

5.07 IXAZOMIB, Capsule 2.3 mg, Capsule 3 mg, Capsule 4 mg, Ninlaro[®], Takeda Pharmaceuticals Australia Pty Ltd.

1 Purpose of submission

- 1.1 The submission requested a Section 100 (Highly Specialised Drug), Authority Required (telephone) listing for ixazomib in combination with lenalidomide and dexamethasone (ILd) 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 histologically-confirmed multiple myeloma who have experienced disease progression with at least one prior therapy
Intervention	Ixazomib in combination with lenalidomide and dexamethasone (ILd). Ixazomib 4 mg orally on Days 1, 8, and 15; plus Lenalidomide 25 mg ^a orally on Days 1-21; plus Dexamethasone 40 mg orally on Days 1, 8, 15, and 22 of each 28-day cycle continuously until disease progression
Comparator	Main comparator: Carfilzomib in combination with dexamethasone (Cd) Secondary comparator: Lenalidomide in combination with dexamethasone (Ld) Secondary near market comparator: Daratumumab in combination with bortezomib and dexamethasone (DBd)
Outcomes	PFS, OS, ORR, Safety/tolerability
Clinical claim	In patients with RRMM, ILd is superior in terms of effectiveness, and non-inferior in terms of safety to Ld. In patients with RRMM, ILd is at least non-inferior in terms of effectiveness and safety to Cd. In patients with RRMM, ILd is non-inferior in terms of effectiveness and safety to DBd.

Source: Table 1-1, pp23,25 of the submission; Moreau, 2016

Cd = carfilzomib + dexamethasone; DBd = daratumumab + bortezomib + dexamethasone; ILd = ixazomib + lenalidomide + dexamethasone; LD = lenalidomide + dexamethasone; ORR = overall response rate; OS = overall survival; PFS = progression free survival; RRMM = relapsed and/or refractory multiple myeloma

^a In TOURMALINE-MM1, for patients with a creatinine clearance of ≤ 50 or 60 mL/min/1.73m² (based on local prescribing information) the dose of lenalidomide was 10 mg.

2 Background

Registration status

- 2.1 Ixazomib in combination with lenalidomide and dexamethasone was TGA registered on the 15th of November 2016 for the treatment of patients with multiple myeloma (MM) who have received at least one prior therapy.
- 2.2 This was the first consideration of ILd 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. Qty	No. of Rpts	DPMQ ^a	Proprietary Name and Manufacturer
Ixazomib, 4 mg oral capsules			Private \$ [REDACTED]	NINLARO®
Ixazomib, 3 mg oral capsules	3	2	Public \$ [REDACTED]	Takeda Pharmaceuticals
Ixazomib, 2.3 mg oral capsules			[\$SPA TBD] ^b	Australia Pty Ltd

Category/Program:	Section 100 – Highly Specialised Drugs Program
PBS indication:	Multiple myeloma
Treatment phase:	Initial
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 not be receiving concomitant PBS-subsidised thalidomide, bortezomib, carfilzomib or pomalidomide, AND Patient must not have previously received this drug for this condition
Treatment phase:	Continuing
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition, AND The treatment must be in combination with lenalidomide and dexamethasone, AND Patient must not develop disease progression while receiving treatment with this drug for this condition, AND Patient must not be receiving concomitant PBS-subsidised thalidomide, bortezomib, carfilzomib or pomalidomide

Source: Table 1-3, Table 1-5 pp35,37,38 of the submission

Abbreviations: AEMP = approved ex-manufacturer price; DPQM = dispensed price for maximum quantity; max = maximum; qty = quantity; SPA = special pricing arrangement; TBD = to be determined

^a DPMQ of \$7,492.62 was reported in the submission, which subsequently referred to this figure as the AEMP. This was updated during the evaluation.

^b Price related to proposed special price arrangement remains to be determined

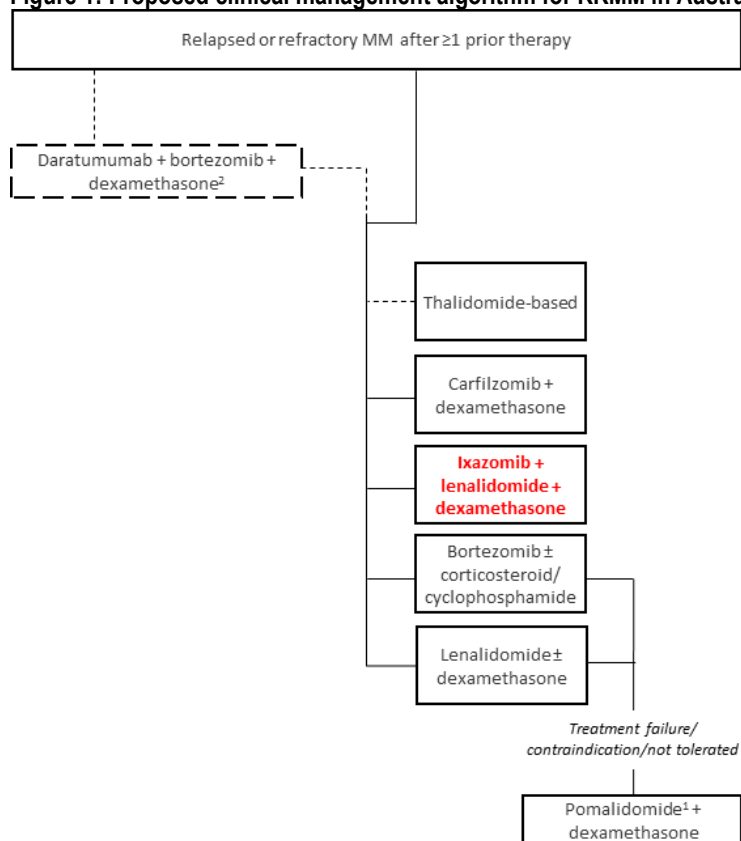
- 3.1 Based on the CMA to Cd, the submission proposed a published approved ex-manufacturer price (AEMP) of \$ [REDACTED].
- 3.2 The submission noted that special pricing arrangements (SPAs) apply to both carfilzomib and lenalidomide and requested a similar arrangement for ixazomib. No effective price was offered for ixazomib at the time of the submission given that the effective prices of the comparators were unknown to the sponsor.
- 3.3 The proposed restrictions were consistent with the TGA indication and the clinical evidence.

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

4 Population and disease

- 4.1 MM is a haematological malignancy characterised by a clonal population of plasma cells in the bone marrow derived from post-germinal-centre B cells. Classification of symptomatic MM is defined by the presence of myeloma-defining events including the presence of myeloma related organ or tissue dysfunction, such as hypercalcaemia, renal insufficiency, anaemia and bone disease (also known as CRAB features). Although long term disease control is possible, MM is an incurable, progressive disease characterised by multiple relapses with each recurrence resulting in a more aggressive disease.
- 4.2 The clinical management algorithms presented in the submission were primarily based on recommendations by the Australian Medical Scientific Advisor Group (MSAG) MM clinical practice guidelines, which were updated in October 2019. The clinical algorithm appeared reasonable and reflected the Australian treatment context. The proposed clinical algorithm provided by the submission included DBd owing to the regimen's consideration at the July 2020 PBAC meeting. However, the requested listing for DBd is specifically for treatment of second-line MM and thus 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 clinical management algorithm for RRMM in Australia



Source: Figure 1-4, p33 of the submission.

Abbreviations: MM = multiple myeloma; RRMM = relapsed and/or refractory multiple myeloma

Notes: The regimen and place in therapy requested in this submission, ixazomib in combination with lenalidomide and dexamethasone for RRMM patients with at least one prior therapy, is highlighted in red.

¹ Experienced treatment failure with lenalidomide and bortezomib, unless contraindicated or not tolerated. Pomalidomide must be used in combination with dexamethasone.

² This combination was considered at the July 2020 PBAC meeting, application appears to be limited to the second line setting in MM (i.e. only as the first therapy in the RRMM setting). Hence, considered as a near market comparator for this submission.

4.3 International guidelines note a preference for triple combination therapy (of either an immunomodulator (IMiD), proteasome inhibitor (PI), and corticosteroid; or a PI, IMiD/monoclonal antibody and corticosteroid) where possible for patients with RRMM (National Comprehensive Cancer Network (NCCN) Myeloma Guidelines Version 3.2021). This is likely to impact the utilisation of newer triple combination therapies (DBd, ILd and elotuzumab plus lenalidomide and dexamethasone) over the currently available double combination therapies in the RRMM setting. In addition, it is difficult to predict how the recent PBS listing of lenalidomide in combination with bortezomib and dexamethasone (LBd) in newly diagnosed MM (NDMM), will affect the use of triple therapy combinations in the RRMM setting.

4.4 Ixazomib is an oral, selective and reversible PI. It preferentially binds and inhibits the chymotrypsin-like activity of the β_5 subunit of the 20S proteasome core of the 26S

proteasome complex. Ixazomib has been shown to reduce cell viability in myeloma cells and disrupt the bone marrow microenvironment. The combination of ixazomib and lenalidomide demonstrated synergistic cytotoxic effects in vitro in MM cell lines.

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

5 Comparator

- 5.1 The submission nominated Cd as the main comparator, lenalidomide plus dexamethasone (Ld) as a secondary comparator and DBd as a near market comparator.
- 5.2 The choice of comparators was based on the assumption that the utilisation of lenalidomide in the newly diagnosed MM population will increase based on the recent PBS listing of lenalidomide containing regimens in newly diagnosed MM and therefore its use is likely to reduce in the RRMM setting. The submission considered that this positioned carfilzomib as a major therapy option in RRMM patients with at least one prior therapy, as carfilzomib was the second most common treatment option for patients with prior exposure to lenalidomide or bortezomib. However, this does not recognise that lenalidomide remains the backbone of ILd; thus, a patient considered eligible for ILd would likely also be considered eligible for Ld. The pre-sub-committee response (PSCR) stated that although all patients considered eligible for ILd would be eligible for Ld, it does not necessarily follow that all Ld patients would be considered eligible for ILd and that Cd was nominated as the main comparator as the patient population expected to access ILd most closely aligns with the population currently receiving Cd given the similar efficacy and tolerability profile of the regimens.
- 5.3 The ESC considered that Cd would be mostly displaced by ILd, 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.
- 5.4 The pre-PBAC response noted that a 10% sample of Medicare data from 2015 to 2019 demonstrated 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 of treatment. The pre-PBAC response stated that this suggested that for many patients, treatment substitution in the third-line setting will represent a replacement, rather than a displacement of therapy. The pre-PBAC response also noted that Cd is currently the most prescribed third-line treatment.
- 5.5 The ESC considered that the impact of the PBAC recommendation of daratumumab was particularly difficult to estimate. As 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 ILd (and Cd and Ld) would most likely be used in the third-line setting, making pomalidomide plus dexamethasone (Pd) another relevant comparator.

- 5.6 Ixazomib is an oral, selective and reversible PI and ILd is the only all oral triple combination therapy. The PBAC considered that this may make it a more attractive treatment option for those in rural/remote areas, or those unable to attend clinics for intravenous or subcutaneous administration.
- 5.7 With reference to the requirements of the National Health Act 1953, Section 101(3B), the PBAC was satisfied that ILd provides, for some patients, a significant improvement in efficacy over Ld, and by extension over bortezomib plus dexamethasone (Bd).
- 5.8 The ESC noted that elotuzumab in combination with lenalidomide and dexamethasone (ELd), 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 There was no hearing for this item.

Consumer comments

- 6.1 The PBAC noted and welcomed the input from individuals (38), health care professionals (1) and organisations (4) via the Consumer Comments facility on the PBS website. The comments from individuals who had received treatment with ixazomib described benefits including that it was an oral triple therapy, had 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.
- 6.2 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 ixazomib and the need for alternative treatments for multiple myeloma patients.

Clinical trials

- 6.3 The submission presented a naïve indirect treatment comparison (ITC) of ILd and Cd informed by two head-to-head randomised control trials (RCTs): TOURMALINE, comparing ILd with Ld (N = 722); and ENDEAVOR, comparing Cd with Bd (N = 929).
- 6.4 A naïve ITC was also presented for the comparison between ILd and DBd. The CASTOR trial (N= 498), comparing DBd with Bd was used to inform this comparison.
- 6.5 Details of the three RCTs presented in the submission are provided in Table 2.

