7.11 DARATUMUMAB, Solution concentrate for I.V. infusion, 100 mg/5mL vial, 400 mg/20 mL vial, Darzalex®, Janssen-Cilag Pty Ltd

1 Purpose of Application

1.1 A major resubmission in November 2019 (item 7.01) requested a Section 100 (Efficient Funding for Chemotherapy) Authority Required (Written) listing for daratumumab, in combination with bortezomib and dexamethasone (DBd), for the treatment of second-line multiple myeloma (MM). The PBAC deferred making a recommendation in November 2019 to seek revisions to the economic model, the estimated financial implications and the proposed Risk Sharing Arrangement (RSA). The sponsor subsequently provided these revisions for consideration at the July 2020 PBAC meeting.

1.2 Daratumumab listing, as DBd, was requested on the basis of a cost-effectiveness analysis versus bortezomib plus dexamethasone (Bd).

1.3 To address equity issues regarding access, along with the revisions, the sponsor had stated that daratumumab monotherapy would be supplied compassionately as a last-line therapy to MM patients who have no other PBS-funded treatment options.

2 Background

Registration status

2.1 Daratumumab was TGA registered on 17th July 2017:

- in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy;
- as monotherapy, for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are refractory to both a PI and an immunomodulatory agent.

2.2 Daratumumab was approved by the TGA in September 2019 for use in combination with bortezomib, melphalan and prednisolone for the treatment of patients with newly diagnosed MM who are ineligible for autologous stem cell transplant (ASCT).

Previous PBAC considerations

2.3 Daratumumab was previously deferred for this indication, second-line MM, by the PBAC at its November 2019 meeting. Another two submissions, for the use of DBd in the treatment of relapsed and/or refractory (RR) MM patients who had received at least one prior therapy, were not recommended by the PBAC in March 2019 and November 2017. The March 2019 resubmission also requested daratumumab monotherapy for highly treatment experienced patients or patients who were refractory to at least three prior lines of therapy.

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

3 Requested listing

Daratumumab as DBd

3.1 All non-pricing aspects of the essential elements for daratumumab 400 mg and 100 mg vials remain unchanged from the previous resubmission.

3.2 The proposed restrictions for daratumumab are presented below. Secretariat suggested additions are in italics and deletions are in strikethrough.

Name, Restriction, Manner of administration and form	Max. Amount	№.of Rpts	DPMA	Proprietary Name and Manufacturer
DARATUMUMAB VIAL, 400 mg and 100 mg	1,920 mg	~~Initial: 13~~ *8* ~~Continuing: 5~~	Published: Public: $11,768.86 Private: $11,972.19 Effective: Public: $[redacted] Private: $[redacted]	DARZALEX® Janssen-Cilag Pty Ltd

Category / Program: Section 100 – Efficient Funding of Chemotherapy (Public/Private hospital)
Prescriber type: ☒Medical Practitioners
Restriction type / Method: ☒Authority Required – non-immediate/delayed assessment by Services Australia (In-writing only via mail/postal service or electronic upload to Hobart)
Episodicity: *Relapsed and/or refractory*
Severity: [blank]
Condition: Multiple myeloma
PBS Indication: *Relapsed and/or refractory* multiple myeloma
Treatment Phase: Initial *treatment as second-line drug therapy for weeks 1 to 9 (administered once weekly)*
Clinical criteria:
The condition must be confirmed by a histological diagnosis
AND
Clinical criteria:
The treatment must be in combination with bortezomib and dexamethasone
AND
Clinical criteria:
Patient must have progressive disease after ~~no more than~~ one prior line of *drug* therapy*, but the treatment must not be commenced beyond the second-line drug treatment setting (i.e. use as third-line drug treatment and beyond is not PBS-subsidised)*

AND
Clinical criteria:
Patients must not be receiving concomitant PBS-subsidised carfilzomib, thalidomide or its analogues
AND
~~**Clinical criteria:**~~
~~Patient must not receive more than eight cycles of treatment under this restriction~~
AND
Clinical criteria:
Patient must ~~not have previously~~ *be* receive~~d~~*ing* ~~PBS subsidised~~ treatment with this drug for ~~this condition~~ *the first time*
Prescriber instructions: *The authority application must be made in writing and must include:* *(1) a completed authority prescription form; and* *(2) a completed Multiple Myeloma daratumumab Authority Application - Supporting Information Form, which includes details of the histological diagnosis of multiple myeloma, prior treatments including name(s) of drug(s) and date of most recent treatment cycle and record of prior stem cell transplant or ineligibility for prior stem cell transplant; details of the basis of the diagnosis of progressive disease or failure to respond; and nomination of which disease activity parameters will be used to assess response* *To enable confirmation of eligibility for treatment, current diagnostic reports of at least one of the following must be provided:* *(a) the level of serum monoclonal protein; or* *(b) Bence-Jones proteinuria - the results of 24-hour urinary light chain M protein excretion; or* *(c) the serum level of free kappa and lambda light chains; or* *(d) bone marrow aspirate or trephine; or* *(e) if present, the size and location of lytic bone lesions (not including compression fractures); or* *(f) if present, the size and location of all soft tissue plasmacytomas by clinical or radiographic examination i.e. MRI or CT-scan; or* *(g) if present, the level of hypercalcaemia, corrected for albumin concentration.* *As these parameters will be used to determine response, results for either (a) or (b) or (c) should be provided for all patients. Where the patient has oligo-secretory or non-secretory multiple myeloma, either (c) or (d) or if relevant (e), (f) or (g) should be provided. Where the prescriber plans to assess response in patients with oligo-secretory or non-secretory multiple myeloma with free light chain assays, evidence of the oligo-secretory or non-secretory nature of the multiple myeloma (current serum M protein less than 10 g per L) must be provided.*
Prescriber instructions: *Progressive disease is defined as at least 1 of the following:* *(a) at least a 25% increase and an absolute increase of at least 5 g per L in serum M protein (monoclonal protein); or* *(b) at least a 25% increase in 24-hour urinary light chain M protein excretion, and an absolute increase of at least 200 mg per 24 hours; or* *(c) in oligo-secretory and non-secretory myeloma patients only, at least a 50% increase of the difference between involved free light chain and uninvolved free light chain; or* *(d) at least a 25% relative increase and at least a 10% absolute increase in plasma cells in a bone marrow aspirate or on biopsy; or* *(e) an increase in the size or number of lytic bone lesions (not including compression fractures); or* *(f) at least a 25% increase in the size of an existing or the development of a new soft tissue plasmacytoma (determined by clinical examination or diagnostic imaging); or* *(g) development of hypercalcaemia (corrected serum calcium greater than 2.65 mmol per L not attributable to any other cause).*
Prescriber instructions: *Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M protein.*
Prescriber instructions: A line of therapy is defined as 1 or more cycles of a planned treatment program. This may consist of 1 or more planned cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner. A new line of therapy starts when a planned course of therapy is modified to include other treatment agents (alone or in combination) as a result of disease progression, relapse, or toxicity, with the exception to this being the need to attain a sufficient response for stem cell transplantation to proceed. A new line of therapy also starts when a planned period of observation off therapy is interrupted by a need for additional treatment for the disease.
***Administrative Advice*:** *Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).*

Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au *Applications for authority to prescribe should be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos* *Or mailed to:* *Services Australia* *Complex Drugs* *Reply Paid 9826* *HOBART TAS 7001*
Administrative Advice: *No increase in the maximum number of repeats may be authorised.*
Administrative Advice: *Special Pricing Arrangements apply*
Administrative Advice: *This drug is not PBS-subsidised for use in patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are refractory to both a PI and an immunomodulatory agent, as monotherapy.*

Name, Restriction, Manner of administration and form	**PBS item code**	**Max. Amount**	**№.of Rpts**	**Manufacturer**
DARATUMUMAB Injection	NEW (Public) NEW (Private)	1920 mg	4	Janssen-Cilag Pty Ltd
Available brands				
Darzalex (daratumumab 100 mg/5 mL injection, 5 mL vial)				
Darzalex (daratumumab 400 mg/20 mL injection, 20 mL vial)				

Category / Program: Section 100 – Efficient Funding of Chemotherapy (Public/Private)
Prescriber type: ☐ ☒Medical Practitioners
Restriction Level / Method: ☒Authority Required – immediate/real time assessment by Services Australia (telephone/online/emergency)
PBS Indication: *Relapsed and/or refractory* multiple myeloma
Treatment Phase: Continuing *treatment of second-line drug therapy for weeks 10 to 24 (administered every 3 weeks)*
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with ~~an authority prescription for~~ this drug for this condition
AND
Clinical criteria:
~~Patient must have previously received PBS-subsidised treatment with this drug in combination with bortezomib and dexamethasone as initial treatment in the current course of treatment~~ *The treatment must be in combination with bortezomib and dexamethasone*
AND
Clinical criteria:
Patient must not *have* develope*d* disease progression while receiving treatment with this drug for this condition
AND
Clinical criteria:
Patient~~s~~ must not be receiving concomitant PBS-subsidised carfilzomib, ~~or~~ thalidomide or its analogues
Prescriber Instructions: *Progressive disease is defined as at least 1 of the following:* *(a) at least a 25% increase and an absolute increase of at least 5 g per L in serum M protein (monoclonal protein); or* *(b) at least a 25% increase in 24-hour urinary light chain M protein excretion, and an absolute increase of at least 200 mg per 24 hours; or*

(c) in oligo-secretory and non-secretory myeloma patients only, at least a 50% increase of the difference between involved free light chain and uninvolved free light chain; or *(d) at least a 25% relative increase and at least a 10% absolute increase in plasma cells in a bone marrow aspirate or on biopsy; or* *(e) an increase in the size or number of lytic bone lesions (not including compression fractures); or* *(f) at least a 25% increase in the size of an existing or the development of a new soft tissue plasmacytoma (determined by clinical examination or diagnostic imaging); or* *(g) development of hypercalcaemia (corrected serum calcium greater than 2.65 mmol per L not attributable to any other cause).*
Prescriber Instructions: *Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M protein.*
Administrative Advice: *Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting the Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday)*
Administrative Advice: *No increase in the maximum number of repeats may be authorised.*
Administrative Advice: *Special Pricing Arrangements apply*
Administrative Advice: *This drug is not PBS-subsidised for use in patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are refractory to both a PI and an immunomodulatory agent, as monotherapy.*

Name, Restriction, Manner of administration and form	***PBS item code***	***Max. Amount***	***№.of Rpts***	***Manufacturer***
DARATUMUMAB *Injection*	*NEW (Public)* *NEW (Private)*	*1920 mg*	*5*	*Janssen-Cilag Pty Ltd*
Available brands				
Darzalex *(daratumumab 100 mg/5 mL injection, 5 mL vial)*				
Darzalex *(daratumumab 400 mg/20 mL injection, 20 mL vial)*				

Restriction Summary: [new]

