5.04 ELOTUZUMAB,

Powder for IV infusion 300 mg, 400 mg,

Empliciti®,

Bristol-Myers Squibb Australia Pty Ltd

1 Purpose of submission

1.1 The submission requested a Section 100 (Efficient Funding of Chemotherapy), Authority Required (telephone) listing for elotuzumab in combination with lenalidomide and dexamethasone (ELd) for the treatment of relapsed and/or refractory multiple myeloma (RRMM).

1.2 Listing was requested on the basis of a cost-minimisation analysis (CMA) versus carfilzomib in combination with dexamethasone (Cd). The key components of the clinical issues addressed by the submission are provided in Table 1.

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

Component	Description
Population	Patients with relapsed or refractory multiple myeloma (RRMM).
Intervention	Elotuzumab in combination with lenalidomide and dexamethasone (ELd) • The recommended dose of elotuzumab is 10 mg/kg administered intravenously once weekly (28-day cycle) on Days 1, 8, 15 and 22 of cycles 1 and 2; and every 2 weeks thereafter on Days 1 and 15. • The recommended dose of lenalidomide is 25 mg orally once daily on Days 1-21 of repeated 28-day cycles, and at least 2 hours after elotuzumab administration when on the same day. • On weeks without elotuzumab, the recommended dose of dexamethasone is 40 mg administered orally on Days 1, 8, 15 and 22 of repeated 28-day cycles; on weeks with elotuzumab, the recommended dose is 28 mg orally (3-24 hours prior to elotuzumab) and 8 mg intravenously (45-90 minutes prior to elotuzumab). Treatment with ELd should continue until disease progression or unacceptable toxicity.
Comparator	Carfilzomib and dexamethasone (Cd)
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 in combination with lenalidomide and dexamethasone was TGA registered on 22 September 2016 for the treatment of patients with multiple myeloma who have received at least one prior therapy.

2.2 This was the first consideration of ELd by the PBAC.

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

3 Requested listing

Name, Restriction, Manner of administration and form	Max Amt	№.of Rpts	Dispensed Price Max Amt	Proprietary Name and Manufacturer
Elotuzumab, vial 400 mg Elotuzumab, vial 300 mg	1,200 mg	Initial:15 Continuing: 11	Published: Public: $5,035.09 Private: $5,144.15 Effective: Public: $[redacted] *($[redacted])* Private: $[redacted] *($[redacted])*	EMPLICITI® Bristol-Myers Squibb Australia Pty Ltd

Category/Program:	Section 100 – Efficient Funding of Chemotherapy
PBS indication:	Relapsed or refractory multiple myeloma
Treatment phase:	Initial and Continuing
Restriction:	Authority Required – Telephone, Electronic
Clinical criteria:	The condition must be confirmed by a histological diagnosis, AND The treatment must be in combination with lenalidomide and dexamethasone, AND Patient must have progressive disease after at least one prior therapy, AND Patient must have undergone or be ineligible for a stem cell transplant, AND Patient must not be receiving concomitant PBS-subsidised carfilzomib, bortezomib, pomalidomide or thalidomide AND Patient must not receive more than six cycles of treatment under this restriction AND Patient must not have previously received this drug for this condition

Source: Table 1.4.2 and Table 1.4.3 of the submission. *Values in italics were re-estimated based on updated mark-ups and fees (July 2020)*

3.1 Based on the CMA, the proposed effective dispensed price per maximum amount (DPMA) of elotuzumab was $[redacted] (public) and $[redacted] (private). The estimated prices were based on cost-minimisation at the DPMA of Cd. CMAs should be conducted using approved ex-manufacturer prices (AEMPs). Pricing agreements are made by Government under the *National Health Act 1953* at the ex-manufacturer level and, as such, the prices would be agreed on this basis. It is not usually the case that pharmacy and wholesaler mark-ups are considered for the purpose of cost-minimisation as they do not relate to the cost of the medicine. When cost-minimised against the AEMP for Cd, the resulting effective DPMAs for elotuzumab were $[redacted] (public) and $[redacted] (private).

3.2 The proposed restrictions were consistent with the TGA indication and the clinical evidence. The trial eligibility criteria for ELOQUENT-2, the pivotal trial for ELd, included restrictions on patients' prior response (including achieving at least a partial response

and not being refractory to prior lenalidomide). In addition, recruitment of patients with prior lenalidomide exposure was restricted to no more than 10% of the study population. The submission stated that this was done for ethical reasons to limit the number of patients in the lenalidomide plus dexamethasone (Ld) control group receiving a regimen from which they may not derive significant benefit. The proposed PBS restrictions do not include these criteria.

3.3 The submission requested an Authority Required (Telephone/Electronic) listing for the initial and continuing treatment. The PBAC considered this to be appropriate.

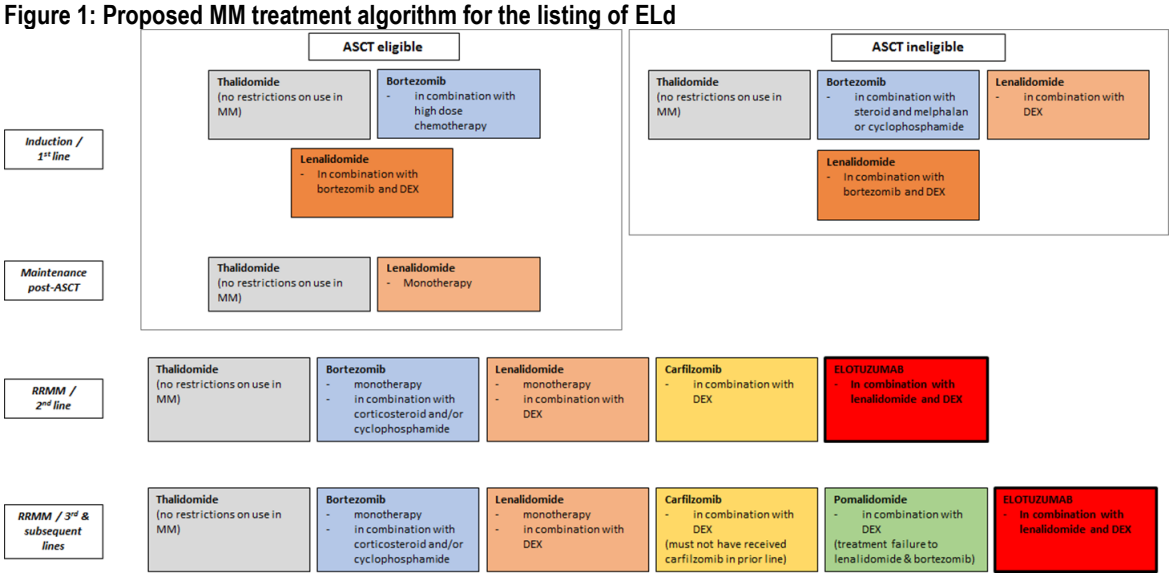
For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 Multiple myeloma (MM) is a B-cell malignancy characterised by the clonal proliferation of malignant plasma B cells within the bone marrow. Clinical complications of progressive MM include recurrent infections, cytopenias, renal failure, hyperviscosity syndrome, hypercalcaemia, bone pain, and pathologic fractures. MM remains incurable; with diminishing duration of response to subsequent lines of therapy with each relapse that tends to be progressively more aggressive.

4.2 The submission requested PBS listing of ELd for the treatment of patients with RRMM. The clinical algorithm presented in the submission proposed that ELd would substitute for Cd. The clinical algorithm (Figure 1) appeared reasonable, with the exception that it did not include the use of daratumumab, bortezomib and dexamethasone (DBd) at the same place in therapy as proposed for ELd. Clinical guidelines presented in the submission noted that DBd would likely be the main triple therapy used in this setting (as the first therapy in RRMM). The ESC considered that the requested listing for DBd, which is specifically for treatment of second-line MM, has the potential to displace current treatments for use later in the treatment pathway. The PBAC considered that DBd, if listed on the PBS, would displace current treatments to the third- and later-line settings.

Figure 1: Proposed MM treatment algorithm for the listing of ELd



Source: Figure 1.2.2, p22 of the submission.
ASCT = autologous stem cell transplant; DEX = dexamethasone; ELd = elotuzumab + lenalidomide + dexamethasone; MM = multiple myeloma; RRMM = relapsed/refractory multiple myeloma.
Note: the proposed treatment regimen (ELd) is indicated in red and is proposed as an alternative in the second and subsequent line treatments settings.

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

5 Comparator

5.1 The submission nominated Cd as the comparator for ELd. At the time of the submission, Cd represented the most recent therapy to be PBS listed for the treatment of RRMM.

5.2 The submission based its decision on the currently established therapeutic relativities and the anticipated changes in utilisation of current agents in the RRMM setting. Cd was recommended based on cost-effectiveness compared to bortezomib plus dexamethasone (Bd; Carfilzomib PSD, July 2017); Ld was recommended based on cost-minimisation versus Bd (Lenalidomide PSD, Nov 2008); and Bd was recommended on a cost-effectiveness basis compared to salvage treatment (Bortezomib PSD, July 2007). Based on PBS utilisation data, Cd appears to have an increasing greater share of new initiations compared to Ld. In addition, utilisation of Ld in RRMM is likely to be impacted by the April 2020 PBS listing of lenalidomide monotherapy as maintenance treatment post-autologous stem cell transplant (ASCT) and the June 2020 PBS listing of lenalidomide with bortezomib and dexamethasone for all newly diagnosed multiple myeloma (NDMM) patients.

5.3 The submission stated that if NDMM treatment included a proteasome inhibitor (such as bortezomib), the RRMM treatment most likely to be used was Ld; whereas, if upfront treatment comprised of an immunomodulatory drug (IMiD, such as

lenalidomide), then it may be more likely that RRMM treatment would include a proteasome inhibitor containing regimen such as carfilzomib. The ESC considered that, as long as there were no safety concerns with either lenalidomide or dexamethasone, there would be no reason that patients who had received lenalidomide in the NDMM setting would not receive treatment that consisted of an IMid (e.g. ELd) in the RRMM setting.

5.4 The ESC considered that Cd would be mostly displaced by ELd, whereas Ld would be replaced; thus, Ld may be the more relevant comparator. However, the ESC noted that the implications of the recent PBS listings of lenalidomide in the first-line setting and the recent PBAC recommendation of daratumumab in the second-line setting were, as yet, unknown and created significant uncertainty around the predicted market shares of lenalidomide and carfilzomib in RRMM.

5.5 The PBAC noted that approximately 40% of patients in each treatment line do not receive subsequent treatment i.e. of all patients who initiate treatment, only 22% will receive a fourth-line treatment and 13% will receive a fifth-line treatment. Therefore, for some patients, treatment substitution in the third-line setting will represent a replacement, rather than a displacement of therapy.

