

National Institute for Health and Clinical Excellence

Multiple technology appraisal of bortezomib and thalidomide for the first-line treatment of multiple myeloma

Celgene Ltd Submission



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EXECUTIVE SUMMARY

Context

- Multiple myeloma is the most common type of primary cancerous bone tumour, characterised by skeletal destruction, renal failure, hypercalcaemia and anaemia. Although incurable, it is treatable. The average age at diagnosis is 68 years and 99% of those diagnosed are older than 40 years of age. In England and Wales in 2009, multiple myeloma is estimated to affect approximately 1,400 males and 1,300 females, with an estimated 3,472 new cases in 2009. Many multiple myeloma patients are too frail to undergo high dose therapy (HDT) and Stem Cell Transplant (SCT), and for decades the treatment of choice for this group had been combined melphalan and prednisone (MP). The need to target older patients with innovative approaches to improve outcomes is recognised as an unmet need.

- Thalidomide is an oral immunomodulatory agent shown to be effective across the spectrum of myeloma disease. Its mechanism of action is not fully understood. In combination with MP, thalidomide is licensed as first line treatment of patients with untreated multiple myeloma, aged ≥ 65 years or ineligible for HDT.
- In this submission, the efficacy, safety and cost-effectiveness of thalidomide in combination with MP (MPT) is assessed first-line in untreated patients aged ≥ 65 years or ineligible for HDT. The interventions in this submission are MPT and bortezomib in combination with MP (VMP) both compared with MP. Inclusion of comparator cyclophosphamide and dexamethasone was not possible due to lack of evidence in the relevant population. The Medical Research Council Myeloma IX trial in multiple myeloma is relevant to the scope of this appraisal; however Celgene does not have access to information from this ongoing study to inform this submission. The submission therefore considers the clinical efficacy, safety and cost-effectiveness of MPT versus VMP versus MP in first line treatment of patients with untreated multiple myeloma, aged ≥ 65 years or ineligible for HDT.

Thalidomide clinical effectiveness

Comparison with MP in untreated multiple myeloma patients

- Significantly improved efficacy and manageable toxicity of the thalidomide combination in this group is demonstrated in three randomised, controlled clinical trials (the IFM 99-06, IFM 01-01, and GIMEMA studies). These were of similar designs but also featured some methodological differences (e.g. patient age, thalidomide or MP dose, regimen or duration, cross-over or use of maintenance therapy). These compare MPT with MP alone in previously untreated elderly multiple myeloma patients aged ≥ 65 years and/or HDT ineligible. MPT was administered as recommended in UK guidelines and thalidomide was given orally, consistent with advice that in older patients ineligible for HDT an oral regimen is preferable to achieve maximum response with minimum toxicity. The thalidomide dose and regimen varied across the trials; study IFM 99-06 evaluated the dose and regimen according to the thalidomide license while IFM 01-01 employed the licensed regimen with a lower dose considered more appropriate in an elderly patient cohort (>75 years of age). The GIMEMA study examined a different dose and regimen to the SPC and the protocol allowed patients in the MP arm to cross-over to MPT on progression.
- Studies IFM 99-06 and IFM 01-01, both using the licensed thalidomide regimen, unanimously showed better overall survival and progression-free survival in

the MPT group; concordance of results represents an increasing confidence in the evidence. The GIMEMA trial showed significantly longer event free survival and response rates but did not a statistically significant OS advantage for MPT versus MP. When comparing median OS in the MPT treatment arms of study IFM 99-06 and the GIMEMA trial, the median OS with MPT in the IFM 99-06 study was almost seven months longer (51.6 months) than in GIMEMA (45 months). The authors concluded that the similar median OS for MPT and MP in the GIMEMA analysis was probably due to the use of more effective salvage regimens in the MP group.

- Two additional unpublished trials (conducted in the Netherlands and the Nordic countries) provide positive evidence for extended progression-free survival for MPT versus MP.
- The positive outcomes of these thalidomide trials, with age and sex distributions of patients consistent with the English and Welsh populations, apply well to English and Welsh patients and are a welcome addition to inform clinical practice.

Comparison with VMP in untreated multiple myeloma patients

Since there are no direct head-to-head studies of MPT versus VMP the clinical evidence supporting this comparison was derived from a mixed treatment comparison (MTC). The base case analysis comprised two thalidomide studies employing the licensed regimen (IFM 99-06 and IFM 01-01) and one VMP study (VISTA).

