

An addendum to this Public Summary Document (PSD) has been included at the end of the document.

**5.07 DARATUMUMAB,
Solution for subcutaneous injection 1,800 mg in
15 mL vial,
Darzalex SC[®],
Janssen-Cilag Pty Ltd.**

1 Purpose of submission

- 1.1 The Category 1 submission requested a Section 100 (Highly Specialised Drug), Authority Required listing for daratumumab subcutaneous (SC), in combination with cyclophosphamide, bortezomib and dexamethasone (CyBorD) for newly diagnosed patients with systemic light-chain AL amyloidosis (herein referred to as AL amyloidosis). The requested listing is for combination therapy for the first 24 weeks, followed by daratumumab SC as monotherapy for treatment from week 25 to a maximum of 96 weeks (24 cycles). The submission requested that patients continue to access daratumumab SC until disease progression or the development of treatment-limiting toxicity, or for a maximum of 24 cycles (i.e. a maximum of 34 injections of daratumumab SC).
- 1.2 Listing was requested on the basis of a cost-utility analysis (CUA) of daratumumab SC + CyBorD versus the submission's main comparator, CyBorD. The submission also presented a secondary CUA versus melphalan and dexamethasone (MDex).
- 1.3 Table 1 summarises the components of the clinical issue addressed by the submission.

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

Component	Description
Population	Patients with newly diagnosed systemic light chain AL amyloidosis
Intervention	<p>Daratumumab SC, administered in combination with bortezomib, cyclophosphamide and dexamethasone (i.e. CyBorD)</p> <p><u>Daratumumab SC:</u> Daratumumab is administered subcutaneously at a dose of 1800 mg over approximately 3-5 minutes. It is administered weekly for the first 2 cycles (each cycle is 4 weeks in duration; a total of 8 doses over weeks 1 to 8), every two weeks from cycles 3 to 6 (a total of 8 doses over week 9 to 24) and then once every 4 weeks from cycle 7 (week 25+) onward until disease progression, the development of treatment-limiting toxicity, or a maximum of 24 cycles (≈2 years) from the first dose of treatment (whichever is first).</p> <p><u>CyBorD:</u> Dexamethasone is given as a 40 mg dose either orally or by IV injection, cyclophosphamide as a 300 mg/m² dose either orally or by IV injection, and bortezomib as a 1.3 mg/m² dose by SC injection. Each is administered once weekly on days 1, 8, 15, 22 of every 4-week cycle for a maximum of 6 cycles.</p>
Comparator	<p>This submission nominates two comparators:</p> <ol style="list-style-type: none"> <u>Regimen that will be replaced in clinical practice (main comparator):</u> Bortezomib-based regimens, mainly bortezomib, cyclophosphamide and dexamethasone (CyBorD) as per the comparator of the pivotal ANDROMEDA trial. <u>CyBorD:</u> Dexamethasone is given as a 40 mg dose either orally or by IV injection, cyclophosphamide as a 300 mg/m² dose either orally or by IV injection, and bortezomib as a 1.3 mg/m² dose by SC injection. Each is administered once weekly on days 1, 8, 15, 22 of every 4-week cycle for a maximum of 6 cycles. <u>Regimen that is PBS listed (supplementary comparator):</u> Melphalan in combination with dexamethasone (MDex). <u>MDex:</u> Melphalan is given as a 10 mg/m² dose orally and dexamethasone as a 40 mg dose orally on days 1 to 4 of each 4-week cycle for generally a maximum of 6 cycles.
Outcomes	Haematological response, organ response, MOD-PFS, OS, AEs
Clinical claim	<p><u>Daratumumab SC + CyBorD vs. CyBorD</u> <u>Efficacy:</u> Compared with CyBorD, daratumumab SC + CyBorD demonstrates superior comparative efficacy based on haematological response and organ response which is anticipated will translate to a superior OS as further follow-up data from the trial become available. <u>Safety:</u> daratumumab SC + CyBorD is associated with additional AEs compared with CyBorD alone and therefore has an inferior safety profile.</p> <p><u>Daratumumab SC + CyBorD vs. MDex</u> <u>Efficacy:</u> Compared with MDex, daratumumab SC + CyBorD demonstrates superior comparative efficacy based on CR, MOD-PFS and OS. <u>Safety:</u> There are limited data to permit comparison of the safety profiles of daratumumab SC + CyBorD and MDex.</p>

Source: Table 1-1, p 11 of the submission

AL = light-chain; AEs = adverse events; CR = complete response; CyBorD = bortezomib, cyclophosphamide and dexamethasone; IV = intravenous; MDex = melphalan in combination with dexamethasone; MOD-PFS = major organ deterioration progression-free survival; OS = overall survival; SC = subcutaneous.

2 Background

Registration status

2.1 The submission was made under the TGA/PBAC Parallel Process. At the time of evaluation for PBAC consideration, the TGA's Delegates Overview and ACM minutes

were available. Daratumumab SC was approved for registration by the TGA on 6 October 2021 for the following indication:

‘in combination with bortezomib, cyclophosphamide and dexamethasone, for the treatment of patients with light chain AL amyloidosis’

2.2 Bortezomib is not TGA indicated for use in patients with AL amyloidosis. The submission stated that the sponsor does not intend to seek TGA approval for bortezomib to be used in patients with AL amyloidosis because the sponsor does not have access to the trial data reported by Kastritis et al. 2020 and because there are no further confirmatory studies for bortezomib in AL amyloidosis.

Previous PBAC consideration

2.3 The PBAC has previously considered and recommended (July 2020) daratumumab (intravenous infusion) in combination with bortezomib and dexamethasone for relapsed/refractory (second line) multiple myeloma (RRMM). Daratumumab SC for RRMM was recommended by the PBAC at July 2021 meeting.

2.4 The PBAC has not previously considered daratumumab SC for AL amyloidosis. This is the first submission to the PBAC from any sponsor for AL amyloidosis.

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

3 Requested listing

Name, restriction, manner of administration, form	Maximum amount	No. of repeats	Dispensed price for maximum amount	Proprietary name and manufacturer
Daratumumab SC				
Initial treatment + Grandfather treatment (1-8 weeks, administered once weekly) Daratumumab, subcutaneous vial 1800 mg	1800 mg	7	Section 100 HSD Published price: Public hospital: \$7,010.28 Private hospital: \$7,058.02	DARZALEX SC®, Janssen-Cilag Pty Ltd
Continuing treatment (Weeks 9 to 24, administered once every 2 weeks) Daratumumab, subcutaneous vial 1800 mg	1800 mg	7	Effective price: Public hospital: \$ [REDACTED] Private hospital: \$ [REDACTED]	
Continuing treatment (Weeks 25 onwards, administered every 4 weeks) Daratumumab, subcutaneous vial 1800 mg	1800 mg	5		

Category / Program:	Section 100 (Highly Specialised Drugs Program)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Systemic light chain amyloidosis
PBS Indication:	Untreated systemic light-chain amyloidosis
Restriction:	<input checked="" type="checkbox"/> Authority Required – Telephone, Electronic
Clinical criteria:	Patients must have a confirmed diagnosis of systemic light-chain amyloidosis,

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	<p>AND The condition must be untreated <i>[initial treatment only]</i>), AND The patient must not have NYHA Class IIIB or Class IV cardiac disease or Mayo stage IIIB disease, AND The treatment must be in combination with bortezomib, cyclophosphamide and dexamethasone, AND The patient must have an Eastern Cooperative Oncology Group Performance Status of 0, 1 or 2 AND; The patient must not have developed disease progression while receiving treatment with this drug for this condition <i>[continuing treatment only]</i>.</p>
Administrative Advice:	Special Pricing Arrangements apply

Source: Table 1-16 and Table 1-17, p58-60 of the submission
NYHA = New York Heart Association

Name, restriction, manner of administration, form	Maximum amount	No. of repeats	Dispensed price for maximum amount	Proprietary name and manufacturer
Bortezomib (for use as part of the daratumumab SC + CyBorD combination)				
Bortezomib, 3.5 mg injection, 1 vial			Section 100 EFC	
Bortezomib, 3 mg injection, 1 vial	3000 mcg	11	Public hospital: \$605.00	VELCADE®, Janssen-Cilag
Bortezomib, 1 mg injection, 1 vial			Private hospital: \$653.29	

Category / Program:	Chemotherapy Items for Public Hospital use
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition:	Systemic light-chain amyloidosis
PBS Indication:	Untreated systemic light-chain amyloidosis
Restriction:	<input checked="" type="checkbox"/> Authority Required – Telephone, Electronic
Treatment phase	Initial and continuing
Clinical criteria:	<p>Patients must have a confirmed diagnosis of systemic light-chain amyloidosis, AND The condition must be untreated <i>[initial treatment only]</i>), AND The patient must not have NYHA Class IIIB or Class IV cardiac disease or Mayo stage IIIB disease, AND The treatment must be in combination with daratumumab, cyclophosphamide and dexamethasone, AND The patient must have an Eastern Cooperative Oncology Group Performance Status of 0, 1 or 2 AND; The patient must not have developed disease progression while receiving treatment with this drug for this condition <i>[continuing treatment only]</i>.</p>
Administrative Advice:	nil

Source: Table 1-16 and Table 1-17, p58-60 of the submission
NYHA = New York Heart Association

- 3.1 The submission requested a Special Pricing Arrangement (SPA), consistent with the price proposed for daratumumab SC for second-line multiple myeloma. The submission requested a rebate of ██████% for daratumumab SC under a Section 100 (Highly Specialised Drugs Program) listing. The proposed published DPMQ for daratumumab SC is \$7,010.28 (public hospital) and \$7,058.02 (private hospital) and the proposed effective DPMQ is \$██████ for the public setting and \$██████ for the private setting. The Pre-Sub-Committee Response (PSCR) agreed with the Secretariat's suggestion to align the listing program of daratumumab SC for AL amyloidosis to that for RRMM, i.e., dual General Schedule and Section 100 (EFC) listings.
- 3.2 The proposed PBS restriction did not explicitly exclude patients with a concurrent diagnosis of AL amyloidosis and multiple myeloma (MM). However, patients in the pivotal trials, ANDROMEDA and Kastritis et al. 2020, were excluded if they had a concurrent diagnosis of AL amyloidosis and multiple myeloma. The PSCR contended that ANDROMEDA had a narrower interpretation of symptomatic MM than the definition of the International Myeloma Working Group (IMWG) and, therefore, considered the requested PBS restriction to be aligned to the evidence. The ESC noted that, despite the ANDROMEDA exclusion criteria stating that patients with previous or current diagnosis of symptomatic MM should be excluded, some patients meeting the IMWG definition of may have been included in the ANDROMEDA trial due to narrower criteria being applied and, the exclusion of only the more severe patients.
- 3.3 The PSCR further contended that according to clinical advice from the Australian Amyloidosis Network (AAN), in clinical practice most patients with a concurrent AL amyloidosis and MM diagnosis would have less than 60% of plasma cells in the bone marrow. However, the PSCR did not comment on the frequency that AL amyloidosis patients also meet the criteria for MM due to the presence of (1) lytic bone disease, OR (2) plasmacytomas, OR (3) hypercalcemia.
- 3.4 The PSCR stated that based on advice from AAN clinicians, patients with a concurrent diagnosis of AL amyloidosis and MM have poorer outcomes and greater clinical need than patients with AL amyloidosis alone, noting that patients with higher levels of plasma cell clones have worse outcomes. Thus, excluding patients with concurrent systemic AL amyloidosis and MM diagnoses from the restriction would represent an inequity of access to daratumumab for these patients. The ESC noted this is particularly relevant to newly diagnosed MM patients, as MM patients can only access daratumumab in the second line setting.
- 3.5 The PSCR argued that patients are almost always diagnosed with AL amyloidosis before MM in clinical practice. However, the ESC considered that the proposed PBS listing may lead to an increase in testing and diagnosis of AL amyloidosis in MM patients and due to the potential for patients with MM and subclinical AL amyloidosis to access front line daratumumab under the proposed PBS listing if the criteria are met. The pre-PBAC response reiterated that the proposed PBS listing for AL

amyloidosis should not exclude patients with a concurrent diagnosis of MM, stating that the median bone marrow plasma cell count of patients in ANDROMEDA was 10%, indicating that at least 50% of patients had a plasma cell level to qualify them for an MM diagnosis. The Secretariat advised that if daratumumab is to have separate listings for MM and AL amyloidosis, for the patient with a diagnosis of both conditions, it would not be immediately apparent to a prescriber as to which PBS listing to apply under. Furthermore, if an existing MM patient was to be re-diagnosed/re-classified to have AL amyloidosis, or vice versa, from an administrative perspective, it would be unclear under which listing the prescriber would continue daratumumab treatment under. These practical implementation issues were inadequately addressed by the submission.

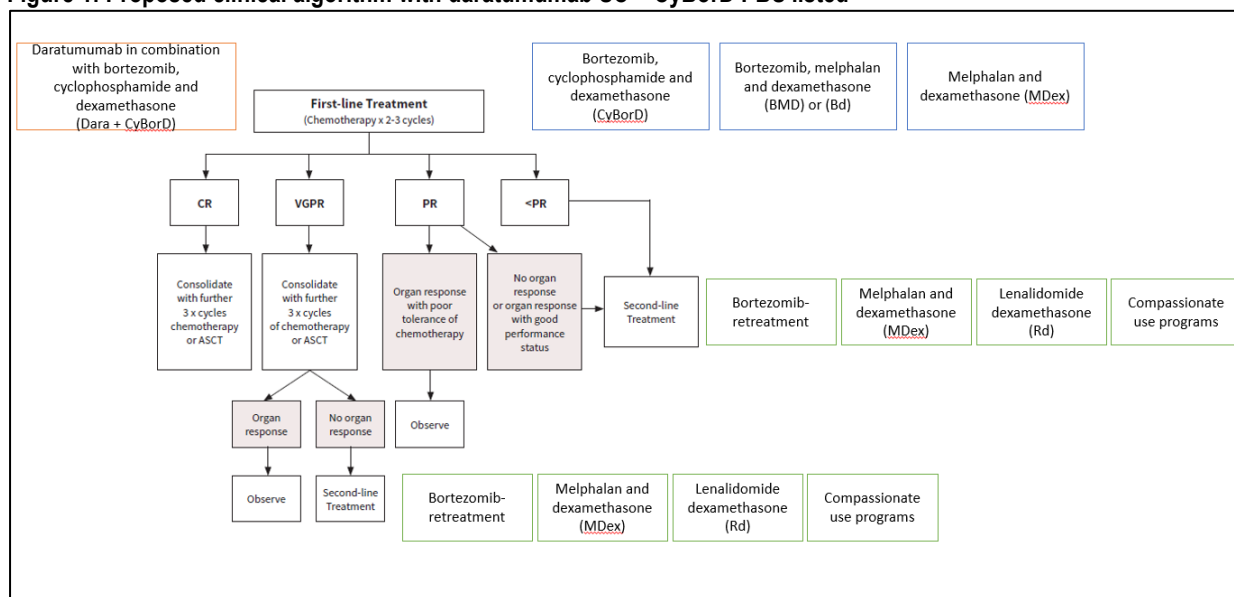
- 3.6 The proposed PBS restriction did not define what constitutes a confirmed diagnosis of AL amyloidosis. In ANDROMEDA, this was defined as having a histopathological diagnosis of AL amyloidosis and having either a monoclonal protein >5 g/L in serum; or dFLC > 50 mg/L, with an abnormal kappa: lambda ratio. The PBAC agreed with the ESC, that the eligibility criteria should stipulate histological confirmation of the diagnosis.
- 3.7 The restriction proposed in the submission required the patient to have no significant cardiac disease as defined in the ANDROMEDA trial (defined as NYHA Class IIIB or Class IV cardiac disease or Mayo stage IIIB). However, the PSCR clarified that the initially proposed clinical criterion that excluded patients with Mayo Stage IIIB, NYHA Class IIIB and IV cardiac disease should be deleted from the restriction, consistent with the TGA indication and clinical advice and provided updated financial estimates. The PBAC considered that this was reasonable.
- 3.8 The proposed restrictions applying to the first 24 weeks of treatment require that patients receive ongoing treatment with CyBorD, consistent with the draft daratumumab PI and the ANDROMEDA trial. The proposed continuing treatment restriction for week 25 onwards requires patients receive ongoing treatment with daratumumab monotherapy consistent with the draft daratumumab PI. The ESC considered that response criteria are clear and well established in clinical practice.
- 3.9 The PBAC considered that the number of proposed restrictions could be simplified as proposed by the Secretariat (i.e. Weeks 1-24, 25+ and grandfather). The PBAC noted that there were an estimated 30 patients who may require non-PBS to PBS transitioning arrangements.
- 3.10 The PBAC also advised that any future proposed restriction limit prescribing to a haematologist.
- 3.11 The submission requested PBS listing of bortezomib to be used as part of the daratumumab SC + CyBorD regimen for 6 cycles for untreated AL amyloidosis. Bortezomib's current PBS listing is restricted to use in multiple myeloma.

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

4 Population and disease

- 4.1 AL amyloidosis refers to a group of rare plasma cell disorders involving the synthesis and abnormal extracellular deposition of misfolded proteins in various organs with resultant damage. AL amyloidosis is among the more common and more severe forms of amyloidosis. It has been estimated that 49% of patients with amyloidosis have the AL amyloid sub-type (Wisniowski et al. 2019). AL amyloidosis involves the slow proliferation of a bone-marrow-residing plasma cell clone and the secretion of unstable immunoglobulin-free light-chains that infiltrate peripheral tissues and result in detrimental end-organ damage. Organs involved usually include the kidneys, heart, gastrointestinal tract, liver and nervous system. Up to 70% of newly diagnosed patients present with cardiac involvement at diagnosis. Cardiac complications account for most deaths in this population.
- 4.2 An Australian observational study of 196 AL amyloidosis patients diagnosed between 1999 and 2013, reported that median survival was 1.2 years (Wisniowski et al. 2019). The increased number and availability of novel agents that effectively target plasma cell clones has seen the median OS in AL amyloidosis significantly improve over the last two decades (MSAG, 2019).
- 4.3 The condition commonly occurs in patients with MM, with up to 15% of MM patients also developing symptomatic AL amyloidosis and up to 38% of newly diagnosed MM patients found to have clinically occult AL amyloidosis. At the time of diagnosis, approximately 10% of patients with AL amyloidosis will meet diagnostic criteria for MM as defined by CRAB (hypercalcemia, renal insufficiency, anaemia, or bone disease) criteria. Another 40 % of AL amyloidosis patients who do not meet the criteria for MM will have 10% or more bone marrow plasmacytosis at diagnosis. Daratumumab is a novel human monoclonal antibody that binds to and inhibits CD38 that is highly expressed on the cell surface of clonal plasma cells that produce the amyloidogenic immunoglobulin light chain. This eliminates the underlying plasma cell clone producing the amyloidogenic light chain that causes organ dysfunction.
- 4.4 The key difference between the current and proposed clinical management pathways proposed by the submission was the addition of daratumumab SC + CyBorD as first-line treatment for patients with AL amyloidosis (see Figure 1). The ESC considered this was reasonable.