5.6 The ESC considered that the impact of the PBAC recommendation of daratumumab was particularly difficult to estimate. As daratumumab, in combination with bortezomib and dexamethasone (DBd), is restricted to the second-line setting only and will likely be the preference of most patients in this setting if available, the ESC noted that ELd (and Cd and Ld) would most likely be used in the third-line setting, making pomalidomide plus dexamethasone (Pd) another relevant comparator. The ESC also noted early evidence[1] suggesting that ELd may be better used before DBd; however, considered that the recommended restriction for daratumumab would ensure DBd is used in the second-line setting.

5.7 Like daratumumab, elotuzumab is a monoclonal antibody with a drug class of L01XC23 that specifically targets the SLAMF7 protein. The submission did not provide trial evidence of the comparison of ELd with DBd other than that contained in a published network meta-analysis. DBd was recommended at the July 2020 PBAC meeting and a PBS listing may impact on the line of treatment at which ELd is used.

5.8 With reference to the requirements of the *National Health Act 1953*, Section 101(3B), the PBAC was satisfied that ELd provides, for some patients, a significant improvement in efficacy over Ld, and by extension, over Bd.

[1] Hoylman E, Brown A, Perissinotti AJ, et al. Optimal sequence of daratumumab and elotuzumab in relapsed and refractory multiple myeloma. Leuk Lymphoma. 2020;61(3):691-698.

5.9 The ESC noted that ixazomib in combination with lenalidomide and dexamethasone (ILd), which was also considered at the November 2020 PBAC meeting, would be a near market comparator.

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

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician described the importance of additional treatment options for patients with RRMM, particularly those that incorporated monoclonal antibodies. The clinician also described the patients who would benefit most from ELd treatment (i.e. those in whom retreatment with a lenalidomide-containing backbone was preferable) and the lack of cumulative side effects.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (40) and organisations (4) via the Consumer Comments facility on the PBS website. The comments from individuals who had received treatment with elotuzumab described benefits including few side effects and improved quality of life. A number of individuals described the benefits of access to new treatment options and the impact this has on quality of life.

6.3 The PBAC noted the advice received from (i) Myeloma Australia, (ii) Myeloma Australia's Medical and Scientific Group (MSAG), (iii) The Leukaemia Foundation, and (iv) Rare Cancers Australia which strongly supported the submission for elotuzumab and the need for alternative treatments for multiple myeloma patients.

Clinical trials

6.4 The submission presented an indirect treatment comparison (ITC) of ELd and Cd informed by two randomised trials: ELOQUENT-2, comparing ELd with Ld (N = 646); and ENDEAVOR, comparing Cd with Bd (N = 929). In forming this comparison, the submission utilised Ld and Bd as the common reference, assuming their equivalence. The submission has assumed that the efficacy of Ld and Bd was the same and did not adjust for any potential difference in their outcomes. Although the PBAC has previously considered non-inferiority between Ld and Bd with respect to efficacy for the purposes of Ld listing in RRMM, the PBAC noted that OS may possibly favour Ld and that there was uncertainty due to the ITC and the differences in the trials used in the comparison (paragraph 12, lenalidomide PSD, November 2008). In consideration of carfilzomib in November 2016, the PBAC stated that it might not be reasonable to assume non-inferior efficacy between Bd and Ld (paragraph 5.3, carfilzomib PSD, November 2016).

6.5 Details of the trials presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
ELOQUENT-2	Clinical Protocol CA204004 v10.0. Title: A Phase 3, Randomized, Open Label Trial of Lenalidomide/dexamethasone With or Without Elotuzumab in Relapsed or Refractory Multiple Myeloma. Revised Protocol No.: 04;	07 May 2014
	Final Clinical Study Report for Study CA204004. Title: A Phase 3, Randomized, Open-Label Trial of Lenalidomide/Dexamethasone With Or Without Elotuzumab in Relapsed or Refractory Multiple Myeloma	11 May 2015
	Addendum 01 Clinical Study Report for Study CA204004. Title: A phase 3, randomized, open-label trial of lenalidomide/dexamethasone with or without elotuzumab in relapsed or refractory multiple myeloma.	02 December 2015
	Addendum 02 Clinical Study Report for Study CA204004. Title: A phase 3, randomized, open-label trial of lenalidomide/dexamethasone with or without elotuzumab in relapsed or refractory multiple myeloma.	15 March 2019
	Dimopoulos MA, Lonial S, Betts KA, Chen C, Zichlin ML, Brun A, et al. Elotuzumab plus lenalidomide and dexamethasone in relapsed/refractory multiple myeloma: extended 4-year follow-up and analysis of relative progression-free survival from the randomized ELOQUENT-2 trial.	Cancer. 2018b;124(20):4032-43.
	Cella D, McKendrick J, Kudlac A, Palumbo A, Oukessou A, Vij R, et al. Impact of elotuzumab treatment on pain and health-related quality of life in patients with relapsed or refractory multiple myeloma: results from the ELOQUENT-2 study.	Annals of Hematology. 2018;97(12):2455-63.
	Dimopoulos MA, Lonial S, White D, Moreau P, Palumbo A, San-Miguel J, et al. Elotuzumab plus lenalidomide/dexamethasone for relapsed or refractory multiple myeloma: ELOQUENT-2 follow-up and post-hoc analyses on progression-free survival and tumour growth.	British Journal of Haematology. 2017b;178(6):896-905.
	Lonial S, Dimopoulos M, Palumbo A, White D, Grosicki S, Spicka I, et al. Elotuzumab therapy for relapsed or refractory multiple myeloma..	New England Journal of Medicine. 2015;373(7):621-31
	NCT. Phase III Study of Lenalidomide and Dexamethasone With or Without Elotuzumab to Treat Relapsed or Refractory Multiple Myeloma. https://clinicaltrialsgov/show/NCT01239797. 2010.	NCT record
	Euctr ES. Ensayo de fase 3, aleatorizado y abierto, de lenalidomida/dexametasona, con o sin elotuzumab, en el mieloma múltiple en recidiva o resistente al tratamiento // A Phase 3, Randomized, Open Label Trial of Lenalidomide/dexamethasone With or Without Elotuzumab in Relapsed or Refractory Multiple Myeloma. http://wwwwhoint/trialsearch/Trial2aspx?TrialID=EUCTR2010-020347-12-ES. 2011.	EUCTR record
	Title: Phase III Study of Lenalidomide and Dexamethasone With or Without Elotuzumab to Treat Relapsed or Refractory Multiple Myeloma	NCT record
ENDEAVOR	Dimopoulos, M. A., et al. (2016). "Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): And randomised, phase 3, open-label, multicentre study."	The Lancet Oncology 17(1): 27-38.
	Dimopoulos, M. A., et al. (2017). "Carfilzomib or bortezomib in relapsed or refractory multiple myeloma (ENDEAVOR): an interim overall survival analysis of an open-label, randomised, phase 3 trial."	The Lancet Oncology 18(10): 1327-1337.
	Goldschmidt, H., et al. (2018). "Carfilzomib-dexamethasone versus subcutaneous or intravenous bortezomib in relapsed or refractory multiple	Leukemia and Lymphoma 59(6): 1364-1374.

Trial ID	Protocol title/ Publication title	Publication citation
	myeloma: secondary analysis of the phase 3 ENDEAVOR study."	
	Orlowski, R. Z., et al. (2019). "Carfilzomib-Dexamethasone Versus Bortezomib-Dexamethasone in Relapsed or Refractory Multiple Myeloma: Updated Overall Survival, Safety, and Subgroups."	Clinical Lymphoma, Myeloma and Leukemia 19(8): 522-530.e521.
	Chng, W. J., et al. (2017). "Carfilzomib-dexamethasone vs bortezomib-dexamethasone in relapsed or refractory multiple myeloma by cytogenetic risk in the phase 3 study ENDEAVOR."	Leukemia 31(6): 1368-1374.
	Dimopoulos, M., et al. (2019). "Carfilzomib vs bortezomib in patients with multiple myeloma and renal failure: A subgroup analysis of ENDEAVOR."	Blood 133(2): 147-155.
	Dimopoulos, M. A., et al. (2019b). "Outcomes for Asian patients with multiple myeloma receiving once- or twice-weekly carfilzomib-based therapy: a subgroup analysis of the randomized phase 3 ENDEAVOR and A.R.R.O.W. Trials."	International Journal of Hematology 110(4): 466-473.
	Moreau, P., et al. (2017b). "Impact of prior treatment on patients with relapsed multiple myeloma treated with carfilzomib and dexamethasone vs bortezomib and dexamethasone in the phase 3 ENDEAVOR study."	Leukemia 31(1): 115-122.
	Moreau, P., et al. (2020). "Once-weekly (70 mg/m2) vs twice-weekly (56 mg/m2) dosing of carfilzomib in patients with relapsed or refractory multiple myeloma: A post hoc analysis of the ENDEAVOR, A.R.R.O.W., and CHAMPION-1 trials."	Cancer Medicine.
	Mateos, M. V., et al. (2018). "Carfilzomib in relapsed or refractory multiple myeloma patients with early or late relapse following prior therapy: A subgroup analysis of the randomized phase 3 ASPIRE and ENDEAVOR trials."	Hematological Oncology 36(2): 463-470.
	NCT (2012). "Phase 3 Study With Carfilzomib and Dexamethasone Versus Bortezomib and Dexamethasone for Relapsed Multiple Myeloma Patients."	NCT record
	Euctr, C. Z. (2012). "A Randomized, Open-label, Phase 3 Study of Carfilzomib Plus Dexamethasone vs Bortezomib Plus Dexamethasone in Patients With Relapsed Multiple Myeloma."	EUCTR record
	Amgen. (2014). Phase 3 Study With Carfilzomib and Dexamethasone Versus Bortezomib and Dexamethasone for Relapsed Multiple Myeloma Patients. In.	NCT record

Source: Table 2.2.3, pp42 – 47 and Att 2. ELd in RRMM_Literature search_aster List (Excel workbook) of the submission.
Note: Conference abstracts for ELOQUENT-2 AND ENDEVOR are not included in the table. A full list of publications is presented in Attachment 2 of the commentary.

6.6 The key features of the direct randomised trials are summarised in Table 3.

Table 3: Key features of the included evidence – indirect comparison

Trial	N	Design/ median follow-up	Risk of bias	Patient population	Outcomes
ELd vs Ld					
ELOQUENT-2	646	Phase III, R, OL PFS: 46.8 months OS: 70.9 months (cut-off 3 Oct 2018)[a]	Low	Patients who had received at least one prior line of therapy (RRMM).	Co-primary endpoints: PFS and ORR Secondary: OS and BPI-SF Exploratory: Safety, TTR, DOR, HRQoL (EORTC QLQ-C30 and QLQ-MY20)
Cd vs Bd					
ENDEAVOR	929	Phase III, R, OL, MC PFS: NR OS: 44.3 months (Cd) and 43.7 months (Bd) (cut-off 19 July 2017)[a]	Low	Patients who had received one to three prior lines of therapy and achieved at least a partial response to at least one previous treatment (RRMM).	Primary: PFS Secondary: OS, ORR and Safety

Source: Table 2.2.4, Table 2.3.1, Table 2.4.3 of the submission.
Bd = bortezomib + dexamethasone; BPI-SF = Brief Pain Inventory-Short Form; Cd = carfilzomib +dexamethasone; DB = double blind; DOR = duration of response; ELd = elotuzumab + lenalidomide + dexamethasone; EMA = European Medicines Agency; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 module; EORTC QLQ-MY20 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire the myeloma specific module; IQR = interquartile range; IRC = independent review committee; ITT = intention to treat; Ld = lenalidomide + dexamethasone; MC = multi-centre; NR = not reported; OL = open label; OS = overall survival; PFS = progression-free survival; R = randomised; TTR = time to response.
[a] The details of the follow-up are provided for the latest data cut-off.

