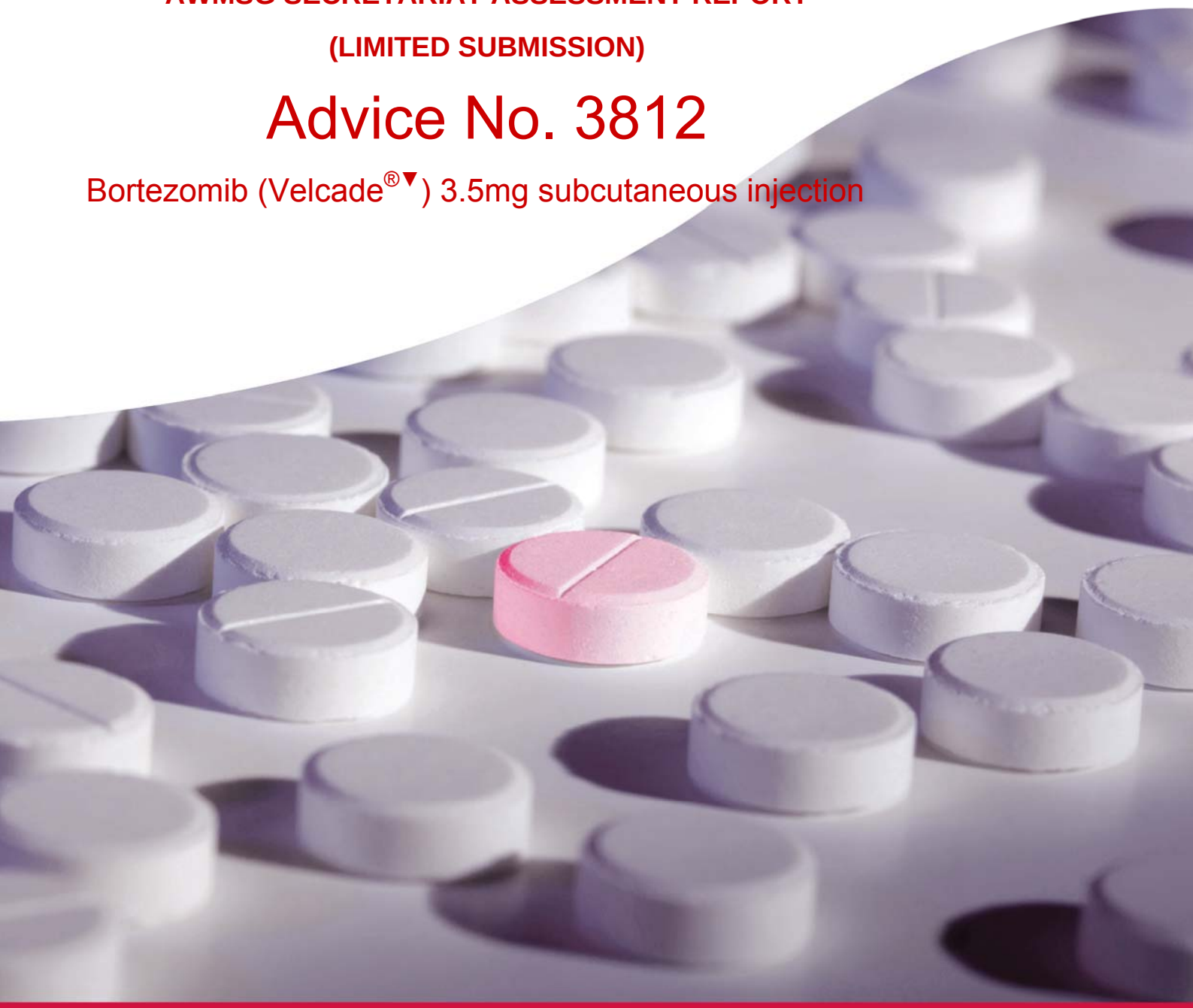
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

(LIMITED SUBMISSION)

Advice No. 3812

Bortezomib (Velcade®▼) 3.5mg subcutaneous injection



In collaboration with the Centre for Health Economics & Medicines Evaluation, Bangor University

AWMSG Secretariat Assessment Report – Advice No. 3812
Bortezomib (Velcade®▼) 3.5 mg subcutaneous injection

This assessment report is based on evidence from a limited submission by Janssen-Cilag Ltd on 4 July 2012[1].

