The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

10 June 2009

VELCADE 3.5 mg, powder for solution for injection
B/1 bottle (CIP code: 564 957-3)
VELCADE 1 mg, powder for solution for injection
B/1 bottle (CIP code: 386 657-9)

Applicant: JANSSEN-CILAG

bortezomib
ATC code: L01XX32

List I
For hospital use only
The treatment must be started and administered under the supervision of a physician qualified and experienced in the use of chemotherapeutic agents.

Date of Marketing Authorisation (centralised procedure): 26 April 2004 - Variations: 26 April 2005 and 29 August 2008

Reason for request: Inclusion on the list of medicines approved for hospital use in the indication extension “in combination with melphalan and prednisone for the treatment of patients with previously untreated multiple myeloma, who are not eligible for high-dose chemotherapy with bone marrow transplantation.”

Medical, Economic and Public Health Assessment Division
1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
bortezomib

1.2. Indications
“VELCADE is indicated in combination with melphalan and prednisone for the treatment of patients with previously untreated multiple myeloma, who are not eligible for high-dose chemotherapy with bone marrow transplantation.

VELCADE is indicated as monotherapy for the treatment of progressive multiple myeloma in patients who have received at least 1 prior therapy and who have already undergone or are unsuitable for bone marrow transplant.”

1.3. Dosage
“VELCADE (bortezomib) is administered by intravenous bolus injection over 3-5 seconds, in combination with oral melphalan and oral prednisone for nine therapeutic cycles of 6 weeks, as described in Table 2. During cycles 1-4, VELCADE is administered twice weekly (on days 1, 4, 8, 11, 22, 25, 29 and 32). During cycles 5-9, VELCADE is administered once weekly (on days 1, 8, 22 and 29).

Table 2 – Recommended dosage regimen for VELCADE in combination with melphalan and prednisone in patients with previously untreated multiple myeloma.

<table>
<thead>
<tr>
<th>Twice weekly VELCADE (Cycles 1-4)</th>
<th>Week</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vc (1.3 mg/m2)</td>
<td>D1</td>
<td>--</td>
<td>--</td>
<td>D4</td>
<td>D8</td>
<td>D11</td>
<td>rest period</td>
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<tr>
<td>m(9 mg/m2)</td>
<td></td>
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<tr>
<td>p(60 mg/m2)</td>
<td>D1</td>
<td>D2</td>
<td>D3</td>
<td>D4</td>
<td>--</td>
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<td>rest period</td>
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<tr>
<td>rest period</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Once weekly VELCADE (Cycles 5-9)</th>
<th>Week</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vc (1.3 mg/m2)</td>
<td>D1</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>D8</td>
<td>rest period</td>
<td>D22</td>
</tr>
<tr>
<td>m(9 mg/m2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>D1</td>
<td>D2</td>
<td>D3</td>
<td>D4</td>
<td>--</td>
<td>rest period</td>
<td>--</td>
</tr>
</tbody>
</table>

Vc = VELCADE; m = melphalan, p=prednisone"
2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2008)
L : Antineoplastic and immunomodulating agents
L01 : Antineoplastics
L01X : Other antineoplastic agents
L01XX : Other antineoplastic agents
L01XX32 : Bortezomib

2.2. Medicines in the same therapeutic category
Comparator medicines
None

2.3. Medicinal products with the same therapeutic aim
- ALKERAN (melphalan)
- ENDOXAN-ASTA (cyclophosphamide)
- ONCOVIN (vincristine)
- BICNU (carmustine)
- INTRONA (alpha 2a interferon)
- THALIDOMIDE PHARMION (thalidomide)
High-dose corticosteroids (prednisone or dexamethasone) are used alone or in combination with cytotoxic agents.
3. ANALYSIS OF AVAILABLE DATA

The dossier comprises two studies:
- one phase I/II dose-ranging study. This will not be considered in this opinion.
- one phase III study (MMY-3002)

3.1. Efficacy

Study MMY-3002 is a randomised, open-label phase III study which assessed VELCADE in combination with melphalan and prednisone (VMP) versus melphalan and prednisone (MP) alone in 682 patients with previously untreated multiple myeloma who were not eligible for high-dose treatment followed by autologous transplantation.

The primary endpoint was the time to progression defined according to the criteria of EBMT (see appendix 1)

The secondary endpoints were progression-free survival, overall survival, the overall response rate (complete response CR and partial response PR), the time to the first response and the duration of the response.

