

**7.05 ELOTUZUMAB,
Powder for I.V. infusion 300 mg
Powder for I.V. infusion 400 mg,
Empliciti®,
Bristol Myers Squibb Australia Pty Ltd**

1 Purpose of Application

- 1.1 The Category 3 resubmission sought a Section 100 (Efficient Funding of Chemotherapy) Authority Required (telephone/online) listing, in combination with lenalidomide and dexamethasone (ELd), for the treatment of relapsed or refractory multiple myeloma (RRMM).

Table 1: Key components of the clinical issue addressed by the resubmission (as stated in the resubmission)

Component	Description
Population	Patients with relapsed or refractory multiple myeloma (RRMM).
Intervention	Elotuzumab in combination with lenalidomide and dexamethasone (ELd), in 28 day cycles consisting of: <ul style="list-style-type: none"> • Elotuzumab: Cycles 1 and 2: 10 mg/kg IV on Days 1, 8, 15 and 22 Cycles 3+: 10 mg/kg IV on Days 1 and 15 • Lenalidomide: 25 mg orally once daily on Days 1 to 21 • Dexamethasone: Cycles 1 and 2: 28 mg orally and 8 mg IV on Days 1, 8, 15 and 22 Cycles 3+: 28 mg orally and 8 mg IV on Days 1 and 15 and 40 mg orally on Days 8 and 22
Comparator	Carfilzomib and dexamethasone (Cd), in 28 day cycles consisting of: <ul style="list-style-type: none"> • Carfilzomib: Cycle 1: 20 mg/m² IV on Days 1 and 2 and 56 mg/m² IV on Days 8, 9, 15, 16 Cycle 2+: 56 mg/m² IV on Days 1, 2, 8, 9, 15, 16 • Dexamethasone: 20 mg orally on Days 1, 2, 8, 9, 15, 16, 22 and 23
Outcomes	Overall survival (OS), progression free survival (PFS), objective response rate (ORR), safety
Clinical claim	In patients with RRMM, ELd is non-inferior in terms of comparative effectiveness and has a different, yet non-inferior, safety profile compared with Cd.

Source: Table 1.1.1 of the submission.

2 Background

Registration status

- 2.1 Elotuzumab was TGA registered on 22 September 2016 for the treatment of patients with multiple myeloma who have received at least one prior therapy, administered in combination with lenalidomide and dexamethasone.

Previous PBAC consideration

- 2.2 This was the second PBAC consideration.

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- 2.3 In November 2020, the PBAC did not recommend the listing of ELd for the treatment of patients with RRMM. The PBAC considered that, due to the nature of the indirect treatment comparison (ITC) and differences between the key trials, the results of the ITC were difficult to interpret and did not adequately demonstrate non-inferiority between ELd and the nominated comparator, carfilzomib plus dexamethasone (Cd), in terms of efficacy or safety. The PBAC therefore considered that the presentation of a cost minimisation analysis could not be supported at this stage.
- 2.4 The table below presents the issues identified by the PBAC during its consideration of elotuzumab in November 2020 and how the July 2021 resubmission addresses those issues.

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Table 1: Issues identified by the PBAC in November 2020 and how the issues are addressed in the July 2021 resubmission

	November 2020 submission	July 2021 resubmission
Treatment algorithm	The PBAC considered that ELd would potentially replace Ld and replace/displace Cd in the third-line setting (paragraph 7.3, Nov 2020 PSD).	Resubmission agreed.
Comparator	Cd was the nominated primary comparator. The PBAC, noting that Ld was the backbone of ELd and that the majority of patients eligible for Ld would also be eligible for ELd, considered that Ld and Cd were relevant comparators (paragraph 7.4, Nov 2020 PSD).	No change.
Clinical evidence	An ITC between ELd (ELOQUENT-2 trial) and Cd (ENDEAVOR trial).	No new evidence presented.
Clinical claim - efficacy	- ELd was non-inferior compared to Cd. The PBAC considered that the nature of the ITC, the differences between the trials and the lack of a nominated non-inferiority margin impacted on the reliability of the comparison. On the basis of these issues together with concerns regarding the equivalence of the comparator arms, the PBAC considered that the results did not adequately demonstrate non-inferiority between ELd and Cd in terms of efficacy (paragraph 7.11, Nov 2020 PSD).	No change.
Clinical claim - safety	- ELd had a different, but non-inferior, safety profile compared to Cd. The PBAC considered that non-inferiority between ELd and Cd in terms of safety was not adequately demonstrated (paragraph 7.13, Nov 2020 PSD).	No change.
Economic analysis	The submission presented a CMA between once cycle of ELd and one cycle of Cd. The PBAC considered that the CMA was not appropriate as the claims of non-inferior efficacy and safety were not supported. The PBAC noted that the uncertainties resulting from the indirect comparison also impacted on the appropriate inputs for the CMA (paragraph 7.14, Nov 2020 PSD).	A revised CMA was presented. See Table 3 for further detail.
Utilisation	The PBAC considered that the eligible patient population was likely underestimated as the submission assumed that ELd would substitute for Cd only. The PBAC considered that ELd would also likely substitute for Ld (paragraph 7.15, Nov 2020 PSD)	No change.
Financial impact	Although cost-minimised to Cd, the cost of listing ELd was estimated to be \$10 million to < \$20 million over the first 6 years. The CMA did not include the loading doses and associated costs of ELd in Cycles 1 and 2. The PBAC considered that the estimated financial impact was underestimated as (i) by assuming that the estimated treatment durations of ELd and Cd were equal (28.6 cycles), Cd use was likely overestimated; and (ii) the proposed substitution rate of ELd for Cd (22% in Year 6) was highly uncertain (paragraph 7.15, Nov 2020 PSD).	Revised estimates were presented with a cost saving of listing ELd of \$0 to < \$10 million over the first 6 years. Loading doses for ELd and dose titration for Cd were included. The resubmission applied a treatment duration of 12 cycles to both ELd and Cd. This may underestimate the treatment duration of ELd. The proposed substitution rate of ELd for Cd was unchanged.

AEMP = approved ex-manufacturer price; Cd = carfilzomib + dexamethasone; CMA = cost-minimisation analysis; DPMA = dispensed price for maximum amount; DPMQ = dispensed price for maximum quantity; ELd = elotuzumab + lenalidomide + dexamethasone; ESC =

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Economic Sub-Committee; ITC = indirect treatment comparison; Ld = lenalidomide + dexamethasone; PBAC = Pharmaceutical Benefits Advisory Committee; PSD = Public Summary Document; RRMM = relapsed and/or refractory multiple myeloma

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

3 Requested listing

3.1 The resubmission did not present further amendments to that proposed in November 2020.

3.2 Secretariat suggested July 2021 additions in *italics* and deletions in ~~strike through~~ to the sponsor’s proposed restriction are shown below.