Concept ID (for internal Dept. use)	
	Category / Program: *Section 100 – Efficient Funding of Chemotherapy (Public/Private)*
	Prescriber type: ☐*Dental* ☒*Medical Practitioners* ☐*Nurse practitioners* ☐*Optometrists* ☐*Midwives*
	Restriction Level / Method: ☒*Authority Required – immediate/real time assessment by Medicare (telephone/online/emergency)*
New 1 (variation of 7906)	***PBS Indication:*** *Relapsed and/or refractory multiple myeloma*
	Treatment Phase: *Continuing treatment of second-line drug therapy from week 25 until disease progression (administered every 4 weeks)*
11365	***Clinical criteria:***
11364	*Patient must have previously received PBS-subsidised treatment with this drug for this condition*
	AND
12908	***Clinical criteria:***
7911	*The treatment must be in combination with dexamethasone*
	AND
21513	***Clinical criteria:***
21512	*Patient must not have developed disease progression while receiving treatment with this drug for this condition*
	AND
22332	***Clinical criteria:***
22331	*Patient must not be receiving concomitant PBS-subsidised bortezomib, carfilzomib, or thalidomide or its analogues*
7922	***Prescriber Instructions:*** *Progressive disease is defined as at least 1 of the following:*

	(a) at least a 25% increase and an absolute increase of at least 5 g per L in serum M protein (monoclonal protein); or *(b) at least a 25% increase in 24-hour urinary light chain M protein excretion, and an absolute increase of at least 200 mg per 24 hours; or* *(c) in oligo-secretory and non-secretory myeloma patients only, at least a 50% increase of the difference between involved free light chain and uninvolved free light chain; or* *(d) at least a 25% relative increase and at least a 10% absolute increase in plasma cells in a bone marrow aspirate or on biopsy; or* *(e) an increase in the size or number of lytic bone lesions (not including compression fractures); or* *(f) at least a 25% increase in the size of an existing or the development of a new soft tissue plasmacytoma (determined by clinical examination or diagnostic imaging); or* *(g) development of hypercalcaemia (corrected serum calcium greater than 2.65 mmol per L not attributable to any other cause).*
7923	***Prescriber Instructions:*** *Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M protein.*
25745 *CAR flag*	***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 the Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday)*
7607	***Administrative Advice:*** *No increase in the maximum number of repeats may be authorised.*
7608	***Administrative Advice:*** *Special Pricing Arrangements apply*
New 7	***Administrative Advice:*** *This drug is not PBS-subsidised for use in patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are refractory to both a PI and an immunomodulatory agent, as monotherapy.*

Name, Restriction, Manner of administration and form	***PBS item code***	***Max. Amount***	***№.of Rpts***	***Manufacturer***
DARATUMUMAB *Injection*	*NEW (Public)* *NEW (Private)*	*1920 mg*	*0*	*Janssen-Cilag Pty Ltd*
Available brands				
Darzalex *(daratumumab 100 mg/5 mL injection, 5 mL vial)*				
Darzalex *(daratumumab 400 mg/20 mL injection, 20 mL vial)*				

Restriction Summary: [new]

Concept ID (for internal Dept. use)	**Category / Program:** Section 100 – Efficient Funding of Chemotherapy (Public/Private hospital)
	Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
	Restriction Level / Method: ☒Authority Required – delayed assessment by Medicare (In-writing only via mail/postal service or electronic upload to Hobart); at least one concept to be marked for 'FULL' assessment
New 1 (variation of 7906)	**PBS Indication:** *Relapsed and/or refractory* multiple myeloma
	Treatment Phase: Grandfather ~~– Initial~~ *treatment (transition from non-PBS supply to PBS-subsidised treatment)*
New 8	**Clinical criteria:**
	Patient must have previously received non-PBS-subsidised treatment with this drug for this condition prior to <date>
	AND
7907	**Clinical criteria:**
	The condition must be confirmed by a histological diagnosis
	AND
New 9	**Clinical criteria:**

New 10	The treatment must be in combination with bortezomib and dexamethasone *if supply is to cover weeks 1 to 24 of treatment; or*
New 11	*The treatment must be in combination with dexamethasone if supply is to cover week 25 of treatment to disease progression*
	AND
New 12 (variation of New 2)	**Clinical criteria:**
	Patient must have *had* progressive disease after ~~no more than~~ one prior line of *drug* therapy, *but not after a second-line of drug therapy, prior to having initiated non-PBS subsidised treatment with this drug for this condition (i.e. non-PBS supply should have commenced as second-line drug therapy)*
	AND
22374	**Clinical criteria:**
22373	Patient~~s~~ must not be receiving concomitant PBS-subsidised *carfilzomib,* thalidomide or its analogues ~~or carfilzomib~~
	AND
New 13	**Clinical criteria:**
New 14 FULL	Patient must not receive more than *the balance of* ~~eight cycles~~ *9 doses (comprising of an original prescription with up to 7 repeats, assuming at least one non-PBS subsidised has been administered in this treatment phase)* ~~of initial treatment in total, including supply under the PBS~~ *if the patient is receiving treatment for weeks 1 to 9; or*
New 15 FULL	*Patient must not receive more than the balance of 5 doses (comprising of an original prescription with up to 4 repeats) if the patient is receiving treatment for weeks 10 to 24; or*
New 16 FULL	*Patient must not receive more than the balance of 6 doses (comprising of an original prescription with up to 5 repeats) if the patient is receiving treatment for weeks 25 to disease progression*
New 17 *(variation of New 4)* *(Details to be refined)* FULL assessment	***Prescriber instructions:*** *The authority application must be made in writing and must include:* *(1) a completed authority prescription form; and* *(2) a completed Multiple Myeloma daratumumab Grandfather treatment Authority Application - Supporting Information Form, which includes details of the histological diagnosis of multiple myeloma, prior treatments including name(s) of drug(s) and date of most recent treatment cycle and record of prior stem cell transplant or ineligibility for prior stem cell transplant; details of the basis of the diagnosis of progressive disease or failure to respond; and nomination of which disease activity parameters will be used to assess response* *To enable confirmation of eligibility for treatment, diagnostic reports of at least one of the following must be provided (if not already provided with the first-line drug treatment authority application):* *(a) the level of serum monoclonal protein; or* *(b) Bence-Jones proteinuria - the results of 24-hour urinary light chain M protein excretion; or* *(c) the serum level of free kappa and lambda light chains; or* *(d) bone marrow aspirate or trephine; or* *(e) if present, the size and location of lytic bone lesions (not including compression fractures); or* *(f) if present, the size and location of all soft tissue plasmacytomas by clinical or radiographic examination i.e. MRI or CT-scan; or* *(g) if present, the level of hypercalcaemia, corrected for albumin concentration.* *As these parameters will be used to determine response, results for either (a) or (b) or (c) should be provided for all patients. Where the patient has oligo-secretory or non-secretory multiple myeloma, either (c) or (d) or if relevant (e), (f) or (g) should be provided. Where the prescriber plans to assess response in patients with oligo-secretory or non-secretory multiple myeloma with free light chain assays, evidence of the oligo-secretory or non-secretory nature of the multiple myeloma (current serum M protein less than 10 g per L) must be provided.*
7922	***Prescriber instructions:*** *Progressive disease is defined as at least 1 of the following:* *(a) at least a 25% increase and an absolute increase of at least 5 g per L in serum M protein (monoclonal protein); or* *(b) at least a 25% increase in 24-hour urinary light chain M protein excretion, and an absolute increase of at least 200 mg per 24 hours; or* *(c) in oligo-secretory and non-secretory myeloma patients only, at least a 50% increase of the difference between involved free light chain and uninvolved free light chain; or* *(d) at least a 25% relative increase and at least a 10% absolute increase in plasma cells in a bone marrow aspirate or on biopsy; or* *(e) an increase in the size or number of lytic bone lesions (not including compression fractures); or*

	(f) at least a 25% increase in the size of an existing or the development of a new soft tissue plasmacytoma (determined by clinical examination or diagnostic imaging); or *(g) development of hypercalcaemia (corrected serum calcium greater than 2.65 mmol per L not attributable to any other cause).*
7923	***Prescriber instructions:*** *Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M protein.*
New 5	**Prescribing Instructions:** A line of therapy is defined as 1 or more cycles of a planned treatment program. This may consist of 1 or more planned cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner. A new line of therapy starts when a planned course of therapy is modified to include other treatment agents (alone or in combination) as a result of disease progression, relapse, or toxicity, with the exception to this being the need to attain a sufficient response for stem cell transplantation to proceed. A new line of therapy also starts when a planned period of observation off therapy is interrupted by a need for additional treatment for the disease.
17098	***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*
7608	***Administrative Advice:*** *Special Pricing Arrangements apply*
25398 draft	***Administrative Advice:*** *This Grandfather restriction will cease to operate from 12 months after the date specified in the Clinical criteria*

Concept ID	~~**Category / Program:** Section 100 – Efficient Funding of Chemotherapy~~
	~~**Prescriber type:** ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives~~
	~~**Restriction Level / Method:**~~ ~~☐Unrestricted benefit~~ ~~☐Restricted benefit~~ ~~☐Authority Required – In Writing~~ ~~☒Authority Required – Telephone/Electronic/Emergency~~ ~~☐Authority Required – Streamlined~~
	~~**Condition:** Multiple myeloma~~
	~~**Treatment Phase:** Grandfather continuing treatment~~
	~~**Clinical criteria:**~~
	~~Patient must have previously received non-PBS-subsidised treatment with this drug in combination with bortezomib and dexamethasone as initial treatment in the current course of treatment prior to <date>~~
	~~**AND**~~
	~~**Clinical criteria:**~~
	~~Patient must not develop disease progression while receiving treatment with this drug for this condition~~
	~~**AND**~~
	~~**Clinical criteria:**~~
	~~Patients must not be receiving concomitant PBS-subsidised thalidomide or its analogues or carfilzomib~~

3.3 The Secretariat suggested some revised wording and that the new listing be presented in three distinct treatment phases to match the dosing schedule in the TGA approved Product Information (i.e. treatment for weeks 1-9, weeks 10-24, and week 25 and beyond) as the requirements for daratumumab to be given in combination with other drugs and the schedule of daratumumab dosing vary according to the week of treatment.

3.4 The pre-PBAC response agreed to the proposed changes to the restriction, but noted that the clinical criterion that 'Treatment must be in combination with

dexamethasone' in the continuing treatment from Week 25 to disease progression restriction (and in the Grandfather restriction) should be removed, as from Week 25 daratumumab is given as monotherapy. The PBAC noted that this change was consistent with the TGA approved Product Information.

3.5 The sponsor requested an Authority Required (written) listing for initial treatment and an Authority Required (telephone/online) listing for continuing treatment. This is consistent with lenalidomide listings for MM, which are currently written Authority Required, but not consistent with carfilzomib (a telephone/immediate assessment type authority for progressive disease after at least one therapy) and bortezomib (a streamlined authority type listing also for progressive disease after at least one therapy). The intent to restrict daratumumab use to the second-line population only could justify a reason for a delayed assessment by Services Australia to check that at least one prior therapy is present in the patient's PBS claims history, but also no more than two prior therapies are evident in the patient's PBS claims history. However, for carfilzomib and bortezomib listings, the criterion that the disease must have progressed after at least one prior therapy did not justify a delayed assessment by Services Australia. Therefore, a daratumumab listing requiring delayed assessment to check the number of prior therapies before granting authority approval would be inconsistent.