6.7 The key difference between the eligibility criteria of the trials was with respect to the prior exposure to either lenalidomide or bortezomib:

- ELOQUENT-2 had strict eligibility criteria for patients with regard to prior lenalidomide exposure, requiring them to have achieved at least a partial response, not be refractory and being limited to no more than 10% of the study population. The ESC considered that the majority of patients would receive prior lenalidomide in the NDMM setting and that the inclusion of this eligibility criteria meant that the ELOQUENT-2 trial was not representative of the likely clinical population.
- ENDEAVOR specified that patients had to have had at least a partial response to bortezomib, were not removed from bortezomib therapy due to toxicity, and were to have had at least a 6-month bortezomib free period prior to study initiation.

The PBAC noted that the differences in eligibility criteria specific to prior use of lenalidomide (ELOQUENT-2) and bortezomib (ENDEAVOR) may have had a potential bearing on the exchangeability of the trials for the quantitative ITC.

6.8 The demographic characteristics across the two trials were similar, with the following exceptions: more ELOQUENT-2 patients were male (59.6% versus 50%), aged 75 years or over (20% versus 15.4%), had an Eastern Cooperative Oncology Group (ECOG) performance status of 2 (9.0% versus 6.7%), and were white (84% versus 75%)

compared with ENDEAVOR trial patients. These differences were not anticipated to affect the comparability of these trials.

6.9 The PBAC noted the following differences between the trials in terms of baseline disease and treatment characteristics:

- A higher proportion of patients in ENDEAVOR had poorer renal function at study entry compared with ELOQUENT-2 (CrCl < 30 mL/min: 6.0% vs. 1.4%). The submission stated that this was likely due to differences in the inclusion criteria of the trials with respect to renal function.
- High risk cytogenetic markers of 17pDel and t(4;14) were present in 31.9% and 9.4% of patients, respectively, in the ELOQUENT-2 trial. While the rates of t(4;14) amongst patients in ENDEAVOR were similar (11.9%); rates of 17pDel were considerably lower than those in ELOQUENT-2 (9.9%). The ESC noted that the higher proportion of patients in the ELOQUENT-2 trial with 17pDel, likely meant that patients in the ELOQUENT-2 trial had a poorer prognosis.
- B2 microglobulin of 3.5 mg/L or more was reported in a higher proportion of patients in ENDEAVOR compared with ELOQUENT-2 (53.1% vs. 44.9%, respectively). Nonetheless, the rate of patients classified as having International Staging System stage 1 disease was similar between trials (43.2% in ELOQUENT-2 and 44.0% in ENDEAVOR).
- In ELOQUENT-2, approximately one third of patients (35.1%) had resistance to their most recent line of therapy (progression during or within 60 days after prior therapy) and 64.7% had relapsed (progression after a period greater than 60 days post last therapy). Response to the most recent line of therapy was not reported in ENDEAVOR although the trial required that all patients had at least a partial response to at least one line of prior therapy.
- Prior treatment with bortezomib was more common amongst patients in the ELOQUENT-2 trial compared with ENDEAVOR (69.7% vs. 54.0%, respectively). Prior use of lenalidomide was more common in ENDEAVOR compared with ELOQUENT-2 (38.1% vs. 5.7%, respectively). The ESC noted patients in the ENDEAVOR trial were more highly pre-treated. The ESC noted that the submission did not provide any information on prior therapy with daratumumab.
- The rates of no prior IMiD therapy were higher in ELOQUENT-2 (47.0% vs. 46.8% in ELd and Ld, respectively) compared to ENDEAVOR (30.0% vs. 25.4% in Cd and Bd, respectively). The difference in prior use of IMiD therapy may affect the comparability of the two trials. The submission presented results from subgroup analyses from the trials to assess the impact of these differences (see paragraphs 6.15 and 6.16).

Comparative effectiveness

ELd versus Ld (ELOQUENT-2 trial)

6.10 The summary of survival outcomes in ELOQUENT-2 is presented in Table 4, with the corresponding Kaplan-Meier plots reported in Figure 2. As noted in the submission, patients in the ELd arm had statistically significantly longer progression free survival (PFS) and overall survival (OS) compared to Ld. The results did not change substantially between the two data-cuts.

Table 4: Results of PFS and OS across the trials

	ELd		Ld		Difference in median, months	P value [a] (log rank test)	HR [b] (95% CI)
	Patients with events, n (%)	Median, months (95% CI)	Patients with events, n (%)	Median, months (95% CI)			
PFS							
29 Oct 2014 – ITT (IRC)	192 (59.8%)	18.5 (16.5, 21.4)	231 (71.1%)	14.3 (12.0, 16.0)	4.2	**0.0001**	**0.68 (0.56, 0.83)**
3 Oct 2018 – ITT (IRC)	268 (83.5%)	19.4 (16.6, 22.2)	290 (89.2%)	14.8 (12.1, 16.6)	4.6	**0.0001**	**0.72 (0.61, 0.85)**
OS							
29 Oct 2015 (all randomised patients)	136 (42.4%)	43.7 (40.3, NE)	159 (48.9%)	39.6 (33.3, NE)	4.1	**0.0257**	**0.77 (0.61, 0.97)**
3 Oct 2018 (all randomised patients)	212 (66.0%)	48.3 (40.3, 51.9)	225 (69.2%)	39.6 (33.3, 45.3)	8.7	**0.0408**	**0.82 (0.68, 0.99)**

Source: Table 2.5.1, Table 2.5.5 of the submission.

CI = confidence interval; ELd = elotuzumab + lenalidomide + dexamethasone; HR = hazard ratio; IMiD = Immunomodulatory drug; IRC = independent review committee; ITT = intention to treat; Ld = lenalidomide + dexamethasone; OS = overall survival; PFS = progression free survival;

[a] 2-sided p-value for stratified log-rank test.

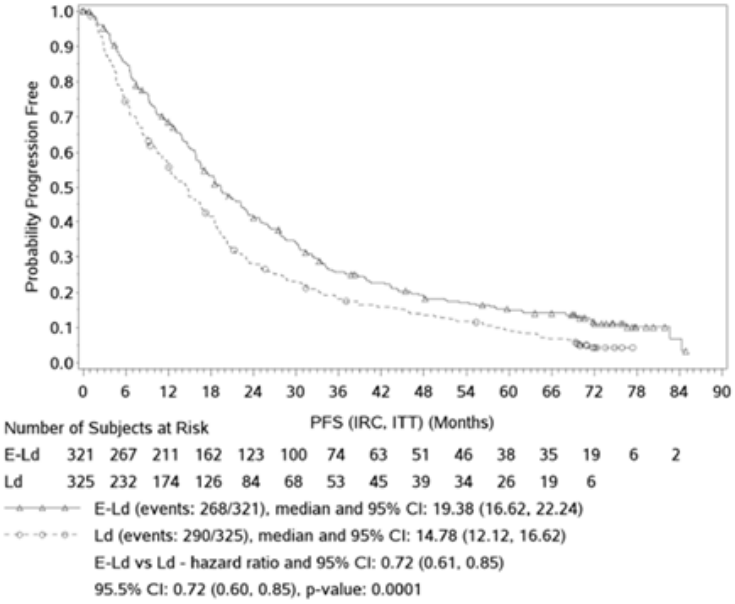
[b] Stratified by B2 microglobulin (<3.5 mg/L vs >= 3.5 mg/L), number of prior lines of therapy (1 vs 2 or 3) and prior IMiD (no vs prior thalidomide only vs other) at randomisation.

Note: ELOQUENT-2 median follow for PFS: 24.5 months (data cut 29 Oct 2014); 46.8 months (data cut 3 Oct 2018); OS: 38.7 months (data cut 29 Oct 2015); 70.9 months (data cut 3 Oct 2018).

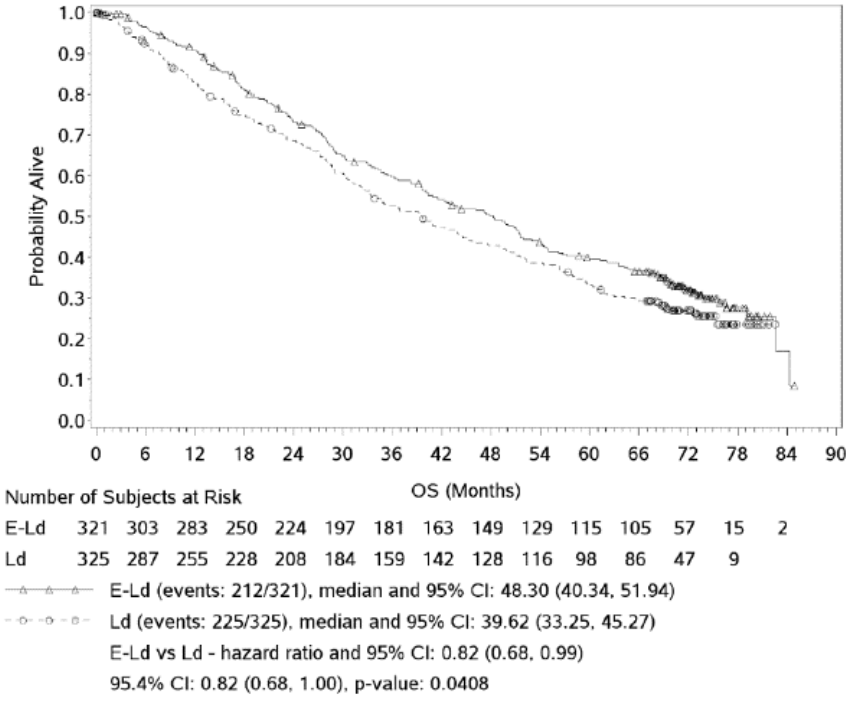
Bold values indicate statistical significance.

Figure 2: Kaplan-Meier curves for (A) PFS and (B) OS, ELOQUENT-2 (3 Oct 2018 data-cut)

A: PFS (median duration of follow-up = 46.8 months)



B: OS (median duration of follow-up = 70.9 months)



Source: Figure 2.5.4, Figure 2.5.8, of the submission.
CI = confidence interval; E-Ld = elotuzumab + lenalidomide + dexamethasone; IRC = independent review committee; KM = Kaplan Meier; Ld = lenalidomide + dexamethasone; NE = not estimable; OS = overall survival; PFS = progression free survival.

