

**6.12 POMALIDOMIDE,  
Capsule 3 mg,  
Capsule 4 mg,  
Pomalyst<sup>®</sup>, Celgene Pty Ltd.**

**1 Purpose of Application**

1.1 The minor submission sought to amend the current wording to the restriction of pomalidomide to include the treatment of patients who have experienced severe intolerance or toxicity to lenalidomide and/or bortezomib for relapsed/refractory multiple myeloma.

**2 Requested listing**

2.1 The submission requested the following changes (shown in **bold**) to the existing initial treatment restriction as below. No change was requested to the continuing treatment restriction.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Manufacturer	Name and
POMALIDOMIDE pomalidomide 3 mg capsule, 21	1	0	\$ [REDACTED]	Pomalyst <sup>®</sup>	Celgene Pty Ltd
pomalidomide 4 mg capsule, 21	1	0	\$ [REDACTED]		

<b>Category / Program</b>	Section 100 – Highly Specialised Drugs Program
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Condition:</b>	Multiple myeloma
<b>PBS Indication:</b>	Multiple myeloma
<b>Treatment phase:</b>	Initial treatment
<b>Restriction Level / Method:</b>	<input checked="" type="checkbox"/> Authority Required - In Writing
<b>Clinical criteria:</b>	The treatment must be in combination with dexamethasone,  AND  Patient must have undergone or be ineligible for a primary stem cell transplant,  AND  Patient must have experienced treatment failure with bortezomib; <b>OR</b>  <b>Patient must have experienced severe intolerance to bortezomib unresponsive to clinically appropriate dose adjustment or scheduling; OR</b>  <b>Patient must be contraindicated to bortezomib,</b>

	<p><b>AND</b></p> <p>Patient must have experienced treatment failure with lenalidomide; <b>OR</b></p> <p><b>Patient must have experienced severe intolerance to lenalidomide unresponsive to clinically appropriate dose adjustment or scheduling; OR</b></p> <p><b>Patient must be contraindicated to lenalidomide,</b></p> <p><b>AND</b></p> <p>Patient must not be receiving concomitant PBS-subsidised thalidomide, lenalidomide or bortezomib.</p>
<p><b>Prescriber Instructions</b></p>	<p>Bortezomib treatment failure is the absence of achieving at least a partial response or as progressive disease during treatment or within 6 months of discontinuing treatment with bortezomib. Lenalidomide treatment failure is progressive disease during treatment or within 6 months of discontinuing treatment with lenalidomide.</p> <p><b>Severe intolerance due to bortezomib is defined as any Grade 3 or 4 toxicity.</b></p> <p><b>Severe intolerance due to lenalidomide is defined as skin rash (Grade 2 or greater), angioedema, exfoliative or bullous rash, suspected Stevens-Johnson syndrome or toxic epidermal necrolysis or other Grade 3 or 4 toxicity.</b></p> <p>Progressive disease is defined as at least 1 of the following: (no changes proposed)</p> <p>(a) at least a 25% increase and an absolute increase of at least 5 g per L in serum M protein (monoclonal protein); or</p> <p>(b) at least a 25% increase in 24-hour urinary light chain M protein excretion, and an absolute increase of at least 200 mg per 24 hours; or</p> <p>(c) in oligo-secretory and non-secretory myeloma patients only, at least a 50% increase of the difference between involved free light chain and uninvolved free light chain; or</p> <p>(d) at least a 25% relative increase and at least a 10% absolute increase in plasma cells in a bone marrow aspirate or on biopsy; or</p> <p>(e) an increase in the size or number of lytic bone lesions (not including compression fractures); or</p> <p>(f) at least a 25% increase in the size of an existing or the development of a new soft tissue plasmacytoma (determined by clinical examination or diagnostic imaging); or</p> <p>(g) development of hypercalcaemia (corrected serum calcium greater than 2.65 mmol per L not attributable to any other cause).</p> <p>Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M protein.</p>
<p><b>Administrative Advice</b></p>	<p>As per existing restriction (no changes proposed)</p>
<p><b>Cautions</b></p>	<p>As per existing restriction (no changes proposed)</p>

**Secretariat suggested wording for the restriction:**

Suggestions and additions proposed by the Secretariat to the requested listing are added in *italics* and suggested deletions are crossed out with ~~strikethrough~~.