3.6 The prescriber instruction seeking details of the histological diagnosis of multiple myeloma, prior treatments including name(s) of drug(s) and date of most recent treatment cycle, is not necessary given that the details of histological diagnosis of multiple myeloma would have been provided to Services Australia when the patient accessed a first-line treatment. Records of prior stem cell transplant or ineligibility for prior stem cell transplant would also be unnecessary in the daratumumab restriction given that the PBS eligibility make no reference to stem cell transplantation. Given the positioning of daratumumab as second-line therapy, the lesser administrative burden associated with non-written Authority Required type listings for carfilzomib and bortezomib, and, the urgency of commencing treatment in a patient who has progressed after first-line treatment, the PBAC considered that an immediate assessment type Authority Required listing (via telephone or online pathways) would be appropriate for this new daratumumab second-line therapy listing.

<u>Bortezomib</u>

3.7 If DBd is PBS listed, the minor resubmission again proposed (i) a simplified PBS restriction for bortezomib, as an Authority Required (Streamlined) item for the treatment of MM; and (ii) a lower effective price for bortezomib. The proposed [redacted] for bortezomib of $[redacted] per mg was unchanged from the previous submission and represents a [redacted]% reduction on the current weighted average effective price of bortezomib of $[redacted] (see Table 1).

3.8 [redacted], and includes an effective price of $[redacted]/mg in the [redacted] (a [redacted]% reduction from the current effective price of $[redacted]/mg).

Table 1: Weighted average effective price per mg of bortezomib

Setting	Effective AEMP of bortezomib ($/mg)	Proportional use of bortezomib (per 2019 utilisation data)
Newly diagnosed transplant ineligible MM	$[redacted]	9.69%
Newly diagnosed transplant eligible MM	$[redacted]	68.42%
Newly diagnosed MM with renal impairment	$[redacted]	1.10%*
RR MM, current price vs proposed price	$[redacted] / $[redacted]	20.79%*
Current weighted average price of bortezomib/mg	$[redacted]/mg	
Proposed weighted average price of bortezomib/mg	**$[redacted]/mg**	

***** These proportions were incorrectly reversed in the minor resubmission, as compared to Attachment 3
AEMP = approved ex-manufacturer price; MM = multiple myeloma; RR = relapsed and/or refractory
Source: Table 2-5, p20 and Attachment 3 of the minor resubmission

3.9 The sponsor also proposed [redacted]

3.10 The proposed restriction for bortezomib is presented below. Secretariat suggested additions are in italics and deletions are in strikethrough.

Name, restriction, manner of administration, form	Maximum amount (units)	No. of repeats	Dispensed price for maximum amount	Proprietary name and manufacturer
BORTEZOMIB, intravenous infusion, powder in vial, 1 mg BORTEZOMIB, intravenous infusion, powder in vial, 3 mg BORTEZOMIB, intravenous infusion, powder in vial, 3.5 mg	3,000 mcg	15	Effective: Public hospital: $[redacted] Private hospital: $[redacted]	VELCADE® Janssen-Cilag Pty Ltd

Concept ID (for internal Dept. use)	**Category / Program: Section 100 – Efficient Funding for Chemotherapy *(Public/Private)*** **Prescriber type:** ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives **Restriction Level / Method:** ☐Unrestricted benefit ☒*Restricted benefit* ☐Authority Required – In Writing ☐Authority Required – Telephone/Electronic/Emergency ☒~~Authority Required - Streamlined~~
7906	**PBS Indication:** Multiple myeloma
	~~**Clinical criteria:**~~
	~~For the treatment of multiple myeloma~~
7608	**Administrative Advice:** Special Pricing Arrangements apply

3.11 The Secretariat proposed that bortezomib for the treatment of MM be listed as a Restricted benefit, given the proposed listing is very brief due to the absence of any

further clinical, treatment, patient criteria or prescriber instructions that may otherwise need to be acknowledged by a prescriber. The PBAC considered that this would be appropriate.

Daratumumab monotherapy

3.12 Table 2 presents the proposed eligibility and ineligibility criteria for the purpose of providing compassionate supply of daratumumab monotherapy. The criteria are based on clinical trials and are narrower than the TGA approved indication.

Table 2: Criteria for the compassionate supply of daratumumab monotherapy

Eligibility criteria:
[redacted]
Ineligibility criteria
[redacted]

ALT = alanine aminotransferase; COPD = chronic obstructive pulmonary disease; ECOG = Eastern Cooperative Oncology Group; FEV1 = forced expiratory volume in 1 second; IMid = immunomodulatory imide drug; IMWG = International Myeloma Working Group; MM = multiple myeloma; ULN = upper limit of normal
Source: Table 2-1, pp13-14 of the minor resubmission

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

4 Comparator

4.1 The previous major submissions proposed Bd as the primary comparator, which was accepted by the PBAC. The comparator was unchanged in this minor resubmission.

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

5 Consideration of the evidence

Sponsor hearing

5.1 There was no hearing for this item as it was a minor submission.

Consumer comments

5.2 The PBAC noted and welcomed the input from individuals (99), health care professionals (1) and organisations (3) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with daratumumab including improved response rates and survival, an improved quality of life and few side effects.

5.3 The PBAC noted the advice received from (i) The Leukaemia Foundation, (ii) Myeloma Australia, and (iii) South East Myeloma Support Group, South Australia, which again supported the submission, outlining the clinical need for DBd in providing optimal management of myeloma and reiterating the patients' views. The PBAC noted that this advice was supportive of the evidence provided in the submission.

Clinical data

5.4 In November 2019 the PBAC considered that the clinical data supported the claims that DBd demonstrated superior efficacy and inferior safety compared to Bd.

5.5 No further clinical data were presented in this minor resubmission. As per the November 2019 resubmission, the economic model presented in the minor resubmission applies data from the interim analysis 5 (IA5) data-cut of the CASTOR trial.

Economic analysis

5.6 The November 2019 resubmission presented two incremental cost-effectiveness ratios (ICERs). Although both applied a 20 year time horizon and adjusted for crossover:

- the first applied an exponential extrapolation to overall survival (OS) (which was the best fit), resulting in an ICER of $45,000 - $75,000 per quality adjusted life year (QALY); whereas
- the second applied a generalised gamma extrapolation to OS (which was the most conservative), resulting in an ICER of $75,000 - $105,000 per QALY.

5.7 In November 2019 the PBAC considered that the economic model for DBd as a second-line MM treatment should use a 15 year time horizon, adjust for crossover and apply the generalised gamma function to OS. In addition, the PBAC considered that the extrapolation of the OS curves should appropriately represent the expected survival estimates, rather than being simply truncated at 15 years (paragraph 7.13, daratumumab Public Summary Document (PSD), November 2019). The PBAC reiterated that an ICER within the range of $45,000 to $75,000 per QALY would be appropriate, as this is what was previously accepted in the July 2017 consideration of carfilzomib plus dexamethasone (para 7.13, daratumumab PSD, November 2019).

5.8 The minor resubmission presented a revised cost-effectiveness analysis which addressed the concerns raised by the PBAC in its evaluation of the November 2019 major resubmission. Table 3 presents a comparison of the key components of the November 2019 economic evaluation and the changes made in this resubmission.

Table 3: The key changes to the November 2019 economic evaluation in the July 2020 minor resubmission

Component	Description	Changes made in the July 2020 minor resubmission
Time horizon	20 years (lifetime) The PBAC considered that a 15 year time horizon could be reasonable for patients treated in the second-line setting, but only if the extrapolation of the OS curves appropriately represented the expected survival estimates, rather than if the curves were simply truncated at 15 years (para 7.12, daratumumab PSD, November 2019)	15 years
Convergence applied?	No The PBAC considered that the generalised gamma extrapolation to the OS Kaplan Meier curves, which resulted in 12.8% of DBd patients alive at 15 years, overestimated survival (para 7.12, daratumumab PSD, November 2019)	Yes, linear convergence factor applied to DBd OS arm from Year 10 to 15
Adjustment for treatment switching	Presented in the base case The PBAC considered that the OS cross-over adjusted analysis, which was adjusted using the IPCW, was appropriate (para 7.7, daratumumab PSD, November 2019)	No change
OS transitions beyond the trial time	Exponential (best fit) Generalised gamma (conservative scenario)	Generalised gamma
Costs	As presented in the November 2019 submission. Bortezomib = $[redacted]/mg Infusion site reactions = $1,320.66	Updated unit costs (e.g., changes to medicine prices, fees and mark-ups) to reflect prices as at 28 January 2020; Updated separations of usage for estimating costs of hospitalisations for specific AEs Bortezomib = $[redacted]/mg Infusion site reactions = $1,192.63

AE = adverse event; DBd = daratumumab + bortezomib + dexamethasone; IPCW = inverse probability of censoring weights; OS = overall survival; PBAC = Pharmaceutical Benefits Advisory Committee; PSD = Public Summary Document
Source: Table 3-1, p23 of the minor resubmission

5.9 Figure 1 presents the Markov traces for the economic model. The impact of convergence reduces the time spent by DBd patients in the progressed alive state, i.e. patients die more quickly than in the no convergence scenario. The Markov traces presented below have a time horizon of 20 years, compared to the model time horizon of 15 years.

Figure 1: Markov traces for the economic evaluation of DBd versus Bd in second-line MM patients (IA5 data-cut; IPCW adjustment for cross-over) with OS convergence (Left panel) and without OS convergence (Right panel)*

Bd = bortezomib + dexamethasone; DBd = daratumumab + bortezomib + dexamethasone; IPCW = inverse probability of censoring weights; MM = multiple myeloma; OS = overall survival; PFS = progression free survival
Source: Figure 3, p19 of the minor resubmission
* Time horizon in figures is 20 years, compared to 15 years in the economic model.

5.10 The results of the stepped economic evaluation, using the published prices of lenalidomide, pomalidomide and carfilzomib, are presented in Table 4.

Table 4: Results of the stepped economic evaluation

	DBd	Bd	Increment
Step 1: Trial based (47 months), with IPCW cross-over adjustment			
Costs	$	$	$
QALYs			
ICER			**$**
Step 2: 20 year time horizon (OS = generalised gamma extrapolation)			
Costs	$	$	$
QALYs			
ICER			**$**
Step 3: 15 year time horizon			
Costs	$	$	$
QALYs			
ICER			**$**
Step 4: Application of linear convergence from Year 10			
Costs	$	$	$
QALYs			
ICER			**$**

Bd = bortezomib + dexamethasone; DBd = daratumumab + bortezomib + dexamethasone; ICER = incremental cost-effectiveness ratio; IPCW = inverse probability of censoring weights; OS = overall survival; QALY = quality-adjusted life year
Source: Tables 3-2 to 3-5, pp31-34 of the minor resubmission

5.11 The base case model resulted in an ICER of $75,000 - $105,000 per QALY.

5.12 Sensitivity analyses presented in the minor resubmission are reported in Table 5.

Table 5: Results of sensitivity analyses presented in the minor resubmission

Parameter	Value used	Incremental cost	Incremental QALY	ICER per QALY
Base case	**-**	**$**		**$**
No adjustment for cross-over (base case: IPCW adjustment)	ITT	$		$
Time horizon (base case = 15 years)	20 years	$		$
Cost of bortezomib (base case = $ /mg)	$ /mg	$		$
Cost of infusion site reactions (base case = $1,192.63)	$1,320.66	$		$
OS extrapolation (base case = generalised gamma)	Exponential	$		$
	Weibull	$		$
	Gompertz	$		$
Convergence type (base case = linear)	None	$		$
	Concave	$		$
	Convex	$		$
	Exponential	$		$

ICER = incremental cost-effectiveness ratio; IPCW = inverse probability of censoring weights; ITT = intention to treat; OS = overall survival; QALY = quality-adjusted life year
Source: Table 3-6, p35 of the minor submission

5.13 The minor resubmission noted that the proposed base case ICER of $75,000 - $105,000 per QALY was not in the range considered appropriate ($45,000 to $75,000 per QALY) by the PBAC in November 2019. The minor resubmission stated that the ICER does not take into consideration the additional QALYs that would result from the compassionate supply of daratumumab monotherapy to patients who have exhausted available PBS treatments at no additional cost to the government, and that overall, the ICER was likely to be lower than that presented in Table 4.