6.11 The results for objective response rate (ORR) are presented in Table 5. Patients in the ELd arm had a statistically significantly higher ORR compared to Ld at both data cuts.

Table 5: Results of ORR in ELOQUENT-2

	ELd		Ld		Difference in median	P value (log rank test)	Hazard ratio[a] (95% CI)
	n/N (%)	Median, months	n/N (%)	Median, months			
29 Oct 2014 data-cut	252/321 (78.5%)	NR	213/325 (65.5%)	NR	NR	**0.0002**	**1.94 (1.36, 2.77)**
10 Aug 2015 data-cut	252/321 (78.5%)	1.87	213/325 (65.5%)	1.87	0	**0.0002**	**1.95 (1.36, 2.78)**

Source: Table 2.5.3 of the submission.
CI = confidence interval; ELd = elotuzumab + lenalidomide + dexamethasone; IMiD = Immunomodulatory drug; IRC = independent review committee; Ld = lenalidomide + dexamethasone; NR = not reported; OR = odds ratio; ORR = objective response rate.
[a] Stratified by B2 microglobulin (<3.5 mg/L vs >= 3.5 mg/L), number of prior lines of therapy (1 vs 2 or 3) and prior IMiD (no vs prior thalidomide only vs other) at randomisation.
Bold values indicate statistical significance.

Cd versus Bd (ENDEAVOR trial)

6.12 The summary of survival outcomes from ENDEAVOR are presented in Table 6, with the corresponding Kaplan-Meier plots in Figure 3.

Table 6: Results of PFS and OS in ENDEAVOR

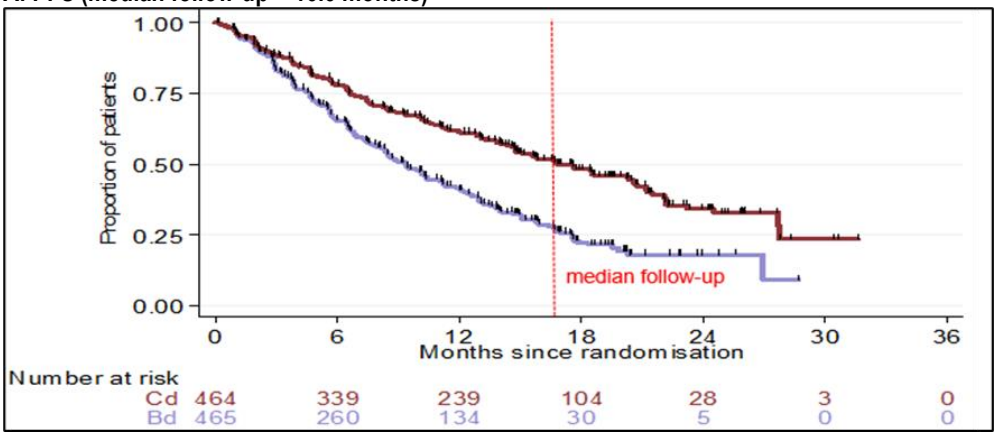
	Cd		Bd		Difference in median, months	P value (log rank test)	HR (95% CI)
	Patients with events, n (%)	Median, months (95% CI)	Patients with events, n (%)	Median, months (95% CI)			
PFS							
10 Nov 2014-IRC	171 (36.9%)	18.7 (15.6, NE)	243 (52.3%)	9.4 (8.4, 10.4)	9.3	**< 0.0001**	**0.53 (0.44, 0.65)**
3 Mar 2016-ORCA	232 (50.0%)	16.8 (14.8, 20.3)	288 (61.9%)	9.3 (8.3, 10.4)	7.5	**< 0.0001**	**0.55 (0.46, 0.65)**
OS							
3 Jan 2017	189 (40.7%)	47.6 (42.5, NE)	209 (44.9%)	40.0 (32.6, 42.3)	7.6	**0.010**	**0.79 (0.65, 0.96)**
19 July 2017	214 (46.1%)	47.8 (41.9, NE)	248 (53.3%)	38.8 (31.7, 42.7)	9.0	**0.0017**	**0.76 (0.63, 0.92)**

Source: Table 2,5,2, Table 2.5.6 of the submission.
Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; CI = confidence interval; HR = hazard ratio; IRC = Independent Review Committee; NE = not estimable; ORCA = Onyx Response Computational Assessment; OS = overall survival; PFS = progression free survival.
Note: ENDEAVOR median follow-up for PFS: 11.5 months (data cut 10 Nov 2014); 16.6 months (data cut 3 March 2016); OS: 37.2 months (data cut 3 Jan 2017); 44 months (data cut 19 July 2017).
Bold values indicate statistical significance.

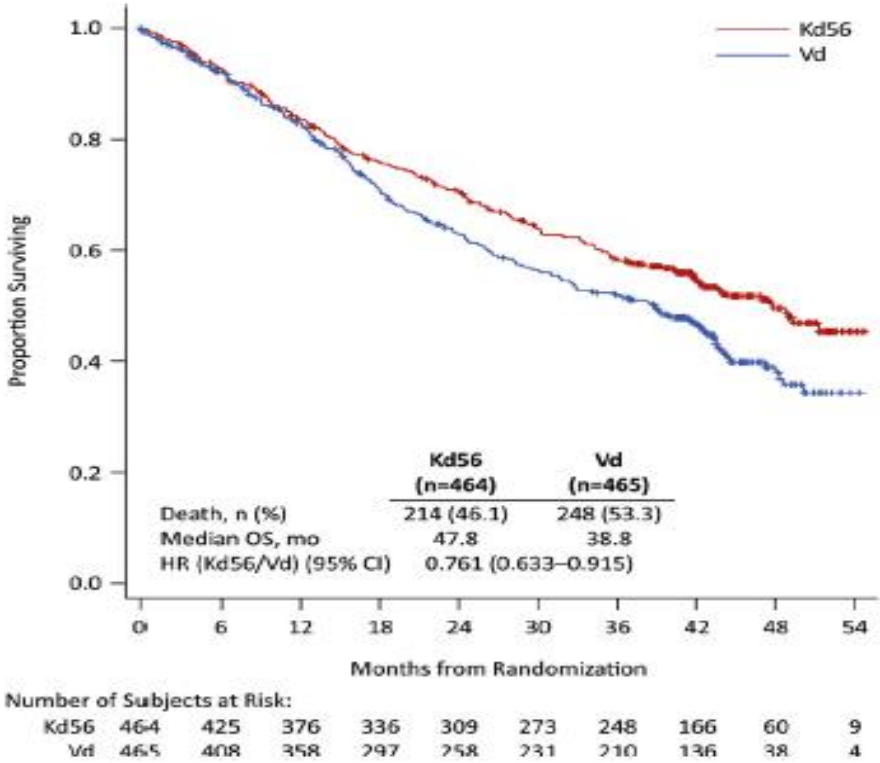
6.13 The patients in the Cd arm of ENDEAVOR had statistically significant improvements in PFS and OS compared to Bd.

Figure 3: Kaplan-Meier curve of (A) PFS (3 March 2016 data-cut) and (B) OS (19 July 2017 data-cut), ENDEAVOR

A: PFS (median follow-up = 16.6 months)



B: OS (median follow-up = 44 months)



Source: Figure 2.5.7, Figure 2.5.8 of the submission.
CI = confidence interval; IRC = independent review committee; KM = Kaplan Meier; Kd56 = carfilzomib + dexamethasone (56 mg/m^2 dose); OS = overall survival; PFS = progression free survival; Vd = bortezomib + dexamethasone.

6.14 The ORR was statistically significantly higher for patients receiving Cd compared with Bd (Table 7).

Table 7: Summary of efficacy results: ORR, ENDEAVOR (10 Nov 2014 data-cut; median OS follow up = 12.2 months)

	Cd		Bd		Difference in median, months	P value (log rank test)	HR (95% CI)
	Patients with events, n (%)	Median, months	Patients with events, n (%)	Median, months			
ORR	357 (76.9%)	1.1	293 (63.0%)	1.1	0	**<0.0001**	**2.03 (1.52, 2.72)**

Source: Table 2.5.4 of the submission.
Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; CI = confidence interval; HR = hazard ratio; IRC = independent review committee; ORR = objective response rate.
Bold values indicate statistical significance.

Subgroup analyses

6.15 The submission presented subgroup analyses from the ELOQUENT-2 and ENDEAVOR trials based on the baseline characteristics of patients to assess the consistency within trials of the treatment effect on PFS. The submission presented results stratified within subgroups; a treatment by subgroup interaction term was not reported and it is unclear if an interaction was included in each subgroup analysis. The results of the analyses for ELOQUENT-2 and ENDEAVOR demonstrated a similar, albeit not significantly different, trend of PFS advantage in favour of ELd/Cd relative to their comparators (Ld and Bd, respectively) with respect to patient characteristics (i.e. age, gender, race) and disease characteristics (i.e. ECOG performance status, creatinine clearance). The results of the test for subgroup differences showed that there were only significantly different results for Cd compared with Bd when stratified by ECOG status in ENDEAVOR.

6.16 The submission presented the subgroup analyses within each trial with respect to the number of prior therapies, with ELd showing improved PFS for two or more prior lines compared to Ld, and Cd showing improvement in PFS for one prior line compared to Bd. Prior lenalidomide (IMiD) treatment was not a treatment effect modifier for PFS in ELOQUENT-2, noting the analysis was based on a small number of patients who received lenalidomide as prior treatment. The submission stated that the results for PFS from ELOQUENT-2 showed that ELd exhibited similar efficacy across subgroups of patients with prior refractory disease compared with relapsed disease. The results of the subgroup analyses showed that prior lenalidomide use and patients who were refractory to lenalidomide had a worse outcome for Cd compared with Bd in ENDEAVOR.

Indirect treatment comparison - ELd versus Cd

6.17 The results of the ITC for the outcomes of PFS and OS are presented in Table 8. The ITC compared ELd to Cd assuming that the efficacy results for Ld and Bd were the same for the purposes of anchoring as a common comparator in the ITC. This may be inappropriate as Ld and Bd are different treatment regimens and, although the PBAC has previously considered Ld and Bd to be non-inferior, the results of the ITC could be confounded by any differences in the efficacy of these two therapies, as well as potential issues of transitivity between the trials. The submission did not adjust the

ITC for differences in efficacy between Ld and Bd. The Pre-Sub-Committee-Response (PSCR) stated that attempts of adjust for any potential differences in outcomes between Ld and Bd would have added uncertainty to the results and limited the transparency of the ITC.

