

6.08 CARFILZOMIB, Powder for injection 10 mg, 30 mg and 60 mg, Kyprolis[®], Amgen Australia Pty Limited

1 Purpose of Application

- 1.1 The minor submission requested the addition of a 70 mg/m² once weekly (70 QW) dosing regimen to the current 56 mg/m² twice weekly (56 BIW) dosing regimen for carfilzomib for use in combination with dexamethasone (Cd) in patients with relapsed or refractory multiple myeloma (RRMM).
- 1.2 The minor submission also requested a change in the restriction level of the carfilzomib PBS listings for both initial and continuing treatment of RRMM from Authority Required (Telephone) to Authority Required (STREAMLINED).

2 Background

Registration status

- 2.1 Carfilzomib was initially TGA registered on 19 December 2016, as dual therapy in combination with dexamethasone or triple therapy in combination with lenalidomide and dexamethasone for the treatment of patients with RRMM who have received at least one prior therapy.
- 2.2 Cd70 QW was approved by the TGA on 16 October 2019. Amendments were made to the dose and method of administration section of the approved Product Information (PI) so that carfilzomib could be administered either once or twice weekly based on the selected regimen (p1, PI).

Previous PBAC consideration

- 2.3 At its July 2017 meeting, the PBAC recommended the Section 100 Authority Required (Telephone) listing of Cd56 BIW in patients with RRMM, and it was PBS listed for MM patients whose disease has relapsed or progressed after at least one prior therapy on 1 January 2018.

For more detail on PBAC's view, see section 6 PBAC outcome.

3 Requested listing

- 3.1 The minor submission requested the following changes to the existing carfilzomib listings:
 - an increase in the maximum amount allowed from 120 mg to 160 mg for both initial and continuing treatment.

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- a change in the restriction level from Authority Required (Telephone) to Authority Required (STREAMLINED) for all carfilzomib PBS listings.

3.2 An abridged version of the requested listings are provided below. Suggestions and additions proposed by the Secretariat are in italics and deletions in strikethrough.

Name, Restriction, Manner of administration and form	PBS item code	Max. amount	No of Rpts	DPMA	Proprietary Name and Manufacturer	
CARFILZOMIB carfilzomib 10 mg injection, 1 vial carfilzomib 30 mg injection, 1 vial carfilzomib 60 mg injection, 1 vial	41229B <i>New listing (Public hospital)</i>	160 mg	478	\$3,468.95	Kyprolis®	Amgen Australia Pty Limited
CARFILZOMIB carfilzomib 10 mg injection, 1 vial carfilzomib 30 mg injection, 1 vial carfilzomib 60 mg injection, 1 vial	41230C <i>New listing (Private hospital)</i>	160 mg	478	\$3,556.09	Kyprolis®	Amgen Australia Pty Limited
Restriction Level / Method:	Authority Required – Streamlined					

- 3.3 The dose of carfilzomib is calculated using the patient’s baseline body surface area (BSA) (p2, PI). Patients with a body surface area > 2.2 m² should receive a dose based upon a body surface area of 2.2 m², resulting in a maximum dose of 154 mg (70 mg x 2.2). Therefore, the submission requested a maximum amount of 160 mg for once weekly treatment. The proposed dispensed price for maximum amount (DPMA) for the requested PBS listings was based on the current ex-manufacturer price per vial.
- 3.4 The submission requested a maximum of 17 repeats for QW treatment, which would provide up to 6 cycles of treatment at 70 mg/m² QW. This is inconsistent with the clinical criteria of ‘Patient must not receive more than 3 cycles of treatment’ under both the current initial and continuing treatment restrictions for carfilzomib. It was also noted during the evaluation that patients are required to be assessed every 3 cycles to ensure that they still qualify for the PBS subsidised treatment with carfilzomib. Therefore, the number of repeats should be reduced.
- 3.5 The pre-PBAC response agreed that Cd70 QW should be new listings on the PBS to help prevent administration of the incorrect dose and improve patient medication management.
- 3.6 The minor submission requested that the authority level for carfilzomib be amended from Authority Required (Telephone) to Authority Required (STREAMLINED) to align with the current authority level for bortezomib. The submission stated it is likely that this would reduce the administrative burden for clinicians and would have no impact on the uptake of carfilzomib. The table below shows the current authority requirements for RRMM treatment.

