

Case study 4

Revlimid and Multiple Myeloma*

Summary

Need

- Revlimid brings benefits to myeloma patients, by slowing disease progressing and lengthening patients lives.
- Myeloma affects 1.3 in every 10,000 people. In the UK just under 5,000 people are diagnosed a year however around half of these will be likely to be prescribed Revlimid.
- The number of patients estimated to be eligible for treatment, and assuming a relatively small amount of uptake is particularly small across the devolved countries (as low as 23 in the first year of use in Scotland). These estimates have also changed over time. This demonstrates uncertainties for manufacturers and the NHS in the final numbers of patients. This also feeds through into uncertainties for the cost to the NHS, and the revenue to Celgene.

R&D

- Revlimid is a derivative of Thalidomide - a sedative drug introduced in the 1950s to treat morning sickness. This illustrates that useful medicines can therefore be developed as knowledge builds over time, including from treatments for unrelated conditions which are unsafe.
- Celgene will need to re-coup R&D costs, but the effective patent life may be relatively short with the first patent for Revlimid due to expire in 2019.

Regulatory approval

- In 2007 Revlimid recieved regulatory approval from the EMA based on two trials, one including 704 patients.
- Approval was faster however in the US (in 2006) but slower in others (in 2008 in Canada and 2010 in Japan).
- Celgene will need to re-coup R&D costs, but the effective patent life may be relatively short with the first patent for Revlimid due to expire in 2019.

Payer approval

- The cost of Revlimid per patient per year is in the region of £40,000. However, the precise cost per patient over their lifetime (sadly typically less than 3 years) is limited to the NHS (only in England in Wales) through a special arrangement where the manufacturer pays for cycles of treatment for patients beyond the 26 cycles that the NHS pays.
- The budget impact of Revlimid to the NHS in Scotland was estimated to be £2.35million in the first year, rising to £3.75million in the fifth year in 2008. In 2010 these were revised down to £920,000 and £2.92million. This illustrates uncertainties for the budget impact for the NHS, but also in revenues to the manufacturer.
- The budget impact of Revlimid to the NHS in Wales was £3million in year one, rising to over £4.2 million by year five of use.
- NICE appraised Revlimid within 2 years of its approval, and has is updating their guidance over

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currently. SMC and AWMSG were both faster providing guidance within a year.

- The ICER for Lenalidomide ranges according to the characteristics of patients and the treatments that they have had prior to Lenalidomide, however they are above £30,000 per QALY that is usually considered the point at which a medicine is no longer offering value for money.
- its original analysis in 2008, also recommends restricted use. The AWMSG did not recommend Revlimid, however their guidance is now superseded by NICE guidance.
- In part, these differences across agencies may be due to differences in the flexibilities now permitted in decision making and the time these were introduced (in some cases after appraisal of Revlimid). NICE (from 2009) is able to recommend products with higher cost per QALY in the context of end of life treatments. AWMSG (from 2011) is also able to recommend products with a higher cost per QALY in the context of end of life treatments. Scotland does not have the exact same guidance, although SMC does allow for some flexibility when there is substantial improvement in life expectancy since 2010. The SMC also explicit allows for a modifier (which can mean acceptance of a higher cost per QALY) when a product has orphan drug status. The NICE recommendation may also be driven by the option for the manufacturer to voluntarily offer Revlimid at a lower cost through a Patient Access Scheme.
- The Patient Access Scheme allows access, and at a lower cost to the NHS, but equally this means lower revenue for the manufacturer.
- Funding is also controversial outside of the UK: in Australia it is not reimbursed under the PBS, and in Canada, Provinces have agreed to fund, but in Quebec that seems to be a provisional decision for second line treatment taken in 2012.

- The views of agencies differ: NICE recommends Lenalidomide in combination with dexamethasone as an option for the treatment of multiple myeloma, only in people who have received two or more prior therapies. The SMC, after a resubmission in 2010 of Future funding is a concern expressed by patients.

Prescription

- Revlimid is just one part of a range of treatments, and clinicians need to use their expertise in determining the treatment options and when to use Revlimid.

Introduction

Revlimid (Lenalidomide) manufactured by Celgene Limited, is a derivative drug of Thalidomide (a sedative drug introduced in the 1950s to treat morning sickness) that was introduced in 2004 (Wikipedia, 2012a). It is an anti-cancer medicine that is used in combination with dexamethasone to treat adults with multiple myeloma whose disease has been treated at least once in the past (EMA, 2012d).

