

7.03 DARATUMUMAB,

**Solution concentrate for I.V. infusion 100 mg in 5 mL,
400 mg in 20 mL,**

Darzalex[®], Janssen-Cilag Pty Ltd

1 Purpose of Application

- 1.1 The resubmission requested a Section 100 listing (Efficient Funding for Chemotherapy) for daratumumab in combination with bortezomib and dexamethasone (DBd) for patients with relapsed or refractory multiple myeloma (RRMM) who had failed at least one prior therapy and as monotherapy for highly treatment experienced patients or patients' refractory after at least three prior lines including a proteasome inhibitor (PI) and an immunomodulatory (IMiD) or who are refractory to both PI and IMiD. A previous submission was rejected by the PBAC at its November 2017 meeting.
- 1.2 The resubmission presented a cost utility analysis comparing DBd with bortezomib plus dexamethasone (Bd). In addition, the resubmission presented non-comparative evidence on the efficacy and safety of daratumumab monotherapy. The key components of the clinical issues addressed by the resubmission are presented in Table 1.

Table 1: Key components of the clinical issue addressed by the resubmission

Component	Description
Population	<u>DBd</u> : Multiple myeloma; patients with RRMM after at least one prior therapy. <u>Daratumumab monotherapy</u> : Multiple myeloma; patients with RRMM after at least three prior lines of therapy which included a proteasome inhibitor and an IMiD (immunomodulator) or are refractory to both a proteasome inhibitor and an IMiD.
Intervention	<u>DBd</u> : Daratumumab is administered as an IV infusion at a dose of 16 mg/kg in combination with bortezomib-based therapies. Daratumumab is administered weekly for the first 3 cycles (3 weekly cycle), every three weeks from cycles 4 to 8 (3 weekly cycle) and then once every 4 weeks from cycle 9 onwards (4 weekly cycle) until disease progression or treatment-limiting toxicity. <u>Daratumumab monotherapy</u> : Daratumumab is administered weekly for the first 2 cycles (each cycle is 4 weeks in duration), every two weeks from cycles 3 to 6 (each cycle is 4 weeks in duration) and then once every 4 weeks from cycle 7 onwards (i.e. each cycle is 4 weeks in duration) until disease progression or the development of treatment-limiting toxicity.
Comparator	<u>DBd</u> : Main comparator - placebo + Bd. <u>Supplementary comparators</u> : carfilzomib + dexamethasone (Cd); bortezomib + dexamethasone + cyclophosphamide (VCd); lenalidomide + dexamethasone (Ld; acknowledged as a potential supplementary comparator). <u>Daratumumab monotherapy</u> : No specific comparator was nominated.
Outcomes	<u>DBd</u> : PFS, OS, ORR, MRD negativity rates <u>Daratumumab monotherapy</u> : PFS, OS, ORR, AEs
Clinical claim	<u>DBd</u> : Efficacy: The clinical claim for DBd presented in the resubmission remained unchanged; in patients with RRMM, DBd is superior for comparative effectiveness compared with Bd as assessed by statistically and clinically significant improvements in PFS, OS and a significantly higher ORR. Safety: As previously accepted by PBAC, the resubmission maintained that DBd was associated with additional AEs compared with Bd, and therefore had an inferior safety profile safety (5.05 daratumumab PBAC Public Summary Document (PSD), paragraph 7.7). <u>Supplementary comparators</u> : Additional clinical claims were made with respect to the supplementary comparators, Cd and VCd in the relevant sections of the submission. No clinical claim was made with respect to Ld by the resubmission due to lack of a direct trial or ability to perform an indirect comparison. <u>Daratumumab monotherapy</u> : No clinical claim was made for daratumumab monotherapy. However, the resubmission noted that daratumumab monotherapy provides benefit for highly treatment experienced and refractory MM patients, although the magnitude of incremental benefit is difficult to determine due to the non-comparative study designs. Daratumumab monotherapy is generally well tolerated with a manageable AE profile.

AE = adverse events; Bd = bortezomib-dexamethasone; Cd = carfilzomib-dexamethasone; DBd = daratumumab-bortezomib-dexamethasone; Ld = lenalidomide-dexamethasone; MRD = minimal residual disease; ORR = overall response rates; OS = overall survival; PFS = progression free survival; RRMM = relapsed and/or refractory multiple myeloma; VCd = bortezomib-cyclophosphamide-dexamethasone

Source: Table 1.2, p.22 Section 1 of the resubmission, Table 1.1, p.4 Section 1 Daratumumab monotherapy appendix of the resubmission and p.22-29 of Daratumumab monotherapy clinical data appendix of the resubmission.

2 Requested listing

2.1 The details of the proposed listings for DBd are summarised in Table 2 and for daratumumab monotherapy, in Table 3. The resubmission proposed that daratumumab be listed under a special pricing arrangement (SPA). The proposed published price for daratumumab was not dependent on the setting in which it was used (combination or monotherapy) but the proposed SPA varied between those settings.

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Table 2: Details of proposed PBS listing for datatumumab in combination with bortezomib and dexamethasone

Name, Restriction, Manner of administration and Form	Max. Qty	No. of Rpts	Dispensed Price for Max.	Proprietary Name and Manufacturer
INITIAL TREATMENT: DARATUMUMAB VIAL, 400 mg and 100 mg	1,920 mg	13	<u>Published</u> Public hospital: \$11,300.89 Private hospital: \$11,497.14 <u>Effective</u> Public hospital: \$ [REDACTED] Private hospital: \$ [REDACTED]	DARZALEX® Janssen-Cilag Pty Ltd
CONTINUING TREATMENT: DARATUMUMAB VIAL, 400 mg and 100 mg	1,920 mg	5	<u>Published</u> Public hospital: \$11,300.89 Private hospital: \$11,497.14 <u>Effective</u> Public hospital: \$ [REDACTED] Private hospital: \$ [REDACTED]	DARZALEX® Janssen-Cilag Pty Ltd

Category/Program:	Section 100 – Efficient Funding for Chemotherapy
PBS indication:	Multiple Myeloma
Treatment phase:	Initial and Continuing
Restriction:	Authority Required - Telephone
Clinical criteria:	<p><u>Initial treatment:</u> The condition must be confirmed by a histological diagnosis AND The treatment must be in combination with bortezomib and dexamethasone. AND Patient must have progressive disease after at least one prior therapy AND Patient must not be receiving concomitant PBS-subsidised thalidomide or its analogues or carfilzomib. AND Patient must not receive more than eight cycles of treatment under this restriction AND Patient must not have previously received PBS-subsidised treatment with this drug for this condition</p> <p><u>Continuing treatment</u> Patient must have previously received PBS-subsidised treatment with an authority prescription for this drug for this condition AND The patient must have previously received PBS-subsidised treatment with this drug in combination with bortezomib and dexamethasone as initial treatment in the current course of treatment 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 or its analogues, bortezomib, or carfilzomib.</p>

Abbreviations: EFC = efficient funding of chemotherapy; Max = maximum; N/A = not applicable; Qty = quantity; Rpts = repeats.
Source: Table 1.8, p.53 Section 1 of the resubmission

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Table 3: Details of proposed PBS listing for daratumumab monotherapy

Name, Restriction, Manner of administration and Form	Max. Qty	No. of Rpts	Dispensed Price for Max.	Proprietary Name and Manufacturer
INITIAL TREATMENT: DARATUMUMAB VIAL, 400 mg and 100 mg	1,920 mg	15	<u>Published</u> Public hospital: \$11,300.89 Private hospital: \$11,497.14 <u>Effective</u> Public hospital: \$ [REDACTED] Private hospital: \$ [REDACTED]	DARZALEX® Janssen-Cilag Pty Ltd
CONTINUING TREATMENT: DARATUMUMAB VIAL, 400 mg and 100 mg	1,920 mg	5	<u>Published</u> Public hospital: \$11,300.89 Private hospital: \$11,497.14 <u>Effective</u> Public hospital: \$ [REDACTED] Private hospital: \$ [REDACTED]	DARZALEX® Janssen-Cilag Pty Ltd

Category/Program:	Section 100 – Efficient Funding for Chemotherapy
PBS indication:	Multiple Myeloma
Treatment phase:	Initial and Continuing
Restriction:	Authority Required - Telephone
Clinical criteria:	<u>Initial treatment</u> The condition must be confirmed by a histological diagnosis AND The treatment must be the sole PBS-subsidised therapy for this condition. AND Patient must have progressive disease after at least three prior lines of therapy which included a proteasome inhibitor and an immunomodulatory agent. OR Patient must have refractory disease to a proteasome inhibitor and an immunomodulatory agent. AND Patient must not receive more than six cycles of treatment under this restriction AND Patient must not have previously received PBS-subsidised treatment with this drug for this condition <u>Continuing treatment</u> The patient must have previously received PBS-subsidised treatment with this drug as sole PBS-subsidised therapy in the current course of treatment AND Patient must not develop disease progression while receiving treatment with this drug for this condition AND The treatment must be the sole PBS-subsidised therapy for this condition

Abbreviations: EFC = efficient funding of chemotherapy; Max = maximum; N/A = not applicable; Qty = quantity; Rpts = repeats.
 Source: Table 1.5, p.11 Daratumumab monotherapy appendix of the resubmission.

- 2.2 The proposed listing of daratumumab in combination with bortezomib and dexamethasone was more restrictive than the TGA indication, which allows use in combination with bortezomib or lenalidomide plus dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.
- 2.3 The resubmission requested the application of grandfathering criteria to patients receiving DBd prior to the commencement of PBS listed supply. The proposed detailed criteria were consistent with those for newly commencing patients, with the addition of the following clinical criteria:

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- Patient must not receive more than <number> cycles of treatment under this restriction; AND
 - Patient must have previously received non-PBS-subsidised treatment with this drug for this condition prior to <date>.
- 2.4 The proposed grandfathering criteria did not specify a total number of cycles of treatment. As initiation therapy is intended to comprise eight cycles of therapy, this criterion could be modified to read: Patient must not receive more than eight cycles of initial treatment in total, including supply under the PBS.
- 2.5 The resubmission did not provide an estimate of the number of potential grandfathered patients, instead it was assumed that they would be captured in the epidemiological approach used to estimate the utilisation estimates. The Pre-Sub-Committee Response (PSCR) advised that as the patient access program would not be opened until the restriction criteria were known, the number of grandfathered patients could not be estimated. The PBAC considered that the patient access program was likely to have high uptake.
- 2.6 The resubmission included an updated “Multiple Myeloma Treatment Package” consisting of a special pricing arrangement for daratumumab and changes to the bortezomib listing:
- Rebated daratumumab at [REDACTED] % for the [REDACTED] infusions when used with bortezomib and at [REDACTED] % for the continuing treatment for DBd, and for initial and continuing treatment for daratumumab monotherapy.
 - Simplified wording for the PBS listing of bortezomib; treatment of multiple myeloma, to be in line with that applied to thalidomide. This change to the bortezomib PBS listing is consistent with recommendations of the May 2018 Multiple Myeloma Stakeholder meeting.
 - Reduction in the price applied to bortezomib:

[REDACTED]

- 2.7 The key differences between the November 2017 “Multiple Myeloma Treatment Package” and that presented in the resubmission were: the proposed additional ■■■% rebate for daratumumab for continuing treatment as DBd; and the additional proposal of a ■■■% rebate for daratumumab in both initial and continuing treatment when used as monotherapy. In addition, the resubmission proposed a ■■■% price reduction for bortezomib across all indications including RRMM (resulting in an overall ■■■% price reduction of bortezomib for RRMM) whereas in the November 2017 submission, a ■■■% reduction was applied to the price of bortezomib for only RRMM.

For more detail on PBAC’s view, see Section 7 PBAC outcome.

3 Background

Registration status

- 3.1 Daratumumab was approved by the TGA on 17th July 2017 for use:
- in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy;
 - as monotherapy, for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are refractory to both a PI and an immunomodulatory agent.
- 3.2 At the time of the PBAC meeting, daratumumab was undergoing evaluation by the TGA for use in combination with bortezomib, melphalan and prednisolone for the treatment of patients with newly diagnosed MM who are ineligible for ASCT.

Previous PBAC consideration

- 3.3 A summary of the matters of concern raised by the PBAC with respect to the November 2017 submission, and how they have been addressed in the March 2019 resubmission is provided in Table 4.
- 3.4 Unlike the November 2017 submission, the resubmission did not request listing of daratumumab for use in combination with lenalidomide and dexamethasone (DLd). The resubmission attributed the decision to exclude this combination to the price of lenalidomide and the lack of control on any price reduction for lenalidomide. The requested listing of daratumumab monotherapy was to address inequity concerns raised by the PBAC in November 2017 for the patient population refractory to bortezomib and lenalidomide.