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Table 1: Current authority requirements for bortezomib, carfilzomib and lenalidomide

	Newly diagnosed MM		Relapsed or refractory MM	
	Initial	Continuing	Initial	Continuing
Bortezomib	Authority Required (STREAMLINED)	Authority Required (STREAMLINED)	Authority Required (STREAMLINED)	Authority Required (STREAMLINED)
Lenalidomide	Authority Required (Written)	Authority Required (Telephone)	Authority Required (Written)	Authority Required (Telephone)
Carfilzomib	-	-	Authority Required (Telephone)	Authority Required (Telephone)

Source: Compiled during the evaluation

3.7 The following table shows PBAC’s previous considerations of the authority requirements for RRMM treatments.

Table 2: Previous PBAC considerations regarding the authority levels for the treatment of MM

Meeting	Recommendation
Carfilzomib PBAC Meeting July 2017	The PBAC recommended the listing of carfilzomib for the treatment of RRMM. The PBAC advised that a telephone authority, rather than a written authority, was appropriate as patients will have already demonstrated that they have multiple myeloma when they received first-line therapy (paragraph 7.10, Carfilzomib PSD, July 2017). The PBAC also noted that there remained a risk of greater than expected utilisation due to greater than expected patient numbers, and of use outside the restriction. Although this use would potentially be clinically appropriate, the cost-effectiveness was unknown. Therefore, the PBAC considered that this would need to be addressed through risk sharing arrangements (paragraph 7.9, carfilzomib PSD, July 2017).
Bortezomib PBAC Meeting March 2018	PBAC supported a streamlined authority listing for bortezomib. The PBAC considered this change in the authority level should be subject to monitoring of use for inappropriate increases in use outside the restrictions (March 2018 PBAC Outcomes – Other matters).
Multiple Myeloma Stakeholder meeting May 2018	PBAC supported simplification of restrictions in the RRMM setting, noting any requested changes would need to be considered in the context of the effective PBS prices (p5, Multiple Myeloma Stakeholder meeting outcome statement).
Lenalidomide PBAC Meeting March 2019	PBAC did not recommend a change to the restriction level of the existing PBS listings for lenalidomide for MM from Authority Required (Written) to Authority Required (STREAMLINED) to align with the authority level for bortezomib. The PBAC considered the proposed increase to the rebate for newly diagnosed symptomatic MM did not sufficiently address the risk of use outside the current PBS indications with a relaxing of the authority level for prescribing and any future proposed price reduction should be based on actual expenditure and consider combined caps across indications” (paragraph 4.4, item 6.13 lenalidomide PSD, March 2019).

3.8 The PBAC recalled its previous advice supporting the simplification of restrictions in the relapsed and refractory setting of MM, noting any requested changes to listings would need to be considered in the context of the effective PBS prices (p5, Multiple Myeloma Stakeholder meeting outcome statement, May 2018). The PBAC considered the submission’s request to lower the authority type to Streamlined and the potential risks around greater than expected utilisation and use outside of the restriction could be managed by the risk sharing arrangements (RSA) currently in place for carfilzomib.

For more detail on PBAC’s view, see section 6 PBAC outcome.

4 Comparator

- 4.1 The minor submission nominated Cd56 BIW as the main comparator. The PBAC considered this was appropriate as the Cd56 BIW dosing regimen would most likely be replaced by the Cd70 QW dosing regimen should it be listed on the PBS.

For more detail on PBAC's view, see section 6 PBAC outcome.

5 Consideration of the evidence

Sponsor hearing

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

Consumer comments

- 5.2 The PBAC noted and welcomed the input from individuals (37) and organisations (3) via the Consumer Comments facility on the PBS website. The comments were supportive of the addition of the once weekly dosing regimen because it would provide flexibility in dosing and fewer hospital visits. The comments also highlighted that treatment with carfilzomib improved quality of life. The comments also noted that patients wanted more treatment options for this debilitating condition.
- 5.3 The PBAC noted the correspondence received from Myeloma Australia, Leukaemia Foundation and South-East Myeloma Support Group, which also included patient input that the organisations had received. These organisations were supportive of having the additional once weekly dosing regimen for carfilzomib because it would allow clinicians to switch between the two dosing regimens based on patient needs, as well as reduce the burden on patients and their carers. The organisations also noted that there is a clinical need for more treatment options for MM as it becomes progressively harder to treat after each relapse as patients become refractory to different treatments.

