or placebo plus dexamethasone. Over 80% of patients enrolled in both studies had been treated with 2 or more types of treatment prior to randomisation including thalidomide (30.1 to 45.5%), bortezomib (4.0 to 11.4%) and stem-cell transplantation (54.3 to 61.5%). The primary efficacy end-point was time to progression (TTP) which was defined as the time from randomisation to the first occurrence of progressive disease or death from progressive disease. The trials appear to be methodologically robust in that they were randomised, blinded, had low rates of loss to follow up and results were analysed using intention to treat principles. In one study (n=353) it is reported that the median TTP was 11.1 months in the combination arm compared with 4.7 months in the dexamethasone arm (p< 0.0001). In the other study (n=351), the median TTP was 11.3 months in the combination arm and 4.7 months in the control arm (p < 0.0001). In one study it is reported that median overall survival (a secondary endpoint) was 29.6 months in the combination arm compared with 20.2 months in control arm, in the other study median overall survival was 20.6 months in the control arm but has not yet been reached in the group that received combination treatment. In both trials complete responses were seen in around 15% of patients that received the combination of lenalidomide and dexamethasone compared with 0.6 to 3.4% of those that received dexamethasone and overall response rates were reported as occurring in 53% and 51% of the combination treatment arms compared with 16 and 19% of the dexamethasone groups (p< 0.0001).

A combined analysis of results from both trials has been published in the Summary of Product Characteristics (SPC) (5) and is reproduced in Table 1:
Lenalidomide (Revlimid) for relapsed or refractory multiple myeloma

1-year Overall Survival rate

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>len/dex (N=353)</th>
<th>placebo/ dex (N=351)</th>
<th>Hazard ratio/odds ratio , 95% CI, p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Time To Progression [weeks] [95% CI]</td>
<td>48.3 [41.1, 60.1]</td>
<td>20.1 [19.9, 20.7]</td>
<td>0.35 [0.29, 0.43], p &lt; 0.001</td>
</tr>
<tr>
<td>Overall Response [n, %]</td>
<td>214 (60.6)</td>
<td>77 (21.9)</td>
<td>0.18 [0.13, 0.25], p &lt; 0.001</td>
</tr>
<tr>
<td>Complete Response [n, %]</td>
<td>53 (15.0)</td>
<td>7 (2.0)</td>
<td>0.12 [0.05, 0.26], p &lt; 0.001</td>
</tr>
<tr>
<td>Partial Response [n, %]</td>
<td>161 (45.6)</td>
<td>70 (19.9)</td>
<td>0.30 [0.21, 0.42], p &lt; 0.001</td>
</tr>
<tr>
<td>Median Progression Free Survival [weeks] [95% CI]</td>
<td>47.3 [36.9, 58.4]</td>
<td>20.1 [18.1, 20.3]</td>
<td>0.38 [0.32, 0.46], p &lt; 0.001</td>
</tr>
<tr>
<td>1-year Overall Survival rate</td>
<td>82%</td>
<td>75%</td>
<td>0.75 [0.59, 0.95], p = 0.015</td>
</tr>
</tbody>
</table>

A further follow-up of these data has been presented at conference (13). This analysis shows that the combination of lenalidomide and dexamethasone is associated with an overall survival of 35 months compared to 31 months in patients that were randomised to receive dexamethasone alone. However the authors point out that of the patients who progressed on dexamethasone alone (prior to unblinding) or discovered they were receiving dexamethasone alone (after unblinding) 47% elected to receive lenalidomide. This makes it very difficult to quantify the true effect of lenalidomide on overall survival. Some unpublished modelling analysis suggests that lenalidomide/ dexamethasone may be associated with a 2.8 year increase in mean survival compared with historical controls (4.7 years vs. 1.9 years) (14).

Sub-group analyses of these trials have also been presented at the 2006 ASCO conference. One compared efficacy in patients that had previously been exposed to thalidomide (n=269) with those that had not (n=423) (15). It was shown that median time to progression in patients previously exposed to thalidomide was 36.9 and 19.7 weeks in patients randomised to the lenalidomide/ dexamethasone combination and dexamethasone alone respectively (p=0.001) and 59 and 20.3 weeks in patients that had not received thalidomide previously (p=0.001). Longer term follow up data on sub-groups has been presented at conference (13) and shows that median overall survival in patients who had received more than one prior treatment was 32.4 months in patients that received the combination of lenalidomide and dexamethasone and 27.3 months in patients that received dexamethasone. For patients that had only received one prior treatment the median overall survival was 35.3 months and had not been reached in the combination group. Again interpretation is complicated by the fact that 47% of patients crossed over to receive lenalidomide.