Figure 1: Proposed clinical algorithm with daratumumab SC + CyBorD PBS listed



Source: Figure 1-20, p 51 of the submission

ASCT = autologous stem cell transplant; CR = complete response; PR = partial response; VGPR = very good partial response

- 4.5 The proposed clinical algorithm was broadly consistent with the proposed PBS restriction, proposed PI, and clinical evidence presented. Some patients with concurrent severe multiple myeloma were excluded from the clinical trials and were not explicitly considered in the clinical management algorithm. The clinical course and treatment of these patients are dependent on which of the two diseases is dominant in terms of end-organ Treatment damage and symptoms (Dispenzieri, 2021).
- 4.6 The main difference in dosing of daratumumab SC between treatment of RRMM and AL amyloidosis is that daratumumab SC is administered once per 3-week cycle for RRMM (for weeks 10-24) and twice per 4-week cycle for AL amyloidosis (for weeks 9-24). Therefore, over the initial 24-week treatment period, RRMM patient would receive 14 doses of daratumumab SC, whilst AL amyloidosis patients would receive 16 doses of daratumumab SC.
- 4.7 Co-administered therapies include corticosteroids (dexamethasone 20 mg), antipyretics (oral paracetamol 500-1000 mg) and antihistamines (oral or IV diphenhydramine 20-50 mg equivalent) taken 1-3 hours prior to daratumumab administration. The costs of the co-administered therapies dexamethasone, paracetamol and montelukast (as the antihistamine) were incorporated into the economic evaluation and financial estimates. These were also consistent with the co-administered therapies used in patients with RRMM (p 6 of the proposed PI).
- 4.8 The ESC noted that four states (NSW, QLD, VIC, WA) have specialist amyloidosis services, which coordinate and assist with diagnosis and management of the majority of Australian patients, including patients from interstate if required. The ESC

considered that some patients may become eligible for autologous stem cell transplantation (ASCT; as shown in Figure 1), however this is a high risk procedure, especially in patients with significant organ involvement, therefore careful selection of patients is important.

- 4.9 The ESC noted that the proposed clinical algorithm was consistent with the MSAG Clinical guidelines and reflective of Australian clinical practice.

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

5 Comparator

- 5.1 The submission nominated CyBorD as the main comparator, as CyBorD is the most commonly used regimen in clinical practice. The nomination of CyBorD as the main comparator was reasonable; however, as bortezomib is not PBS-listed for use in patients with AL amyloidosis, the cost-effectiveness of CyBorD has not been established by the PBAC. The submission did not attempt to demonstrate the cost-effectiveness of CyBorD. The ESC considered the nomination of CyBorD as main comparator to be appropriate, noting that CyBorD has not been evaluated by the PBAC for this indication, and that bortezomib is not TGA registered for this indication. The long term clinical outcomes and cost-effectiveness of CyBorD have not been assessed by the PBAC which adds considerable uncertainty to the cost-effectiveness of daratumumab.

- 5.2 The submission nominated MDex as a secondary comparator. This was reasonable as MDex has an unrestricted PBS listing and is recommended for first-line treatment of AL amyloidosis by the clinical guidelines (MSAG, 2019) if bortezomib based therapies are unavailable (through private or hospital funding, compassionate supply or clinical studies) or are contraindicated (e.g. neuropathy). The submission estimated that 8% of patients with AL amyloidosis are treated with MDex. The ESC considered MDex to be an appropriate secondary comparator, and noted it is used for this indication in clinical practice if bortezomib is not available to the patient.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor provided a hearing for this item. The presenting clinician was an investigator on the ANDROMEDA study and discussed the benefits of daratumumab therapy. The clinician supported the use of haematologic response as a surrogate endpoint for survival for patients with amyloidosis. The clinician also noted that MOD-PFS in ANDROMEDA was almost entirely driven by haematological progression. The

PBAC considered that the hearing was informative as it provided a clinical perspective on treating this disease.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (21) and organisations (3) via the Consumer Comments facility on the PBS website. The comments from individuals gave insight into the symptoms and impact of amyloidosis, and gave accounts of marked improvement in function and quality of life (QoL) on daratumumab therapy.
- 6.3 The advice received from Myeloma Australia’s Medical and Scientific Advisory Group (MSAG) summarised the ANDROMEDA results and indicated support for the proposed listing. The Leukaemia Foundation provided support for the listing and highlighted the lack of TGA or PBS listed treatments, and described the poor prognosis and high unmet need associated with the disease.
- 6.4 The advice received from the Australian Amyloidosis Network (AAN) commented on the high unmet need in the population and the strong correlation between haematologic response and both organ function and OS, stating that “the factor being measured to assess response, the immunoglobulin free light chain, is not only a surrogate of the underlying tumour mass but is actually the cause of the disease”. The AAN also requested that Mayo Stage IIIB and renal failure patients (CrCl < 20 ml/min) should be included in the PBS listing despite exclusion from the trial.

Clinical trials

- 6.5 The evidential basis of the submission was informed by two clinical trials. ANDROMEDA was a randomised, open-label trial, which directly compared the efficacy and safety of daratumumab SC + CyBorD to CyBorD alone in 388 patients with newly diagnosed AL amyloidosis. Kastritis et al. 2020 was a randomised, open-label trial, which compared the efficacy of bortezomib, melphalan and dexamethasone (BMDex) with MDex alone in 109 newly diagnosed patients with AL amyloidosis.
- 6.6 The submission conducted an indirect treatment comparison (ITC) between daratumumab SC + CyBorD (ANDROMEDA) and MDex (Kastritis et al. 2020), using the common comparator, bortezomib-based regimens (CyBorD in ANDROMEDA and BMDex in Kastritis et al. 2020).
- 6.7 Details of the trials presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Daratumumab SC + CyBorD vs. CyBorD		
ANDROMEDA (NCT03201965)	A Randomized Phase 3 Study to Evaluate the Efficacy and Safety of Daratumumab in Combination with CyBorD Compared with CyBorD in Newly Diagnosed Systemic AL Amyloidosis. Protocol 54767414AMY3001 Primary Analysis Clinical Study Report	October 2019, August 2020
	Palladini, Kastritis, <i>et al.</i> Daratumumab plus CyBorD for patients with newly diagnosed AL amyloidosis: safety run-in results of ANDROMEDA.	The Journal of the American Society of Hematology 2020, 136(1), pp.71-80.
	Kastritis, Palladini, <i>et al.</i> Daratumumab-Based Treatment for Immunoglobulin Light-Chain Amyloidosis.	New England Journal of Medicine 2021, 385(1), pp.46-58.
Daratumumab SC + CyBorD vs. MDex (via common comparator, bortezomib-based regimens (CyBorD/ BMDex))		
Kastritis et al. 2020 (NCT01277016)	A randomized open-label multicentre phase III trial of MDex versus BMDex for untreated patients with systemic light-chain amyloidosis. Protocol AC-004-EU	January 2013
	Kastritis, Leleu, <i>et al.</i> Bortezomib, melphalan, and dexamethasone for light-chain amyloidosis.	Journal of Clinical Oncology 2020, 38(28), pp.3252-3260.

Source: Table 2-5, p76 of the submission

AL = light-chain; BMDex = bortezomib, melphalan and dexamethasone; CyBorD = cyclophosphamide, bortezomib and dexamethasone; MDex = melphalan and dexamethasone; SC = subcutaneous injection

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

Table 3: Key features of the included evidence

Trial	N	Design/duration	Risk of bias	Patient population	Outcome	Use in modelled evaluation
Dara + CyBorD vs. CyBorD						
ANDROMEDA	388	OL, MC, R 11.4 months	Low	Newly diagnosed AL amyloidosis ^a . MM patients were excluded.	CR, VGPR, Overall HR, OS, OrRR, MOD-PFS, HRQoL	Response category at 6 months; EQ5D5L utility weights
BMDex vs. MDex						
Kastritis et al., 2020	109	OL, MC, R 50 months	Low	Newly diagnosed AL amyloidosis who were not eligible for ASCT. MM patients were excluded.	Overall HR, OS, OrRR, PFS, HRQoL	OS HR
Indirect Comparison: Dara + CyBorD vs. MDex, via common comparator, bortezomib regimens (CyBorD/BMDex)						
ANDROMEDA	Dara + CyBorD vs. CyBorD				CR, MOD-PFS/PFS;	Not used
Kastritis et al., 2020	BMDex vs. MDex				OS	

Source: Constructed during evaluation

AL = light-chain; ASCT = autologous stem cell transplantation; BMDex = bortezomib, melphalan, dexamethasone; CR = complete hematologic response; CyBorD = cyclophosphamide, bortezomib, and dexamethasone; Dara = daratumumab subcutaneous; DB = double blind; EQ5D-5L = European Quality of Life Five Dimensions Questionnaire; HR = hematologic response; HRQoL = health-related quality of life; MC = multi-centre; MDex = melphalan, dexamethasone; MOD-PFS = major organ deterioration progression free survival; MM = multiple myeloma; OL = open label; OS = overall survival; OrRR = organ response rate; R = randomised control trial; PFS = progression free survival; VGPR = very good partial response

^a Patients in ANDROMEDA were able to undergo ASCT after 6 cycles of treatment

- 6.9 At the time of the second interim analysis (corresponding to data presented in the submission), the median follow-up in ANDROMEDA was 11.4 months. The data was only 43.5% mature, as 87 of the 200 prespecified major organ deterioration progression-free survival (MOD-PFS)¹ events had occurred. Hence, the data may be too immature to demonstrate a survival benefit. The ESC noted that the PSCR provided an updated analysis of the ANDROMEDA study, based on a median follow-up period of 25.8 months, sourced from an abstract provided with the PSCR (Comenzo et al 2021), and proposed for presentation at the American Society of Hematology (ASH) meeting in December 2021.
- 6.10 The PSCR and abstract (Comenzo et al 2021) indicated that OS data and updated MOD-PFS data will be analysed after approximately 200 events have occurred, which the submission had estimated to occur in first quarter of 2023.
- 6.11 At the time of second interim analysis, 10% (N = 19/193) of patients in the daratumumab SC + CyBorD arm and 42% (N = 79/188) in the CyBorD had commenced subsequent non-cross resistant anti-plasma cell therapies This was defined as subsequent treatment with melphalan, ASCT, lenalidomide, and daratumumab for

¹ MOD-PFS is a composite endpoint for death, the clinical manifestation of end-stage cardiac failure, the clinical manifestation of end-stage renal failure and/or development of hematologic disease progression.

patients randomised to the CyBorD arm². Of the 79 CyBorD patients who received non-cross-resistant subsequent therapy, 48 (61%) received intravenous daratumumab as monotherapy or in combination with other therapies. The submission applied inverse-probability of censoring weights to adjust for crossover in the present analysis for the surrogate outcome, MOD-PFS, as well as alternate analysis methodologies which showed that the results were robust to the methods applied to control for subsequent treatment. Treatment crossover is likely to confound overall survival and MOD-PFS, in future analyses.

- 6.12 Eligibility criteria for ANDROMEDA and Kastritis et al. 2020 were broadly consistent with the proposed PBS listing as patients were required to (i) be untreated; (ii) have no significant cardiac disease; and (iii) have Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) ≤ 2 . Inconsistent with ANDROMEDA, the proposed PBS restriction does not require patients to have at least one organ impacted by AL amyloidosis and does not restrict use based on ASCT eligibility.
- 6.13 The submission assumed common comparators, CyBorD and BMDex had equivalent efficacy and safety. The submission did not attempt to demonstrate the biological plausibility of this assumption. The MSAG clinical guidelines for AL amyloidosis state that ‘bortezomib is the most active agent in AL amyloidosis’ and therefore that ‘bortezomib based regimens are the preferred front-line therapy’ and that ‘CyBorD and BMD (ex) are the optimal initial treatment regimens for newly-diagnosed AL amyloidosis’ (MSAG, 2019). However, the clinical practice guidelines also note that cyclophosphamide is stem cell sparing compared to melphalan (MSAG, 2019). This may provide patients with the possibility of greater treatment flexibility in the future and ultimately improve long-term outcomes for patients in whom CyBorD is administered as first-line treatment.
- 6.14 Differences between the trials which may impact the transitivity included:
- the submission assumed the comparators CyBorD and BMDex had equivalent efficacy and safety; and
 - median follow-up in Kastritis et al. 2020 was 50 months, compared to 11.4 months for ANDROMEDA. The proportion of patients with events in the common comparator arm were not comparable for the outcomes: complete haematological response (CyBorD = 18% vs. BMDex = 23%), MOD-PFS response (CyBorD = 28% vs. BMDex = 52%), and overall survival (CyBorD = 15% vs. BMDex = 32%).

² Non-cross resistant anti-plasma cell therapy was defined as high dose melphalan and ASCT, melphalan plus dexamethasone, or any new combination regimen that included at least 1 new component other than 1 of the assigned study drugs received (ie, bortezomib plus lenalidomide for both treatment arms and daratumumab for the CyBorD arm).

Comparative effectiveness

Daratumumab SC + CyBorD vs CyBorD

6.15 For the primary endpoint of the ANDROMEDA trial, patients in the daratumumab SC + CyBorD treatment arm reported a statistically significant improvement in the overall complete response rate compared to patients treated with CyBorD (odds ratio (OR) = 5.13; 95% confidence interval (CI): 3.22, 8.16; $p < 0.0001$). The proportion of patients having a complete/very good partial response and overall response were significantly greater in the daratumumab SC + CyBorD treatment arm compared to the CyBorD treatment arm for both data cuts (median of 11.4 months and 25.8 months follow-up; see Table 4).

Table 4: Hematologic response in the ANDROMEDA trial (median follow-up = 11.4 months and 25.8 months) – intention-to-treat population

Outcome	Dara + CyBorD	CyBorD	Odds ratio (95% CI)	Dara + CyBorD	CyBorD	Odds ratio (95% CI)
Median follow-up	11.4 months			25.8 months		
CR	104/195 (53%)	35/193 (18%)	5.13 (3.22, 8.16)	116/195 (60%)	37/193 (19%)	6.03 (3.80, 9.58)
VGPR	49/195 (25%)	60/193 (31%)	0.74 (0.48, 1.16)	38/195 (20%)	60/193 (31%)	0.54 (0.34, 0.86)
PR	26/195 (13%)	53/193 (28%)	0.41 (0.24, 0.68)	25/195 (13%)	52/193 (27%)	0.40 (0.24, 0.68)
No response	8/195 (4%)	38/193 (20%)	0.17 (0.08, 0.39)	8/195 (4%)	37/193 (19%)	0.18 (0.08, 0.40)
Disease progression	0/195	0/193	NE	8/195 (4%)	7/193 (4%)	1.14 (0.40, 3.20)
CR and VGPR	153/195 (79%)	95/193 (49%)	3.75 (2.40, 5.85)	154/195 (79%)	97/193 (50%)	3.74 (2.39, 5.86)
Overall response (CR+VGPR+PR)	179/195 (92%)	148/193 (77%)	3.40 (1.85, 6.26)	179/195 (92%)	149/193 (77%)	3.40 (1.85, 6.26)
% patients in CR at 6 months	97/195 (50%)	27/193 (14%)	6.09 (3.70, 10.03)	-	-	-
% patients in CR at 12 months	55/195 (28%)	14/193 (7%)	5.24 (2.77, 9.90)	-	-	-

Source: Table 2-28 and Table 2-32, p131-136 of the submission and Table 1 of the PSCR

CI = confidence interval; CR = complete response; CyBorD = cyclophosphamide, bortezomib and dexamethasone; Dara = daratumumab subcutaneous; NE = not estimable; PR = partial response; VGPR = very good partial response; **bold** = statistically significant at p -value < 0.05

6.16 The proportion of patients with a response was significantly higher with daratumumab SC + CyBorD than CyBorD at 6 months (OR = 6.09; 95 CI: 3.70, 10.03) and at 12 months follow-up (OR = 5.24; 95% CI: 2.77, 9.90). The percent of patients in CR was lower at 12 months compared with 6 months. The ESC noted that haematologic responses remained superior for daratumumab SC + CyBorD compared with CyBorD alone in the updated analysis with 25.8 months median follow-up.

6.17 Table 5 presents the rates of cardiac and renal responses in the ANDROMEDA trial at 6, 12- and 18-months follow-up.

Table 5: Organ response in ANDROMEDA, without censoring for subsequent therapies (median follow-up = 11.4 months and 25.8 months) – intention-to-treat population

Event	Dara + CyBorD	CyBorD	Absolute difference	Hazard ratio (95% CI)	Dara + CyBorD	CyBorD
Median follow up	11.4 months				25.8 months	
Cardiac response						
Overall	58/118 (49%)	39/117 (33%)	16%	1.93 (1.14, 3.28)	-	-
- 6 months	49/118 (42%)	26/117 (22%)	20%	2.44 (1.35, 4.42)	42%	22%
- 12 months	34/118 (29%)	15/117 (13%)	16%	2.62 (1.32, 5.20)	-	-
- 18 months	8/118 (7%)	5/117 (4%)	3%	1.56 (0.49, 4.91)	53%	24%
Renal response						
Overall	83/117 (71%)	45/113 (40%)	31%	3.69 (2.12, 6.39)	-	-
- 6 months	63/117 (54%)	31/113 (27%)	27%	3.34 (1.88, 5.94)	54%	27%
- 12 months	35/117 (30%)	18/113 (16%)	14%	2.43 (1.27, 4.64)	-	-
- 18 months	5/117 (4%)	5/113 (4%)	0%	1.00 (0.27, 3.68)	58%	26%

Source: Table 2-37 – Table 2-39, p 146-148 and Table 3 of the PSCR

CI = confidence interval; CyBorD = cyclophosphamide, bortezomib and dexamethasone; Dara = daratumumab subcutaneous

6.18 Patients treated with daratumumab + CyBorD had statistically significantly superior cardiac and renal responses at 6- and 12-months follow-up. However, at 18-months follow-up daratumumab + CyBorD treatment benefit in terms of cardiac and renal response was no longer statistically significant, potentially due to the small number of patients with follow-up beyond 12 months. The ESC noted that cardiac and renal responses were superior for daratumumab SC + CyBorD compared with CyBorD alone in the updated analysis provided in the PSCR.

6.19 Patients treated with daratumumab + CyBorD were significantly less likely to have a MOD-PFS event than patients treated with CyBorD (hazard ratio (HR) = 0.58; 95% CI: 0.36, 0.93, see Table 6).