5.14 The minor resubmission stated that the duration of daratumumab monotherapy received by more than 600 Australian patients following PBS subsidised treatment with pomalidomide as part of the sponsor's compassionate supply program (median = months; mean = months) was similar to the duration of pomalidomide, despite being used in a later stage of MM. The minor resubmission stated that this provides support to the claim that the compassionate supply of daratumumab monotherapy provides health-related quality of life benefits through time spent in the progression free state. These arguments were reiterated in the pre-PBAC response.

Drug cost/patient/course

5.15 The estimated drug cost per patient per course is presented in Table 6.

Table 6: Drug cost per patient for DBd

	DBd*		Bd	
	Within trial analysis	**CUA**	**Within trial analysis**	**CUA**
Mean dose/injection	Dara: 1,161 mg Bort: 1.92 mg Dex: 4 mg	Dara: 1,161 mg Bort: 1.92 mg Dex: 4 mg	Bort: 2.05 mg Dex: 4 mg	Bort: 2.05 mg Dex: 4 mg
Mean duration	23.6 months	NR	4.5 months	NR
Median duration	24.0 months	[redacted] months	5.2 months	[redacted] months
Cost/patient/cycle	Cycles 1-3 (DBd): $[redacted] Cycles 4-8 (DBd): $[redacted] Cycles > 8 (Dd): $[redacted]	Cycles 1-3 (DBd): $[redacted] Cycles 4-8 (DBd): $[redacted] Cycles > 8 (Dd): $[redacted]	(Bd) $[redacted]	(Bd) $[redacted]
Cost/patient/course	$[redacted] a	$[redacted] b	$[redacted] c	$[redacted] d

Bd = bortezomib + dexamethasone; Bort = bortezomib; CUA = cost utility analysis; Dara = daratumumab; DBd = daratumumab + bortezomib + dexamethasone; Dd = daratumumab + dexamethasone; Dex = dexamethasone; MMTP = Multiple Myeloma Treatment Package; NR = not reported; SPA = Special Pricing Arrangement;

Source: Compiled during evaluation. MMTP prices were used in estimating DBd costs, current SPA prices were used in estimating Bd cost.

* Daratumumab dosing = Cycles 1-3 (i.e. weeks 1-9): daratumumab is given every 7 days; Cycles 4-8 (i.e. weeks 10-24): daratumumab is given every 21 days; Cycles > 8 (i.e. weeks > 25): daratumumab is given every 28 days

a. The cost/patient/course was based on mean duration of 23.6 months (103 weeks) which included 8 initial cycles and 20 continuing cycles with daratumumab, 8 cycles of bortezomib, and 8 initial cycles and 20 continuing cycles of dexamethasone.

b. The cost/patient/course was based on median duration of [redacted] months ([redacted] weeks) which included 8 initial cycles and 22 continuing cycles with daratumumab, 8 cycles of bortezomib, and 8 initial cycles and 22 continuing cycles of dexamethasone.

c. The cost/patient/course was based on mean duration of 4.5 months (20 weeks) which included 7 cycles of bortezomib, and 7 cycles of dexamethasone.

d. The cost/patient/course was based on median duration of [redacted] months ([redacted] weeks) which included 11 cycles of bortezomib, and 11 cycles of dexamethasone.

Estimated PBS usage & financial implications

5.16 Previous daratumumab submissions presented utilisation and financial impact estimates for the listing of DBd on the PBS based on a mixed epidemiological and market share approach.

5.17 In November 2019, the PBAC considered:

- that the estimates for the number of patients initiating DBd second-line treatment presented in the November 2019 resubmission (less than 10,000 in Year 1 and approximately less than 10,000 in Years 4 to 6) were overestimated (paragraph 7.14, daratumumab PSD, November 2019).
- that the assumed uptake rates (78% in Year 1 and 81% in Year 6) should be amended to 50% in Year 1, increasing to 90% over the forward estimates (paragraph 7.15, daratumumab PSD, November 2019);
- that it was appropriate to include continuing patients, and for each yearly initiating cohort, the time to treatment discontinuation derived from the Kaplan Meier estimates in the economic model should be applied (paragraph 7.15, daratumumab PSD, November 2019); and

- updated financial estimates should include additional information around the estimated cost offsets, including any reduction in the costs of other medicines (paragraph 7.19, daratumumab PSD, November 2019).

5.18 The minor submission presented a revised financial estimates model for the PBS listing of DBd as a second-line treatment for MM based on patient level PBS utilisation data provided by the DUSC Secretariat. The key inputs are presented in Table 7.

Table 7: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Second-line incident population	Logarithmic extrapolation of DUSC Secretariat PBS/RPBS utilisation data	Reasonable
Uptake rate	50% in Year 1 increasing linearly to 90% in Year 6	As recommended by PBAC in November 2019
Duration of DBd treatment	Application of the Kaplan-Meier time to treatment discontinuation from the economic model (extrapolated from the CASTOR trial) to each annual cohort of patients initiation therapy	As recommended by PBAC in November 2019
Cost of daratumumab (effective price)	100 mg = $[redacted] 400 mg = $[redacted]	Unchanged from November 2019
Cost of bortezomib (effective price)	3 mg = $[redacted]	Unchanged from November 2019
Market shares of first, second and third and later-lines of therapy with and without DBd	Based on advice from Australian MM clinicians	Consistent with advice received at the PBAC multiple myeloma clinical consultation held in October 2019

DBd = daratumumab + bortezomib + dexamethasone; DUSC = Drug Utilisation Sub-Committee; MM = multiple myeloma; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

5.19 The DUSC Secretariat PBS/RPBS utilisation data for MM provided the number of eligible patients across each line of therapy, and the utilisation of each treatment in each line of therapy.

5.20 The revised model also estimates the change in use and cost of other MM medicines resulting from the PBS/RPBS listing of DBd in the RR setting, as well as the impact of PBS listing DBd as a second-line treatment on the relative use of bortezomib and lenalidomide in the newly diagnosed setting.

5.21 The base case financial estimates do not include lenalidomide as a maintenance treatment post ASCT or first-line lenalidomide in combination with bortezomib and dexamethasone (RVd). However, the minor resubmission provided two alternate scenario analyses:

- Alternative base case 1: The use of lenalidomide as maintenance treatment post ASCT (PBS listed 1 April 2020) is included, but the use of RVd is not, reflecting the PBS listings at the time of the minor resubmission. No further information relating to this analysis is presented in the overview as it is not applicable to the current situation; and

- Alternative base case 2: Both the use of lenalidomide as maintenance treatment post ASCT and the use of RVd (PBS recommended, not PBS listed at the time of the minor resubmission but listed on 1 June 2020) are included. This analysis is representative of the current situation. Further information regarding this analysis is presented in paragraphs 5.53 to 5.56 and Tables 22 and 23. In addition, results from Alternative base case 2 are presented, where applicable, alongside the base case analyses below. The PBAC considered that this analysis best represented the current situation.

Estimated use and cost of daratumumab in the second-line setting

5.22 The model uses a market share approach. To estimate the number of patients eligible for initiating DBd the historical number of second-line initiations from the full PBS/RPBS data set were extrapolated to future years using a logarithmic function (Figure 2). This resulted in an 8.1% reduction in DBd eligible, second-line patients over the six-year forward estimates compared to the November 2019 resubmission.

Figure 2: Extrapolation of number of second-line treatment initiations

Source: Figure 4-1, p43 of the minor resubmission

5.23 Based on advice from the PBAC the revised model applied an uptake rate of 50% in Year 1, linearly increasing to 90% in Year 6.

5.24 Kaplan Meier treatment duration data from the CASTOR trial was used to estimate the duration of daratumumab treatment.

5.25 The estimated cost of daratumumab to the PBS/RPBs is presented in Table 8.

Table 8: Estimated daratumumab utilisation and cost to the PBS/RPBS (effective price)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Eligible 2nd-line patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DBd uptake	50%	58%	66%	74%	82%	90%
DBd initiations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Initial dara prescriptions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Continuing dara prescriptions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total dara prescriptions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost of dara to the PBS/RPBS	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]
Alternative base case 2 Total dara prescriptions **Cost to PBS/RPBS**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
November 2019 DBd initiations Total dara prescriptions Cost to PBS/RPBS	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]	$ [redacted]

dara = daratumumab; DBd = daratumumab + bortezomib + dexamethasone; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme
Source: Tables 4-1 to 4-4, pp43-45 of the minor resubmission

The redacted table shows that at Year 6, the estimated number of patients was less than 10,000 and the net cost to the PBS would be more than $100 million.

5.26 Using the effective price, the cost of daratumumab is estimated to be $30 million - $60 million in Year 1, increasing to more than $100 million in Year 5 and totalling more than $100 million over the first five years of listing. This is an 19.9% reduction over the five year period compared to the November 2019 resubmission (more than $100 million), which has been driven by the changes to the number of initiating patients and the uptake rate, as the proposed price has not changed.

5.27 The cost of daratumumab in Alternative base case 2 is $30 million - $60 million in Year 1, increasing to more than $100 million in Year 5 and totalling more than $100 million over the first five years of listing. This is a 32.2% reduction over the five year period compared to the November 2019 resubmission (more than $100 million).

Estimated change in use and cost of other MM treatments

5.28 In November 2019, the PBAC requested that any updated financial estimates provide additional information around the estimated cost offsets, including any reduction in the costs of other medicines (paragraph 7.19, daratumumab PSD, November 2019).

5.29 If listed, DBd is expected to replace current therapies in the second-line setting, displacing some to the third or later-line settings. In addition, as daratumumab in combination with lenalidomide and dexamethasone (DLd) is not proposed for PBS listing, the second-line listing of DBd might result in an increased use of lenalidomide relative to bortezomib in the newly diagnosed setting.

5.30 The revised model estimates the:

- change in use and cost of other MM therapies in the RR setting as a result of PBS listing of DBd as a second-line treatment;
- impact of the changing relative use of lenalidomide and bortezomib in the newly diagnosed setting; and
- combined total impact of listing DBd on the PBS.