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Table 4: Summary of outstanding matters of concern

Component	PBAC matter of concern	How the resubmission addressed it
Clinical evidence		
Requested listing	Preference to have DBd, DLd and daratumumab monotherapy listed (paragraphs 7.1, 7.2, PSD, Nov-17).	Not addressed: proposed listing of DBd and daratumumab monotherapy, although no basis for the monotherapy listing was provided in the submission.
Comparator	Requested inclusion of Ld, Cd and VCd as supplementary comparators (paragraph 7.4, PSD, Nov-17).	Partially addressed: Cd and VCd included. Ld was acknowledged but no comparative data provided.
Clinical data	Immature data with median of 13.3 months of follow-up (paragraphs 7.6, 7.11, PSD, Nov-17).	Partially addressed: used longer-term data with median follow-up of approx. 31 months provided in the resubmission and limited data with a median follow-up of 40 months presented in the PSCR.
Indirect comparison of DBd to Cd	Suggested comparison between Bd naïve subgroups for the indirect comparison between DBd and Cd to address confounding factors (paragraph 7.8, PSD, Nov-17).	Addressed: used CASTOR longer-term data and performed additional efficacy subgroup analysis where data were available for Cd.
Efficacy of DBd in patients with or without prior bortezomib use	Noted DBd was less effective in terms of the point estimates for improvements in PFS in patients with prior bortezomib use compared to those without in the ITT population (paragraph 6.12, PSD, Nov-17).	Addressed: The point estimate PFS results for prior/no prior bortezomib were more similar in the ITT population at the IA4 data-cut. In addition, the resubmission presented a new subgroup analysis in the second-line population for patients with or without prior bortezomib use, and both subgroups experienced similar improvements in PFS.
Economic issues		
Approach	To exclude the proportionate use of alternatives from the economic model (paragraph 7.9, PSD, Nov-17).	Addressed: used one model structure that considered 100% use of alternatives.
Time horizon	Proposed the use of a shorter 10-15 year time horizon (paragraph 7.10, PSD, Nov-17).	Not addressed: maintained 20-year time horizon and reiterated the previous justification
Financial issues		
Financials	Adjust number of cycles of Bd included in the model to reflect PBS current listing of up to 11 cycles (paragraph 6.36, PSD, Nov-17).	Addressed: used 11 cycles of Bd for a proportion of patients likely to use it.
Change in use of other medicines	Likelihood of increase in Ld use in first line treatment and outside its current indication due to listing of DBd only (paragraphs 6.59, 7.3, 7.12, PSD, Nov-17).	Addressed: Incorporated potential increase in the utilisation of Ld in first line transplant eligible patients due to listing of daratumumab.
Eligible patient population	Underestimation of the size of prevalent MM patients (paragraph 6.62, PSD, Nov-17).	Partially addressed: projected the size of prevalent MM patients using the ABS-projected growth rate for 60+ year age segment which is representative of the mean incidence age of RRMM. This lead to 6.6% more patients being treated compared to the November 2017 submission.
Discontinuation of daratumumab	Time-to-treatment discontinuation extrapolations in Section 3 were based on short-term trial data and may not reflect the typical duration of daratumumab therapy for these patients. Longer time on therapy with daratumumab would increase the cost to Government (paragraph 6.62, PSD, Nov-17).	Not addressed: Discontinuation from daratumumab was not explicitly modelled and the method utilised to estimate duration of treatment underestimates the scripts and patient numbers.

Bd = bortezomib-dexamethasone; Cd = carfilzomib-dexamethasone; DBd = daratumumab- bortezomib-dexamethasone; DLd = daratumumab-lenalidomide-dexamethasone; ICER = incremental cost effectiveness ratio; Ld = lenalidomide-dexamethasone; MM = multiple myeloma; Nov = November; PFS = progression free survival; PSD = public summary document; VCd = bortezomib-cyclophosphamide-

dexamethasone.

Source: Daratumumab November 2017 Public Summary Document and resubmission March 2019 – see right hand column for details.

For more detail on PBAC’s view, see Section 7 PBAC outcome.

4 Population and disease

- 4.1 Multiple myeloma (MM) is a cytogenetically heterogeneous clonal plasma cell proliferative disorder characterised by an abnormal serum and/or urine immunoglobulin. As MM progresses and patients relapse following initial treatment, the presence of subclonal populations of malignant plasma cells becomes increasingly prevalent. Typical clinical features include bone disease (and bone loss) with skeletal pain, impaired renal function, anaemia, fatigue, hypercalcaemia, recurrent and/or persistent bacterial infection, and/or hyperviscosity of the blood.
- 4.2 The resubmission requested PBS listing of daratumumab in combination with bortezomib and dexamethasone (DBd) for the treatment of patients with RRMM with progressive disease after at least one prior therapy. Daratumumab monotherapy was requested in fourth and subsequent lines of treatment of RRMM. The clinical algorithm presented considered that DBd would substitute for Bd, Cd and Ld. The resubmission noted that listing DBd only was unlikely to change the choice of first line therapy due to the appropriateness of using bortezomib-based regimens across the first and second-line settings and DBd being highly effective. The major change between the current and proposed algorithm is the addition of daratumumab as a triple therapy (DBd) for use as a second-line agent after progression. However, it may reasonably be assumed that the proposed DBd listing may lead to greater use of first-line lenalidomide. The MM Stakeholder meeting outcomes¹ from May 2018 state:

“Should a restriction be approved for only one therapy for combination use (eg. only lenalidomide or bortezomib in combination with daratumumab), this would still be of clinical benefit, however MSAG stated that this was not optimal and would lead to an unsatisfactory outcome for patients particularly for those who appeared to respond better to the backbone treatment not available for use in combination.”

This also impacts the subsequent choice of third-line treatment.

For more detail on PBAC’s view, see Section 7 PBAC outcome.

5 Comparator

- 5.1 The resubmission nominated Bd as the main comparator for DBd. The resubmission noted that daratumumab is used as an add-on therapy and, if PBS listed, combination use of daratumumab with bortezomib and dexamethasone (i.e. DBd) is most likely to replace bortezomib-based regimens without daratumumab. The ESC considered the

¹ <http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/pbac-stakeholder-meetings/Multiple-myeloma-May-2018.pdf>

nominated comparator was reasonable, noting it was accepted by the PBAC at the November 2017 meeting (paragraph 7.4, Daratumumab PSD, November 2017)

- 5.2 The resubmission nominated carfilzomib plus dexamethasone (Cd), bortezomib plus cyclophosphamide plus dexamethasone (VCd) and lenalidomide plus dexamethasone (Ld) as secondary comparators. At its November 2017 meeting, the PBAC had requested the addition of VCd and Ld as supplementary comparators for DBd. The ESC considered the nominated secondary comparators were appropriate.
- 5.3 The ESC advised that nominated comparators would be displaced, rather than replaced, by DBd.
- 5.4 The resubmission did not nominate a comparator for daratumumab monotherapy. However, the resubmission noted that the ESC (October 2017) had previously stated that pomalidomide may be a likely comparator. The PSCR stated that a comparator for monotherapy was not formally nominated as the use of daratumumab monotherapy was likely to be limited. In addition, the PSCR stated that as daratumumab is used predominantly as a combination therapy, it was unlikely that data which reliably informs the incremental effectiveness of daratumumab monotherapy will ever become available. The ESC considered that the absence of a comparator for daratumumab monotherapy meant it was not possible to assess its comparative clinical efficacy, safety or cost-effectiveness in the RRMM setting and this made pricing considerations difficult. The PBAC noted that the sponsor had not provided the information required, including a clinical comparison and economic evaluation, to enable it to consider a listing for daratumumab monotherapy. The PBAC further noted the sponsor had provided a clinical comparison and economic evaluation for daratumumab versus pomalidomide to the UK National Institute for Health and Care Excellence (NICE) and considered an equivalent analysis should have been included in the PBAC submission.²

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 sponsor reiterated information presented in the pre-PBAC response including that the use of the second-line subgroup population and a 20 year time horizon, truncated at 15 years, in the economic evaluation were appropriate. The sponsor also reiterated that they are unable to reduce the requested price for daratumumab due to pricing constraints, and that a Risk Sharing Arrangement (RSA) would be proposed if daratumumab was recommended to reduce the ICER and the magnitude of the budget impact, but

² National Institute for Health Care and Excellence (NICE). Daratumumab monotherapy for treating relapsed and refractory multiple myeloma: Final appraisal determination. Available at: <https://www.nice.org.uk/guidance/ta510/documents/final-appraisal-determination-document-2>

provided no detail. The PBAC considered that the hearing was not informative as it did not add to the evidence presented in the submission.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (166), health care professionals (1) and organisations (3) via the Consumer Comments facility on the PBS website. The vast majority of the comments described a range of benefits of treatment with daratumumab including improved survival, an improved quality of life and fewer side effects.
- 6.3 The PBAC noted the advice received from the Leukaemia Foundation, Myeloma Australia and the Medical and Scientific Group (MSAG) of Myeloma Australia which outlined the clinical need for DBd and daratumumab monotherapy in providing optimal management of myeloma and reiterated the patients' views. The PBAC noted that this advice was supportive of the evidence provided in the submission. MSAG also highlighted its disappointment that there was no proposal for the combination of daratumumab plus lenalidomide and dexamethasone.

Clinical trials

- 6.4 As per the November 2017 submission, the resubmission was based the CASTOR trial (N = 498), a head-to-head trial comparing DBd to Bd. The resubmission presented longer-term data (interim analysis 4 (IA4), median follow-up = 31.2 months) in addition to the 120-day safety update (120dsu, median follow-up = 13.3 months, as provided in the November 2017 submission) as the pivotal evidence for the evaluation. Limited data from the IA5 data-cut (median follow-up = 40 months) was presented in the PSCR.
- 6.5 The clinical claim was based on subgroup analyses of patients who had received only one prior treatment (this was termed the 'second-line' population). The rationale for presenting these analyses, which was reiterated in the PSCR, was that incident RRMM patients would receive DBd in clinical practice. Additionally, as the proposed restriction limited patients to receiving daratumumab only once, the PSCR stated that the efficacy of DBd as a second-line treatment was relevant and reflective of the proposed restriction. Although the subgroup was not pre-specified, the PSCR stated that second-line patients constituted the largest segment in the CASTOR trial when split by line of therapy (46-48% of the ITT population) and that the results for the second-line outcomes were strongly statistically and clinically significant in favour of DBd. The ESC considered that it would have been more appropriate to base the clinical claim on the ITT population (patients who had received at least one prior therapy) as this was consistent with the proposed PBS restriction.
- 6.6 The resubmission presented an indirect comparison between DBd and the secondary comparator Cd and a descriptive comparison between DBd and VCd. The comparisons were:

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- DBd (CASTOR, N = 498) and Cd (ENDEAVOR, N = 929), with Bd as the common reference arm, and
 - DBd (CASTOR, N = 498) and VCd (Kropff 2017; NCT00813150, N = 93), with Bd as the common reference arm.
- 6.7 The resubmission did not provide any comparative data for DBd and Ld, stating that there were no direct trials of Bd and Ld that would allow an indirect comparison. However, a multi-step indirect comparison could have been performed using MM010 (Ld vs d) and APEX (Bd vs d), together with CASTOR (DBd vs Bd).
- 6.8 The resubmission presented two non-comparative non-randomised open-label trials as clinical evidence for daratumumab monotherapy GEN501 and SIRIUS.
- 6.9 Details of the trials presented in the submission are provided in Table 5.

