Scottish Medicines Consortium

thalidomide, 50mg hard capsule (Thalidomide Pharmion®)

No. (525/08)

Celgene Ltd

05 December 2008

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

thalidomide (Thalidomide Pharmion®) is accepted for use within NHS Scotland in combination with melphalan and prednisone, as first line treatment of patients with untreated multiple myeloma, aged 65 years or over or ineligible for high dose chemotherapy. Thalidomide is prescribed and dispensed according to the Thalidomide Pharmion Pregnancy Prevention Programme.

In the pivotal trial in patients aged 65 to 75 years, at 51.5 months median follow-up, the addition of thalidomide to melphalan and prednisone gave an overall survival advantage of 18.4 months.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

Thalidomide, in combination with melphalan and prednisone, as first line treatment of patients with untreated multiple myeloma, aged ≥65 years or ineligible for high dose chemotherapy. Thalidomide is prescribed and dispensed according to the Thalidomide Pharmion Pregnancy Prevention Programme.

Dosing information

The recommended oral dose is 200mg per day. A maximum number of 12 cycles of 6 weeks should be used. The dose can be lowered by 50% according to tolerability.

There are recommended dose modifications if peripheral neuropathy is experienced and guidance on management if there is a thromboembolic event. No specific dose adjustments are recommended for the elderly.

Thalidomide treatment must be initiated and monitored under the supervision of physicians with expertise in managing immunomodulatory or chemotherapeutic agents and a full understanding of the risks of thalidomide therapy and monitoring requirements.

Product availability date

30 June 2008

Thalidomide for the treatment of multiple myeloma was granted orphan status by the European Medicines Agency in November 2001.

The Medicines and Healthcare products Regulatory Agency granted approval of the pregnancy prevention programme in May 2008.

Summary of evidence on comparative efficacy

Multiple myeloma (MM) is a haematological cancer in which immature malignant plasma cells (myeloma cells) accumulate in and eventually destroy the bone marrow. The pathological effect of this accumulation is an increasingly dysfunctional bone marrow, causing cytopenias, which lead to bacterial infections and anaemia, and osteolytic lesions. Thalidomide is anti-angiogenic with immunomodulatory and anti-inflammatory activity; its mechanism of action has not been fully elucidated.

Evidence for this indication came from a pivotal study and two supportive studies. All were randomised phase III trials in patients who had not been previously treated for multiple myeloma; two were open-label and one was double-blind. Patients in the pivotal trial were aged between 65 and 75, or less than 65 but ineligible for a treatment intensification protocol with bone marrow transplant conditioning. They also had Durie-Salmon stage II or III MM, or stage I with high-risk disease. There were 2 (of 3) treatment arms of interest; the third arm received reduced-intensity stem cell transplantation using melphalan 100mg/m^2 which is not a standard regimen in the UK and will not be discussed further. The first group received "conventional" oral treatment of melphalan and prednisone (MP) (at 0.25mg/kg/day and 2mg/kg/day respectively) given for 4 days every 6 weeks for 12 cycles. The second group received MP with the addition of thalidomide 200mg/day continuously until the 4th day of the 12th MP cycle, increasing to a maximum of 400mg/day, based on tolerability and response. All patients received sodium clodronate in addition; no thromboprophylaxis was given. The primary end-point was overall survival (OS), defined as the time in months from

randomisation to death from any cause. Secondary efficacy variables included progression-free survival (PFS), survival after progression (SAP), best response rate and toxicity. Time to event end-points were calculated using Kaplan-Meier survival methods. The primary analysis population was the Intention to Treat (ITT) population.

A total of 447 patients (the ITT population) was randomised across the three arms in a ratio of 3:2:2; the relevant arms are the first two. Enrollment was stopped after an unplanned, third interim analysis. The numbers of patients in the ITT population randomised to each relevant arm were 196 (MP) and 125 (MPT). Median follow-up was 51.5 months and median duration of thalidomide treatment was 11 months; mean daily dose was 238mg. Mean age across the trial was 70 years, with 41% over this age. Demographic characteristics were similar in the 2 relevant treatment arms. Overall survival was a statistically significant 18.4 months longer in the MPT group, compared to the MP group (51.6 vs 33.2 months; hazard ratio (HR):0.59; 95% confidence intervals (CI): 0.46 to 0.81). PFS and best response rates were all significantly better in the MPT group; for SAP the difference was not significant. Less than half (55/126, 44%) of patients at first progression on MP received rescue with thalidomide alone or in combination; 18% (10/55) of patients at first progression on MPT received thalidomide-based rescue. Second-line treatment with bortezomib was received by 2% (3/126) of MP patients and 13% (7/55) of MPT patients.