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Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
TOURMALINE NCT01564537	TOURMALINE MM-1 Interim 1 CSR. A Phase 3, Randomised, Double-Blind, Multicentre Study Comparing Oral MLN9708 Plus Lenalidomide and Dexamethasone Versus Placebo Plus Lenalidomide and Dexamethasone in Adult Patients With Relapsed and/or Refractory Multiple Myeloma. Clinical Study Report C16010. Data cut-off date 30 October 2014 TOURMALINE MM-1 Interim 1 TFLs. Tables and figures referred to but not included in the text. Clinical Study Report C16010	May 2015
	TOURMALINE MM-1 Interim 2 CSR. A Phase 3, Randomised, Double-Blind, Multicentre Study Comparing Oral MLN9708 Plus Lenalidomide and Dexamethasone Versus Placebo Plus Lenalidomide and Dexamethasone in Adult Patients With Relapsed and/or Refractory Multiple Myeloma. Clinical Study Report C16010. Clinical Study Report C16010 Addendum 1. Data cut-off date 12 July 2015 TOURMALINE MM-1 Interim 2 TFLs. Statistical tables and figures. Clinical Study Report C16010 Addendum 1	January 2016
	Moreau, P., et al. Oral Ixazomib, Lenalidomide, and Dexamethasone for Multiple Myeloma.	New England Journal of Medicine 2016; 374(17): 1621-1634 https://dx.doi.org/10.1056/NEJMoa1516282
	Gupta, N., et al. Dose and Schedule Selection of the Oral Proteasome Inhibitor Ixazomib in Relapsed/Refractory Multiple Myeloma: Clinical and Model-Based Analyses.	Target Oncol 2017; 12(5): 643-654 10.1007/s11523-017-0524-3
	Kumar, S., et al. Management of adverse events associated with ixazomib plus lenalidomide/dexamethasone in relapsed/refractory multiple myeloma.	Br J Haematol 2017; 178(4): 571-582 10.1111/bjh.14733
	Mateos, M. V., et al. Impact of prior therapy on the efficacy and safety of oral ixazomib-lenalidomide-dexamethasone vs. placebo-lenalidomide-dexamethasone in patients with relapsed/refractory multiple myeloma in TOURMALINE-MM1.	Haematologica 2017; 102(10): 1767-1775
	Hari, P., et al. Healthcare resource utilisation with Ixazomib or placebo plus lenalidomide-dexamethasone in the randomised, double-blind, phase 3 Tourmaline-MM1 study in relapsed/refractory multiple myeloma (RRMM).	Journal of Medical Economics 2018; 21(8): 793-798 10.1080/1396998.2018.1474745
	Leleu, X., et al. Patient-reported health-related quality of life from the phase III TOURMALINE-MM1 study of ixazomib-lenalidomide-dexamethasone versus placebo-lenalidomide-dexamethasone in relapsed/refractory multiple myeloma.	Am J Hematol 2018; 93(8): 985-993. 10.1002/ajh.25134
	Dash, A. B., et al. Clinical benefit of ixazomib plus lenalidomide-dexamethasone in myeloma patients with non-canonical NF-kappaB pathway activation.	European Journal of Haematology 2020; 29: Online ahead of print. https://dx.doi.org/10.1111/ejh.13435
	Di Bacco, A., et al. c-MYC expression and maturity phenotypes are associated with outcome benefit from addition of ixazomib to lenalidomide-dexamethasone in myeloma.	Eur J Haematol 2020; 07: 07. 10.1111/ejh.13405
ENDEAVOR NCT01568866	Dimopoulos, M. A., et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): and randomised, phase 3, open-label, multicentre study.	Lancet Oncology 2016; 17(1): 27-38
	Chng, W. J., et al. Carfilzomib-dexamethasone vs bortezomib-dexamethasone in relapsed or refractory multiple myeloma by cytogenetic risk in the phase 3 study ENDEAVOR.	Leukemia

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Trial ID	Protocol title/ Publication title	Publication citation
		2017; 31(6): 1368-1374. https://dx.doi.org/10.1038/leu.2016.390
	Dimopoulos, M. A., et al. Carfilzomib or bortezomib in relapsed or refractory multiple myeloma (ENDEAVOR): an interim overall survival analysis of an open-label, randomised, phase 3 trial.	Lancet Oncology 2017; 18(10): 1327-1337. https://dx.doi.org/10.1016/S1470-2045(17)30578-8
	Ludwig, H., et al. Carfilzomib and dexamethasone vs bortezomib and dexamethasone in patients with relapsed multiple myeloma: results of the phase 3 study ENDEAVOR (NCT01568866) according to age subgroup.	Leukemia & Lymphoma 2017; 58(10): 2501-2504. https://dx.doi.org/10.1080/10428194.2017.1298755
	Moreau, P., et al. 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 2017; 31(1): 115-122. https://dx.doi.org/10.1038/leu.2016.186
	Goldschmidt, H., et al. Carfilzomib-dexamethasone versus subcutaneous or intravenous bortezomib in relapsed or refractory multiple myeloma: secondary analysis of the phase 3 ENDEAVOR study.	Leukemia & Lymphoma 2018; 59(6): 1364-1374. https://dx.doi.org/10.1080/10428194.2017.1376743
	Mateos, M. V., et al. Carfilzomib in relapsed or refractory multiple myeloma patients with early or late relapse following prior therapy: A subgroup analysis of the randomised phase 3 ASPIRE and ENDEAVOR trials.	Haematological Oncology 2018; 36(2): 463-470. https://dx.doi.org/10.1002/hon.2499
	Dimopoulos, M., et al. Carfilzomib vs bortezomib in patients with multiple myeloma and renal failure: a subgroup analysis of ENDEAVOR.	Blood 2019; 133(2): 147-155. https://dx.doi.org/10.1182/blood-2018-06-860015
	Dimopoulos, M. A., et al. Outcomes for Asian patients with multiple myeloma receiving once- or twice-weekly carfilzomib-based therapy: a subgroup analysis of the randomised phase 3 ENDEAVOR and A.R.R.O.W. Trials.	International Journal of Haematology 2019; 110(4): 466-473. https://dx.doi.org/10.1007/s12185-019-02704-z
	Ludwig, H., et al. Health-related quality of life in the ENDEAVOR study: carfilzomib-dexamethasone vs bortezomib-dexamethasone in relapsed/refractory multiple myeloma.	Blood Cancer Journal 2019; 9(3): 23. https://dx.doi.org/10.1038/s41408-019-0181-0
	Orlowski, R. Z., et al. Carfilzomib-Dexamethasone Versus Bortezomib-Dexamethasone in Relapsed or Refractory Multiple Myeloma: Updated Overall Survival, Safety, and Subgroups.	Clinical lymphoma, myeloma & leukemia 2019; 19(8): 522-530.e521. https://dx.doi.org/10.1016/j.clml.2019.04.018
CASTOR NCT02136134	Palumbo, A., et al. Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma.	New England Journal of Medicine 2016; 375(8): 754-766. https://dx.doi.org/10.1056/NEJMoa1606038
	Spencer, A., et al. Daratumumab plus bortezomib and dexamethasone versus bortezomib and dexamethasone in relapsed or refractory multiple myeloma: updated analysis of CASTOR.	Haematologica 2018; 103(12): 2079-2087. https://dx.doi.org/10.3324/haematol.2018.194118
	Mateos, M. V., et al. Daratumumab-based regimens are highly effective and well-tolerated in relapsed or refractory multiple myeloma	Haematologica

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Trial ID	Protocol title/ Publication title	Publication citation
	regardless of patient age: subgroup analysis of the phase 3 CASTOR and POLLUX studies..	2020; 105(2): 468-477. https://dx.doi.org/10.3324/haematol.2019.217448
TOURMALINE – China continuation study ^a NCT01564537	Hou, J., et al. Randomised, double-blind, placebo-controlled phase III study of ixazomib plus lenalidomide-dexamethasone in patients with relapsed/refractory multiple myeloma: China Continuation study.	J Hematol Oncol 2017; 10(1): 137. 10.1186/s13045-017-0501-4

Source: Table 2-3 pp49-50 of the submission

^a The submission did not consider this study to be directly applicable to Australian, and was excluded in step 3 of the literature screening

6.6 The submission excluded one study comparing ILd with Ld; the China Continuous Study (CCS), a regional expansion of the global TOURMALINE trial. In this trial, Chinese patients were randomised to receive either ILd or Ld (57 versus 58 patients). The CCS population was considered to have a higher proportion of patients with advanced/refractory MM. The submission did not consider CCS to be directly applicable to the Australian setting and was excluded in Step 3 of the literature screening. This seemed reasonable, in the context of differences in the clinical profile of MM and treatment patterns in China (p2, Hou et al, 2017).

6.7 The key features of the direct RCTs are summarised in Table 3.

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

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
ILd vs Ld					
TOURMALINE	722	Phase III, R, DB, MC PFS: 14.8 months (ILd) and 14.6 months (Ld) OS: 14.8/23.3 months (ILd) and 14.6/22.9 months (Ld) ^a	Low ^d	Patients who had received one to three prior lines of therapy (RRMM). ^e	Primary: PFS Key secondary: OS Other secondary: ORR, TTP ^f , Pain response rate ^f , QoL ^f
Cd vs Bd					
ENDEAVOR	929	Phase III, R, OL, MC PFS: 11.9 months (Cd) and 11.1 months (Bd) OS: 12.5/44.3 months (Cd) and 11.9/43.7 months (Bd) ^b	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, DOR, incidence of Grade ≥ 2 neuropathy ^f and Safety
DBd vs Bd					
CASTOR	498	Phase III, R, OL, MC PFS: 7.4/19.4 months OS: 13.0 months ^c	Low	Patients who had received at least one prior line of therapy and achieved at least a partial response to one or more previous therapies, and had documented progressive disease based on IMWG criteria (RRMM).	Primary: PFS Secondary: OS, ORR, DOR, TTR ^f , TTP ^f

Source: Table 2-12 p69 of the submission

Abbreviations: Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; DB = double blind; DBd = daratumumab + bortezomib + dexamethasone; DOR = duration of response; ILd = ixazomib + lenalidomide + dexamethasone; IMWG = International Myeloma Working Group; Ld = lenalidomide + dexamethasone; MC = multi-centre; OL = open label; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; R = randomised; RRMM = relapsed and/or refractory multiple myeloma; QoL = quality of life; TTP = time to progression; TTR = time to response

^a TOURMALINE data cut off for IA1 was 30th October 2014, median follow-up was 14.8 for ILd vs 14.6 months for the Ld arm; Addendum 1 was 12th July 2015, median follow-up was 23.3 for ILd vs 22.9 months for the Ld arm.

^b ENDEAVOR data cut off for IA1 was 10th November 2014, median follow-up for PFS was 11.9 vs Cd and 11.1 months for Bd and median follow-up for OS was 12.5 for Cd vs 11.9 months for Bd; IA3 was 19th July 2017, median follow-up was 44.3 for Cd vs 43.7 months for the Bd arm.

^c The median follow-up in the CASTOR trial was based on the whole trial population.

^d A high proportion of patients (60%) in both treatment arms of TOURMALINE were censored at the time of data cut-off for primary analysis of PFS (64% ILd vs, 57% Ld). The results of sensitivity analyses conducted with respect to the handling of missing data and censoring were consistent with the primary analyses, with statistically significant prolonged median PFS in ILd compared to Ld (p127 TOURMALINE IA1 CSR).

^e Patients with primary refractory disease were eligible.

^f The submission did not present the results from these endpoints as part of the clinical evaluation in Section 2.5

6.8 The overall risk of bias for both TOURMALINE and ENDEAVOR was considered to be low.

6.9 The key differences between the eligibility criteria of TOURMALINE and ENDEAVOR included:

- TOURMALINE allowed patients with a creatinine clearance (CrCl) of ≥ 30 mL/min (with lenalidomide dose modifications at CrCl ≤ 60 mL/min or 50 mL/min according to local practice), whilst ENDEAVOR had a lower threshold for renal function, allowing enrolment of patients with a CrCl ≥ 15 mL/min.