Lenalidomide, the active substance in Revlimid, is an immunomodulating agent, which affects the activity of the immune system. It works by blocking the development of tumour cells, prevents the growth of blood vessels within tumours and also stimulates some of the specialised cells of the immune system to attack the cancerous cells (EMA, 2012d). This lengthens the time that people with multiple myeloma can live without the cancer getting worse.

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Need

Myeloma is classified as a rare disease with a prevalence rate of 1.3 per 10,000 people (COMP and EMASS, 2011). An estimated 103,000 people across the world were diagnosed with myeloma in 2008, accounting for around 1% of all cancers diagnosed, and around 12% of all haematological cancers diagnosed (Cancer Research UK, 2012). In the UK multiple myeloma is the 14th most common cancer among men, and the 17th most common cancer among women, and accounts for more than 1% of all cancers in each sex. In 2009, 2,714 (57%) men and 2,070 (43%) women were diagnosed with myeloma in the UK (Cancer Research UK, 2012).

In England, approximately 2,100 people are likely to be prescribed Revlimid (NICE, 2009a). In Scotland, the manufacturer assumed in 2008 that the net number of patients who could be initiating treatment in year one was 75, 40 in year 2, 48 in year 3, 56 in year 4 and 63 in year 5 (SMC, 2008c). By 2010, they suggested that there could be 234 eligible patients in year one and 370 in year five. Assuming update of 10% in year one, rising to 50% by year five, the number of patients who could be initiating treatment would then be 23 patients starting treatment in year one and 51 patients starting treatment in year five (SMC, 2010d). In Wales, the manufacturer estimated that 106 patients could be eligible and initiate treatment (AWMSG, 2008a).

The lifetime risk of developing myeloma is around 1 in 115 for men and 1 in 155 for women (Cancer Research UK, 2012).

Multiple myeloma disproportionately affects older adults (the median age in 2010 was 70 years) and is rarely diagnosed in those under 40 years old (Renshaw et al, 2010). Incidence rates increase steadily with age and peak in those aged 85 and over (Cancer Research UK, 2012).

It has been argued by several research groups that incidence for multiple myeloma has remained stable, and that any increases are largely owing to improved diagnostic techniques and data registration, especially

in older groups. But the cancer is often misdiagnosed or under-reported due to intermittent and non-specific symptoms – a problem which occurs in developed and developing countries alike (Cancer Research UK, 2012).

Data from the Haematological Malignancy Research Network (HMRN) region for 2004-2009 have found that there is lower incidence of the cancer in lower socio-economic groups in the UK, however rather than reflecting disease aetiology, it is suggested that this is compatible with the theory that socio-economic factors can impact on the likelihood of recognising symptoms and/or seeking medical attention (Cancer Research UK, 2012).

Cancer Research UK (2012) studies on the cancer by ethnicity, covering 2002-2006, found that myeloma was almost twice as common in black people as in white and Asian people .

Multiple myeloma is incurable and may not cause any symptoms in its early stages (Science Daily, 2010). However, it usually causes a wide range of symptoms and complications as it develops. The most common of these include:

- bone pain;
- bone fractures;
- fatigue;
- anaemia;
- infection;
- hypercalcaemia;
- kidney damage (NHS, 2011).

Multiple myeloma is incurable, but it can be managed (McNutt, 2009). Doctors may describe multiple myeloma as smoldering, Stage I, Stage II, or Stage III. The various stages takes into consideration whether

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the cancer is causing problems with the individuals' bones or kidneys. Once it this has been identified, a doctor can assess which treatment is most appropriate. Treatment options Include:

- 'watchful waiting' (people with smoldering myeloma or Stage I myeloma, for example, may be able to put off having cancer treatment. In doing so, you can avoid the side effects of treatment until you have symptoms);
- induction therapy (or the initial therapy, which is the first in a series of therapeutic measures to treat a disease. With myeloma these could be chemotherapy, targeted therapy using drugs that block the growth of myeloma cells, or certain steroids) (Medicine Net, undated);
- stem cell transplant;
- a combination of methods (Medicine Net, undated).

Research and development

Revlimid is a derivative of thalidomide. Thalidomide was once used to treat morning sickness during pregnancy but was banned in the early 1960s after causing birth defects (Pollock, 2005). Thalidomide, intended as a treatment for multiple myeloma, is an accepted therapy, but has been shown to carry poor prognosis. Lenalidomide (Revlimid) has been shown to improve overall survival in myeloma without thalidomide (Wikipedia, 2012a).