<b>Category / Program</b>	Section 100 – Highly Specialised Drugs Program (Public & Private Hospitals)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Condition:</b>	Multiple myeloma
<b>PBS Indication:</b>	Multiple myeloma
<b>Treatment phase:</b>	Initial treatment
<b>Restriction Level / Method:</b>	<input checked="" type="checkbox"/> Authority Required - In Writing
<b>Clinical criteria:</b>	<p>The treatment must be in combination with dexamethasone, AND Patient must have undergone or be ineligible for a primary stem cell transplant, AND Patient must have experienced treatment failure with bortezomib, <i>unless contraindicated or not tolerated according to the Therapeutic Goods Administration (TGA) approved Product Information; OR</i> <del>Patient must have experienced severe intolerance to bortezomib unresponsive to clinically appropriate dose adjustment or scheduling; OR</del> <del>Patient must be contraindicated to bortezomib,</del> AND Patient must have experienced treatment failure with lenalidomide, <i>unless contraindicated or not tolerated according to the TGA approved Product Information; OR</i> <del>Patient must have experienced severe intolerance to lenalidomide unresponsive to clinically appropriate dose adjustment or scheduling; OR</del> <del>Patient must be contraindicated to lenalidomide,</del> AND Patient must not be receiving concomitant PBS-subsidised thalidomide, lenalidomide or bortezomib.</p>
<b>Prescriber Instructions</b>	<p>Bortezomib treatment failure is the absence of achieving at least a partial response or as progressive disease during treatment or within 6 months of discontinuing treatment with bortezomib. Lenalidomide treatment failure is progressive disease during treatment or within 6 months of discontinuing treatment with lenalidomide.</p> <p><del>Severe intolerance due to bortezomib is defined as any Grade 3 or 4 toxicity. Severe intolerance due to lenalidomide is defined as skin rash (Grade 2 or greater), angioedema, exfoliative or bullous rash, suspected Stevens-Johnson syndrome or toxic epidermal necrolysis or other Grade 3 or 4 toxicity.</del></p> <p><i>If treatment with either bortezomib or lenalidomide is contraindicated according to the relevant TGA-approved Product Information. The application must provide details of the contraindication.</i></p> <p><i>If intolerance to either bortezomib or lenalidomide treatment develops during the relevant period of use which is of a severity to necessitate withdrawal of the treatment, the application must provide details of the nature and severity of this intolerance.</i></p>

	Progressive disease defined as per existing restriction (no changes proposed)
<b>Administrative Advice</b>	As per existing restriction (no changes proposed)
<b>Cautions</b>	As per existing restriction (no changes proposed)

*For more detail on PBAC’s view, see section 7 “PBAC outcome”*

### **3 Background**

- 3.1 Pomalidomide (in combination with dexamethasone) is TGA registered for the treatment of patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.
- 3.2 A major submission for pomalidomide seeking listing for treatment of patients with multiple myeloma who have previously received and failed, or are intolerant to treatment with lenalidomide or bortezomib was rejected by the PBAC at the July 2014 meeting on the basis that cost-effectiveness had not been demonstrated. The PBAC also considered that the words “or are intolerant to” should be removed from the proposed restriction, so that the restriction could read “for treatment of patients with multiple myeloma who have previously received and failed treatment with lenalidomide and bortezomib.”
- 3.3 At the November 2014 meeting, pomalidomide was recommended for listing for patients who have received and failed prior treatment with both bortezomib and lenalidomide (with reference to “or are intolerant to” removed from the restriction).
- 3.4 At the March 2016 meeting, the PBAC rejected the request to change the definition of treatment failure of bortezomib and lenalidomide and amend the listing to include patients who have ‘experienced severe intolerance or toxicity to bortezomib (or lenalidomide), unresponsive to clinically appropriate dose adjustment’. The PBAC considered that the issue was not whether pomalidomide is effective in these populations, but whether pomalidomide is cost-effective against the additional comparators that would apply in those circumstances (for example re-use of lenalidomide or bortezomib with adjusted scheduling). At this meeting, the PBAC also recommended changes to the restriction for lenalidomide to enable a treatment holiday, which it considered would address some of the issues raised in the submission. This recommendation is yet to be implemented.