MEDICINAL PRODUCT Medicinal product pack	Dispensed price for Max. Amount	PBS item code	Max. Amount	No. of Rpts
ELOTUZUMAB Injection	<p><u>Published:</u> Public: \$5,035.09 Private: \$5,144.15</p> <p><u>Effective:</u> Public: \$ [REDACTED] Private: \$ [REDACTED]</p>	NEW (Public) NEW (Private)	1,200 mg	15 (initial) 9 <i>(initial)</i>
Available brands				
Empliciti (elotuzumab 300 mg injection, 1 vial)				
Empliciti (elotuzumab 400 mg injection, 1 vial)				
Category/Program: Section 100 (Efficient Funding of Chemotherapy – Public/Private hospitals)				
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
Restriction type: <input checked="" type="checkbox"/> Authority Required – immediate/real-time assessment by Services Australia (telephone/online)				
Episodicity: N/A-Relapsed and/or refractory				
Severity: Patients must have received at least one prior therapy				
Condition: Multiple M myeloma				
PBS Indication: Relapsed <i>and/or</i> refractory multiple myeloma				
Treatment phase: Initial treatment				
Clinical criteria:				
The condition must be confirmed by a histological diagnosis,				
AND				
Clinical criteria:				
The treatment must be in combination with lenalidomide and dexamethasone,				
AND				
Clinical criteria:				
Patient must have progressive disease after at least one prior therapy,				
AND				
Clinical criteria:				
Patient must have undergone or be ineligible for a stem cell transplant,				
AND				
Clinical criteria:				
Patient must not be receiving concomitant PBS-subsidised <i>treatment with each of (i) bortezomib, (ii) carfilzomib, (iii) pomalidomide, or (iv) thalidomide</i>				
AND				
Clinical criteria:				
Patient must not receive more than six cycles of treatment under this restriction				
AND				
Clinical criteria:				

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Patient must not have previously received this drug for this condition
Definitions Prescriber 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).
Definitions Prescriber instructions: Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M protein.
Prescribing Instructions: Provide details of the histological diagnosis of multiple myeloma, prior treatments including name(s) of drug(s) and date of most recent treatment cycle; the basis of the diagnosis of progressive disease or failure to respond; and which disease activity parameters will be used to assess response once only through the Authority application for lenalidomide.
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Special Pricing Arrangements apply

MEDICINAL PRODUCT Medicinal product pack	Dispensed price for Max. Amount	PBS item code	Max. Amount	No. of Rpts
ELOTUZUMAB Injection	Published: Public: \$5,035.09 Private: \$5,144.15 Effective: Public: \$ Private: \$	NEW (Public) NEW (Private)	1,200 mg	11 (continuing) 5 (continuing)
Available brands				
Empliciti (elotuzumab 300 mg injection, 1 vial)				
Empliciti (elotuzumab 400 mg injection, 1 vial)				
Category/Program: Section 100 (Efficient Funding of Chemotherapy – Public/Private hospitals)				
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
Restriction type: <input checked="" type="checkbox"/> Authority Required – immediate/real-time assessment by Services Australia (telephone/online)				
Episodicity: N/A Relapsed and/or refractory				
Severity: Patients must have received at least one prior therapy				
Condition: Multiple M myeloma				
PBS Indication: Relapsed and/or refractory multiple myeloma				
Treatment phase: Continuing treatment				
Clinical criteria: Patient must have previously received PBS-subsidised treatment with an authority prescription for this drug for this condition,				
AND				
Clinical criteria: The treatment must be in combination with lenalidomide and dexamethasone,				
AND				
Clinical criteria: Patient must not have developed disease progression while receiving treatment with this drug for this condition,				

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AND
Clinical criteria:
Patient must not be receiving concomitant PBS-subsidised <i>treatment with each of (i) bortezomib, (ii) carfilzomib, (iii) pomalidomide, or (iv) thalidomide</i>
AND
Clinical criteria:
Patient must not receive more than six cycles of treatment per continuing treatment course authorised under this restriction
Prescriber instructions:
<i>Progressive disease is defined as at least 1 of the following:</i>
<i>(a) at least a 25% increase and an absolute increase of at least 5 g per L in serum M protein (monoclonal protein); or</i>
<i>(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</i>
<i>(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</i>
<i>(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</i>
<i>(e) an increase in the size or number of lytic bone lesions (not including compression fractures); or</i>
<i>(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</i>
<i>(g) development of hypercalcaemia (corrected serum calcium greater than 2.65 mmol per L not attributable to any other cause).</i>
Prescriber instructions:
<i>Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M protein.</i>
Administrative Advice:
<i>Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting the Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday)</i>
Administrative Advice: <i>No increase in the maximum number of repeats may be authorised.</i>
Administrative Advice: <i>Special Pricing Arrangements apply</i>

- 3.3 The proposed listing of elotuzumab aligned with the TGA indication, which requires use in combination with lenalidomide plus dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior line of therapy.
- 3.4 The maximum amount of elotuzumab, 1,200 mg, is consistent with the dosing (10 mg/kg) as per the approved Product Information and based on a 120 kg patient. The sponsor's proposed maximum repeat values of 15 (initial treatment) and 11 (continuing treatment) provide enough doses for 6 months treatment for both initial and continuing treatment. The comparator, carfilzomib, has a PBS listing that provides a maximum of 3 months therapy (3 x 28-day treatment cycles) in each of the initial and continuing treatment phases. Maximum repeat figures that would provide treatment cover for 3 months and/or cycles in each treatment phase: 9 repeats for initial treatment (= 10 doses in total to cover 8 doses over cycles 1-2, plus 2 doses to cover cycle 3); and 5 repeats for continuing treatment (= 6 doses in total to cover the 2 doses per cycle over 3 cycles) were therefore proposed by the Secretariat. The pre-PBAC response agreed that the number of repeats should provide no more than 3 months therapy (3 x 28 day treatment cycles).
- 3.5 The sponsor requested an immediate assessment type Authority Required listing for initial and continuing treatment. The PBAC considered this appropriate. The existing PBS listing for lenalidomide (in combination with dexamethasone) for the initial treatment of progressive disease is a written-only type Authority Required listing. To obtain the lenalidomide plus dexamethasone (Ld) portion of ELD on the PBS, separate

lenalidomide restrictions for use in combination with elotuzumab (see paragraph 6.12) would be required, as the existing lenalidomide listing in progressive disease is specific to use as dual therapy (see PBS item codes 5783J/9642L – 5mg capsules , 5784K/9643M – 10 mg capsules, 5785L/9644N – 15 mg capsules, 5786M/9645P – 25 mg capsules).

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

4 Comparator

- 4.1 The resubmission acknowledged that the RRMM treatment landscape was evolving with the PBS listing of daratumumab, in combination with bortezomib and dexamethasone (DBd), as a second-line treatment of MM. The resubmission noted that DBd uptake in the second-line setting will be high, displacing ELd and Cd to the third-line setting.
- 4.2 The resubmission again nominated Cd as the main comparator. In November 2020, the PBAC noted that as Ld was the backbone of ELd, the majority of patients who were considered eligible for Ld, i.e. those in whom retreatment with a lenalidomide-containing backbone is preferable compared to a proteasome inhibitor (e.g. those with pre-existing peripheral neuropathy or cardiac issues), would also likely be considered eligible for ELd.
- 4.3 The resubmission stated that the recent PBS listings of lenalidomide monotherapy (as maintenance treatment post autologous stem cell transplant (ASCT)) and of lenalidomide in combination with bortezomib and dexamethasone (as first-line treatment) would result in lenalidomide being used earlier in the treatment algorithm. Therefore, the resubmission stated that this would result in an increasing market share for Cd in the third and later line settings. The resubmission therefore considered that Cd was the most reasonable comparator and basis for the cost-minimisation analysis (CMA).
- 4.4 The PBAC again considered that Ld and Cd were relevant comparators, with ELd potentially replacing Ld and replacing/displacing Cd in the third-line setting.

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.