- Patients were not eligible for TOURMALINE if they had peripheral neuropathy of Grade 1 with pain or Grade > 2, whilst in ENDEAVOR patients were not eligible if they had significant neuropathy (defined as Grades 3/4 or Grade 2 with pain).
- 6.10 The PBAC noted that these differences in the eligibility criteria may have allowed patients with more advanced MM or more heavily pre-treated patients to be enrolled in ENDEAVOR compared with TOURMALINE.
- 6.11 The baseline demographic characteristics were similar between the intent to treat (ITT) populations of TOURMALINE and ENDEAVOR with respect to age (median range: 66-65 years across the arms of both trials) and Eastern Cooperative Oncology Group (ECOG) performance status, with the majority of patients in both trials having an ECOG performance status of 0 or 1 (TOURMALINE: 95% ILd vs 93% Ld and ENDEAVOR: 93% Cd versus 94% Bd). The following differences were noted between the two trials with respect to the baseline disease characteristics:
- A higher proportion of patients in TOURMALINE were International Staging System (ISS) stage I (ILd: 63% versus Ld: 64%) compared to ENDEAVOR (44% in both Cd and Bd arms). Higher stages of ISS are indicative of more severe disease.
 - Consistent with the eligibility criteria, a higher mean CrCl was observed in TOURMALINE patients (ILd: 83.0 mL/min versus Ld: 81.7 mL/min) compared to ENDEAVOR (Cd: 76.7 mL/min versus Bd: 75.1 mL/min).
 - More patients in TOURMALINE had only one prior line of therapy (ILd: 62% versus Ld: 60%) compared to those in ENDEAVOR (50% in both arms), and thus fewer patients had three lines of prior therapy (ILd: 11% versus Ld: 9%) compared to ENDEAVOR (Cd: 16% versus Bd: 19%).
 - More patients in TOURMALINE had prior therapy with bortezomib compared to ENDEAVOR (69% versus 54%), but fewer patients in TOURMALINE compared to ENDEAVOR had prior therapy with lenalidomide (12% versus 38%). The ESC noted that the submission did not provide any information on prior therapy with daratumumab.
- 6.12 Based on these differences the PBAC noted that it appeared that patients in ENDEAVOR had more severe (higher ISS stage and lower mean creatinine clearance) and advanced disease (with more prior therapy).

Comparative effectiveness

PFS outcome

6.13 A summary of the PFS results from TOURMALINE and ENDEAVOR is presented in Table 4.

Table 4: Results of PFS in TOURMALINE and ENDEAVOR (ITT)

	TOURMALINE IA1 ^a		ENDEAVOR IA1 ^b	
	ILd (N = 360)	Ld (N = 362)	Cd (N = 464)	Bd (N = 465)
Events, n (%) ^c	129 (35.8)	157 (43.4)	171 (36.9)	243 (52.3)
Median, months (95% CI)	20.6 (17.02, NE)	14.7 (12.9, 17.58)	18.7 (15.6, NE)	9.4 (8.4, 10.4)
Difference in median PFS, months	5.9 ^d		9.3 ^d	
HR (95% CI)	0.74 (0.59, 0.94)		0.53 (0.44, 0.65)	
p-value	0.012		< 0.0001	

Source: Table 2-12 p69 of the submission

Abbreviations: Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; CI = confidence interval; HR = hazard ratio; IA1 = interim analysis 1; ILd = ixazomib + lenalidomide + dexamethasone; Ld = lenalidomide + dexamethasone; n = number of participants reporting data; N = total participants in group; NE = not estimable; PFS = progression free survival;

^a TOURMALINE data cut off for IA1 was 30th October 2014, median follow-up was 14.8 for ILd vs 14.6 months for the Ld arm.

^b ENDEAVOR data cut off for IA1 was 10th November 2014, median follow-up for PFS was 11.9 months Cd and 11.1 months for Bd.

^c Events of disease progression or death

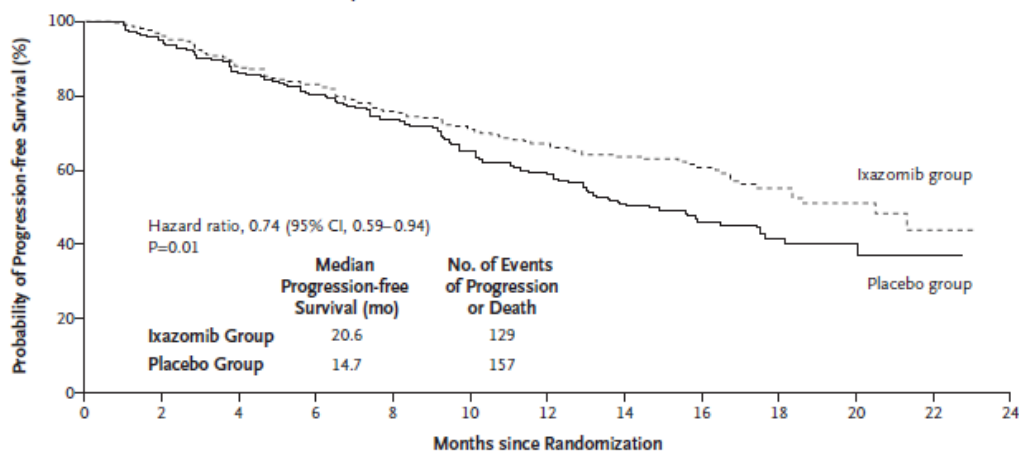
^d Results presented in the submission were rounded to the nearest month which was likely to bias results in favour of TOURMALINE as TOURMALINE was rounded up to 6 months and ENDEAVOR rounded down to 9 months.

Bold text indicates a statistically significant difference.

- 6.14 The median PFS in TOURMALINE was longer in the ILd arm (20.6 months) compared to the Ld arm (14.7 months; HR = 0.74, 95% CI: 0.59, 0.94). 64% of patients were censored in the ILd arm and 57% in the Ld arm, predominantly due to no documented death or progressive disease (ILd: 54% versus Ld: 44%). The results of sensitivity analyses for PFS with respect to the handling of missing data and censoring were consistent with the primary analyses, with statistically significant prolonged median PFS for ILd compared to Ld.
- 6.15 In ENDEAVOR, the median PFS was statistically significantly longer in the Cd arm (18.7 months) compared to the Bd arm (9.4 months; HR = 0.53, 95% CI: 0.44, 0.65).
- 6.16 The Kaplan-Meier (KM) estimates for PFS for the ITT population are presented in Figure 2 for TOURMALINE and Figure 3 for ENDEAVOR. The KM plot for PFS from the TOURMALINE trial shows separation of the curves beyond 8 months. The KM plot for PFS from the ENDEAVOR trial showed an earlier and greater separation of the curves at approximately 3 months. However, this could be due to the difference in efficacy between the comparator arms (i.e. Ld and Bd) in the two trials.

Figure 2: Kaplan-Meier analysis of PFS for TOURMALINE (IA1)

A Progression-free Survival in the Intention-to-Treat Population



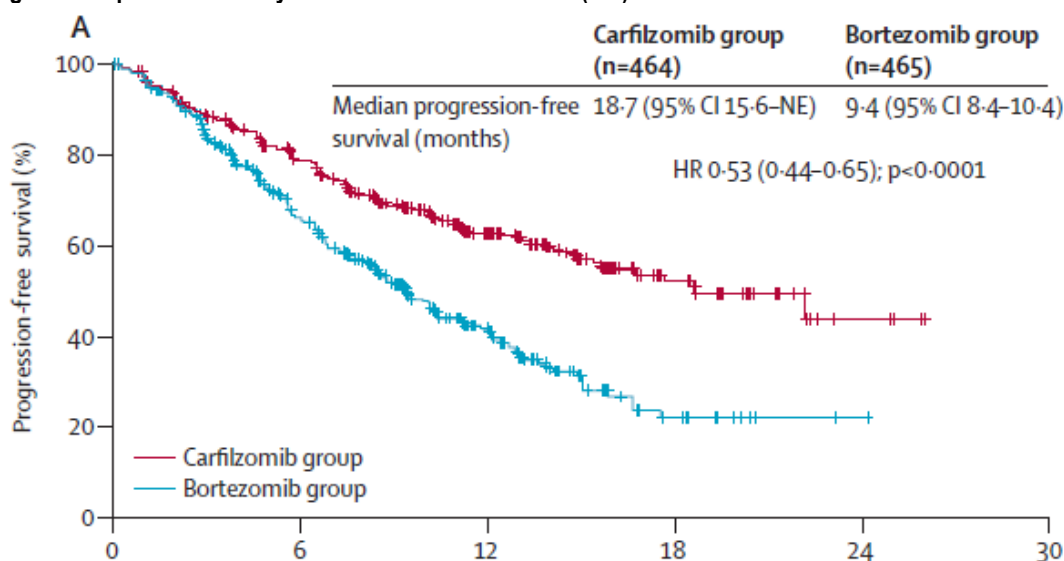
No. at Risk

Ixazomib group	360	345	332	315	298	283	270	248	233	224	206	182	145	119	111	95	72	58	44	34	26	14	9	1	0
Placebo group	362	340	325	308	288	274	254	237	218	208	188	157	130	101	85	71	58	46	31	22	15	5	3	0	0

Source: Figure 2-5 p70 of the submission

Abbreviations: CI = confidence interval; mo = months PFS = progression free survival

Figure 3: Kaplan-Meier analysis of PFS for ENDEAVOUR (IA1)



Source: Figure 2-7 p71 of the submission

Abbreviations: CI = confidence interval; HR = hazard ratio; NE = not estimable; PFS = progression free survival

Overall survival (OS) outcome

6.17 A summary of the overall survival (OS) results from TOURMALINE and ENDEAVOR is presented in Table 5.

Table 5: Results of OS in TOURMALINE and ENDEAVOR (ITT)

OS	TOURMALINE ^a				ENDEAVOR ^b			
	IA1		Addendum 1		IA1		IA3	
	ILd (N = 360)	Ld (N = 362)	ILd (N = 360)	Ld (N = 362)	Cd (N = 464)	Bd (N = 465)	Cd (N = 464)	Bd (N = 465)
Events, n (%)	51 (14.2)	56 (15.5)	81 (22.5)	90 (24.9)	75 (16.2)	88 (18.9)	214 (46.1)	248 (53.3)
Median, months (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (30.9, NE)	NE	24.3	47.8 (41.9, NE)	38.8 (31.7, 42.7)
Difference in median OS, months	NA		NA		NA		9.0	
HR (95% CI)	0.90 (0.62, 1.32)		0.87 (0.64, 1.18)		0.79 (0.58, 1.08)		0.76 (0.63, 0.92)	
p-value	0.586		0.359		0.13		0.0017	

Source: Table 2-13 p75 of the submission; Figure S2, p14 Dimopoulos et al, 2016 Supplementary Appendix

Abbreviation: Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; CI = confidence interval; HR = hazard ratio; IA1 = interim analysis 1; ILd = ixazomib + lenalidomide + dexamethasone; Ld = lenalidomide + dexamethasone; n = number of participants reporting data; N = total participants in group; NA = not applicable; NE = not estimable; OS = overall survival

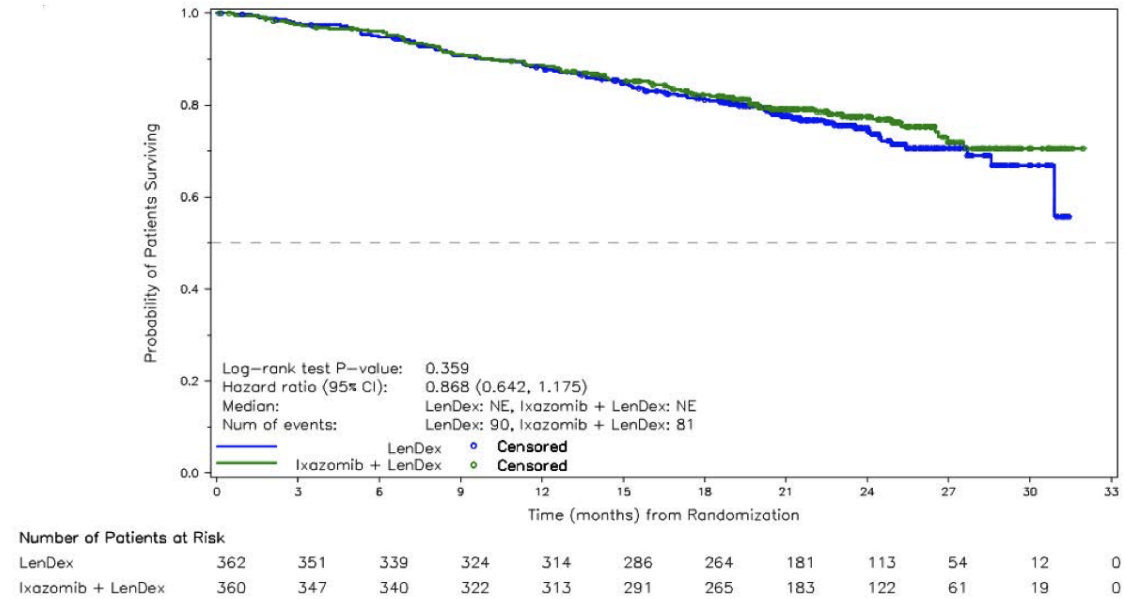
^a TOURMALINE data cut off for IA1 was 30th October 2014, median follow-up was 14.8 for ILd vs 14.6 months for the Ld arm; Addendum 1 was 12th July 2015, median follow-up was 23.3 for ILd vs 22.9 months for the Ld arm

^b ENDEAVOR data cut off for IA1 was 10th November 2014, median follow-up for OS was 12.5 for Cd vs 11.9 months for Bd; IA3 was 19th July 2017, median follow-up was 44.3 for Cd vs 43.7 months for the Bd arm.