Initially Revlimid was developed to treat multiple myeloma, however further research also found it could be effective in treating myelodysplastic syndromes (MDS) – a class of hematological disorders (Wikipedia, 2012a). Celgene received approval from the FDA in December 2005 to market Revlimid for the treatment of patients with transfusion-dependent anemia due to Low- or Intermediate-1-risk MDS associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities

(Wikipedia, 2012b). In 2010 that patent was challenged by pharmaceutical company Natco (The Pharma Letter, 2010). Celgene Europe Ltd. submitted an application for approval for MDS as an indication in 2006 (EMA, 2007b). In 2012 the company has decided to withdraw its application for an extension of the indication for Revlimid (EMA, 2012e).

Although there has been significant research on Revlimid, the exact mechanism of action is not understood (NICE, 2009a).

There are numerous patents related to Revlimid. The first patent is due to expire in October 2019.

Regulatory approval

Revlimid was awarded orphan drug status in 2003. It was subsequently approved by the EMA in 2007 for use in multiple myeloma (EMA, 2012d).

Approval of Revlimid was made on the basis of results from two trials in which pre-planned interim analyses of both studies showed that lenalidomide/dexamethasonewas were statistically significantly superior to dexamethasone alone. Updated results made after the authorisation confirmed the significant benefit it had over placebos (EMA, 2012c)

One of the trials, on which EMA approval was based, included 704 patients with multiple myeloma. In both trials, Revlimid in combination with dexamethasone was compared with a placebo. The primary measure of effectiveness was progression free survival (essentially how long before the disease got worse). From the combined results of both trials, it took, on average, 48.3 weeks for the disease to get worse in patients taking Revlimid, compared with 20.1 weeks in those taking placebo (EMA, 2012d). The results also found that from the time of diagnosis, survival without treatment is between 6 to 12 months versus 3 years with chemotherapy. Approximately 25% of patients survive 5 years or longer, with fewer than 5% surviving longer than 10 years (EMA, 2012d).

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The measures being taken to ensure the safe use of Revlimid include Celgene providing letters and educational kits for healthcare workers, and brochures for patients, explaining the fact that it is expected to be harmful to the unborn child, detailing the steps that need to be taken for the medicine to be used safely (EMA, 2012d).

In addition to that the company will supply cards for patients to ensure that all appropriate safety measures have been taken by each patient, educational materials will be provided for each Member State in the EU and Revlimid capsules will include boxes with a warning that lenalidomide is expected to be harmful to the unborn child (EMA, 2012d).

Revlimid was also approved in the US by the FDA in 2006 (Pazdur, undated). Concerns however have been raised about an increased second primary malignancies (new types of cancer) in patients with newly-diagnosed multiple myeloma who received Revlimid. FDA have added information to the drug label in 2012 to warn clinicians and patients on this risk (US Department of Health and Human Services, 2012).

Revlimid was also approved in Canada in 2008, and in Japan in 2010 (Canada Newswire, 2012).

Payer approval

25 mg capsules of Lenalidomide costs £4,368 per 21 capsules exclusive of VAT (2009 price in the UK). If, for example, lenalidomide is continued for ten 28-day cycles without dose reduction, the cost would be £43,680 per patient (NICE, 2010e).

However, the real cost per patient paid by the NHS depends upon the patients' response and any locally negotiated discount. Celgene has agreed a Patient Access Scheme where they will pay when patients receive more than 26 cycles of Revlimid (NICE, 2010e). This means that the prescribing clinician believes that the patient is still deriving benefit from

the treatment after 26 cycles. We discuss the scheme in more detail below as it is linked to the NICE appraisal. However, this scheme essentially caps the amount per patient that the NHS will pay. Correspondingly it also limits the revenue that Celgene can make from sales for individual patients, and also means that they bear the costs of any further cycles. This will not be the same cost as the cost per cycle sold to the NHS, but rather the marginal cost of production.

Revlimid is excluded from Payment by Results and hence the high cost has to be paid for outside of the national tariff (Medicines Management Team for Coastal West Sussex, 2012).

Revlimid has been appraised by all the three key UK agencies: NICE, SMC and AWMSG. In short the findings are:

- NICE recommends Lenalidomide in combination with dexamethasone as an option for the treatment of multiple myeloma, only in people who have received two or more prior therapies;
- SMC recommends restricted use;
- AWMSG does not recommend Revlimid;

We look at these in more detail below.

NICE

NICE appraised Revlimid beginning in May 2008¹, and produced final guidance in 2009 (TA171) (NICE, 2009a). In that guidance NICE recommends Lenalidomide in combination with dexamethasone as an option for the treatment of multiple myeloma, only in people who have received two or more prior therapies (NICE, 2009a). They also recommend further research to understand the survival benefits of Lenalidomide.