The second trial was double-blind, placebo-controlled and had a similar design to the pivotal trial. However, patients in this study were aged 75 or over. Treatment doses were slightly different with melphalan prescribed at 0.2mg/kg/day and thalidomide at 100mg/day; the prednisone dose was the same at 2mg/kg/day. Again, no thromboprophylaxis was given. As with the pivotal trial, the primary end-point was overall survival, with secondary end-points being PFS, response to treatment and toxicity.

Patients (n = 232) were randomised and 229 analysed (113 in the MPT group and 116 in the MP-placebo group) as the ITT population. Again, enrollment was stopped after a second interim analysis. Median age was 78.5 years with 36% aged 80 or over. Median follow-up was 24 months. Median OS (± standard error) was 45.3 ± 1.6 months for the MPT group and 27.7 ± 2.1 months in the MP-placebo group, the benefit being significant. Significant improvements in median PFS and response rates were also reported for the MPT group. After relapse in the placebo arm, 77% of patients received thalidomide. Survival time after progression was similar in the two groups.

In the third trial, patients were >65 years, or younger if unable to undergo transplantation. Again the two arms were MP versus MPT. The doses were slightly different however: melphalan was 4mg/m^2 and prednisone was 40mg/m^2 and they were given for 7 days every 4 weeks for 6 cycles. Thalidomide was given as 100mg/day and after completion of the 6 cycles, could be given as maintenance therapy until progression. The thalidomide dose could be reduced by 50% or discontinued if required due to adverse events. An amendment during enrollment allowed approximately half the patients in the MPT group to receive thromboprophylaxis for 4 cycles.

The primary end-points were clinical response rates and PFS. Secondary end-points included OS, prognostic factors and time to first response. Again the population analysed was an ITT one and survival data was analysed using the Kaplan Meier method. Patients (n = 331) were randomised; 164 received MP and 167 MPT. The median duration of thalidomide therapy was 9.6 months and median follow-up in both groups was 38 months. Demographic data in both groups were similar, with a median age of 72 years. Response rates were statistically significantly better across all definitions of response (complete, very good partial and partial); with the complete response rate being 15.6% compared to 3.7% in the MPT and MP groups respectively. Median PFS was statistically significantly longer for the MPT patients, at 21.8 months, compared to 14.5 months for the MP group (HR 0.63;

95% CI 0.48 to 0.81). Median OS was similar for the two groups at 45.0 months for the MPT group and 47.6 months for the MP group. Median SAP was shorter in the MPT group than in the MP group. Salvage regimes were given to 48% (81/167) of MPT patients (with 22% (37/167) receiving thalidomide and/or bortezomib) and 57% (93/164) of MP patients (with 42% (68/164) received thalidomide and/or bortezomib).

Summary of evidence on comparative safety

In the pivotal trial, significantly more patients in the MPT group n=122 (98%) experienced at least one adverse event (AE) vs n=154 (80%) in the MP group. Fifty six patients (45%) in the MPT group withdrew from the study because of an AE vs 15 patients (7.8%) in the MP group. The most common AEs were neutropenia (the MPT group reported significantly more), anaemia, thrombocytopenia and infections. Somnolence and constipation occurred significantly more often in the MPT group. Grade 3 peripheral neuropathy occurred significantly more often in the MPT group at 6%, whereas none in the MP arm reported this severity of the side-effect (neither group reported grade 4). The incidence of thromboembolism was significantly greater in the MPT group; 12% compared to 4% in the MP group.

In the second trial, 42% of the MPT group discontinued treatment due to toxicity compared to 11% of the MP group. Some grade 2-4 toxicities were significantly increased with MPT: peripheral neuropathy (20% vs 5%), neutropenia (23% vs 9%) and depression (7% vs 2%). DVT rates (6% vs 4%) and somnolence (6% vs 3%) were not significantly increased in the thalidomide group.

In the third trial, grade 3-4 AEs occurred in 55% of the MPT group and in 22% of the MP group. At the follow-up period reported thus far for this trial, no figures were given for AEs in the MP group. Thromboembolism (at 11%) and peripheral neuropathy, cardiac events and infections (all at 10%) are reported as being the most common AEs. In an earlier analysis at just over a year, a significant reduction in thromboembolism in the group of MPT patients who received thromboprophylaxis, compared to those who did not, was seen.