Estimated change in use and cost of second, third and later-line therapies

5.31 Table 9 presents the historical market share of second-line initiations, as provided by the DUSC Secretariat (2014 to 2019), and the projected market share over the forward estimates period in the absence of PBS listed DBd, as assumed in the minor resubmission from advice provided by the DUSC Secretariat based on a consultation with Australian MM clinicians (2020 to 2025). Table 10 presents the market shares in the presence of PBS listed DBd.

Table 9: Historical and predicted market share of second-line initiations in the absence of DBd

	2014	2015	2016	2017	2018	2019	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Bortezomib	28.0%	25.4%	21.2%	17.9%	21.2%	25.6%						
Lenalidomide	36.5%	30.7%	29.0%	27.5%	41.6%	44.6%						
Thalidomide	35.5%	43.9%	49.8%	54.5%	27.2%	20.0%						
Carfilzomib	0.0%	0.0%	0.0%	0.0%	9.5%	8.3%						
Pomalidomide	0.0%	0.0%	0.0%	0.0%	0.6%	1.5%						

DBd = daratumumab + bortezomib + dexamethasone
Source: Tables 4-5 and 4-6, pp46-47 or the minor resubmission

Table 10: Historical and predicted market share of second-line initiations in the presence of DBd

	2014	2015	2016	2017	2018	2019	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
DBd	-	-	-	-	-	-						
Bortezomib	28.0%	25.4%	21.2%	17.9%	21.2%	25.6%						
Lenalidomide	36.5%	30.7%	29.0%	27.5%	41.6%	44.6%						
Thalidomide	35.5%	43.9%	49.8%	54.5%	27.2%	20.0%						
Carfilzomib	0.0%	0.0%	0.0%	0.0%	9.5%	8.3%						
Pomalidomide	0.0%	0.0%	0.0%	0.0%	0.6%	1.5%						

DBd = daratumumab + bortezomib + dexamethasone
Source: Tables 4-5 and 4-7, pp46-47 of the minor resubmission

5.32 In the presence of PBS listed DBd it was assumed that the use of lenalidomide and carfilzomib in the second-line setting would decrease. There is a net increase in the use of bortezomib which is driven by its use in combination with daratumumab.

5.33 Tables 11 and 12 present the third and later-line market shares in the absence and presence of PBS listed DBd.

Table 11: Historical and predicted market share of third and later-line initiations in the absence of DBd

	2014	2015	2016	2017	2018	2019	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Bortezomib	51.7%	35.6%	26.7%	23.1%	14.4%	14.3%	[redacted]					
Lenalidomide	46.9%	48.1%	48.7%	54.5%	42.0%	38.1%						
Thalidomide	1.3%	2.0%	1.5%	1.1%	0.5%	0.5%						
Carfilzomib	0.0%	0.0%	0.0%	0.0%	27.2%	26.0%						
Pomalidomide	0.0%	14.4%	23.2%	21.3%	15.9%	21.2%						

DBd = daratumumab + bortezomib + dexamethasone
Source: Tables 4-8 and 4-9, pp48-4-97 or the minor resubmission

Table 12: Historical and predicted market share of third and later-line initiations in the presence of DBd

	2014	2015	2016	2017	2018	2019	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Bortezomib	51.7%	35.6%	26.7%	23.1%	14.4%	14.3%	[redacted]					
Lenalidomide	46.9%	48.1%	48.7%	54.5%	42.0%	38.1%						
Thalidomide	1.3%	2.0%	1.5%	1.1%	0.5%	0.5%						
Carfilzomib	0.0%	0.0%	0.0%	0.0%	27.2%	26.0%						
Pomalidomide	0.0%	14.4%	23.2%	21.3%	15.9%	21.2%						

DBd = daratumumab + bortezomib + dexamethasone
Source: Tables 4-8 and 4-10, pp48-4-97 or the minor resubmission

5.34 Each year, a portion of the prevalent patients from the previous year continue to be supplied the same therapy, while a portion start the next line of treatment. In the second, third and later-line settings, a portion of patients also die each year. This is informed by the PBS 10% sample analysis, and is the same approach followed in the previous submissions.

5.35 Table 13 presents the change in the number of prescriptions dispensed and the cost of MM therapies, other than daratumumab in the RR setting (second, third and later-lines). There is a net increase in the use of bortezomib which is driven by its use in combination with daratumumab. The use of carfilzomib and lenalidomide was expected to decrease due to replacement and displacement by DBd, as well as a delay in patients progressing to third-line therapy. The minor resubmission used the proposed effective weighted price of bortezomib across all settings and the published prices of the other therapies (lenalidomide, carfilzomib and pomalidomide).

Table 13: Estimated change in second, third and later-line prescriptions dispensed and cost if DBd is PBS listed

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Change in prescriptions dispensed						
Bortezomib						
Lenalidomide						
Thalidomide						
Carfilzomib						
Pomalidomide						
Change in cost						
Bortezomib	$	$	$	$	$	$
Lenalidomide	-$	-$	-$	-$	-$	-$
Thalidomide	-$	-$	-$	-$	-$	-$
Carfilzomib	-$	-$	-$	-$	-$	-$
Pomalidomide	$	-$	-$	-$	-$	-$
Total change	**-$**	**-$**	**-$**	**-$**	**-$**	**-$**

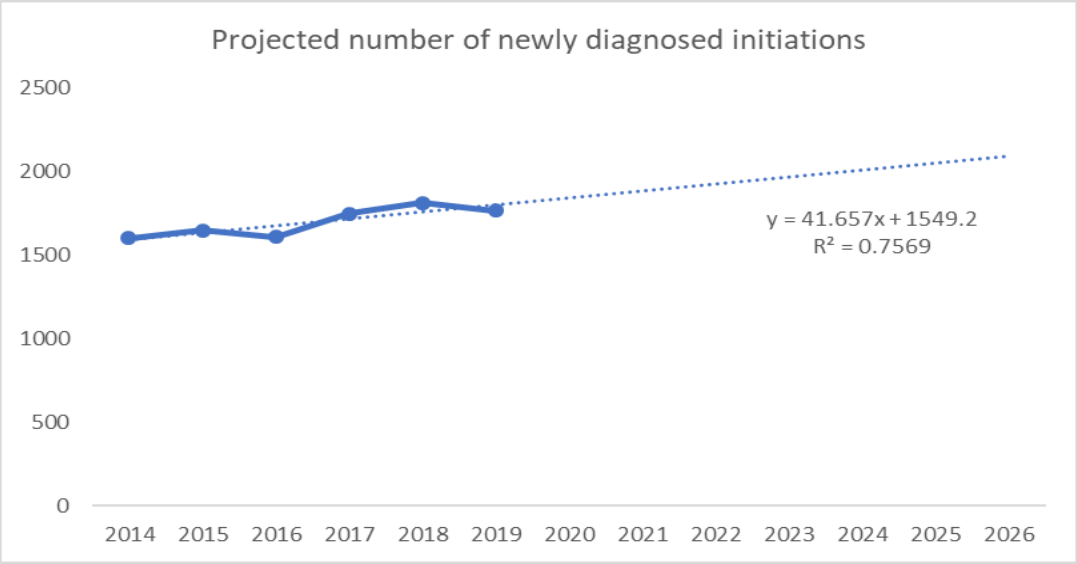
DBd = daratumumab + bortezomib + dexamethasone; PBS = Pharmaceutical Benefits Scheme
Source: Tables 4-11 and 4-12, p50 of the minor submission

5.36 The minor resubmission, using published prices for lenalidomide, carfilzomib and pomalidomide and the proposed effective price of bortezomib, estimated that the PBS listing of DBd would result in a more than $100 million reduction in current second, third and later-line therapies over the first six years.

Estimated change in use and cost of first-line therapies

5.37 The minor resubmission projected the number of newly diagnosed patients initiating therapy based on a linear extrapolation of the historical initiations in this setting (Figure 3). This resulted in less than 10,000 newly diagnosed MM patients in Year 1, increasing to less than 10,000 in Year 6.

Figure 3: Extrapolation of number of newly-diagnosed treatment initiations



Source: Figure 4-2, p51 of the minor resubmission

5.38 Table 14 presents the historical market share of first-line initiations, as provided by the DUSC Secretariat (2014 to 2019), and their projected market share over the forward estimates period in the absence of PBS listed DBd, as assumed in the minor resubmission from information provided by the DUSC Secretariat based on advice from a consultation with Australian MM clinicians (2020 to 2025). Table 15 presents the market shares in the presence of PBS listed DBd.

Table 14: Historical and predicted market share of first-line initiations in the absence of DBd

	2014	2015	2016	2017	2018	2019	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Bortezomib (TE) no lenalidomide maintenance	25.9%	29.9%	28.0%	25.0%	29.7%	22.7%	[redacted]					
Bortezomib (TI)	41.4%	45.5%	50.1%	41.2%	42.0%	47.9%	[redacted]					
Lenalidomide	0.0%	0.0%	0.0%	24.7%	25.4%	27.9%	[redacted]					
Thalidomide	32.8%	24.6%	21.9%	9.1%	2.9%	1.6%	[redacted]					

DBd = daratumumab + bortezomib + dexamethasone; TE = transplant eligible; TI = transplant ineligible
Source: Tables 4-13 and 4-14, pp51-52 or the minor resubmission

Table 15: Historical and predicted market share of first-line initiations in the presence of DBd

	2014	2015	2016	2017	2018	2019	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Bortezomib (TE) no lenalidomide maintenance	25.9%	29.9%	28.0%	25.0%	29.7%	22.7%	[redacted]					
Bortezomib (TI)	41.4%	45.5%	50.1%	41.2%	42.0%	47.9%	[redacted]					
Lenalidomide	0.0%	0.0%	0.0%	24.7%	25.4%	27.9%	[redacted]					
Thalidomide	32.8%	24.6%	21.9%	9.1%	2.9%	1.6%	[redacted]					

DBd = daratumumab + bortezomib + dexamethasone; TE = transplant eligible; TI = transplant ineligible
Source: Tables 4-13 and 4-15, pp51-52 of the minor resubmission

5.39 It is expected that if DBd is PBS listed in the second-line, the relative use of lenalidomide compared to bortezomib in the newly diagnosed setting will increase by a larger extent than if DBd is not PBS listed.

5.40 The estimated number of patients initiating each therapy in the newly diagnosed setting joins the pool of prevalent patients supplied the therapy in this setting each year. The proportion of patients who continue to be supplied the same therapy in the following year is derived from the full PBS/RPBS utilisation data and the proportion of patients transitioning out of the first-line setting or dying is derived from the PBS 10% sample analysis. From the net number of prevalent patients supplied a therapy each year, the number of prescriptions dispensed for the therapy is estimated based on the ratio of the number of prescriptions dispensed to the number of prevalent patients supplied the therapy derived from the full PBS/RPBS utilisation data.

5.41 Table 16 presents the change in the number of prescriptions dispensed and the cost of MM therapies in the newly diagnosed setting. The minor resubmission used the proposed effective weighted price of bortezomib across all settings and the published prices of the other therapies.