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Table 5: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials		
CASTOR (NCT02136134)	MMY3004: Phase 3 Study Comparing Daratumumab, Bortezomib, and Dexamethasone (DVd) vs Bortezomib and Dexamethasone (Vd) in Subjects with Relapsed or Refractory Multiple Myeloma. Clinical study Report (CSR) 120-Day Safety Update Interim analysis 4	27 July 2016 20 October 2016 11 January 2018
Publications	Palumbo, A., Chanan-Khan, A., Weisel K., et al. Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma. Palumbo, A., Chanan-Khan, A., Weisel K., et al. Phase III randomised controlled study of daratumumab, bortezomib, and dexamethasone (DVd) versus bortezomib and dexamethasone (Vd) in patients (pts) with relapsed or refractory multiple myeloma (RRMM): CASTOR study. Weisel, K., Palumbo, A., Chanan-Khan, A., et al. Phase 3 randomised study of daratumumab, bortezomib and dexamethasone (DVd) vs bortezomib and dexamethasone (Vd) in patients (pts) with relapsed or refractory multiple myeloma (RRMM): CASTOR. Palumbo, A., Dimopoulos, MA., Reece, DE., et al. Twin randomised studies of daratumumab (DARA; D) plus standard of care (lenalidomide/dexamethasone or bortezomib/dexamethasone [DRd or DVd]) versus Rd or Vd alone in relapsed or refractory multiple myeloma (MM): 54767414MMY3003 (Pollux) and 54767414MMY3004 (Castor). Mateos, M., Estell, J., et al. Efficacy of daratumumab, bortezomib, and dexamethasone versus bortezomib and dexamethasone in relapsed or refractory multiple myeloma based on prior lines of therapy: updated analysis of CASTOR Avet-Loiseau, H., Casneuf, T., et al. Evaluation of minimal residual disease (MRD) in relapsed/refractory multiple myeloma (RRMM) patients treated with daratumumab in combination with lenalidomide plus dexamethasone or bortezomib plus dexamethasone. Chanan-Khan A., Lentzsch S., Quach H., et al. Daratumumab, bortezomib, and dexamethasone versus bortezomib and dexamethasone alone for relapsed or refractory multiple myeloma based on prior treatment exposure: updated efficacy analysis of CASTOR. Spencer, A, et al. Daratumumab plus bortezomib and dexamethasone versus bortezomib and dexamethasone in relapsed or refractory multiple myeloma: updated analysis of CASTOR ^a Spencer, A, et al. Daratumumab, bortezomib, and dexamethasone (DVD) versus bortezomib and dexamethasone (VD) in relapsed or refractory multiple myeloma (RRMM): Updated efficacy and safety analysis of castor Iida, S, Lentzsch, S, et al. Safety and efficacy of daratumumab in combination with bortezomib and dexamethasone in Japanese patients with relapsed or refractory multiple myeloma. Lentzsch, S, Quach, H, et al. Daratumumab, bortezomib, and dexamethasone versus bortezomib and dexamethasone for relapsed/refractory multiple myeloma (RRMM) patients: an update of overall survival in castor. Lentzsch, S, Weisel, K, et al. Daratumumab, bortezomib and dexamethasone (DVd) vs bortezomib and dexamethasone (Vd) in	New England Journal of Medicine. 2016; 375(8):754-66 Journal of Clinical Oncology. 2016; 34, (suppl LBA4) Annals of Oncology. 2016; 27 (Supplement 6): vi313–vi327 Journal of Clinical Oncology. 2015; 33 (15 Suppl): TPS8609 Blood. 2016; 128 (22); 1150 Blood. 2016; 128 (22), 246 Blood. 2016; 128 (22), 3313 Haematologica .2018; 103 doi:10.3324/haematol.2018.194118 Blood. 2017; 130: 3145 International Journal of Haematology. 2018; 107(4):460-467 Blood. 2017; 130: 1852 Journal of Clinical Oncology. 2017; 35(no. 15_suppl): 8036

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Trial ID	Protocol title/ Publication title	Publication citation
	relapsed or refractory multiple myeloma (RRMM): Efficacy and safety update (CASTOR). Mateos, M, Spencer, A, et al. Updated efficacy and safety analysis of daratumumab, bortezomib, and dexamethasone (DVD) versus bortezomib and dexamethasone (VD) for re-lapsed or refractory multiple myeloma (RRMM; CASTOR). Weisel, K, Lentzsch, S, et al. Efficacy and safety of daratumumab, bortezomib and dexamethasone (DVD) versus bortezomib and dexamethasone (VD) in relapsed or refractory multiple myeloma (RRMM): Updated analysis of castor.	Haematologica. 2017; 103(S1): 30 Annals of Oncology. 2016; 27(suppl 6): vi313-vi327
Non-randomised studies		
GEN501	Daratumumab (HuMax-CD38) Safety Study in Multiple Myeloma – Open-label, Dose-Escalation Followed by Open-Label, Single-Arm Study Clinical Study Report with addendums.	14 May 2015
Publications	Lokhorst, H.M., Plesner, T., Laubach, J.P. et al. Targeting CD38 with Daratumumab Monotherapy in Multiple Myeloma. Usmani, S., Weiss, B., Plesner, T. et al. Clinical efficacy of daratumumab monotherapy in patients with heavily pre-treated relapsed or refractory multiple myeloma.	New England Journal of Medicine. 2015; 373:1207-19. Blood. 2016; 128(1); 37-44.
SIRIUS (MMY2002)	An Open-label, Multicenter, Phase 2 Trial Investigating the Efficacy and Safety of Daratumumab in Subjects with Multiple Myeloma Who Have Received at Least 3 Prior Lines of Therapy (Including a Proteasome Inhibitor and IMiD) or are Double Refractory to a Proteasome Inhibitor and an IMiD Clinical Study Report with addendums.	12 May 2015
Publications	Lonial, S., Weiss, B., Usmani, S. et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial. Usmani, S., Weiss, B., Plesner, T. et al. Clinical efficacy of daratumumab monotherapy in patients with heavily pre-treated relapsed or refractory multiple myeloma.	Lancet. 2016; 387: 1551-60 Blood. 2016; 128(1); 37-44

a. This was identified during evaluation. However, the median follow-up was 19.4 months, which is less than the most updated data (31.2 months) that was used in the resubmission.

Source: Table 2.4, p.9 Section 2a of the November 2017 submission (information not presented in the resubmission); Table 2.5, p12 Section 2 of the resubmission; Table 2.1, p.3 Daratumumab monotherapy clinical data appendix of the resubmission.

6.10 The key features of the included evidence are summarised in the Table 6.

Table 6: Key features of the included evidence

Trial	N	Design/ duration of follow-up	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
Direct randomised trial (DBd)						
CASTOR	DBd: 251 Bd: 247 N: 498	Phase 3, OL, RCT, MC Nov 2017: 120 dsu: 13.3 months Mar 2018: IA4: 31.2 months PSCR: IA5: 40 months	Low	Received ≥ 1 previous lines of therapy ^a	PFS, OS, ORR, MRD, PROs, safety	All outcomes used (MRD used to justify time horizon) except ORR.
Non randomised studies (Daratumumab monotherapy)						
GEN501	Part 1: 32 Part 2: 72 N:104	Phase 1/2, OL, single-arm, MC divided in 2 parts CSR short term data: 10.2 months Long term follow-up: 35.3 months	Low to high ^b	Received ≥ 2 prior lines of therapy ^c	Safety, ORR, PFS, OS, DOR, TTR	No modelled evaluation was presented for daratumumab monotherapy
SIRIUS	Part 1: 59 Part 2: 65 N:104	Phase 2, OL, single-arm, MC, divided in 2 parts CSR short term data: 9.3 months Long term follow-up: 36.7 months	Low to high ^b	Received ≥ 3 prior lines of therapy ^c	ORR, PFS, OS, DOR, TTR	

Bd = bortezomib-dexamethasone; CSR = clinical study report; DBd = daratumumab-bortezomib-dexamethasone; DOR = duration of response; IA4 = interim analysis 4; IA5 = interim analysis 5; MC = multi-centre; MRD = minimal residual disease; OL = open label; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PSCR = pre-Sub-Committee response; RCT = randomised controlled trial; TTR = time to response; 120 dsu: 120 day safety update.

a. Documented MM and received ≥ 1 previous lines of therapy. At least a partial response to ≥ 1 previous therapies. Documented PD according to IMWG criteria during or after completion of last regimen.

b. risk of confounding, selection and performance bias was high whilst risk of bias due to detection, attrition, reporting and misclassification was low.

c. Documented MM, who were relapsed or refractory to at least 2 (GEN501) or 3 (SIRIUS) prior lines of therapy using IMWG criteria

Source: compiled during the evaluation.

Comparative effectiveness

DBd versus Bd

- 6.11 The resubmission presented updated progression free survival (PFS) and overall survival (OS) results (from the IA4 data-cut), which provided an additional 17.9 months of data over the 120dsu. The results from the updated data continued to demonstrate significant improvements in PFS and OS for DBd compared to Bd; see Table 7, and Figure 1 and Figure 2 for the corresponding Kaplan-Meier curves.
- 6.12 In the November 2017 submission (120dsu data cut), the median PFS was 7.1 months (95% CI: 6.2, 7.7) for the Bd arm and was not reached in the DBd treatment arm. In the resubmission (IA4 data cut), median PFS was reached for the DBd arm, 16.7 months (95% CI: 13.4, 19.4), resulting in a difference in median PFS of 9.6 months. The estimated hazard ratios (HRs) were similar for both data-cuts (120dsu: HR = 0.33; 95% CI: 0.26, 0.43 vs IA4 data-cut: HR = 0.32; 95% CI: 0.25, 0.40).
- 6.13 The median OS was not reached for either arm at the IA4 data-cut, implying that the CASTOR data remained immature and may not accurately reflect the magnitude of clinical benefit or longer-term risks of death associated with daratumumab-based regimens. The estimated HRs for OS implied that the [REDACTED] % reduction in the risk of death from any cause was less than at the at the 120dsu data cut (37%). The resubmission considered that this observed difference in HR resulted from the higher number of patients ([REDACTED]%) in the Bd arm who had switched onto a daratumumab-

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based regimen at the IA4 data-cut compared to at the 120dsu data-cut (█%). This improved OS in the Bd arm.

6.14 The PSCR provided additional OS data from interim analysis 5 (IA5) which had a median duration of follow-up of 40 months. The reduction in the risk of death at IA5 was █% (compared to █% at IA4 and █% at 120dsu) in the ITT population. The PSCR claimed that the data provided at the IA5 data-cut demonstrated that DBd was associated with a long-term OS benefit over Bd in RRMM patients.

6.15 The updated data provided for the DLd vs Ld comparison (interim analysis 3 – IA3) also showed a similar effect for PFS and a reduced effect for OS (when compared with 120dsu data). The resubmission stated that the reduced effect in OS was due to higher proportion of patients (█%) crossing over in the Ld arm to use a daratumumab-based regimen at the IA3 data cut compared to █% at the 120dsu data-cut.

Table 7: Results of progression free survival and overall survival in the CASTOR trial (ITT population)

	DBd n/N (%)	DBd Median time to event, mths (95% CI)	Bd n/N (%)	Bd Median time to event, mths (95% CI)	Diff. in median	P value (log rank test)	Hazard ratio (95% CI)
November 2017 submission: 120-day safety update^{a,b}							
PFS	100/251 (39.8%)	NE (12.6, NE)	177/247 (71.7%)	7.1 (6.2, 7.7)	NE	< 0.0001	0.33 (0.26, 0.43)
OS	37/251 (14.7%)	NE (NE, NE)	58/247 (23.5%)	NE (NE, NE)	NE	0.029	0.63 (0.42, 0.96)
March 2019 resubmission: Interim-analysis 4 (IA4)^{b,c}							
PFS	172/251 (68.5%)	16.7 (13.14, 19.38)	204/247 (82.6%)	7.1 (6.21, 7.66)	9.6	< 0.0001	0.32 (0.25, 0.40)
OS	█	█	█	█	█	█	█
PSCR: Interim-analysis 5 (IA5)^e							
OS	█	█	█	█	█	█	█

Bd = bortezomib-dexamethasone; CI = confidence interval; DBd = daratumumab-bortezomib-dexamethasone; ITT = intention-to-treat; mths = months NE = not evaluable; OS = overall survival; PFS = progression free survival; PSCR = pre-Sub-Committee response

a. median follow-up for CASTOR is 13.3 months

b. PFS measured by computerised algorithm.

c. median follow-up at IA4 is 31.2 months.