Clinical trials

- 5.4 The minor submission was based on a naïve indirect comparison of three studies given no direct comparison between Cd70 QW and Cd56 BIW was available:
- ARROW: a randomised, phase 3, open-label, multicentre study comparing Cd70 QW to Cd27 BIW in adult patients with RRMM who received two to three prior lines of treatment, which provides the pivotal clinical evidence for Cd70 QW.
 - CHAMPION-1: a phase 1/2, single-arm dose escalation study, which provides supporting evidence for Cd70 QW.
 - ENDEAVOR: a randomised, phase 3 study comparing the cost-effectiveness of Cd to Bd in RRMM patients with 1-3 prior lines of treatment, which was

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previously considered by the PBAC as the pivotal evidence for Cd56 BIW (carfilzomib Public Summary Document (PSD), July 2017).

5.5 Details of the trials presented in the submission are provided in the table below.

Table 3: Trials presented in the submission

	ARROW	CHAMPION-1	ENDEAVOR
Number of subjects	478	118	929
Design	Phase 3 Randomised 1:1 active-controlled study	Phase 1/2 Single-group, dose escalation and dose-expansion study	Phase 3 Randomised 1:1 active-controlled study
Carfilzomib dosing regimen	Cd 70/20 mg/m ² once weekly	Cd 70/20 mg/m ² once weekly	Cd 56/20 mg/m ² twice weekly
Comparator dosing regimen	Cd 27/20 mg/m ² twice weekly	None	Bd 1.3 mg/m ² twice weekly
Patient population	RRMM	RRMM	RRMM
Prior treatment	2-3 lines	1-3 lines	1-3 lines
Geographic regions	Asia-Pacific, Europe and North America	United States	Asia-Pacific, Brazil, Europe, Israel, and North America

Abbreviation: Cd: carfilzomib with dexamethasone; Bd: bortezomib with dexamethasone; RRMM: relapsed and refractory multiple myeloma
 Note: CHAMPION-1 is a bridge study between ARROW and ENDEAVOR as CHAMPION-1 evaluated the same dose regimen as ARROW and a similar patient population as ENDEAVOR. All studies were open-label. All have a completed final analysis Clinical Study Report (CSR) however, ARROW and CHAMPION-1 studies have patients still on treatment or in long-term follow-up.

Clinical claim

5.6 The minor submission claimed that based on the evidence presented, Cd70 QW is non-inferior to Cd56 BIW in terms of efficacy and safety.

5.7 The TGA Clinical Evaluator Report noted Cd70 QW was associated with similar toxicity to that observed with Cd56 BIW. It was also associated with superior efficacy. The new regimen therefore has a favourable benefit-risk balance compared to the low dose regimen.

Economic analysis

5.8 The minor submission presented a cost-minimisation analysis (CMA) of Cd70 QW compared to Cd56 BIW.

5.9 The minor submission estimated the equi-effective doses (cumulative) as 4969 mg for Cd70 QW and 7278 mg for Cd56 BIW based on the time on treatment until progression of disease in adults with RRMM who received 2-3 prior lines of treatment from ARROW and ENDEAVOR.

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Table 4: Summary of equi-effective doses (with wastage)

	Cd70 weekly (ARROW)	Cd56 twice-weekly (ENDEAVOR)
Average no. of infusions per patient	40 (1 x 20 mg/m ² ; 39 x 70 mg/m ²)	74 (2 x 20 mg/m ² ; 72 x 56 mg/m ²)
Average dose (mg) per infusion, with wastage	126.4	100.0
Cumulative mg per patient	4969	7278
Therapeutic relativity: (Weekly Cd70: twice-weekly Cd56)	1:1.465	

Source: Table 3.2-1 of minor submission based on trial-based vial usage analysis

5.10 The minor submission proposed reducing the current special pricing arrangement (SPA) rebate for carfilzomib from █% to █%. The results of the stepped CMA, with the █% rebate applied in step 6, are presented in the table below.