Bold text indicates a statistically significant difference.

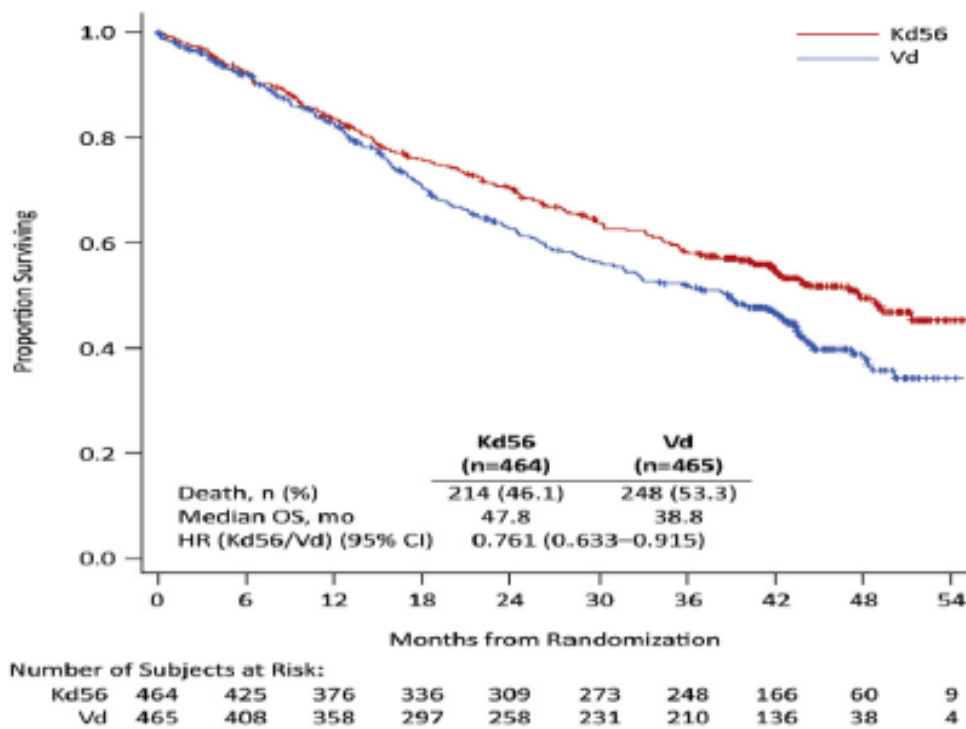
- 6.18 The ESC noted median OS had not been reached for either arm of TOURMALINE at the Addendum 1 (23-month) analysis. The difference in OS between ILd and Ld was not statistically significant different (HR = 0.87, 95% CI: 0.64, 1.18).
- 6.19 ENDEAVOR had a follow-up period sufficient to observe median OS. The median OS was 9.0 months longer in the Cd arm compared to the Bd arm and the difference in OS was statistically significant (HR = 0.76, 95% CI: 0.63, 0.92).
- 6.20 The KM estimates for OS for the ITT populations are presented in Figure 4 for TOURMALINE and Figure 5 for ENDEAVOR. In TOURMALINE, the KM plot shows a slight separation of the curves at approximately 21 months but they come together at approximately 28 months before appearing to separate again (subject to censoring and low numbers at risk at the end of the curve). The KM plot for ENDEAVOR shows a consistent separation of the curves from approximately 12 months. Apparent differences in the incremental OS noted from these curves may be due to the difference in efficacy between the comparator arms (i.e. Ld and Bd) in the two trials.

Figure 4: Kaplan-Meier analysis of OS for TOURMALINE (Addendum 1)



Source: Figure 2.2.a p26 TOURMALINE Addendum 1 CSR
 Abbreviations: CI = confidence interval; LenDex = lenalidomide + dexamethasone; NE = not estimable; Num = number; OS = overall survival

Figure 5: Kaplan-Meier analysis of OS for ENDEAVOR (IA3)



Source: Figure 2-11 p76 of the submission
 Abbreviations: CI = confidence interval; HR = hazard ratio; Kd56 = carfilzomib + dexamethasone; mo = months; OS = overall survival; Vd = bortezomib + dexamethasone

Overall response rate (ORR) outcome

6.21 A summary of the overall response rate (ORR) results from TOURMALINE and ENDEAVOR is presented in Table 6.

Table 6: Results of ORR in TOURMALINE and ENDEAVOR (ITT)

ORR	TOURMALINE ^a				ENDEAVOR ^b	
	IA1		Addendum 1		IA1	
	ILd (N = 360)	Ld (N = 362)	ILd (N = 360)	Ld (N = 362)	Cd (N = 464)	Bd (N = 465)
ORR (CR + PR) n, (%)	282 (78.3)	259 (71.5)	283 (78.6)	265 (73.2)	NR (77)	NR (63)
OR (95% CI)	1.44 (1.03, 2.03)		1.35 (0.96, 1.19)		2.03 (1.52, 2.72)	
p-value	0.035		0.089		< 0.0001	
Time to response, months						
Median (95%CI) ^c	1.1 (1.05, 1.74)	1.9 (1.84, 1.94)	1.1 (1.05, 1.74)	1.9 (1.84, 1.94)	1.1 (NR) ^d	1.1 (NR) ^d
HR (95% CI)	1.24 (1.05, 1.48)		1.23 (1.04, 1.46)		NR	
p-value	0.009		0.012		NR	
Duration of response (≥ partial response), months						
Median (95% CI)	20.5 (16.2, NE)	15.0 (12.0, NE)	26.0 (22.5, NE)	21.7 (17.8, NE)	21.3 (21.3, NE)	10.4 (9.3, 13.8)

Source: Compiled for the Commentary, Table 2-15, 2-16 and 2-17 pp77,78,79 of the submission; Table 14.3.1.5G p1255 TOURMALINE IA1 TFLs

Abbreviation: Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; CI = confidence interval; CR = complete response; HR = hazard ratio; IA = interim analysis 1; ILd = ixazomib + lenalidomide + dexamethasone; IQR = interquartile range; Ld = lenalidomide + dexamethasone; n = number of participants reporting data; N = total participants in group; NE = not estimable; NR = not reported; OR = odds ratio; ORR = overall response rate; PR = partial response

^a TOURMALINE data cut off for IA1 was 30th October 2014, median follow-up was 14.8 for ILd vs 14.6 months for the Ld arm; Addendum 1 was 12th July 2015, median follow-up was 23.3 for ILd vs 22.9 months for the Ld arm

^b ENDEAVOR data cut off for IA1 was 10th November 2014, median follow-up for PFS was 11.9 for Cd vs 11.1 months for Bd.

^c For TOURMALINE, the median time to response in patients who had a response at IA1 was 1.0 months (95%CI 0.99, 1.08) in ILd and 1.1 months (95%CI 0.99, 1.22) in Ld (HR 1.21; 95%CI 1.01, 1.44). The median time to response in patients who had a response at Addendum 1 was 1.0 months (95%CI 0.99, 1.08) in Ld and 1.1 months (95%CI 0.99, 1.28) in Ld (HR 1.27; 95%CI 1.07, 1.52).

^d In ENDEAVOR the IQR for median time to response was reported instead, Cd (1.0, 2.0) and Bd (1.0, 1.9).

Bold text indicates a statistically significant difference.

6.22 The response rate in TOURMALINE was higher for ILd compared to Ld at both IA1 (78.3% versus 71.5%; odds ratio (OR) = 1.44, 95% CI: 1.03, 2.03) and Addendum 1 (78.6% versus 73.2%; OR = 1.35, 95% CI: 0.96, 1.19). At Addendum 1, more patients receiving ILd achieved a complete response (ILd: 14.7% versus Ld: 10.2%) or a stringent complete response (ILd: 3.3% versus Ld: 1.1%; OR = 1.35), however the proportion of stable disease was lower in ILd (10.3%) compared to Ld (14.6%). Among patients who responded, time to response was rapid in both treatment arms (ILd: 1.1 months versus Ld: 1.9 months; HR = 1.23). The median duration of response in patients with a partial response or better was 26.0 months for ILd and 21.7 months for Ld.

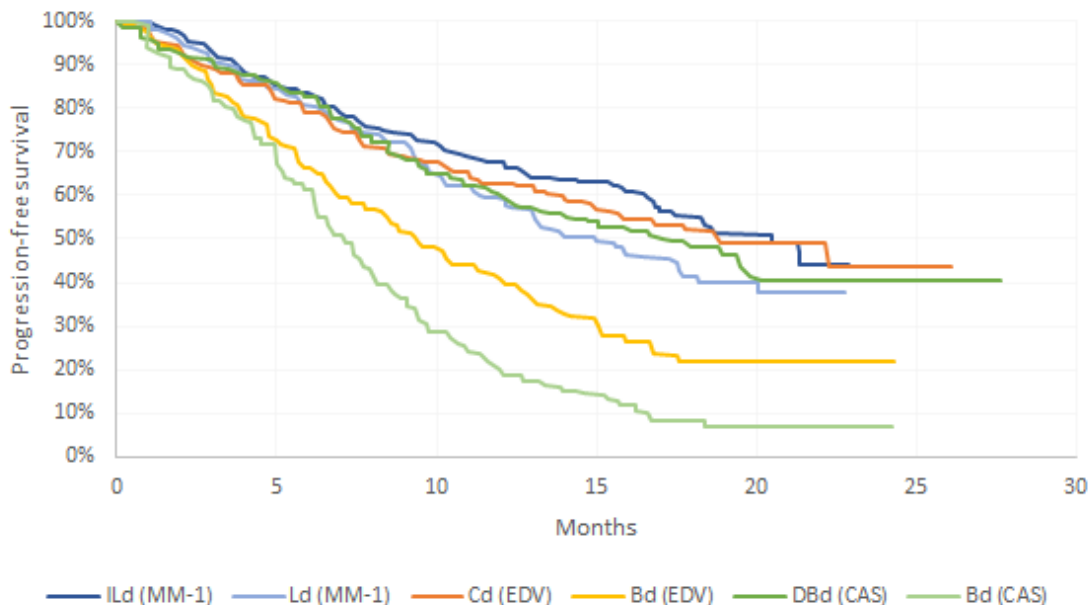
6.23 The proportion of patients achieving an overall response in ENDEAVOR was significantly higher in the Cd arm (77%) compared to the Bd arm (63%; OR = 2.03, 95% CI: 1.52, 2.72). This was consistent with patients achieving a complete response (11% versus 4%) and very good partial response (42% versus 22%; Dimopoulos, 2016) in the Cd and Bd arms respectively. The median time to response was 1.1 months in both the Cd arm (IQR: 1.0, 2.0) and the Bd arm (IQR: 1.0, 1.9). The median duration of

response in patients with a partial response or better was double for the Cd arm (21.3 months) compared to the Bd arm (10.4 months).

Indirect treatment comparison (ITC) – ILd versus Cd

- 6.24 The submission presented a naïve ITC given that the comparator arm in TOURMALINE (Ld) was different to that of ENDEAVOR (Bd). The submission stated that based on the previous PBAC consideration and network meta-analyses, the combination of Ld is likely to be more efficacious than Bd in RRMM, and thus the assumed relativity between Ld and Bd may disadvantage ILd when evaluating the relative effectiveness of this regimen compared to Cd. To support this claim, the submission presented an overlay of the KM curves for PFS from the included trials which demonstrated that Ld performed better than Bd (see Figure 6, noting the inclusion of the data from CASTOR for DBd). The PBAC considered that due to the differences between the trials, the overlay of the KM curves for PFS was not informative.
- 6.25 At the time of considering lenalidomide for RRMM, the PBAC noted that OS may possibly favour Ld over Bd, however there was uncertainty due to the ITC, and the differences in the trials used for comparison (p7, Lenalidomide Public Summary Document (PSD), November 2008 PBAC meeting). The PBAC subsequently considered that it might not be reasonable to assume non-inferior efficacy between Bd and Ld for this reason (paragraph 5.3, carfilzomib PSD, November 2016).

Figure 6: KM curves for PFS for TOURMALINE (IA1), ENDEAVOR (IA1) and CASTOR (median follow-up 19.4 months)



Source: Figure 2-12 p89 of the submission

Abbreviations: Bd = bortezomib + dexamethasone; CAS = CASTOR; Cd = carfilzomib + dexamethasone; DBd = daratumumab + bortezomib + dexamethasone; EDV = ENDEAVOR; ILd = ixazomib + lenalidomide + dexamethasone; Ld = lenalidomide + dexamethasone; MM-1 = TOURMALINE; PFS = progression free survival

6.26 The results of the naïve ITC of ILd vs Cd are presented in Table 7. The submission used various data cut off points to compare the key outcomes. The median durations of follow-up for PFS and ORR were longer in TOURMALINE (14.8 months and 23.3 months ILd, respectively) compared to ENDEAVOR (11.9 months Cd for both PFS and ORR analyses). The more mature data cut off and median duration of follow-up from TOURMALINE for these key outcomes may bias the results in favour of TOURMALINE (noting the potential for confounding from differences in baseline treatment characteristics and differences in the efficacy of the within-trial comparators).