Table 8: 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)

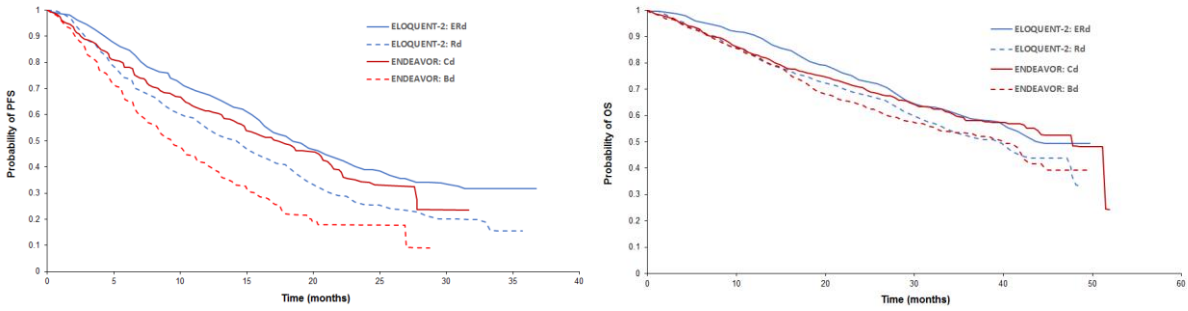
Source: Table 2.6.3, Table 2.6.4, Table 2.6.1, Table 2.6.2 of the submission.
Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; CI = confidence interval; ELd = elotuzumab + lenalidomide + dexamethasone; HR = hazard ratio; IRC = independent review committee; ITT = intention to treat; 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

6.18 The ESC noted that a non-inferiority margin was not nominated by the submission. There were no statistically significant differences between ELd and Cd in terms of PFS or OS. The results of the ITC demonstrated a numerical advantage in PFS in favour of Cd relative to ELd (HR = 1.236; 95% CI: 0.95, 1.61). Comparatively, a numerical advantage in OS was noted in favour of ELd relative to Cd (HR = 0.975; 95% CI: 0.72, 1.32).

6.19 The submission presented an overlay of the Kaplan-Meier plots for PFS and OS (Figure 4) from the ELOQUENT-2 and ENDEAVOR trials to demonstrate that there were no significant differences between ELd and Cd. The PBAC considered that due to the differences in between the trials, the overlay of the Kaplan-Meier curves for PFS and OS were not informative.

Figure 4: Overlay of Kaplan-Meier curves[a] for (A) PFS and (B) OS from the ELOQUENT-2[b] and ENDEAVOR[c] trials

A: PFS **B: OS**



Source: Figure 2.6.5, Figure 2.6.4 of the submission.
Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; ELd = elotuzumab + lenalidomide + dexamethasone; Ld = lenalidomide + dexamethasone; PFS = progression free survival.
[a] Data from the published Kaplan-Meier curves were extracted using digitising software and replotted
[b] PFS data based on ELOQUENT-2 median follow up 24.5 months (data cut 29 Oct 2014), and OS data based on median follow-up 38.7 months (data cut 29 Oct 2015)
[c] PFS data based on ENDEAVOR median follow-up 16.6 months (data cut 3 March 2016), and OS data based median follow-up 37.2 months (data cut 3 Jan 2017)

6.20 The incremental difference in OS was greater for ELd relative to Ld as the CD and Bd curves did not separate until month 15.

6.21 There are potential transitivity issues between the ELOQUENT-2 and ENDEAVOR trials which are outlined in paragraph 6.6 and 6.9. The submission stated that the relative treatment effect in terms of PFS was more pronounced in the ENDEAVOR trial compared with ELOQUENT-2 and therefore the assumption that Bd and Ld are equi-effective may be overly conservative and bias the results of the ITC in favour of Cd. The submission assumed that the efficacy results for Ld and Bd were the same, and did not include adjustments for differences in efficacy between Ld and Bd.

Comparative harms

ELd versus Ld – ELOQUENT trial

6.22 The summary of key safety outcomes from ELOQUENT-2 is presented in Table 9. Treatment with ELd was associated with more serious adverse everts (AEs) and Grade 3-4 AEs compared to treatment with Ld.

Table 9: Summary of safety outcomes from ELOQUENT-2 (3 Oct 2018 data cut-off; median OS follow up of 70.9 months)

ELOQUENT-2	ELd n with event/N (%)	Ld n with event/N (%)	RR (95% CI)
Median treatment duration	17 months	12 months	
Patients with any AE	316/318 (99.4%)	314/317 (99.1%)	1.00 (0.99, 1.02)
Patients with serious AE	238/318 (74.8%)	194/317 (61.2%)	**1.22 (1.10, 1.36)**
Patients with Grade 3-4 AE	244/318 (76.7%)	217/317 (68.5%)	**1.12 (1.02, 1.23)**
Patients with AE leading to discontinuation	114/318 (35.8%)	104/317 (32.8%)	1.09 (0.88, 1.36)
Patients with Grade 5 AE	45/318 (14.2%)	45/317 (14.2%)	1.00 (0.68, 1.46)
Deaths	212/318 (66.7%)	225/317 (71.0%)	0.94 (0.85, 1.04)
Deaths within 60 days of last dose	44/318 (13.8%)	45/317 (14.2%)	0.97 (0.66, 1.43)

Source: Table 2.5.8 of the submission.
AE = adverse event; CI = confidence interval; ELd = elotuzumab + lenalidomide + dexamethasone; Ld = lenalidomide + dexamethasone; RR = relative risk
Bold values indicate statistically significant results.

6.23 The most frequently reported Grade 3-4 AEs in the ELOQUENT-2 trial were neutropenia, anaemia, pneumonia, thrombocytopenia, fatigue and cataracts; however, the differences were not statistically significantly between the ELd and Ld arms. The ESC noted that there was a statistically significant higher risk of lymphopenia (RR =2.24; 95% CI: 1.16, 4.35) and deep vein thrombosis (DVT; RR = 2.62; 95% CI: 1.18, 5.82) with ELd treatment compared to Ld. The submission stated that post-hoc analysis found no significant differences in the incidences of any specified serious AEs. Grade 3-4 DVTs were more likely to occur in patients treated with ELd. As DVTs are a known side-effect of Ld, the increase in the risk for ELd relative to Ld may be due to the addition of elotuzumab. There was a significantly higher risk in the ELd arm with respect to AEs and serious AEs of special interest (infections and infestations of any grade and Grade 3-4) compared to Ld. The submission stated that elotuzumab has the potential to affect immune cells and increase the risk of infection due to the expression pattern of SLAMF7.

6.24 The costs of using growth-colony stimulating factors (G-CSF) associated with neutropenia were included in the CMA. Cost of aspirin and enoxaparin, and cost of dexamethasone, diphenhydramine, ranitidine and paracetamol to prevent thromboembolic events and infusion reactions, respectively, were also included in the CMA.

<u>Cd versus Bd – ENDEAVOR trial</u>

6.25 The summary of AEs reported in ENDEAVOR is presented in Table 10. Treatment with Cd was associated with more Grade 3+ and serious AEs than Bd; however, Bd was associated with more dose reductions.

Table 10: Summary of safety outcomes from ENDEAVOR (19 July 2017 data cut-off; median OS follow-up of 37.2 months)

	Cd n with event/N (%)	Bd n with event/N (%)	RR (95% CI)*
Patients with any AE	457/463 (98.7%)	451/456 (98.9%)	1.00 (0.98, 1.01)
Patients with Grade 3+ AE	379/463 (81.9%)	324/456 (71.1%)	**1.15 (1.07, 1.24)**
Patients with serious AE	279/463 (60.3%)	183/456 (40.1%)	**1.50 (1.31, 1.72)**
Patients with AE leading to discontinuation	137/463 (29.6%)	121/456 (26.5%)	1.12 (0.91, 1.37)
Patients with AE leading to PI dose reduction	138/463 (29.8%)	226/456 (49.6%)	**0.60 (0.51, 0.71)**
Patients with AE leading to death	32/463 (6.9%)	22/456 (4.8%)	1.43 (0.85, 2.43)
Patients with any AE	457/463 (98.7%)	451/456 (98.9%)	1.00 (0.98, 1.01)

Source: Table 2.5.9 of the submission.
Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; CI = confidence interval; PI = protease inhibitor; RR = risk ratio
Bold values indicate statistically significant results.

6.26 The most frequently reported Grade 3-4 AEs in ENDEAVOR were anaemia, hypertension, dyspnoea, diarrhoea and pyrexia. In terms of serious AEs, there was at least a 2% difference in the rates of pyrexia (4.1% versus 0.7%; RR = 6.24, 94% CI: 1.86, 20.93) and dyspnoea (3.9% versus 0.2%; RR = 17.73, 95% CI: 2.38, 132.2) in the Cd arm as compared to the Bd arm.

6.27 At the latest data-cut (19 July 2017), AEs (all grades) of special interest which occurred in a statistically higher proportion of patients in the Cd arm compared with Bd included: hypertension (32.4% vs. 10.1%), cardiac failure (11.0% vs. 3.5%); acute renal failure (10.8% vs. 6.4%) and infections and infestations (79.5% vs. 70.0%). Peripheral neuropathy was more common in the Bd arm compared with Cd (54.6% vs. 21.0%).

6.28 The PBAC has previously accepted that Cd has a different safety profile compared with Bd (paragraph 7.7, carfilzomib PSD, November 2016 and paragraph 6.13, carfilzomib PSD, July 2017). The PBAC has also noted that based on the 3rd Jan 2017 data cut-off the clinical data indicate a reduction in the rates of peripheral neuropathy, but an increase in serious cardiovascular AEs for Cd compared to Bd (paragraph 7.4, carfilzomib PSD, July 2017). This was supported by the 19th July 2017 data cut-off.

Safety ITC – ELd versus Cd

6.29 The submission presented a naïve ITC for the comparison of safety between ELd and Cd. The safety was compared at the end of follow-up of treatment, which for ELOQUENT-2 was 17 months (73 weeks), and for ENDEAVOR, 48 weeks. In addition, ELOQUENT-2 patients were followed for 60 days after the last study dose, and ENDEAVOR patients for 30 days after the last study dose. Thus, the comparisons may favour Cd due to the longer duration of exposure, and hence potential to accumulate more toxicity events, for ELd within ELOQUENT-2.

6.30 There was consistency between the ELd and Cd arms in terms of the incidence of patients experiencing at least one AE (99.4% vs. 98.7%); serious AE (65.4% vs. 60.3%); Grade 3-5 AE (87.4% vs. 81.9%) and AE leading to discontinuation (26.1% vs 29.6%).

6.31 The reported Grade 3-4 AEs that occurred in a higher proportion of ELd patients compared with Cd patients (≥ 5% difference in either treatment arm) were: neutropenia (27.0% vs 2.4%); pneumonia (15.1% vs. 8.4%); cataracts (10.1% vs 2.4%); and DVT (6.6% vs 0.9%), despite ELd patients receiving anti-thrombotic prophylaxis. Conversely, the following Grade 3-4 AEs were reported in a higher proportion of Cd patients compared with ELd patients (≥ 5% difference in either treatment arm): hypertension (14.5% vs 2.2%); and decreased lymphocyte count (6.3% vs 0.3%).