*For more detail on PBAC’s view, see section 7 “PBAC outcome”*

### **4 Clinical place for the proposed therapy**

- 4.1 Multiple myeloma is a rapidly progressive disease for which there is no effective cure. The primary goals of treatment are to control the disease, maximise quality of life and prolong survival.
- 4.2 Pomalidomide was proposed as a last line option for the treatment of multiple myeloma for patients who have failed lenalidomide and bortezomib or are intolerant to treatment with bortezomib or lenalidomide after clinically appropriate dose

adjustment.

- 4.3 The minor submission stated that in clinical practice, there are circumstances outlined in the relevant Product Information where initiation or continuation of treatment with lenalidomide or bortezomib with further dose modification or adjusted scheduling is not appropriate.

## **5 Comparator**

- 5.1 The minor submission nominated salvage therapy (high dose dexamethasone; HDD) or palliative care as the comparators (as per the July 2014 submission) on the basis that the requested restriction has been revised to only include patients who are intolerant to bortezomib or lenalidomide with clinically appropriate dose adjustment. The PBAC previously accepted that HDD was the appropriate main comparator in this context, while noting that other salvage therapies would also be replaced in practice (paragraph 7.3, pomalidomide Public Summary Document, July 2014).

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 There was no hearing for this item as it was a minor submission.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from health care professionals (3) via the Consumer Comments facility on the PBS website. The comments highlighted the need for treatment options for patients who are intolerant to lenalidomide and/or bortezomib.
- 6.3 The PBAC noted and welcomed the letter from Myeloma Australia which expressed its support for the amending the current pomalidomide restriction. The letter described pomalidomide as an effective treatment option for patients who have progressed on lenalidomide and bortezomib. It emphasised that there are patients intolerant or contraindicated to treatment with either bortezomib or lenalidomide for whom there are limited treatment options and a poor prognosis.

### ***Clinical trials***

- 6.4 As a minor submission no new clinical data was presented.
- 6.5 The PBAC noted that no data had been provided to provide evidence that treatment with pomalidomide would be safe in patients who were intolerant to lenalidomide. The PBAC was of the view that this was an important consideration, as some of the side effects could be drug class effects. Therefore, the PBAC considered that the safety of pomalidomide treatment in the proposed setting had not been established.

### ***Clinical need***

- 6.6 The minor submission stated that patients who have not failed but are intolerant or contraindicated to lenalidomide or bortezomib are currently unable to access

pomalidomide on the PBS and have no other effective PBS subsidised treatment options. The sponsor claimed that the continued need to provide access to pomalidomide through internal access programs following the PBS listing of pomalidomide and amendments to allow re-treatment with lenalidomide demonstrates that there is a clinical need that is not met by the current PBS restriction for pomalidomide.

### ***Economic analysis***

- 6.7 There was no economic analysis presented in the minor submission.
- 6.8 The PBAC considered that the cost-effectiveness of pomalidomide treatment in this setting had not been established.
- 6.9 The PBAC recalled that at the March 2016 meeting it questioned whether pomalidomide in this setting is cost-effective against the additional comparators that would apply in those circumstances (for example re-use of lenalidomide or bortezomib with adjusted scheduling). The submission claimed that because the proposed listing only includes patients who are intolerant to bortezomib or lenalidomide even with clinically appropriate dose adjustment, these additional comparators do not apply. The PBAC also recalled that it previously considered that the incremental cost-effectiveness ratio (ICER) of \$45,000/ quality adjusted life-year (QALY) - \$75,000/QALY was at the high end of what would be considered cost-effective for pomalidomide in this indication, and recommended the listing on the basis of high clinical need.