Thalidomide is highly teratogenic and thus is accompanied by a mandatory pregnancy prevention plan, the Thalidomide Pharmion Pregnancy Prevention Programme. This was designed to educate patients and professionals and monitor thalidomide use, with the aim of preventing exposure of unborn children to thalidomide

Summary of clinical effectiveness issues

The licence and trials specify the use of prednisone. This is not available in the UK where a direct substitution of prednisolone for prednisone is made: the two are considered dose-equivalent.

This treatment is already widely used in Scotland, being prescribed on a named-patient compassionate use basis as an unlicensed product.

The increased rate of infection in MPT groups was unexpected, as thalidomide has no myelosuppressive properties.

There were some methodological differences across the three studies. MP and thalidomide doses were not consistent, nor were treatment periods. The licensed thalidomide dose comes from the pivotal study, with no specific recommendations in the licence to reduce the

dose for the elderly, as used in the second trial. Use of thalidomide maintenance therapy was only allowed in the third trial, and this was the only one to introduce thromboprophylaxis. Different salvage regimes were used in the third trial, with different uptake rates, which may account for the lack of significant increase in overall survival in the MPT group, unlike in the other 2 studies.

The second trial, in an older population, has only been reported as a conference abstract.

There is an administrative requirement associated with the compulsory Pregnancy Prevention Programme.

Summary of comparative health economic evidence

The manufacturer submitted a trial-based cost-utility analysis comparing melphalan, prednisone and thalidomide (MPT) with melphalan and prednisone (MP) alone in the first line treatment of patients with multiple myeloma aged ≥65 years or ineligible for high dose therapy. The comparator is currently used in Scotland and therefore was appropriate. A lifetime horizon was adopted and survival analysis modelling was performed to extrapolate survival estimates beyond the end of the trial, resulting in an estimated incremental gain in life years of 1.43 years per patient for the MPT regimen. Resource use and adverse event treatment costs were based on expert opinion from six Scottish haematologists experienced in treating multiple myeloma. Utility estimates for disease states were based on a published study in multiple myeloma patients and adverse event disutilities were from a literature survey.

The predominant cost difference between the two regimens related to drug acquisition costs, being £15,041 for MPT and £201 for MP over 5 years. The results of the model indicated an additional QALY gain of 0.92 QALYs for MPT and a base case incremental cost per QALY gained of £17,847 based on patients receiving an average of 7 cycles of treatment. Accounting for thromboprophylaxis and adverse event disutilities increased the cost per QALY gained to closer to £20,000 in sensitivity analysis. The pivotal trial used to provide data for these estimates was conducted in patients aged 65 to 75 and therefore the base case ICER did not give any evidence to support the cost-effectiveness of the treatment in older patients. Additional sensitivity analysis was however provided to address this issue and indicated a cost per QALY of £12,060 for patients aged over 75. This figure was lower than the base case estimate mainly as a consequence of the reduced dosing and therefore reduced drug costs in elderly patients.

The strength of the single trial-based evaluation in patients aged 65-75 years was that it was performed with the recommended licensed starting dose for thalidomide of 200mg/day, had an overall follow-up of >51 months and demonstrated clear overall survival benefits for MPT over MP. Also, the use of Scottish experts for estimating resource use for routine disease management appears well performed.

The analysis showed some sensitivity to the survival data used in the base case; if for example the hazard ratio for the risk of progression was increased by 20%, the base case ICER increased to £24,161.

Additionally, the administrative costs associated with the Pregnancy Prevention Plan do not seem to have been factored in to the analysis.

Despite these concerns, the economic case was demonstrated.

Summary of patient and public involvement

Patient Interest Group Submission: Myeloma UK.

Additional information: guidelines and protocols

The British Committee for Standards in Haematology published "Guidelines on the diagnosis and management of multiple myeloma 2005". At this time, the addition of thalidomide to MP was only being explored for the current indication, although it was felt that preliminary data suggested an improved response rate but an increased incidence of side effects, particularly thromboembolism.