Table 5: Results of the stepped CMA

Step	Description of step	No. of infusions [mg] Total cost ^{ab} (\$/patient) Cd56 BIW	No. of infusions [mg] Total cost (\$/patient) Cd70 QW	Cost saving (\$/patient)
1 ^a	Per-protocol (the standard treatment protocol) use of carfilzomib, with no wastage, at the current rebate of █%	20 mg/m ² x 2 infusions [20 x 1.8 ^c x 2 = 72 mg] 56 mg/m ² x 78 infusions [56 x 1.8 x 78 = 7862.40 mg] \$ █	20 mg/m ² x 1 infusion [20 x 1.8 x 1 = 36 mg] 70 mg/m ² x 39 infusions [70 x 1.8 x 39 = 4914 mg] \$ █	█
2	Per-protocol use of carfilzomib, with wastage (as step 1, accounting for wastage)	20 mg/m ² x 2 infusions [40 x 2 = 80 mg] 56 mg/m ² x 78 infusions [110 x 78 = 8580 mg] \$ █	20 mg/m ² x 1 infusion [40 x 1 = 40 mg] 70 mg/m ² x 39 infusions [130 x 39 = 5070 mg] \$ █	█
3	Trial-based vial usage, with wastage (as step 1, trial-based vial usage accounting for wastage)	20 mg/m ² x 2 infusions [40.6 x 2 = 81.24 mg] 56 mg/m ² x 78 infusions [100 x 78 = 7800 mg] \$ █	20 mg/m ² x 1 infusion [40.6 x 1 = 40.6 mg] 70 mg/m ² x 39 infusions [126.4 x 39 = 4929.6 mg] \$ █	█
4	Number of carfilzomib infusions as in trials	20 mg/m ² x 2 infusions [40.6 x 2 = 81.24 mg] 56 mg/m ² x 72 infusions [100 x 72 = 7200 mg] \$ █	20 mg/m ² x 1 infusion [40.6 x 1 = 40.6 mg] 70 mg/m ² x 39 infusions [126.4 x 39 = 4929.6 mg] \$ █	█
5	Proportion of Cd70 QW patients changed from 100% to █%	20 mg/m ² x 2 infusions [40.6 x 2 = 81.24 mg] 56 mg/m ² x 72 infusions [100 x 72 = 7200 mg] \$ █ (current – 100% patients using Cd56 BIW)	20 mg/m ² x 1 infusion [40.6 x 1 = 40.6 mg] 70 mg/m ² x 39 infusions [126.4 x 39 = 4929.6 mg] at uptake rate of █% \$ █ (█% patients using Cd56 BIW and █% Cd70 QW)	█

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			$\% \times \$78,908.03 + \% \times$	
6	New proposed rebate of $\%$ for price of carfilzomib (BASE CASE)	\$	\$	-\$
7	Infusion cost ^d (MBS 13915)	74 infusions x \$66.10 x $\%$ = \$	40 infusions x \$66.10 x $\%$ = \$	\$1348.44 - \$ = \$

Source: compiled by the Secretariat based on Table 3.4-1 and Table 3.4-2, p79, 83 of the submission.

^a total cost was calculated using the published ex-manufacturer price of \$634.48 for carfilzomib 30 mg vial and applicable fees and mark-ups under the Efficient Funding of Chemotherapy (EFC) initiative in the public and private hospital settings, which included the preparation fee (\$85.06) in the public and private settings, and the ready prepared dispensing fee (\$7.39), distribution fee (\$27.02), diluent fee (\$5.35) and mark ups at 1.4% of the drug cost in the private hospital setting only. The number of infusions for BIW was calculated as twice the number of weekly infusions.

^b the weightings across private (67.6%) and public (32.4%) hospital settings were based on calculations from the July 2017 PBAC meeting assuming that this ratio has unlikely changed markedly over time.

^c mean body surface area (BSA) for patients is 1.8 m² (base case value of a mean BSA in ARROW) that was used to calculate amount of carfilzomib for each infusion when patients are treated using the amount specified in the standard treatment protocol ('per-protocol' calculations).

^d Administration/infusion costs of \$66.10 based on MBS item 13915.