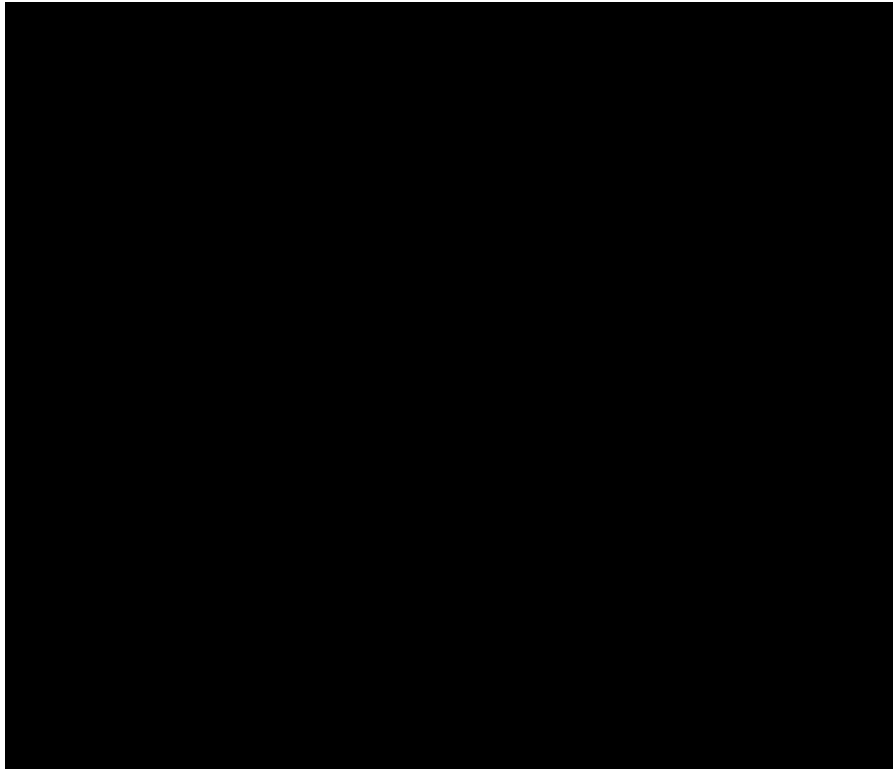
d. p-value was verified from source during evaluation

e. median follow-up at IA5 is 40 months

Bold indicates a statistically significant difference.

Source: Table 2.26, p.52 Section 2a of the November 2017 submission (information not presented in the resubmission); Table 3.2, p.8 Section 3; Table 2.28, p.58 Section 2a of the November 2017 submission (information not presented in the resubmission). Table 2.10, p.22, Table 2.11, p.24, Table 2.13, p.27, Table 2.19, p.40 Section 2 of the resubmission; Table 2.14, p.29 Section 2 CASTOR IA4 data TEPFFS01 TEPFFS01_1PL_PRIMID_MAF, TEPFFS01_1PL_PRLINA_2_MAF, Janssen internal analyses, Submission Figures Excel file, Appendix 4 of the resubmission; compiled during the evaluation and Table 1, p5 of the PSCR

Figure 1: Kaplan-Meier Curve of PFS (CASTOR IA4, ITT population, computerised algorithm)

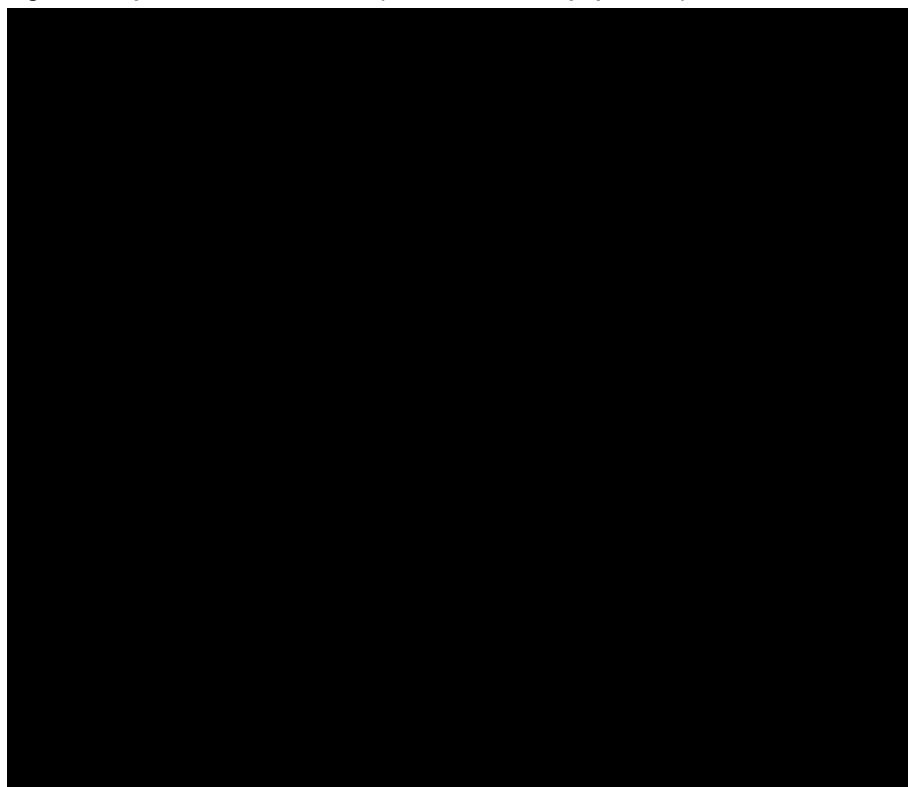


CI = confidence intervals; DVd = daratumumab-bortezomib-dexamethasone; ITT = intention-to-treat; PFS = progression free survival; Vd = bortezomib-dexamethasone

Note: median follow-up for CASTOR is 31.2 months.

Source: Figure 2.2, p.23 Section 2 of the resubmission.

Figure 2: Kaplan-Meier curve of OS (CASTOR IA4, ITT population)



DVd = daratumumab-bortezomib-dexamethasone; ITT = intent-to-treat; OS = overall survival; Vd = bortezomib-dexamethasone.
Note: median follow-up is 31.2 months.
Source: Figure 2.7, p.35 Section 2 of the resubmission.

- 6.16 The PFS and OS results for the subgroup of patients who had received only one prior therapy are presented in Table 8, with Kaplan Meier plots presented in Figure 3 and Figure 4. The resubmission highlighted statistically significant differences in favour of DBd for both PFS (HR = 0.23; 95% CI: 0.16, 0.33 and OS (HR = [REDACTED]; 95% CI: [REDACTED], [REDACTED]). The ESC noted that this subgroup population did not match the requested indication (at least one prior therapy), was not a predefined subgroup analysis, the complement to the subgroup was not reported and there were no treatment by subgroup interactions presented.
- 6.17 The PSCR presented OS data for the second-line population at IA5. A median OS of [REDACTED] months had been reached in the Bd arm. The HR at the IA5 data cut was similar to that at the IA4 data cut.

Table 8: Results of OS and PFS in the second-line population of CASTOR

	DBd n/N (%)	DBd Median time to event, mths (95% CI)	Bd n/N (%)	Bd Median time to event, mths (95% CI)	Diff. in median	P value (log rank test)	Hazard ratio (95% CI)
Interim analysis 4 (IA4)^a							
PFS	71/122 (58.2%)	27.01 (21.19, 30.62)	94/113 (83.2%)	7.92 (6.77, 9.03)	19.09	< 0.0001	0.23 (0.16,0.33)
OS							
PSCR: Interim-analysis 5 (IA5)^b							
OS							

Bd = bortezomib-dexamethasone; CI = confidence interval; DBd = daratumumab-bortezomib-dexamethasone; NE = not estimable; PFS = progression free survival; OS = overall survival

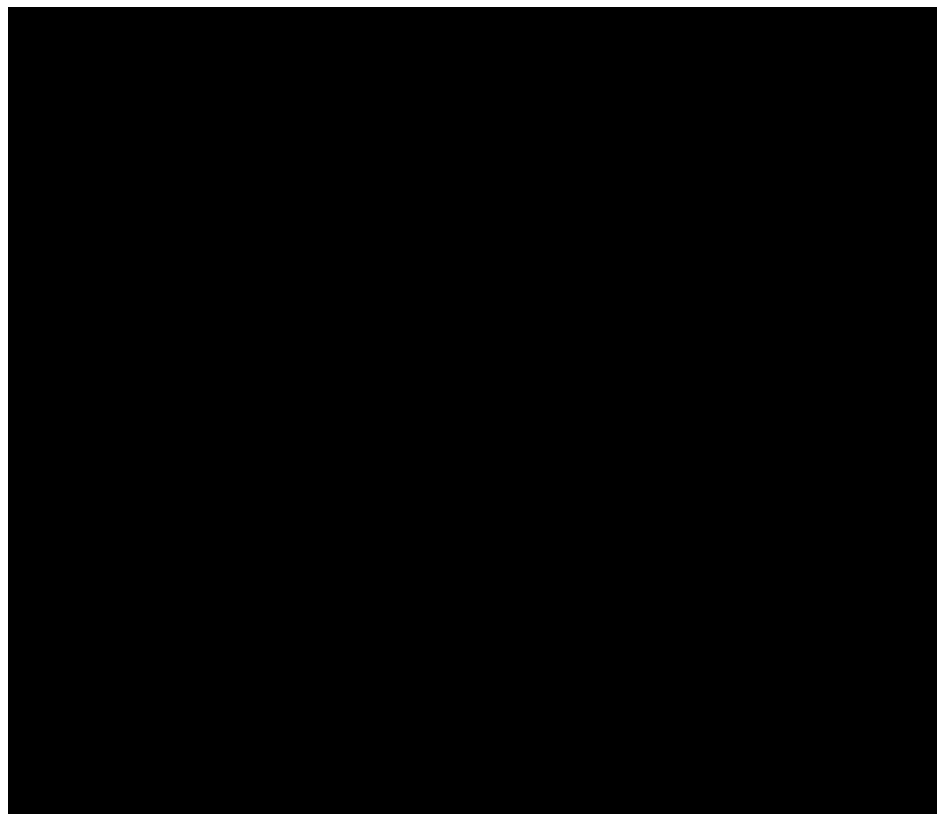
a. median follow-up for CASTOR IA4 is 31.2 months.

b. median follow-up at IA5 is 40 months

Bold indicates a statistically significant difference.

Source: Table 2.11, p.24 and Table 2.15, p.30 of the resubmission.

Figure 3: Kaplan-Meier Curve of PFS in the second-line population of CASTOR (IA4, computerised algorithm)

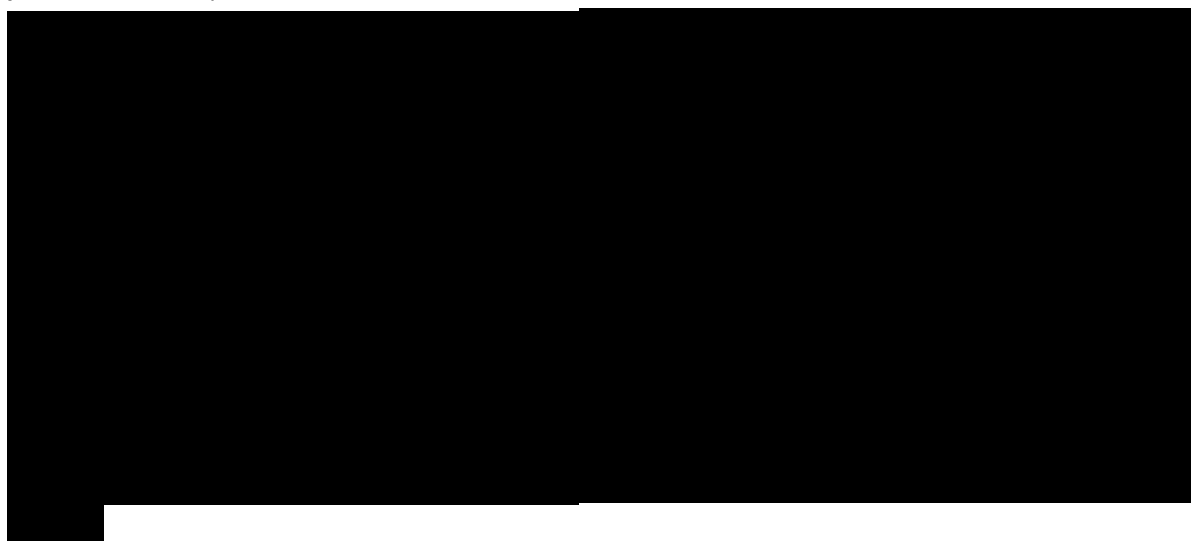


CI = confidence intervals; DVd = daratumumab-bortezomib-dexamethasone; PFS = progression free survival.

Note: median follow-up for is 31.2 months

Source: Figure 2.3, p.25 Section 2 of the resubmission.

Figure 4: Kaplan-Meier curve of OS in the second-line population of CASTOR (LEFT panel: IA4 data cut^a; RIGHT panel: IA5 data cut^b)



DVd = daratumumab-bortezomib-dexamethasone; OS = overall survival; Vd = bortezomib-dexamethasone.

a. median follow-up at IA4 is 31.2 months

b. median follow-up at IA5 is 40 months

Source: Figure 2.5, p.35 Section 2 of the resubmission and Figure 1, p5 of the PSCR.