Table 6: Major organ deterioration-progression free survival in ANDROMEDA (median follow-up = 11.4 months)

Outcome	Dara + CyBorD	CyBorD	Absolute difference	HR (95% CI)
IPCW method for patients who commenced non-cross resistant anti-plasma cell therapy				
Progressed, n (%)	34/195 (17%)	53/193 (28%)	-	0.58 (0.36, 0.93)
Intention-to-treat population				
Progressed, n (%)	34/195 (17%)	53/193 (28%)	-	0.57 (0.37, 0.87)
Kaplan-Meier Estimates				
Median MOD-PFS, months (95% CI)	NE (NE, NE)	NE (18.66, NE)	NE	-
% not progressed at 6 months (95% CI)	87% (81%, 91%)	83% (77%, 88%)	5%	-
% not progressed at 12 months (95% CI)	82% (75%, 87%)	71% (62%, 77%)	11%	-
% not progressed at 18 months (95% CI)	79% (70%, 85%)	63% (52%, 72%)	16%	-

Source: Table 2-31, p133 of the submission, Table TEFMPFS01A, 1073 of the ANDROMEDA CSR

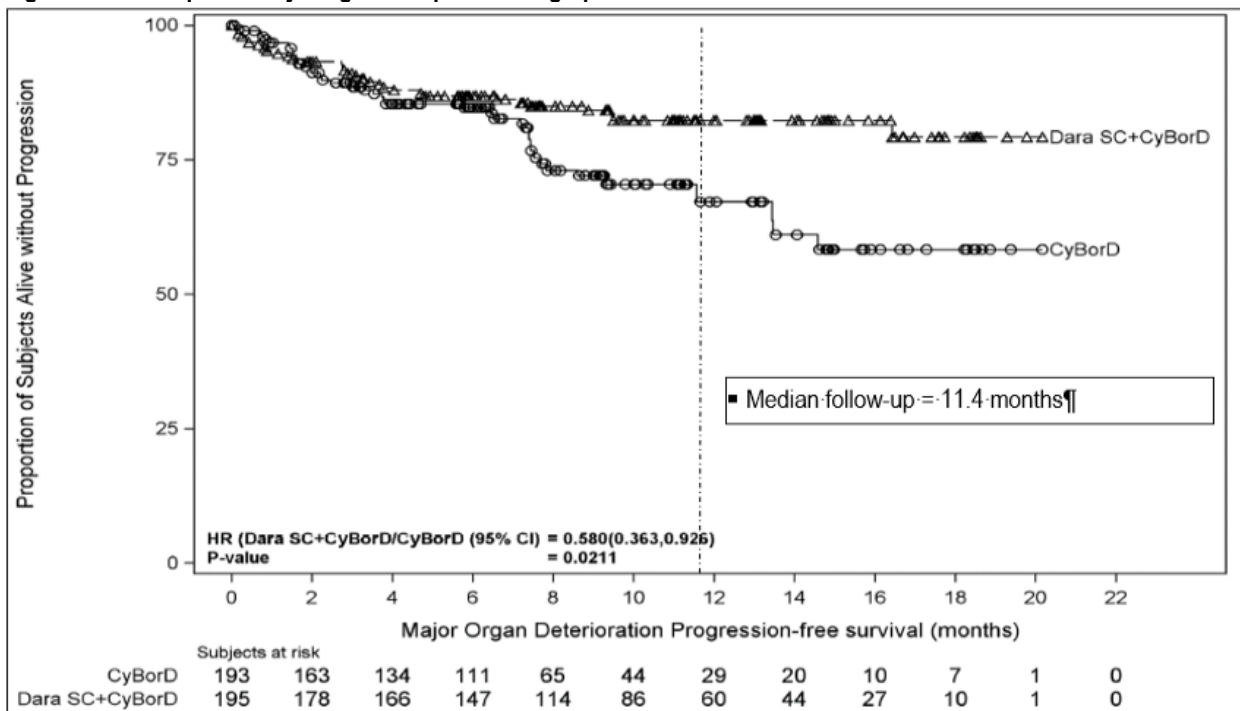
CI = confidence interval; CyBorD = cyclophosphamide, bortezomib and dexamethasone; Dara = daratumumab subcutaneous; HR = hazard ratio; IPCW = inverse probability of censoring weight; MOD-PFS = major organ deterioration progression-free survival; NE = not estimable, **Bold** = statistically significant; *italics* = conducted by the evaluation

6.20 The separation of the Kaplan-Meier curve at approximately seven months (Figure 2) suggested a clear treatment benefit of daratumumab SC + CyBorD in terms of MOD-PFS. However, the nominal p-value of 0.0211, did not cross the prespecified stopping boundary (p = 0.00136), with 87 MOD-PFS events observed representing 43.5% of the

200 planned events and median MOD-PFS was not reached in either treatment arm (p95 of the CSR).

- 6.21 The submission stated that inverse-probability of censoring weights (IPCW) were employed to adjust for patients undergoing treatment with subsequent non-cross resistant, anti-plasma cell therapy. The Advisory Committee on Medicines (ACM) also advised that the IPCW method was ‘a valid statistical technique in this scenario given the nature of the data and that this is an interim analysis’ (ACM minutes). Additionally, the submission appropriately presented various methods of calculating the hazard ratio for MOD-PFS, which showed the results were robust to the methods employed to control for subsequent treatment. The ESC noted that the IPCW method was used in the MOD-PFS analysis to adjust for patients undergoing treatment with subsequent therapy. The ESC considered this appropriate and noted that other adjustment methods demonstrated similar results.

Figure 2: Inverse probability weighted Kaplan-Meier graph for MOD-PFS



Source: ANDROMEDA CSR, Figure 7, p 96

CI = confidence interval; CyBorD = cyclophosphamide, bortezomib and dexamethasone; Dara = daratumumab subcutaneous; HR = hazard ratio; MOD-PFS = major organ deterioration-progression free survival

- 6.22 The results for overall survival are presented in Table 7 and Figure 3.

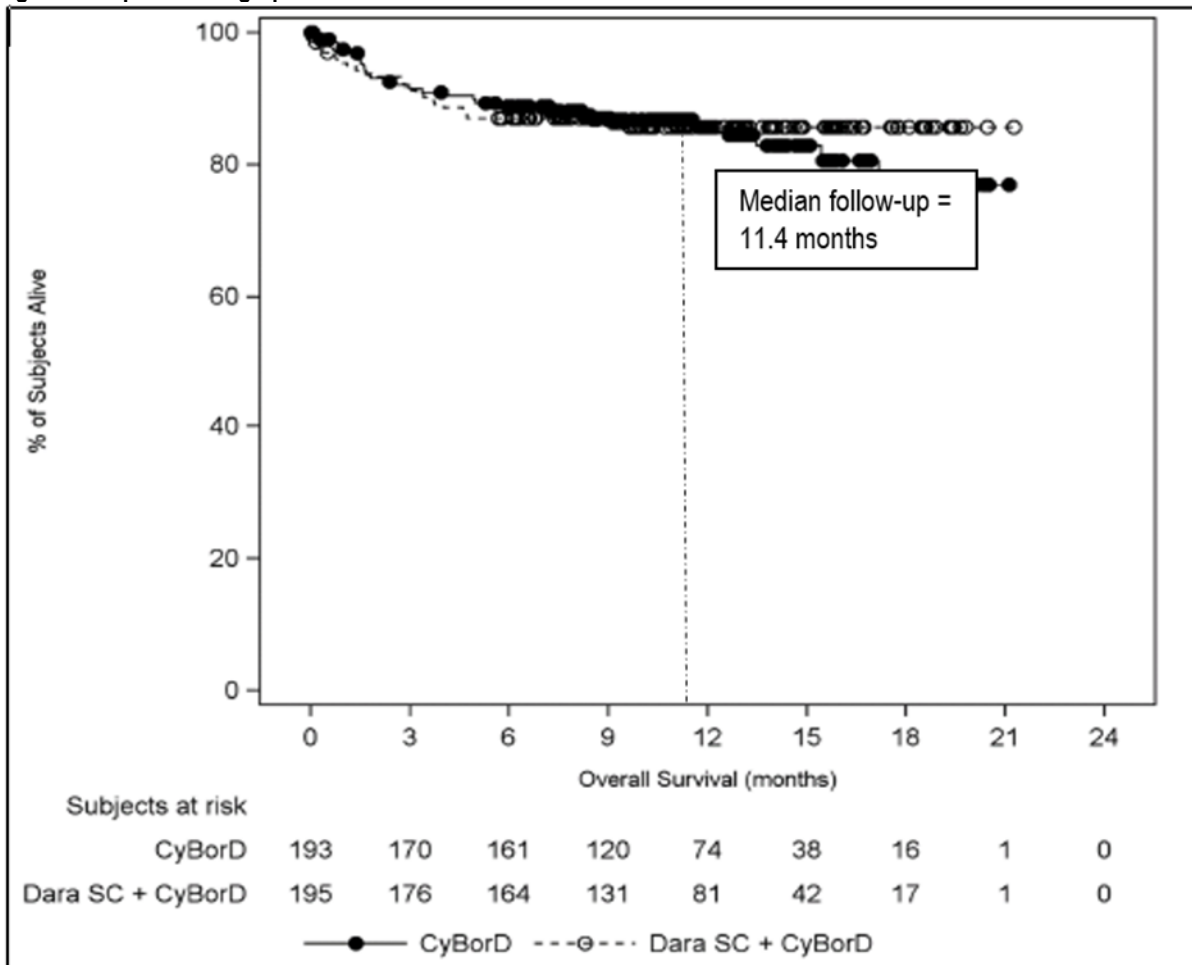
Table 7: Overall survival in ANDROMEDA (median follow-up = 11.4 months) – intention-to-treat population

Outcome	Dara + CyBorD	CyBorD	Absolute difference	HR (95% CI)
Deaths, n/N (%)	27/195 (14%)	29/193 (15%)	-	0.90 (0.53, 1.53)
Median months OS (95% CI)	NE (NE, NE)	NE (15.44, NE)	NE	-
% alive at 6 months (95% CI)	87% (81%, 91%)	89% (83%, 93%)	-2%	-
% alive at 12 months (95% CI)	86% (80%, 90%)	86% (79%, 90%)	0%	-
% alive at 18 months (95% CI)	86% (80%, 90%)	77% (65%, 85%)	9%	-

Source: Table 2-35, p 143 of the submission, Table 2-31, p133 of the submission, Table TEFMPFS01A, p1073 of the ANDROMEDA CSR, Table 21, p103 of the ANDROMEDA CSR

CI = confidence interval; CyBorD = cyclophosphamide, bortezomib and dexamethasone; Dara = daratumumab subcutaneous e; HR = hazard ratio; OS = overall survival; NE = not estimable, **Bold** = statistically significant; *italics* = conducted by the evaluation

Figure 3: Kaplan-Meier graph for overall survival in the ANDROMEDA trial



Source: Figure 2-14, p144 of the submission ANDROMEDA CSR, Figure 10, p104

CyBorD = cyclophosphamide, bortezomib and dexamethasone; Dara SC = daratumumab subcutaneous

6.23 At the time of the second interim analysis (as presented in the submission), there were 27 deaths (14%) in the daratumumab SC + CyBorD arm and 29 deaths (15%) in the CyBorD arm. The hazard ratio for survival was 0.91 (95% CI: 0.54, 1.53). The ESC noted

that median survival was not reached in either arm at the time of analysis, suggesting survival data are immature.

- 6.24 In regard to overall survival, the ESC considered it is biologically plausible that a rapid haematological response and stabilisation or recovery of organ function, in particular as measured by cardiac response, would influence OS.

Daratumumab vs. MDex (ITC)

- 6.25 Table 8 presents the indirect comparison of MOD-PFS/PFS for daratumumab SC + CyBorD compared with MDex.

Table 8: Indirect comparison of Dara +CyBorD vs. MDex, via the common comparator, bortezomib based regimens for the outcome – complete hematologic response

Comparison	Trial	Intervention n/N (%)	Bortezomib based regimens n/N (%)	Odds Ratio (95% CI)	Relative Risk (95% CI)
Dara +CyBorD vs. CyBorD- ITT	ANDROMEDA	104/195 (53%)	35/193 (18%)	5.13 (3.22, 8.16)	2.94 (2.12, 4.08)
	Median follow-up (months)	11.4	11.4	-	-
MDex vs BMDex- MITT	Kastritis et al. 2020	11/ 56 (20%)	12/53 (23%)	0.84 (0.33, 2.1)	0.87 (0.42, 1.79)
	Median follow-up (months)	50	50	-	-
Indirect estimate of Dara + CyBorD vs. MDex effect adjusted for the common comparator, bortezomib based regimens (CyBorD / BMDex)				6.18 (2.2, 17.31)	3.39 (1.53, 7.52)

Source: Table 2-66, p181 of the submission

BMDex = bortezomib, melphalan, and dexamethasone; CI = confidence interval; CR = complete response; CyBorD = cyclophosphamide, bortezomib and dexamethasone; Dara = daratumumab subcutaneous; MDex = melphalan and dexamethasone; **bold** = statistically significant at p-value <0.05

- 6.26 The results of the ITC suggested that patients treated with daratumumab SC + CyBorD were 6.18 times more likely to have a complete response after or during treatment than patients treated with MDex (OR = 6.18; 95% CI: 2.2, 17.31). However, it should be noted that the common event rates were higher in Kastritis et al. 2020 (23%) than ANDROMEDA (18%). Further, the results of the ITC were confounded by the exchangeability issues between the trials. In particular, the longer follow-up data available for Kastritis et al. 2020 compared to ANDROMEDA (median of 50 months vs. 11.4 months).
- 6.27 The results of the ITC suggested a statistically significant improvement in the rates of MOD-PFS for patients receiving daratumumab SC + CyBorD compared with MDex (HR = 0.27; 95% CI: 0.14, 0.53). However, as the MOD-PFS/PFS events in the common comparator arm in the trials were not comparable (CyBorD = 28% vs. BMDex = 52%) and there were exchangeability issues between trials the results should be interpreted with caution. See Table 9.

Table 9: Results of the indirect comparison, Dara + CyBorD vs. MDex, via the common comparator, bortezomib based regimens (CyBorD/ BMDex) for MOD-PFS/PFS

Trial	Outcome	Dara + CyBorD/ MDex	CyBorD/ BMDex	HR (95% CI)
ANDROMEDA (Dara +CyBorD vs. CyBorD) - IPCW	Progressed	34/195 (17%)	53/193 (28%)	-
	Median follow-up (months)	11.11	11.9	0.58 (0.36, 0.93)
Kastritis et al. 2020 (MDex vs BMDex) - MITT	Progressed	44/56 (90%)	28/53 (52%)	-
	Median follow-up (months)	50	50	2.17 (1.35, 3.57)
Indirect comparison: Dara + CyBorD vs. MDex				0.27 (0.14, 0.53)

Source: Table 2-66, p 182 of the submission

BMDex = bortezomib, melphalan, and dexamethasone; CI = confidence interval; CR = complete response; CyBorD = cyclophosphamide, bortezomib and dexamethasone; Dara + CyBorD = daratumumab subcutaneous and cyclophosphamide, bortezomib and dexamethasone; HR = hazard ratio; IPCW = inverse probability of censoring weights; MDex = melphalan and dexamethasone; MITT = modified intention to treat. bold = statistically significant at p-value <0.05

6.28 Patients treated with daratumumab SC + CyBorD had a significant reduction in the risk of death compared to patients treated with MDex (HR = 0.29, 95% CI: 0.14, 0.62). However, as the death rate in the common comparator arm in the trials were not comparable (CyBorD = 15% vs. BMDex = 32%) the results should be interpreted with caution. See Table 10.

Table 10: Results of the indirect comparison, Dara + CyBorD vs. MDex, via the common comparator, bortezomib based regimens (CyBorD/ BMDex) for overall survival

Trial	Outcome	Dara + CyBorD/ MDex	CyBorD/ BMDex	HR (95% CI)
ANDROMEDA (Dara +CyBorD vs. CyBorD) - ITT	Deaths	27/195 (14%)	29/193 (15%)	-
	Median follow-up (months)	11.11	11.9	0.90 (0.53, 1.53)
Kastritis et al. 2020 (MDex vs BMDex) - MITT	Deaths	31/56 (53%)	17/53 (32%)	-
	Median follow-up (months)	50	50	2.00 (1.11, 3.70)
Indirect comparison: Dara + CyBorD vs. MDex				0.29 (0.14, 0.62)

Source: Table 2-27, p 182 of the submission

BMDex = bortezomib, melphalan, and dexamethasone; CI = confidence interval; CR = complete response; CyBorD = cyclophosphamide, bortezomib and dexamethasone; Dara + CyBorD = daratumumab subcutaneous and cyclophosphamide, bortezomib and dexamethasone; HR = hazard ratio; ITT = intention to treat; MDex = melphalan and dexamethasone; MITT = modified intention-to-treat population; MOD-PFS = major organ deterioration-progression free survival; bold = statistically significant at p-value <0.05

6.29 The PSCR argued that while the rates of CR were different between CyBorD and BMDex, the absolute difference was relatively small at 5%. The ESC noted that the PSCR did not comment on the much larger discrepancies seen for MOD-PFS and OS (see Table 9 and Table 10). The ESC considered that although, the results of the ITC suggested statistically significant differences, in terms of complete haematological response, MOD-PFS and OS, in favour of daratumumab SC + CyBorD compared to MDex, the results of the ITC were uncertain given the potential transitivity issues identified with the indirect comparison.

Comparative harms

Daratumumab SC + CyBorD vs CyBorD

6.30 A summary of adverse events in ANDROMEDA is presented in Table 11.

Table 11: Key safety outcomes reported in ANDROMEDA

Summary of TEAEs	Dara + CyBorD	CyBorD	RR (95% CI)
Safety analysis set	193	188	-
Any TEAE	189/193 (98%)	185/188 (98%)	1.00 (0.22, 4.51)
- At least one related to daratumumab	110/193 (57%)	1/188 (1%) ^a	NE
Maximum toxicity grade			-
- Grade 3	79/193 (41%)	83/188 (44%)	0.93 (0.62, 1.39)
- Grade 4	18/193 (9%)	16/188 (9%)	1.10 (0.54, 2.22)
- Grade 5	22/193 (11%)	15/188 (8%)	1.43 (0.72, 2.85)
Any serious TEAE	83/193 (43%)	68/188 (36%)	1.19 (0.79, 1.80)
- At least one related to daratumumab	24/193 (12%)	0/188	NE
- Cardiac disorders	30/193 (16%)	25/188 (13%)	1.17 (0.66, 2.07)
Patients with TEAE with the outcome resulting in death	22/193 (11%)	15/188 (8%)	1.43 (0.72, 2.85)
- Cardiac disorders resulting in death	14/193 (7%)	8/188 (4%)	1.46 (0.58, 3.66)
Patients with >1 TEAEs leading to discontinuation of trial treatment	8/193 (4%)	8/188 (4%)	0.97 (0.36, 2.65)

Source: Table 2-51, p 161 of the submission

CI = confidence interval CyBorD = cyclophosphamide, bortezomib and dexamethasone; daratumumab SC = daratumumab subcutaneous; NE = not estimable; TEAEs = treatment emergent adverse events; RR = relative risk; *italics* = calculated during the evaluation; **bold** = statistically significant at p-value < 0.05

^a One site reported at least 1 AE as related to daratumumab in error, for 1 patient randomised to CyBorD arm

6.31 The median duration of treatment in ANDROMEDA was longer in the daratumumab SC + CyBorD arm (9.6 months) compared to the CyBorD arm (5.3 months). Over this period, nearly all patients in both arms experienced at least 1 treatment-emergent adverse event (TEAE). The overall incidence of serious TEAEs (43% and 36%), Grade 5 TEAEs (11% and 8%) and TEAE resulting in death (11% and 8%) were all numerically higher in the daratumumab SC + CyBorD arm compared with CyBorD.

Daratumumab SC + CyBorD vs MDex

6.32 The submission did not present any comparative clinical evidence to demonstrate the comparative safety of daratumumab SC + CyBorD to MDex, due to the difference in reporting methods between the trials. Kastritis et al. 2020 reported the number of events observed during the trial, whilst ANDROMEDA reported the number of patients with adverse events.