Note:

- i. Step 1 showed the cost saving if all patients use Cd70 QW at the current rebate of $\%$ assuming that the number of carfilzomib infusions for Cd56 BIW (2 infusions x 20 mg/m² + 78 infusions x 56 mg/m²) is double that for Cd70 QW (40 infusions x 70 mg/m²).
- ii. Step 2 changed the dispensing assumption for carfilzomib to be per-protocol with wastage taking account that carfilzomib dispensing requires a whole number of vials).
- iii. Step 3 changed the dispensing assumption for carfilzomib to be as in the ARROW and ENDEAVOR trials, taking account of wastage (dispensing of whole vials).
- iv. Step 4 changed the number of carfilzomib infusions from being in a 2:1 ratio to being that observed in ENDEAVOR compared with ARROW.
- v. Step 5 changed the proportion of patients who would switch to Cd70 QW if it were available from all patients to $\%$ of patients.
- vi. Step 6 applied the proposed rebate of $\%$ in the submission. This is the base case for the cost-minimisation.
- vii. Step 7 showed the effect of the cost offset for the reduced number of infusions of carfilzomib.

5.11 The submission considered that the average cost per patient at the equi-effective doses for each dosing regimen would likely be cost-neutral when the proposed rebate of $\%$ and the assumption of $\%$ uptake for Cd70 QW are applied. The CMA estimated a net saving of \$ per patient to the Government taking into account the cost offsets for the reduced number of infusions (MBS item 13915) for Cd70 QW, but these cost savings were not incorporated to calculate the base case in the CMA. The submission also considered that the use of Cd70 QW would be higher than $\%$ in which case the revised effective price would likely result in a cost saving.

5.12 The minor submission claimed the revised SPA rebate of $\%$ is the cost-neutral price based on a CMA comparing Cd70 QW to Cd56 BIW. The submission claimed that at a rebate of $\%$ the life-time per patient cost of treatment with Cd70 QW equalled the life-time per patient cost of treatment with Cd56 BIW at the current rebate of $\%$. As a result, the revised rebate of $\%$ reflected the weighted average rebate for Cd70 QW and Cd56 BIW on the assumption that $\%$ of patients would use Cd70 QW (i.e. $\% \times \% + \% \times \%$). The evaluation noted the calculation was reliant on an uncertain uptake rate with no evidentiary basis, given the extent of use for the once weekly dosing regimen was not known. The submission's proposal for a weighted rebate across carfilzomib use for both dosing regimens resulted in an

increase to the effective price of carfilzomib and required that there is at least ■% uptake of Cd70 QW for the effective price increase to be cost-neutral. The pre-PBAC response (p1) presented an alternative approach and proposed that the different rebates of ■% and ■% be applied to the Cd56 BIW and Cd70 QW listings respectively to mitigate the uncertainty around the estimated uptake of Cd70 QW.

Estimated PBS usage & financial implications

- 5.13 The minor submission estimated that the new dosing regimen will result in a cost saving to the PBS/RPBS of \$0 to < \$10 million in Year 6 of listing, with a total net saving to the PBS/RPBS of approximately \$10 million to < \$20 million over the first 6 years of listing at effective prices, excluding the MBS costs.
- 5.14 The estimated utilisation and financial impact of the addition of Cd70 QW are summarised in the table below.

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Table 6: Estimated use and financial implications

	2021	2022	2023	2024	2025	2026
Estimated extent of use						
Number of patients treated ^a						
Estimated financial implications of Cd56 BIW (100%) (current situation)						
Number of services ^b						
Cost to PBS/RPBS less copayments ^c (published prices)	\$	\$	\$	\$	\$	\$
Cost to PBS/RPBS less copayments ^c (effective prices)	\$	\$	\$	\$	\$	\$
Estimated financial implications for Cd56 BIW (% uptake) and Cd70 QW (% uptake)						
Number of services ^d						
Cost to PBS/RPBS less copayments ^e (published prices)	\$	\$	\$	\$	\$	\$
Cost to PBS/RPBS less copayments ^e (effective prices)	\$	\$	\$	\$	\$	\$
Net financial implications						
Net cost to PBS/RPBS (published prices)	-\$	-\$	-\$	-\$	-\$	-\$
Net cost to PBS/RPBS (effective prices)	-\$	-\$	-\$	-\$	-\$ 587,878	-\$
Net cost to MBS ^f	-\$	-\$	-\$	-\$	-\$	-\$
Net cost to Government (effective prices)	-\$	-\$	-\$	-\$	-\$	-\$

Source: compiled by the Secretariat; Table 4.2-1, Table 4.2-3, Table 4.2-4, Table 4.2-6, Table 4.2-7, Table 4.2-8, Table 4.2-12, Table 4.4-1, Table 4.5-2, Table 4.5-3 (pp86-89, 91 and 94-95 of the submission).