- 6.18 The PSCR argued that the use of the second-line subgroup population would not affect the clinical claim; however, the ESC noted the HR for OS, which was statistically significant in the subgroup population, was not statistically significant in the ITT analysis. The pre-PBAC response noted that the HR was statistically significant in the ITT population at the 120dsu data-cut (HR = 0.63; 95% CI: 0.42, 0.96), which was not confounded by treatment switching in the Bd arm. The pre-PBAC response stated that the loss of statistical significance at IA4 data-cut was due to the high use of daratumumab in the Bd arm.
- 6.19 At the November 2017 PBAC meeting, the PBAC “noted that while the improvement in PFS for patients who had previous bortezomib was statistically significant (HR = [REDACTED]; 95% CI: [REDACTED]), based on the point estimates, DBd was less effective in these patients [compared to DBd in patients who had not received prior bortezomib (HR = [REDACTED]; 95% CI: [REDACTED])]” (paragraphs 6.12 and 7.3, Daratumumab PSD, November 2017). The November 2017 results were in the ITT population at the 120dsu data-cut. Results in the ITT population at the IA4 data-cut indicated that PFS point estimates were more similar in those who had received prior bortezomib (HR = [REDACTED]; 95% CI: [REDACTED], [REDACTED]) and those who had not (HR = [REDACTED]; 95% CI: [REDACTED], [REDACTED]). The resubmission conducted additional subgroup analyses for the second-line population based on prior therapies, including for prior bortezomib exposure. The results in the resubmission showed that the rate of progression was similar in patients who had (HR = [REDACTED]; 95% CI: [REDACTED]) or had not (HR = [REDACTED]; 95% CI: [REDACTED];) been exposed to bortezomib.
- 6.20 The resubmission presented additional analysis of the OS data to account for the higher survival rates observed in the [REDACTED]% patients in the Bd arm who switched to a

daratumumab-based regimen after disease progression. However, the resubmission did not base this analysis on any standardised statistical methods, instead OS in the Bd arm was estimated using the results from the 120dsu data-cut and in the DBd arm OS results from the IA4 data-cut were used. This assumed that the 120dsu data for the Bd arm better represented the OS among Bd patients (i.e. they were free of crossover). The resubmission justified its approach on the basis of immortal time bias, treatment switch bias and as multiple types of daratumumab regimens used as subsequent treatment in the Bd arm. The estimated OS was statistically significantly different in favour of DBd compared to Bd, and resulted in a reduction in the risk of death of ■% for the crossover analysis compared with ■% in the analysis using only IA4 data (i.e. not 'adjusting' for the effects of crossover). The evaluation considered that the use of the two-stage estimation (TSE), the rank preserving structural failure time model (RPSFTM) and inverse probability of censoring weights (IPCW) to account for cross-over were not appropriate in this setting due to the lack of baseline data; however, the ESC considered the appropriateness of the methods adopted in the resubmission could not be ascertained due to the absence of information on the characteristics of patients at the time of switching. The PSCR had stated that the characteristics of the patients at the time of switching were not collected in the CASTOR trial and therefore, it was not possible to implement the TSE method to adjust the survival of Bd patients who received daratumumab. The ESC considered the method used in the submission was uncommon and its reliability remained uncertain.

- 6.21 QoL data were collected until a median follow up of 7.4 months, as described in the November 2017 submission, using the EORTC QLQ-C30 and EuroQoL EQ-5D-5L questionnaires. There were no statistically significant differences in the median time to worsening and time to improvement for EORTC QLQ-C30 and EuroQoL EQ-5D-5L (utility scores or VAS)). The November 2017 submission presented the mean utility scores as calculated from the individual patient data. The resubmission noted that DBd is generally tolerated and any additional AEs did not result in impairment of patients' HRQOL.

Indirect treatment comparison between DBd and Cd

- 6.22 The indirect comparison between DBd and Cd, which used Bd as a common comparator, demonstrated that there was a statistically significant difference in PFS in favour of DBd (HR = ■; 95% CI: ■) in the ITT analysis.
- 6.23 Although the OS point estimate favoured DBd, the ESC noted that the result did not reach statistical significance (HR = ■; 95% CI: ■). The OS remained statistically insignificant when incorporating the resubmission's analysis that accounted for crossover in the Bd arm of CASTOR (HR = ■; 95% CI: ■). The ESC was unsure if the absence of a difference in OS was due to the lack of differences between the treatments or due to underlying differences between the trials.

Descriptive comparison between DBd and VCd

- 6.24 Based on a descriptive comparison, the resubmission claimed that DBd was superior to VCd in terms of efficacy, given that DBd was superior to Bd in the CASTOR trial in

terms of PFS and OS and that VCd was similar to Bd in Kropff, 2017 in terms of PFS (HR = 0.71; 95% CI: 0.43, 1.19; p = 0.196) and OS (HR = 0.85; 95% CI: 0.41, 1.73; p= 0.645). This evaluation considered that claim was inconclusive given the descriptive nature of this comparison.

Daratumumab monotherapy

6.25 No comparative data were presented for daratumumab monotherapy. Evidence from two small non-comparative clinical trials (GEN501 and SIRIUS) demonstrated that daratumumab provided some benefits in terms of PFS, OS and overall response rate (ORR) in highly treatment experienced and refractory patients. The median PFS and OS from GEN502 was 6.2 months (95% CI: 4.2, 11.6) and 34.3 (95% CI: 19.9, NE) respectively at a median follow-up of 35.3 months. The median PFS and OS from SIRIUS was 3.7 months (95% CI: 2.8, 4.6) and 18.60 (95% CI: 13.7, 24.0) at a median follow-up of 36.7 months. The ORR was 30.4% at median follow-up of 36.6 months in a pooled analysis of both trials. The evidence from GEN501 and SIRIUS was subject to potential transitivity issues including differences between the proportion with a clinical benefit at their respective interim analyses (45.2% vs. 34.0%), the median prior therapies (4 vs. 5) and duration of treatment (5.4 months vs. 2.8 months). The safety of daratumumab monotherapy was consistent with daratumumab when used in combination as DBd.

Comparative harms

DBd

6.26 The safety profile of daratumumab at the IA4 data-cut was relatively unchanged compared to at the 120 dsu (Table 9). Overall, treatment with DBd was associated with more adverse events than Bd. In the November 2017 assessment, the PBAC considered that the clinical claim of inferior safety of DBd compared to Bd was supported by the data presented and that the similar and relatively low discontinuation rates in both DBd and Bd arms of CASTOR implied that the toxicity of daratumumab was manageable (paragraph 6.28, Daratumumab PSD, November 2017).

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Table 9: Summary of key adverse events in the trials

Trial ID: CASTOR	DBd n /N (%)	Bd n /N (%)	Risk Difference (95% CI)	Relative risk (95% CI)
November 2017 submission: 120dsu ^a				
Any AE, n (%)	240/243 (98.8%)	226/237 (95.4%)	3.41 (0.39, 6.42)	1.04 (1.00, 1.07)
Grade 3 and 4 AEs	193/243 (79.4%)	149/237 (62.9%)	16.55 (8.58, 24.53)	1.26 (1.12, 1.42)
Any serious AE, n (%)	118/243 (48.6%)	81/237 (34.2%)	14.38 (5.67, 23.10)	1.42 (1.14, 1.77)
≥1 AE related to discontinuation of all study treatment, n (%)	22/243 (9.1%)	22/237 (9.3%)	-0.23 (-5.39, 4.93)	0.98 (0.56, 1.71)
Total no. deaths within 30 days of last dose, n (%)	14/243 (5.8%)	13/237 (5.5%)	0.28 (-3.85, 4.40)	1.05 (0.50, 2.19)
March 2019 resubmission: IA4 ^b				
Any AE, n (%)	██████ (██%)	██████ (██%)	████ (████, █████)	████ (████, █████)
Grade 3 or 4 AE, n (%)	██████ (██%)	██████ (██%)	████ (████, █████)	████ (████, █████)
Any serious AE, n (%)	██████ (██%)	██████ (██%)	████ (████, █████)	████ (████, █████)
Any AE leading to discontinuation of study treatment, n (%)	██████ (██%)	██████ (██%)	████ (████, █████)	████ (████, █████)
Grade 3 or 4 AE, n (%)	██████ (██%)	██████ (██%)	████ (████, █████)	████ (████, █████)
Deaths	██████ (██%)	██████ (██%)	████ (████, █████)	████ (████, █████)

Abbreviations: 120dsu = 120-day safety update; AE = adverse event; Bd = bortezomib-dexamethasone; CI = confidence intervals; DBd = daratumumab-bortezomib-dexamethasone; IA4 = interim analysis 4.

Note: risk difference > 0 favours Bd over DBd.

a. median follow-up is 13.0 months.

b. median follow-up is 31.2 months.

Bold indicates a statistically significant difference.

Source: Table 2.44, p. 92 Section 2a of the November 2017 submission (information not presented in the resubmission); Table 2.28, p. 59 Section 2 of the resubmission.

Supplementary comparators (Cd and VCd)

6.27 The resubmission claimed that the ITC results comparing adverse events for DBd and Cd showed non-inferior safety with an overlapping but different and manageable profile.

6.28 The resubmission claimed DBd was non-inferior to VCd in comparative safety. The evaluation considered this claim was inconclusive given the descriptive nature of the comparison.

Benefits/harms

6.29 A summary of the comparative benefits and harms for DBd vs Bd is presented in Table 10.

Table 10: Summary of comparative benefits and harms for DBd vs Bd (ITT population, IA4 data-cut)

Benefits						
	DBd, N = 251	Bd, N = 247	Absolute difference		HR (95% CI)	
Progression events						
Number of events (%)	172 (68.5%)	204 (82.6%)	-			
Median months	16.7	7.1	9.6 months		0.32	
Not progressed at 30 months,%	29.1	4.0	25.1		(0.25, 0.40)	
Deaths						
Number of events (%)						
Median months						
Alive at 30 months,%						
Harms						
	DBd, n/N	Bd, n/N	RR (95% CI)	Event rate/100 patients*		RD (95% CI)
				DBd	Bd	
Any AE						
IA4 data-cut						
Grade 3 and 4 AE						
IA4 data-cut						
Any serious AE						
IA4 data-cut						
AE leading to discontinuation of study treatment						
IA4 data-cut						

Abbreviations: AE = adverse event; Bd = bortezomib-dexamethasone; CI = confidence intervals; DBd = daratumumab-bortezomib-dexamethasone; IA4 = interim analysis 4; NE = not estimable; RD = risk difference; RR = risk ratio.

Note: * Median follow-up for CASTOR is 31.2 months for IA4 data-cut.

Source: Table 2.10, p.22, Table 2.17, p.34, Section 2, Table 2.28, p. 59 Section 2 of the resubmission; CASTOR IA4 data TEFPFS01 TEFPFS01_1PL_PRIMID_MAF, TEFPFS01_1PL_PRLINA_2_MAF, Janssen internal analyses, Submission Figures Excel file, Appendix 4 of the resubmission and compiled during the evaluation. The absolute difference, event rate and RR were calculated during the evaluation. Bold indicates a statistically significant difference.

6.30 On the basis of the direct evidence presented in CASTOR, for every 100 patients treated with DBd:

- Approximately fewer patients would have progressed than if treated with Bd at months after the start of treatment.
- Approximately additional patients would be alive than if treated with Bd at months after the start of treatment.
- Approximately additional patients would have any AE than if treated with Bd over a median duration of exposure of months.
- Approximately additional patients would have a Grade 3 and 4 AE than if treated with Bd over a median duration of exposure of months.
- Approximately additional patients would have any serious AE than if treated with Bd over a median duration of exposure of months.

Daratumumab monotherapy

- 6.31 As no comparator was nominated for daratumumab monotherapy, and hence no comparative data was presented, a benefit/harms table was not possible.