6.32 The pre-PBAC response acknowledged that ELd had a different safety profile to Cd, but stated that the similar rates of discontinuation due to AEs across the ELd and Cd treatment arms (26.1% vs 29.6%) suggested that the AE profile of ELd was manageable. In addition, the pre-PBAC response stated that the difference in DVT incidence was not a reason to deny an otherwise effective treatment option, but rather a reason to adhere to DVT prophylactic guidelines.

Benefits/harms

6.33 A summary of the benefits and harms was not presented given the non-inferiority nature of the claim.

Clinical claim

6.34 On the basis of the ITC, the submission claimed that ELd was non-inferior in terms of effectiveness compared to Cd.

6.35 The ITC assumed that Ld and Bd were the same in terms of efficacy. The results of the ITC for both PFS and OS were not statistically significantly different, with PFS being numerically in favour of Cd (HR = 1.236; 95% CI: 0.95, 1.61) and OS numerically in favour of ELd (HR = 0.975; 95% CI: 0.72, 1.32). However, a lack of a statistically significant difference between the proposed medicine (ELd) and the comparator (Cd) does not adequately establish non-inferiority; this would have required that the confidence limits of the difference in treatment effect do not include a clinically meaningful difference favouring the comparator (PBAC Guidelines, v5.0, 2016, Section 2.4.5, p 39).

6.36 The ESC noted that it was difficult to assess the claim of non-inferior efficacy in terms of PFS and OS due to the nature of the ITC, the lack of a stated non-inferiority margin and the transitivity issues between the trials.

6.37 The PBAC considered that the claim of non-inferior comparative effectiveness was not adequately supported by the data.

6.38 The submission claimed that on the basis of a naïve ITC that ELd has a different, yet non-inferior, safety profile relative to Cd. Although the durations of follow-up differed between the trials and may have favoured Cd, this claim might not be supported as ELd resulted in a higher frequency of Grade 3-4 AEs (including neutropenia, pneumonia, thrombocytopenia, lymphopenia, cataracts and DVT) compared to Cd.

The ESC considered that the higher occurrence of DVTs in ELd patients was a particular concern, considering they were receiving anti-thrombotic prophylaxis. The ESC considered the data did not support the claim of non-inferior safety.

6.39 The PBAC considered that the claim of different, yet non-inferior, comparative safety was not adequately supported by the data.

Economic analysis

6.40 The submission presented a CMA comparing ELd to Cd.

6.41 The CMA applied a median dose intensity (DI; reported in mg/kg/week) for ELd from ELOQUENT-2 at 38.7 months median follow-up (29th Oct 2015 data-cut), and a median relative DI (RDI; reported as a percentage) for Cd from ENDEAVOR at 37.2 months median follow up (3rd Jan 2017 data cut). The use of these data was appropriate given that the ITC for OS was based on these data cuts.

6.42 The submission stated that the 'steady state' for ELd was assumed from Cycle 3 of the ELOQUENT-2 trial and for Cd from Cycle 2 of the ENDEAVOR trial. However, as the DI for Cd in the 'steady state' was not available, the submission applied the dose intensity calculated over all cycles to the Cd arm of the CMA. This is likely to have biased the analysis in favour of ELd as the higher exposure (and dose intensity) during the first two cycles of ELd (elotuzumab was given once per week in Cycles 1 and 2, and once per fortnight in Cycles 3+) was excluded. The PSCR stated that the PBAC Guidelines, v5.0, 2016 advise that dose intensity from the 'steady state' is applied to ensure all potential confounders including, but not limited to, different discontinuation rates and different titration (or loading) schedules do not impact on the potential pricing. The ESC noted that the Guidelines state that 'For medicines that are ongoing, the 'steady state' dose comparison is generally most relevant. Calculate equi-effective doses at steady state (ie the average dose after dose titrations are complete and after excluding participants who discontinue the medicine).' The ESC noted that the Guidelines do not make reference to loading doses and considered that ELd is not an ongoing treatment, as patients cease treatment when they progress. Therefore, the ESC considered that it would be appropriate to compare the total cost per patient, including loading doses, for ELd and Cd.

6.43 The DIs reported in ELOQUENT-2 excluded exposure in patients who discontinued treatment. Thus, the estimated DIs did not reflect the mean dose exposure for ELd and may have led to an overestimation of the equi-effective doses (see the sensitivity analysis below). The DI for dexamethasone in ENDEAVOR was not available, therefore the carfilzomib RDI was applied to both carfilzomib and dexamethasone in the Cd regimen.

6.44 The submission assumed a 'steady state' dose intensity and a wastage estimate for both elotuzumab and carfilzomib. The median weekly DIs were applied for ELd (4.81 mg/kg/week for elotuzumab; 114.84 mg/week if the starting dose was 25 mg/day or

49.71 mg/week if the starting dose was less than 25 mg/day for lenalidomide; and 33.82 mg/week of dexamethasone). The median DI applied for Cd was based on an RDI of 91% (50.69 mg/m^2 for carfilzomib and 18.2 mg for dexamethasone).

6.45 The resultant equi-effective doses per cycle, as estimated by the submission, were:

1,544 mg of elotuzumab, 416 mg of lenalidomide and 135 mg of dexamethasone = 601 mg of carfilzomib and 146 mg of dexamethasone

6.46 The submission did not incorporate the length of treatment for each regimen into the estimation of the equi-effective doses. Although the mean duration of treatment (DOT) for ELd was not reported in ELOQUENT-2 at the 29 Oct 2015 data-cut (median duration of follow-up 38.7 months), the mean and median number of cycles received at this data-cut were 22.3 cycles (22.3*28/(365/12) = 20.5 months treatment) and 19 cycles (19*28/(365/12) = 17.5 months treatment) respectively. The mean DOT for Cd was not reported in the ENDEAVOR trial, but the median DOT was 48 weeks or 12 cycles (12*28/(365/12) = 11.0 months treatment) at the 3rd Jan 2017 data-cut (median duration of follow-up 37.2 months). Thus, the comparable median durations of treatment, based upon the data cuts which were used to inform the ITC and the claim of non-inferiority, were 19 cycles (17.5 months treatment) of ELd and 12 cycles (11.0 months treatment) of Cd. The difference in duration of therapy appears to reflect differences in the distribution over time of patient discontinuations; at 38.7 months follow-up, 74.0% of patients in the ELOQUENT-2 trial had discontinued ELd, whereas 89.4% of patients in ENDEAVOR had discontinued Cd at the comparable 37.2 months follow-up. As the median duration of ELd treatment in the ELOQUENT-2 was longer than the median duration of Cd treatment in the ENDEAVOR trial, this favoured ELd. The effects of including median DOT in the CMA is tested in the sensitivity analyses. The PSCR stated that if the differences in treatment duration were considered to be real effects, as opposed to naïve comparisons, then the difference in progression free survival would result in a claim of superior efficacy for ELd over Cd. Rather, the differences were likely due to differences in the patient populations and/or the conduct and follow-up of the respective trials. The PSCR stated that for consistency with the clinical claim of non-inferiority, the CMA therefore assumes the same duration of treatment for the two regimens.

6.47 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 (19 cycles/17.5 months) and Cd (12 cycles/11.0 months) in the trials 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.

6.48 The submission included additional costs and/or cost offsets associated with differences per cycle in the administration of ELd ($[redacted]) and Cd ($[redacted]) and

management of AEs and the use of prophylactic medications ($[redacted] for ELd vs $[redacted] for Cd). The ESC noted that the inclusion of these costs and/or cost offsets was appropriate.

6.49 The CMA presented by the submission was inappropriately based on the effective DPMQs/DPMAs for lenalidomide, carfilzomib and dexamethasone. The Sponsor noted that it was aware of the effective prices for the comparator therapies and applied those values in its estimates. Results based on the effective AEMPs are presented below.

Table 11: Cost-minimised price of elotuzumab re-estimated using AEMP prices for carfilzomib and lenalidomide

Row	Parameter	Inputs	Source/calculation
A	Cd drug costs per cycle (ex-man)	$[redacted]	Carfilzomib ex-man $ * 6 doses per cycle + dexamethasone ex-man $ * 1.2133 packs per cycle
B	Lenalidomide and dexamethasone drug costs per cycle (ex-man)	$[redacted]	Lenalidomide ex-man $ * 0.79 packs per cycle + dexamethasone ex-man $ (oral and IV)
C	Difference in prescribing and administration costs	-$[redacted]	
	Prescribing and administration costs: ELd	$[redacted]	
	Prescribing and administration costs: Cd	$[redacted]	
D	Difference in safety management costs	$[redacted]	
	Safety management costs: ELd	$[redacted]	
	Safety management costs: Cd	$[redacted]	
E	Difference concomitant treatment costs	$[redacted]	
	Concomitant treatment costs: ELd	$[redacted]	
	Concomitant treatment costs: Cd	$[redacted]	
F	Cost of elotuzumab per cycle (AEMP)	$[redacted]	A-B-C-D-E
G	'Steady state' doses per cycle	2	TGA PI elotuzumab
H	Cost of elotuzumab per dose	$[redacted]	F/G
I	Actual volume per dose, mg	771.8	*Estimated by submission using patient weight from ELOQUENT-2*
J	300 mg vials per dose	1.35	*Estimated by submission using patient weight from ELOQUENT-2*
K	400 mg vials per dose	0.92	*Estimated by submission using patient weight from ELOQUENT-2*
L	Cost-min weighted AEMP: 300 mg vial	$[redacted]	Calculated (H/I) x 300
M	Cost-min weighted AEMP: 400 mg vial	$[redacted]	Calculated (H/I) x 400
	Cost-min AEMP: 1,200 mg	$[redacted]	= J*4 vials or K*3 vials
	Cost -min weighted DPMA: 1,200 mg	$[redacted]	Private/public
	Cost-min private DPMA: 1,200 mg	$[redacted]	70% private hospital
	Cost-min public DPMA: 1,200 mg	$[redacted]	30% public hospital

Source: Table 3.4.4 of the submission. *Cost in italics was re-estimated based on the updated AHI, preparation fees, MBS item fees and PBS (DPMQ/DPMA) prices for July 2020.*

AEMP = approved ex-manufacturer's price; Cd = carfilzomib + dexamethasone; DPMA = dispensed price per maximum amount; ELd = elotuzumab + lenalidomide + dexamethasone; ex-man = ex-manufacturers price; IV = intravenous infusion; PI = product information; TGA = Therapeutic Goods Administration.

6.50 Applying the effective AEMPs of the comparators as the basis for the cost-minimisation, the AEMP for elotuzumab was $[redacted] per 1,200 mg, with DPMA of $[redacted] (private) and $[redacted] (public).