1.0 PRODUCT AND APPRAISAL DETAILS

Licensed indication under consideration	Bortezomib (Velcade®▼) as monotherapy is indicated for the treatment of adult patients with progressive multiple myeloma who have received at least 1 prior therapy and who have already undergone or are unsuitable for bone marrow transplantation. Bortezomib (Velcade®▼) in combination with melphalan and prednisone is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for high-dose chemotherapy with bone marrow transplant[2]. This submission concerns the use of bortezomib administered as a subcutaneous injection for the above indications.
Marketing authorisation date	20 September 2012[2].
Comparators	Bortezomib (Velcade®▼) intravenous injection.
Limited submission details	Bortezomib (Velcade®▼) for the above indication met the following criteria for eligibility for a limited submission: • New formulation with a pro-rata or lower cost per treatment. • Anticipated usage in NHS Wales is considered to be of minimal budgetary impact.

2.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

2.1 Summary of evidence provided

The company submission provides details of an open-label, multicentre, randomised phase III trial, which compared the efficacy and safety of subcutaneous (SC) bortezomib (n = 148) versus intravenous (IV) bortezomib (n = 74) in patients with relapsed multiple myeloma[1,3]. In this study, patients received up to eight 21-day cycles of bortezomib 1.3 mg/m^2. Treatment was as monotherapy for cycles 1–4; patients who had a suboptimal response were additionally administered oral dexamethasome (20 mg) from cycle 5 onwards. After four treatment cycles, SC bortezomib demonstrated non-inferiority to IV bortezomib in terms of overall response rate* (ORR); ORR was 42.5% (31/73 patients) and 42.1% (61/145 patients) in the IV and SC groups respectively (ORR difference −0.4%, 95% CI −14.3 to 13.5, p = 0.002)[1,3]. Results were similar for all other measured efficacy endpoints after four and eight cycles[1,3].

* ORR is defined as complete response (CR: a negative immunofixation on both serum and urine, maintained for a minimum of six weeks) plus partial response (PR: 50% decrease in serum paraprotein)[3,4].

Grade 3 or higher adverse events (AEs) were reported in 57% of patients in the SC group and 70% of patients in the IV group. Discontinuation of treatment due to AEs was seen in 22% and 27% of patients in the SC and IV groups, respectively[1,3]. Overall, when compared to IV bortezomib, SC bortezomib demonstrated an improved safety profile[1].

2.2 Points to note

- In October 2007, bortezomib 3.5 mg IV injection was recommended as an option by the National Institute for Health and Clinical Excellence (NICE)[5] for the treatment of multiple myeloma in people who are at first relapse having received one prior therapy and who have undergone, or are unsuitable for, bone marrow transplantation[5]. In July 2011, NICE published a multiple technology appraisal of bortezomib and thalidomide for the first line treatment of multiple myeloma; this recommends bortezomib as an option for the first line treatment of multiple myeloma if thalidomide is either contraindicated or not tolerated[6].
- The study presented in the company submission demonstrated the efficacy and safety of SC bortezomib in treatment experienced patients[1,3]. Treatment naïve patients were not included in the study, and no other evidence to support the efficacy of SC bortezomib within this population has been provided. However, the company conclude that there are no notable differences in pharmacokinetic and pharmacodynamic properties between IV and SC bortezomib, and SC administration is therefore considered to be appropriate for use in all lines of therapy within the licensed indication of bortezomib.
- The company anticipates that all patients currently treated with IV bortezomib are expected to switch to SC administration[1].
- SC administration of bortezomib could be advantageous to patients with poor venous access. It could eliminate the need for repeated IV access or insertion of long-term central venous access devices thereby improving convenience for patients and their physicians[3].
- SC bortezomib and IV bortezomib are administered as different concentrations (2.5 mg/ml for SC versus 1 mg/ml for IV administration) and thus have different reconstitution volumes (3.5 mg in 1.4 ml 0.9% sodium chloride for SC versus 3.5 mg in 3.5 ml 0.9% sodium chloride for IV)[1,7]. Dose calculations for the SC formulation may be more complex than for the IV formulation.

3.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

3.1 Budget impact evidence

The company anticipates SC bortezomib to displace IV bortezomib for the first-line treatment of patients with multiple myeloma and for the treatment of patients at first relapse[1]. Based on the NICE costing template for bortezomib[6], which reports the incidence of multiple myeloma as 0.010% and 0.007% for males and females respectively, the company estimates that there will be 201 new cases of multiple myeloma diagnosed in year one in Wales, rising to 206 cases in five years. Assuming that 20% of these patients will be eligible for treatment with bortezomib[6], the company estimates that the number of patients receiving bortezomib as a first-line treatment will be around 35 in year one, rising to 36 in year five. It is also assumed that 38% of patients diagnosed with multiple myeloma each year in Wales

will be at first relapse and that 67% of these patients will be eligible for treatment with bortezomib. The number of patients receiving bortezomib at first relapse is estimated to be 51 in year one, rising to 53 in year five. The total number of patients treated each year with bortezomib in Wales, therefore, is expected to increase from 86 in year one to 89 in year five.