Additional information: previous SMC advice

Following a full submission, the Scottish Medicines Consortium (SMC) issued advice in October 2008: pegylated liposomal doxorubicin (Caelyx®) is not recommended for use within NHS Scotland in combination with bortezomib for the treatment of progressive multiple myeloma in patients who have received at least one prior therapy and who have already undergone or are unsuitable for bone marrow transplant. Results from an interim analysis showed that pegylated liposomal doxorubicin plus bortezomib significantly increased the time to progression compared to bortezomib monotherapy. At the time of the interim analysis only 31% of patients in the combination arm had reached the primary endpoint. The manufacturer did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Following a full submission, the Scottish Medicines Consortium (SMC) issued advice in May 2008: lenalidomide (Revlimid®) is not recommended for use within NHS Scotland in combination with dexamethasone for the treatment of multiple myeloma in patients who have received at least one prior therapy. Lenalidomide plus dexamethasone significantly increased the time to disease progression compared with dexamethasone alone in multiple myeloma patients who had been treated with at least one prior therapy. The manufacturer did not present a sufficiently robust case and in addition the manufacturer's justification of the treatment's cost in relation to its health benefits was not sufficient to gain acceptance by SMC. The licence holder has indicated their intention to resubmit.

Following a resubmission, the Scottish Medicines Consortium (SMC) issued advice in August 2007: bortezomib (Velcade®) is not recommended for use within NHS Scotland as mono-therapy for the treatment of progressive multiple myeloma in patients who have received at least one prior therapy and who have already undergone or are unsuitable for bone marrow transplantation. Bortezomib, compared to high dose dexamethasone, prolonged time to disease progression by 2.7 months and improved survival in patients who had progressive multiple myeloma despite previous justification of the treatment's cost in relation to its health benefits was not sufficient to gain acceptance by SMC and they did not present a sufficiently robust economic analysis.

Following a full submission, the Scottish Medicines Consortium (SMC) issued advice in October 2004: bortezomib (Velcade®) is accepted for use within NHS Scotland for the treatment of patients with multiple myeloma who have received at least two prior therapies, have demonstrated disease progression on the last therapy and who are refractory to alternative licensed treatments for this stage of the disease. Bortezomib produced a disease response in approximately one third of these patients in an open-label uncontrolled study.

Any other use of bortezemib should only take place within the context of a controlled study. The manufacturers are encouraged to mount an observational study in collaboration with haemato-oncologists to gain more information on the benefits and risks of this therapy.

Additional information: comparators

As standard first-line treatment in this population and the comparator used in the trials, MP is used. A direct substitution of prednisolone for prednisone has been made: prednisone is not available in the UK and the two are considered dose equivalent. As there are no formal recommended dose regimens for these combinations, those described in the pivotal trial have been used.

Cost of relevant comparators

Drug	Dose regimen	Cost per cycle (£)	Cost per course (£) (12 cycles)
melphalan prednisolone thalidomide *	**0.25mg/kg orally for days 1-4 every 6 weeks 2mg/kg orally for days 1-4 every 6 weeks 200-400mg orally daily for 6 weeks****	**1808 to 3603**	**20,072 to 39,994**
melphalan prednisolone	0.25mg/kg orally for days 1-4 every 6 weeks 2mg/kg orally for days 1-4 every 6 weeks	17 to 21	201 to 254

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 7th October 2008. * Price from manufacturer on 28th August 2008.
**Note that thalidomide is given daily throughout the 12 cycles, but finishes on day 4 of the 12th cycle.

Additional information: budget impact

The manufacturer provided a complex budget impact analysis under two scenarios. The estimates were based on market research data which suggest that 54% of eligible patients are currently receiving thalidomide first line. Based on an estimated 179 additional patients being treated with thalidomide, the additional costs ranged from £0.32m to £3.2m in year 1 to £0.77m to £3.4m in year 5. These assumed that 60% of eligible patients would receive MPT in year 1 rising to 70% of eligible patients in year 5, and that patients would receive an average of 7 cycles as per the economic model. The scenarios assumed that existing thalidomide use is of the manufacturer's product but current practice across Scotland is variable with some use of a less expensive unlicensed preparation. The true net drug budget impact in practice is likely to be at the upper end of the company estimates i.e. around £3m per annum.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 14 November 2008.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted references were supplied with the submission.

Facon T, Mary JY, Hulin C, Benboubker L, Attal M, Pegourie B, et al. Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomised trial. Lancet. 2007 Oct 6;370(9594):1209–18.

Hulin C, Facon T, Rodon P, Hulin C, Facon T, Rodon P. Melphalan-prednisone-thalidomide (MP-T) demonstrates a significant survival advantage in elderly patients > 75 years with multiple myeloma compared with melphalan-prednisone (MP) in a randomized, double-blind, placebo-controlled trial, IFM 01/01. Blood 2007;110:abstract 75.

Palumbo A, Bringhen S, Liberati AM, Caravita T, Falcone A, Callea V, et al. Oral melphalan, prednisone, and thalidomide in elderly patients with multiple myeloma: updated results of a randomized, controlled trial. Blood. 2008 May 27:(in press).