6.51 The results of sensitivity analyses are presented in Table 12.

Table 12: Sensitivity analyses (based on CMA using the effective AEMPs of lenalidomide, carfilzomib and dexamethasone)

Parameter	AEMP for 1,200 mg elotuzumab
Base case:	[redacted]
Altering DIs for ELd (base case: based on median doses from Cycle 3 onwards)	
DIs for ELd based on mean doses from Cycle 3 onwards	[redacted]
DIs for ELd based on median doses from all cycles[b]	[redacted]
DIs for ELd based on mean doses from all cycles[c]	[redacted]
Altering RDIs for Cd (base case = 91%)	
RDI for Cd = 93%[d] (from earlier data cut with OS median follow up of 12.5 months; median DOT of 39.9 weeks)	[redacted]
Excluding cost offsets (safety and concomitant treatment)	[redacted]
Incorporating DOT of ELd and Cd[e]	[redacted]

AEMP = approved ex-manufacturer's price; Cd = carfilzomib + dexamethasone; CMA = cost minimisation analysis; DI = dose intensity; DOT = duration of treatment; OS = overall survival; RDI = relative dose intensity; SA = sensitivity analyses.

Note:

[a] Based on mean 3+ cycles DIs the revised equi-effective doses are: 1,516 mg of elotuzumab, 383 mg of lenalidomide and 122 mg of dexamethasone = 601 mg of carfilzomib and 146 mg of dexamethasone

[b] Based on median all cycles DIs the revised equi-effective doses are: 1,676 mg of elotuzumab, 416 mg of lenalidomide and 137 mg of dexamethasone = 601 mg of carfilzomib and 146 mg of dexamethasone

[c] Based on the mean all cycles DIs the revised equi-effective doses are: 1,637 mg of elotuzumab, 383 mg of lenalidomide and 124 mg of dexamethasone = 601 mg of carfilzomib and 146 mg of dexamethasone

[d] Based on RDI of 93% for Cd the revised equi-effective doses are: 1,544 mg of elotuzumab, 416 mg of lenalidomide and 135 mg of dexamethasone = 612 mg of carfilzomib and 149 mg of dexamethasone.

[e] Duration of treatment for ELd was based on median 19 cycles (29 Oct 2015 data cut) and median of 12 cycles for Cd (3 Jan 2017 data-cut)

6.52 Incorporating the median DOTs for ELd and Cd into the CMA has the largest impact on the proposed cost-minimised price of elotuzumab. This is primarily because, over the longer DOT for ELd (19 cycles), Ld accounts for 88.5% of the comparative cost of Cd (from the shorter 12 cycles). This leaves only 11.5% of the Cd drug cost to allocate to the elotuzumab component, resulting in a substantially lower estimate of the price for elotuzumab (all other cost offsets for treatment administration, prophylactic medications and safety were also adjusted for the difference in the duration of therapy).

Drug cost/patient/cycle

6.53 Applying the equi-effective doses estimated in the submission, the cost of ELd per cycle was estimated to be $[redacted], with the cost of elotuzumab equalling $[redacted]. This was based on an estimated AEMP of $[redacted] per 1,200 mg, reflecting the AEMP prices for carfilzomib, lenalidomide and dexamethasone and updated for AHI, preparation fees, MBS items and PBS (DPMQ) prices for July 2020.

Table 13: Drug cost per patient for ELd and Cd

	ELd			Cd		
	Trial dose and duration	**CMA**	**Financial estimates**	**Trial dose and duration**	**CMA**	**Financial estimates**
Dose/cycle (based on median DI/ RDI)	Elo: 1,676 mg[a] Len: 416 mg[b] Dex: 137 mg[a]	Elo: 1,544 mg[c] Len: 416 mg[b] Dex: 135 mg[c]	Elo: 1,544 mg[c] Len: 416 mg[b] Dex: 135 mg[c]	Carf: 601 mg Dex:146 mg	Carf: 601 mg Dex:146 mg	Carf: 601 mg Dex:146 mg
Frequency/cycle	Elo: Cycles 1 and 2: 10 mg/kg once per week; Cycles 3+: 10 mg/kg once every two weeks. Len: 25 mg daily (Days 1-21) Dex: on days without Elo 40 mg orally once per week; on days with Elo 28 mg orally plus 8 mg IV. 28-day cycle			Carf: Cycle 1: 20 mg/m^2 (on days 1 and 2) and 56 mg/m^2 (on days 8, 9, 15, 16); Cycles 2+: 56 mg/m^2 (on days 1,2, 8, 9, 15, 16) Dex: 8 times per cycle 28-day cycle		
Median DOT	19 cycles[d]	1 cycle	28.6 cycles[e] (mean)	12 cycles[f]	1 cycle	28.6 cycles[e] (mean)
Cost/patient/cycle	ELd: $[redacted] Elo: $[redacted] Len: $[redacted] Dex 4mg: $4.70 Dex 8 mg: $2.95	ELd: $[redacted] Elo: $[redacted] Len: $[redacted] Dex 4 mg: $4.70 Dex 8 mg: $2.95	ELd: $[redacted] Elo: $[redacted] Len: $[redacted] Dex 4 mg: $4.70 Dex 8 mg: $2.95	Cd: $[redacted] Carf $[redacted] Dex: $5.90	Cd: $[redacted] Carf $[redacted] Dex: $5.90	Cd: $[redacted] Carf: $[redacted] Dex: $5.90
Cost/patient/course	ELd: $[redacted] Elo:$ [redacted] Len: $[redacted] Dex: $148	ELd: $[redacted]	ELd: $[redacted] Elo: $[redacted] Len: $[redacted] Dex: $220	Cd: $[redacted] Carf: $[redacted] Dex: $70	Cd: $[redacted]	Cd: $[redacted] Carf: $[redacted] Dex: $168

Source: Section 3 workbook, sheet 3a of the utilisation-and-cost-model. Italicised values have been calculated.
Carf = carfilzomib; Cd = carfilzomib + dexamethasone; CMA = cost-minimisation analysis; Dex = dexamethasone; DI = dose intensity; DOT = duration of treatment; Elo = elotuzumab; ELd = elotuzumab + lenalidomide + dexamethasone; IV = intravenous; Len = lenalidomide; RDI = relative dose intensity
[a] Based on median DI for all cycles of treatment and AEMP prices for carfilzomib, lenalidomide and dexamethasone.
[b] DI for lenalidomide was based on weighted average of two starting doses (25 mg/day or <25 mg/day) which was irrespective of the cycle
[c] Based on median DI for cycle 3+ of treatment and AEMP prices for carfilzomib, lenalidomide and dexamethasone.
[d] Median number of cycles in ELOQUENT-2 (29 Oct 2015 data-cut)
[e] Mean number of cycles in ELOQUENT-2 (3 Oct 2018 data-cut)
[f] Based on median number of cycles in the ENDEAVOR trial (Dimopoulous et al., 2017)

Estimated PBS usage & financial implications

6.54 This submission was not considered by DUSC.

6.55 The submission presented a mixed model approach combining epidemiology and market share data to estimate the financial implications of the proposed listing. This was reasonable given that the submission presented a CMA.

6.56 The estimated ELd eligible population was based on historical PBS utilisation of carfilzomib. This may not be reasonable as it is likely that ELd would also be used in patients currently receiving Ld. The ESC considered that the market shares of Cd and Ld would be difficult to estimate considering the recent PBS listings of lenalidomide and the recent PBAC recommendation for second-line DBd. The ESC did consider that Cd would likely be displaced, rather than replaced in the treatment algorithm, though

due to the number of lines of therapy available, estimating the patient numbers would also be difficult.

6.57 The estimated treatment durations of ELd and Cd were assumed to be equal and were based on the mean number of ELd cycles reported in ELOQUENT-2 at the latest data-cut, 3rd October 2018, median follow-up of 70.9 months (i.e. 28.6 cycles). This likely overestimates Cd use. The equi-effective doses of ELd and Cd were based on ELOQUENT-2 and ENDEAVOR presented in the CMA. As stated above, the calculation of the equi-effective doses may have favoured elotuzumab as it excluded the first two cycles of high-intensity therapy for ELd, resulting in a higher cost-minimised price relative to Cd (for which all cycles of therapy were included).

6.58 The submission presented financial estimates for the use of ELd as only the first treatment in the RRMM setting. This may lead to an underestimate of the utilisation of ELd in Australia, as the requested listing and the TGA approved usage is for MM after at least one prior therapy. The patients in ELOQUENT-2 were not restricted to one prior line of therapy, with the median number of prior regimens being 2 (range 1-4).

6.59 The key inputs for the financial estimates are presented in Table 14.

Table 14: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Eligible patients (Cd treated patients)	Year 1: 1,072 to Year 6: 1,208 Estimated patients treated with carfilzomib scripts from 10% PBS sample (2018), assumed 22 scripts per patients, estimated number of Cd patients in 2019 (10% PBS sample (Prospection Pharmdash)); an assumed population growth for 2020-2026 to estimate	Eligible patient population may be larger as it is likely that ELd would also be used in patients currently receiving Ld.
Assumed substitution rate	10% (Year 1) – 22% (Year 2)	The proposed substitution rate is unsupported, the ESC considered the rates to be highly uncertain.
Market growth	0% due to listing of elotuzumab	Appropriate.
Patients treated with ELd	Year 1: <500 to Year 6: <500	-
DOT	28.6 cycles for both ELd and Cd. Based on mean number of cycles in ELOQUENT-2 at 3 October 2018 data-cut (median follow-up = 70.9 months)	Equal DOTs likely overestimates Cd use.
Scripts per course of treatment	ELd ELO = 61.2, LEN = 22.7, DEX (4mg) = 27.1, DEX (8mg) = 10.3 Cd CAR = 171.6, DEX (4mg) = 34.7 Based on ELOQUENT- 2 and ENDEAVOR.	Likely overestimates Cd use compared to ELd use.
Elotuzumab	Elotuzumab 400 mg - Published: *$1,650.01* Effective: *$[redacted]*	AEMP for carfilzomib and lenalidomide were known to the sponsor. However, the CMA has incorrectly estimated the cost-minimised price for elotuzumab by applying DMPA/DPMQ prices for carfilzomib, lenalidomide and dexamethasone.
Other medicine included in therapy	Lenalidomide 25 mg - Published: *$5,961.70* Effective: *$[redacted]* Dexamethasone 4 mg: $4.84 Dexamethasone 8 mg: $8.60	
Comparator	Carfilzomib (10mg) - Published: *$326.27* Effective: *$[redacted]* Dexamethasone (4 mg, 30): *$16.68*	
MBS items	MBS Item 13915 (administration of cytotoxic chemotherapy): *$67.10* MBS Item 105 (professional attendance by a specialist): *$45.00* An MBS benefit of 80% applied in the submission.	MBS Items are appropriate.

Source: Table 4.1.1 o the submission.

CAR = carfilzomib; Cd = carfilzomib+ dexamethasone; CMA = cost minimisation analysis; DEX = dexamethasone; DPMA = dispensed price per maximum amount; ELd = elotuzumab + lenalidomide + dexamethasone; ELO = elotuzumab; LEN = lenalidomide; MBS = Medicare Benefit Schedule.

Values in italics were re-estimated based on the updated AHI preparation fees and MBS item fees for July 2020.