Table 7: Results of the ITC of ILd vs Cd

Trial ID	Basis of comparison	Direct HR/OR (95%CI) ILd vs Ld or Cd vs Bd	Indirect estimate of effects
PFS			
TOURMALINE IA1 ^a	ITT	HR = 0.74 (0.59, 0.94)	Not available
ENDEAVOR IA1 ^b	ITT	HR = 0.53 (0.44, 0.65)	
OS			
TOURMALINE Addendum 1 ^c	ITT	HR = 0.87 (0.64, 1.18)	Not available
ENDEAVOR IA3 ^d	ITT	HR = 0.76 (0.63, 0.92)	
ORR			
TOURMALINE Addendum 1 ^c	ITT	OR = 1.35 (0.96, 1.19)	Not available
ENDEAVOR IA1 ^b	ITT	OR = 2.03 (1.52, 2.72)	

Source: Table 2-30, 2-30, 3-33 pp90,91 of the submission

Abbreviation: Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; CI = confidence interval; HR = hazard ratio; IA1 = interim analysis 1; IA3 = interim analysis 3; ILd = ixazomib + lenalidomide +dexamethasone; ITT = intent to treat; Ld = lenalidomide + dexamethasone; PFS = progression free survival; OS = overall survival; OR = odds ration; ORR = overall response rate

^a TOURMALINE data cut off for IA1 was 30th October 2014, median follow-up for PFS was 14.8 for ILd vs 14.6 months for the Ld arm.

^b ENDEAVOR data cut off for IA1 was 10th November 2014, median follow-up was 11.9 months vs Cd and 11.1 months for Bd.

^c TOURMALINE data cut off for Addendum 1 was 12th July 2015, median follow-up was 23.3 for ILd vs 22.9 months for the Ld arm

^d ENDEAVOR data cut off for IA3 was 19th July 2017, median follow-up was 44.3 for Cd vs 43.7 months for the Bd arm.

6.27 Based on a naïve comparison of the two trials, the HR for PFS from ENDEAVOR (HR = 0.53; 95% CI: 0.44, 0.65) was more favourable than that from TOURMALINE (HR = 0.74; 95% CI: 0.59, 0.94). The submission attributed the relative difference in median PFS between ILd vs Ld (TOURMALINE) compared to Cd vs Bd (ENDEAVOR) to the higher median PFS in the Ld arm of TOURMALINE, and argued that the median PFS for the ILd arm (20.6 month, 95% CI: 17.02, NE) and Cd arm (18.7 months, 95% CI: 15.6, NE; Table 4) were comparable.

6.28 The direct OR for ORR from ENDEAVOR (OR = 2.03; 95% CI: 1.52, 2.72) was also more favourable than that from TOURMALINE (OR = 1.35; 95% CI: 0.96, 1.19). The submission noted that a higher treatment effect was seen for the Ld arm of TOURMALINE, reducing the relative benefit for the ILd arm, and that the absolute ORR values were comparable between ILd (78.6%) and Cd (77%; Table 6). However, the results of the naïve ITC were subject to bias and cannot be readily interpreted due to

differences in the baseline disease characteristics between the trials and in the efficacy between the comparator arms.

- 6.29 The submission did not consider that conducting an ITC for OS would be useful as at the latest available follow-up period, the OS data for TOURMALINE was still immature. The ESC noted that the analyses provided in the submission were from the Addendum 1 datacut conducted in July 2015. The pre-PBAC response stated that results from the final analysis of TOURMALINE were expected no later than quarter 3 of 2021.

Comparative harms

ILd Safety

- 6.30 A summary of the adverse events (AEs) at Addendum 1 from TOURMALINE (data cut off: 12th July 2015, median follow-up 23.3 months for ILd versus 22.9 months for Ld) is presented in Table 8.

Table 8: Summary of adverse events in TOURMALINE (Safety Population)

n (%)	ILd (N = 361)	Ld (N = 359)	RD (95% CI) ^f	RR (95%CI) ^f
Any AE	355 (98)	357 (99)	-0.01 (-0.03, 0.00)	0.99 (0.97, 1.00)
Grade ≥ 3 AE	267 (74)	247 (69)	0.05 (-0.01, 0.12)	1.07 (0.98, 1.18)
TRAE ^a	335 (93)	329 (92)	0.01 (-0.03, 0.05)	1.01 (0.97, 1.06)
Grade ≥ 3 TRAE ^a	218 (60)	190 (53)	0.07 (0.00, 0.15)	1.14 (1.00, 1.30)
Any SAE	168 (47)	177 (49)	-0.03 (-0.10, 0.05)	0.94 (0.81, 1.10)
TRSAE ^a	92 (25)	92 (26)	0.00 (-0.007, 0.06)	0.99 (0.77, 1.28)
AE resulting in dose modification ^{b,c}	271 (75)	250 (70)	0.05 (-0.01, 0.12)	1.08 (0.98, 1.18)
AE resulting in dose reduction ^b	203 (56)	181 (50)	0.06 (-0.01, 0.13)	1.12 (0.97, 1.28)
AE resulting in discontinuation of any drug ^b	91 (25)	73 (20)	0.05 (-0.10, 0.11)	1.24 (0.95, 1.63)
AE resulting in discontinuation of the full regimen ^d	60 (17)	50 (14)	0.03 (-0.03, 0.08)	1.19 (0.84, 1.69)
AE-related death ^e	4 (1)	3 (1)	0.00 (-0.01, 0.02)	1.33 (0.30, 5.88)

Source: Table 2-18 p80 of the submission

Abbreviations: AE = adverse event; CI = confidence interval; ILd = ixazomib + lenalidomide +dexamethasone; Ld = lenalidomide + dexamethasone; n = number of participants reporting data; N = total participants in group; RD = risk difference; RR = relative risk; SAE = serious adverse event; TRAE = treatment related adverse event; TRSAE = treatment related serious adverse event

^a AE assessed by the investigator that was related to any drug in the drug combination (placebo/ixazomib, lenalidomide, or dexamethasone) was considered to be treatment related.

^b Of ≥ 1 of the three agents in the drug regimen

^c Dose modification included dose delay, dose reduction, and drug discontinuation, the latter which could represent discontinuation of an individual drug in the combination or a discontinuation of the full treatment regimen.

^d Discontinuation of full study drug regimen data was presented for the ITT population (N = 360 for ILd vs N = 362 for Ld)

^e Death during treatment period are defined as deaths that occurred within 30 days of the last dose of study drug.

^f RD and RR was calculated during the evaluation

- 6.31 The overall rates of any AEs, serious adverse events (SAEs) and treatment related AEs (TRAEs) were similar across both arms of TOURMALINE. The rates of Grade ≥ 3 AE and TRAEs were higher in the ILd arm (74% and 60%) compared to the Ld arm (69% and 53% respectively). None of the differences in aggregate events reported in the summary of AEs were statistically significant.
- 6.32 Grade ≥ 3 thrombocytopenia occurred more frequently in the ILd arm compared to the Ld arm (15% versus 6%). This difference was statistically significant. Other

statistically significant occurrences of Grade ≥ 3 AEs included diarrhoea (ILd: 6% versus Ld: 3%) and hypokalaemia (ILd: 4% versus Ld: 1%). The rates of SAEs were similar across both arms (1%).

Cd Safety

6.33 A summary of the AEs at IA3 from ENDEAVOR (data cut off: 19th July 2017, median follow-up 44.3 months for Cd versus 43.7 months Bd) is presented in Table 9.

Table 9: Summary of adverse events in ENDEAVOR (Safety Population)

n (%)	Cd (N = 463)	Bd (N = 456)	RD (95% CI) ^a	RR (95% CI) ^b
Any AE	457 (98.7)	451 (98.9)	0.00 (-0.02, 0.01)	1.00 (0.98, 1.01)
Grade ≥ 3 AE	379 (81.9)	324 (71.1)	0.11 (0.05, 0.16)	1.15 (1.07, 1.24)
Any SAE	279 (60.3)	183 (40.1)	0.20 (0.14, 0.26)	1.50 (1.31, 1.72)
Dose reduction of drug ^b	138 (29.8)	226 (49.6)	-0.02 (-0.26, -0.14)	0.60 (0.51, 0.71)
Discontinuation of treatment	137 (29.6)	121 (26.5)	0.03 (-0.03, 0.09)	1.12 (0.91, 1.37)
AE-related death	32 (6.9)	22 (4.8)	0.02 (-0.01, 0.05)	1.43 (0.85, 2.43)

Source: Table 2-21 p82 of the submission

Abbreviations: AE = adverse event; Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; CI = confidence interval; n = number of participants reporting data; N = total participants in group; RD = risk difference; RR = relative risk; SAE = serious adverse event

^a RD and RR was calculated during the evaluation

^b Carfilzomib or bortezomib

Bold text indicates a statistically significant difference.

6.34 Grade ≥ 3 AEs and SAEs were more frequent in the Cd arm (81.9% and 60.3%) compared to the Bd arm (71.1% and 40.1%, respectively). Among the commonly occurring Grade ≥ 3 events, anaemia (Cd: 17.3% versus Bd: 10.1%), pyrexia (Cd: 3.0% versus Bd: 0.7%), hypertension (Cd: 4.9% versus Bd: 3.3%) and dyspnoea (Cd: 3.3% versus Bd: 2.2%) were more frequent in the Cd arm compared to the Bd arm and these results were statistically significantly different. Grade ≥ 3 diarrhoea rates were lower in the Cd arm (4.1%) compared to the Bd arm (8.8%). Of the events of interest that were statistically significant, cardiac failure rates were more frequent with Cd (6.0%) compared to Bd (2.0%), but rates of peripheral neuropathy were lower with Cd (2.4%) compared to Bd (9.6%).

Indirect treatment comparison (ITC) – ILd versus Cd

6.35 A comparison of AEs reported in TOURMALINE and ENDEAVOR is presented in Table 10.

Table 10: Summary of adverse events in TOURMALINE and ENDEAVOR (Safety Population)

	TOURMALINE Addendum 1 ^a		ENDEAVOR IA3 ^b	
	ILd (N = 361)	Ld (N = 359)	Cd (N = 463)	Bd (N = 456)
Any AE	355 (98)	357 (99)	457 (98.7)	451 (98.9)
Grade ≥ 3 AE	267 (74)	247 (69)	379 (81.9)	324 (71.1)
Any SAE	168 (47)	177 (49)	279 (60.3)	183 (40.1)
AE resulting in discontinuation of the full regimen ^c	60 (17)	50 (14)	137 (29.6)	121 (26.5)
AE-related death ^d	4 (1)	3 (1)	32 (6.9)	22 (4.8)
Grade ≥3 AE occurring in ≥10% of patients in one arm				
Neutropenia	74 (20)	71 (20)	NR	NR
Thrombocytopenia	55 (15)	22 (6)	NR	NR
Anaemia	34 (9)	48 (13)	80 (17.3)	46 (10.1)
Hypertension	4 (1)	11 (3)	69 (14.9)	15 (3.3)

Source: Table 2-33 p92 of the submission

Abbreviations: AE = adverse event; Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; CI = confidence interval; IA3 = interim analysis 3; ILd = ixazomib + lenalidomide +dexamethasone; Ld = lenalidomide + dexamethasone; n = number of participants reporting data; N = total participants in group; SAE = serious adverse event

^a TOURMALINE data cut off for Addendum 1 was 12th July 2015, median follow-up was 23.3 for ILd vs 22.9 months for the Ld arm

^b ENDEAVOR data cut off for IA3 was 19th July 2017, median follow-up was 44.3 for Cd vs 43.7 months for the Bd arm.

^c Discontinuation of full study drug regimen data in TOURMALINE was presented for the ITT population (N = 360 for ILd vs N = 362 for Ld)

^d In TOURMALINE The total number of on-study deaths was 15 in the ILd arm and 23 in the Ld arm, however of the 38 on-study deaths, 7 were reported to have been related to the trial regimen (p112, TOURMALINE Addendum 1 CSR).

6.36 The median duration of follow-up at the data points for the safety analysis for the two trials varied substantially. The median follow-up in TOURMALINE (ILd: 23.3 months versus Ld: 22.9 months) was almost half the duration of follow-up in ENDEAVOR (Cd: 44.3 months versus Bd: 43.7 months). At the points of follow-up, 37.8% of the ILd arm and 36.7% of the Ld arm of TOURMALINE and 7.8% of Cd arm and 6.5% of Bd arm of ENDEAVOR were still on treatment. Thus, patients in the ENDEAVOR trial had greater potential to experience AEs. This is likely to bias the comparison of safety in favour of TOURMALINE.