There is also a Phase II study in which 101 patients were randomised to receive lenalidomide at a dose of 15mg twice daily or 30mg once daily for 3 weeks in a 4 weekly cycle (16). Dexamethasone (40mg daily for 4 days every 2 weeks) was added if there was progression at 4 weeks or if the disease was stable at 8 weeks. Most patients had been treated previously with thalidomide. 83 patients were eligible for assessment and it was shown that a complete response (defined as a >75% reduction in paraprotein levels) was achieved in 5 (6%), a partial response (defined as a 50-75% decrease in paraprotein levels) was achieved in 15 (16%), a minimal response (defined as a 25-50% decrease in paraprotein levels) was achieved in 12 (14%) and stable disease (defined as a >25% decrease in paraprotein levels) in 39 (47%) of patients. Twelve patients (14%) progressed despite treatment with lenalidomide. Dexamethasone was added to 30% of patients at 4 weeks.

### Safety

Animal data has indicated that lenalidomide may not have the teratogenic potential that thalidomide is known to have, as lenalidomide was nonteratogenic in the New Zealand rabbit preclinical model, the most sensitive animal model for thalidomide-associated teratogenicity (2). This is not, however, a guarantee of lack of teratogenic effects in humans and in the US the drug has been licensed with the following black box warning (1).

**Warning: Potential for human birth defects**

Lenalidomide is an analogue of thalidomide. Thalidomide is a known human teratogen that causes severe life-threatening human birth defects. If lenalidomide is taken during pregnancy, it may cause birth defects or death to an unborn baby. Females should be advised to avoid pregnancy while taking Revlimid (lenalidomide).

In the UK lenalidomide is only available under a special restricted distribution programme called Pregnancy Prevention Programme. In this programme the drug can only be prescribed and dispensed by hospitals and pharmacies registered with the programme and the drug must only be dispensed to registered patients that meet all the conditions stipulated (including a confirmed negative pregnancy test if that is relevant).

In the US the drug has also got a black box warning about deep vein thrombosis and pulmonary embolism as follows (2):

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May 2008

London New Drugs Group—APC/DTC Briefing
This drug has demonstrated a significantly increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients with multiple myeloma who were treated with REVLIMID (lenalidomide) combination therapy. Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. It is not known whether prophylactic anticoagulation or antplatelet therapy prescribed in conjunction with REVLIMID (lenalidomide) may lessen the potential for venous thromboembolic events. The decision to take prophylactic measures should be done carefully after an assessment of an individual patient’s underlying risk factors.

In the combined analysis of adverse events presented in the Medication Guide (2) it is reported that Grade 3 or 4 DVT was reported in 6.9% of patients treated with the combination compared with 2.9% of patients treated with dexamethasone. Similarly it is reported that pulmonary embolism was reported in 3.5% of patients treated with the combination compared with 0.9% of patients treated with dexamethasone monotherapy and overall 12% of the combination arm and 4% of the dexamethasone arm experienced a thrombotic or thromboembolic event. Presented below in Table 2 is a combined analysis of the Grade 3/4 adverse effect data presented in the published trial reports.

### Table 2: incidence of Grade 3/4 adverse events seen in published clinical trials

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Lenalidomide/ dexamethasone (n=353)</th>
<th>Dexamethasone (n=350)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>35.4%</td>
<td>3.4%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>13%</td>
<td>6.3%</td>
</tr>
<tr>
<td>Anaemia</td>
<td>10.8%</td>
<td>6%</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>3.4%</td>
<td>0</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>13%</td>
<td>4%</td>
</tr>
<tr>
<td>Pulmonary embolism (as part of above)</td>
<td>4%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Respiratory tract infection</td>
<td>7.6%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Other infections</td>
<td>15.6%</td>
<td>9.1%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6.5%</td>
<td>4.9%</td>
</tr>
</tbody>
</table>

Other significant adverse effects listed in the SPC include fatigue (27.2%), asthenia (17.6%), constipation (23.5%), muscle cramp (20.1%), thrombocytopenia (18.4%), anaemia (17.0%), diarrhoea (14.2%) and rash (10.2%).

