

## 6.15 CARFILZOMIB

### Powder for I.V. infusion 10 mg, Kyprolis®, Amgen Australia Pty Ltd

#### 1 Purpose of Application

- 1.1 To request an amendment to the restriction for pomalidomide (sponsored by Celgene Pty Limited) to allow the use of any proteasome inhibitor (bortezomib or carfilzomib) prior to treatment with pomalidomide.

#### 2 Requested listing

- 2.1 The proposed changes to the pomalidomide listing are presented below with additions in italics and strikethrough for deletions.

Name, restriction, manner of administration, form	Maximum quantity (packs)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
POMALIDOMIDE				
pomalidomide 3 mg capsule, 21	1	0	\$10,500.00 (published)	Pomalyst®
pomalidomide 4 mg capsule, 21	1	0	\$10,547.29 (published)	Celgene Pty Ltd

<b>PBS Indication:</b>	Multiple myeloma
<b>Treatment phase:</b>	Initial
<b>Clinical criteria:</b>	<p>Clinical criteria:</p> <ul style="list-style-type: none"> <li>• The treatment must be in combination with dexamethasone, AND</li> <li>• Patient must have undergone or be ineligible for a primary stem cell transplant, AND</li> <li>• Patient must have experienced treatment failure with lenalidomide, unless contraindicated or not tolerated according to the Therapeutic Goods Administration (TGA) approved Product Information, AND</li> <li>• Patient must have experienced treatment failure with <del>bortezomib</del> a proteasome inhibitor (<i>bortezomib or carfilzomib</i>), unless contraindicated or not tolerated according to the Therapeutic Goods Administration (TGA) approved Product Information, AND</li> <li>• Patient must not be receiving concomitant PBS-subsidised bortezomib, carfilzomib or thalidomide or its analogues.</li> </ul>
<b>Prescriber instruction</b>	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. <i>Carfilzomib treatment failure is progressive disease during treatment or within 6 months of discontinuing treatment with lenalidomide.</i>

For more detail on PBAC’s view, see section 5 PBAC outcome.

### 3 Background

- 3.1 At the multiple myeloma stakeholder meeting in May 2018, clinicians raised concerns about the lack of flexibility in prescribing, particularly for being able to switch therapy from bortezomib to lenalidomide. In the relapsed and refractory setting it was raised that there were inconsistencies in prescribing requirements e.g. there are barriers to use of pomalidomide other than in patients who had failed lenalidomide and bortezomib, whereas carfilzomib can be used after 1 – 3 lines of prior therapy (Outcome statement – Multiple myeloma meeting 23 May 2018, p4).
- 3.2 When carfilzomib received a positive PBAC recommendation in July 2017, there was no flow-on change to the pomalidomide restriction to allow access after failure of carfilzomib. To access PBS funded pomalidomide patients are required to have failed both lenalidomide and bortezomib.

### 4 Requested change

#### *Sponsor hearing*

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

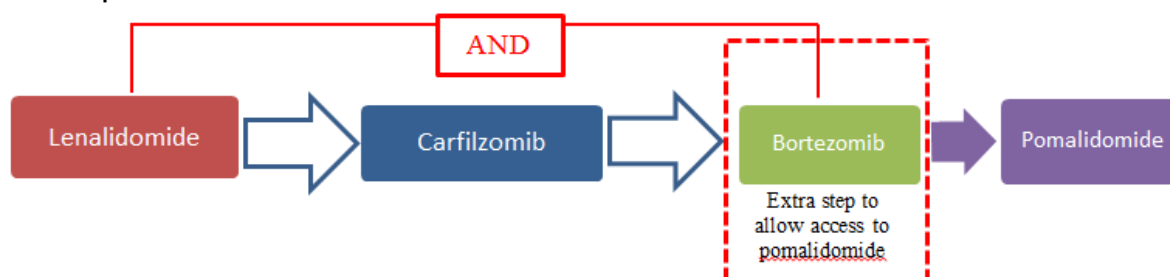
#### *Consumer comments*

- 4.2 The PBAC noted that no consumer comments were received for this item.

#### *Treatment algorithm*

- 4.3 This submission noted that patients who progress on carfilzomib and require subsequent pomalidomide may require an additional line of therapy with bortezomib if they have not received prior bortezomib, in order to access pomalidomide (see Figure 1). Alternatively, in some circumstances, patients may be given bortezomib rather than carfilzomib in order to allow subsequent access to pomalidomide.