6.37 Noting the large differences in median follow-up, the PSCR provided a comparison of adverse events at a median follow-up of 15 months for TOURMALINE and 11 months for ENDEAVOR to further support the claim that ILd was at least non-inferior in terms of safety compared to Cd.

Table 11: Summary of adverse events in TOURMALINE (median follow-up = 15 months) and ENDEAVOR (median follow-up = 11 months)

	TOURMALINE		ENDEAVOR	
	ILd (N = 360)	Ld (N = 360)	Cd (N = 463)	Bd (N = 456)
Any AE	351 (97.5)	355 (98.6)	455 (98.3)	447 (98.0)
Grade ≥ 3 AE	243 (67.5)	221 (61.4)	339 (73.2)	305 (66.9)
Any SAE	143 (39.7)	158 (43.9)	224 (48.4)	162 (35.5)
AE resulting in discontinuation of treatment	46 (12.8)	39 (10.8)	65 (14.0)	73 (15.7)
AE-related death	12 (3.3)	17 (4.7)	22 (4.8)	21 (4.6)
Grade ≥3 AE occurring in ≥10% of patients in one arm				
Neutropenia	67 (18.6)	58 (61.1)	10 (2.2)	10 (2.2)
Thrombocytopenia	48 (13.3)	19 (5.3)	39 (8.4)	43 (9.4)
Anaemia	31 (8.6)	45 (12.5)	67 (14.5)	45 (9.9)
Hypertension	8 (2.2)	3 (0.8)	41 (8.9)	12 (2.6)

Source: Table 1, p2 of the PSCR

Abbreviations: AE = adverse event; Bd = bortezomib + dexamethasone; Cd = carfilzomib + dexamethasone; CI = confidence interval; IA3 = interim analysis 3; ILd = ixazomib + lenalidomide + dexamethasone; Ld = lenalidomide + dexamethasone; SAE = serious adverse event

6.38 The PBAC noted that the safety profiles of ILd and Cd differed, with neutropenia (18.6%) and thrombocytopenia (13.3%) the most commonly reported Grade ≥ 3 AEs for ILd and anaemia (14.5%) and hypertension (8.9%) the most commonly reported Grade ≥ 3 AEs for Cd.

Benefits/harms

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

Clinical claim

6.40 On the basis of the naïve ITC, the submission claimed ILd was non-inferior in terms of effectiveness and safety compared with Cd.

6.41 The submission did not estimate measures of relative effect as part of the naïve ITC, on the basis that any additional efficacy benefits associated with Ld would be expected to disadvantage ILd when compared to Cd.

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

6.43 The PBAC considered that the claim of non-inferior comparative effectiveness was not adequately supported by the data due to the reasons highlighted by the ESC in paragraph 6.42.

6.44 The PBAC considered that the claim of non-inferior comparative safety was not adequately supported by the data due to the nature of the naïve ITC, the transitivity issues between the trials and the differing safety profiles of ILd and Cd.

6.45 The submission claimed superiority of ILd in terms of efficacy and non-inferiority in terms of safety when compared to Ld. Results from TOURMALINE showed statistically significant improvement in PFS for ILd compared to Ld. Thus, on the basis of these data, ILd could be considered superior in terms of PFS compared to Ld, although the data for OS remained immature. The data from TOURMALINE showed that ILd was associated with more toxicity events than Ld, including Grade ≥ 3 thrombocytopenia, diarrhoea and hypokalaemia.

Economic analysis

6.46 The submission presented a CMA comparing ILd to Cd. The key components and assumptions of the CMA are presented in Table 12.

Table 12: Key components and assumptions of the cost-minimisation analysis

Component	Claim or assumption
Therapeutic claim: effectiveness	Non-inferior PFS and likely non-inferior ORR and OS in patients with MM following disease progression with at least one prior treatment
Therapeutic claim: safety	At least non-inferior safety with a tolerable but different profile of AE
Evidence base	ITC based on TOURMALINE and ENDEAVOR
RDI (%) ^a	ILd: ixazomib 93.1%; lenalidomide 84.7%; dexamethasone 84.3% Cd: carfilzomib 91.0%; dexamethasone 91.0% ^b
Equi-effective doses	6,974.4 mg carfilzomib and 1,747.2 mg dexamethasone are equivalent to 134.1 mg ixazomib, 5,336.1 mg lenalidomide and 1,618.6 mg dexamethasone
Direct medicine costs	Carfilzomib AEMP (1 x 60 mg vial) = \$1,268.94 Lenalidomide AEMP (21 x 25 mg tablet) = \$5,928.74 Dexamethasone AEMP (30 x 4 mg tablet) = \$4.84
Other costs or cost offsets	Cost of IV infusion services for carfilzomib - \$67.10 (MBS item 13915)

Source: Table 3-1 p102 of the submission

Abbreviations: AE = adverse events; AEMP = approved ex-manufacturer price; Cd = carfilzomib + dexamethasone; ILd = ixazomib + lenalidomide + dexamethasone; ITC = indirect treatment comparison; IV = intravenous; MBS = Medicare Benefits Schedule; PFS = progression free survival; ORR = overall response rate; OS = overall survival; RDI = relative dose intensity

Cost in italics was re-estimated based on the updated MBS item fee from July 2020.

^a The submission applied a median RDI from the ENDEAVOR trial for Cd and the mean RDI for ILd based on the TOURMALINE trial. The median RDI for TOURMALINE were: ixazomib 97.4%, lenalidomide 93.8% and dexamethasone 92.8%; Table 14.1.1.4A, Table 14.1.1.4B, Table 14.1.1.4C pp84,89,94 TOURMALINE IA1 TFLs).

^b Dimopoulos et al, only stated the relative dose intensity for the proteasome inhibitor (carfilzomib) and not dexamethasone, the submission does not state and alternate source for the dexamethasone RDI.

6.47 The dosing schedules for ILd and Cd were based on the dosage regimens from the draft product information for ixazomib and the product information for carfilzomib (twice weekly regimen) and were consistent with the respective regimens in the trials and outlined in Table 1.

6.48 The submission presented a CMA in which the equi-effective doses were calculated by applying the mean relative dose intensity (RDI) for ILd from the TOURMALINE trial (at 14.8 months median follow-up) and the median RDI for Cd from the ENDEAVOR trial (at 37.5 months median follow-up). As the mean RDI for ILd was less than the median RDI at the same follow-up, the equi-effective doses of ILd are likely to be underestimated. The PSCR acknowledged that the application of median RDIs for both ILd

and Cd was reasonable. The results of a sensitivity analysis applying the median RDI for ILd are presented below.

6.49 The CMA assumed the same median treatment duration, 12.0 cycles, for both therapies, which was the median duration of Cd therapy in ENDEAVOR (at median follow-up of 37.5 months for Cd, data cut off 3rd January 2017). This may not have been reasonable as:

- the median durations of treatment used to inform the claim of non-inferiority (PFS outcome) were based on observations with a median duration of treatment of 13.0 months for ILd (median duration of follow-up 14.8 months) and 10.0 months for Cd (median duration of follow-up 11.9 months);
- the discontinuation rates varied between ILd and Cd. At 14.8 months follow-up, 44.7% of patients had discontinued ILd in TOURMALINE, whereas at 11.9 months follow-up, 75.5% of patients had discontinued Cd in ENDEAVOR. Thus, the difference in median duration of treatment also reflected an underlying difference in the distribution of treatment discontinuation; and
- the RDI for Cd (91% at a median duration of treatment of 12.0 cycles) applied by the submission differed from the RDI at a median duration of treatment of 10.0 months used to inform the primary analysis for PFS, which was 93%.

The results of the sensitivity analyses incorporating differences in the duration of therapy and the RDI are presented below.

6.50 The PSCR presented additional data from Australian patients receiving ILd via a named patient program. Patients were required to meet the same criteria of the TOURMALINE trial and were therefore considered to be representative of the proposed PBS population. The PSCR reported that for the < 500 patients, the median treatment duration was 11.0 months. The PSCR provided an additional sensitivity analysis in which median RDIs were used for both ILd (97.4% for ixazomib, 93.8% for lenalidomide and 92.8% for dexamethasone) and Cd (91.0% for both carfilzomib and dexamethasone), the median duration of treatment for ILd was 11.0 months and the median duration of treatment for Cd was 10.0 months.

6.51 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 time of PFS for ILd (13 months) and Cd (10 months) in the trials differed and that there was also a large difference in the number of discontinuations, with ILd appearing to be better tolerated than Cd. Overall, the ESC considered the uncertainties associated with the non-inferiority claim impacted on the CMA.

6.52 Although the submission included administration costs, no additional costs or cost offsets were included in the CMA. The PBAC noted that the CMA did not adjust for the

differing safety profiles or the differences in the associated costs of managing AEs for ILd and Cd.

- 6.53 With respect to concomitant medications, 96% of patients in TOURMALINE who received ILd received concomitant antithrombotic agents (comprising a mix of aspirin - 78%, enoxaparin - 24%, nadroparin - 7%, warfarin - 6 % and dalteparin - 5%), 74% received drugs for peptic ulcer and gastro-oesophageal reflux, 64% received direct acting antivirals, and 61% received analgesics and antipyretics. All patients in ENDEAVOR received antiviral and proton pump inhibitor therapies. The ESC noted that the differences in requirements for concomitant prophylactic therapies, in particular anticoagulation therapies, between ILd and Cd may have affected the CMA but that they were excluded by the submission.

Results of the CMA

- 6.54 The submission presented a CMA based on the published AEMP of its comparator. Results of the economic evaluation are summarised in Table 13 and 14.

Table 13: Results of the cost-minimisation analysis (Cd)

Row	Parameter	Input	Source/calculation
Carfilzomib			
A	Ex-manufacturer price	\$1,268.94	PBS item 11230C and 11229B
B	Total pack size, mg	60	Calculated
C	RDI, %	91.0%	ENDEAVOUR trial ^b
	Administered dose, mg		
D	Cycle 1	471.2	Calculated ^a
E	Cycle 2+	591.2	Calculated ^a
F	Median duration of therapy, cycles	12.0	As per submission ^d
G	Total dose administered, mg	6,974.4	D+(F-1)*E
H	Drug cost per treatment course	\$147,500.51	A/B*G
	Additional costs of treatment		
I	IV infusion	\$4,831.20	MBS item 13915*6 infusions/cycle*F
Dexamethasone			
J	Ex-manufacturer price	\$4.84	PBS item 2507Y
K	Total pack size, mg	120	Calculated
L	RDI, %	91.0%	Submission assumed same as carfilzomib ^b
M	Administered dose, mg	145.6	Calculated ^c
N	Median duration of therapy, cycles	12.0	As per submission ^d
O	Total dose administered, mg	1,747.2	M*N
P	Drug cost per treatment course	\$70.47	J/K*O
Q	Total Cost of Cd	\$152,402.18	H+I+P

Source: Table 3-5 p106 of the Submission

Abbreviations: Cd = carfilzomib + dexamethasone; CMA = cost-minimisation analysis; IA = interim analysis; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RDI = relative dose intensity

^a Calculated by the submission based on twice weekly regimen dosing as per carfilzomib product information, and wastage costs based on TOURMALINE baseline BSA characteristics (TOURMALINE IA1 Table 14.1.1.2 TFLs)

^b This is based on the median RDI in ENDEAVOR

^c Calculated by the submission based on the recommended dose as per carfilzomib product information per cycle x RDI

^d The submission based the CMA on a comparable median treatment duration of 12 cycles, based on the data reported at IA1 of TOURMALINE (median duration of treatment 13.0 cycles for ILd) and the data reported at IA2 of ENDEAVOR (median duration of treatment 12.0 cycles for Cd).