Consumer comments

- 5.2 The PBAC noted and welcomed the input from individuals (20) and organisations (4) via the Consumer Comments facility on the PBS website. The comments from individuals described the benefits of access to new treatment options and the impact

this has on quality of life.

- 5.3 The PBAC noted the advice received from (i) Myeloma Australia, (ii) Myeloma Australia’s Medical and Scientific Advisory Group (MSAG), (iii) the Leukaemia Foundation and (iv) Rare Cancers Australia which supported the submission for elotuzumab and the need for alternative treatments for MM patients.

Clinical claim

- 5.4 The resubmission did not present any additional efficacy or safety data.
- 5.5 The resubmission again claimed that ELd was non-inferior in terms of comparative effectiveness and has a different, yet non-inferior, safety profile compared to Cd.
- 5.6 The November 2020 submission presented an ITC between ELd (ELOQUENT-2 trial, ELd versus Ld) and Cd (ENDEAVOR trial, Cd versus bortezomib plus dexamethasone (Bd)), and assumed that the efficacy results of Ld and Bd were equivalent for the purposes of anchoring as a common comparator. Although the PBAC had previously considered Ld and Bd to be non-inferior (lenalidomide Public Summary Document (PSD), November 2008), it noted that in November 2016 it had stated that it may not be reasonable to assume non-inferior efficacy between Ld and Bd (paragraph 5.3, carfilzomib PSD, November 2016).

Table 2: Summary of results of the indirect comparison for PFS and OS, between ELOQUENT-2 and ENDEAVOR

	Median duration of follow-up	ELd or Cd n/N (%)	Ld or Bd n/N (%)	Absolute difference	HR ^c (95% CI)
PFS					
ELOQUENT-2 (29 Oct 2017) ^a ELd vs Ld	24.9 months	192/321 (59.8%)	231/325 (71.1%)	11.3%	0.68 (0.56, 0.83)
ENDEAVOR (3 March 2016) ^b Cd vs Bd	16.6 months	232/464 (50.0%)	288/465 (61.9%)	11.9%	0.55 (0.46, 0.65)
Indirect comparison ELd vs. Cd					1.236 (0.95, 1.61)
OS					
ELOQUENT-2 (29 Oct 2015) ELd vs Ld	38.7 months	136/321 (42.4%)	159/325 (48.9%)	6.5%	0.77 (0.61, 0.97)
ENDEAVOR (3 Jan 2017) Cd vs Bd	37.2 months	189/464 (40.7%)	209/465 (44.9%)	4.2%	0.79 (0.65, 0.96)
Indirect comparison ELd vs. Cd					0.975 (0.72, 1.32)

Source: Table 8, p16, Elotuzumab Public Summary Document (PSD, November 2020)

Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; CI = confidence interval; ELd = elotuzumab + lenalidomide + dexamethasone; HR = hazard ratio; IRC = independent review committee; ITT = intention to treat; Ld = lenalidomide + dexamethasone; n = number of participants reporting data; N = total participants in group; ORCA = Onyx Response Computational Assessment; OS = overall survival; PFS = progression free survival.

a. IRC assessed; ITT definition of PFS

b. ORCA generated; ITT population

c. Performed using the Bucher ITC method

- 5.7 In November 2020 the PBAC noted that the results of the ITC favoured Cd relative to ELd in terms of progression free survival (PFS). Overall, the PBAC considered that the

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nature of the ITC, the differences between the trials, including eligibility differences and transitivity issues, and the lack of a nominated non-inferiority margin impacted on the results of the comparison and that non-inferiority between ELd and Cd in terms of efficacy was not adequately demonstrated (paragraphs 7.9, 7.10 and 7.11, elotuzumab PSD, November 2020).

- 5.8 In November 2020 the PBAC considered that non-inferiority between ELd and Cd in terms of safety was not adequately demonstrated by the results of a naïve ITC (paragraphs 7.12 and 7.13, elotuzumab PSD, November 2020).

Economic analysis

- 5.9 In November 2020 the PBAC considered that the CMA between ELd and Cd was not appropriate as the claims of non-inferior efficacy and safety were not supported (paragraph 7.14, elotuzumab PSD, November 2020).

- 5.10 The November 2020 submission presented a CMA based on the cost per cycle. The resubmission presented a revised CMA based on the per patient costs over 12 cycles of ELd and Cd. In November 2020, the ESC considered that if the claim of non-inferiority was accepted, then the length of PFS, and thus the treatment durations applied in the CMA, should be similar. The ESC noted that the median treatment durations for ELd in ELOQUENT-2 (19 cycles/17.5 months) and Cd in ENDEAVOR (12 cycles/11.0 months) differed and that there was also a difference in the number of discontinuations, with ELd appearing to be better tolerated than Cd. Overall, the ESC considered the uncertainties associated with the non-inferiority claim impacted on the CMA (paragraph 6.47, elotuzumab PSD, November 2021).

- 5.11 Changes to the revised CMA are outlined in the table below.

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Table 3: Changes to the CMA from November 2020 to July 2021

November 2020 CMA (from the elotuzumab PSD)	Revised July 2021 CMA
Loading and titration doses	
The dose intensity calculated over all cycles, including titration, from the ENDEAVOR trial was applied to the Cd arm, whereas the dose intensity for ELd was calculated from Cycle 3 onwards using the ELOQUENT-2 trial. This excluded the higher exposure and dose intensity of ELd in Cycles 1 and 2.	Revised analysis incorporated loading doses for elotuzumab (ELOQUENT-2 trial) and titration doses for carfilzomib (ENDEAVOR trial).
Length of treatment	
The length of treatment was not incorporated into the estimation of the equi-effective doses, instead per cycle costs were applied. The comparable median durations of treatment, based on the data cuts which were used to inform the ITC and the claim on non-inferiority, were 19 cycles of ELd and 12 cycles of Cd.	The revised analysis was based on per patient costs to account for loading/titration doses and considered a similar duration of treatment for ELd and Cd, in line with the median duration of treatment for Cd of 12 cycles from the ENDEAVOR trial. The resubmission stated that the assumption of 12 cycles of treatment inherently biased against ELd as the impact of the loading/titration doses is increased, favouring Cd.
AE costs	
Costs of \$92.01 and \$35.35 for ELd and Cd respectively were applied per cycle to account for differences in safety and toxicity management.	Updated costs of \$105.83 and \$36.64 for ELd and Cd respectively were applied per cycle. The resubmission stated that given the claim of non-inferior safety the higher costs related to AEs applied to the ELd arm biased the CMA in favour of Cd.
AEMP vs DPMA/DPMQ prices	
Effective DPMA/DPMQs were applied for lenalidomide, carfilzomib and dexamethasone.	AEMPs were used for all costs.
Equi-effective doses	
1,544 mg elotuzumab + 416 mg lenalidomide + 135 mg dexamethasone = 601 mg carfilzomib + 146 mg dexamethasone	22,357 mg elotuzumab + 4,990 mg lenalidomide = 7,084 mg carfilzomib ^a
AEMP of elotuzumab and lenalidomide	
Elotuzumab: corrected CMA - \$ [REDACTED] submission - \$ [REDACTED]	Elotuzumab: \$ [REDACTED]
Lenalidomide: \$ [REDACTED]	Lenalidomide: \$ [REDACTED]

Source: Section 2 of the July 2021 resubmission and elotuzumab PSD, November 2020

AE = adverse event; AEMP = approved ex-manufacturer price; Cd = carfilzomib + dexamethasone; CMA = cost-minimisation analysis; DPMA = dispensed price for maximum amount; DPMQ = dispensed price for maximum quantity; ELd = elotuzumab + lenalidomide + dexamethasone; ITC = indirect treatment comparison

^a The resubmission stated that dexamethasone was not incorporated in the equi-effective doses because it is comparatively inexpensive and has very similar doses for both the ELd and Cd regimens (11 mg or approximately \$2 difference per cycle).