Within the SPC (5) clinicians are also advised to monitor the complete blood cell count, including white blood cell count with differential count, platelet count, haemoglobin, and haematocrit. These measurements should be performed at baseline, every week for the first 8 weeks of lenalidomide treatment and monthly thereafter to monitor for cytopenias. It is advised that the major dose limiting toxicities of lenalidomide include neutropenia and thrombocytopenia. Therefore, co-administration of lenalidomide with other myelosuppressive agents should be undertaken with caution. It is also noted that since lenalidomide is substantially excreted by the kidney, care should be taken in dose selection and monitoring of renal function is advised in patients with renal impairment. Also cases of hypothyroidism have been reported and monitoring of thyroid function should be considered. Finally as lenalidomide is structurally related to thalidomide, which is known to induce severe peripheral neuropathy. At this time, the neurotoxic potential of lenalidomide associated with long-term use cannot be ruled out.

Knight et al elaborate further on the thrombosis issue in a letter published in the New England Journal of Medicine (17). They note that in the study conducted in the United States and Canada, 23% of the patients that received the combination plus erythropoietin developed thrombosis compared with 5% in the patients treated with the combination but not erythropoietin. In the group that received dexamethasone alone thrombosis developed in 7% of those also treated with erythropoietin and 1% of those that were not. In another letter the authors state that in an ongoing ECOG trial comparing lenalidomide plus high-dose dexamethasone (regimen used in the Phase III trials discussed above) and lenalidomide plus low-dose dexamethasone (40mg on Days 1, 8, 15 and 22 every 4 weeks) in newly diagnosed multiple myeloma it was observed that 18.2% of the high-dose group and 3.7% of the low-dose group developed thromboembolic events (18). Also in a recently published letter in Blood the same authors state that the National Cancer Therapy Evaluation Program in the US now recommend routine thromboprophylaxis when lenalidomide and erythropoietin are used concurrently and in the ECOG trial it is now recommended...
that all patients receiving lenalidomide plus dexamethasone should receive routine thromboprophylaxis with aspirin as the minimum mandatory prophylaxis and a recommendation to consider low-molecular weight heparin or warfarin in patients receiving high-dose dexamethasone (19).

Comparison with thalidomide

There are no published studies comparing lenalidomide with thalidomide directly. For the treatment of MM, thalidomide has been studied as a single agent, in combination with dexamethasone, and in combination with chemotherapy. Its use in both newly diagnosed and relapsed, refractory MM have been investigated, although again research has mainly focussed on relapsed/refractory disease. In a systematic review of Phase II studies of thalidomide as a single agent for relapsed, refractory MM it is reported that a CR/PR response rate of 29% was seen in 1629 patients (20). Higher response rates of the order of 60% have been reported for combined therapy with thalidomide and dexamethasone or thalidomide, dexamethasone and cyclophosphamide (7). There are also trial data showing responses to thalidomide and dexamethasone combination in patients who have previously been refractory to thalidomide alone (7).

2006 Guidelines on the management of MM from the British Committee for Standards in Haematology state that for relapses/progressive disease the most appropriate therapy must be determined on an individual basis, but that thalidomide may be an appropriate choice for some patients, with the addition of dexamethasone if there is no response after 6-8 weeks. For initial treatment of MM they state that thalidomide should only be used in the context of a clinical trial, and for maintenance therapy in the plateau phase following initial chemotherapy the role of thalidomide remains unclear (7).

Adverse effects of thalidomide

Venous thromboembolism (VTE) has also emerged as an important complication of thalidomide therapy in this setting and, like lenalidomide, it was considered necessary to issue a black box warning in the US. Within the Thalomid package insert it is reported that in one controlled study of thalidomide plus dexamethasone in patients with multiple myeloma found that 22.5% of patients that received the combination developed a venous thromboembolic event compared with 4.9% of those patients that received dexamethasone alone (21). Some of the other Grade 3 or 4 adverse events seen in that controlled trial are listed in Table 3:

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Thalidomide plus dexamethasone (n=102)</th>
<th>Dexamethasone alone (n=102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperglycaemia</td>
<td>15.7%</td>
<td>18.7%</td>
</tr>
<tr>
<td>Hypocalcaemia</td>
<td>14.7%</td>
<td>4.9%</td>
</tr>
<tr>
<td>Hyponatraemia</td>
<td>12.8%</td>
<td>14.7%</td>
</tr>
<tr>
<td>Hyperkalaemia</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Neuropathy-sensory</td>
<td>3.9%</td>
<td>1%</td>
</tr>
<tr>
<td>Neuropathy-motor</td>
<td>7.9%</td>
<td>5.9%</td>
</tr>
<tr>
<td>Confusion</td>
<td>8.8%</td>
<td>4.9%</td>
</tr>
<tr>
<td>Decreased haemoglobin</td>
<td>15.6%</td>
<td>5.9%</td>
</tr>
<tr>
<td>Decreased leucocytes</td>
<td>6.9%</td>
<td>3%</td>
</tr>
<tr>
<td>Decreased neutrophils</td>
<td>12.7%</td>
<td>10.7%</td>
</tr>
<tr>
<td>Constipation</td>
<td>7.8%</td>
<td>1%</td>
</tr>
<tr>
<td>Rash</td>
<td>3.9%</td>
<td>2%</td>
</tr>
</tbody>
</table>

