**NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE**

**MULTIPLE TECHNOLOGY APPRAISAL**

# Bortezomib and thalidomide for the first-line treatment of multiple myeloma

## Bortezomib (VELCADE®▼)

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## 1. EXECUTIVE SUMMARY

Background and management of multiple myeloma

- Multiple myeloma (MM) is an incurable progressive haematological cancer. As well as reducing life expectancy MM causes significant morbidity. The symptoms include painful backache, lytic bone lesions leading to fractures, renal failure, susceptibility to serious infections and severe fatigue.
- At presentation first line treatment consisting of chemotherapy followed by high-dose therapy with stem cell transplant (HDT-SCT) is considered the standard of care for patients younger than 65 years of age. For older and/or less fit patients in whom HDT is not planned initial therapy should consist of either a thalidomide-containing regimen in combination with an alkylating agent and steroid such as MPT or CTDa, or bortezomib in combination with melphalan and prednisolone (VMP). (Draft UK myeloma Forum guidelines, 2009).
- The aim of MM treatment is to control the disease, maximize quality of life and prolong survival.
- Bortezomib received its marketing authorisation for use in combination with MP for previously untreated multiple myeloma in patients not eligible for HDT-SCT in September 2008.
- Thalidomide is licensed for use in newly diagnosed multiple myeloma as part of the MPT combination, although in UK clinical practice it is more commonly used in an unlicensed combination with cyclophosphomide and dexamethasone attenuated (CTDa).
- Bortezomib (Velcade®) is a first in class dipeptidyl boronic acid that works by reversible inhibition of the proteasome, a multienzyme complex present in all cells that selectively degrades intracellular proteins. As well as exerting direct actions on multiple myeloma cells, bortezomib modifies the tumour microenvironment by interfering with interactions between MM cells and bone-marrow cells and by inhibiting the production of growth and survival factors (Terpos *et al*, 2008).
- This submission addresses the use of bortezomib and thalidomide in combination regimens with an alkylating agent and a steroid for the first-line treatment of multiple myeloma, as per the NICE final scope
- All potential comparisons between VMP, MPT, CTDa and MP have been considered as the relevant combinations.

Clinical evidence for bortezomib and thalidomide-based regimens

- The efficacy and safety of VMP versus MP was assessed in VISTA, largest randomised trial ever conducted in multiple myeloma, including 682 patients with previously untreated multiple myeloma who were not candidates for HDT-SCT. (San Miguel 2008)
- Five randomized studies have compared the efficacy and safety of MPT to MP in elderly patients with newly diagnosed multiple myeloma. (Facon 2007, Palumbo 2006 and 2008, Hulin 2009, Gulbrandsen 2008, Wijermans 2008) while one study is assessing the CTDa regimen (Myeloma IX, non-intensive arm, Owen 2009).

*Response rate*

- In the VISTA study an unprecedented complete response rate of 30% was observed

with VMP versus 4% with MP after a median follow-up of 16.3months. Median time to response was shorter with VMP (1.4 months) versus MP (4.2 months). In addition the median duration of response was longer with VMP (19.9 months) versus MP (13.1 months). The overall response rate was 71% with VMP versus 35% with MP.

- In comparison the efficacy of thalidomide, as determined by complete response rates, ranged from 2% (Wijermans 2008) to 15.6% with MPT (Palumbo 2006) and 22.5% with CTDa (Owen 2009). In the MP arm complete response rates ranged from 1% (Hulin 2009) to 6.2% (Owen 2009). The overall response rates ranged from 42% (Gulbrandsen 2008) to 76% (Facon 2007 and Hulin 2009) with MPT and to 82.5% with CTDa. In the MP arm the overall response rate ranged from 28% (Gulbrandsen 2008) to 48.2% (Owen, 2009).

*Disease Progression*

- In the VISTA trial VMP showed a statistically significant improvement in the median time to progression (TTP) versus MP (24.0 months vs. 16.6 months; hazard ratio HR =0.48, p<0.001) after a median follow-up of 16.9 months. Progression free survival was significantly prolonged by MPT versus MP in all studies except the one conducted by Gulbrandsen; ranges were from 13 months (Wijermans 2008) to 27.5 months (Facon 2007) in the MPT arm and from 10 months (Wihermans 2008) to 18.5 months (Hulin 2009) in the MP arm. The study by Gulbrandsen did show a significant improvement in median TTP for MPT vs. MP.