Benefits/harms

6.33 A summary of the comparative benefits and harms for daratumumab SC + CyBorD versus CyBorD, based on the results of ANDROMEDA is presented in Table 12.

Table 12: Summary of comparative benefits and harms for daratumumab SC + CyBorD versus CyBorD

Trial	Dara + CyBorD	CyBorD	OR (95% CI)	Event rate/100 patients		RD (95% CI)
				Dara + CyBorD	CyBorD	
Benefits						
Overall complete hematologic response – intention-to-treat population						
ANDROMEDA	104/195 (53%)	35/193 (18%)	5.13 (3.22, 8.16)	53.3	18.1	35% (26%, 44%)
Major organ deterioration-progression free survival (IPCW method) in ANDROMEDA (median duration of follow-up: 11.4 months)						
Event	Dara + CyBorD	CyBorD	Absolute Difference		HR (95% CI)	
Progressed, n (%)	34/195 (17%)	53/193 (28%)	-		0.58 (0.36, 0.93)¹	
Median MOD- PFS, months (95% CI)	NE (NE, NE)	NE (18.66, NE)	NE			
% not progressed at 6 months (95% CI)	87% (81%, 91%)	83% (77%, 88%)	4%		-	
% not progressed at 12 months (95% CI)	82% (75%, 87%)	71% (62%, 77%)	11%		-	
Overall survival in ANDROMEDA (median duration of follow-up: 11.4 months) – intention to treat population						
Deaths, n/N (%)	27/195 (14%)	29/193 (15%)	-		0.90 (0.53, 1.53)	
Median months OS (95% CI)	NE (NE, NE)	NE (NE, NE)	NE			
% alive at 6 months (95% CI)	87% (81%, 91%)	89% (83%, 93%)	-2%		-	
% alive at 12 months (95% CI)	86% (80%, 90%)	86% (79%, 90%)	0%		-	
Harms reported in ANDROMEDA (median duration of treatment in the daratumumab SC + CyBorD arm = 9.6 months vs. CyBorD arm = 5.3 months).						
Adverse Event	Dara + CyBorD	CyBorD	RR (95% CI)	Event rate/100 patients		RD (95% CI)
				Dara + CyBorD	CyBorD	
Any serious TEAE	83/193	68/188	1.19 (0.79, 1.8)	43.0	36.2	7% (-3%, 17%)
Patients with TEAE with the outcome resulting in death	22/193	15/188	1.43 (0.72, 2.85)	11.4	8.0	3% (-3%, 9%)
Patients with >1 TEAEs leading to treatment discontinuation	8/193	8/188	0.97 (0.36, 2.65)	4.2	4.3	0% (-4%, 4%)
Peripheral sensory neuropathy	60/193	37/188	1.58 (0.99, 2.53)	31.1	19.7	11% (3%, 20%)
Dyspnoea	44/193	32/188	1.34 (0.81, 2.23)	22.8	17.0	6% (-2%, 14%)
Thrombocytopenia	33/193	22/188	1.46 (0.82, 2.61)	17.1	11.7	5% (-2%, 12%)
Neutropenia	21/193	12/188	1.87 (0.90, 3.87)	10.9	6.4	4% (-1%, 10%)
Cardiac failure	12/193	8/188	1.46 (0.58, 3.66)	6.2	4.3	2% (-3%, 6%)
Cardiac arrest	7/193	3/188	2.27 (0.58, 8.92)	3.6	1.6	2% (-1%, 5%)

Source: Constructed during evaluation from Table 4, Table 5, Table 6, Table 7, Table 10, Table 2.5.11 of this Commentary; Table 21, p103 of the ANDROMEDA CSR; Table 2-57, p167 of the submission

CI = confidence interval CyBorD = cyclophosphamide, bortezomib and dexamethasone; daratumumab SC + CyBorD = daratumumab subcutaneous and cyclophosphamide, bortezomib and dexamethasone; HR = hazard ratio; IPCW = inverse probability of censoring weights; NE = not estimable; OR = odds ratio; RD = risk difference; RR = relative risk; **bold** = statistically significant at p-value < 0.05

Note: ¹ inverse probability of censoring weight was applied for patients who commenced non-cross resistant anti-plasma cell therapy

6.34 On the basis of the direct evidence presented by the submission from ANDROMEDA, for every 100 patients treated with daratumumab SC + CyBorD in comparison with CyBorD in newly diagnosed patients with AL amyloidosis:

- Approximately 35 additional patients will achieve a complete haematologic response over a median duration of follow-up of 11.4 months.

- Approximately 11 fewer patients will experience a major organ deterioration PFS event at 12-months follow-up.
- Approximately 11 additional patients will experience peripheral sensory neuropathy over a median duration of follow up of 11.4 months.

6.35 Table 13 presents the benefits of daratumumab SC + CyBorD compared to the submission’s supplementary comparator, MDex, based on the results of ITC, via the common comparator, bortezomib-based regimens (i.e. CyBorD/BMDex).

6.36 The submission presented no comparative safety evidence, comparing daratumumab + CyBorD with MDex. Accordingly, the harms component of this table was not presented.

Table 13: Indirect comparison of comparative benefits for daratumumab SC + CyBorD vs. MDex, via the common comparator, bortezomib based regimens (CyBorD/BMDex)

Trial	Dara + CyBorD	CyBorD / BMDex	RR (95% CI)	Event rate/100 patients*		RD (95% CI)		
				Dara + CyBorD	CyBorD / BMDex			
Benefits								
Overall complete response rates reported in ANDROMEDA vs. Kastritis et al. 2020								
Trial	Dara + CyBorD	MDex	CyBorD / BMDex	Odds Ratio (95% CI)	Event rate/100 patients*		RD (95% CI)	
ANDROMEDA	104/195	-	35/193	5.13 (3.22, 8.16)	53.3	-	18.1	35% (26%, 44%)
Kastritis et al. 2020	-	11/56	12/53	0.84 (0.33, 2.1)	-	19.6	22.6	-3% (-18%, 12%)
Indirect comparison: Dara + CyBorD vs. MDex				6.18 (2.2, 17.31)	-		38% (20%, 56%)	
Major organ deterioration-progression free survival reported in ANDROMEDA (median duration of follow-up: 11.4 months) vs. Kastritis et al. 2020 (median duration of follow-up: 50 months)								
Trial	Dara + CyBorD / MDex		CyBorD / BMDex	HR (95% CI)				
ANDROMEDA (Dara +CyBorD vs. CyBorD)	34/195 (17%)		53/193 (28%)	0.58 (0.36, 0.93)				
Kastritis et al. 2020 (MDex vs BMDex)	44/56 (90%)		28/53 (52%)	2.17 (1.35, 3.57)				
Indirect comparison: Dara + CyBorD vs. MDex				0.27 (0.14, 0.53)				
Overall survival reported in ANDROMEDA (median duration of follow-up: 11.4 months) vs. Kastritis et al. 2020 (median duration of follow-up: 50 months)								
Trial	Dara + CyBorD / MDex		CyBorD / BMDex	HR (95% CI)				
ANDROMEDA (Dara +CyBorD vs. CyBorD)	27/195 (14%)		29/193 (15%)	0.90 (0.53, 1.53)				
Kastritis et al. 2020 (MDex vs BMDex)	31/56 (53%)		17/53 (32%)	2.00 (1.11, 3.70)				
Indirect comparison: Dara + CyBorD vs. MDex				0.29 (0.14, 0.62)				

Source: Constructed during evaluation from Table, Table 8, Table 9 of this Commentary.

BMDex = bortezomib, melphalan, and dexamethasone; CI = confidence interval; CyBorD = cyclophosphamide, bortezomib and dexamethasone; daratumumab SC CyBorD = daratumumab subcutaneous; HR = hazard ratio; MDex = melphalan, and dexamethasone; NE = not estimable; RD = risk difference; RR = relative risk; **bold** = statistically significant at p-value < 0.05

- 6.37 On the basis of indirect comparison, the evidence presented by the submission, for every 100 patients treated with daratumumab SC + CyBorD over a median follow up of 11.4 months in comparison with MDex over a median follow up of 50 months:
- Approximately 38 additional patients would have a complete hematologic response.

Clinical claim

Efficacy and safety of daratumumab SC + CyBorD vs CyBorD

- 6.38 The submission described daratumumab SC + CyBorD as superior in terms of effectiveness compared with CyBorD based on: (1) complete and very good partial hematologic response, (2) MOD-PFS, and (3) cardiac and renal responses. The submission claimed that the superiority of these surrogate outcomes would translate into superior long-term survival. The PBAC considered that the primary clinical claim for daratumumab SC + CyBorD versus CyBorD was supported by the evidence presented for the surrogate outcomes.
- 6.39 The submission claimed that the data was too immature to demonstrate a survival benefit as only 87 of the 200 prespecified MOD-PFS events had occurred (data was 43.5% mature). The submission presented a modelled analysis to demonstrate the relationship between haematological response and survival outcomes. The PBAC agreed with the ESC that the data were immature. In addition, the PBAC considered that the submission's claim of superior long-term survival was probably reasonable; however, the magnitude of effect remained uncertain due to the relatively short duration of follow-up to date.
- 6.40 The submission claimed that daratumumab SC + CyBorD was inferior in terms of safety compared to CyBorD alone. The PBAC considered that this clinical claim was supported by the clinical evidence.

Efficacy and safety of daratumumab SC + CyBorD vs MDex

- 6.41 The submission claimed that compared with MDex, daratumumab SC + CyBorD demonstrated superior comparative efficacy based on the results of the ITC in terms of complete haematological response, MOD-PFS and OS. The PBAC considered that the clinical claim made by the submission was uncertain given the potential transitivity issues identified with the indirect comparison. In particular, the longer follow-up data available for Kastiris et al. 2020 (median of 50 months vs. 11.4 months for ANDROMEDA) limits the ability to draw conclusions from the results of the ITC.
- 6.42 The submission made no clinical claim with regards to comparative safety of daratumumab SC + CyBorD compared to MDex. The submission considered the results were non-informative due to the difference in reporting methods between the trials. The ESC considered that this was reasonable.

Economic analysis

- 6.43 The submission presented two cost-utility analyses.
- 6.44 Firstly, the submission presented a modelled economic evaluation based on the randomised trial, ANDROMEDA, comparing the listing of daratumumab SC + CyBorD with the primary comparator, CyBorD alone. CyBorD alone is the most commonly utilised standard of care and is a reasonable comparator, however it is not PBS listed and the cost-effectiveness of CyBorD has not been assessed by the PBAC. The PSCR stated that although not explicitly presented in the submission, the economic model could be used to estimate the cost effectiveness of CyBorD versus MDex. The PSCR claimed that CyBorD is cost-effective at its current PBS price versus MDex, with an ICER of \$5,000 to < \$15,000/QALY. The ESC considered this estimate was uncertain due to the structural and parametric uncertainties associated with the model. Further, the ESC noted an alternative approach would be to remove the costs associated with CyBorD in the comparator arm. Whilst this approach is considered exploratory and extreme, removal of treatment costs and AE costs from the CyBorD arm results in an ICER of \$55,000 to < \$75,000/QALY vs \$55,000 to < \$75,000/QALY in the base case (submission model).
- 6.45 The submission presented a supplementary modelled economic evaluation comparing daratumumab SC + CyBorD to the secondary comparator, MDex (PBS listed as an unrestricted benefit in the General Schedule). While the submission presented the results of an indirect comparison of two randomised trials (ANDROMEDA and Kastritis et al. 2020) to demonstrate the superiority of daratumumab SC + CyBorD compared to MDex, these results were not used in the modelled economic evaluation. This may have been reasonable given the potential transitivity issues identified with the indirect comparison. The evaluation of MDex relied on the same inputs as CyBorD with the exception of treatment costs and an adjustment of OS using the HR of MDex vs. BMDex from Kastritis et al. (2020). The application of the HR from Kastritis et al. (2020) relies on an assumption of equivalence between CyBorD and BMDex which was not demonstrated by the submission. The direction of bias is unclear.
- 6.46 A summary of model structure, key inputs and rationale are presented below.

Table 14: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	Daratumumab SC + CyBorD vs. CyBorD and MDex
Outcomes	Life years gained, quality-adjusted life years
Time horizon	25 years in the model base case vs. 6 months in ANDROMEDA and 36 months from an observational study, Palladini et al. (2012) (total 42 months). The submission relied on 6 months of trial data, 36 months of observational data, and the remaining 21.5 years was based on extrapolation.
Methods used to generate results	Partitioned survival model. The pre-PBAC response clarified that that the model was not a conventional partitioned survival analysis, rather it was a simple decision analysis.
Health states	<p><u>Response</u>: achieving and maintaining a response, loss of response from start of subsequent therapy, ASCT or death</p> <p><u>Post loss of response</u>: discontinued treatments of interest and progressed to subsequent treatment</p> <p><u>Death</u>: absorbing death state.</p> <p>The response health state included patients who responded to treatment or maintained a response off-treatment. In ANDROMEDA, patients discontinued treatment if haematological response was suboptimal or worsening organ function, which occurs before progression. The ANDROMEDA trial measured MOD-PFS which was defined as haematologic PD, major organ deterioration, initiation of any subsequent non-cross resistant anti-plasma cell therapy, or death, whichever comes first. It may have been more appropriate to apply MOD-PFS in the model.</p>
Cycle length	1 month
Transition probabilities	<p><u>Time to loss of response</u>: KM estimates of time to subsequent pharmacological treatment, ASCT or death from ANDROMEDA daratumumab SC + CyBorD and CyBorD. Assumed same transitions associated with MDex and CyBorD.</p> <p><u>Time to post loss of response</u>: difference between proportion alive and proportion remaining in responding health state.</p> <p><u>Time to death</u>: Assumed surrogacy relationship between haematological response to treatment CR, VGPR, PR and NR to OS. The treatment group and response category specific transitions from ANDROMEDA inform the OS transitions to CR, VGPR, PR and NR for the first 6 cycles (6 months). Thereafter, estimates of survival from Palladini et al. (2012) inform the OS transitions based on response at 6 months. Assumed same KM curve with MDex and CyBorD with HR applied from Kastritis et al. (2020).</p> <p><u>Cardiac failure</u>: The rates of cardiac progression per month from ANDROMEDA were applied to patients who remained alive on treatment and were assumed to be living with cardiac failure at a given cycle.</p> <p>The submission relied on the translation of surrogate outcome, haematological response to OS. The submission relied on observational study Palladini et al. (2012) for the time to death transition using estimates landmarked at 6 months by response category. The indirect comparison results (between daratumumab SC + CyBorD and MDex on the basis of CyBorD/BMD common comparator) were not relied on for the modelling of time to death for MDex.</p>
Extrapolation methods	<p>Time to subsequent treatment: parametric model fitted to each treatment arm with Weibull selected in base case for based on goodness of fit, parametric model fitted from when 20% remaining at risk.</p> <p>OS: exponential extrapolation applied after 42 months based on 36 months of data from Palladini et al. (2012).</p> <p>TTD: parametric model fitted to each treatment arm with Gompertz selected in base case for based on goodness of fit, parametric model fitted from when 20% remaining at risk.</p>
Health related quality of life	ANDROMEDA: Response (0.733), loss of response (0.664). US-based Medical Expenditure Panel Survey cardiac failure (-0.1034)

Source: Table 3.1, p. 205-206 of the submission.

ASCT = autologous stem cell transplant; BMD = bortezomib, melphalan and dexamethasone; CR = complete response; CyBorD = cyclophosphamide; bortezomib and dexamethasone; HR = hazard ratio; KM = Kaplan Meier; MDex = melphalan and dexamethasone; MOD-

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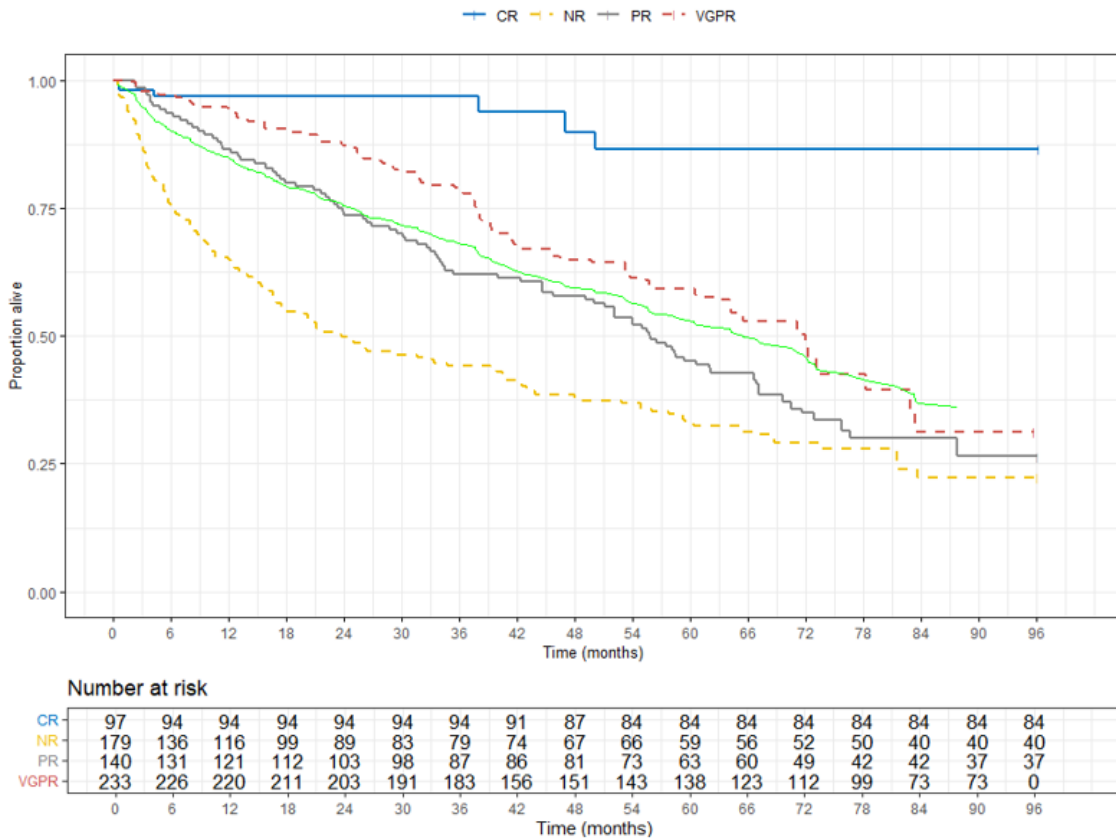
PFS = major organ deterioration-progression free survival; NR = no response; OS = overall survival; PD = progressive disease; PR = partial response; SC = subcutaneous; TTD = time to treatment discontinuation; VGPR = very good or partial response.