Figure 1: Current treatment pathway in progressed multiple myeloma in patients receiving carfilzomib to allow access to pomalidomide

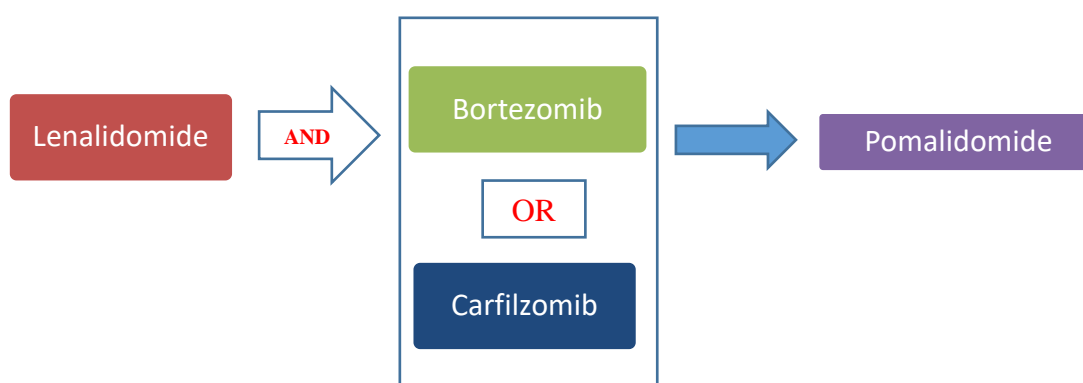


Note: Lenalidomide and carfilzomib can be use as 2<sup>nd</sup> (first relapse) or 3<sup>rd</sup> (second relapse) line and vice versa.  
Source: Figure 2, minor submission, p2.

- 4.4 The submission proposed a change to the wording of the listing of pomalidomide to

allow use after lenalidomide and any protease inhibitor (PI) i.e. either bortezomib or carfilzomib. The revised treatment algorithm is shown below in Figure 2. It was suggested this change to the PBS restriction would allow for optimal patient treatment, reducing the treatment burden patients and reducing the unnecessary cost incurred by the sub-optimal interim use of bortezomib in some patients. No estimates of the financial impact of the change were provided with the submission.

Figure 2: Proposed treatment pathway in progressed multiple myeloma to allow access to pomalidomide (changed listing criteria for pomalidomide)



Note: Lenalidomide, bortezomib and carfilzomib can be use as 2<sup>nd</sup> (first relapse) or 3<sup>rd</sup> (second relapse) line and vice versa.  
Source: Figure 3, minor submission, p2.

For more detail on PBAC’s view, see section 5 PBAC outcome.

### Clinical evidence

Table 1: Trials and associated reports presented in the resubmission

Trial ID/First Author	Protocol title/ Publication title	Publication citation
ENDEAVOR	Dimopoulos MA, Moreau P, Palumbo A, et al. Goldschmidt H, Niesvizky R, et al. Carfilzomib or bortezomib in relapsed or refractory multiple myeloma (ENDEAVOR): an interim overall survival analysis of an open-label, randomised, phase 3 trial.	<i>Lancet Oncol</i> 2017; 18:1327–37.
	Dimopoulos MA, Moreau P, Palumbo A, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study.	<i>Lancet Oncol</i> 2016; 17:27–38.
Tomer et al (2013)	Tomer MM, Allan JN, Boyer A, Rossi AC, et al. Sequence Impact Of Pomalidomide and Carfilzomib On Treatment Response In Relapsed Multiple Myeloma.	<i>Blood</i> 2013;122:1954-.

Source: references in minor submission, p4.

4.5 The ENDEAVOR trial was presented as the pivotal trial evidence in the July 2017 PBAC submission. In the minor submission, the data from the ENDEAVOR study was used to show that approximately 16% of patients previously on carfilzomib were subsequently treated with pomalidomide (24% of bortezomib patients were subsequently treated

with pomalidomide) thereby supporting the use of pomalidomide post carfilzomib. The PBAC did not consider that these data, which demonstrated use in patients progressing on the trial, established either the need or the efficacy of pomalidomide treatment immediately following carfilzomib.