- The efficacy outcome examined in the MTC was time to progression (progression free survival [PFS] where TTP was not provided). For this binary measure, separate analyses were run for each 6 month interval up to 30 months where data were available. Overall, in our base case analysis MPT and VMP were more effective than MP in achieving PFS. MPT was slightly more effective than MP in achieving post progression survival (PPS); however, at each time point the credibility intervals for the odds ratios included 1.0. The point estimates are very slightly better for MPT versus VMP at all time points except 24 months. There were no data to compare MP with VMP in PPS.

Patient Subgroups

Scrutiny of subgroup data from both thalidomide evidence base and the VISTA study would suggest there is no significant impact of subgroups on clinical outcomes. There is also insufficient data to make meaningful conclusions between thalidomide and bortezomib in view of the different subgroups assessed across the studies

Thalidomide safety

- MPT was associated with higher rates of toxicity than MP alone. The most common grade 3-4 adverse events (AEs) included neutropenia, thrombocytopenia, anaemia, thromboembolism, peripheral neuropathy, somnolence, infections and constipation.
- Importantly, peripheral neuropathy and risks of thromboembolism can be managed or even prevented with appropriate thalidomide dose reduction or recommended VTE antithrombotic prophylaxis, respectively. Higher incidences of infections on MPT could be reduced by regularly assessing patients, monitoring for fever of unknown origin and promptly administering prophylactic antibiotics. Constipation can be improved with increased fluid and dietary fibre intake and use of appropriate laxatives while mild cases of dry skin and pruritus can be resolved with non-alcohol moisturisers.
- Thalidomide is highly teratogenic and exposure to this drug may therefore cause severe birth defects. Consequently, thalidomide is accompanied by a mandatory Risk Management Plan. Since women of child-bearing potential are likely to constitute <5% of the patients eligible to receive thalidomide in relation to this thalidomide indication, the sponsor is reassured that safety concerns of this nature are unlikely to impact significantly in clinical practice. The thalidomide SPC reflects these findings and recommendations.
- While the AEs expected in clinical practice may be serious (reflecting the gravity of the underlying malignant disease), they were considered acceptable given their manageability, thereby allowing patients to continue their treatment and benefit from the clear superiority of MPT compared with MP in terms of important clinical outcomes such as OS, PFS, EFS and RR.
- In the VISTA trial, VMP was associated with higher rates of toxicity than MP alone. AEs with VMP versus MP were consistent with the established profiles of toxic events associated with bortezomib and MP; the rate of peripheral neuropathy on VMP was consistent with other studies.
- AEs were not assessed in the meta-analysis because they were inconsistently reported; for example grades 2-4 versus grades 3-4, or the reported AEs differed by study. Rather, a study by study account of AEs was assessed in the submission.

Thalidomide cost effectiveness

- The comparator in the economic analysis was MP as used in the pivotal IFM 99-06 trial and VMP. A lifetime Markov model was developed using data from a MTC of the two main MPT trials (IFM 99-06 and IFM 01-01) and VISTA, the pivotal trial for bortezomib (Velcade) in combination with MP (VMP). The model was adapted from a model for NHS Scotland and informed by a comprehensive systematic literature search and expert opinion in order that treatment pathways and model input variables reflect current clinical practice for England and Wales. Overall survival (OS) was not included in the model. Rather, the outcomes of interest (derived from the MTC) are the survival time both before (PFS) and after progression (PPS) in order to apply different utility values to pre-progression (with and without AEs) and post progression. The approach was in accord with the NICE reference case and the cost-base year is 2008.
- MPT resulted in an incremental gain of 1.09 life-years compared to MP and an additional 0.85 QALYs gained. The resulting ICERs were £18,188 and £23,381, respectively.
- The incremental gain in life-years for VMP over MPT was 0.11 (£200,237/life years gained) and 0.09 gain in QALYs gained (£303,845/QALY gained). Multiple univariate sensitivity analyses indicated the findings were robust to varying key parameters. Ranges in the incremental cost-effectiveness ratios were calculated using the MTC credibility intervals rather than using a probabilistic sensitivity analysis. For MPT versus MP the range was £16,586 to £33,275 per incremental QALY gained and for VMP versus MPT the range was £148,873 to £1,000,435/QALY gained. The results of MPT versus MP were consistent with previous analyses. Thus, MPT represents a cost-effective therapy in previously untreated multiple myeloma in England and Wales.

Conclusion

- Treatment of patients with multiple myeloma who are aged ≥ 65 years and who are not candidates for HDT remains a challenge, with a huge unmet need to prolong survival and enhance quality of life. On the basis of this submission, thalidomide represents a clinically acceptable and cost-effective use of NHS resources in England and Wales.