Clinical claim

DBd versus Bd

- 6.32 The resubmission claimed that DBd demonstrated superior efficacy compared to Bd, based on the subgroup analyses of patients who had received only one prior therapy at the IA4 data cut of the CASTOR trial and supported by analyses of the ITT population. The ESC considered that the data presented in the resubmission supported the claim of superior efficacy; however, noted that the HR for OS, which was statistically significant in the subgroup analysis was not statistically significant for the ITT population. The ESC considered that this subgroup did not reflect the proposed PBS listing which was for RRMM patients who had received at least one prior therapy. In addition, although the data were more mature compared to those presented in the November 2017 submission (median follow-up of 31.2 months versus 13.3 months), median OS had not been reached in either the DBd or Bd arms (although it was reached for Bd in the IA5 data cut presented in the PSCR). The ESC therefore considered that the continued immaturity of the data made it difficult to quantify the magnitude of benefit of DBd compared to Bd and may not accurately reflect the longer-term comparative risks of progression or death associated with daratumumab-based therapies.
- 6.33 The resubmission claimed that DBd had inferior safety to Bd. The PBAC previously concluded that “...the submission’s claim of inferior safety of DBd over Bd was supported by the data. However the PBAC noted that the similar and relatively low discontinuation rates in both arms of the trial suggested that the toxicity was manageable” (paragraph 6.28, Daratumumab PSD, November 2017).
- 6.34 The PBAC considered that the claim that DBd was superior to Bd in terms of comparative effectiveness was reasonable, noting that the second-line subgroup did not accurately reflect the proposed PBS population, the magnitude of the OS benefit was uncertain due to the immaturity of the data and the difference in OS in the ITT population was not statistically significant.
- 6.35 The PBAC considered that the claim of inferior comparative safety remained reasonable.

DBd versus Cd

- 6.36 The resubmission claimed that DBd compared to Cd was superior in terms of PFS (statistically significant), with a clinically significant trend towards superior OS (not statistically significant), and non-inferior in comparative safety, based on an indirect comparison between the CASTOR and ENDEAVOR trials. Subject to the potential issues of transitivity between CASTOR and ENDEAVOUR (such as differences in duration of follow-up, ISS staging and higher rate of progression in Bd arm for CASTOR), the ESC

considered that the evidence provided in the resubmission partially supported this claim.

- 6.37 The resubmission claimed that DBd was non-inferior in terms of comparative safety to Cd, with the indirect comparison suggesting an overlapping but different and manageable adverse event profile for DBd.
- 6.38 The PBAC considered that the claim that DBd was superior compared to Cd in terms of PFS, demonstrated a trend towards superior OS and was non-inferior in terms of safety was partially supported by the data. The PBAC remained concerned that there was no statistically significant OS benefit.

DBd versus VCd

- 6.39 The resubmission claimed that DBd was superior to VCd in terms of efficacy, given that DBd was superior to Bd in CASTOR and VCd was similar to Bd in Kropff, 2017. The resubmission claimed that DBd was non-inferior to VCd in comparative safety. The evaluation considered that these claims were inconclusive given the descriptive nature of this comparison.

Daratumumab monotherapy

- 6.40 The resubmission did not make a clinical claim for daratumumab monotherapy. However, it concluded that “Daratumumab monotherapy provides benefit for highly treatment experienced and refractory MM patients, although the magnitude of incremental benefit is difficult to determine due to the non-comparative study designs. Daratumumab monotherapy is generally well tolerated with a manageable adverse event profile”. Evidence from two small non-comparative clinical trials (GEN501 and SIRIUS) demonstrated that daratumumab provided some benefits in terms of PFS, OS and ORR in highly treatment experienced and refractory patients. The safety of daratumumab monotherapy was consistent with daratumumab when used in combination as DBd. The ESC considered daratumumab monotherapy in fourth line RRMM would likely be beneficial for a small number of patients.
- 6.41 The PBAC noted that the sponsor had not provided a clinical comparison with an appropriate comparator and hence, it was not possible to assess the comparative effectiveness or safety of daratumumab monotherapy.

Economic analysis

- 6.42 The resubmission presented a cost-utility analysis of DBd compared to Bd relying on the second-line subgroup from CASTOR as the base-case. The ESC noted that the resubmission did not present the cost-effectiveness of daratumumab monotherapy. The key points from the economic evaluation are summarised in Table 11.

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Table 11: Summary of model structure and rationale

Component	Summary
Time horizon	Lifetime horizon (20 years) in the model base-case versus 31 months in CASTOR. The pre-PBAC response truncated the time horizon to 15 years.
Outcomes	LYG and QALY
Methods used to generate results	Partitioned survival model, incorporating a cohort expected value analysis.
Health states	Three: progression free, progressive disease and death.
Cycle length	1 month.
Transition probabilities (area under the curve)	<p>Consistent with PBAC advice, the longer-term IA4 data-cut was used. IA4 had median follow-up of 31.2 months. The time points (months) from which extrapolations began were based on when less than 20% of patients at risk remained, as follows:</p> <p>ITT:</p> <ul style="list-style-type: none"> • DBd = PFS 30.36, OS 33.3, TTD 29.8 months • Bd = PFS 10.9, OS 31.4, TTD 5.3 months <p>Second-line subgroup (base-case):</p> <ul style="list-style-type: none"> • DBd = PFS 31.6, OS 33.3, TTD 31.3 months • Bd = PFS 11.9, OS 33.0, TTD 5.4 months <p>The functional forms applied for the extrapolations were as follows:</p> <p>ITT and second-line subgroup (base-case):</p> <ul style="list-style-type: none"> • PFS to PD = Weibull • Survival to death = Exponential • TTD = DBd Exponential; Bd Weibull

Bd = bortezomib-dexamethasone; DBd = daratumumab-bortezomib-dexamethasone; IA4 = interim-analysis 4; OS = overall survival; PBAC = Pharmaceutical Benefits Advisory Committee; PD = progressive disease; PFS = progression free survival; QALY = quality adjusted life year, TTD = time to treatment discontinuation

Source: Table 3.1, p.7-8 Section 3 of the resubmission.

6.43 A summary of the key drivers of the model is shown in Table 12.

Table 12: Key drivers of the model

Description	Method/Value	Impact Base: \$ [redacted]*
CASTOR population	Base-case is based on a sub-group population who received DBd as second-line treatment only. This was not consistent with the proposed PBS restriction. The ESC considered use of the ITT population as the base-case more appropriate.	High, favours DBd ICER: \$ [redacted] using ITT population
Time horizon	Model adopts a 20-year time horizon, which it supports with data from the PBS/Australia Cancer Database to support patient longevity in this indication. The PBAC previously stated that greater confidence in establishing cost effectiveness would be derived by limiting the time horizon to 10 years (paragraph 7.10. Daratumumab PSD, Nov 2017). The pre-PBAC response truncated the time horizon to 15 years.	High, favours DBd ICER: 31 months = \$ [redacted]; 10 years = \$ [redacted]; 15 years = \$ [redacted]

DBd = daratumumab-bortezomib-dexamethasone; ESC = Economic Sub-Committee; ICER = incremental cost-effectiveness ratio; ITT = intention-to-treat; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PSCR = pre-Sub-Committee response; PDS = public summary document; RRMM = relapsed or refractory multiple myeloma

* Updated ICER presented in the PSCR which corrected an error in the model in which dispensed prices were calculated from an outdated public hospital preparation fee, which was different to that used in the financial estimates.

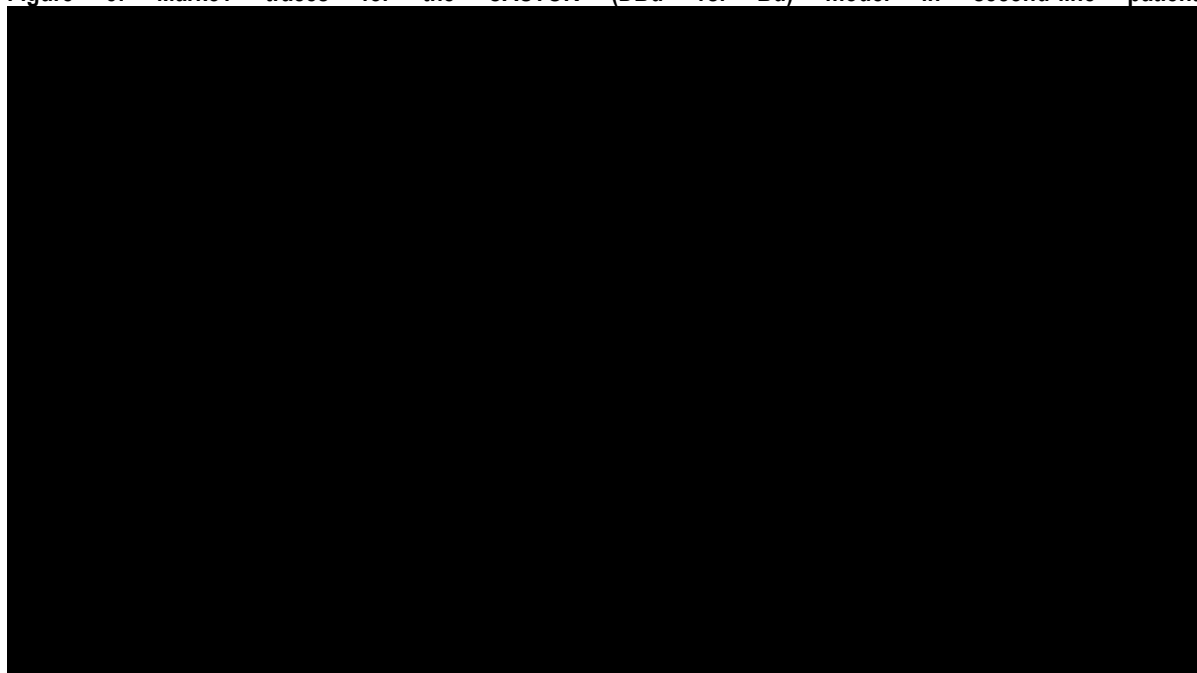
Source: Table 3.15-16, p.68-69 and 72-73, Table 3.19, p.79 Section 3 of the resubmission.

The redacted table shows ICERs in the range of \$75,000/QALY – more than \$200,000/QALY.

6.44 A stepped economic evaluation was presented (see Table 13). The resubmission presented Step 1 as a within trial analysis (with 31 months follow-up) and Step 2 extrapolated to the time horizon of 20 years. The resubmission nominated the results which used the second-line subgroup population as the base-case. In the November 2017 submission, the results from the ITT population formed the base-case.

6.45 Traces for the model results are presented in Figure 5.

Figure 5: Markov traces for the CASTOR (DBd vs. Bd) model in second-line patients



Bd = bortezomib-dexamethasone; DBd = daratumumab-bortezomib-dexamethasone; PFS = progression free survival.

Note: Model time horizon 20 years (240 months)

Source: Fig traces base case IA4 1PL tab, RR MM Economic model DBd vs Bd - Excel.

6.46 The ESC noted that the Markov traces indicated that █% (█%) of patients who received DBd as a second line treatment would be alive at 20 years (15 years). The ESC considered that this was clinically implausible. The ESC noted that if the ITT population was used the proportion of patients estimated to be alive at 20 years (15 years) was █% (█%) (OS extrapolations IA4 tab, Excel workbook).