^a Patient numbers were estimated in the July 2017 PBAC meeting for Cd56 BIW until 2023, and the submission estimated thereafter assuming 2% growth to be consistent with population growth.

^b Assuming an average of 56 infusions per patient for Cd56 BIW per year

^c The average cost per infusion for Cd56 BIW using average dose per infusion of 102.19 mg at the current rebate of % were \$2,246.28, \$2,316.29 (published prices) and \$, \$ (effective prices) for public and private hospital settings respectively.

^d The number of infusions for Cd70 QW was calculated based on the ratio of 72:39 (1.85:1), which was estimated to be 30.3 (56/1.85). The average dose per infusion allowing for wastage were 126.4 mg and 102.19 mg for Cd70 QW and Cd56 BIW respectively.

^e The weighted average cost per infusion for Cd70 QW and Cd56 BIW using average dose per infusion of 126.4 mg and 102.19 mg at the proposed rebate of % were \$2,553.49, \$2,627.80 (published prices) and \$, \$ (effective prices) for public and private hospital settings respectively.

^f Administration/infusion costs of \$66.10 based on MBS item 13915.

The redacted table shows that at Year 6, the estimated number of patients was 500 to < 5,000 and there would be a net cost saving for the PBS/RPBS.

5.15 The estimated number of patients was based on the patient numbers previously considered by the PBAC in the July 2017 meeting for the listing of Cd56 BIW for RRMM and formed the basis of the current Risk Sharing Arrangement (RSA). The patient numbers were based on PBS sample data (2014 -15) and estimated up to 2023. The estimated number of patients from 2024 were extrapolated from the number of PBS items processed between January 2018 to November 2019 for item codes 11229B and 11230C, assuming a growth rate of 2% per year given that the carfilzomib PBS market

was stable. The growth rate was considered to be reasonable given the absence of more mature data for the current listings and the current early trend towards a plateau in use.

- 5.16 The minor submission assumed that the number of patients initiating on carfilzomib and time on treatment were not expected to be impacted by the requested changes in the PBS restrictions, and ■% of these patients would use Cd70 QW in Year 1 increasing to ■% by Year 6 given that uptake of Cd70 QW is expected to be high and rapid.

Financial management - Risk Sharing Arrangements

- 5.17 There is currently an RSA in place for carfilzomib for the treatment of RRMM. The submission noted that the first full year of implementation for the requested changes would be in 2021, when carfilzomib will be in the fourth year of the current Deed.
- 5.18 The financial estimates under a revised scenario where Cd70 QW is available were compared to the current scenario (Cd56 BIW only) based on the agreed expenditure caps to assess the impact of the use of the 70 mg/m² QW dosing regimen. The minor submission noted the revised financial estimates for Cd70 QW were below the expenditure caps of \$■■■■ and \$■■■■ under the current Deed of Agreement for 2021 and 2022, respectively.
- 5.19 As a minor submission, the clinical evidence, economic analysis and financial estimates were not independently evaluated.

For more detail on PBAC's view, see section 6 PBAC outcome.

6 PBAC Outcome

- 6.1 The PBAC recommended the addition of the 70 mg/m² once weekly (70 QW) dosing regimen to the existing 56 mg/m² twice weekly (56 BIW) dosing regimen where carfilzomib is used in combination with dexamethasone (Cd) for the treatment of patients with RRMM. The PBAC considered that the Cd 70 QW is likely to be comparable to that of Cd56 BIW for RRMM on the basis of effectiveness and safety.
- 6.2 The PBAC recommended a new Section 100 (Efficient Funding of Chemotherapy) listing of carfilzomib to allow for once weekly dosing. Additionally, the PBAC made the following recommendations for the requested listing:
- The requested maximum amount of 160 mg for once weekly treatment was appropriate as it would provide sufficient amount for treatment.
 - The requested maximum repeats should be reduced to 8 to restrict the use of carfilzomib up to 3 cycles. This is consistent with the current clinical criteria of 'Patient must not receive more than 3 cycles of treatment' under both the initial and continuing treatment restrictions for carfilzomib.