- 6.47 The submission assumed an extrapolated benefit of time to subsequent therapy beyond the 24-month treatment period in the time on response health state (based on time to subsequent therapy transition probability). At the end of the model time horizon of 25 years, 1.7% of patients remained in the responding health state in the daratumumab SC + CyBorD arm horizon after receiving 24 months of daratumumab SC. The assumed continued treatment effect favoured daratumumab SC + CyBorD. The application of an exponential extrapolation (base case Weibull) reduced the proportion of patients in the daratumumab SC + CyBorD arm in the responding health state to 0.1% and increased the ICER from \$55,000 to < \$75,000/QALY gained (base case) to \$55,000 to < \$75,000/QALY gained, although, this is likely still an overestimation of treatment benefit. The application of a convergence factor to time to subsequent treatment between daratumumab SC + CyBorD and CyBorD/MDex also increased the ICER (see Table 18).
- 6.48 The model time horizon of 25 years was optimistic given the average age of patients entering the model was 63 years, based on ANDROMEDA. A median survival of 1.2 years was reported in observational data from Wisniowski et al. (2019) for amyloidosis without a monoclonal antibody which is suggestive of AL amyloidosis. The economic model relied on 6 months of trial data with an additional 36 months of observational data from Palladini et al. (2012), and therefore consisted of 21.5 years of extrapolation. The extensive extrapolation of the time horizon (to 25 years) with premature OS data resulted in a high degree of uncertainty with respect to the model outputs. The PSCR argued that a 25-year time horizon was clinically plausible and justified, stating that survival rates have improved over time as a consequence of more effective therapies becoming available (i.e. bortezomib). Similarly, the PSCR claimed that survival will be improved by the addition of daratumumab, beyond that observed by Wisniowski 2019. Further, the PSCR stated that 52.8% of patients in ANDROMEDA were aged between 34-64 years, thereby supporting the proposed time-horizon.
- 6.49 Despite OS data from ANDROMEDA not demonstrating a statistically significant difference, the model generated a survival advantage of daratumumab + CyBorD. Modelled survival was based on the translation of the surrogate outcome, haematological response (VGPR or better) and OS.
- 6.50 The submission conducted a meta-analysis to support the statistical association between the surrogate outcome haematological response VGPR+ and OS. The submission conducted a literature search of studies that reported VGPR+ and OS and relied on six studies for the analysis (Palladini et al. (2012), Kastritis et al. (2020, retrospective analysis), D'Souza et al. (2016), Sachchitanantham et al. (2015), Palladini et al. (2014) and Venner et al. (2014)) and reported measures of association at 12 months, 24 months, 36 months and 48 months. While the meta-analysis

demonstrated an association between haematologic response and OS, without RCT evidence the relationship is subject to considerable uncertainty, particularly as the submission assumed that the relationship between haematological response and OS was treatment agnostic, i.e. the studies did not necessarily include daratumumab or CyBorD. The submission did not report meta-analysis results of OS by category of haematological response.

- 6.51 Modelled survival was based on single data source, Palladini et al. (2012) at 6 months. Exponential extrapolations were applied to the different response categories to result in average overall survivals of 12.4 years for complete response, 8.6 years for very good partial response, 4.6 years for partial response and 2.6 years for no response. The use of Palladini et al. (2012) was not justified given six studies were relied on for the association analysis between haematological response and OS. The PSCR stated that Palladini et al. (2012) was used in the base case as it was the largest of the six studies used in the association analysis. In Palladini et al. (2012) at 36 months, 61.8% of patients with very good partial response+ were alive, compared to 79.6% in Venner et al. (2014) and 50.3% in Sachchithanatham et al. (2015) which was also landmarked at 6 months. It may have been more reasonable to apply a weighted average approach between the studies landmarked at 6 months. For very good partial response+ this equated to survival of 60.9%. The ESC noted that the choice of survival estimate source is a model driver, with the use of European Myeloma Network observational data at 3 months (used by the submission to validate the model and presented as a sensitivity analysis) increasing the ICER by 17% compared to CyBorD and 7.7% compared to MDex.
- 6.52 The PSCR stated that the European Myeloma Network (EMN) data could not be included in the association analysis due to becoming available close to the submission cut-off; however the data were presented as a scenario analysis to provide greater certainty in the base case. The PSCR stated that the EMN data reflected a large cohort and followed patients over a considerable period; and the proportion alive at 36-months in the EMN cohort was 68.2%.
- 6.53 The ESC considered that the evidence suggested an association between haematologic response and OS, which was supported by the EMN data (see Figure 4); however, uncertainty remained in terms of the long term survival estimates applied in the model, particularly as the submission assumed that benefits are treatment agnostic. The PBAC noted that a relationship between haematological response and survival outcomes was accepted; however, considered the incremental benefit associated with daratumumab remained uncertain in the longer term.

Figure 4: Overall survival of European Myeloma Network registry cohort (3-month landmark)



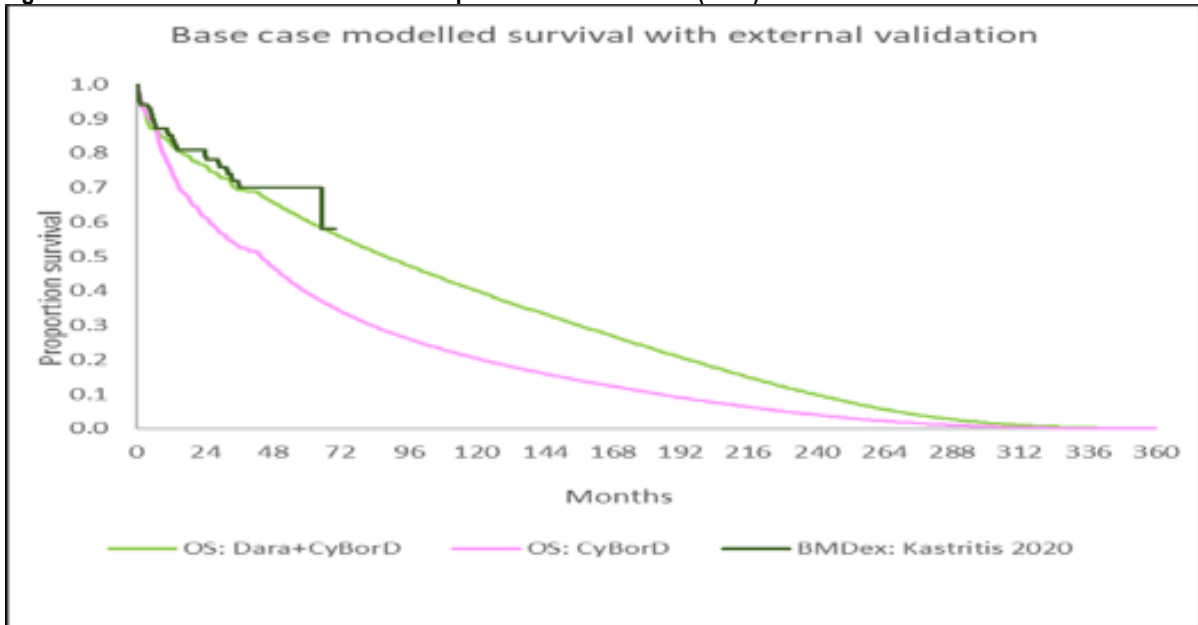
Source: PSCR, Figure 2.

CR = complete response; NR = no response; PR = partial response; VGPR = very good partial response

6.54 For time to death, an exponential extrapolation was applied from 42 months (6 months ANDROMEDA data + 36 months Palladini et al. 2012 data). No other extrapolation distributions were tested, and it was unclear if the application of an exponential distribution was appropriate. The PSCR argued that the application of different parametric functions within the model would have required a different model structure with added complexity and uncertainty. The ESC did not agree with the PSCR and advised that different extrapolation functions should have been tested. The submission presented an external validation using Wisniowski et al. (2019) and Kastritis et al. (2020) of the survival estimates for the base case model. The survival estimates from Wisniowski et al. (2019) for those diagnosed from 2011 to 2014 were more optimistic than predicted by the base case model for CyBorD. Based on these survival estimates it is possible that the modelled survival for CyBorD is underestimated and applying these in the model would increase the ICER (however this was not reported in the submission). The digitised KM estimates from BMDex in Kastritis et al. (2020) were more optimistic than predicted by the base case model for

daratumumab SC + CyBorD (and the comparators) (see Figure 5). However, the impact of using OS of BMDex Kastritis et al. (2020) on the ICER was not reported.

Figure 5: Base case modelled survival compared to Kastritis et al. (2020)

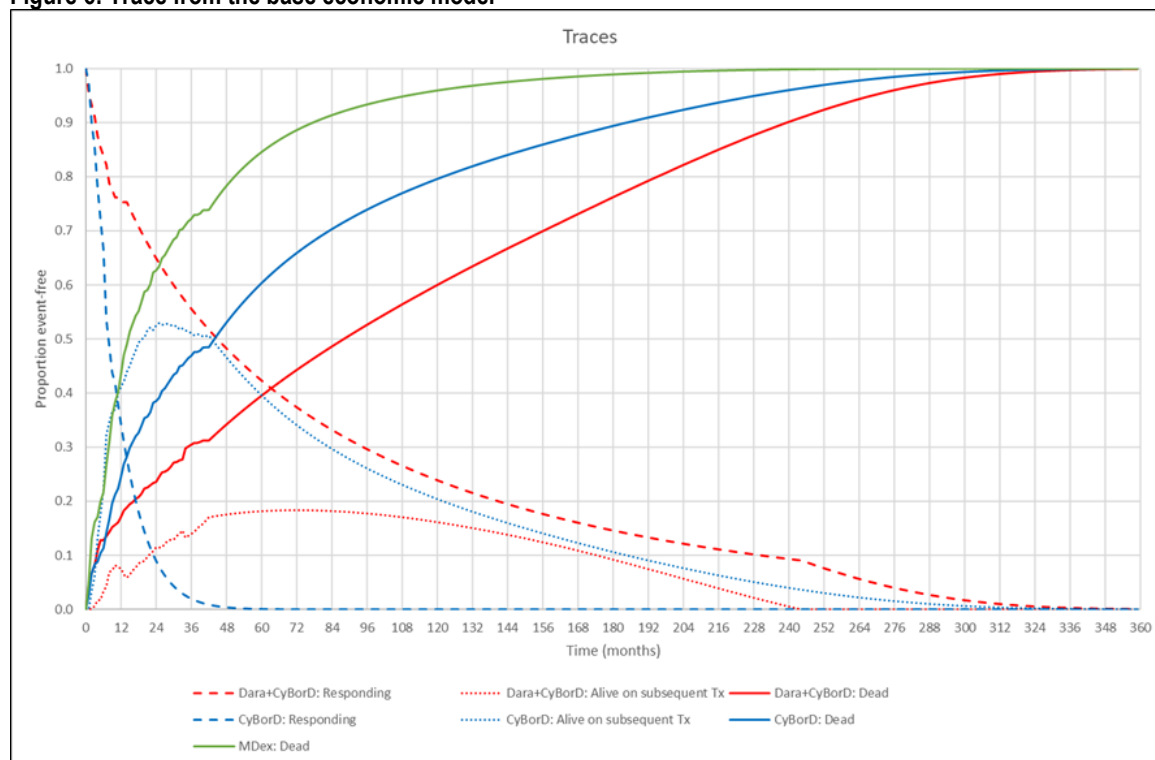


Source: Figure 3.22, p.257 of the submission.

BMDex = bortezomib, melphalan and dexamethasone; Dara = daratumumab subcutaneous; OS = overall survival.

6.55 The model trace is presented below. By the end of the model time horizon of 25 years (300 months), in the daratumumab SC + CyBorD arm 1.7% of patients in the remain in the responding health state, with the remaining in the death health state. By the end of the model time horizon in the CyBorD arm, 0.6% of patients remain in the post-loss of response health state with the remaining in the death health state. Finally, in the MDex arm, all patients were in the death health state at the end of the time horizon.

Figure 6: Trace from the base economic model



Source: Figure 3.28, p.271 of the submission.

CyBorD = cyclophosphamide, bortezomib and dexamethasone; Dara = daratumumab subcutaneous; MDex = melphalan and dexamethasone; Tx = treatment.

6.56 The disaggregated summary of health outcomes is presented in Table 15. This highlights the impact of the time spent in the health states. In the daratumumab SC + CyBorD arm the majority of the QALYs gained are from the response health state, whilst in the comparator arms, the majority of QALY gain was from the loss of response health state. There were more CyBorD patients in the loss of response health state which indicates that the incremental benefit is being driven by the survival transitions rather than the time to subsequent treatment transitions. The survival transitions are uncertain as derived from Palladini et al. (2012) rather than the ANDROMEDA trial.

6.57 Cardiac failure could occur when a patient was in either the response or the loss of response health state and measured a worsening of disease.

Table 15: Disaggregated summary of health outcomes included in the economic evaluation, discounted

	QALY			Incremental outcome		% of total incremental outcome	
	Daratumumab SC + CyBorD	CyBorD	MDex	vs. CyBorD	vs. MDex	vs. CyBorD	vs. MDex
Response	3.60	0.65	0.65	2.95	2.95	175%	93%
Loss of response	1.08	2.38	0.89	-1.30	0.19	-77%	6%
Cardiac failure	-0.18	-0.21	-0.21	0.04	0.04	2%	1%
Total	4.51	2.82	1.33	1.69	3.18	100%	100%

Source: Table 3.24, p.277 of the submission and calculated during the evaluation.

CyBorD = cyclophosphamide, bortezomib and dexamethasone; dara = daratumumab; MDex = melphalan and dexamethasone; QALY = quality adjusted life year; SC = subcutaneous.

6.58 The key drivers of the model are included in Table 16 and the results of the stepped economic evaluation in Table 17.

Table 16: Key drivers of the model

Description	Method/Value	Impact vs. CyBorD Base case: █ ¹ /QALY gained	Impact vs. MDex Base case: █ ³ /QALY gained
Extrapolation for time to subsequent treatment - convergence	Treatment effect continued beyond the 6 month trial period (with maximum 2 years treatment) for up to 25 years. Base case model assumed no convergence of time to subsequent treatment for daratumumab SC + CyBorD to comparators.	High, favours daratumumab SC. Use of convergence factor beginning at 36 and ending at 72 months increased ICER to █ ¹ /QALY gained.	Moderate, favours daratumumab SC. Use of convergence factor beginning at 36 and ending at 72 months increased ICER to █ ³ /QALY gained.
Source of survival estimate	Base case model used a single survival estimate of observational study of Palladini et al. (2012) at 6 months.	High, favours daratumumab SC. Use of EMN at 3 months increased the ICER to █ ¹ /QALY gained.	Moderate, favours daratumumab SC. Use of EMN at 3 months increased the ICER to █ ³ /QALY gained.
Time horizon	Base case model of 25 years relied on trial data of 6 months. Observational data from Wisniewski et al. (2019) reported median survival of 1.2 years for amyloidosis without a monoclonal antibody (suggestive of AL).	High, favours daratumumab SC. Use of 10 year or 15 year time horizon increased ICER to █ ² /QALY and █ ¹ /QALY, respectively.	Moderate, favours daratumumab SC. Use of 10 year or 15 year time horizon increased ICER to █ ⁴ and █ ³ /QALY, respectively.

Source: Source: Table 3.25, p.279 of the submission and estimated during the evaluation changing B6 'Inputs' to 15 using the Excel spreadsheet "Systemic AL amyloidosis Economic Model".

AL = light chain; CyBorD = cyclophosphamide, bortezomib and dexamethasone; EMN = European Myeloma Network; ICER = incremental cost-effectiveness ratio; MDex = melphalan and dexamethasone; QALY = quality adjusted life year; SC = subcutaneous.

The redacted values correspond to the following ranges:

¹ \$55,000 to < \$75,000

² \$75,000 to < \$95,000

³ \$35,000 to < \$45,000

⁴ \$45,000 to < \$55,000

Table 17: Results of the stepped economic evaluation

Step and component	Dara + CyBorD	CyBorD	MDex	Increment Dara + CyBorD vs. CyBorD	Increment Dara + CyBorD vs. MDex
Step 1: trial-based costs and outcomes, time horizon 0.5 years					
Costs (\$)		\$22,924	\$6,465		
LYG	0.46	0.46	0.43	-0.01	0.03
Incremental cost/extra LYG gained				Dominated	²
Step 2: trial and Palladini et al. (2012) 6 month landmarked OS, time horizon extended to 3.5 years, undiscounted					
Costs (\$)		\$37,345	\$23,784		
LYG	2.75	2.37	1.66	0.38	1.09
Incremental cost/extra LYG gained				³	⁴
Step 3: trial and Palladini et al. (2012) 6 month landmarked OS, time horizon extended to 3.5 years, discounting (5%) included					
Costs (\$)		\$36,764	\$23,130		
LYG	2.60	2.25	1.60	0.34	1.00
Incremental cost/extra LYG gained				³	⁵
Step 4: trial and Palladini et al. (2012) 6 month landmarked OS, time horizon extended to 25 years, discounting (5%) included					
Costs (\$)		\$47,718	\$29,871		
LYG	6.54	4.47	2.23	2.07	4.31
Incremental cost/extra LYG gained				⁶	⁷
Step 5: trial and Palladini et al. (2012) 6 month landmarked OS, time horizon extended to 25 years, discounting (5%) included, utility weights applied					
Costs (\$)		\$47,718	\$29,871		
QALYs	4.51	2.82	1.33	1.69	3.18
Incremental cost/extra QALY gained (base case)				¹	⁸

Source: Table 3.22, Table 3.23 and Table 3.34, p.275-277 of the submission.

CyBorD = cyclophosphamide, bortezomib and dexamethasone; Dara = daratumumab subcutaneous; MDex = melphalan and dexamethasone; LYG = life year gained; OS = overall survival; QALY = quality adjusted life year; vs. = versus.

The redacted values correspond to the following ranges:

¹ \$55,000 to < \$75,000

² > \$1,055,000

³ \$255,000 to < \$355,000

⁴ \$95,000 to < \$115,000

⁵ \$115,000 to < \$135,000

⁶ \$45,000 to < \$55,000

⁷ \$25,000 to < \$35,000

⁸ \$35,000 to < \$45,000

6.59 The results of key univariate / multivariate sensitivity analyses are summarised below.

Table 18: Sensitivity analyses

Analyses (base case)	CyBorD				MDex			
	Incr cost (\$)	Incr QALY	ICER	%	Incr cost (\$)	Incr QALY	ICER	%
Base case	████████	1.69	████████ ²	0	████████	3.18	████████ ⁵	0
Dara SC cost (EFC) ^{a, b}	████████	1.69	████████ ²	-3.2%	████████	3.18	████████ ⁵	-2.7%
Time horizon (25 years)								
• 5 years ^a	████████	0.56	████████ ⁴	194.8%	████████	1.20	████████ ¹	149.6%
• 10 years ^a	████████	1.15	████████ ³	43.3%	████████	2.28	████████ ³	34.0%
• 15 years ^a	████████	1.49	████████ ²	11.4%	████████	2.86	████████ ⁵	8.6%
• 20 years	████████	1.65	████████ ²	2.0%	████████	3.11	████████ ⁵	1.4%
Time to subsequent therapy extrapolation (Weibull)								
• Exponential	████████	1.56	████████ ²	9.4%	████████	3.05	████████ ⁵	5.1%
Time to subsequent therapy (no convergence) ^a								
• Start: 24, end:60 months	████████	1.47	████████ ²	19.2%	████████	2.96	████████ ⁵	10.9%
• Start: 36, end:72 months	████████	1.50	████████ ²	16.2%	████████	2.99	████████ ⁵	9.3%
Time to subsequent therapy (no convergence) and time horizon ^a								
• 24 to 60 month, 15 years	████████	1.30	████████ ³	33.0%	████████	2.67	████████ ⁷	20.4%
• 36 to 72 months, 15 years	████████	1.33	████████ ³	29.3%	████████	2.70	████████ ⁷	18.6%
Time to death (Palladini et al. (2012) at 6 months)								
• Palladini et al. at 3 months	████████	1.66	████████ ²	1.3%	████████	3.22	████████ ⁵	-1.8%
• EMN at 3 month	████████	1.44	████████ ²	17.0%	████████	2.95	████████ ⁵	7.7%
Modelling cardiac failure ^a								
Removed cost and disutility	████████	1.65	████████ ²	2.5%	████████	3.14	████████ ⁵	1.4%
Utility value loss of response (0.719, base =0.644) and response (0.735, base =0.733) ^a	████████	1.59	████████ ²	6.3%	████████	3.20	████████ ⁵	-0.7%
Complete response for dara SC at 6 months (0.503)								
• 10% increase – 0.553	████████	1.87	████████ ²	-9.7%	████████	3.36	████████ ⁵	-5.4%
• 10% decrease – 0.453	████████	1.51	████████ ²	12.1%	████████	3.00	████████ ⁵	6.1%
Discounting (5%)								
• 0%	████████	2.53	████████ ⁵	-30.4%	████████	4.64	████████ ⁶	-27.1%
• 3.5%	████████	1.89	████████ ²	-9.7%	████████	3.53	████████ ⁵	-8.6%

Source: Table 3.25, p.279-280 of the submission and Excel spreadsheet 'Systemic AL amyloidosis Economic Model'

CyBorD = cyclophosphamide, bortezomib and dexamethasone; EFC = efficient funding of chemotherapy; EMN = European Myeloma Network; HSD = highly specialised drug; ICER = incremental cost-effectiveness ratio; Incr = incremental; MDex = melphalan and dexamethasone; QALY = quality adjusted life year.