5.12 Table 4 presents the calculation of the equi-effective doses.

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Table 4: Calculation of the equi-effective doses

Cycles	Dosing regimen	Dispensed as	Total milligrams
Elotuzumab (28 day cycle)			
1 and 2	10 mg/kg on days 1,8,15,22	300 mg vials: 1.396 per dose 400 mg vials: 0.951 per dose (100% dose intensity)	3,196 mg per cycle
3+	10 mg/kg on days 1,15	300 mg vials: 1.389 per dose 400 mg vials: 0.954 per dose (96.2% dose intensity)	1,597 mg per cycle
Total exposure over 12 cycles (3,196 mg x 2 + 1,597 mg x 10)			22,357 mg
Lenalidomide (28 day cycle)			
1+	25 mg/day on days 1 to 21	25 mg x 16.6 days (79.2% dose intensity)	416 mg per cycle
Total exposure over 12 cycles (416 mg x 12)			4,990 mg
Carfilzomib (28 day cycle)			
1	20 mg/m ² on days 1,2 56 mg/m ² on days 8,9,15,16	10 mg vials: 3.91 per dose (days 1,2) 10 mg vials: 10.01 per dose (days 8,9,15,16) (91% relative dose intensity)	479 mg
2+	56 mg/m ² on days 1,2,8,9,15,16	10 mg vials: 10.01 per dose (91% relative dose intensity)	601 mg
Total exposure over 12 cycles (479 + 601 x 11)			7,084 mg

Source: Table 1 of the resubmission

- 5.13 The resubmission again assumed a ‘steady state’ dose intensity and a wastage estimate for both elotuzumab and carfilzomib. Median weekly dose intensities were applied for elotuzumab (10 mg/kg/week for Cycles 1 and 2 and 4.81 mg/kg/week for Cycle 3 and beyond) and lenalidomide (114.84 mg/week for patients starting at the recommended 25 mg dose and 103.95 mg/week for patients starting at less than the 25 mg dose). A relative dose intensity of 91% was applied to carfilzomib (18.2 mg/m² in Cycle 1 and 50.96 mg/m² in Cycles 2 and beyond).
- 5.14 The equi-effective doses were estimated over 12 cycles of therapy as:
- $$22,357 \text{ mg elotuzumab} + 4,990 \text{ mg lenalidomide} = 7,084 \text{ mg carfilzomib}$$
- 5.15 The revised CMA did not incorporate exposure to dexamethasone, which the resubmission stated was almost identical for both the ELd and Cd regimens (11 mg or approximately \$2 difference per cycle).
- 5.16 In the November 2020 submission, the steady state approach resulted in 1 mg carfilzomib equating to 2.57 mg elotuzumab and 0.69 mg lenalidomide. The revised per patient approach resulted in 1 mg carfilzomib equating to 3.16 mg elotuzumab and 0.70 mg lenalidomide. The revised equivalent doses were more conservative and resulted in a lower price for ELd.
- 5.17 The revised CMA, which incorporates the effective prices for elotuzumab and lenalidomide and the effective price for carfilzomib, is presented below. The equi-effective dose of carfilzomib was based on the ENDEAVOR trial in which patients received 56 mg/m² twice weekly. It was therefore appropriate to apply the effective

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approved ex-manufacturer price (AEMP) of carfilzomib which corresponded to this regimen.

Table 5: CMA between elotuzumab and lenalidomide and carfilzomib

Row	Parameter	Value	Reference/notes
Carfilzomib			
A	Cycles per patient	12	-
B	Exposure, inclusive of wastage	7,084 mg	Table 4
C	Price per mg	\$ [REDACTED]	AEMP = \$ [REDACTED] for 120 mg
D	Total drug costs	\$ [REDACTED]	B x C
E	Administrations per cycle (IV infusion)	6	Cd dosing regimen
F	Administrations per patient (IV infusion)	72	A x E
G	Administration unit cost (IV infusion)	\$111.40	MBS item 13950
H	Total administration costs	\$8,020.80	F x G
I	AE costs per cycle	\$36.64	-
J	Total AE costs	\$439.68	A x I
K	Total cost per patient	\$ [REDACTED]	D + H + J
Elotuzumab			
A'	Cycles per patient	12	-
B'	Exposure, inclusive of wastage	22,357 mg	Table 4
C'	Price per mg	\$ [REDACTED]	Proposed effective price
D'	Total drug costs	\$ [REDACTED]	B' x C'
E'	Administrations per cycle (IV infusion, elotuzumab)	4 in cycles 1,2; 2 in cycles 3+	ELd dosing regimen
F'	Administrations per cycle (IV injection, dexamethasone)	4 in cycles 1,2; 2 in cycles 3+	ELd dosing regimen
G'	Administrations per patient (IV infusion, elotuzumab)	28	4 x 2 + 2 x 10
H'	Administrations per patient (IV injection, dexamethasone)	28	4 x 2 + 2 x 10
I'	Administration unit cost (IV infusion)	\$111.40	MBS item 13950
J'	Administration unit cost (IV injection)	\$45.00	MBS item 105
K'	Total administration costs	\$4,379.20	G' x I' + H' x J'
L'	AE costs per cycle	\$105.83	-
M'	Total AE costs	\$1,269.91	A' x M'
N'	Total cost per patient	\$ [REDACTED]	D' + K' + M'
Lenalidomide			
O'	Total lenalidomide costs for cost neutrality	\$ [REDACTED]	K - N'
P'	Exposure	4,990 mg	Table 4
Q'	Price per mg	\$ [REDACTED]	O'/P'
R'	AEMP per PBS item (25 mg x 21)	\$ [REDACTED]	Q' x 25 x 21
S'	Current effective AEMP per PBS item (25 mg x 21)	\$ [REDACTED]	
T'	Proposed price change for lenalidomide	-10%	

Source: Table 2of the resubmission

AE = adverse event; AEMP = approved ex-manufacturer price; Cd = carfilzomib + dexamethasone; ELd = elotuzumab + lenalidomide + dexamethasone; IV = intravenous; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme

5.18 The revised price proposal includes a price reduction of 10% to lenalidomide which is specific to its use in combination with elotuzumab (i.e. the current prices of lenalidomide for the currently PBS listed indications would remain unchanged). The resubmission did not indicate whether the proposed lenalidomide price reduction applied to all strengths of lenalidomide, to account for dose reductions, or just the 25 mg strength. The PBAC considered that the price reduction should apply to all

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strengths of lenalidomide used in combination with elotuzumab. In addition, the sponsor did not indicate whether the price reduction would be implemented via separate lenalidomide restrictions for use in combination with elotuzumab or via a weighted price. The pre-PBAC response stated that separate lenalidomide restrictions would be preferred to ensure utilisation of ELd can be appropriately monitored.