6.47 The PSCR claimed that the use of a 20 year time horizon was justified as:

- the IA4 data was substantially more mature than that presented in the November 2017 submission (31.2 months versus 13.3 months), thereby providing greater certainty of the cost-effectiveness of DBd. Furthermore, the IA5 data cut, with a median follow-up of almost four years, did not support shortening the time horizon to 10 years;
- a higher rate of patients achieved minimal residual disease (MRD) negativity with DBd. The PSCR stated that, using the IA5 data cut and at a sensitivity threshold of 10^{-5} , █% of DBd patients achieved MRD negativity compared to █% of patients treated with Bd. The PSCR claimed that patients who achieve MRD negativity are observed to have increased survival compared to MRD positive patients and that after a median follow-up of 40 months, nearly all patients who achieved MRD negativity remained alive. The PSCR considered that as a significantly higher proportion of patients achieved MRD negativity with DBd, particularly in the second-line setting, combined with their prolonged survival, further justified a 20 year time horizon; and

- the indirect comparisons of OS between DBd and carfilzomib supported a claim of superiority.
- 6.48 The ESC noted that the PBAC had previously considered that although some patients may be alive beyond 10 years, and possibly 15 years, the extrapolation of immature trial data to 20 years substantially increased the uncertainty in terms of the cost-effectiveness estimates and that greater confidence would be derived by limiting the time horizon to 10 years (paragraph 7.10, Daratumumab PSD, November 2017). The ESC considered that the use of a 20 year time horizon continued to result in substantial uncertainty with the respect to the cost-effectiveness estimates, noting the extrapolation of immature OS IA4 trial data from a median follow-up of 31.2 months. The ESC again noted that the PBAC had previously accepted a 10 year time horizon when considering carfilzomib in the RRMM setting (PSD, July 2017) and a 15 year time horizon when considering lenalidomide in newly diagnosed patients (PSD, November 2015) and considered the use of a 20 year time horizon in the RRMM setting clinically implausible. Further, the ESC noted that the indirect treatment comparison between DBd and Cd did not demonstrate that DBd was superior in terms of OS. The pre-PBAC response proposed truncating the time horizon at 15 years to inform the base-case economic model to alleviate concerns regarding uncertainty in the ICER. The pre-PBAC response considered that a 10 year time horizon was too conservative as it was estimated that $\geq 20\%$ of current second-line patients will survive beyond 10 years and thus would not reflect the true cost-effectiveness of the DBd in clinical practice. The PBAC reiterated its opinion that the appropriate time horizon was 10 years, which it had previously accepted for carfilzomib, noting that the evidence provided in the resubmission did not support a gain in OS for DBd over Cd.
- 6.49 The resubmission justified the use of the second-line subgroup as the base case on the basis that incident RRMM patients will use DBd as a second line therapy, and therefore, this subgroup of RRMM patients is representative of the population of patients who will access DBd on the PBS. The resubmission considered that the subgroup was the most appropriate group of patients to include in the model and would reflect the cost-effectiveness of DBd at steady state. The PSCR further argued that as the CASTOR ITT population did not reflect the distribution of patients who will use DBd in Australia, it should not inform the base case. The ESC considered that, although the use of the second-line subgroup may reflect use of DBd in the future should it be listed and become the dominant treatment option, it is not representative of the proposed PBS population, which is for patients who have received at least one prior therapy. The ESC considered that the CASTOR ITT population more accurately reflected the proposed PBS restriction than the second-line subgroup, and was therefore the most appropriate data to inform the base case of the economic model.
- 6.50 The resubmission presented a supplementary cost-effectiveness analysis using the ITT data from the IA4 data-cut for DBd and 120dsu data-cut for Bd as a way to address the bias from the high use of daratumumab as subsequent therapy in the Bd arm from the IA4 data-cut (see paragraph 6.20). The ICER from the supplementary analysis was lower (\$105,000/QALY - \$200,000/QALY gained) than the ICER from the corresponding

ITT analyses using data from the IA4 data-cut for both the DBd and Bd arm (\$105,000/QALY - \$200,000/QALY gained). The difference in ICERs was due to fewer QALYs gained for Bd in the supplementary cost-effectiveness analysis. While such a difference is to be expected if the effect of crossover (longer OS) was adjusted for the Bd arm, the combination of data from the IA4 data-cut for DBd and 120dsu for Bd may have favoured DBd given the longer duration of follow-up.

- 6.51 The ESC considered that a revised base case should use the IA4, ITT population data and a time horizon of 10 years. This resulted in an ICER of \$105,000/QALY - \$200,000/QALY. The ESC advised that, in addition, it may be appropriate to revise the model structure so that the survival curves converge within the model time horizon.
- 6.52 The PSCR stated that an updated base case economic model informed by the IA5 data would be provided prior to the PBAC meeting. Instead, the pre-PBAC response proposed a revised base case, using the IA4, second-line treatment only subgroup population and a 15 year time horizon. This resulted in an ICER of \$75,000/QALY - \$105,000/QALY. If the ITT population was used, the ICER was \$105,000/QALY - \$200,000/QALY and if the ITT population was used and there was adjustment for treatment switching, the ICER was \$105,000/QALY - \$200,000/QALY.

Table 13: Results of the stepped economic evaluation

Data	Costs			QALY			ICER
	DBd	Bd	Incr	DBd	Bd	Incr	
IA4, ITT population (>= 1 prior therapy)							
Step 1: CASTOR (31-month follow-up)							
Step 2: Extrapolated to 20 years							
Supplementary analysis: IA4, ITT pop used for DBd arm, 120dsu, ITT pop used for Bd arm							
IA4, 2nd-line treatment only subgroup (1 prior therapy)							
Step 1: CASTOR (31-month follow-up)							
Step 2: Extrapolated to 20 years – Base case*							
ESC revised base cases*							
IA4, ITT pop for DBd and Bd arms; extrapolated to 10 years							
IA4, ITT pop for DBd arm, 120dsu, ITT pop for Bd arm, extrapolated to 10 years							
pre-PBAC response – 15 year time horizon							
Base-case: IA4, 2nd-line treatment subgroup							
IA4, ITT pop for DBd and Bd arms							
IA4, ITT pop for DBd arm, 120dsu, ITT pop for Bd							

Bd = bortezomib-dexamethasone; DBd = daratumumab-bortezomib-dexamethasone; ICER = incremental cost-effectiveness ratio; Incr = increment; pop = population; PSCR = pre-Sub-Committee response; QALY = quality adjusted life year.

* Updated ICER presented in the PSCR which corrected an error in the model in which dispensed prices were calculated from an outdated public hospital preparation fee, which was different to that used in the financial estimates.

Source: Table 3.15-16, p.68-69 and 72-73, Section 3 of the resubmission; and the pre-PBAC response.

- 6.53 The PBAC considered that a revised base case ICER should be informed by the ITT population of the IA5 (or most recent) data-cut and utilise a 10 year time horizon, with scenarios adjusting/not adjusting for crossover. The PBAC recalled that it recommended Cd on the basis of superior efficacy compared to Bd and noted that the ICER for carfilzomib (July 2017) was in the range of \$45,000/QALY to \$75,000 per QALY. The PBAC considered an ICER within this range would be appropriate for DBd.

6.54 Results of univariate sensitivity analyses specified by the resubmission and additional analyses conducted during the evaluation are presented in Tables 14 and 15. The ICER was most sensitive to variations in the time horizon, the CASTOR population used and the comparison accounting for the potential effects of crossover.

Table 14: Results of univariate sensitivity analyses, DBd vs. Bd in the second-line treatment only subgroup

Parameter	Base	Value	Incr cost	Incr QALY	ICER
Base-case (Second-line subgroup)	-	-			
Time horizon	20 years	15 years			
Time horizon	20 years	10 years			
Time horizon	20 years	5 years			
Extrapolation function for OS	Exponential	Weibull			
Extrapolation function for TTD DBd	Gompertz	Exponential			

Bd = bortezomib-dexamethasone; DBd = daratumumab-bortezomib-dexamethasone; ICER = incremental cost-effectiveness ratio; Incr = incremental; OS = overall survival; QALY = quality-adjusted life year; TTD = time to treatment discontinuation

Source: Table 3.19, p.79 Section 3 of the resubmission and compiled during the evaluation using Excel spreadsheet "RR MM – Economic Model DBd vs Bd" using sheets "DBd LY calc IA4 PL1" and "Results Step 1-2 IA4 2nd line" and "Inputs"

The redacted table shows ICERs in the range of \$45,000/QALY – more than \$200,000/QALY.

Table 15: Results of univariate sensitivity analyses, DBd vs. Bd for the ESC nominated revised base-cases

Parameter	Base	Value	Incr cost	Incr QALY	ICER
IA4, ITT pop for DBb and Bd arms, 10 year time horizon base case	-	-			
Time horizon	10 years	5 years			
Time horizon	10 years	15 years			
Extrapolation function for OS	Exponential	Weibull			
IA4, ITT pop for DBd arm, 120dsu ITT pop for Bd arm, 10 year time horizon	-	-			
Time horizon	10 years	5 years			
Time horizon	10 years	15 years			
Extrapolation function for OS	Exponential	Weibull			

Bd = bortezomib-dexamethasone; DBd = daratumumab-bortezomib-dexamethasone; ESC = Economic Sub-Committee; IA4 = interim analysis 4; ICER = incremental cost-effectiveness ratio; Incr = incremental; ITT = intention-to-treat; OS = overall survival; QALY = quality-adjusted life year; TTD = time to treatment discontinuation

Source: Table 3.19, p.79 Section 3 of the resubmission and compiled during the evaluation using Excel spreadsheet "RR MM – Economic Model DBd vs Bd" using sheets "DBd LY calc IA4 PL1" and "Results Step 1-2 IA4 2nd line" and "Inputs"

The redacted table shows ICERs in the range of \$105,000/QALY – more than \$200,000/QALY.

Drug cost/patient/course

6.55 From the model, which estimated an average time on DBd treatment of [redacted] months for the ITT population, the undiscounted cost of daratumumab was \$ [redacted] per patient and the undiscounted cost of bortezomib was \$ [redacted] (for an average of 6.3 months treatment). These costs included the application of the proposed "MM Treatment Package".

6.56 From the model, the cost of the bortezomib in the comparator arm, Bd, was estimated to be \$ [redacted] (for an average of [redacted] months treatment). As this assumed that daratumumab was not listed, the "MM treatment package" was not applied.

Application of the “MM Treatment Package” results in a \$ [REDACTED] saving in the cost of bortezomib.

Estimated PBS usage & financial implications

6.57 This resubmission was considered by DUSC. The resubmission used a mixed epidemiological and market share approach to estimate the utilisation and financial impact of listing DBd and daratumumab monotherapy. The approach in the resubmission to estimating the financial impact of listing daratumumab for RRMM was modified from that presented in November 2017 in that it included estimates of the patient numbers and therapies for first-line and subsequent lines of MM treatment. This modification was included to address the PBAC’s concerns that the November 2017 estimates had not accounted for the impact of the PBS listing of DBd on the use of first-line therapies (i.e., lenalidomide and bortezomib), and to estimate the financial impact of a listing for daratumumab monotherapy.

6.58 The estimated use and financial implications of listing daratumumab as DBd and monotherapy are presented in Table 16.

Table 16: 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]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Number of scripts dispensed ^a	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Estimated financial implications of daratumumab at dispensed prices						
Cost to PBS/RPBS	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Copayments	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Cost to PBS/RPBS less copayments	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Estimated financial implications of daratumumab and bortezomib at dispensed prices						
Cost to PBS/RPBS less copayments	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Estimated financial implications for other medicines (bortezomib, lenalidomide, thalidomide, pomalidomide, carfilzomib, dexamethasone, pegfilgrastim, hydrochlorothiazide)						
Cost to PBS/RPBS less co-payments – dara listed	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Cost to PBS/RPBS less co-payments – dara not listed	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Cost to PBS/RPBS less co-payments – net changes	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Net financial implications no copayments (effective price for bortezomib and dispensed prices for other medicine)						
Net cost to PBS/RPBS	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Net cost to MBS	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Net cost to PBS/RPBS/MBS	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

^a Assuming in the initial period of 2.5 scripts/month for DBd and 2.9 scripts/month for daratumumab monotherapy as estimated by the resubmission. Assuming in the continuing period 1.1 scripts/month for both DBd and daratumumab monotherapy.

Compiled during the evaluation as the patient numbers on treatment at December each year as reported from the ‘Monthly model (dara)’ sheet of the Excel spreadsheet ‘Daratumumab RRMM financial estimates’.

Source: Text p.30, Section 4 of the resubmission. Table 4.12, p.33; Table 4.19-4.21, p.42-43 and Table 4.26, p.49 Section 4 of the resubmission. Excel Spreadsheet ‘Daratumumab_RRMM_financial_estimates’ ‘4.2 Use and cost of dara’ summing co-payment amounts and ‘4.3 Change Use and Cost Other’ and summation of Year 1 to 6 based on ‘Summary Tables’ during the evaluation and ‘Monthly model (dara)’.