^a. Treatment cost of daratumumab SC to HSD S100 change public cost from to \$████████ to \$████████ and private cost from \$████████ to \$████████. The analysis of convergence of time to subsequent therapy/Response curves was based on the convergence slope (13308.75) by estimating the exponent of the linear estimate between the corresponding time to subsequent values of daratumumab SC + CyBorD (Start) to CyBorD (end) during the 2 years and 5 years time periods, and convergence index (-0.2801) the results (proportion) for time to subsequent values for daratumumab SC + CyBorD are estimated in column CR in worksheet "Costs and Outcomes" during the evaluation. The convergence slope and convergence index for the 3 years and 6 years time periods are 2872.83 and -0.237, respectively. Cardiac failure: Change treatment cost to "No" and change disutility to 0. Utility value: Combining the no response and progression utility values returned a utility value of 0.719 (weighted average of 0.726, n=486 and 0.664, n=62). Combining the remaining response category utility values of partial response, very good partial response and complete response yielded a weighted mean utility score of 0.735.

^b. The submission base case included the cost of daratumumab subcutaneous based on EFC mark-ups rather than the HSD Section 100 mark-ups.

The redacted values correspond to the following ranges:

¹ \$95,000 to < \$115,000

² \$55,000 to < \$75,000

³ \$75,000 to < \$95,000

⁴ \$155,000 to < \$255,000

⁵ \$35,000 to < \$45,000

⁶ \$25,000 to < \$35,000

⁷ \$45,000 to < \$55,000

6.60 The ESC considered that the estimated cost-effectiveness of daratumumab as presented in the submission was likely underestimated and was underpinned by uncertainties in the clinical data, particularly with regard to extrapolation of outcomes beyond the period of trial data which is evident in the stepped analysis (see Table 17). In addition, the ESC considered that some elements of design and assumptions used in the base case were poorly supported. The ESC's key concerns included that:

- the model design was based on an assumed relationship of a surrogate endpoint to OS informed by an unconnected study;
- the model time horizon of 25 years relied on extensive extrapolation and was optimistic given a median survival of 1.2 years for patients with light chain AL amyloidosis has been reported in the Australian observational study by Wisniewski et al. (2019). Furthermore, a comparison of survival in the comparator arm with the Wisniewski et al. (2019) study performed as external validation, suggests that survival in the comparator arm may be underestimated by the extrapolation, thereby favouring daratumumab. The pre-PBAC response maintained that a 25 year time horizon was appropriate, stating that Wisniewski et al (2019) reported that approximately 20% of patients survive beyond 15 years and this was likely to have improved with the use of more effective therapies such as bortezomib;
- there was selective use of data to inform surrogate to OS relationship;
- the model applied an exponential distribution for OS extrapolation applied from 42 months (6 months ANDROMEDA + 36 months Palladini) and did not test other approaches; and
- the model assumed the treatment effect continued beyond the 6 month trial period (with maximum 2 years treatment) for up to 25 years.

6.61 The ESC noted that multivariate sensitivity analyses with a shorter time horizons (15 years) and convergence of treatment effect resulted in ICERs of approximately \$75,000 to < \$95,000/QALY (for the comparison with CyBorD), with the continued use of an exponential OS extrapolation and single modelled survival estimate from Palladini (2012). The ESC considered that a more appropriate base case would include following changes:

- Application of a shorter time horizon (10 and 15 years);
- Application of convergence to the treatment effect curves;

- Calculation of the survival estimate by using a weighted average approach using the six studies in the association analysis and the EMN data; and
- Allowing alternative OS extrapolation functions to be assessed and reported.

Daratumumab SC in combination with CyBorD: cost/patient/course

Table 19: Drug cost per patient for proposed and comparator drugs (proposed effective price for daratumumab)

	Daratumumab SC + CyBorD			CyBorD		MDex	
	Trial dose and duration	Model	Financial estimates	Trial dose and duration	Model	Trial dose and duration	Model
Mean dose	Da:1,800 mg C: 300 mg/m ² B:1.3mg/m ² D:40 mg	Da:1,800mg C:500mg B:3 mg D:40 mg	Da:1,800mg Cy:500 mg B:3 mg D:40 mg	C:300 mg/m ² B:1.3 mg/m ² D:40 mg	C:500 mg B:3 mg D:152.3 mg/mth	M:10 mg/m ² D:40 mg	M:2 mg D:160 mg/mth
Mean duration, months	9.7	18.21	18.3	4.4	4.88	Median cycles: 5	5.16 ^f
Cost/patient/cycle (\$)	██████ ^{a,g}	██████ ^{a,g}	██████ ^{b,g}	\$3,072 ^c	\$3,072 ^c	\$102	\$102
Cost/patient/course (\$)	██████	██████ ^d	██████ ^e	\$13,517	\$15,001	\$510	\$526
Cost/patient/cycle (corrected) ^{d,g} (\$)	-	██████ ^d	-	-	\$3,186	-	\$102

Source: Section 2.4 of the submission. Using spreadsheet 'Costs and Outcomes' in the economic model workbook, and 'Drug utilisation' in the financial estimates workbook. Italicised values have been calculated.

Weight based dosing by body surface area for bortezomib and melphalan. All weighted costs are based on 34.6%:65.4% public/private split. B = bortezomib; C = cyclophosphamide; CyBorD = cyclophosphamide, bortezomib and dexamethasone; D = Dexamethasone; Da = daratumumab; M = melphalan; MDex = melphalan and dexamethasone; SC = subcutaneous.

^a Based on 4 injections of daratumumab, cyclophosphamide, bortezomib and one dose of dexamethasone in Cycle 1. Daratumumab SC based on EFC mark-ups applied in the economic model of the submission.

^b Based on 4 injections of daratumumab, cyclophosphamide, bortezomib and dexamethasone in Month 1. Daratumumab SC based on HSD-S100 mark-ups applied in the financial estimates of the submission.

^c Based on 4 injections of cyclophosphamide and bortezomib and one dose of dexamethasone in Cycle 1.

^d Cost of daratumumab is without administration, blood typing, pre-injection or post-injection medicines. Cell BM in 'Costs and Outcomes'.

^e Based on daratumumab administered doses of 27.8 scripts per 24 week course consisting of 14.67 scripts in initial 6 cycles (91.71% compliance), 5.3 scripts in continuing 7-12 cycles (75.9% compliance) and 7.8 scripts in continuing cycles 13-24 (70.7% compliance). Based on cyclophosphamide and bortezomib doses of 21.5 scripts per 6 week course consisting of 24 scheduled doses with 89.7% compliance. Based on dexamethasone administered doses of 73.7 scripts per 24 week course consisting of 42.6 scripts in Year 1 (82.0% compliance) and 31.1 in Year 2 (70.6% compliance).

^f Mean duration of treatment in economic model for MDex based on area under the curve analysis sum D8:D13 in 'Costs and Outcomes' in model

^g The weighted effective price of daratumumab applied in the economic model was \$██████ per injection. The corrected weighted effective price using HSD S100 mark-ups is \$██████. The weighted effective price of bortezomib applied in the economic model was \$██████, in the financial estimates was \$630.72 and the revised prices based on updated mark-ups are \$636.56. The price of cyclophosphamide applied in the economic model was \$██████ based on 4327R and 7226H. The price of cyclophosphamide applied in the financial estimates was \$155.65 based on 1266P and this was revised to \$155.71 in the corrected estimate. The price of dexamethasone applied in the economic and financial model was \$17.27 and this was revised to \$17.33 in the corrected estimate.

6.62 The expected cost of daratumumab SC + CyBorD per patient per course is \$██████. This was based on a weighted effective price of daratumumab of \$██████ and a mean duration of treatment of 18.21 months. For cyclophosphamide and bortezomib weighted effective prices of \$██████ and \$██████ respectively were applied for a mean duration of 6 cycles.

- 6.63 The submission applied the EFC mark-up in estimating the cost of daratumumab SC. This was inconsistent with the proposed PBS restriction (HSD S100). Application of HSD S100 mark-ups would have reduced the cost of daratumumab SC to a weighted effective price of \$ [REDACTED]. The use of daratumumab SC EFC mark-ups in the economic model was not consistent with the use of daratumumab SC HSD S100 mark-ups in the financial estimates.

Estimated PBS usage & financial implications

- 6.64 This submission was considered by DUSC. The submission used an epidemiological approach to estimate the financial implications associated with the proposed listing of daratumumab SC in combination with CyBorD.

Table 20: Estimation of number of treated patients, prescriptions and key inputs

Data	Value	Year 1 ^a	Source and Comment
Eligible population			
Incident patients	-	188	Wisniowski et al. (2019) and ABS data (2012 – 2030). Expert clinician advice for 15% increase in diagnosis rate.
Prevalent patients	-	31	Wisniowski et al. (2019) median survival estimate and clinical expert advice for 8%. The inclusion of prevalent patients in the financial estimates is inconsistent with the TGA indication of newly diagnosed patients. There is uncertainty in the assumed 8% of untreated prevalent patients.
Treatment utilisation			
Eligibility without Mayo Stage IIIB or no ECOG 3+ - initiating	75%	141	Australian Amyloidosis Network This was reasonable with regard to ECOG status. Although the estimates provided in the submission did not exclude patients with cardiac disease (defined as Mayo Stage IIIB, NYHA Class IIIB/IV); these were included in the revised restriction provided in the PSCR. The PSCR provided updated utilisation estimates.
Uptake rate - initiating	95%	134	Assumption
Uptake rate - prevalent	95%	29	Assumption It was unclear if the uptake for prevalent patients who were previously untreated would be as high.
Costs			
Daratumumab	Published: \$7,010.28 (public), \$7,058.02 (private) \$ (weighted). Effective: \$ (public), \$ (private), \$ (weighted)	Requested DPMQ, weighted for public (65.37%) and private (34.63%)	Based on updated HSD S100 mark-ups: Published: Public = \$7,010.28; private = \$7,058.06 and weighted = \$. Effective: Public = \$; private = \$ and weighted = \$
Bortezomib	\$604.50 (public) \$644.65 (private) \$ (weighted)	PBS item 12219D and 12227M weighted for public (65.37%) and private (34.63%) - injection	Based on updated mark-ups: Public = \$605.00; Private: \$653.29 and weighted \$
Cyclophosphamide	\$155.65	PBS item 1266P - oral	General Schedule DPMQ = \$155.71
Dexamethasone	\$17.27	PBS item 2507Y - oral	General Schedule DPMQ=\$17.33
MBS costs – daratumumab injection	\$111.40	MBS item 13950	-
Time to treatment discontinuation	Monthly probabilities	ANDROMEDA as estimated for Section 3 of the submission	-

Source: Section 4.1 of the submission. Excel spreadsheet 2a. Patients – incident and Drug utilisation in “Utilisation cost model – daratumumab AL amyloidosis”

ABS = Australian Bureau of Statistics; DPMQ = dispensed price for maximum quantity; ECOG = Eastern Cooperative Oncology Group; HSD S100 = highly specialised drugs Section 100; MBS = Medicare Benefits Schedule; NYHA = New York Heart Association; PBS = Pharmaceutical Benefits Scheme.

^a Number of treated patients estimated at each step in Year 1 of the financial estimates.

6.65 The estimated use and financial implications of daratumumab SC + CyBorD are presented below. The PSCR provided new financial estimates reflecting the applicable mark-up and fees for the proposed dual General Schedule and Section 100 (EFC) listings and which include Mayo Stage IIIB patients.

Table 21: Estimated use and financial implications (proposed effective price for daratumumab)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use - submission						
Number of initiating patients	1	1	1	1	1	1
Number of scripts dispensed ^a - dara SC	2	2	2	2	2	2
Number of scripts dispensed ^b - CyBorD	3	3	3	3	3	3
Estimated financial implications of daratumumab SC						
Cost to PBS/RPBS less co-payments	4	4	4	4	4	4
Estimated financial implications for CyBorD (in combination with daratumumab SC)						
Cost to PBS/RPBS less co-payments	5	5	5	5	5	5
Net financial implications (daratumumab in combination with CyBorD)						
Net cost to PBS/RPBS	4	4	4	4	4	4
Net cost to MBS	5	5	5	5	5	5
Net cost to PBS/RPBS/MBS	4	4	4	4	4	4
Estimated extent of use – PSCR (updated to include dual program listings and Mayo Stage IIIB patients)						
Number of initiating patients	1	1	1	1	1	1
Number of daratumumab scripts	2	2	2	2	2	2
Estimated financial implications of daratumumab SC						
Cost to PBS/RPBS less co-payments	4	4	4	4	4	4
Net financial implications (daratumumab in combination with CyBorD)						
Net cost PBS/RPBS	4	4	4	4	6	6
MBS cost (Item 13950)	5	5	5	5	5	5
Net cost to PBS/RPBS/MBS	4	6	4	6	6	6

Source: Table 4.1 p.288, Table 4.5 p.291, Table 4.7 p.292 and Table 4.10 p.294 of the submission.

Source: Table 4 in PSCR, and Excel spreadsheet 'Utilisation cost model – daratumumab AL amyloidosis 20210922 (PSCR)

CyBorD = cyclophosphamide, bortezomib and dexamethasone; dara SC = daratumumab subcutaneous; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Schedule of Pharmaceutical Benefits; SC = subcutaneous.

^a Assuming 14.67 scripts of daratumumab SC per year for initiating patients, 5.31 scripts of daratumumab SC per year for Year 1 incident and prevalent patients and 7.77 scripts of daratumumab SC for continuing patients in Year 2 as estimated by the submission.

^b Assuming 20.80 scripts of bortezomib per year for initiating patients, 3.70 scripts per year for initiating patients, 14.21 scripts per year for initiating patients and 12.23 scripts per year for continuing patients.

The redacted values correspond to the following ranges:

¹ < 500

² 500 to < 5,000

³ 5,000 to < 10,000

⁴ \$10 million to < \$20 million

⁵ \$0 to < \$10 million

⁶ \$20 million to < \$30 million

6.66 Based on the proposed effective price for daratumumab and the updated estimates provided in the PSCR, the total cost to the PBS/RPBS of listing daratumumab SC +

CyBorD was estimated to be \$20 million to < \$30 million in Year 6 (\$10 million to < \$20 million for daratumumab and \$0 to < \$10 million for CyBorD), and a total of \$100 million to < \$200 million in the first 6 years of listing. The PBAC noted that the MBS costs were reduced in the estimates provided in the PSCR without explanation.

- 6.67 The submission estimated increased costs associated with use of CyBorD in combination with daratumumab by assuming cyclophosphamide and bortezomib were administered for up to 6 cycles and dexamethasone for up to 24 cycles.
- 6.68 Although DUSC considered that the estimates presented in the submission were likely to be reasonable, they identified the following areas of uncertainty:
- The application of a 15% increased diagnosis rate, which resulted in an increased incidence rate of 7.2% over the two years, was uncertain. It was probable that the consequence of listing daratumumab SC + CyBorD would be earlier diagnosis (rather than increasing incidence) for some patients and therefore, the magnitude of any market growth remained uncertain. In the EMN report, for patients diagnosed post-2010, the time from first symptoms to diagnosis was a median of 5.0 months and a mean of 11.6 months. The pre-PBAC response clarified that the 15% relative increase (phased over the first 2 years) in incident patients was intended to reflect the patients being diagnosed more rapidly following the PBS listing of daratumumab SC due to greater awareness and an effective treatment being PBS listed. The incidence of the disease and the patient presentation to doctors were assumed to remain unchanged.
 - The financial estimates were consistent with the proposed PBS restriction in that previously diagnosed untreated prevalent patients were included. However, the proportion of prevalent patients deemed untreated and therefore eligible for daratumumab SC + CyBorD was uncertain. The sponsor acknowledged that the AL amyloidosis prevalent population in the financial estimates was lower than the prevalence estimate in the US by Quock et al. (2018)³ which was based on hospitalisation claims for any type of amyloidosis, and included a larger proportion of patients aged ≥ 65 years compared with the US population. In comparison, the submission estimate was derived using Australian data from histopathology reports.
 - The submission did not adjust the estimates to account for patients with a concurrent diagnosis of MM (up to 15% of MM patients will develop symptomatic AL amyloidosis) that already have access to daratumumab via the PBS.

³ Quock TP, Yan T, Chang E, Guthrie S, Broder MS. Healthcare resource utilization and costs in amyloid light-chain amyloidosis: a real-world study using US claims data. *J Comp Eff Res.* 2018 Jun;7(6):549-559.

6.69 There was a ‘grandfather’ restriction in Section 1.4 of the listing. The estimation of these patients was not explicitly incorporated into the financial estimates.

Quality Use of Medicines

6.70 The sponsor noted that the quality use of daratumumab factors for AL amyloidosis are that outcomes are regularly monitored, and the risks of misuse and/or overuse will be minimised. The submission did not provide any education materials in the submission but noted the responsibilities for the appropriate use of daratumumab in practice.

Financial Management – Risk Sharing Arrangements

6.71 The sponsor proposed a Risk-Sharing Arrangement (RSA) with annual subsidisation caps set at the level of the base case utilisation estimates presented in the submission. A rebate rate of █% for the Commonwealth Payment above the annual subsidisation cap was proposed. The value of the proposed subsidisation cap amounts to a total of \$80 million to < \$90million over the five-year RSA period, based on the PSCR utilisation estimates.

6.72 The pre-PBAC response reiterated that the sponsor does not consider it appropriate to exclude patients with a concurrent diagnosis of MM from the estimates.