- 5.19 The revised CMA resulted in reductions to the prices of both elotuzumab and lenalidomide relative to the November 2020 submission (see Table 6). The July 2021 resubmission incorrectly cited the private effective dispensed price for maximum amount (DPMA) for elotuzumab proposed in the November 2020 submission (\$ [REDACTED]) as the November 2020 AEMP and claimed that the proposed elotuzumab price in July 2021 was a 25% reduction on this price. If the AEMP for elotuzumab, calculated (and corrected) during evaluation of the CMA in the November 2020 submission, was used, the reduction in the proposed elotuzumab price was 7.7%.

Table 6: Proposed AEMPs for elotuzumab and lenalidomide

	November 2020	July 2021	Reduction
Elotuzumab 1,200 mg (maximum amount) – as per resubmission	\$ [REDACTED] (\$ [REDACTED] per mg)	\$ [REDACTED] (\$ [REDACTED] per mg)	-24.8%
Elotuzumab 1,200 mg (maximum amount) – corrected during evaluation ^a	\$ [REDACTED] (\$ [REDACTED] per mg) ^a	\$ [REDACTED] (\$ [REDACTED] per mg)	-7.7%
Lenalidomide capsules 25 mg x 21	\$ [REDACTED]	\$ [REDACTED]	-10%

Source: Table 3 of the resubmission

AEMP = approved ex-manufacturer price; DPMA = dispensed price for maximum amount

^a The July 2021 resubmission incorrectly cited the private effective DPMA proposed in the November 2020 submission as the November 2020 AEMP for elotuzumab. The actual AEMP, calculated and corrected during evaluation of the CMA of the November 2020 submission, presented results in a price reduction of 7.7%

Drug cost/patient/cycle: \$ [REDACTED] (elotuzumab + lenalidomide, from cycle 3+)

- 5.20 Applying the equi-effective doses estimated in the resubmission, the cost of 12 cycles of elotuzumab plus lenalidomide was estimated to be \$ [REDACTED] (elotuzumab = \$ [REDACTED]; lenalidomide = \$ [REDACTED]). This was based on an average dose of elotuzumab of approximately 798 mg and a weighted DPMA of \$ [REDACTED] per 1,200 mg. The average dose of lenalidomide on Days 1 to 21 was 19.8 mg and the weighted dispensed price for maximum quantity (DPMQ) was \$ [REDACTED] (21 tablets x 25 mg).

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Table 7: Drug cost per patient for ELd and Cd

	ELd		Cd	
	CMA	Financial estimates	CMA	Financial estimates
Dose/cycle	ELO Cycles 1, 2: 3,196 mg ^a Cycles 3+: 1,597 mg ^a LEN Cycles 1+: 416 mg ^b	ELO Cycles 1, 2: 3,087 mg ^c Cycles 3+: 1,544 mg ^c LEN Cycles 1+: 416 mg ^b DEX Cycles 1, 2: oral: 95.2 mg ^d IV: 27.2 mg ^d Cycles 3+: oral: 116 mg ^d IV: 13.6 mg ^d	CARF Cycle 1: 479 mg ^e Cycles 2+: 601 mg ^e	CARF Cycle 1: 479 mg ^e Cycles 2+: 601 mg ^e DEX Cycles 1+: 146 mg ^e
Cycle length	28 days		28 days	
Number of cycles	12	12	12	12
Cost/patient/cycle	ELO Cycles 1, 2: \$ [redacted] ^f Cycles 3+: \$ [redacted] ^f LEN Cycles 1+: \$ [redacted] ^g Cycles 1, 2: \$ [redacted] Cycles 3+: \$ [redacted]	ELO Cycles 1, 2: \$ [redacted] ^f Cycles 3+: \$ [redacted] ^f LEN Cycles 1+: \$ [redacted] ^g DEX Cycles 1,2: \$ [redacted] ^h Cycles 3+: \$ [redacted] ^h Cycles 1, 2: \$ [redacted] Cycles 3+: \$ [redacted]	CARF Cycle 1: \$ [redacted] Cycles 2+: \$ [redacted]	CARF Cycle 1: \$ [redacted] Cycles 2+: \$ [redacted] DEX Cycles 1+: \$21 ^h
Cost/patient/course	\$ [redacted] Elo: \$ [redacted] Len: \$ [redacted]	\$ [redacted] Elo: \$ [redacted] Len: \$ [redacted] Dex: \$ [redacted]	\$ [redacted] Carf: \$ [redacted]	\$ [redacted] Carf: \$ [redacted] Dex: \$ [redacted]

Source: March 21 ELd RRMM_CMA – Excel workbook and Mar21 ELd in RRMM_Section 4_BIM – Excel workbook.

Carf = carfilzomib; Cd = carfilzomib + dexamethasone; CMA = cost-minimisation analysis; Dex = dexamethasone; Elo = elotuzumab; ELd = elotuzumab + lenalidomide + dexamethasone; IV = intravenous; Len = lenalidomide

* Dose intensities applied as per the CMA

^a Average dose = 798 mg

^b Dose intensity = 79.2%

^c Average dose = 772 mg

^d Dose intensity = 85%

^e Dose intensity = 91%

^f Weighted DPMA for elotuzumab 1,200 mg was \$ [redacted] (30.4% public; 69.6% private)

^g Weighted DPMQ for lenalidomide 25 mg x 21 was \$ [redacted] (30.4% public; 69.6% private)

^h Weighted DPMQ for dexamethasone 4 mg oral x 30 was \$ [redacted] and 8 mg IV x 5 was \$ [redacted] (30.4% public; 69.6% private)

ⁱ Weighted DPMA for carfilzomib 120 mg was \$ [redacted] (30.4% public; 69.6% private)

Estimated PBS utilisation and financial implications

5.21 In November 2020, the PBAC noted that although cost minimised to Cd, the cost of listing ELd on the PBS was estimated in the submission to be approximately \$10 million to < \$20 million over the first six years. In addition, the PBAC considered that the estimated financial impact of listing elotuzumab on the PBS was underestimated (paragraph 7.15, elotuzumab PSD, November 2020).

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5.22 The structure of the utilisation and financial estimates was the same as in the November 2020 submission, i.e. a mixed model approach combining epidemiology and market-share data has again been used. The prices applied in the July 2021 financial estimates have been updated to reflect the revised CMA.

Table 8: Prices applied in the July 2021 financial estimates

	Pack/Volume/Formulation	AEMP	Source
Elotuzumab	Max amt: 1,200 mg	\$ [REDACTED]	Proposed price
Lenalidomide	25 mg x 21 capsules	\$ [REDACTED]	Proposed price
Dexamethasone	4 mg x 30 tablets	\$4.84	PBS item 2507Y
Dexamethasone	8 mg vial	\$8.60	PBS item 1291Y
Carfilzomib	Max amt: 120 mg	\$ [REDACTED]	PBS item 11229B (effective price)

Source: Table 5 of the resubmission

AEMP = approved ex-manufacturer price; amt = amount; Max = maximum

5.23 In November 2020, the PBAC considered that the submission likely overestimated Cd use by assuming that the estimated treatment durations of ELd and Cd were equal (28.6 cycles based on the mean number of cycles in ELOQUENT-2) (paragraph 7.15, elotuzumab PSD, November 2020). The duration of treatment for both ELd and Cd has been revised down to 12 cycles in July 2021 to align with the revised CMA and is based on the median duration of treatment in the ENDEAVOUR trial. This may underestimate the utilisation of ELd.