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- No flow-on restriction changes would be required for the current listings of dexamethasone for a 40 mg once weekly dosing regimen, given that the maximum quantity of 5 vials for the 8 mg/2 mL injection would provide 40 mg of dexamethasone under the unrestricted PBS benefit.
- 6.3 The PBAC considered it would be appropriate to lower the restriction authority type from Authority Required (Telephone) to Authority Required (STREAMLINED) for all carfilzomib PBS listings in both initial and continuing treatment of RRMM. The PBAC considered this would help simplify RRMM restrictions and improve access to MM treatment, consistent with its recommendations at the Multiple Myeloma Stakeholder meeting in May 2018. The PBAC noted its previous concern regarding the risk of leakage outside the restriction, however considered that any financial cost to Government that may result from this change would be managed by the current risk sharing arrangement (RSA) for carfilzomib.
- 6.4 The PBAC considered Cd56 BIW to be the appropriate comparator as nominated in the submission.
- 6.5 The PBAC noted the minor submission presented a naïve indirect comparison of three clinical trials (ARROW, CHAMPION-1, and ENDEAVOR) in RRMM patients with 1-3 prior lines of treatment (except ARROW where the patient cohort received 2 to 3 prior lines of treatment) in the absence of clinical data comparing Cd70 QW to Cd56 BIW. The PBAC considered that, based on the available evidence, the effectiveness and safety of the 70 mg/m² QW dosing regimen is likely to be comparable to that of the 56 mg/m² BIW dosing regimen when used with dexamethasone for RRMM.
- 6.6 The PBAC considered the cost minimisation analysis should be based on the equi-effective doses (cumulative) of 4969 mg for Cd70 QW and 7278 mg for Cd56 BIW.
- 6.7 The PBAC accepted the weighted average rebate of ■% proposed in the submission to be applied across all carfilzomib listings. The PBAC considered that there may be some cost savings to the Government associated with the addition of Cd70 QW at the break-even weighted average price for carfilzomib due to reduced administration and dispensing fees from fewer scripts dispensed for Cd70 QW compared to Cd56 BIW. However, the magnitude of these savings is uncertain given that costs are sensitive to the uptake of Cd70 QW. The PBAC advised that the impact of this uncertainty could also be minimised by the current RSA for carfilzomib.
- 6.8 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because the carfilzomib once weekly dosing regimen is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over the carfilzomib twice weekly dosing regimen, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by *the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met.

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6.9 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

7 Recommended listing

7.1 Add new item:

Name, Restriction, Manner of administration and form	PBS item code	Max. amount	No of Rpts	Proprietary Name and Manufacturer	
CARFILZOMIB carfilzomib 10 mg injection, 1 vial carfilzomib 30 mg injection, 1 vial carfilzomib 60 mg injection, 1 vial	New (Public) New (Private)	160 mg	8	Kyprolis®	Amgen Australia Pty Limited
Concept ID (for internal Dept. use)	Category / Program: Section 100 – Efficient Funding of Chemotherapy {public and private hospitals}				
	Restriction Type / Method: Authority Required – Streamlined (new code)				
[7906]	Indication: Multiple myeloma				
[NEW]	Treatment Phase: Initial treatment - once weekly treatment regimen				
[7908]	Clinical criteria:				
[7907]	The condition must be confirmed by a histological diagnosis				
	AND				
[12908]	Clinical criteria:				
[7911]	The treatment must be in combination with dexamethasone				
	AND				
[7914]	Clinical criteria:				
[7913]	Patient must have progressive disease after at least one prior therapy				
	AND				
[19705]	Clinical criteria:				
[19704]	Patient must have undergone or be ineligible for a stem cell transplant				
	AND				
[18135]	Clinical criteria:				
[18069]	Patient must not have previously received this drug for this condition				
	AND				
[21518]	Clinical criteria:				
[21540]	Patient must not be receiving concomitant PBS-subsidised bortezomib, thalidomide or its analogues				
	AND				
[21499]	Clinical criteria:				
[21498]	Patient must not receive more than three cycles of treatment under this restriction				
[7922]	Prescribing Instructions: Progressive disease is defined as at least 1 of the following: (a) at least a 25% increase and an absolute increase of at least 5 g per L in serum M protein (monoclonal protein); or (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 (c) in oligo-secretory and non-secretory myeloma patients only, at least a 50% increase in the difference between involved free light chain and uninvolved free light chain; or (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 (e) an increase in the size or number of lytic bone lesions (not including compression fractures); or				

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	(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 (g) development of hypercalcaemia (corrected serum calcium greater than 2.65 mmol per L not attributable to any other cause).
[7923]	Prescribing Instructions: Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M protein.
[7607]	Administrative Advice: No increase in the maximum number of repeats may be authorised.
[21501]	Administrative Advice: No increase in the maximum amount or number of units may be authorised.
[7608]	Administrative Advice: Special Pricing Arrangements apply.