### ***Estimated PBS usage & financial implications***

- 6.10 The minor submission did not provide estimates of utilisation for the proposed patient population. The minor submission indicated that less than 10,000 patients who meet the proposed criteria were provided pomalidomide via an access program between June 2016 and November 2016. This was considered the minimum number of patients that would access PBS subsidy for this indication.
- 6.11 The minor submission estimated that the number of patients initiating pomalidomide in year 2 of the risk share arrangement would be less than half of the patient cap. The submission argued that because the actual Commonwealth expenditure on pomalidomide is expected to be lower than the estimates in the pomalidomide risk share agreement, any additional expenditure due to extending the pomalidomide listing was already captured within the original financial estimates and the current deed. Risk share arrangement caps set the upper limit of Government expenditure for the drug in a particular year of the deed; they do not commit the Government to a certain level of expenditure. Amending the listing to provide subsidy for additional patients will result in an additional cost to Government. As with all requests to include a new population for PBS subsidy, this must be considered cost-effective and the financial impact estimated.
- 6.12 The pre-PBAC response estimated an additional less than 10,000 patients in year 1, increasing to less than 10,000 patients in year 5, with a net cost to the PBS of \$10 -

\$20 million (published) over the first five years of listing. However, these estimates could not be verified.

*For more detail on PBAC's view, see section 7 "PBAC outcome"*

## **7 PBAC Outcome**

- 7.1 The PBAC rejected the request to amend the current restriction for pomalidomide to include the treatment of patients who have experienced severe intolerance or toxicity to lenalidomide and/or bortezomib for relapsed/refractory multiple myeloma based on unknown cost-effectiveness. The PBAC also noted that the safety of pomalidomide in patients previously experiencing a severe toxicity when treated with lenalidomide was uncertain, as were the utilisation estimates.
- 7.2 The submission did not provide any safety data on the use of pomalidomide in patients with severe intolerance to lenalidomide. The PBAC considered there was a high risk that patients experiencing severe intolerance to lenalidomide would experience similar adverse effects on treatment with pomalidomide, given lenalidomide and pomalidomide have similar mechanisms of action. The PBAC also noted that the submission did not present any data to support efficacy of pomalidomide in the proposed treatment setting.
- 7.3 The PBAC considered that the cost-effectiveness of pomalidomide in this treatment setting was unknown. Further, the PBAC recalled that at the November 2014 meeting when it recommended pomalidomide for treatment of patients who have received and failed prior treatment with both bortezomib and lenalidomide, it considered the ICER to be at the high end of what they would consider cost-effective.
- 7.4 The PBAC noted that utilisation for Year 1 of the deed was only 51.24% of Cap 1 (\$10 - \$20 million). The PBAC considered that these data may indicate that the mean treatment duration of pomalidomide is shorter than expected and may suggest that pomalidomide was less effective in practice than modelled as part of the original submission. The PBAC considered that given pomalidomide was recommended with an ICER at the high end of what would be considered cost-effective, a lower than expected effectiveness may raise concerns about the ongoing cost-effectiveness of the current PBS-listing of pomalidomide. The PBAC therefore requested the Department review the utilisation of pomalidomide to determine whether further evaluation was required.
- 7.5 The PBAC recalled its previous recommendation at the March 2016 meeting to amend the restriction for lenalidomide to enable re-treatment with lenalidomide after a "treatment holiday". The PBAC noted that its recommendation is yet to be implemented. The PBAC considered that implementation of the recommendation would address some of the remaining clinical need.
- 7.6 The PBAC noted that this submission is not eligible for an Independent Review; Independent Review is not available in response to a request to modify or extend an existing listing.

**Outcome:**  
Rejected

**8 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

**9 Sponsor's Comment**

The sponsor had no comment.