5.24 Table 9 presents the estimated extent of use, cost of ELd to the PBS/RPBS and the net financial implications to the PBS/RPBS and MBS.

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Table 9: Estimated use and financial implications of listing ELd on the PBA/RPBS

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients initiating ELd	1	1	1	1	1	1
Number of prescriptions dispensed:						
Elotuzumab 300/400 mg vial	2	2	3	3	3	3
Lenalidomide 25 mg x 21	2	2	2	2	2	2
Dexamethasone 4 mg tablet	2	2	2	2	2	2
Dexamethasone 8 mg vial	1	2	2	2	2	2
Drug costs						
Cost of ELd to PBS/RPBS	\$ 4	\$ 5	\$ 5	\$ 6	\$ 6	\$ 6
Less patient copayments	\$ 4	\$ 4	\$ 4	\$ 4	\$ 4	\$ 4
Total cost of ELd	\$ 4	\$ 5	\$ 5	\$ 6	\$ 6	\$ 6
Cost of Cd to PBS/RPBS	\$ 4	\$ 5	\$ 5	\$ 6	\$ 6	\$ 6
Less patient copayments	\$ 4	\$ 4	\$ 4	\$ 4	\$ 4	\$ 4
Total cost of Cd	\$ 4	\$ 5	\$ 5	\$ 6	\$ 6	\$ 6
Estimated net financial implications						
Net cost to PBS	\$ 4	-\$ 4	-\$ 4	-\$ 4	-\$ 4	-\$ 4
Net cost to RPBS	\$ 4	-\$ 4	-\$ 4	-\$ 4	-\$ 4	-\$ 4
Net cost to PBS/RPBS	\$ 4	-\$ 4	-\$ 4	-\$ 4	-\$ 4	-\$ 4
Net cost to MBS at 80% rebate	-\$ 4	-\$ 4	-\$ 4	-\$ 4	-\$ 4	-\$ 4
November 2020 submission						
Net cost to PBS/RPBS	\$ 4	\$ 4	\$ 4	\$ 4	\$ 4	\$ 4

Source: Tables 4 to 8 of the resubmission and Mar21 ELd in RRM_Section 4_BIM – Excel workbook and Table 15 of the elotuzumab Public Summary Document (PSD), November 2020

Cd = carfilzomib + dexamethasone; ELd = elotuzumab + lenalidomide + dexamethasone; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

The redacted values correspond to the following ranges:

¹ < 500

² 500 to < 5,000

³ 5,000 to < 10,000

⁴ \$0 to < \$10 million

⁵ \$10 million to < \$20 million

⁶ \$20 million to < \$30 million

5.25 The patient estimates remained the same as in the November 2020 submission with 500 to < 5,000 patients estimated to initiate ELd over the first six years of listing (Year 1: < 500; Year 6: < 500). ELd was again expected to completely substitute for the use of Cd. In November 2020, the utilisation estimates were for the use of ELd as a second line treatment only (paragraph 6.58, elotuzumab PSD, November 2020). The resubmission acknowledged that, following the PBS listing of DBd, ELd would likely be displaced to the third line setting. This may affect the patient estimates.

5.26 As per paragraph 5.23, the prescription estimates have been updated to reflect the 12 cycle treatment durations of both ELd and Cd and the prices of elotuzumab and lenalidomide have been updated to reflect those calculated in the revised CMA. Although changes in the revised CMA resulted in an average dose of elotuzumab of approximately 798 mg, like the November 2020 submission, the resubmission applied an average of 772 mg of elotuzumab per dose.

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- 5.27 The cost of ELd to the PBS/RPBS is expected to be \$90 million to < \$100 million over six years (Year 1: \$0 to < \$10 million; Year 6: \$20 million to < \$30 million). This listing is expected to result in a saving of \$100 million to < \$200 million on the utilisation of existing PBS/RPBS listings of carfilzomib over the first six years of listing. The estimated net financial impact to the PBS/RPBS for the listing of ELd was a saving of \$0 to < \$10 million over six years (Year 1: \$0 to < \$10 million; Year 6: -\$0 to < \$10 million).
- 5.28 The resubmission stated that the cost in Year 1 of \$0 to < \$10 million was a function of the initial loading doses of ELd and the titration doses of Cd. The resubmission stated that the cost savings in Years 2 to 6 were due to the higher dispensing fees and mark-up associated with Cd; however, the saving appears to be primarily due to the lower prices of elotuzumab and lenalidomide applied in the estimates compared to November 2020.
- 5.29 The savings to the MBS were associated with the reduced administration costs of ELd compared to Cd.
- 5.30 Issues with respect to the utilisation and financial estimates identified by the PBAC in November 2020 and not addressed in the resubmission included that:
- ELd was assumed to substitute for Cd only, whereas the PBAC considered that ELd would also likely substitute for Ld (paragraph 7.15, elotuzumab PSD, November 2020);
 - as per paragraph 5.25, estimates were presented for the use of ELd in the second line of treatment only. The proposed restriction does not restrict ELd use to one prior line of therapy and therefore it could be used in later lines (paragraph 6.58, elotuzumab PSD, November 2020); and
 - the assumed substitution rate of Cd by ELd (22% in Year 6), which was considered highly uncertain, was unchanged (paragraph 7.15, elotuzumab PSD, November 2020).

Financial Management – Risk Sharing Arrangements

- 5.31 The resubmission did not present a Risk Sharing Arrangement (RSA) for ELd. The resubmission stated that the sponsor would be willing to enter into a RSA for expenditure of elotuzumab and lenalidomide for this indication, either by joining the existing RSA for carfilzomib or through a new RSA.

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

6 PBAC Outcome

- 6.1 The PBAC recommended elotuzumab as a Section 100 (Efficient Funding of Chemotherapy) Authority Required listing for multiple myeloma that has progressed after at least one prior therapy, when administered in combination with lenalidomide

and dexamethasone (ELd). Listing of ELd was recommended on a cost minimisation bases against carfilzomib plus dexamethasone (Cd). Although no new clinical evidence was presented in the resubmission, the PBAC considered that a claim of non-inferior efficacy may be reasonable, noting the uncertainty with the indirect treatment comparison (ITC) reflected in the available clinical evidence and that a statistically significant gain in overall survival (OS) was demonstrated for ELd over lenalidomide plus dexamethasone (Ld), the magnitude of which was similar to that observed for Cd over bortezomib plus dexamethasone (Bd). The PBAC considered the revisions to the cost minimisation analysis (CMA), including the revised equi-effective doses, to be reasonable.