6.60 A summary of the estimated use and financial implications for the proposed listing of ELd for the treatment of RRMM on the PBS is presented in Table 15.

Table 15: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of scripts dispensed[a] - elotuzumab	[redacted][2]	[redacted][3]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
Number of scripts dispensed[a] - lenalidomide	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][3]	[redacted][3]	[redacted][3]
Number of scripts dispensed[a] – Dex 4 mg (tablet)	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][3]	[redacted][3]	[redacted][3]
Number of scripts dispensed[a] – Dex 8 mg (IV)	[redacted][1]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Estimated financial implications of ELd						
Cost to PBS/RPBS less copayments	$[redacted][5]	$[redacted][6]	$[redacted][7]	$[redacted][8]	$[redacted][9]	$[redacted][9]
Estimated financial implications for Cd						
Cost to PBS/RPBS less copayments	-$[redacted][5]	-$[redacted][6]	-$[redacted][7]	-$[redacted][8]	-$[redacted][8]	-$[redacted][8]
Net financial implications						
Net cost to PBS/RPBS	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]
Net cost to MBS	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]	-$[redacted][5]
Net cost to PBS/RPBS/MBS	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]	$[redacted][5]

Source: Source: Table 4.2.1, Table 4.2.2; Table 4.2.3; Table 4.2.4; Table 4.2.5, Table 4.2.11, Table 4.3.5, Table 4.5.2, Table 4.5.3 of the submission.

Values *in italics were re-estimated based on the updated AHI and preparation fees, and MBS item fees (where appropriate) for July 2020.*

Cd = carfilzomib + dexamethasone; Dex = dexamethasone; ELd = elotuzumab + lenalidomide + dexamethasone; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RRMM = relapsed refractory multiple myeloma.

[a] Assuming 28.6 cycles per patient as estimated by the submission (ELOQUENT-2).

The redacted values correspond to the following ranges:

[1] <500

[2] 500 to < 5,000

[3] 5,000 to < 10,000

[4] 10,000 to < 20,000

[5] $0 to < $10 million

[6] $10 million to < $20 million

[7] $30 million to < $40 million

[8] $40 million to < $50 million

[9] $50 million to < $60 million

6.61 The total cost to the PBS/RPBS of listing elotuzumab was estimated to be $0 to < $10 million in Year 6, with a total cost of $10 million to < $20 million in the first 6 years of listing.

6.62 The estimated financial impact of listing elotuzumab on the PBS is likely to be underestimated as the submission assumed that the DOTs of ELd and Cd were equal. In addition, the submission assumed that ELd would substitute for Cd only. In reality, it is likely that some patients currently receiving Ld would receive ELd, though the ESC considered that calculating the market shares of Cd and Ld would be difficult.

6.63 The submission stated that the positive net cost to the PBS/RPBS can be explained by different administration profiles and different loading dose periods for ELd and Cd. The explanation provided by the submission did not appear to support the difference in the positive net-cost. Rather, the additional cost to PBS/RPBS was associated with the approach used in the CMA to calculate the equi-effective doses that excluded the loading doses, and the associated costs, of ELd in Cycles 1 and 2. A lower cost-minimising price for elotuzumab would result if the equi-effective doses included ELd use from Cycles 1 and 2, decreasing the positive net-cost estimates contained in the submission.

6.64 The submission acknowledged the uncertainty associated with the substitution rates of ELd for Cd and the average duration of treatment with Cd and conducted sensitivity analyses in which the uptake rates were doubled/halved and which reduced the duration of Cd treatment from ENDEAVOR (Table 16). The net cost to the PBS/RPBS was most sensitive to the estimated duration of Cd treatment; when DOT with Cd was reduced to 18.1 cycles (estimated by the submission and based on comparative proportions from the ELOQUENT-2 trial) compared to the base case which assumed use as per ELOQUENT-2 (28.6 cycles) the net cost to Government increased to $20 million to < $30 million in Year 6 (due to fewer cost-offsets).

Table 16: Sensitivity analyses results (Net Impact PBS/RPBS/MBS effective)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Base case	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]
Increase uptake rate (doubled)	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]
Reduce uptake rate (halved)	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]
DOT Cd = 18.1 cycles[a] (base case = 28.6 cycles)	$[redacted][1]	$[redacted][1]	$[redacted][2]	$[redacted][2]	$[redacted][3]	$[redacted][3]
Elotuzumab AEMP (400 mg vial) = $809.62[b] (base case = $879.28)	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]

Source: Table 4.6.2 of the submission. Values *in italics were re-estimated during evaluation.*
AEMP = approved ex-manufacturer price; Cd = carfilzomib + dexamethasone; DI = dose intensity; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.
[a] The submission assumed that for ELd a median of 19 cycles at 38.7 months median follow-up = a mean of 26.8 cycles at 70.9 months median follow-up; therefore, for Cd a median of 12 cycles at 37.2 months median follow-up = mean of 18.1 cycles at a comparable follow-up of 70.9 months, i.e. 18.1 = 26.8 * 12/19
[b] Based on DI for all cycles in ELOQUENT-2 (as estimated during evaluation)
The redacted values correspond to the following ranges
[1] *$0 to < $10 million*
[2] *$10 million to < $20 million*
[3] *$20 million to < $30 million*

Quality Use of Medicines

6.65 The submission provided an overview of current and planned actions to support the safe and effective use of elotuzumab. These included physician education and nursing and pharmacy in-services regarding the mechanism of action of elotuzumab. A pharmacovigilance plan addressing adverse events is to be presented.

Financial Management – Risk Sharing Arrangements

6.66 The submission did not present a risk sharing arrangement (RSA) for ELd. However, the submission stated the Sponsor is willing to work with the PBAC and Department of Health to implement an appropriate RSA. The pre-PBAC response reiterated that the Sponsor was willing to join the current RSA and annual subsidisation caps for Cd.

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

7 PBAC Outcome

7.1 The PBAC did not recommend the listing of elotuzumab, in combination with lenalidomide and dexamethasone (ELd), for the treatment of patients with relapsed and/or refractory multiple myeloma (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.

7.2 The PBAC noted that the comments from consumers and from Myeloma Australia, Myeloma Australia's Medical and Scientific Group (MSAG), The Leukaemia Foundation, and Rare Cancers Australia were all in support of the requested listing for ELd, describing the ongoing need for additional treatment options for RRMM patients.

7.3 The PBAC considered that the clinical place in therapy of ELd, as proposed by the requested PBS restriction, was appropriate based on the current PBS listings, but noted that if daratumumab in combination with bortezomib and dexamethasone (DBd) is listed on the PBS and restricted to the second-line setting it will likely displace the other RRMM treatments to the third-line setting. 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 in the third-line setting.

7.4 The PBAC noted that the submission nominated Cd as the primary comparator. 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. The PBAC considered that if DBd was not listed on the PBS, then Ld and Cd were relevant comparators. The PBAC acknowledged that the implications of the recent PBS listings of lenalidomide in the first-line setting were unknown and created significant uncertainty around the predicted market shares of Ld and Cd in RRMM.

7.5 The PBAC noted that the submission presented an ITC between ELd and Cd informed

by the ELOQUENT-2 (ELd versus Ld) and ENDEAVOR (Cd versus Bd) trials.

7.6 The PBAC noted that the results of the ELOQUENT-2 trial indicated that patients treated with ELd had significantly longer PFS (HR = 0.68; 95% CI: 0.56, 0.83 at 24.5 months median follow-up) and OS (HR = 0.77; 95% CI: 0.61, 0.97 at 38.7 months median follow-up) compared to those treated with Ld.

7.7 The PBAC noted that the results of the ENDEAVOR trial indicated that patients treated with Cd had significantly longer PFS (HR = 0.55; 95% CI: 0.46, 0.65 at 16.6 months median follow-up) and OS (HR = 0.79; 95% CI: 0.65, 0.96 at 37.2 months median follow-up) compared to those treated with Bd.

7.8 The PBAC noted that the results of the ITC comparison, based on the data cuts stated in paragraphs 7.6 and 7.7 for the ELOQUENT-2 and ENDEAVOR trials, favoured Cd relative to ELd in terms of PFS (HR = 1.236; 95% CI: 0.95, 1.61) with similar OS (HR = 0.975; 95% CI: 0.72, 1.32).

7.9 The PBAC considered that there were eligibility differences (paragraph 6.7) and transitivity issues (paragraph 6.9) between the trials which limited the comparability of the trials and made interpretation of the ITC difficult. The PBAC also noted that no non-inferiority margin was nominated.

7.10 The PBAC noted that the submission assumed that the comparator arms of the trials (Ld in ELOQUENT-2 and Bd in ENDEAVOR) were equivalent and therefore did not adjust for any potential differences in the outcomes. The PBAC considered that the results of the ITC were likely to be confounded by differences in the efficacy of the comparator arm therapies, noting that in November 2016 it had stated that it may not be reasonable to assume non-inferior efficacy between Bd and Ld (paragraph 5.3, carfilzomib PSD, November 2016).

7.11 Overall, the PBAC considered that the nature of the ITC, the differences between the ELOQUENT-2 and ENDEAVOR 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.

7.12 The PBAC noted that the submission presented a naïve ITC for the comparison of safety between ELd and Cd. The PBAC noted that safety was compared at the end of follow-up of treatment, which differed considerably (ELOQUENT = 73 weeks; ENDEAVOR = 48 weeks) and may have biased the results in favour of Cd. The PBAC noted that the reported rates of Grade 3-4 adverse events (AEs) which were higher for ELd compared to Cd were neutropenia (27.0% vs 2.4%), pneumonia (15.1% vs 8.4%), cataracts (10.1% vs 2.4%) and DVT (6.6% vs 0.9%). The rates of Grade 3-4 AEs which were higher for Cd were hypertension (14.5% vs 2.2%) and decreased lymphocyte count (6.3% vs 0.3%).

7.13 Overall, the PBAC considered that non-inferiority between ELd and Cd in terms of safety was not adequately demonstrated.

7.14 The PBAC noted that the submission presented a cost minimisation analysis (CMA) between one cycle of ELd and one cycle of Cd based on the claims of non-inferior efficacy and safety. The PBAC considered the CMA between ELd and Cd 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.

7.15 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 $17.1 million over the first six years due to the CMA inappropriately not including the loading doses and associated costs of ELd in Cycles 1 and 2. The PBAC considered that the estimated financial impact of listing elotuzumab on the PBS was underestimated as the:

- submission likely overestimated Cd use by assuming that the estimated treatment durations of ELd and Cd were equal;
- proposed substitution rate of ELd for Cd (22% in Year 6) was highly uncertain; and
- eligible patient population was likely to be underestimated as the submission assumed that ELd would substitute for Cd only. The PBAC considered that ELd would also likely substitute for Ld.

7.16 The PBAC considered that any future resubmission should be a major resubmission and address the uncertainties surrounding the clinical claims.

7.17 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Rejected

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

The sponsor had no comment.