Cost in italics was re-estimated based on the updated MBS item fee from July 2020

Table 14: Results of the cost-minimisation analysis (ILd)

Row	Parameter	Input	Source/calculation
Lenalidomide			
A	Ex-manufacturer price	\$5,713.12	Calculated ^a
B	Total pack size, mg	Variable	
C	RDI, %	84.7%	TOURMALINE trial ^b
D	Administered dose, mg	█	Calculated ^c
E	Mean duration of therapy, cycles	█	As per submission ^g
F	Total dose administered, mg	█	E*F
G	Drug cost per treatment course	\$ █	A*E ^d
Dexamethasone			
H	Ex-manufacturer price	\$4.84	PBS item 2507Y
I	Total pack size, mg	120	Calculated
J	RDI, %	84.3%	TOURMALINE trial ^b
K	Administered dose, mg	█	Calculated ^d
L	Mean duration of therapy, cycles	█	As per submission ^g
M	Total dose administered, mg	█	K*L
N	Drug cost per treatment course	\$ █ ^e	H/I*M
Ixazomib			
O	Ex-manufacturer price	\$ █	U/S/Q
P	Total pack size, mg	█	
Q	RDI, %	93.1%	TOURMALINE trial ^b
R	Administered dose, mg	█	Calculated ^f
S	Mean duration of therapy, cycles	█	As per submission ^g
T	Total dose administered, mg	█	R*S
U	Drug cost per treatment course	\$ █	V-(G+N)
V	Total Cost of ILd	\$152,402.18	Row Q of Table 3.4.2

Source: Table 3-5 p106 of the Submission

Abbreviations: CMA = cost-minimisation analysis; IA = interim analysis; ILd = ixazomib + lenalidomide + dexamethasone; PBS = Pharmaceutical Benefits Scheme; RDI = relative dose intensity

^a Calculated by the submission based on lenalidomide dose modifications in TOURMALINE (adjusted for RDI) and the published AEMP for the various doses of lenalidomide.

^b The RDI for the ILd regimen in the CMA is based on the mean RDI from TOURMALINE

^c Calculated by the submission based on the recommended dose as per ixazomib draft product information per cycle x RDI

^d Calculated by the submission based on the recommended dose as per ixazomib draft product information per cycle x RDI

^e Table 3-5 p106 of the submission, reported \$68.28, this was corrected during the evaluation to reflect the ('Section 3 CMA Workbook – Takeda Australia - Ixazomib.xlsx')

^f Calculated by the submission based on the recommended dose as per ixazomib draft product information per cycle x RDI

^g The submission based the CMA on a comparable median treatment duration of 12 cycles, based on the data reported at IA1 of TOURMALINE (median duration of treatment 13.0 cycles for ILd) and the data reported at IA2 of ENDEAVOR (median duration of treatment 12.0 cycles for Cd).

Cost in italics was re-estimated based on the updated MBS item fee from July 2020

6.55 The total cost of the Cd regimen over 12 cycles, based on the estimated equi-effective dose (see Table 12), was estimated to be \$152,402. The submission estimated the total cost of the Ld component of ILd was \$█. Thus, the cost of the ixazomib component of the ILd regimen at the published AEMP level was \$█ (see Table 14). This resulted in a corresponding AEMP for ixazomib of \$█.

6.56 The results of the sensitivity analyses conducted to test the effects of applying mean versus median RDI for ILd, of applying durations of therapy based on the PFS outcomes which supported the clinical claim of non-inferiority and of applying the respective

RDI at the point of clinical analysis are presented in Table 15. The largest change in the total cost of ixazomib was observed when variations to the duration of therapy were applied. The equi-effective doses when the durations of therapy for ILd and Cd were consistent with the clinical evidence were: 5,792.0 mg carfilzomib and 1,456.0 mg dexamethasone over 13 cycles is equivalent to 145.2 mg ixazomib, 5,780.8 mg lenalidomide and 1,753.4 mg dexamethasone over 10 cycles.

Table 15: Sensitivity analyses ixazomib AEMP

Parameter	Total cost of Cd	Total cost of Ld ^f	Total cost of ixazomib ^g	Ixazomib AEMP estimation ^h
Base case (12 cycles of ILd and Cd, mean RDI from TOURMALINE, median from ENDEAVOUR) ^a	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Comparison of median RDI from TOURMALINE and median ENDEAVOR ^b	Based on relative distribution of lenalidomide (matched to median RDI) as per submission	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
	Assumed flat lenalidomide recommended dose of 25 mg ^c	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Duration of therapy consistent with clinical claim of non-inferior PFS (13.0 cycles of ILd and 10.0 cycles of Cd) ^d	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Duration of therapy consistent with clinical claim of non-inferior PFS (13.0 cycles of ILd and 10.0 cycles of Cd) and RDI at PFS analysis of 93% ^{d,e}	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
Duration of therapy as per base case and RDI at PFS analysis of 93% ^e	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
PSCR sensitivity analysis (median RDIs from TOURMALINE and ENDEAVOR; 11 cycles of ILd and 10 cycles of Cd)	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: calculated during evaluation and Table 2, p4 of the PSCR

Abbreviations: AEMP = approved ex-manufacturer price; Cd = carfilzomib + dexamethasone; CMA = cost minimisation analysis; IA1 = interim analysis 1; IA2 = interim analysis 2; ILd = ixazomib + lenalidomide + dexamethasone; Ld = lenalidomide + dexamethasone; RDI = relative dose intensity

^a The base case consisted of the mean RDI for TOURMALINE at data cut off for IA1 (data cut off: 30th October 2014, median follow-up was 14.8 for ILd), which was ixazomib 93.1%; lenalidomide 84.7%; dexamethasone 84.3%. The RDI for ENDEAVOR at data cut off for IA2 was 91% for carfilzomib (data cut off: 3rd January 2017; median follow-up 37.5 months).

^b This scenario compared the median RDI for TOURMALINE (ixazomib 97.4%, lenalidomide 93.8% and dexamethasone 92.8%; Table 14.1.1.4A, Table 14.1.1.4B, Table 14.1.1.4C pp84,89,94 TOURMALINE IA1 TFLs) with the median RDI for ENDEAVOR.

^c This scenario disregarded the relative distribution of lenalidomide and assumed that the recommended starting dose was 25 mg (irrespective of baseline renal function).

^d The equi-effective doses were calculated to be: 5,792.0 mg carfilzomib and 1,456.0 mg dexamethasone are equivalent to 145.2 mg ixazomib, 5,780.8 mg lenalidomide and 1,753.4 mg dexamethasone

^e The RDI from ENDEAVOR for carfilzomib at the primary analysis for PFS was 93%, the submission applied the RDI (IA1: 10th November, median follow-up 11.9 months), the submission applied a RDI (91%) from IA2.

^f As part of ILd backbone.

^g Calculated as the total cost of Cd minus the total cost of Ld.

^h Calculated as the total cost of ixazomib divided by the duration of therapy.

Drug cost/patient/course

6.57 A summary of the drug cost per patient for ILd and Cd is provided in Table 16. Based on the CMA, the cost/patient/course for a patient treated with ILd was estimated to be \$ [REDACTED] with the corresponding AEMP for ixazomib being \$ [REDACTED] (cost per cycle, based on 12.0 cycles of therapy). This was less than the cost per patient per

course arising from the financial estimates where patients were assumed to receive 13 cycles of therapy.

Table 16: Drug cost per patient for proposed and comparator drugs (based on published AEMP)

	ILd			Cd ^g		
	Trial dose and duration	CMA	Financial estimates	Trial dose and duration	CMA	Financial estimates
RDI ^a	Ixa: 93.1% Len: 84.7% Dex: 84.3%	Ixa: 93.1% Len: 84.7% Dex: 84.3%	Ixa: 100.0% Len: 84.7% Dex: N/A ^b	Car: 91.0% Dex: 91.0%	Car: 91.0% Dex: 91.0%	Car: 100% Dex: N/A ^b
Median duration of therapy ^c	13.0 cycles	12.0 cycles	13.04 cycles	10.0 cycles	12.0 cycles	13.04 cycles
Total dose administered ^d	Ixa: 145 mg Len: 5,781 mg Dex: 1,753 mg	Ixa: 134 mg Len: 5,336 mg Dex: 1,619 mg	Ixa: 156 mg Len: 5,799 mg Dex: 1,759 mg	Car: 5,792 mg Dex: 1,456 mg	Car: 6,974 mg Dex: 1,747 mg	Car: 8,340 mg Dex: 1,899 mg
Cost/patient/cycle ^e	<i>ILd: \$ [REDACTED]</i>	<i>ILd: \$ [REDACTED]</i>	<i>ILd: \$ [REDACTED]</i>	Cd: \$ 12,255	Cd: \$12,298	Cd: \$13,532
	Ixa: \$ [REDACTED] Len: \$ [REDACTED] Dex: \$ [REDACTED]	Ixa: \$ [REDACTED] Len: \$ [REDACTED] Dex: \$ [REDACTED]	Ixa: \$ [REDACTED] Len: \$ [REDACTED] Dex: \$ [REDACTED]	Car: \$12,249 Dex: \$6	Car: \$12,929 Dex: \$6	Car: \$13,526 Dex: \$6
Cost/patient/course ^f	<i>ILd: \$ [REDACTED]</i>	<i>ILd: \$ [REDACTED]</i>	<i>ILd: \$ [REDACTED]</i>	Cd: \$122,553	Cd: \$147,571	Cd: \$176,454
	Ixa: \$ [REDACTED] Len: \$ [REDACTED] Dex: \$ [REDACTED]	Ixa: \$ [REDACTED] Len: \$ [REDACTED] Dex: \$ [REDACTED]	Ixa: \$ [REDACTED] Len: \$ [REDACTED] Dex: \$ [REDACTED]	Car: \$122,494 Dex: \$59	Car: \$147,501 Dex: \$70	Car: \$176,378 Dex: \$77

Source: Section 3 workbook. Italicised values have been calculated.

^a The submission applied a median RDI from the ENDEAVOR trial for Cd and the mean RDI for ILd based on the TOURMALINE trial. The median RDI for TOURMALINE were: ixazomib 97.4%, lenalidomide 93.8% and dexamethasone 92.8%; Table 14.1.1.4A, Table 14.1.1.4B, Table 14.1.1.4C pp84,89,94 TOURMALINE IA1 TFLs).

^b The submission did not include dexamethasone in the financial estimates, as dexamethasone is a concomitant treatment in both ILd and Cd and the submission did not expect the addition of ixazomib to the PBS to increase the total number of patients treated. The RDI of dexamethasone were assumed the same as the trial for the cost/patient/cycle and cost/patient/course calculations.

^c The median duration of therapy from the clinical trials reflect the data cut offs for the clinical claim for non-inferiority based on PFS outcomes.

^d Calculated based on recommended dose per cycle x RDI x duration of therapy

^e Cost per patient per cycle was estimated based on cost of treatment per patient divided by a 12 (as the course of treatment is based on 12 cycles of therapy)

^f A course was considered to equate to the median duration of therapy

^g The cost per patient does not incorporate the costs associated with the infusion of Cd, but is only based on drug costs.

Estimated PBS usage & financial implications

6.58 This submission was not considered by DUSC.

6.59 The submission applied a market share approach to the estimation of the financial implications. This was reasonable given the assumption of non-inferiority relative to Cd. An overview of the data sources and assumptions used to populate the financial estimates is provided in Table 17.

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Table 17: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Treatment utilisation		
Substitution rate	Carfilzomib – Year 1: 5.0% to Year 6: 33.3% Lenalidomide – Year 1: 2.5% to Year 6: 5.0% Assumed by the submission.	The ESC considered these assumptions to be highly uncertain. The PBAC considered that the assumptions were not well supported. The financial estimates were highly sensitive to varying the rates of substitution.
Scripts dispensed	Year 1: [redacted] to Year 6: 5 [redacted] Calculated based on estimated annual rate of growth. Market share and size were derived from PBS statistics January 2019 to December 2019, submission assumptions and population growth rates from ABS 2018 data.	
Costs		
Proposed medicine	Published: \$7,492.62 Requested AEMP price for ixazomib (all strengths)	The submission did not include dexamethasone in the financial estimates, as no change was expected in its use since dexamethasone is a concomitant treatment with all regimens included in the model, and the addition of ixazomib to the PBS was not expected to increase the total number of patients treated. This was reasonable.
Other medicine included in therapy	Published: \$4,495.22 Lenalidomide 5 mg PEMP \$4,704.42 Lenalidomide 10 mg PEMP \$5,486.60 Lenalidomide 15 mg PEMP \$5,928.74 Lenalidomide 25 mg PEMP	
Comparator	Published: \$1,268.94 Carfilzomib 60 mg: 11229B, 11230C; \$4,495.22 Lenalidomide 5 mg: 5783J, 9642L; \$4,704.42 Lenalidomide 10 mg: 5784K, 9642M; \$5,486.60 Lenalidomide 15 mg: 5785L, 9644N; \$5,928.74 Lenalidomide 25 mg 5786M, 9645P	
Patient co-payment	PBS = \$18.00; RPBS = \$5.88 Sourced from the Medicare Statistics website. Carfilzomib and lenalidomide (in RRMM setting) PBS scripts processed from January 2019 to December 2019.	
MBS costs	MBS item 13915 (administration of cytotoxic chemotherapy) – \$67.10	Attributed to the Cd regimen for IV administration.