- 6.2 The PBAC noted the consumer comments which supported the listing of elotuzumab on the PBS for the treatment of RRMM.
- 6.3 The PBAC considered that ELd would most likely be used as third- and later-line treatment due to the recent listing (January 2021) of daratumumab, for use in combination with bortezomib and dexamethasone (DBd), on the PBS for use as second-line treatment only. Noting international guidelines (e.g. NCCN Myeloma Guidelines version 3.2021) which indicate a preference for triple combination therapies, the PBAC considered that ELd would potentially replace Ld and replace/displace Cd as third-line treatment.
- 6.4 The PBAC accepted Cd as the primary comparator in progressive disease where the patient has received at least one prior therapy, noting that the use of lenalidomide was increasing in the first line setting as maintenance therapy and as part of triple therapy in combination with bortezomib and dexamethasone (LBd).
- 6.5 The PBAC recalled that the results of the ELOQUENT-2 trial (ELd versus Ld) indicated that patients treated with ELd had significantly longer progression free survival (PFS, HR = 0.68; 95% CI: 0.56, 0.83) and overall survival (OS, HR = 0.77; 95% CI: 0.61, 0.97) compared to Ld.
- 6.6 The PBAC noted the ITC for the PFS outcome numerically favoured Cd (HR = 1.24; 95% CI: 0.95, 1.61), although the reliability of this comparison was unclear given the difference in PFS for Ld in ELOQUENT-2 (median 14.8 months) and Bd in ENDEAVOR (median 9.3 months). The PBAC noted that the OS outcome was approximately equal to one (HR = 0.98; 95% CI: 0.72, 1.32). The PBAC recalled that it had previously considered that, due to the nature of the ITC, the differences between the ELOQUENT-2 and ENDEAVOR trials and the lack of nominated non-inferiority margins, the claim of non-inferiority between ELd and Cd in terms of efficacy was not adequately supported. Although no new clinical evidence was presented in the resubmission, the PBAC considered that a claim of non-inferior efficacy may be reasonable, noting that the uncertainty with the ITC reflected the available clinical evidence, and that a statistically significant gain in OS was demonstrated for ELd over Ld, the magnitude of which was similar to that observed for Cd over Bd.

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- 6.7 In terms of safety, the PBAC again noted the increase in deep vein thrombosis for ELd versus Ld, and versus Cd. The PBAC further noted the cost of thromboembolic prophylaxis with ELd was accounted for in the CMA.
- 6.8 The PBAC noted that the following changes were made to the calculation of the equi-effective doses: (i) incorporation of ELd loading doses; and (ii) treatment durations of 12 cycles per patient for both ELd and Cd. The PBAC considered that the equi-effective doses for ELd and Cd over 12 cycles of therapy (excluding dexamethasone) were:
- 22,357 mg elotuzumab + 4,990 mg lenalidomide = 7,084 mg carfilzomib
- 6.9 Although the uncertainties resulting from the ITC continued to impact the CMA, the PBAC considered that the changes to the calculation of the equi-effective doses meant that the results of the revised CMA, which resulted in a 7.7% price reduction in the proposed price of elotuzumab compared to November 2020, were reasonable. The PBAC noted that the revised CMA also included a proposed 10% price reduction for lenalidomide 25 mg when used in combination with elotuzumab. The PBAC considered that it would be appropriate for the lenalidomide price reduction to apply to all strengths of lenalidomide when used in combination with elotuzumab to include potential dose reductions.
- 6.10 The PBAC noted that the resubmission presented updated financial estimates which applied a duration of treatment for both ELd and Cd of 12 cycles, to align with the CMA. The PBAC considered that this may be a reasonable estimate of the average treatment duration when used as third line treatment. The PBAC considered the claimed cost saving versus Cd to be uncertain, although accepted that the listing of ELd was likely to be approximately cost neutral.
- 6.11 The PBAC considered that it would be appropriate for the expenditure on elotuzumab and lenalidomide for this indication to be included in the existing Risk Sharing Arrangement for carfilzomib.
- 6.12 The PBAC recommended that elotuzumab be listed on the PBS as an immediate assessment type Authority Required listing and provide a maximum of 3 months therapy per treatment phase to align with Cd's listing. The PBAC noted that additional lenalidomide listings would be required to outline the circumstance of Ld subsidy within ELd use. The PBAC recommended that these separate lenalidomide listings also be immediate assessment type Authority Required listings.
- 6.13 The PBAC advised that elotuzumab was not suitable for prescribing by nurse practitioners.
- 6.14 The PBAC advised that elotuzumab should not be exempt from the early supply rule.
- 6.15 The PBAC advised that, under Section 101(3BA) of the *National Health Act 1953*, elotuzumab should not be treated as interchangeable on an individual patient basis with any other drug.

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- 6.16 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because ELd is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over Cd, 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.
- 6.17 The PBAC noted that this submission was not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

7 Recommended listing

7.1 Add new medicinal product as follows:

MEDICINAL PRODUCT Medicinal product pack	PBS item code	Max. Amount	No. of Rpts	Sponsor
ELOTUZUMAB Injection	NEW (Public) NEW (Private)	1,200 mg	9	Bristol-Myers Squibb Australia Pty Ltd
Available brands				
Empliciti (elotuzumab 300 mg injection, 1 vial)				
Empliciti (elotuzumab 400 mg injection, 1 vial)				
Restriction Summary [new] / Treatment of Concept: [new]				
	Category/Program: Section 100 (Efficient Funding of Chemotherapy – Public/Private hospitals)			
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners			
	Restriction type: <input checked="" type="checkbox"/> Authority Required – immediate/real-time assessment (telephone/online PBS Authorities system)			
	PBS Indication: Relapsed and/or refractory multiple myeloma			
	Treatment phase: Initial treatment			
	Clinical criteria:			
	The condition must be confirmed by a histological diagnosis,			
	AND			
	Clinical criteria:			
	The treatment must be in combination with lenalidomide and dexamethasone,			
	AND			
	Clinical criteria:			
	Patient must have progressive disease after at least one prior therapy,			
	AND			
	Clinical criteria:			
	Patient must have undergone or be ineligible for a stem cell transplant			
	AND			
	Clinical criteria:			
	Patient must not have previously received this drug for this condition			
	AND			
	Clinical criteria:			
	Patient must not be receiving concomitant PBS-subsidised treatment with any of: (i) bortezomib, (ii) carfilzomib, (iii) daratumumab, (iv) pomalidomide, (v) thalidomide			

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	<p>Prescriber 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).</p>
	<p>Prescriber instructions: Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M protein.</p>
	<p>Administrative advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.</p>
	<p>Administrative Advice: No increase in the maximum number of repeats may be authorised.</p>
	<p>Administrative Advice: Special Pricing Arrangements apply</p>

MEDICINAL PRODUCT Medicinal product pack	PBS item code	Max. Amount	№.of Rpts	Sponsor
ELOTUZUMAB Injection	NEW (Public) NEW (Private)	1,200 mg	5	Bristol-Myers Squibb Australia Pty Ltd
Available brands				
Empliciti (elotuzumab 300 mg injection, 1 vial)				
Empliciti (elotuzumab 400 mg injection, 1 vial)				
Restriction Summary [new] / Treatment of Concept: [new]				
Category/Program: Section 100 (Efficient Funding of Chemotherapy – Public/Private hospitals)				
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
Restriction type: <input checked="" type="checkbox"/> Authority Required – immediate/real-time assessment (telephone/online PBS Authorities system)				
PBS Indication: Relapsed and/or refractory multiple myeloma				
Treatment phase: Continuing treatment				
Clinical criteria:				
Patient must have previously received PBS-subsidised treatment with this drug for this condition,				
AND				
Clinical criteria:				
The treatment must be in combination with lenalidomide and dexamethasone,				
AND				
Clinical criteria:				
Patient must not have developed disease progression while receiving treatment with this drug for this condition,				
AND				
Clinical criteria:				
Patient must not be receiving concomitant PBS-subsidised treatment with any of: (i) bortezomib, (ii) carfilzomib, (iii) daratumumab, (iv) pomalidomide, (v) thalidomide				
Prescriber 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				

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	(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).
	Prescriber instructions: Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M protein.
	Administrative advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply

7.2 Add new lenalidomide Treatment phase listing to permit use in elotuzumab + lenalidomide + dexamethasone triple combination therapy as follows:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. Qty (units)	Max. Qty (packs)	No. of Rpts	Available brands	Sponsor
LENALIDOMIDE						
lenalidomide 5 mg capsule, 21	New (Public) / (Private)	21	1	2	Revlimid	Celgene Pty Ltd
lenalidomide 10 mg capsule, 21	New (Public) / (Private)	21	1	2	Revlimid	Celgene Pty Ltd
lenalidomide 15 mg capsule, 21	New (Public) / (Private)	21	1	2	Revlimid	Celgene Pty Ltd
lenalidomide 25 mg capsule, 21	New (Public) / (Private)	21	1	2	Revlimid	Celgene Pty Ltd
Restriction Summary [new] / Treatment of Concept: [new]						
	Category/Program: Section 100 (Highly Specialised Drugs Program) – Public/Private hospitals					
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
	Restriction type: <input checked="" type="checkbox"/> Authority Required – immediate/real-time assessment (telephone/online PBS Authorities system)					
	PBS Indication: Relapsed and/or refractory multiple myeloma					
	Treatment phase: Triple combination therapy consisting of elotuzumab, lenalidomide and dexamethasone					
	Treatment criteria:					
	Patient must be undergoing concurrent treatment with elotuzumab obtained through the PBS					
	AND					
	Treatment criteria:					
	Patient must not be undergoing simultaneous treatment with this drug obtained under another PBS listing					
	Administrative advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.					
	Administrative Advice: Special Pricing Arrangements apply					

7.3 Flow on changes to the carfilzomib, daratumumab and pomalidomide listings in progressive multiple myeloma to exclude simultaneous use with elotuzumab, are as follows:

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MEDICINAL PRODUCT: CARFILZOMIB	
Affected Restriction Summary Numbers: 11196 (Initial treatment – twice weekly treatment regimen) and 11197 (Continuing treatment – twice weekly treatment regimen)	
Medicinal product pack (Trade product):	PBS item number
carfilzomib 60 mg injection, 1 vial (Kyprolis) carfilzomib 30 mg injection, 1 vial (Kyprolis) carfilzomib 10 mg injection, 1 vial (Kyprolis)	11229B (Public) / 11230C (Private)
Affected Restriction Summary Numbers: 11198 (Initial treatment – once weekly treatment regimen) and 11291 (Continuing treatment – once weekly treatment regimen)	
carfilzomib 60 mg injection, 1 vial (Kyprolis) carfilzomib 30 mg injection, 1 vial (Kyprolis) carfilzomib 10 mg injection, 1 vial (Kyprolis)	12244K (Public) / 12243J (Private)
Relevant change:	
	Clinical criteria:
	Patient must not be receiving concomitant PBS-subsidised bortezomib, thalidomide or its analogues
	Patient must not be receiving concomitant PBS-subsidised treatment with any of: (i) bortezomib, (ii) daratumumab (iii) elotuzumab, (iv) lenalidomide, (v) pomalidomide, (vi) thalidomide
MEDICINAL PRODUCT: DARATUMUMAB	
Affected Restriction Summary Numbers / Treatment of Concept: 11142 (Initial treatment), 11076 (Continuing treatment – Weeks 10 – 24)	
medicinal product pack (Trade product):	PBS item number
daratumumab 100 mg/5 mL injection, 5 mL vial daratumumab 400 mg/20 mL injection, 20 mL vial	12228N (Public) / 12230Q (Private): Init. tx Wk 1-9 12220E (Public) / 12225K (Private): Cont. tx Wk 10 – 24
Relevant change:	
	Clinical criteria:
	Patient must not be receiving concomitant PBS-subsidised carfilzomib, thalidomide or its analogues
	Patient must not be receiving concomitant PBS-subsidised treatment with any of: (i) carfilzomib, (iii) elotuzumab, (iv) lenalidomide, (v) pomalidomide, (vi) thalidomide
Affected Restriction Summary Numbers / Treatment of Concept: 11075 (Continuing treatment – Weeks 25 onwards)	
medicinal product pack (Trade product):	PBS item number
daratumumab 100 mg/5 mL injection, 5 mL vial daratumumab 400 mg/20 mL injection, 20 mL vial	12231R (Public) / 12226L (Private)
Relevant change:	
	Clinical criteria:
	Patient must not be receiving concomitant PBS-subsidised bortezomib, carfilzomib or thalidomide or its analogues
	Patient must not be receiving concomitant PBS-subsidised treatment with any of: (i) bortezomib, (ii) carfilzomib, (iii) elotuzumab, (iv) lenalidomide, (v) pomalidomide, (vi) thalidomide
Affected Restriction Summary Numbers / Treatment of Concept: 11131 (Grandfather arrangements)	
medicinal product pack (Trade product):	PBS item number
daratumumab 100 mg/5 mL injection, 5 mL vial daratumumab 400 mg/20 mL injection, 20 mL vial	12229P (Public) / 12221F (Private)
Relevant change:	
	Clinical criteria:
	Patient must have met all initial treatment PBS-eligibility criteria applying to a non-grandfathered patient prior to having commenced treatment with this drug, which are: (i) the condition was confirmed by histological diagnosis, (ii) the treatment is/was being used as part of triple combination therapy with bortezomib and dexamethasone, (iii) the condition progressed (see definition of progressive disease below) after one prior therapy, but not after more than two prior lines of therapies (i.e. this drug was commenced as second-line treatment), (iv) the treatment

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	was/is not to be used in combination with PBS-subsidised carfilzomib, thalidomide or its analogues, and (v) the patient had never been treated with this drug
	Patient must have met all initial treatment PBS-eligibility criteria applying to a non-grandfathered patient prior to having commenced treatment with this drug, which are: (i) the condition was confirmed by histological diagnosis, (ii) the treatment is/was being used as part of triple combination therapy with bortezomib and dexamethasone, (iii) the condition progressed (see definition of progressive disease below) after one prior therapy, but not after more than two prior lines of therapies (i.e. this drug was commenced as second-line treatment), (iv) the treatment was/is not to be used in combination with PBS-subsidised carfilzomib, elotuzumab, thalidomide or its analogues, and (v) the patient had never been treated with this drug

MEDICINAL PRODUCT: POMALIDOMIDE	
Affected Restriction Summary Numbers / Treatment of Concept: 7951 / 7952 (Initial treatment), 7817 / 7791 (Continuing treatment)	
medicinal product pack (Trade product):	PBS item number
pomalidomide 4 mg capsule, 21 (Pomalyst)	10386P (Private) / 10387Q (Public)
pomalidomide 3 mg capsule, 21 (Pomalyst)	10417G (Private) / 10406Q (Public)
Relevant change:	
	Clinical criteria:
	Patient must not be receiving concomitant PBS-subsidised bortezomib, carfilzomib or thalidomide or its analogues
	Patient must not be receiving concomitant PBS-subsidised treatment with any of: (i) bortezomib, (ii) carfilzomib, (iii) daratumumab (iv) elotuzumab, (v) lenalidomide, (vi) thalidomide

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

Bristol-Myers Squibb Australia (BMSA) welcomes the positive recommendation for the listing of elotuzumab in combination with lenalidomide and dexamethasone (ELd), for the treatment of relapsed or refractory multiple myeloma (RRMM). BMSA would like to acknowledge the contribution of individuals and organisations in conveying the need for alternative treatments for MM patients.