Name, Restriction, Manner of administration and form	PBS item code	Max. amount	No of Rpts	Proprietary Name and Manufacturer	
CARFILZOMIB carfilzomib 10 mg injection, 1 vial carfilzomib 30 mg injection, 1 vial carfilzomib 60 mg injection, 1 vial	New (Public) New (Private)	160 mg	8	Kyprolis®	Amgen Australia Pty Limited
Concept ID (for internal Dept. use)	Category / Program: Section 100 – Efficient Funding of Chemotherapy {public and private hospitals}				
	Restriction Type / Method: Authority Required – Streamlined (new code)				
[7906]	Indication: Multiple myeloma				
[NEW]	Treatment Phase: Continuing treatment - once weekly treatment regimen				
[11365]	Clinical criteria:				
[11364]	Patient must have previously received PBS-subsidised treatment with this drug for this condition				
	AND				
[12908]	Clinical criteria:				
[7911]	The treatment must be in combination with dexamethasone				
	AND				
[21503]	Clinical criteria:				
[21502]	Patient must not develop disease progression while receiving treatment with this drug for this condition				
	AND				
[21518]	Clinical criteria:				
[21540]	Patient must not be receiving concomitant PBS-subsidised bortezomib, thalidomide or its analogues				
	AND				
[21505]	Clinical criteria:				
[21504]	Patient must not receive more than 3 cycles of treatment per continuing treatment course authorised under this restriction				
[7922]	Prescribing Instructions: Progressive disease is defined as at least 1 of the following: (a) at least a 25% increase and an absolute increase of at least 5 g per L in serum M protein (monoclonal protein); or (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 (c) in oligo-secretory and non-secretory myeloma patients only, at least a 50% increase in the difference between involved free light chain and uninvolved free light chain; or (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 (e) an increase in the size or number of lytic bone lesions (not including compression fractures); or (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 (g) development of hypercalcaemia (corrected serum calcium greater than 2.65 mmol per L not attributable to any other cause).				
[7923]	Prescribing Instructions:				

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	Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M protein.
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7.2 Amend the treatment phase criteria for the restrictions of the 56 mg/m² twice weekly dosing regimen.

Restriction Summary [7360] / Treatment of Concept: [7355]

Name, Restriction, Manner of administration and form	PBS item code	Max. amount	No of Rpts	Proprietary Name and Manufacturer	
CARFILZOMIB carfilzomib 10 mg injection, 1 vial carfilzomib 30 mg injection, 1 vial carfilzomib 60 mg injection, 1 vial	11229B (Public) 11230C (Private)	120 mg	17	Kyprolis®	Amgen Australia Pty Limited
Category / Program:	Section 100 – Efficient Funding of Chemotherapy {public and private hospitals}				
Restriction Type / Method:	Authority Required – Streamlined				
Indication:	Multiple myeloma				
Treatment Phase:	Initial treatment - <i>twice weekly treatment regimen</i>				

Restriction Summary [7356] / Treatment of Concept: [7348]

Name, Restriction, Manner of administration and form	PBS item code	Max. amount	No of Rpts	Proprietary Name and Manufacturer	
CARFILZOMIB carfilzomib 10 mg injection, 1 vial carfilzomib 30 mg injection, 1 vial carfilzomib 60 mg injection, 1 vial	11229B (Public) 11230C (Private)	120 mg	17	Kyprolis®	Amgen Australia Pty Limited
Category / Program:	Section 100 – Efficient Funding of Chemotherapy {public and private hospitals}				
Restriction Type / Method:	Authority Required – Streamlined				
Indication:	Multiple myeloma				
Treatment Phase:	Continuing treatment - <i>twice weekly treatment regimen</i>				

This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor’s Comment

Amgen are pleased that the current PBS listing for carfilzomib will be expanded to provide all eligible patients with relapsed refractory multiple myeloma the flexibility of once weekly or twice weekly dosing and the ability switch between these two regimens according to need.