Table 22: Risk-sharing arrangement for daratumumab SC in AL amyloidosis

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 1-5
Number of daratumumab SC scripts	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Commonwealth Payment (value of the subsidisation cap)	█ ³	█ ³	█ ³	█ ³	█ ³	█ ⁴
PSCR updated values (includes dual program listings and Mayo Stage IIIB patients)						
Number of daratumumab SC scripts	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ²
Commonwealth Payment (value of the subsidisation cap)	█ ³	█ ³	█ ³	█ ³	█ ³	█ ⁵

Source: Table 4.13, p.297 of the submission.

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² 20,000 to < 30,000

³ \$10 million to < \$20 million

⁴ \$70 million to < \$80 million

⁵ \$80 million to < \$90 million

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

7 PBAC Outcome

7.1 The PBAC did not recommend daratumumab SC, for use in combination with cyclophosphamide, bortezomib and dexamethasone (CyBorD) for the treatment of patients with newly diagnosed systemic light-chain AL amyloidosis. The PBAC recognised that there are no treatments on the PBS available specifically for this

condition, and it considered that the addition of daratumumab SC plus CyBorD offered high added therapeutic value. However, the PBAC considered that there were uncertainties in the cost-effectiveness analysis and financial estimates, particularly due to the overlap between patients with AL amyloidosis and multiple myeloma (MM). The PBAC considered that these uncertainties could be managed through a re-specified economic analysis that included more conservative assumptions, and a risk sharing arrangement (RSA).

- 7.2 The PBAC noted the consumer comments highlighting the poor prognosis of AL amyloidosis and the high and unmet need for effective new therapies. The PBAC noted the comments provided in the sponsor hearing that supported the use of haematologic response as a surrogate endpoint for survival for patients with AL amyloidosis.
- 7.3 The PBAC advised that the nomination of CyBorD alone as the main comparator was reasonable given that it is the therapy most likely to be replaced in clinical practice, although bortezomib was not PBS listed for this indication. The PBAC noted that melphalan plus dexamethasone (MDex), which is PBS listed, was nominated as a secondary comparison. The PBAC agreed with the submission that MDex is used in less than 10% of patients.
- 7.4 The PBAC noted that the submission was based on one head-to-head randomised controlled trial comparing daratumumab SC + CyBorD to CyBorD alone in 388 patients with newly diagnosed AL amyloidosis (ANDROMEDA). The submission also presented an indirect treatment comparison (ITC) between daratumumab SC + CyBorD (ANDROMEDA) and MDex (Kastritis et al. 2020), using a common comparator of bortezomib-based regimens (CyBorD in ANDROMEDA and BMDex in Kastritis et al. 2020).
- 7.5 The PBAC noted that the primary outcome of ANDROMEDA was complete haematologic response, with secondary outcomes including haematologic and organ response, overall survival (OS) and major organ deterioration progression free survival (MOD-PFS), which was a composite endpoint of clinically observable endpoints including: death, cardiac failure, end-stage renal failure and/or haematologic disease progression.
- 7.6 The PBAC noted that the median follow-up in ANDROMEDA was 11.4 months. The PBAC considered that the data were too immature to demonstrate a survival benefit. The PBAC noted that the PSCR provided updated data for haematological and organ response with a median follow up of 25.8 months. The PBAC noted that the duration of follow-up remained short; however, considered that the updated data was informative as it demonstrated that haematologic, cardiac and renal response outcomes were sustained over a longer period.

- 7.7 With regard to efficacy outcomes, the PBAC noted that the incidence of complete response (CR) was significantly higher with daratumumab SC + CyBorD than CyBorD at 6-months and 12 months, and remained superior for daratumumab SC + CyBorD compared with CyBorD alone in the updated analysis at 25.8 months median follow-up (see paragraph 6.16). The PBAC noted that the haematological response outcomes from ANDROMEDA at 6 months provided the key efficacy inputs used in the economic model. Patients treated with daratumumab SC + CyBorD had statistically significantly superior cardiac and renal responses at 6-, 12- and 18 months follow-up (paragraph 6.18). Patients treated with daratumumab + CyBorD were significantly less likely to have a MOD-PFS event than patients treated with CyBorD (see paragraph 6.19). The PBAC noted that difference in OS between study arms at 11.4 months follow-up was not statistically significant (see paragraph 6.23).
- 7.8 Overall, the PBAC considered that the submission's claim that daratumumab SC + CyBorD was superior in terms of effectiveness compared with CyBorD based on: (i) complete and very good partial hematologic response, (ii) MOD-PFS, and (iii) cardiac and renal responses, was supported by the evidence presented. The PBAC considered that the submission's claim of superior long-term survival, which was based on a modelled analysis to demonstrate the relationship between haematological response and survival outcomes, was probably reasonable; however, due to the immaturity of the data in ANDROMEDA, the magnitude of the survival benefit associated with daratumumab SC remained uncertain.
- 7.9 In terms of safety, the PBAC noted that the overall incidence of serious treatment emergent adverse events (TEAEs), Grade 5 TEAEs and TEAE resulting in death were all numerically higher in the daratumumab SC + CyBorD arm compared with CyBorD (see paragraph 6.31). The PBAC agreed with the submission's claim that daratumumab SC + CyBorD was inferior in terms of safety compared to CyBorD alone.
- 7.10 With regards to the secondary comparison, the PBAC noted the ITC presented in the submission comparing daratumumab SC + CyBorD with MDex. The PBAC considered that the results of the ITC were confounded by exchangeability issues between the trials, in particular, the longer follow-up data available for Kastritis et al. 2020 compared to ANDROMEDA (median of 50 months vs. 11.4 months), and the differing results in the common comparator arms, particularly for MOD-PFS and OS outcomes. The PBAC considered that the submission's claim that daratumumab SC + CyBorD demonstrated superior efficacy compared with MDex was reasonable; however, the magnitude of the benefit was uncertain due to transitivity issues in the ITC.
- 7.11 The PBAC noted that the submission presented a primary cost utility analysis based on the ANDROMEDA trial comparing daratumumab SC + CyBorD with CyBorD alone and a supplementary cost utility analysis comparing daratumumab SC + CyBorD with MDex. The PBAC considered the results from the primary analysis between daratumumab SC + CyBorD and CyBorD to be more reliable as the supplementary analysis relied on the unsupported assumption of equivalence between CyBorD and

BMDex and the superiority of daratumumab SC + CyBorD over MDex, the magnitude of which was uncertain. The PBAC acknowledged that the primary analysis required acceptance that CyBorD was a cost-effective treatment compared with MDex or that daratumumab SC + CyBorD remained cost-effective with removal of the cost of CyBorD from the comparator arm, and noted the analyses in paragraph 6.44.

7.12 The PBAC considered the base case incremental cost effectiveness ratio (ICER) of daratumumab SC + CyBorD versus CyBorD of \$55,000 to < \$75,000 per quality adjusted life year (QALY) was likely underestimated and was underpinned by uncertainties in the clinical data, particularly with regard to extrapolation of outcomes beyond the period of trial data which is evident in the stepped analysis (see Table 17). The key concerns were that:

- The time horizon of 25 years relied on extensive extrapolation and was poorly supported, particularly considering the short duration of follow-up and immaturity of the data in the ANDROMEDA trial;
- Although no OS difference was observed in the clinical data, the model assumed a survival advantage for daratumumab SC + CyBorD. This was based on the translation of the surrogate outcome, haematological response (VGPR or better), to OS and relied on data from a single data source, Palladini et al 2012, landmarked at 6 months. The PBAC noted that use of observational data from the European Myeloma Network (EMN) at 3 months increased the ICER by 17%;
- The model applied an exponential distribution for OS extrapolation applied from 42 months (6 months ANDROMEDA + 36 months Palladini); however, as no other extrapolations could be tested it was not possible to determine if this favoured daratumumab; and
- The model assumed the treatment effect continued beyond the 6-month trial period (with maximum 2 years treatment) for up to 25 years.

7.13 The PBAC considered that the some of the uncertainty in the model could be addressed by the application of more conservative assumptions, including a time horizon of no more than 20 years, convergence of the time to subsequent treatment extrapolations from 24 to 60 months and use of the EMN data to inform the translation of the haematologic response to OS. The PBAC noted the ICER for this scenario increased to \$75,000 to < \$95,000 per QALY and did not consider daratumumab to be cost-effective at the price proposed in the submission.

7.14 With regards to the financial estimates, the PBAC noted the revised estimates submitted with the PSCR (see Table 21) and PBAC advised it would be appropriate for the estimates to include Mayo Stage IIIB patients consistent with the TGA indication. The PBAC noted that although DUSC considered that utilisation estimates to be reasonable, there was some uncertainty relating to the overlapping AL amyloidosis and MM patient populations and considered that this impacted on the financial

estimates as it was determined that patients would be eligible to access one course of daratumumab per lifetime (see paragraph 7.16).

- 7.15 The PBAC considered that the financial risks associated with the overlapping AL amyloidosis and MM populations could be addressed with a combined RSA for both indications in which the expenditure caps appropriately account for patients diagnosed with both indications, regardless of whether this occurs concurrently or sequentially. The PBAC considered that the estimates presented in the PSCR, adjusted for overlap between the populations, should form the basis of the revisions to the RSA.
- 7.16 With regards to the proposed restriction, the PBAC considered that patients with concurrent MM, should be allowed to access daratumumab if AL amyloidosis is proven on biopsy. However, the PBAC advised that a patient should only be eligible to access one course of daratumumab (either IV or SC form) per lifetime, and wording to reflect this would be required to be added to both the proposed AL amyloidosis restriction and the MM listing.
- 7.17 The PBAC noted that bortezomib would also need to be PBS listed to enable use of daratumumab SC + CyBorD. If daratumumab SC is recommended, the PBAC considered bortezomib should be recommended as a restricted benefit in line with the current bortezomib listings. The PBAC suggested that a simplified restriction tied to daratumumab SC and reliant on the daratumumab SC restriction to provide detailed eligibility criteria would be appropriate. The PBAC advised that it could be stated that the patient must fulfil the PBS criteria for daratumumab for AL amyloidosis. A maximum of 23 repeats would be required to cover bortezomib for 6 cycles of CyBorD.
- 7.18 The PBAC considered the outstanding issues could be easily resolved in a simple resubmission for daratumumab SC. The PBAC also considered daratumumab SC addresses a high and urgent unmet clinical need and was expected to provide a substantial and clinically relevant improvement in efficacy, over any alternative therapies. Therefore, the PBAC considered an early resolution pathway would be acceptable. If the sponsor accepts this pathway, the following changes may address these outstanding issues without requiring further re-evaluation:
- A revised economic analysis which applies the more conservative assumptions outlined in paragraph 7.13 and price reduction to achieve an ICER of approximately \$55,000 to < \$75,000/QALY;
 - A revised RSA which meets the criteria outlined above and in paragraph 7.15; and
 - A revised proposed restriction that meets the criteria outlined in Section 3 and paragraph 7.16.

The early resolution resubmission must be lodged by week 7 of the current PBAC cycle or the next cycle. If the issues cannot be addressed by the sponsor in a simple

resubmission and the early resolution timing is not acceptable, the standard re-entry timing is available in the next cycle.

- 7.19 The PBAC advised that should the sponsor choose the standard re-entry pathway, the resubmission would be required to address the concerns expressed about the economic model in the ESC Advice. For example, the model should have a reduced time horizon of 15-20 years, with convergence applied, and improved modelling of the uncertainty associated with the use of a surrogate outcome to predict overall survival. Furthermore, the resubmission should consider using data from other studies, including the EMN data, model alternative approaches to extrapolation, and model the impact of updated clinical data based on a longer-follow-up period where possible. The overlap in patients with AL amyloidosis and MM would also need to be addressed in the financial estimates.
- 7.20 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Not recommended

Addendum to the November 2021 PBAC PSD:

7.01 DARATUMUMAB, Solution for subcutaneous injection 1,800 mg in 15 mL vial, Darzalex SC[®], Janssen-Cilag Pty Ltd.

8 Background

- 8.1 An early resolution resubmission was provided that sought to address the PBAC's concerns from its November 2021 meeting at which the PBAC did not recommend daratumumab subcutaneous (SC), in combination with cyclophosphamide, bortezomib and dexamethasone (CyBorD), for newly diagnosed patients with systemic light-chain AL amyloidosis (herein referred to as AL amyloidosis).

9 Consideration of the evidence

- 9.1 At the November 2021 meeting, the PBAC did not recommend daratumumab SC + CyBorD but considered that the early resolution pathway would be appropriate if the following issues were addressed:
- Economic model: a price reduction to give an incremental cost effectiveness ratio (ICER) of approximately \$55,000 to < \$75,000 per quality adjusted life year (QALY) once -
 - the time horizon was reduced from 25 years to ≤ 20 years;
 - the time to subsequent treatment extrapolations were converged from 24 to 60 months; and
 - European Myeloma Network (EMN) data were used to inform the translation of the haematologic response to OS
 - Risk Sharing Arrangement (RSA): present a combined RSA for daratumumab use in both AL amyloidosis and second-line multiple myeloma (MM) -
 - in which the expenditure caps appropriately accounted for patients diagnosed with both indications; and
 - which were based on estimates provided in the PSCR, adjusted for overlap.
 - Restriction: allowed patients to receive only one course of daratumumab per lifetime, regardless of the indication by –
 - presenting revised restrictions for AL amyloidosis and second-line MM.

- 9.2 The early resolution resubmission made the three changes to the economic model as requested by the PBAC in November 2021 and summarised in paragraph 9.1. These changes resulted in an ICER of \$75,000 to < \$95,000 per QALY versus CyBorD alone.
- 9.3 The early resolution resubmission proposed no change to the published or effective prices of daratumumab SC. The proposed prices were the same as the price of daratumumab SC for RRMM (published approved ex-manufacturer price (AEMP) = \$7,010.28; effective AEMP = \$). Instead of reducing the proposed effective price of daratumumab SC to give an ICER of approximately \$55,000 to < \$75,000 per QALY, the early resolution resubmission based the economic analysis on the net cost of daratumumab after application of the proposed RSA in which the financial caps were set below the estimated level of utilisation. If the estimates of expected use are accurate, the average effective ex-manufacturer price for daratumumab per injection would be \$. Incorporation of this price into the updated economic model resulted in an ICER of \$55,000 to < \$75,000 per QALY (Table 23 below).

Table 23: Results of the economic evaluation

	Dara + CyBorD	CyBorD	Increment
Resubmission model with actual effective price (\$)			
Total costs (discounted)	\$	\$	\$
Total QALYs (discounted)	4.24	3.04	1.19
ICER per QALY			\$ ¹
Resubmission model with proposed average effective price (\$)			
Total costs (discounted)	\$	\$	\$
Total QALYs (discounted)	4.24	3.04	1.19
ICER per QALY			\$ ²

Source: Resubmission Table 3-3.

CyBorD = cyclophosphamide, bortezomib and dexamethasone; Dara = daratumumab subcutaneous; ICER = incremental cost effectiveness ratio; LYG = life year gained; OS = overall survival; QALY = quality adjusted life year; vs. = versus.

The redacted values correspond to the following ranges:

¹\$75,000 to < \$95,000

²\$55,000 to < \$75,000

- 9.4 The estimated financial impact of listing daratumumab on the PBS for the treatment of AL amyloidosis, based on the estimates provided in the November 2021 PSCR (includes dual program listings and Mayo Stage IIIB patients), is presented in Table 24. The estimated net cost to the PBS/RPBS of daratumumab was \$100 million to < \$200 million over the first 6 years of listing.

Table 24: Estimated financial impact of listing daratumumab on the PBS for AL amyloidosis (AEMP = \$)*

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Eligible patients	1	1	1	1	1	1
Prescriptions	2	2	2	2	2	2
Cost of dara to the PBS/RPBS	\$ ³	\$ ³	\$ ³	\$ ³	\$ ³	\$ ³
Net cost of dara+CyBorD to PBS/RPBS	\$ ³	\$ ⁴	\$ ³	\$ ⁴	\$ ⁴	\$ ⁴

Source: Table 4-5, p36 and Table 4-8, p39 of the early resolution resubmission

AEMP = approved ex-manufacturer price; CyBorD = cyclophosphamide + bortezomib + dexamethasone; dara = daratumumab

* Results in the early resolution resubmission are approximately 1.5% higher than those in the November 2021 PSCR due to a shift in Year 1 from 2022 to 2023.

The redacted values correspond to the following ranges:

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¹< 500

²500 to < 5,000

³\$10 million to < \$20 million

⁴\$20 million to < \$30 million

9.5 As requested by the PBAC in November 2021, the early resolution resubmission proposed a combined RSA for daratumumab across second-line MM and untreated systemic AL amyloidosis, with an annual subsidisation cap adjusted for overlap between the two patient populations and one course of daratumumab therapy per patient per lifetime. It was proposed that the listing for AL amyloidosis would join the existing MM RSA in its third year, and a rebate of 19.2% for daratumumab use above the combined subsidisation caps would apply (which aligns with the current rebate for daratumumab in MM).

9.6 The subsidisation caps for the AL amyloidosis listing are set lower than the utilisation estimates (the number of prescriptions was reduced by 19.2%; Table 25). The submission assumed the existing MM RSA would be revised from the start of Year 3 of the Deed which corresponds to 1 January 2023. The Secretariat provided estimates for Years 5 and 6 of the AL amyloidosis subsidisation cap, based on the assumption that the number of prescriptions would be reduced by 19.2%. The PBAC noted if a listing for daratumumab for AL amyloidosis was to occur before or after 1 January 2023 that the AL amyloidosis estimates and the existing MM estimates would need to be realigned based on the actual listing date.

Table 25: RSA subsidisation cap for daratumumab in AL amyloidosis

Year of AL amyloidosis listing	Year 1	Year 2	Year 3	Year 4	Year 5
Year of MM RSA	Year 3	Year 4	Year 5	-	-
Proposed AL amyloidosis daratumumab RSA caps					
Prescriptions ^a	1	1	1	1	1
Value of cap	\$ 2	\$ 2	\$ 2	\$ 2	\$ 2
Estimated AL amyloidosis daratumumab utilisation and financial estimates					
Prescriptions ^b	1	1	1	1	1
Net cost to PBS/RPBS	\$ 2	\$ 2	\$ 2	\$ 2	\$ 2
19.2% rebate payment	\$ 3	\$ 3	\$ 3	\$ 3	\$ 3
Net cost to PBS/RPBS after rebate	\$ 2	\$ 2	\$ 2	\$ 2	\$ 2
Reduction in net cost to PBS/RPBS	19.2%	19.2%	19.2%	19.2%	19.2%

Source: Table 4-13, p43 of the early resolution resubmission

MM = multiple myeloma; RSA = risk sharing arrangement

a The number of prescriptions as estimated in Table 24 were reduced by 19.2% for the RSA cap. Years 4 and 5 of AL amyloidosis listing were estimated by the Secretariat

b As per Table 24

The redacted values correspond to the following ranges:

¹500 to < 5,000

²\$10 million to < \$20 million

³\$0 to < \$10 million

9.7 The early resolution resubmission stated that a commissioned market research survey of 20 haematologists in 2021 that was included as part of the November 2021 submission indicated that almost all of the 38% of patients with concurrent AL

amyloidosis and MM would have AL amyloidosis diagnosed first. The resubmission modelled the progression of these patients to the second-line MM setting (where they will not be eligible for daratumumab again), using the progression free survival (PFS) Kaplan-Meier estimates of the daratumumab SC + CyBorD arm from the economic analysis for the AL amyloidosis listing. Based on this method, 23.8% of the initial patient cohort was estimated to progress in Year 1, with the addition of 10.3% of patients in Year 2 and 9.6% in Year 3. As presented below, it was estimated that < 500 patients treated with daratumumab for AL amyloidosis would progress to second-line MM and will no longer be eligible for daratumumab, within the first year of listing (Table 26).