Source: Table 4-2, 4-4, 4-11 pp108, 117,122 of the submission

Abbreviations: ABS = Australian Bureau of Statistics; AEMP = approved ex-manufacturer price; IV = intravenous infusion; MBS = Medicare Benefit Schedule; PBS= Pharmaceutical Benefits Scheme; PEMP = proportional ex-manufacturer price; RPBS = Repatriation Schedule of Pharmaceutical Benefits; RRMM = relapsed refractory multiple myeloma

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

The redacted values correspond to the following ranges:

¹40,000 to <50,000

²50,000 to <60,000

6.60 The submission assumed use of lenalidomide prior to first relapse would increase following the recent PBS listings of lenalidomide monotherapy as maintenance treatment post-autologous stem cell transplant (ASCT) and of LbD for NDMM patients. This would potentially reduce the use of lenalidomide in the RRMM setting, matched by a corresponding increase in utilisation of carfilzomib. However, this does not recognise that lenalidomide remains the backbone of ILd, thus a patient considered eligible for Ld would also likely be considered eligible for ILd.

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6.61 A summary of the estimated extent of use (prescriptions) for ixazomib and substitution for its comparators is provided in Table 18.

Table 18: Estimated ixazomib script volume and proportion of medicines affected by ixazomib

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated ixazomib script volume						
Net PBS/RPBS	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Proportion of medicines affected by ixazomib						
Carfilzomib – all strengths ^a						
Proportion affected by ixazomib	5.00%	25.00%	33.33%	33.33%	33.33%	33.33%
Net effect – PBS/RPBS	-█ ¹	-█ ²	-█ ²	-█ ³	-█ ³	-█ ³
Lenalidomide 5 mg						
Proportion affected by ixazomib	2.50%	4.00%	5.00%	5.00%	5.00%	5.00%
Net effect – PBS/RPBS	-█ ⁴	-█ ⁴	-█ ⁴	-█ ⁴	-█ ⁴	-█ ⁴
Lenalidomide 10 mg						
Proportion affected by ixazomib	2.50%	4.00%	5.00%	5.00%	5.00%	5.00%
Net effect – PBS/RPBS	-█ ⁴	-█ ⁴	-█ ⁴	-█ ⁴	-█ ⁴	-█ ⁴
Lenalidomide 15 mg						
Proportion affected by ixazomib	2.50%	4.00%	5.00%	5.00%	5.00%	5.00%
Net effect – PBS/RPBS	-█ ⁴	-█ ⁴	-█ ⁴	-█ ⁴	-█ ⁴	-█ ⁴
Lenalidomide 25 mg						
Proportion affected by ixazomib	2.50%	4.00%	5.00%	5.00%	5.00%	5.00%
Net effect – PBS/RPBS	-█ ⁴	-█ ⁴	-█ ⁴	-█ ⁴	-█ ⁴	-█ ⁴

Source: Table 4-7,4-11 pp119-122 of the submission

Abbreviations: PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Schedule of Pharmaceutical Benefits

^a The submission expected that one service of ixazomib and one service of lenalidomide was expected to substitute for six services of carfilzomib

The redacted values correspond to the following ranges:

¹500 to <5,000

²5,000 to <10,000

³10,000 to <20,000

⁴<500

6.62 A summary of the financial implications of the proposed listing of ILd for the treatment of RRMM on the PBS is presented in Table 19.

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Table 19: Estimated financial implications of listing ILd on the PBS/RPBS

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
ILd						
Cost to PBS (less patient co-payment)	\$ ██████ ¹	\$ ██████ ²	\$ ██████ ³	\$ ██████ ³	\$ ██████ ³	\$ ██████ ³
Cost to RPBS (less patient co-payment)	\$ ██████ ¹	\$ ██████ ¹	\$ ██████ ¹	\$ ██████ ¹	\$ ██████ ¹	\$ ██████ ¹
Total cost of ILd	\$ ██████ ¹	\$ ██████ ²	\$ ██████ ³	\$ ██████ ³	\$ ██████ ³	\$ ██████ ³
Substituted medicines						
Cost to PBS (less patient co-payment)	-\$ ██████ ¹	-\$ ██████ ³	-\$ ██████ ²	-\$ ██████ ³	-\$ ██████ ³	-\$ ██████ ³
Cost to RPBS (less patient co-payment)	-\$ ██████ ¹	-\$ ██████ ¹	-\$ ██████ ¹	-\$ ██████ ¹	-\$ ██████ ¹	-\$ ██████ ¹
Total cost of substituted medicines	-\$ ██████ ¹	-\$ ██████ ²	-\$ ██████ ³	-\$ ██████ ³	-\$ ██████ ³	-\$ ██████ ³
Net cost to PBS/RPBS						
Net cost to PBS	\$ ██████ ¹	\$ ██████ ¹	\$ ██████ ¹	\$ ██████ ¹	\$ ██████ ¹	\$ ██████ ¹
Net cost to RPBS	\$ ██████ ¹	\$ ██████ ¹	\$ ██████ ¹	\$ ██████ ¹	\$ ██████ ¹	\$ ██████ ¹
Net cost to PBS/RPBS	\$ ██████ ¹	\$ ██████ ¹	\$ ██████ ¹	\$ ██████ ¹	\$ ██████ ¹	\$ ██████ ¹
Cost to other Govt budgets						
Net cost to MBS	-\$ ██████ ¹	-\$ ██████ ¹	-\$ ██████ ¹	-\$ ██████ ¹	-\$ ██████ ¹	-\$ ██████ ¹
Net cost to Govt budgets	-\$ ██████ ¹	-\$ ██████ ¹	-\$ ██████ ¹	-\$ ██████ ¹	-\$ ██████ ¹	-\$ ██████ ¹

Source: Table 4-16 p127 of the submission

Abbreviations: MBS = Medicare Benefit Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Schedule of Pharmaceutical Benefits

Cost in italics was re-estimated based on the updated MBS item fee from July 2020.

The redacted values correspond to the following ranges:

1\$0 to <\$10 million

2\$20 to <\$30 million

3\$30 million to <\$40 million

- 6.63 The total net cost of listing ixazomib was estimated to be \$0 to <\$10 million over the first 6 years of listing.
- 6.64 Although the submission requested grandfathering provisions for ixazomib for a small number of Australian patients who are currently receiving treatment via a compassionate access scheme, the estimates of the use of ixazomib in that patient population were not presented in the financial cost model workbook.
- 6.65 The submission acknowledged that some uncertainties existed in the forecasting of respective market shares of the substituted therapies, in light of recent PBAC recommendations (e.g. DBd), which may lead to changes in the current treatment landscape for MM. The substitution rates adopted in the financial estimates were not well supported. Furthermore, the estimates assumed a higher substitution rate for Cd compared to Ld, contradictory to historical market data, based on predictions associated with recent PBS listings. A sensitivity analysis was conducted during the evaluation which assumed a lower substitution rate for Cd and higher substitution rate for Ld (Table 20). It was not possible to test the impact on the financial implications of

potential differences in the duration of therapy (see the CMA discussion) as this was not incorporated into the structure of the financial impact workbook.

- 6.66 The ESC considered that the market shares of the different therapies would be very 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. Finally, the ESC considered that as ILd is an oral triplet therapy, uptake could be high, particularly in rural and remote areas.

Table 20: Sensitivity analyses results (Net Impact PBS/RPBS/MBS)

	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
Modified Substitution rate ^a	\$ [redacted] ¹	\$ [redacted] ¹	\$ [redacted] ¹	\$ [redacted] ¹	\$ [redacted] ¹	\$ [redacted] ¹

Source: Table 4-16 p127 of the submission

Abbreviations: Cd = carfilzomib + dexamethasone; Ld = lenalidomide + dexamethasone; MBS = Medicare Benefit Schedule; PBS= Pharmaceutical Benefits Scheme; RPBS = Repatriation Schedule of Pharmaceutical Benefits

Cost in italics was re-estimated based on the updated MBS item fee from July 2020.

^a The sensitivity analysis assumes a lower substitution rate for Cd (maximum of 20% by Year 3) and a higher substitution rate for Ld (maximum 10% over available lenalidomide market by year 2).

The redacted values correspond to the following ranges:

¹\$0 to <\$10 million

- 6.67 The financial estimates are based on the twice weekly carfilzomib regimen. However, the weekly regimen received a positive PBAC recommendation at the July 2020 PBAC Meeting.

Quality Use of Medicines

- 6.68 The submission did not present a quality use of medicines section. However, a planned strategy for the safe and effective use of ixazomib would be important with respect to the complex dosing regimen of ILd (and associated co-commitment supportive medications). Thus, health care professional education on the mechanism of action, identification and management of adverse effect symptoms, dose modifications in light of laboratory results are considered necessary at the prescribing and dispensing stage.

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

7 PBAC Outcome

- 7.1 The PBAC did not recommend ixazomib, in combination with lenalidomide and dexamethasone (ILd), for the treatment for patients with relapsed and/or refractory multiple myeloma (RRMM). The PBAC considered that, due to the nature of the naïve indirect treatment comparison (ITC) and differences between the key trials, the results of the naïve ITC were difficult to interpret and did not adequately demonstrate non-

- inferiority between ILd 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 ILd, describing the ongoing need for additional treatment options for RRMM patients.
 - 7.3 The PBAC noted that as ixazomib was an oral capsule, ILd was an entirely oral triple therapy which may have advantages for rural and remote patients.
 - 7.4 The PBAC considered that the clinical place in therapy of ILd, 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 ILd would potentially replace Ld and replace/displace Cd in the third-line setting.
 - 7.5 The PBAC noted that the submission nominated Cd as the primary comparator, and lenalidomide plus dexamethasone (Ld) and DBd as secondary comparators. 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.
 - 7.6 The PBAC noted that the submission presented a naïve ITC between ILd and Cd informed by the TOURMALINE (ILd versus Ld) and ENDEAVOUR (Cd versus Bd) trials. The PBAC noted that there were a number of eligibility criteria differences (see paragraph 6.9) and transitivity issues (paragraph 6.11) between the trials which may have resulted in patients in the ENDEAVOUR trial having more severe (higher ISS stage and lower mean creatinine clearance) and more advanced (more prior therapies) disease at baseline.
 - 7.7 The PBAC noted that the hazard ratio for progression free survival (PFS) for Cd versus Bd from ENDEAVOR (HR = 0.53; 95% CI: 0.44, 0.65) was more favourable than that for ILd versus Ld from TOURMALINE (HR = 0.74; 95% CI: 0.59, 0.94). As the submission presented a naïve ITC, with no comparison between the comparator arms (Ld for TOURMALINE and Bd for ENDEAVOR), the PBAC considered that the results of the naïve ITC were difficult to interpret.
 - 7.8 The PBAC noted that the hazard ratio for overall survival (OS) was statistically significant for Cd versus Ld from ENDEAVOR (HR = 0.76; 95% CI: 0.63, 0.92), but was not statistically significant for ILd versus Ld from TOURMALINE (HR = 0.87; 95% CI: 0.64, 1.18). However, the PBAC considered that the data from the TOURMALINE trial

were too immature to assess efficacy in terms of OS.

- 7.9 Overall, the PBAC considered that the claim that ILd was non-inferior compared to Cd in terms of efficacy was not supported by the available data due to the nature of the naïve ITC, the differences across the trial patient populations, the more favourable PFS results for Cd (vs Bd) compared with ILd (vs Ld) and the more certain OS results for Cd.
- 7.10 The PBAC noted that neutropenia and thrombocytopenia were the most commonly reported Grade ≥ 3 adverse events (AEs) for ILd and that anaemia and hypertension were the most commonly reported Grade ≥ 3 AEs for Cd. The PBAC noted that although the safety profiles of ILd and Cd appeared to differ, the nature of the naïve ITC meant it was not possible to ascertain whether the differences were likely to be meaningful. The PBAC considered that the naïve ITC did not support the claim that ILd was non-inferior to Cd in terms of safety.
- 7.11 The PBAC considered the cost minimisation analysis (CMA) between ILd 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.
- 7.12 The PBAC noted that although cost minimised to Cd, the net cost of listing ILd on the PBS was estimated in the submission to be approximately \$0 to <\$10 million over the first six years of listing. The PBAC considered that the estimated net financial impact of listing ixazomib on the PBS was underestimated as (i) ILd would displace, rather than replace, a proportion of Cd use; (ii) the duration of use of Cd was potentially overestimated; and (iii) the substitution for Ld was potentially underestimated.
- 7.13 The PBAC considered that any future resubmission should be a major resubmission and address the uncertainties surrounding the clinical claims.
- 7.14 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

Takeda Australia wishes to thank the patients, clinicians, and organisations who took time to provide their experience of ixazomib during the PBAC process. Takeda believes ixazomib can be a valuable part of the management of multiple myeloma. We will continue to work with the Department of Health and the PBAC so that Australian patients may access ixazomib through the PBS.