- 4.6 This minor submission also presented results from a study by Tomar et al, 2013 (note, this study has not previously been presented to PBAC and was not evaluated for this minor submission). Tomar examined the safety and efficacy in a subset of patients who had received carfilzomib prior to a pomalidomide based regimen (clarithromycin, pomalidomide and dexamethasone [ClAPD]) (CP) compared to a subgroup of patients who received carfilzomib after pomalidomide (ClAPD) (PC). Patients were heavily pre-treated. Both regimens appear to have equally effective response regardless of sequence in salvage chemotherapy (see Table 2). The use of carfilzomib after pomalidomide is not reflective of the usual treatment pathway of PBS patients.

**Table 2: Results showing that pomalidomide is effective after patients have progressed on carfilzomib (Tomar et al, 2013)**

	CP (n=14)		PC (n=20)	
	% response to Cfz	% response to Pom	% response to Pom	% response to Cfz
CR	0	0	5	0
VGPR	7	14	10	0
PR	64	28	45	40
SD	14	28	25	40
PD	14	28	15	20
ORR	71	42	6	40
≥VGPR	7	14	15	0

Abbreviations: Cfz = carfilzomib; Pom = pomalidomide; CR – complete response; VGPR = very good partial response; PR = partial response; stable disease; PR = progressive disease; ORR = overall response rate; ≥VGPR.

Source: Table 3, minor submission, p4

For more detail on PBAC’s view, see section 5 PBAC outcome.

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

- 4.7 No financial estimates of the proposed restriction change were provided. However, the minor submission claimed the current pathway requires a subgroup of patients who receive carfilzomib to have an additional treatment step i.e. receive bortezomib, in order to progress to pomalidomide. By reducing this unnecessary step, the proposed listing would reduce cost to the PBS. In addition, removing this step would also reduce the peripheral neuropathy burden associated with bortezomib.

For more detail on PBAC’s view, see section 5 PBAC outcome.

## **5 PBAC Outcome**

- 5.1 The PBAC decided not to recommend a change to the pomalidomide restriction to enable access to pomalidomide after use of carfilzomib, rather than bortezomib, specifically. The PBAC considered that while there is merit in the request, the deficiencies in stakeholder consultation, evidence evaluation and cost assessment preclude a positive recommendation.
- 5.2 The PBAC considered the data from the ENDEVOUR trial showing use of pomalidomide

after carfilzomib in approximately 16% of patients did not establish the need or efficacy of this sequence of treatments. Also, the Tomar et al study was a small, unevaluated trial and the subgroup analysis did not provide data on durability of responses. The PBAC considered it was unclear from the evidence presented whether the responses to pomalidomide immediately following carfilzomib were statistically or clinically meaningful.

- 5.3 The PBAC noted the submission's concern that the current treatment algorithm may require patients who progress on carfilzomib and require subsequent pomalidomide to be treated with an additional line of therapy with bortezomib, if they have not received prior bortezomib, in order to access pomalidomide. The PBAC considered bortezomib was unlikely to be effective after failure of carfilzomib, although it may still be effective in patients who cease carfilzomib due to toxicity.
- 5.4 The proposed restriction change may improve the chances that clinicians would choose carfilzomib over bortezomib in the second-line setting post lenalidomide. However, the PBAC considered there may be unintended consequences, such as inappropriately requiring carfilzomib before pomalidomide if patients are intolerant to bortezomib, or accepting, as proposed in the restriction, that patients naïve to bortezomib and intolerant to carfilzomib could access pomalidomide. The PBAC noted that the original pomalidomide recommendation was based on modest activity in patients whose myeloma was refractory to both lenalidomide and bortezomib, and the tight restriction reflected this evidence and the high incremental cost effectiveness of the pomalidomide listing.
- 5.5 The PBAC noted the proposed change to the pomalidomide restriction was not supported by trial evidence, and there is a risk of loss of cost-effectiveness for pomalidomide use. The PBAC also noted that no costings were provided for the change to the pomalidomide restriction.
- 5.6 The PBAC considered another deficiency of the submission was the lack of evidence for there being a major need for this change from the patient or clinical community.
- 5.7 The PBAC noted the request for change was not from the sponsor of pomalidomide, and that any such change would require consultation with the sponsor.
- 5.8 The PBAC noted that this submission is not eligible for an Independent Review.

**Outcome:**

Rejected

## **6 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.

**7 Sponsor's Comment**

The sponsor had no comment.