Table 26: Estimation of the number of patients with concurrent AL amyloidosis and MM which progresses to the second-line setting

Year of AL amyloidosis listing	Year 1	Year 2	Year 3
Year of MM RSA	Year 3	Year 4	Year 5
Number of eligible AL amyloidosis patients ^a	¹	¹	¹
Proportion with concurrent MM ^b	38.0%	38.0%	38.0%
Number of AL amyloidosis patients with concurrent MM	¹	¹	¹
Number of patients with concurrent AL amyloidosis and MM diagnoses progressing to second-line MM (and no longer eligible for daratumumab in 2 nd line MM)	¹	¹	¹

Source: Table 4-14, p45 of the early resolution resubmission

MM = multiple myeloma

a Patient numbers in the early resolution resubmission are approximately 1.5% higher than those in the November 2021 PSCR due to a shift in Year 1 from 2022 to 2023.

b Commissioned market research survey of 20 haematologists in 2021 (included in November 2021 submission)

The redacted values correspond to the following ranges:

1 < 500

9.8 The resubmission proposed a revised subsidisation cap for the MM listing which was reduced by excluding patients with concurrent AL amyloidosis and MM diagnoses progressing to second-line MM as estimated above. The estimated reduction in the value of the subsidisation cap is shown in Table 27.

Table 27: Changes to the existing second-line MM RSA

Year of MM RSA	Year 3	Year 4	Year 5
Number of daratumumab initiations			
Original second-line MM RSA	¹	¹	¹
Revised second-line MM RSA	¹	¹	¹
Number of daratumumab prescriptions under the subsidisation caps			
Original second-line MM RSA	²	³	³
Revised second-line MM RSA	²	³	³
Value of the subsidisation caps			
Original second-line MM RSA	\$ ⁴	\$ ⁵	\$ ⁵
Revised second-line MM RSA	\$ ⁴	\$ ⁶	\$ ⁵
Reduction in value of the subsidisation cap	\$ ⁷	\$ ⁷	\$ ⁷

Source: Table 4-15, p46 of the early resolution resubmission

MM = multiple myeloma; RSA = risk sharing arrangement

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The redacted values correspond to the following ranges:

- ¹500 to < 5,000
- ²10,000 to < 20,000
- ³20,000 to < 30,000
- ⁴\$60 million to < \$70 million
- ⁵\$80 million to < \$90 million
- ⁶\$70 million to < \$80 million
- ⁷\$0 to < \$10 million

9.9 If the subsidisation cap for AL amyloidosis and the revised subsidisation cap for second-line MM were added to form a new combined RSA, this would result in an increase over the 3 year period in which the caps were combined of \$30 million to < \$40 million and a net increase in the total cost of daratumumab of \$30 million to < \$40 million (Table 28).

Table 28: Daratumumab subsidisation caps and net cost of daratumumab on the PBS/RPBS

Year of AL amyloidosis listing	Year 1	Year 2	Year 3
Year of MM RSA	Year 3	Year 4	Year 5
Value of the new subsidisation caps (AL amyloidosis and MM)			
Number of daratumumab prescriptions under the subsidisation cap	■ ¹	■ ¹	■ ¹
Increase from the current MM RSA	%	%	%
Total value of the subsidisation cap (AL amyloidosis and MM)	\$ ■ ²	\$ ■ ³	\$ ■ ⁴
Increase from the current MM RSA	%	%	%
Net cost of daratumumab on the PBS/RPBS (AL amyloidosis and MM)			
Total cost of daratumumab after the RSA in second-line MM	\$ ■ ²	\$ ■ ⁵	\$ ■ ³
Total cost of daratumumab after the RSA	\$ ■ ⁵	\$ ■ ³	\$ ■ ⁴
Change in total cost of daratumumab due to the AL amyloidosis listing ^a	\$ ■ ⁶	\$ ■ ⁷	\$ ■ ⁷

Source: Table 4-16, p46 and Table 4-17, p47 of the early resolution resubmission

MM = multiple myeloma; RSA = risk sharing arrangement

^a Total cost of daratumumab exceeds the RSA expenditure caps as the proposed rebate for use beyond the caps is ■%

The redacted values correspond to the following ranges:

- ¹20,000 to < 30,000
- ²\$70 million to < \$80 million
- ³\$90 million to < \$100 million
- ⁴\$100 million to < \$200 million
- ⁵\$80 million to < \$90 million
- ⁶\$0 to < \$10 million
- ⁷\$10 million to < \$20 million

9.10 Consistent with previous advice, the resubmission proposed dual General Schedule and Section 100 (EFC) listings for daratumumab SC (aligned with the listing program arrangements of daratumumab SC for RRMM). In terms of the proposed restriction, the early resolution resubmission provided updated restrictions for daratumumab in AL amyloidosis restricts patients to one course of daratumumab per lifetime. The resubmission stated that as patients who have concurrent disease are almost always diagnosed with AL amyloidosis first, the additional restriction criterion would be redundant for the second-line MM listing; however, the sponsor was amenable to including it in the MM restriction.

10 PBAC Outcome

- 10.1 The PBAC recommended the listing of daratumumab subcutaneous (SC), for use in combination with cyclophosphamide, bortezomib and dexamethasone (CyBorD), for the treatment of patients with newly diagnosed systemic light-chain AL amyloidosis. The PBAC recognised that there are no treatments on the PBS available specifically for this condition, and it considered that the addition of daratumumab SC plus CyBorD offered a high added therapeutic value. The PBAC considered that the revised economic analysis, which included more conservative assumptions, and a risk sharing arrangement (RSA), based on reduced financial estimates which also accounted for the overlap between patients with AL amyloidosis and multiple myeloma (MM), were acceptable.
- 10.2 The PBAC noted that the resubmission implemented the three changes to the economic model that had been requested at the November 2021 meeting to reflect more conservative assumptions (time horizon reduced from 25 to ≤ 20 years; time to subsequent treatment extrapolations converged from 24 to 60 months; and European Myeloma Network (EMN) data used to inform translation of haematologic response to OS). The PBAC noted that these changes resulted in an ICER of \$75,000 to $< \$95,000$ per QALY.
- 10.3 The PBAC noted that the resubmission proposed an RSA in which the subsidisation caps for AL amyloidosis were set lower than the utilisation estimates (the number of prescriptions per year was reduced by $\% \blacksquare$) resulting in a 19.2% reduction in net cost of daratumumab SC to PBS/RPBS, as shown in Table 25. The PBAC noted that if (i) the expenditure caps were exceeded as estimated; and (ii) the reduced effective ex-manufacturer price which reflected the net effective price after payment of cap rebates (i.e. $\$ \blacksquare$) was incorporated into the economic model, then the ICER was reduced to \$55,000 to $< \$75,000$ per QALY. The PBAC noted that this ICER would only be achieved if the use of daratumumab for AL amyloidosis was as predicted or greater. The PBAC considered that it was unknown if the ICER of \$55,000 to $< \$75,000$ per QALY would be realised as it relied on predicted use which is inherently uncertain. Further, with a combined RSA for AL amyloidosis and MM, achieving the lower ICER is contingent on the predicted use in both indications being accurate. The Committee noted that the ICER increased up to \$75,000 to $< \$95,000$ per QALY if use was less than predicted and, in the context of the high clinical need for a small patient population, the PBAC considered daratumumab to be cost-effective provided the RSA was based on the use of daratumumab for AL amyloidosis as outlined in Table 25.
- 10.4 The PBAC noted that the incorporation of the proposed effective approved ex-manufacturer price (AEMP) of daratumumab SC (AEMP = $\$ \blacksquare$) into the financial impact model resulted in an estimated net cost of daratumumab SC to PBS/RPBS of \$100 million to $< \$200$ million over 6 years (\$40 million to $< \$50$ million over 3 years), and a net cost of daratumumab SC + CyBorD to PBS/RPBS of \$100 million to $< \$200$ million

over 6 years.

- 10.5 The PBAC noted that the resubmission proposed an RSA that was consistent with the advice provided at the November 2021 meeting. A combined RSA for daratumumab use in AL amyloidosis and second-line MM was proposed for 3 years, which was based on the estimates of AL amyloidosis utilisation presented in the pre-sub-committee response (PSCR) considered at the November 2021 meeting. The combined cap was reduced to account for overlap between the indications and assumed that patients diagnosed with both indications would receive only one course of daratumumab per lifetime. The resubmission proposed that the AL amyloidosis indication would join the existing MM RSA in its third year (2023), and that a rebate of 1% would apply above the combined cap threshold, consistent with the current rebate for MM. The PBAC noted expert advice that indicated that almost all patients with concurrent AL amyloidosis and MM would be diagnosed with AL amyloidosis first. The PBAC considered that the rebate of 1% was appropriate and the estimates to reduce second line MM usage of daratumumab by < 500 patients in Year 1, < 500 in Year 2 and < 500 in Year 3 were reasonable.
- 10.6 The PBAC noted that adding daratumumab SC for AL amyloidosis to the daratumumab MM RSA as proposed would result in an estimated net \$30 million to < \$40 million increase in the total cost to the PBS/RPBS for daratumumab over the remaining 3 years of the RSA and considered the estimates to be reasonable. However, the PBAC also noted that for MM the use of daratumumab to date was less than predicted in the July 2020 submission. The PBAC noted that with a combined RSA for AL amyloidosis and MM, the use in one indication may compensate for the use in the other i.e. use below that expected for MM would reduce the rebates paid for AL amyloidosis and vice versa. The PBAC advised that if the overlap between the indications could be appropriately accounted for across separate RSAs for each indication (i.e. the MM cap was reduced by the estimates in Table 27), then keeping separate RSAs would be a preferable approach as it would prevent cross subsidisation across the indications.
- 10.7 Regarding the proposed restrictions, the following advice was provided by the PBAC:
- Noting that the early resolution resubmission provided updated restrictions for daratumumab in AL amyloidosis in which patients were limited to one course of daratumumab (IV or SC) per lifetime, the PBAC considered that a similar criterion should be added to the second-line MM restrictions. This PBS noted that this would result in flow-on restriction changes to the existing daratumumab listings.
 - The number of repeats for the continuing (week 25+) and grandfather listings should be 5, not 7 as proposed in the submission, for closest alignment to 104 weeks (2 years) duration of treatment in the absence of disease progression as recommended by the Product Information.

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- The clinical criterion that “Patients must have a confirmed histological diagnosis of systemic light-chain amyloidosis” should be included in the initial listing.
- Flow-on changes to the bortezomib PBS indication will be required to allow PBS-funded bortezomib to be used as part of the daratumumab SC + CyBorD regimen. Bortezomib’s current PBS indication is restricted to use in MM.
- The PBAC noted that the November 2021 submission estimated that 30 patients may require non-PBS to PBS transitioning arrangements and advised that a grandfather restriction was appropriate.

10.8 The PBAC advised that daratumumab is not suitable for prescribing by nurse practitioners.

10.9 The PBAC recommended that the Early Supply Rule should not apply.

10.10 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were met. Specifically, the PBAC found that in the circumstances of its recommendation for daratumumab:

- The treatment is expected to provide a substantial and clinically relevant improvement in efficacy over currently available treatments;
- The treatment is expected to address a high and urgent unmet clinical need as there are no treatments on the PBS specifically for this condition; and
- It would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A on the basis of the preceding findings.

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

Outcome:

Recommended

11 Recommended listing

11.1 Amend existing listing as follows:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
DARATUMUMAB					
daratumumab 1.8 g/15 mL injection, 15 mL vial	New (EFC – Related Ben.) New (Gen. Sch)	1	1	15	Darzalex SC
Category / Program: <input checked="" type="checkbox"/> Section 100 –Efficient Funding of Chemotherapy– Related Benefits (Code CT) <input checked="" type="checkbox"/> General Schedule (Code GE)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					

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	Restriction type: <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)
	Administrative Advice: The intravenously administered presentation of this drug is not PBS-listed for this indication at the request of the sponsor.
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.
	Indication: Systemic light chain amyloidosis
	Treatment Phase: Initial treatment from week 0 to week 24
	Clinical criteria: The condition must have histological evidence consistent with a diagnosis of systemic light-chain amyloidosis – retain this in the patient's medical records
	AND
	Clinical criteria: Patient must be untreated with this drug, irrespective of whether the diagnosis has been re-classified (e.g. multiple myeloma/amyloidosis)
	AND
	Clinical criteria: Patient must have an WHO/Eastern Cooperative Oncology Group (ECOG) performance status of no higher than 2 at the time of treatment initiation with this drug.
	Treatment criteria Must be treated by a haematologist (this does not exclude treatment via a multidisciplinary team, but the PBS authority application must be sought by the treating haematologist)
	AND
	Treatment criteria: Patient must be undergoing concomitant treatment limited to each of: (i) bortezomib, (ii) cyclophosphamide, (iii) dexamethasone, at certain weeks of treatment as outlined in the drug's approved Product Information

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
DARATUMUMAB					
daratumumab 1.8 g/15 mL injection, 15 mL vial	New (EFC – Related Ben.) New (Gen. Sch)	1	1	5	Darzalex SC
Category / Program: <input checked="" type="checkbox"/> Section 100 –Efficient Funding of Chemotherapy– Related Benefits (Code CT) <input checked="" type="checkbox"/> General Schedule (Code GE)					

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	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction type: <input checked="" type="checkbox"/> Authority Required (online PBS Authorities system / telephone)
	Administrative Advice: The intravenously administered presentation of this drug is not PBS-listed for this indication at the request of the sponsor.
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.
	Indication: Systemic light chain amyloidosis
	Treatment Phase: Continuing treatment from week 25 onwards (administered once every four weeks)
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition,
	Treatment criteria:
	Must be treated by a haematologist (this does not exclude treatment via a multidisciplinary team, but the PBS authority application must be sought by the treating haematologist)
	AND
	Treatment criteria:
	Patient must not receive more than 24 cumulative months of PBS subsidised treatment with this drug for this condition
	AND
	Treatment criteria:
	Patient must be undergoing continuing treatment that does not extend treatment duration beyond whichever comes first: (i) disease progression, (ii) 24 cumulative months from the first administered dose, once in a lifetime
	Category / Program:
	<input checked="" type="checkbox"/> Section 100 –Efficient Funding of Chemotherapy– Related Benefits (Code CT)
	<input checked="" type="checkbox"/> General Schedule (Code GE)
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction type: <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)
	Indication: Systemic light chain amyloidosis
	Treatment Phase: Transitioning from non-PBS to PBS-subsidised supply – ‘Grandfather’ arrangements
	Clinical criteria:
	Patient must be continuing treatment with this drug that was commenced as non-PBS subsidised supply prior to [insert listing date]
	AND

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	Clinical criteria:
	The condition must have histological evidence consistent with a diagnosis of systemic light-chain amyloidosis – retain this in the patient's medical records
	AND
	Clinical criteria:
	Patient must be untreated with this drug, irrespective of whether the diagnosis has been re-classified (e.g. multiple myeloma/amyloidosis)
	AND
	Clinical criteria:
	Patient must have an WHO/Eastern Cooperative Oncology Group (ECOG) performance status of no higher than 2 at the time of treatment initiation with this drug.
	Treatment criteria:
	Must be treated by a haematologist (this does not exclude treatment via a multidisciplinary team, but the PBS authority application must be sought by the treating haematologist)
	AND
	Treatment criteria:
	Patient must be undergoing concomitant treatment limited to each of: (i) bortezomib, (ii) cyclophosphamide, (iii) dexamethasone, at certain weeks of treatment as outlined in the drug's approved Product Information
	AND
	Treatment criteria:
	Patient must not receive more than 24 cumulative months of PBS subsidised treatment with this drug for this condition
	AND
	Treatment criteria:
	Patient must be undergoing continuing treatment that does not extend treatment duration beyond whichever comes first: (i) disease progression, (ii) 24 cumulative months from the first administered dose, once in a lifetime
	Administrative advice:
	Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria.
	Administrative advice:
	This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.

11.2 Add new indication for bortezomib to the existing multiple myeloma restriction as follows:

MEDICINAL PRODUCT Form	PBS item code	Max. Amount	No. of Rpts
BORTEZOMIB Injection	12227M (Public) 12219D (Private)	3000 mcg	15
Available brands			
BORTEZOMIB-TEVA (bortezomib 3.5 mg injection, 1 vial)			
Bortezom (bortezomib 3.5 mg injection, 1 vial)			

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Bortezomib Accord (bortezomib 1 mg injection, 1 vial)	
Bortezomib Accord (bortezomib 3.5 mg injection, 1 vial)	
Bortezomib Juno (bortezomib 1 mg injection, 1 vial)	
Bortezomib Juno (bortezomib 2.5 mg injection, 1 vial)	
Bortezomib Juno (bortezomib 3.5 mg injection, 1 vial)	
Bortezomib Sandoz (bortezomib 3.5 mg injection, 1 vial)	
Bortezomib-Dr.Reddy's (bortezomib 3.5 mg injection, 1 vial)	
DBL Bortezomib (bortezomib 1 mg injection, 1 vial)	
DBL Bortezomib (bortezomib 2.5 mg injection, 1 vial)	
DBL Bortezomib (bortezomib 3 mg injection, 1 vial)	
DBL Bortezomib (bortezomib 3.5 mg injection, 1 vial)	
Velcade (bortezomib 1 mg injection, 1 vial)	
Velcade (bortezomib 3 mg injection, 1 vial)	
Velcade (bortezomib 3.5 mg injection, 1 vial)	
	Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction type: <input checked="" type="checkbox"/> Restricted benefit
	Indication: Systemic light chain amyloidosis
	Treatment Phase: Administration on Days 1, 8, 15 and 22 of six 28-day (4-weeks) treatment cycles in total
	Treatment criteria:
	Patient must be undergoing concurrent treatment with PBS-subsidised daratumumab for this PBS-indication

11.3 Update daratumumab’s existing restrictions to limit access to lifetime as follows:

Add the new eligibility criterion to daratumumab initial treatment restrictions with a multiple myeloma indication - RRMM	
<p>EFC listings of the IV daratumumab vials: PBS item codes: 1220E, 12221F, 12225K, 12226L, 12228N, 12229P, 12230Q, 12231R • daratumumab 400 mg/20 mL injection, 20 mL vial, and • daratumumab 100 mg/5 mL injection, 5 mL vial</p> <p>EFC listings of the SC daratumumab vials: PBS item codes: 12673B, 12682L, 12746W • daratumumab 1.8 g/15 mL injection, 15 mL vial</p> <p>General Schedule listings of the SC daratumumab vials: PBS item codes: 12683M, 12704P, 12725R, 12755H • daratumumab 1.8 g/15 mL injection, 15 mL vial</p>	
Insert	Clinical criteria:
	Patient must be untreated with this drug, irrespective of whether the diagnosis has been re-classified (e.g. multiple myeloma/amyloidosis)

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

12 Context for Decision

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

13 Sponsor's Comment

The sponsor had no comment.