¹ The earliest date included in the key documents history on the NICE website (NICE, 2010f)

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NICE drew on both the manufacturer's submission and a review of that submission by an independent academic Evidence Review Group (ERG). The underpinning analysis was complex, needing to account for the different types of treatment that some patients may receive before taking Revlimid, leading to 4 separate groups of patients identified in the economic modelling. The modelling drew on a variety of sources of data: the clinical trials (to capture the clinical benefits and side effects), utility values (which in theory capture the impact on health related quality of life of patients) from published literature, and resource use data collected from specialists. This analysis suggested that (NICE, 2009a):

- For the subgroup with one prior therapy, ICER was £46,865 per QALY gained for lenalidomide compared with dexamethasone.
- For patients who had received two or more prior therapies the ICER was £24,584 per QALY gained.
- In the subgroup of patients who had received prior thalidomide, the ICERs were £38,861 per QALY gained for patients with only one prior therapy and £22,589 per QALY gained for patients who had received two or more prior therapies.

These estimates were low in comparison to re-worked estimates from the ERG. They suggested (NICE, 2009a):

- For the subgroup who had received one prior therapy where the comparator was dexamethasone, the ICER increased from £46,865 to £69,500 per QALY gained.
- For the subgroup of patients who had received two or more prior therapies, the ICER increased from £24,584 to £47,100 per QALY gained.

- For patients who had received prior thalidomide, the ICER increased from £38,861 to £56,500 per QALY gained if they had received only one prior therapy and from £22,589 to £43,600 per QALY gained if they had received two or more prior therapies.

During the appraisal process the manufacturer disagreed with some of the changes suggested by the ERG, such as the approach to estimating overall survival (NICE, 2009a). This changed some of the estimates of the cost per QALY, and the addition of the Patient Access Scheme also changed the likely costs to the NHS per patient. For example, assuming median survival of 2.7 years, the cost per patient was estimated to fall from £59,800 to £51,800 over the lifetime of their treatment. A Patient Access Scheme can be offered voluntarily by a company to allow patient access to high cost treatments (NICE, 2011c). Such schemes must be approved by the Patient Access Scheme Liaison Unit, within NICE. PASLU provides guidance on the workability of schemes. This is a further input to the deliberations of the NICE Appraisal Committee.

In their deliberations, the Appraisal Committee noted that there were gaps in knowledge, such as the effectiveness and scale of use of thalidomide (which can be prescribed off license) (NICE, 2009a). This affects the choice of comparator, since Revlimid may or may not be used instead of thalidomide, and affects the certainty surrounding the benefits since there is little evidence on the difference, if any, between Revlimid and thalidomide on clinical outcomes. They also reviewed the ICERs, and focused on the revised estimates resulting from changes made to the economic modelling and the impact of the Patient Access Scheme. The key ICERs were:

- £43,800 per QALY gained for the subgroup of patients who had received two or more prior therapies.

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- £41,300 per QALY gained for the subgroup who had received two or more prior therapies including thalidomide.
- The Appraisal Committee were also able to draw on guidance on End of Life, which can place a higher weight on the benefits from treatment when:
- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.
- No alternative treatment with comparable benefits is available through the NHS.
- The treatment is licensed or otherwise indicated for small patient populations.
- And that estimates of the extension to life are robust and that the assumptions used in the reference case economic modelling are plausible, objective and robust.

The Committee felt that these conditions were met (NICE, 2009a). In effect, this allows the Committee to recommend a product at higher cost effectiveness ratios than are normally accepted.

The final guidance from NICE changed from the provisional guidance issued and consulted on in November 2008 that Revlimid was not recommended for use (NICE, 2010g). However, there was no Patient Access Scheme offered by the manufacturer at this time, which did reduce the costs of Revlimid. The Patient Access Scheme was included in a second round of provisional guidance issued and consulted on in January 2009 (NICE, 2010g). Guidance on end of life was not formally mentioned at this stage, however this guidance to Appraisal Committees was

also published in January 2009 (NICE, 2010g). Guidance on end of life was consulted on during December 2008 (NICE, 2009b) and so the Appraisal Committee would have been aware of this developing guidance at the time they were considering Revlimid. Given this, it's hard to disentangle the relative importance of either the Patient Access Scheme, or the end of life guidance, on the change in recommendation. No Patient Access Scheme exists in Scotland (Myeloma UK, 2010).

The development of NICE guidance (2012c) on the use of Revlimid was subject to considerable media interest, including the focus of a BBC documentary *'The Price of Life'*. There was also coverage in the press, including for example a headline that "NHS drug ban hands 'death sentence' for thousands of cancer sufferers" (Hope, 2008)

NICE is currently looking at the use of Lenalidomide for newly diagnosed multiple myeloma and use of Lenalidomide as maintenance treatment of multiple myeloma after autologous stem cell transplantation, with guidance expected during 2013 (ID474 (NICE, 2012a) and ID475 (NICE, 2012b)).