Table 16: Estimated change in first-line prescriptions dispensed and cost if DBd is PBS listed

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Change in prescriptions dispensed						
Bortezomib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lenalidomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Thalidomide	0	0	0	0	0	0
Change in cost						
Bortezomib	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Lenalidomide	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Thalidomide	$0	$0	$0	$0	$0	$0
Total change	**$**[redacted]	**$**[redacted]	**$**[redacted]	**$**[redacted]	**$**[redacted]	**$**[redacted]

DBd = daratumumab + bortezomib + dexamethasone; PBS = Pharmaceutical Benefits Scheme
Source: Tablets 4-16 and 4-17, p53 of the minor submission

5.42 The minor resubmission estimated that the PBS listing of DBd would result in a $30 million - $60 million increase in first-line therapies over the first six years.

Estimated total cost offsets

5.43 Table 17 presents the estimated overall change in the number of prescriptions (excluding daratumumab) resulting from PBS listing DBd in the second-line setting.

Table 17: Total change in number of other MM therapy prescriptions dispensed

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Bortezomib (ND)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lenalidomide (ND)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bortezomib (RR)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lenalidomide (RR)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Thalidomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Carfilzomib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pomalidomide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total change in other therapy prescriptions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

MM = multiple myeloma; ND = newly diagnosed; RR = relapsed and/or refractory
Source: Table 4-18, p54 of the minor resubmission

5.44 The minor resubmission estimated that the number of prescriptions dispense for MM therapies other than daratumumab would increase by 10,000 - 50,000 over the six-year forward estimates period. The net increase is primarily driven by the increase in the number of bortezomib prescriptions in the RR setting.

5.45 Table 18 presents the estimated overall change in the cost of MM therapies (excluding daratumumab) resulting from PBS listing DBd in the second-line setting. The minor resubmission used the proposed effective weighted price of bortezomib across all settings and the published prices of the other therapies.

Table 18: Total change in the cost of other MM therapies

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Bortezomib (ND)	$	$	$	$	$	$
Lenalidomide (ND)	$	$	$	$	$	$
Bortezomib (RR)	$	$	$	$	$	$
Lenalidomide (RR)	-$	-$	-$	-$	-$	-$
Thalidomide	-$	-$	-$	-$	-$	-$
Carfilzomib	-$	-$	-$	-$	-$	-$
Pomalidomide	$	-$	-$	-$	-$	-$
Total change in other therapy costs	**-$**	**-$**	**-$**	**-$**	**-$**	**-$**

MM = multiple myeloma; ND = newly diagnosed; RR = relapsed and/or refractory
Source: Table 4-19, p54 of the minor resubmission

5.46 The minor resubmission estimated that the cost of MM therapies other than daratumumab would be reduced by more than $100 million over the six-year forward estimates period. The net reduction was primarily driven by the reduced use of lenalidomide and carfilzomib in the RR setting.

Change in the cost of bortezomib

5.47 The change in the cost of bortezomib was driven by two factors:

- The net increase in use (the use of bortezomib in the second-line setting as part of DBd exceeds the reduction in first-line use); and
- The proposed reduction in the effective price in the if DBd is PBS listed.

5.48 Table 19 presents the estimated saving in the cost of bortezomib with the proposed of bortezomib across all settings.

Table 19: Change in cost of bortezomib

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Change in cost - current pricing	$	$	$	$	$	$
Change in cost - proposed pricing	$	$	$	$	$	$
Impact of proposed price reduction	-$	-$	-$	-$	-$	-$

Source: Table 4-20, p55 of the minor resubmission

5.49 If daratumumab is listed on the PBS for second-line therapy, the implementation of the proposed of bortezomib across all settings is estimated to result in a cost saving of $30 million - $60 million over the first six years, compared to if daratumumab was PBS listed and the current pricing structure was retained.

Estimated net financial implications

5.50 Table 20 presents the estimated net cost to the PBS/RPBS if daratumumab is listed on the PBS as a second-line therapy. The minor resubmission used the proposed effective price of daratumumab and the proposed effective weighted price of bortezomib across all settings and the published prices of the other therapies. The PBAC noted

that the financial estimates are subject to variation when the appropriate effective prices are applied to all therapies.

Table 20: Estimated net financial implications of listing DBd on the PBS/RPBS

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Cost of daratumumab	$	$	$	$	$	$
Change in other therapy costs	-$	-$	-$	-$	-$	-$
Net impact on PBS + RPBS	**$**	**$**	**$**	**$**	**$**	**$**
Alternative base case 2	**$**	**$**	**$**	**$**	**$**	**$**
November 2019 submission	$	$	$	$	$	$

DBd = daratumumab + bortezomib + dexamethasone; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

Source: Table 4-21, p56 of the minor submission

5.51 The minor resubmission estimated that listing DBd as a second-line MM therapy would result in a net cost to the PBS/RPBS of $30 million - $60 million in Year 1, increasing to $60 million - $100 million in Year 6 and totalling more than $100 million over the first six years for less than 10,000 initiating patients. In November 2019 the total cost over the first six years of listing was more than $100 for approximately less than 10,000 initiating patients.

5.52 The minor resubmission estimated that the listing of DBd as a second-line MM therapy would result in a net increase in costs for the MBS of less than $10 million in Year 1, less than $10 million in Year 6 and totalling less than $10 million over the first six years. The total net cost to Government in presented in Table 21.

Table 21: Net financial implications of listing DBd to Government.

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Net impact on PBS	$	$	$	$	$	$
Net impact on RPBS	$	$	$	$	$	$
Net impact on MBS	$	$ 9	$	$	$	$
Net impact on health budget	**$**	**$**	**$**	**$**	**$**	**$**

DBd = daratumumab + bortezomib + dexamethasone; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

Source: Table 4-24, p58 of the minor resubmission

Alternate analyses

Alternative base case 2

5.53 Alternative base case 2 reflects the PBS listings at the time of the PBAC consideration of the daratumumab resubmission, i.e. both lenalidomide use as a maintenance treatment post ASCT (PBS listed 1 April 2020) and first-line use of RVd (PBS recommended August 2019, PBS listed 1 June 2020) are included.

5.54 The minor resubmission expects that the availability of both lenalidomide maintenance post ASCT and RVd in the first-line setting will result in an increase in the use of both lenalidomide and bortezomib. It was expected that the majority of post-transplant patients would receive lenalidomide maintenance treatment. In the

transplant ineligible setting, the use of RVd was modelled to increase rapidly and largely replace doublet lenalidomide or bortezomib-based therapies. Overall, the RVd market share across both transplant eligible and transplant ineligible settings was modelled to start at 45.6% in Year 1 and increase to 65.6% in Year 6. As the majority of transplant ineligible patients will likely receive RVd or bortezomib followed by lenalidomide maintenance, the PBS listing of DBd was not expected to influence the use of lenalidomide in the first-line setting (see Table 22).

Table 22: Market share assumptions in the first-line setting with lenalidomide maintenance post ASCT and RVd available with/without DBd available in the second-line setting

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Without DBd in 2nd-line						
Bortezomib (TE) lenalidomide maintenance						
Bortezomib (TI)						
Lenalidomide						
Thalidomide						
Bortezomib + lenalidomide (TI)						
Bortezomib (TE) lenalidomide maintenance						
Bortezomib + lenalidomide (TE)						
With DBd in 2nd-line						
Bortezomib (TE) no lenalidomide maintenance						
Bortezomib (TI)						
Lenalidomide						
Thalidomide						
Bortezomib + lenalidomide (TI)						
Bortezomib (TE) lenalidomide maintenance						
Bortezomib + lenalidomide (TE)						

ASCT = autologous stem cell transplant; DBd = daratumumab + bortezomib + dexamethasone; RVd = lenalidomide + bortezomib + dexamethasone; TE = transplant eligible; TI = transplant ineligible
Source: Table 4-27, p61 of the minor resubmission

5.55 The minor resubmission assumed that the use of lenalidomide as maintenance treatment post ASCT and RVd would result in a delayed progression and thus, a decrease in the number of patients eligible for and initiating DBd as a second-line treatment. The pre-PBAC response stated that the patient numbers initiating second-line DBd in Alternative base case 2 were likely to be underestimated as the uptake assumptions applied to lenalidomide use, which were based on expert clinician input, were optimistic. The PBAC considered that the assumptions were reasonable given the absence of usage data.

5.56 The estimated utilisation and financial implications for daratumumab as DBd in the second-line setting with the first-line use of lenalidomide maintenance post ASCT and RVd are presented in Table 23.

Table 23: Estimated utilisation and financial implications of daratumumab in alternative base case 2

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Daratumumab prescriptions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% change versus base case	0.0%	-10.4%	-16.7%	-19.2%	-19.2%	-17.6%
Cost of daratumumab	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
% change versus base case	0.0%	-10.4%	-16.7%	-19.2%	-19.2%	-17.6%
Net cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
% change versus base case	1.3%	-9.9%	-12.0%	-8.9%	-5.4%	-3.4
Net cost for the health budget	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
% change versus base case	0.9%	-11.2%	-14.7%	-13.9%	-12.1%	-9.7%

PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme
Source: Table 4-28, p61 of the minor resubmission

Financial Management – Risk Sharing Arrangements

5.57 In the November 2019 PSD the PBAC noted that the proposed RSA consisted of two subsidisation caps beyond which [redacted]% and [redacted]% rebates would apply. The PBAC considered that a single subsidisation caps beyond which a higher rebate would apply would be appropriate.

5.58 The minor resubmission proposed a revised RSA with a single subsidisation cap beyond which a rebate of [redacted]% would apply. The subsidisation cap is set below the estimated number of base case daratumumab prescriptions in second-line MM and is similar the numbers estimated in Alternative base case 2 (see Table 24). The pre-PBAC response stated that irrespective of the scenario used, the proposed RSA reduces the costs of second-line daratumumab to the PBS to between more than $100 million and more than $100 million over five years.

Table 24: The proposed RSA for daratumumab

Year	Year 1	Year 2	Year 3	Year 4	Year 5	Year 1-5
Number of dara prescriptions – base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of dara prescriptions – Alternative base case 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subsidisation cap	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Value of subsidisation cap	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Base case						
Cost of dara without RSA	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost of dara with RSA	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Change in cost due to RSA	-4.3%	-11.5%	-12.5%	-15.9%	-21.5%	-15.0%
Alternative base case 2						
Cost of dara without RSA	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost of dara with RSA	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Change in cost due to RSA	-4.3%	-3.0%	-	-	-6.4%	-2.8%

dara = daratumumab; RSA = risk sharing arrangement
Source: Table 5-1, p64 of the minor resubmission

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

6 PBAC Outcome

6.1 The PBAC recommended the listing of daratumumab, for use in combination with bortezomib and dexamethasone (DBd), as a second-line treatment for patients with multiple myeloma (MM), on the basis that it should be available only under special arrangements under the Section 100 – Efficient Funding of Chemotherapy program. The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of daratumumab would be acceptable if the incremental cost effectiveness ratio (ICER) was reduced to be less than $75,000 per quality adjusted life year (QALY).

6.2 The PBAC was satisfied that DBd provides, for some patients, a significant improvement in efficacy over bortezomib plus dexamethasone (Bd).

6.3 The PBAC noted the large number of consumer comments that described a range of benefits associated with DBd treatment including improved survival, improved quality of life and fewer side effects compared to currently available treatments.