In the US it is advised that patients are examined monthly for the first 3 months of thalidomide therapy to detect early signs of peripheral neuropathy and then periodically thereafter (21). It is also advised that consideration should be given to electrophysiological testing, consisting of measurement of sensory nerve action potential (SNAP) amplitudes at baseline and thereafter every 6 months in an effort to detect asymptomatic neuropathy.
Lenalidomide (Revlimid) for relapsed or refractory multiple myeloma

May 2008

London New Drugs Group—APC/DTC Briefing

Ongoing studies

There are several phase III studies currently underway in this area (personal communication). Ongoing studies are investigating:

- lenalidomide/dexamethasone vs. dexamethasone alone in patients with newly diagnosed MM (n=500)
- lenalidomide/dexamethasone vs. lenalidomide/low-dose dexamethasone in patients with MM (n=412)
- lenalidomide/bortezomib vs. bortezomib in patients with relapsing/progressing MM on total therapy III (n=315)

Estimated financial implications and cost effectiveness

To treat a patient with lenalidomide 25mg daily for 21 days for one 28-day cycle costs £4,368 (excluding VAT). Therefore to treat a patient with 11 cycles (median duration of treatment in the two published Phase III studies) would cost up to £48,000.

No published health economic analyses were identified. One health economic analysis assessing its economic utility in patients treated with one previous line of therapy has recently been presented at conference and makes the following claims (22). It is currently not possible to appraise the validity of these data:

- Lenalidomide plus dexamethasone is associated with a discounted gain of 2.53 years in life expectancy compared with dexamethasone alone (4.53 vs 2 years)
- Lenalidomide plus dexamethasone is associated with a discounted gain of 1.8 quality adjusted life years compared with dexamethasone alone (3.19 vs 1.39 years)
- Lenalidomide is associated with an incremental cost per life year gained of £20,648 and an incremental cost per QALY gained of £28,980

NICE estimate that there are about 2000 patients in England currently eligible for bortezomib and 785 new patients that would be eligible each year equating to a prevalence of around 4 cases per 100,000 population and an incidence of around 1.6 cases per 100,000 population (8), this is probably similar to the population that might then go on to receive lenalidomide. Alternatively, data from Cancer Research UK estimate that the mortality incidence from multiple myeloma is 2.8 people per 100,000 population – again it could be assumed that is the population that might be offered lenalidomide as a salvage therapy. So if we assume that between 1.6 and 2.8 patients per 100,000 population receive lenalidomide every year for an average 11 cycles this could increase costs by between £76,800 and £134,400 per 100,000 population (excluding VAT).

Issues for consideration

- NICE have considering the role of bortezomib in the treatment of relapsed/ refractory MM and stated that it should only be used in patients at first relapse- does this recommendation mean that lenalidomide should only be considered in patients who have relapsed or are refractory after two or more treatments?
- At present there would not appear to be any fully published data that quantifies the impact of lenalidomide on quality of life and therefore it is not currently possible to make any reliable assessment of its cost-effectiveness.
- The UK-relevant economic analysis currently available to support the use of lenalidomide is limited to a conference poster assessing use as a second-line treatment only. As such it is difficult to make any real assessment of the rigour or relevance of this analysis.
- Lenalidomide is licensed to be used within a restricted access programme – this will have service implications although many of these will already have been worked through if centres are already using the Pharmion brand of thalidomide.
- Thromboembolic risk needs to be clarified and thromboprophylaxis will probably be necessary in many patients – current Phase III studies that use low-dose dexamethasone all include aspirin as routine prophylaxis but there are some indications that more aggressive approaches may be necessary (and are recommended within the product license).
- There are currently no RCTs which allow a direct comparison of lenalidomide with thalidomide or bortezomib, it is therefore difficult to define its role in the treatment pathway compared to these agents.
- Lenalidomide treatment could result in hospital admissions for treatment of neutropenia / thrombocytopenia related adverse events and this will have additional cost implications. Conversely since lenalidomide is an oral therapy its use instead of an agent like bortezomib may reduce the need for hospital day case visits.
References

8. NICE. Bortezomib for relapsed multiple myeloma. NICE website (link: last accessed 14.3.08)
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The document reflects the views of LNDG and may not reflect those of the reviewers