*Overall survival*

- In the VISTA trial, a 35% reduction in the risk of death was observed with VMP as compared to MP after a median follow-up of 36 months. Median overall survival was not reached in the VMP group vs. 43.1 months in the MP group (HR=0.653, p=0.00084). Patients with VMP had a higher survival rate at 3 years than patients on MP (68.5% vs. 54.0%, respectively) despite the use of a bortezomib-containing regimen in 50% of subjects in the MP treatment group as part of their subsequent therapy and the potential dilution of treatment benefit on survival.

- Of the five studies that compared MPT and MP, two demonstrated a significant survival advantage in favour of MPT (Facon 2007: median survival of 51.6 months for MP vs. 33.2 months for MP, HR=0.59, 95%CI 0.16-0.81); Hulin 2009: median survival of 44 months for MPT vs. 29.1 months for MP, HR=0.68, p=0.0028). The studies by Palumbo and Wijermans did not show a statistically significant survival difference between MPT and MP (Palumbo, 2008: median survival for MPT 47.6 vs. 45 months for MP HR=1.04, 95% CI 0.76–1.44; Wijermans 2008: median survival of 37 months for MPT vs. 30 months for MP, p=0.16). The study by Gulbrandsen et al reported a median survival of 29 months for MPT and 33 months for MP.

- Preliminary results from the only published trial comparing CTDa to MP (Owen *et al*, 2009) reported no significant difference in survival between the two arms, although median survival itself was not reported.

*Other analyses*

- In the VISTA study time to next therapy was significantly longer with VMP (28.1 months) compared with MP (19.2 months) (HR=0.53, p<0.000001) after a median follow-up of 25.9 months.

- The addition of bortezomib to MP (VMP) did not negatively affect patient-reported outcomes (PROs) over the long term. PROs were assessed by the EQ5D and EORTC QLQ C30until disease progression.

- Prespecified subgroup analyses of time to progression, overall survival and overall response rate showed that the superior efficacy of VMP over MP did not show evidence of significant heterogeneity by prognostic subgroups (e.g. age ≥75 years, impaired renal function or high-risk cytogenetic profiles).
- On September 24th 2009, the CHMP adopted the positive opinion to add the following change in the SmPC Section 5.1 - Pharmacodynamic Properties: 'Data from *in vitro*, *ex-vivo*, and animal models with Bortezomib suggest that it increases osteoblast differentiation and activity and inhibits osteoclast function. These effects have been observed in patients with multiple myeloma affected by an advanced osteolytic disease and treated with bortezomib.'
- The safety profile of VMP was consistent with the known safety profiles of VELCADE and MP; no new safety concerns emerged. Consistent with historical observations, reversibility of peripheral neuropathy was documented in the majority of cases (improvement in 74%, resolution in 56%).
- To compare the effectiveness of VMP to MP, MPT and CTDa, available data was synthesized and an indirect comparison was undertaken.

Cost-effectiveness of VMP, MPT, CTDa

- A cost-utility decision-analytic model was constructed based around three different survival states: stable disease with no response or progression, response without progression, and progression. Baseline values were based on MP treatment and treatment effects for VMP, MPT and CTDa were modelled relative to MP using the results of the indirect comparison. Second-line therapy was assumed to consist of bortezomib plus high dose dexamethasone (HDD), HDD alone, or CTD, and third-line treatment was assumed to be lenalidomide plus dexamethasone. Utility data came from published EQ-5D data for the three different progression states. The perspective was that of the NHS, and the time horizon was thirty years
- Base-case results from the model demonstrated that VMP is more costly, but more effective than comparator treatments. The ICER for VMP versus MP was estimated as £10,498. The ICER for VMP versus MPT and VMP versus CTDa were estimated at £11,907 and £10,411 respectively.
- One-way sensitivity analysis demonstrated that the ICER are most sensitive to changes in the dose and duration of thalidomide, however the ICERs remained below £20 000. The ICERs are also sensitive to a Gompertz extrapolation for the survival and to the HR for overall survival for VMP vs. MP, MPT vs. MP and CTDa vs. MP but again the ICERs remained below £20,000.
- In scenario analyses varying the use of subsequent therapies, VMP shows higher effectiveness and costs than MP, MPT and CTDa.
- The cost-effectiveness acceptability curve showed that with a willingness-to-pay threshold of £30 000, VMP has a 75% probability of being cost-effective.