6.4 The PBAC recalled that it had previously considered the proposed clinical place in therapy as a second-line treatment only was reasonable provided daratumumab monotherapy was available to eligible patients in later-line settings on a compassionate basis. The PBAC considered that the compassionate supply of daratumumab to all eligible MM patients who have no other PBS-funded treatment options addressed concerns regarding equity of access.

6.5 The PBAC, noting that no new clinical data was provided in the minor resubmission, recalled that it had previously considered that DBd provided important clinical benefits over the nominated comparator, Bd, albeit with an inferior safety profile.

6.6 The PBAC recalled that in November 2019 it had considered that the economic model for DBd as a second-line MM treatment should apply a 15 year time horizon in which the extrapolation of the overall survival (OS) curves appropriately represented the expected survival estimates, adjust for crossover, apply the generalised gamma function to OS and result in an ICER within the range of $45,000 to $75,000 per QALY, for consistency with the ICER previously accepted in the July 2017 consideration of carfilzomib plus dexamethasone for the treatment of relapsed and/or refractory (RR) MM.

6.7 The PBAC noted that the minor resubmission presented a revised economic model which applied a 15 year time horizon, applied a linear convergence factor to the DBd OS arm from Year 10 to Year 15, adjusted OS for crossover, applied the generalised gamma function to extrapolate OS and updated resource costs. The PBAC noted that these changes resulted in an ICER of $75,000 - $105,000 per QALY (using the published prices of lenalidomide, pomalidomide and carfilzomib).

6.8 The PBAC noted that the minor resubmission argued that the proposed ICER did not take into consideration the additional QALYs that would result from the

compassionate supply of daratumumab monotherapy. The PBAC considered that the cost-effectiveness of daratumumab monotherapy as a last line therapy was unknown and considered that any benefit was likely to be small, and relevant to only a small subset of patients, compared to the second-line use of DBd.

6.9 The PBAC reiterated that for daratumumab to be cost-effective, the ICER for DBd as a second line treatment would need to be in the range of $45,000 to $75,000 per QALY.

6.10 In terms of the utilisation estimates, the PBAC noted that the minor resubmission had appropriately presented revised estimates based on patient level PBS utilisation data provided by the DUSC Secretariat. The PBAC also noted that these estimates appropriately included the estimated change in use and cost of other drugs in the RR MM setting, and of bortezomib and lenalidomide in the newly diagnosed setting, resulting from the PBS-listing of DBd in the second-line setting.

6.11 The PBAC considered that the utilisation estimates in Alternative base case 2, which included the first-line use of lenalidomide as maintenance treatment post-autologous stem cell transplant (ASCT) and in combination with bortezomib and dexamethasone (RVd) appropriately represented the current situation. The PBAC noted that based on the estimated expenditure in Alternative base case 2, listing daratumumab on the PBS/RPBS would cost approximately more than $100 million over the first five years of listing. The PBAC considered that Alternative base case 2 estimates were informed by a robust analysis of the current use of MM medicines through the PBS and were the most accurate reflection of the likely utilisation in this market should DBd list on the PBS.

6.12 The PBAC noted the minor resubmission proposed a Risk Sharing Arrangement (RSA) which consisted of a single subsidisation cap, beyond which an [redacted]% rebate would apply. The PBAC noted that the base case estimates in combination with the RSA as proposed in the submission resulted in a significant reduction of the net cost for daratumumab [redacted]. However, the PBAC noted that the base case was no longer appropriate due to the subsequent listing changes as described in paragraph 6.11. Application of the sponsor's proposed RSA to the Alternative base case 2 estimates would reduce the PBS/RPBS cost for listing daratumumab to approximately more than $100 million, a saving of [redacted]% over the first five years of listing. The PBAC considered that to achieve [redacted] listing for daratumumab, it would be appropriate to apply a further reduction to the Alternative base case 2 estimates of daratumumab utilisation [redacted], and that this approach would set an appropriate basis for an RSA.

6.13 The PBAC noted the cost-effectiveness of DBd relied on a price reduction for bortezomib as outlined in paragraphs 3.7 and 3.8.

6.14 The PBAC noted that the restriction is considered complex due to existing variance in the type of authority approval methods for MM listed drugs and a desire from the Department to address these variances systematically and correct them if needed. The

PBAC noted that flow-on changes would be required to the current bortezomib listings to allow combination use with daratumumab's second-line MM treatment only indication. The PBAC further recommended that all of the MM indications for bortezomib could be simplified into a single restricted benefit listing, subject to daratumumab being listed and the revised weighted prices for each of the bortezomib MM indications and their weightings are agreed to between the Department and sponsor.

6.15 The PBAC recommended that a 'grandfather' listing be in place for 12 months to transition any non-PBS subsidised supply to PBS-subsidise supply provided that the patient would have met the initial treatment criteria applying to a non-grandfathered patient.

6.16 The PBAC advised that daratumumab is not suitable for prescribing by nurse practitioners as antineoplastic agents are currently considered to be out of scope for prescribing by nurse practitioners.

6.17 The PBAC advised that the Early Supply Rule should not apply to daratumumab.

6.18 Under Section 101(3BA) of the *National Health Act 1953*, the PBAC advised that daratumumab should not be treated as interchangeable with any other drugs on an individual patient basis.

6.19 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met. Specifically the PBAC found that:

a) Treatment with daratumumab is expected to provide a substantial and clinically relevant improvement in efficacy over alternative therapies.
b) Treatment with daratumumab is not expected to address a high and urgent unmet clinical need.
c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

6.20 The PBAC advised that this submission would not meet the criteria for an Independent Review as it received a positive recommendation.

Outcome:
Recommended

7 Recommended listing

7.1 Add new medicinal product:

Name, Restriction, Manner of administration and form	PBS item code	Max. Amount	№.of Rpts	Manufacturer
DARATUMUMAB Injection	NEW (Public) NEW (Private)	1920 mg	8	Janssen-Cilag Pty Ltd
Available brands				
Darzalex (daratumumab 100 mg/5 mL injection, 5 mL vial)				
Darzalex (daratumumab 400 mg/20 mL injection, 20 mL vial)				

Restriction Summary [new] / Treatment of Concept: [new]

Concept ID (for internal Dept. use)	**Category / Program:** Section 100 – Efficient Funding of Chemotherapy (Public/Private hospital)
	Prescriber type: ☒Medical Practitioners
	Restriction Type / Method: ☒Authority Required –immediate, real time assessment by Services Australia (online/telephone)
	Episodicity: Relapsed and/or refractory
	Severity: [blank]
	Condition: multiple myeloma
New 1 (variation of 7906)	**PBS Indication:** Relapsed and/or refractory multiple myeloma
	Treatment Phase: Initial treatment as second-line drug therapy for weeks 1 to 9 (administered once weekly)
7907	**Clinical criteria:**
	The condition must be confirmed by a histological diagnosis
	AND
25200 draft	**Clinical criteria:**
25199	The treatment must be in combination with bortezomib and dexamethasone
	AND
7914	**Clinical criteria:**
7913	Patient must have progressive disease after at least one prior therapy
	AND
NEW	**Clinical criteria:**
	Patient must not have progressive disease after 2 prior lines of drug therapy (i.e. use as third-line drug treatment and beyond is not PBS-subsidised)
	AND
22374	**Clinical criteria:**
22373	Patients must not be receiving concomitant PBS-subsidised carfilzomib, thalidomide or its analogues
	AND
18135	**Clinical criteria:**
18069	Patient must not have previously received this drug for this condition
7922	**Prescriber instructions:** Progressive disease is defined as at least 1 of the following: (a) at least a 25% increase and an absolute increase of at least 5 g per L in serum M protein (monoclonal protein); or (b) at least a 25% increase in 24-hour urinary light chain M protein excretion, and an absolute increase of at least 200 mg per 24 hours; or (c) in oligo-secretory and non-secretory myeloma patients only, at least a 50% increase of the difference between involved free light chain and uninvolved free light chain; or

	(d) at least a 25% relative increase and at least a 10% absolute increase in plasma cells in a bone marrow aspirate or on biopsy; or (e) an increase in the size or number of lytic bone lesions (not including compression fractures); or (f) at least a 25% increase in the size of an existing or the development of a new soft tissue plasmacytoma (determined by clinical examination or diagnostic imaging); or (g) development of hypercalcaemia (corrected serum calcium greater than 2.65 mmol per L not attributable to any other cause).
7923	**Prescriber instructions:** Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M protein.
Edit 22724	**Prescribing Instructions:** Details of: the histological diagnosis of multiple myeloma, prior treatments including name(s) of drug(s) and date of most recent treatment cycle; the basis of the diagnosis of progressive disease or failure to respond; and which disease activity parameters will be used to assess response must be documented in the patient's medical records. Confirmation of eligibility for treatment with current diagnostic reports of at least one of the following must be documented in the patient's medical records: (a) the level of serum monoclonal protein; or (b) Bence-Jones proteinuria - the results of 24-hour urinary light chain M protein excretion; or (c) the serum level of free kappa and lambda light chains; or (d) bone marrow aspirate or trephine; or (e) if present, the size and location of lytic bone lesions (not including compression fractures); or (f) if present, the size and location of all soft tissue plasmacytomas by clinical or radiographic examination i.e. MRI or CT-scan; or (g) if present, the level of hypercalcaemia, corrected for albumin concentration. As these parameters must be used to determine response, results for either (a) or (b) or (c) should be documented for all patients. Where the patient has oligo-secretory or non-secretory multiple myeloma, either (c) or (d) or if relevant (e), (f) or (g) must be documented in the patient's medical records. Where the prescriber plans to assess response in patients with oligo-secretory or non-secretory multiple myeloma with free light chain assays, evidence of the oligo-secretory or non-secretory nature of the multiple myeloma (current serum M protein less than 10 g per L) must be documented in the patient's medical records.
New 5	**Prescriber instructions:** A line of therapy is defined as 1 or more cycles of a planned treatment program. This may consist of 1 or more planned cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner. A new line of therapy starts when a planned course of therapy is modified to include other treatment agents (alone or in combination) as a result of disease progression, relapse, or toxicity, with the exception to this being the need to attain a sufficient response for stem cell transplantation to proceed. A new line of therapy also starts when a planned period of observation off therapy is interrupted by a need for additional treatment for the disease.
25745 CAR	**Administrative Advice:** Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).
7607	**Administrative Advice:** No increase in the maximum number of repeats may be authorised.
7608	**Administrative Advice:** Special Pricing Arrangements apply
New 6	**Administrative Advice:** This drug is not PBS-subsidised for use in patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are refractory to both a PI and an immunomodulatory agent, as monotherapy.