Patients in the VMP group received i.v. VELCADE at a dose of 1.3 mg/m² twice weekly (weeks 1, 2, 4 and 5, this being D1, D4, D8, D11, D22, D25, D29 and D32) for 4 6-week cycles (8 doses per cycle) and then i.v. VELCADE at a dose of 1.3 mg/m² once weekly (weeks 1, 2, 4 and 5, this being D1, D8, D22, and D29) for 5 6-week cycles (4 doses per cycle) combined with oral melphalan 9 mg/m² and oral prednisone 60 mg/m² (once daily, D1 to D4 of each 6-week cycle).

Patients in the MP group received 9 cycles of melphalan 9 mg/m² and prednisone 60 mg/m² (once daily, D1 to D4 of each 6-week cycle).

In each group, treatment was continued for a maximum of 9 cycles (54 weeks) and was discontinued in the event of disease progression or unacceptable toxicity associated with the treatment or if the patient withdrew consent.

Results:

The median age of the patients was 71 years. About two thirds of patients had remained in good general condition.

Forty-seven percent (47%) of patients had multiple myeloma ISS (International Staging System) stage II and 34% had stage III.

The results are from the 3rd interim analysis scheduled in the protocol.

The median time to progression (primary endpoint) was 20.7 months in the VMP group versus 15.0 months in the MP group (HR = 0.540; p = 0.000002).

The median progression-free survival time was 18.3 months in the VMP group and 14.0 months in the MP group (HR = 0.609; p = 0.00001).

2 The European Group for Blood and Marrow Transplantation
3 Progression-free survival was defined as the time interval between the date of randomisation and the date of the first signs of disease progression, relapse or death from any cause, whichever was the first to occur. Patients without disease progression or relapse were ignored at the date of the last follow-up.
4 Complete and partial responses were defined according to the EBMT criteria presented in appendix 1.
Following a median follow-up of 16.3 months, 45 patients (13%) had died in the VMP group and 76 (23%) in the MP group. The median overall survival was not reached in the two groups.

The 1-year survival rate was estimated at 89.1% in the VMP group and 81.8% in the MP group. At 2 years, the estimate was 82.6% for the VMP group and 69.5% for the MP group (HR = 0.607; p = 0.00782).

The global response rate was 71% with 30% complete response in the VMP group and 35% with 4% complete response in the MP group (p< 10^{-10}).

The median time to the first response was 1.4 months in the VMP group and 4.2 months in the MP group (p< 10^{-10}).

The median duration of overall response (CR and PR) was 19.9 months in the VMP group and 13.1 months in the MP group.

3.2. Adverse effects
The incidence of grade 3 adverse events was higher in the VMP group (53%) than in the MP group (44%). The incidence of grade 4 adverse events was similar in both groups: 28% in the VMP group and 27% in the MP group. In each group, fatal grade 5 events were reported in 27 patients (8%).

Treatment was discontinued due to an adverse event in 15% of the VMP group and 14% of the MP group.

The adverse events that were most frequently reported during study MMY-3002 concerned the haematological and lymphatic systems (VMP: 82%, MP: 77%):
- the incidence of anaemia was 43% in the VMP group and 55% in the MP group
- the incidence of thrombocytopenia was 52% in the VMP group and 47% in the MP group. Grades ≥ 3 haemorrhages were reported in 3% of patients in each group;
- the incidence of neutropenia (VMP: 49%, MP: 46%) was similar in the two groups. The incidence of febrile neutropenia was 2% in the VMP group and 4% in the MP group.

Two types of non-haematological toxicity were more common in the VMP group:
- grades ≥ 3 gastrointestinal disorders (16% vs 3%);
- peripheral neuropathy (46% vs 1% of which 13% vs 0% of grades ≥ 3).

3.3. Conclusion
The efficacy and safety of VELCADE as first-line treatment of multiple myeloma in patients aged over 65 years were assessed in an open-label, randomised phase III study comparing the combination Melphalan-Prednisone (MP) with the combination VELCADE-Melphalan-Prednisone (VMP).

The interim analysis performed at 16.3 months’ follow-up showed that the VMP combination prolonged the median time to progression (primary endpoint) by 5.7 months: 20.7 months in the VMP group versus 15.0 months in the MP group (HR = 0.540; p = 0.000002).

The global response rate was 71% with 30% complete response in the VMP group and 35% with 4% complete response in the MP group (p< 10^{-10}).

The 2-year survival rate was estimated at 82.6% in the VMP group and 69.5% in the MP group (HR = 0.607; p=0.00782).