Between 1st April 2011 and 20th December 2011, there have been 62 applications approved for Revlimid by the Cancer Drugs Fund (Rarer Cancers Foundation, 2011). The Cancer Drugs Fund is a ring fenced fund for medicines that have either been considered cost ineffective by NICE, or are going through the NICE process and only applies in England (DH, 2010b). However, it's unclear if these applications are for myeloma or for MDS.

SMC

SMC first published guidance on the use of Revlimid in 2008. They did not recommend use of Revlimid. They did not recommend Revlimid because although there was evidence of an increase in the time to disease progression, the manufacturer did not present a sufficiently robust case. Overall the cost in relation

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to health benefits was not sufficient for the SMC to recommend use (SMC, 2010b). The manufacturers submission to SMC suggested a cost per QALY of £28,980. SMC note that the estimates of cost effectiveness were uncertain and that survival was a key driver of the resulting ICERs.

The budget impact in 2008 was estimated to be £2.35 million in the first year, rising to £3.75 million in the fifth year (SMC, 2008a).

However following a re-submission in 2010 the SMC recommend restricted use of Revlimid. They now recommend that Revlimid is used when patients have received at least two prior lines of therapy. This reflected evidence of the survival benefits for this subgroup of patients, and SMC guidance also cites the orphan status of Revlimid (2008b). The manufacturers re-submission suggested a cost per QALY of £34,286, rising to £41,381 using Scottish costs (SMC, 2010a). SMC now has a policy, introduced in 2010, which allows for ‘modifiers’ to be taken into account which can result in acceptance of higher levels of uncertainty and/or higher cost per QALY estimates. One of those modifiers is the orphan status of a product, where SMC will accept a greater level of uncertainty reflecting limited evidence on efficacy. Substantial improvement in life expectancy is also included within this guidance (SMC, 2012).

The budget impact in 2010 was estimated to be £862,000 in the first year, rising to £2.73 million in the fifth year for the cost of Revlimid. Adding in costs for monitoring, medical management and adverse events the budget impact rose to £920,000 and £2.92million respectively (SMC, 2010a).

AWMSG

Although AWMSG guidance is now superseded by NICE guidance (TA171 discussed above), AWMSG had previously appraised Revlimid in 2008. They did not recommend use. The key factor cited for not recommending Revlimid was an unproven case for cost effectiveness. The manufacturers submission to

AWMSG suggested a cost per QALY of £28,943 rising to £34,770 accounting for costs of monitoring and complications (AWMSG, 2008b).

The budget impact estimates for year 1 were just over £3 million in year one, rising to over £4.2 million by year five (including VAT) (AWMSG, 2008b).

AWMSG guidance predated their policy on ultra-orphan products (published during 2011) (which means around 60 patients in Wales in practice so arguably would not have been relevant even if in place during the time that Revlimid was appraised) (AWMSG, 2011b). It also predated their policy on life extending, end of life medicines (published in 2011) (AWMSG, undated).

International funding

Revlimid has been considered by the Pharmaceutical Benefits Advisory Committee (PBAC) who determine reimbursement by the Pharmaceutical Benefits Scheme (PBS). They have rejected listing of Revlimid. PBAC rejected the manufacturers submission for reimbursement on the basis of a high uncertain clinical effectiveness (as at 2011) (Australian Government, Department of Health and Ageing, 2011).

Revlimid has also been considered by Canadian Provinces. Although there is now funding in all Provinces, patients have raised concerns about funding being described as being through ‘a pilot’ and subject to further price negotiations with the manufacturer in the Province of Quebec (as at February 2012) (Canada Newswire, 2012). Patients have also suggested that second line funding approval in Quebec was the result of allowing patients to present personally to the decision making committee (Canada Newswire, 2012).

Media reports suggest that although approval and funding may be for other positions in the treatment pathway, in practice Revlimid is now widely used across Europe and the US for first line treatment

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(Fernando, 2012). That illustrates how practice can vary from guidelines issued.

Prescription

Clinicians need to carefully consider the use of Revlimid including, and especially, for women during pregnancy. Dosing requires an expert understanding of an individual patient's condition, including whether the cancer is causing problems to a patient's bones or kidneys (EMA, 2012d).

Revenue for Revlimid was \$1.28 billion in 2012 (Reuters, 2012). Based on our searches, we have not been able to find a breakdown of UK sales.