- 6.59 The net cost of daratumumab and bortezomib to the PBS/RPBS without the ‘MM Treatment Package’ over the first six years of listing, during which less than 10,000 patients would be initiated, was substantially more than \$100 million. With the application of the ‘MM Treatment Package’ this was reduced to substantially more than \$100 million. The pre-PBAC response provided updated estimates based on the DUSC advice (see paragraph 6.60 below). These resulted in slightly fewer patients being treated over the first six years of listing and a net cost, with the application of the ‘MM Treatment Package’, of substantially more than \$100 million.
- 6.60 DUSC considered the patient numbers to be underestimated, and the uptake and cost offsets to be overestimated. The main issues were:
- The resubmission did not present the survey questions or additional characteristics of the clinicians included in the market research from ‘So What Research’ used to estimate the uptake of daratumumab for RRMM patients once PBS listed. DUSC commented that the reliability of these data to inform uptake assumptions was uncertain and could not be appraised.
 - DUSC considered that it was unlikely bortezomib would be 100% replaced by daratumumab. The pre-PBAC response acknowledged that there may be some use of bortezomib monotherapy and therefore increased the market share of bortezomib from 0% to 3-6% and correspondingly reduced the uptake of DBd.
 - The methods used to estimate the duration of treatment artificially reduced the estimated patient numbers. DUSC considered discontinuation due to death was accounted for in the model. DUSC considered that adjusting for the time to discontinuation of treatment (TTD) by dividing it by the median time to subsequent therapy or death (i.e. multiplying TTD by the proportion of 78%) artificially reduced the estimated patient numbers and should have been removed from the estimates, and that duration of therapy (other than due to death) should have been accounted for in a different way. The pre-PBAC response acknowledged that the method of applying TTD in the financial estimates artificially reduced the number of treated patients and thus, the utilisation of daratumumab, and removed the multiplication of TTD by 78%.
 - The listing of DBd and daratumumab monotherapy was assumed to replace lenalidomide, thalidomide, pomalidomide and carfilzomib utilisation in subsequent lines. DUSC considered that it was unlikely that replacement would occur to the extent assumed, and considered daratumumab would displace those therapies within the six years represented in the model. The pre-PBAC response stated that the resubmission did not assume that DBd replaced other therapies, instead it assumed that the costs of these treatments were likely to be displaced to beyond the six-year timeframe.

Quality Use of Medicines

- 6.61 The resources proposed in the resubmission (brochures) to support the quality use of medicines were unchanged from the November 2017 submission.

Financial Management – Risk Sharing Arrangements

- 6.62 When considering the financial management of daratumumab in November 2017, the PBAC considered that there were risks associated with the duration of therapy for continuing daratumumab treatment, the number of patients continuing treatment, the replacement of comparator regimens in ongoing treatment, use of daratumumab monotherapy and the exposure of the number of grandfathered patients. The PBAC therefore advised that a Risk Sharing Arrangement (RSA), based on total expenditure or the number of cycles, would be required for listing (paragraph 6.65, Daratumumab PSD, November 2017).
- 6.63 The PSCR and pre-PBAC response stated that an RSA which caps the cost of daratumumab to the PBS and reduces the magnitude of the budget impact would be proposed after the financial estimates have been reviewed by the PBAC.
- 6.64 The sponsor hearing requested that PBAC consider managing the ICER and the large budget impact through the RSA. The PBAC noted that no details were provided regarding the proposed RSA and again advised that utilisation caps based on total expenditure or the number of cycles would be required for assessment before a listing would be considered. The PBAC considered it would be inappropriate to establish a cost-effective price using the RSA when the price offered was so far from producing an acceptable ICER and the estimated utilisation and potential uptake are uncertain. In addition, achieving cost effectiveness through an RSA requires certainty in the patient number and duration of therapy as the cost effective cost is not achieved until the RSA cap is triggered.

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

7 PBAC Outcome

DBd

- 7.1 The PBAC did not recommend the listing of daratumumab for use in combination with bortezomib and dexamethasone (DBd) in relapsed or refractory multiple myeloma (RRMM), on the basis of a high and uncertain cost-effectiveness ratio. The PBAC was also concerned about the very high estimated financial implications. The PBAC acknowledged the clinical need for additional treatments for RRMM and considered that daratumumab is an effective treatment; however, at the price proposed it was not a cost-effective treatment, even in the scenario proposed in the resubmission which included overly optimistic model assumptions regarding its benefits due to the use of a subgroup of the trial population, an uncertain adjustment for crossover and a benefit sustained over 15 to 20 years.
- 7.2 The PBAC noted the consumer comments received in support of a PBS listing and considered that these reflected the clinical need for additional treatment options for patients with RRMM.
- 7.3 The PBAC considered that the clinical place in therapy of DBd, as proposed in the requested PBS restriction, was appropriate, based on the available evidence.

However, the PBAC remained concerned that listing DBd only without the option of daratumumab plus lenalidomide and dexamethasone (DLd) would result in possible inequity as some patients may respond better to a lenalidomide combination backbone. The PBAC also noted a PBS listing for DBd only would either result in a higher proportion of patients receiving lenalidomide plus dexamethasone (Ld) in first-line or patients receiving the same backbone therapy (i.e. Bd) in first- and second-line.

- 7.4 The PBAC noted that, consistent with the November 2017 submission, bortezomib in combination with dexamethasone (Bd) was appropriately nominated as the main comparator for DBd. The PBAC noted that carfilzomib plus dexamethasone (Cd), bortezomib plus cyclophosphamide and dexamethasone (VCd) and lenalidomide plus dexamethasone (Ld) were appropriately nominated as secondary comparators. However, the PBAC noted that no comparative data were provided for the comparison with Ld.
- 7.5 The PBAC noted that updated data were presented from the CASTOR trial in the resubmission. The PBAC noted that the original submission presented data from the 120 day safety update (120 dsu) data cut (median follow-up = 13.3 months); whereas the resubmission presented data from the Interim analysis 4 (IA4) data cut (median follow-up = 31.2 months) and the Pre-Sub-Committee response (PSCR) presented limited data from the Interim analysis 5 (IA5) data cut (median follow-up = 40 months). The PBAC noted that the limited efficacy data presented in the PSCR (IA5) suggested a similar magnitude of effect to that presented in the resubmission based on the IA4 data.
- 7.6 The PBAC noted that the clinical claim presented in the resubmission was based on a subgroup of patients from the CASTOR trial who received DBd or Bd as a second-line treatment only and supported by data from the ITT population. The resubmission claimed this was appropriate on the basis that this was the population in which DBd is most effective and in which use is most likely to occur. The PBAC noted that the second-line subgroup population was not consistent with the proposed PBS population (patients who have received at least one prior therapy) and considered that it was more appropriate to base the clinical claim on the intention to treat (ITT) population.
- 7.7 The PBAC considered that the evidence presented in the resubmission supported a claim of superior efficacy, noting that the hazard ratio for overall survival in the ITT population was likely confounded by cross-over. The PBAC noted that median overall survival had been reached in the Bd arm at the IA5 data cut (median = █████ months; HR = █████; 95% CI: █████).
- 7.8 The PBAC noted the crossover adjustment used in the resubmission resulted in a reduction in the risk of death of █████%, but that the methodology for this adjustment was not based on any standardised statistical methods. Instead OS data from the IA4 data-cut was used to inform the DBd arm and data from the 120dsu data-cut was used for the Bd arm. The PBAC noted that the lack of baseline data for patients who switched meant it was not possible to use the IPCW and RPSFT methods. The PBAC

considered that without baseline data, which is required to make some judgement as to whether there was no unmeasured confounder and the distribution of baseline predictors of survival, it was not possible to evaluate the reliability of the method used to adjust overall survival which resulted in the reduction in the risk of death increasing from ■■■% to ■■■%.

- 7.9 The PBAC considered that the claim of inferior safety remained reasonable.
- 7.10 The PBAC considered that the indirect treatment comparison between DBd and Cd was informative, but noted that there were a number of differences between the CASTOR and ENDEAVOUR patient populations which made the non-significant OS outcome difficult to interpret. The PBAC again noted that in order to recommend DBd at a higher price than Cd, it would need to be satisfied that DBd provides, for some patients, a significant improvement in efficacy or reduction in toxicity over Cd. The PBAC did not consider that this had been adequately established by the data presented in the submission.
- 7.11 The PBAC considered that the economic analysis provided by the resubmission was favourable to DBd treatment and that the overall survival gains with DBd treatment were large in comparison to that observed in the trial and hence uncertain. The PBAC noted that the treatment landscape in multiple myeloma is rapidly changing and expected survival rates for patients have improved. However, the PBAC noted that, using the second-line subgroup population, ■■■% (■■■%) of DBd patients were modelled to be alive at 20 years (15 years) and considered that this was clinically implausible. The PBAC also considered that the persistent treatment effect (i.e. the curves did not converge) over the 20 year (15 year) time horizon was not adequately supported by the data.
- 7.12 The PBAC identified two key issues with the economic analyses presented in the resubmission:
- The time horizon of the model was 20 years in the resubmission, and truncated to 15 years in the pre-PBAC response. The PBAC recalled that it had previously considered that although some patients might be alive beyond 10 years, and possibly 15 years, the extrapolation of immature trial data to 20 years substantially increased the uncertainty of the cost-effectiveness estimates, and that greater confidence would be derived by limiting the time horizon to 10 years. The PBAC acknowledged that the time horizon was truncated at 15 years in the pre-PBAC response, but reiterated that a 10 year horizon, as presented in the July 2017 consideration of carfilzomib in the RRMM setting, would be more appropriate and reduce uncertainty; and
 - The base case analysis used the second-line subgroup, which suggested superior efficacy, rather than the ITT population. Although the resubmission claimed that the use of the subgroup would reflect the cost-effectiveness of DBd at steady state, the PBAC considered that the cost-effectiveness of DBd should be representative of its use at the time of potential listing. Therefore, the PBAC considered that use of the ITT population, which more accurately reflected the

proposed PBS population at the time of listing, should be used to inform the base case of the economic model.

- 7.13 The PBAC considered that the base case ICER for DBd, using a 15 year time horizon and the second-line subgroup population, of \$75,000/quality adjusted life year (QALY) – \$105,000/QALY was high, highly uncertain and likely to be underestimated. The PBAC noted that use of the ITT population, no adjustment for cross over and a 10 year time horizon produced an ICER of \$105,000/QALY - \$200,000/QALY. The PBAC considered a more appropriate base case would incorporate a time horizon of 10 years and utilise the IA5 ITT population and include scenario analyses with and without adjustment for crossover. The PBAC noted that the ICER for Cd (July 2017) was in the range of \$45,000/QALY to \$75,000/QALY and considered an ICER within this range would be appropriate for DBd.

Daratumumab monotherapy

- 7.14 The PBAC was unable to consider the listing of daratumumab monotherapy as a fourth-line treatment in RRMM as no comparative clinical or economic data were provided.
- 7.15 The PBAC considered that the clinical place in therapy of daratumumab monotherapy, as proposed in the requested PBS restriction, was appropriate. The PBAC considered that there was a high clinical need for daratumumab monotherapy and that it was important treatment option to provide equitable access for a small number of patients who had progressed to later stage RRMM.
- 7.16 The PBAC noted that no comparator was nominated for daratumumab monotherapy and that no economic analysis was presented. The PBAC noted that ESC had previously considered that pomalidomide would be a potentially relevant comparator (October 2017). The PBAC noted the NICE technology appraisal guidance document in which daratumumab monotherapy was indirectly compared with pomalidomide plus dexamethasone and considered an equivalent analysis should have been included in this resubmission to allow the Committee to make a recommendation based on the clinical efficacy, safety and cost-effectiveness of daratumumab monotherapy.

DBd and daratumumab monotherapy

- 7.17 The PBAC noted that the financial implications of listing daratumumab appropriately considered both the use of DBd as per the proposed PBS restriction, i.e. in all patients who had received at least one line of prior therapy, and the use of daratumumab monotherapy.
- 7.18 The PBAC noted that although the DUSC considered the patient numbers to be underestimated, the updated estimates provided in the pre-PBAC response inappropriately included fewer initiating patients.
- 7.19 The PBAC noted that the pre-PBAC response updated the estimated cost of listing DBd as a second-line treatment and daratumumab monotherapy as a fourth line therapy over the first six years, and adopting the resubmission's proposed Multiple Myeloma

Treatment Package, was substantially more than \$100 million. The PBAC noted that the resubmission estimated that less than 10,000 patients would initiate this non-curative treatment over the same time period. The PBAC considered that the opportunity cost of the requested listings was very high, particularly considering the high and uncertain ICER for DBd therapy and the lack of a cost-effectiveness analysis for daratumumab monotherapy. The PBAC noted the Special Pricing Arrangement (SPA), in the form of the Multiple Myeloma Treatment Package, but considered that this did not mitigate the risks associated with the duration of therapy for continuing patients. The PBAC noted that although a Risk Sharing Arrangement (RSA) was proposed, no detail was provided. The PBAC considered that a clear, evaluable proposal based on total expenditure or the number of cycles per patient would be helpful.

7.20 The PBAC considered that any future resubmission could be a minor submission if, the changes to the economic model requested by the PBAC (a time horizon of 10 years, using the IA5 ITT population, with scenario analyses with and without adjustment for crossover) resulted in an ICER within the requested range (\$45,000 to \$75,000). A detailed RSA may be proposed, however, the cost-effectiveness of daratumumab must be reasonably achieved with the price offered, not the RSA. Should the resubmission present additional data that would require evaluation, a major submission would be required.

7.21 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 in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

The sponsor had no comment.