Two types of non-haematological toxicity were more common in the VMP group:
- grades ≥ 3 gastrointestinal disorders (16% vs 3%),
- and grades ≥ 3 peripheral neuropathy (13% vs 0%).
4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit
Multiple myeloma is a blood disease that is almost always fatal, with a short median survival (3 to 5 years);
The efficacy/adverse effects ratio of VELCADE is high.
It is intended for palliative treatment;
It is a first-line treatment;
There are alternative medications;

Public health benefit:
The public health burden of multiple myeloma in the population relevant for the indication considered is moderate.
The availability of treatments enabling an improved survival of patients with multiple myeloma is a public health need.
In light of the available data, the combination of VELCADE, melphalan and prednisone has a large impact on morbidity and mortality, and quality of life data do not show a deterioration in the quality of life. The transferability of the results is acceptable.
The combination of VELCADE, melphalan and prednisone is a therapeutic alternative in the first-line treatment of multiple myeloma.
Consequently, the proprietary product VELCADE, when combined with melphalan and prednisone, is expected to benefit public health in this indication. This benefit is moderate.

The actual benefit is substantial.

4.2. Improvement in actual benefit (IAB)
VELCADE, when added to the combination of melphalan and prednisone, provides a moderate (level III) improvement in actual benefit with respect to efficacy when compared with the combination of melphalan and prednisone alone in the first-line treatment of patients with multiple myeloma who are not eligible for high-dose chemotherapy with bone marrow transplantation.

4.3. Therapeutic use
The current classification of myeloma established according to the criteria of the International Myeloma Workshop Group\(^5\) distinguishes two categories of patients: asymptomatic patients, for whom simple monitoring is generally considered sufficient, and symptomatic patients (bone involvement, renal failure, hypercalcaemia, anaemia, intercurrent infections, amyloidosis), who require management that is adjusted for age and comorbidities.
First-line treatment includes the following alternative: is the patient eligible for high-dose treatment after induction chemotherapy has resulted in complete or partial remission? It has been shown that intensification following autologous transplantation has significantly increased 5-year survival in patients aged less than 70 years\(^6\). After this intensification, a

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consolidation treatment can increase the rate of remission (namely it can decrease the tumour mass), prolong the duration of the response and improve survival\textsuperscript{7}.

Patients who are aged \( \geq 65 \) years or are ineligible for intensification are treated with combinations including at least one alkylating agent such as melphalan (M) and one corticosteroid such as prednisone (P): this is the classic MP regimen (28-day cycles including 4 days of treatment with M 0.25 mg/kg and P 1 mg/kg). This Alexanian\textsuperscript{8}-like regimen, which results in less than 50\% of good responses (decrease in the monoclonal peak > 50\%), was improved by the addition of thalidomide (T). The rate of good responses is thus increased to nearly 80\%.

The addition of bortezomib to the melphalan-prednisone combination, in light of the available results, constitutes a new method for the first-line treatment of multiple myeloma in patients aged over 65 years or in whom high-dose chemotherapy is contraindicated. In the absence of a direct comparison, the role of bortezomib with regard to thalidomide remains to be established.

4.4. Target population
The target population for VELCADE consists of patients with untreated symptomatic multiple myeloma who are aged over 65 years or in whom high-dose chemotherapy is contraindicated.

According to data from the French Institute for Public Health Surveillance (Institut national de veille sanitaire, INVS)\textsuperscript{9}, the incidence of multiple myeloma in France increased from 3,565 new cases per year in 2000 to 4,516 in 2005.

Of these patients, 3,327 were aged 65 years or older.

The percentage of patients who are asymptomatic and thus for whom simple monitoring is relevant is estimated to be between 15\textsuperscript{10,11} and 20\%\textsuperscript{12}.

The target population for VELCADE in this indication extension would be of about 2,600 to 2,800 patients per year.

4.5. Recommendations of the Transparency Committee
The Transparency Committee recommends inclusion on the list of medicines approved for hospital use and various public services in this extension of indication.