Name, Restriction, Manner of administration and form	PBS item code	Max. Amount	№.of Rpts	Manufacturer
DARATUMUMAB Injection	NEW (Public) NEW (Private)	1920 mg	4	Janssen-Cilag Pty Ltd
Available brands				
Darzalex (daratumumab 100 mg/5 mL injection, 5 mL vial)				
Darzalex (daratumumab 400 mg/20 mL injection, 20 mL vial)				

Restriction Summary: [new]

Concept ID (for internal Dept. use)	
	Category / Program: Section 100 – Efficient Funding of Chemotherapy (Public/Private)
	Prescriber type: ☒Medical Practitioners
	Restriction type / Method: ☒Authority Required – immediate, real time assessment by Services Australia (online/telephone)
New 1 (variation of 7906)	**PBS Indication:** Relapsed and/or refractory multiple myeloma
	Treatment Phase: Continuing treatment of second-line drug therapy for weeks 10 to 24 (administered every 3 weeks)
11365	**Clinical criteria:**
11364	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	AND
25200	**Clinical criteria:**
25199	The treatment must be in combination with bortezomib and dexamethasone
	AND
21513	**Clinical criteria:**
21512	Patient must not have developed disease progression while receiving treatment with this drug for this condition
	AND
22374	**Clinical criteria:**
22373	Patient must not be receiving concomitant PBS-subsidised carfilzomib, thalidomide or its analogues
7922	**Prescriber Instructions:** Progressive disease is defined as at least 1 of the following: (a) at least a 25% increase and an absolute increase of at least 5 g per L in serum M protein (monoclonal protein); or (b) at least a 25% increase in 24-hour urinary light chain M protein excretion, and an absolute increase of at least 200 mg per 24 hours; or (c) in oligo-secretory and non-secretory myeloma patients only, at least a 50% increase of the difference between involved free light chain and uninvolved free light chain; or (d) at least a 25% relative increase and at least a 10% absolute increase in plasma cells in a bone marrow aspirate or on biopsy; or (e) an increase in the size or number of lytic bone lesions (not including compression fractures); or (f) at least a 25% increase in the size of an existing or the development of a new soft tissue plasmacytoma (determined by clinical examination or diagnostic imaging); or (g) development of hypercalcaemia (corrected serum calcium greater than 2.65 mmol per L not attributable to any other cause).
7923	**Prescriber Instructions:** Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M protein.
25745 CAR	**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 the Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday)
7607	**Administrative Advice:** No increase in the maximum number of repeats may be authorised.
7608	**Administrative Advice:** Special Pricing Arrangements apply
New 7	**Administrative Advice:**

	This drug is not PBS-subsidised for use in patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are refractory to both a PI and an immunomodulatory agent, as monotherapy.

Name, Restriction, Manner of administration and form	**PBS item code**	**Max. Amount**	**№.of Rpts**	**Manufacturer**
DARATUMUMAB Injection	NEW (Public) NEW (Private)	1920 mg	5	Janssen-Cilag Pty Ltd
Available brands				
Darzalex (daratumumab 100 mg/5 mL injection, 5 mL vial)				
Darzalex (daratumumab 400 mg/20 mL injection, 20 mL vial)				

Restriction Summary: [new]

Concept ID (for internal Dept. use)	**Category / Program:** Section 100 – Efficient Funding of Chemotherapy (Public/Private)
	Prescriber type: ☒Medical Practitioners
	Restriction type / Method: ☒Authority Required – immediate/real time assessment by Services Australia (telephone/online)
New 1 (variation of 7906)	**PBS Indication:** Relapsed and/or refractory multiple myeloma
	Treatment Phase: Continuing treatment of second-line drug therapy from week 25 until disease progression (administered every 4 weeks)
11365	**Clinical criteria:**
11364	Patient must have previously received PBS-subsidised treatment with this drug for this condition
	AND
21513	**Clinical criteria:**
21512	Patient must not have developed disease progression while receiving treatment with this drug for this condition
	AND
22332	**Clinical criteria:**
22331	Patient must not be receiving concomitant PBS-subsidised bortezomib, carfilzomib, thalidomide or its analogues
7922	**Prescriber Instructions:** Progressive disease is defined as at least 1 of the following: (a) at least a 25% increase and an absolute increase of at least 5 g per L in serum M protein (monoclonal protein); or (b) at least a 25% increase in 24-hour urinary light chain M protein excretion, and an absolute increase of at least 200 mg per 24 hours; or (c) in oligo-secretory and non-secretory myeloma patients only, at least a 50% increase of the difference between involved free light chain and uninvolved free light chain; or (d) at least a 25% relative increase and at least a 10% absolute increase in plasma cells in a bone marrow aspirate or on biopsy; or (e) an increase in the size or number of lytic bone lesions (not including compression fractures); or (f) at least a 25% increase in the size of an existing or the development of a new soft tissue plasmacytoma (determined by clinical examination or diagnostic imaging); or (g) development of hypercalcaemia (corrected serum calcium greater than 2.65 mmol per L not attributable to any other cause).
7923	**Prescriber Instructions:** Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M protein.
25745 CAR	**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 the Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday)
7607	**Administrative Advice:** No increase in the maximum number of repeats may be authorised

7608	**Administrative Advice:** Special Pricing Arrangements apply
New 7	**Administrative Advice:** This drug is not PBS-subsidised for use in patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are refractory to both a PI and an immunomodulatory agent, as monotherapy.

Name, Restriction, Manner of administration and form	**PBS item code**	**Max. Amount**	**№.of Rpts**	**Manufacturer**
DARATUMUMAB Injection	NEW (Public) NEW (Private)	1920 mg	7	Janssen-Cilag Pty Ltd
Available brands				
Darzalex (daratumumab 100 mg/5 mL injection, 5 mL vial)				
Darzalex (daratumumab 400 mg/20 mL injection, 20 mL vial)				

Restriction Summary [new] / Treatment of Concept: [new]

Concept ID (for internal Dept. use)	**Category / Program:** Section 100 – Efficient Funding of Chemotherapy (Public/Private hospital)
	Prescriber type: ☒Medical Practitioners
	Restriction Type / Method: ☒Authority Required – immediate, real time assessment by Services Australia (online or telephone application)
	Episodicity: Relapsed and/or refractory
	Severity: [blank]
	Condition: multiple myeloma
New 1 (variation of 7906)	**PBS Indication:** Relapsed and/or refractory multiple myeloma
	Treatment Phase: Transitioning from non-PBS to PBS subsidised supply – 'Grandfather' treatment
	Clinical criteria:
New GF	Patient must have received non-PBS-subsidised treatment with this drug for this condition prior to [insert listing date here]
	AND
New GF	**Clinical criteria:** Patient must have met all initial treatment PBS-eligibility criteria applying to a non-grandfathered patient prior to having commenced treatment with this drug, which are: (i) the condition was confirmed by histological diagnosis, (ii) the treatment is/was being used as part of triple combination therapy with bortezomib and dexamethasone, (iii) the condition progressed (see definition of progressive disease below) after one prior therapy, but not after more than two prior lines of therapies (i.e. this drug was commenced as second-line treatment), (iv) the treatment was/is not to be used in combination with PBS-subsidised carfilzomib, thalidomide or its analogues, and (v) the patient had never been treated with this drug
	AND
21513	**Clinical criteria:**
21512	Patient must not have developed disease progression while receiving treatment with this drug for this condition
7922	**Prescriber instructions:** Progressive disease is defined as at least 1 of the following: (a) at least a 25% increase and an absolute increase of at least 5 g per L in serum M protein (monoclonal protein); or (b) at least a 25% increase in 24-hour urinary light chain M protein excretion, and an absolute increase of at least 200 mg per 24 hours; or (c) in oligo-secretory and non-secretory myeloma patients only, at least a 50% increase of the difference between involved free light chain and uninvolved free light chain; or (d) at least a 25% relative increase and at least a 10% absolute increase in plasma cells in a bone marrow aspirate or on biopsy; or (e) an increase in the size or number of lytic bone lesions (not including compression fractures); or (f) at least a 25% increase in the size of an existing or the development of a new soft tissue plasmacytoma (determined by clinical examination or diagnostic imaging); or

	(g) development of hypercalcaemia (corrected serum calcium greater than 2.65 mmol per L not attributable to any other cause).
7923	**Prescriber instructions:** Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M protein.
Edit 22724	**Prescribing Instructions:** Details of: the histological diagnosis of multiple myeloma, prior treatments including name(s) of drug(s) and date of most recent treatment cycle; the basis of the diagnosis of progressive disease or failure to respond; and which disease activity parameters will be used to assess response must be documented in the patient's medical records. Confirmation of eligibility for treatment with current diagnostic reports of at least one of the following must be documented in the patient's medical records: (a) the level of serum monoclonal protein; or (b) Bence-Jones proteinuria - the results of 24-hour urinary light chain M protein excretion; or (c) the serum level of free kappa and lambda light chains; or (d) bone marrow aspirate or trephine; or (e) if present, the size and location of lytic bone lesions (not including compression fractures); or (f) if present, the size and location of all soft tissue plasmacytomas by clinical or radiographic examination i.e. MRI or CT-scan; or (g) if present, the level of hypercalcaemia, corrected for albumin concentration. As these parameters must be used to determine response, results for either (a) or (b) or (c) should be *documented* for all patients. Where the patient has oligo-secretory or non-secretory multiple myeloma, either (c) or (d) or if relevant (e), (f) or (g) must be documented in the patient's medical records. Where the prescriber plans to assess response in patients with oligo-secretory or non-secretory multiple myeloma with free light chain assays, evidence of the oligo-secretory or non-secretory nature of the multiple myeloma (current serum M protein less than 10 g per L) must be documented in the patient's medical records.
New 5	**Prescriber instructions:** A line of therapy is defined as 1 or more cycles of a planned treatment program. This may consist of 1 or more planned cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner. A new line of therapy starts when a planned course of therapy is modified to include other treatment agents (alone or in combination) as a result of disease progression, relapse, or toxicity, with the exception to this being the need to attain a sufficient response for stem cell transplantation to proceed. A new line of therapy also starts when a planned period of observation off therapy is interrupted by a need for additional treatment for the disease.
17098	**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
25398 draft	**Administrative Advice:** This Grandfather restriction will cease to operate from 12 months after the date specified in the Clinical criteria
25745 CAR	**Administrative Advice:** Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).
7607	**Administrative Advice:** No increase in the maximum number of repeats may be authorised.
7608	**Administrative Advice:** Special Pricing Arrangements apply
New 6	**Administrative Advice:** This drug is not PBS-subsidised for use in patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are refractory to both a PI and an immunomodulatory agent, as monotherapy.

7.2 Condense all existing bortezomib multiple myeloma listings to one single multiple myeloma Restricted benefit listing as follows:

Name, restriction, manner of administration, form	Max. amount	No. of repeats	Proprietary name and manufacturer
BORTEZOMIB, intravenous infusion, powder in vial, 1 mg BORTEZOMIB, intravenous infusion, powder in vial, 3 mg BORTEZOMIB, intravenous infusion, powder in vial, 3.5 mg	3,000 mcg (to be confirmed)	15 (to be confirmed)	VELCADE Janssen-Cilag Pty Ltd

Concept ID (for internal Dept. use)	
	Category / Program: Section 100 – Efficient Funding for Chemotherapy (Public/Private)
	Prescriber type: ☒ Medical Practitioners
	Restriction Type: ☒Restricted benefit
7906	**PBS Indication:** Multiple myeloma
7608	**Administrative Advice:** Special Pricing Arrangements apply

These restrictions may be subject to further review. Should there be any changes made to the restrictions the Sponsor will be informed.

8 Context for Decision

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

9 Sponsor's Comment

The sponsor had no comment.