The company estimates that the annual cost of treatment with SC bortezomib (based on an average of 32 vials per course of treatment)[6] will be £24,396 per patient per year for both first-line and first relapse patients. Given that the manufacturer rebates the full cost of bortezomib for relapsed patients with less than a partial response to treatment according to the Velcade®▼ Response Scheme (VRS), the total cost of treatment with bortezomib SC injection will be £2,095,305 in year one rising to £2,153,403 in year five (£9,105,169 over five years). The anticipated number of patients treated with SC bortezomib and associated costs are summarised in Table 1.

Due to non-inferiority in efficacy of SC bortezomib compared to IV bortezomib (section 2.1), identical prices and administration schedules, the company estimates that displacement of IV bortezomib by SC formulation will not incur any additional costs. The company anticipates potential savings in the use of NHS resources, such as medical equipment as well as the release of staff time and capacity, due to changes in the route of administration for bortezomib, although these are not incorporated into the budget impact analysis.

Table 1. Company-reported costs associated with use of bortezomib SC injections for the treatment of patients multiple myeloma

	Year 1	Year 2	Year 3	Year 4	Year 5
Patients eligible for first-line treatment	35	35	35	35	36
Patients eligible for treatment at first relapse	51	52	52	52	53
Acquisition costs for first-line treatment	£847,143	£853,174	£859,342	£865,010	£870,632
Acquisition costs for treatment at first relapse	£1,248,163	£1,257,050	£1,266,137	£1,247,489	£1,282,771
Rebate cost (VRS)	-£299,559	-£301,680	-£303,848	-£305,840	-£307,815
Total cost	£2,095,305	£2,110,224	£2,125,479	£2,139,499	£2,153,403
VRS: Velcade®▼ Response Scheme.					

3.2 AWTTC critique of the budget impact analysis

Budget impact estimates presented by the company consider bortezomib acquisition costs only and do not consider potential opportunities for cost savings owing to reduced use of medical resource and staff time with SC administration. Assuming that bortezomib SC injection is delivered in the same doses with the same administration schedules, and priced at parity with IV bortezomib, no additional costs for NHS Wales are anticipated.

3.3 Comparative unit costs

According to the company submission[1] SC bortezomib (£762.38 per 3.5 mg vial) will displace IV bortezomib (£762.38 per 3.5 mg vial)[8]. Therefore, there will be no

difference in acquisition costs between the two routes of administration, as discussed in Section 3.1.

4.0 ADDITIONAL INFORMATION

4.1 Appropriate place for prescribing

AWTTC is of the opinion that, if given a positive recommendation, SC bortezomib 3.5 mg is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

Treatment with SC bortezomib must be initiated and administered under the supervision of a physician qualified and experienced in the use of chemotherapeutic agents[2].

4.2 AWMSG review

This assessment report will be considered for review three years from the date of Ministerial ratification (as disclosed in the Final Appraisal Recommendation).

4.3 Evidence search

Date of evidence search: 6 July 2012 and 9 July 2012.
Date range of evidence search: No date limits were applied to database searches.

REFERENCES

1 Janssen-Cilag Ltd. Form C: Limited appraisal submission. Bortezomib (Velcade®). 2012.

2 Janssen-Cilag Ltd. Velcade®. Summary of Product Characteristics. Sep 2012. Available at: http://www.medicines.org.uk/EMC/medicine/15593/SPC/VELCADE+3.5+mg+powder+for+solution+for+injection./. Accessed Sep 2012.

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4 Blade J, Samson D, Reece D et al. Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. *Br J Haematol* 1998; 102 (5): 1115-23.

5 National Institute for Health and Clinical Excellence. Technology Appraisal 129. Bortezomib monotherapy for relapsed multiple myeloma. Oct 2007. Available at: http://publications.nice.org.uk/bortezomib-monotherapy-for-relapsed-multiple-myeloma-ta129. Accessed Jul 2012.

6 National Institute for Health and Clinical Excellence. Technology appraisal 228. Bortezomib and thalidomide for the first-line treatment of multiple myeloma. 2011. Available at: http://publications.nice.org.uk/bortezomib-and-thalidomide-for-the-firstline-treatment-of-multiple-myeloma-ta228/guidance. Accessed Jul 2012.

7 Janssen-Cilag Ltd. Velcade®. Summary of Product Characteristics. Sep 2011. Available at: http://www.medicines.org.uk/EMC/medicine/17109/SPC/Velcade+3.5mg+powder+for+solution+for+injection/. Accessed Jul 2012.

8 British Medical Association, Royal Pharmaceutical Society of Great Britain. *British National Formulary. No. 64.* Sep 2012.