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\textsuperscript{8} Alexanian R, Bergsagel DE, Migliore PJ, Vaughn WK, Howe CD. Melphalan therapy for plasma cell myeloma. Blood 1968;31:1-10
\textsuperscript{9} Évolution de l'incidence et de la mortalité par cancer en France de 1980 à 2005; Fiche Myélome Multiple et Maladies Immunoprolifératives (Changes in the incidence and mortality of cancer in France from 1980 to 2005; Multiple Myeloma and Immunoproliferative Diseases file) INVS 30/01/2008: http://www.invs.sante.fr/surveillance/cancers/estimations_cancers/donnees_localisation/myelome/myelome.pdf
### Table 5: Disease Response Criteria (Continued)

<table>
<thead>
<tr>
<th>Response</th>
<th>Criteria for Response$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Progressive Disease (PD) (for subjects not in CR)</strong></td>
<td>Requires one or more of the following:</td>
</tr>
<tr>
<td></td>
<td>• $&gt;25%$ increase$^d$ in the level of serum monoclonal paraprotein, which must also be an absolute increase of at least $5, \text{g/L (500 mg/dL)}$ and confirmed on a repeat investigation</td>
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<tr>
<td></td>
<td>• $&gt;25%$ increase$^d$ in 24-hour urinary light chain excretion, which must also be an absolute increase of at least $200, \text{mg/24 h}$ and confirmed on a repeat investigation</td>
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<tr>
<td></td>
<td>• $&gt;25%$ increase$^d$ in plasma cells in a bone marrow aspirate or on trephine biopsy, which must also be an absolute increase of at least $10%$</td>
</tr>
<tr>
<td></td>
<td>• Definite increase in the size of existing lytic bone lesions or soft tissue plasmacytoma$^e$</td>
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<tr>
<td></td>
<td>• Development of new bone lesions or soft tissue plasmacytomas (not including compression fracture)</td>
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<td></td>
<td>• Development of hypercalcemia (corrected serum calcium $&gt;11.5, \text{mg/dL or 2.8 mmol/L not attributable to any other cause})$</td>
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<td><strong>Relapse from CR</strong></td>
<td>Requires at least one of the following:</td>
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<tr>
<td></td>
<td>• Reappearance of serum or urinary paraprotein on immunofixation or routine electrophoresis confirmed by at least 1 follow-up and excluding oligoclonal immune reconstitution</td>
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<td></td>
<td>• $\geq5%$ plasma cells in the bone marrow aspirate or biopsy</td>
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<td>• Development of new lytic bone lesions or soft tissue plasmacytomas or definite increase in the size of residual bone lesions (not including compression fracture)</td>
</tr>
<tr>
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<td>• Development of hypercalcemia (corrected serum calcium $&gt;11.5, \text{mg/dL or 2.8 mmol/L not attributable to any other cause})$</td>
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</table>

$^a$ Adapted from the criteria reported by Blade et al.$^{49}$
$^b$ According to Blade et al.,$^{49}$ if absence of the monoclonal protein is sustained for 6 weeks it is not necessary to repeat the bone marrow examination. In subjects with nonsecretory or oligosecretory myeloma the marrow examination (including 6 week follow-up examination) will be required.
$^c$ According to Blade et al.$^{49}$ skeletal X-rays are not required for the definition of response, but if performed there must be no evidence of progression of bone disease (no increase in size or number of lytic bone lesions).
$^d$ The reference point for calculating any increase should be the lowest prior value documented at baseline or during the study unless the lowest prior value is considered to be spurious.
$^e$ A definite increase in size is defined as at least a $50\%$ increase in the product of the greatest perpendicular dimensions.
$^f$ Other clinical data may be needed to assess the cause of the hypercalcemia before attributing it to myeloma disease progression.
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<td>(for subjects not in CR)</td>
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<td>• &gt;25% increase(^d) in 24-hour urinary light chain excretion, which must also be an absolute increase of at least 200 mg/24 h and confirmed on a repeat investigation.</td>
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<td>• &gt;25% increase(^e) in plasma cells in a bone marrow aspirate or on trephine biopsy, which must also be an absolute increase of at least 10%.</td>
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<td>• Definite increase in the size of existing lytic bone lesions or soft tissue plasmacytomas(^e).</td>
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\(^a\) Adapted from the criteria reported by Blade et al\(^3\)  
\(^b\) According to Blade et al., if absence of the monoclonal protein is sustained for 6 weeks it is not necessary to repeat the bone marrow examination. In subjects with nonsecretory or oligosecretionary myeloma the marrow examination (including 6 week follow-up examination) will be required.  
\(^c\) According to Blade et al.,\(^3\), skeletal X-rays are not required for the definition of response, but if performed there must be no evidence of progression of bone disease (no increase in size or number of lytic bone lesions).  
\(^d\) The reference point for calculating any increase should be the lowest prior value documented at baseline or during the study unless the lowest prior value is considered to be spurious.  
\(^e\) A definite increase in size is defined as at least a 50% increase in the product of the greatest perpendicular dimensions.  
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