

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

1 Purpose of Application

- 1.1 The Category 2 submission requested an Authority Required – Section 100 (Highly Specialised Drugs Program) listing for daratumumab subcutaneous (SC) flat dosing regimen, in combination with bortezomib and dexamethasone (DBd), for the treatment of second-line multiple myeloma (MM).
- 1.2 The place in therapy is consistent with the current PBS restriction of daratumumab intravenous (IV), for use as DBd, as a second-line MM treatment which was recommended in July 2020 (paragraph 6.1, daratumumab, Public Summary Document (PSD), July 2020).
- 1.3 Listing was requested on the basis of a cost-minimisation analysis between the 1,800 mg SC flat dosing regimen and the current 16 mg/kg IV weight-based dosing regimen.

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

Component	Description
Population	Multiple myeloma; patients with relapsed or refractory disease after one prior line of therapy (i.e., second line MM patients).
Intervention	Daratumumab administered as a subcutaneous (SC) injection at a dose of 1,800 mg in all patients irrespective of weight in combination with bortezomib and dexamethasone. Daratumumab is administered weekly for the first 3 cycles (each cycle is 3 weeks in duration), every three weeks from Cycles 4 to 8 (each cycle is 3 weeks in duration) and then once every 4 weeks from Cycle 9 onwards (i.e. each cycle is 4 weeks in duration) until disease progression or treatment-limiting toxicity.
Comparator	Daratumumab administered as an intravenous (IV) infusion at a dose of 16 mg/kg in combination with bortezomib and dexamethasone. Daratumumab IV is administered as per the same schedule as daratumumab SC.
Outcomes	Efficacy (overall response rate, progression-free survival, overall survival), pharmacokinetics (maximum C_{trough}) and safety/tolerability.
Clinical claim	In patients with RRMM multiple myeloma (second-line MM), daratumumab SC provides non-inferior efficacy, pharmacokinetics and safety/tolerability, with a reduced incidence of IRRs compared with weight-based 16 mg/kg daratumumab IV dosing

Source: Table 1.1 of the submission.

IRR = infusion related reaction, IV = intravenous; MM = multiple myeloma, RRMM = relapsed and/or refractory multiple myeloma; SC = subcutaneous.

2 Background

Registration status

- 2.1 Daratumumab SC formulation was TGA registered on 8 September 2020. The TGA registration is:

- in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with MM who have received at least one prior therapy;
- as monotherapy, for the treatment of patients with MM 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;
- 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).

3 Requested listing

Name, Restriction, Manner of administration and form	Max. Amt	No. of Rpts	Dispensed Price for Max. Amt	Proprietary Name and Manufacturer
INITIAL TREATMENT DARATUMUMAB SUBCUTANEOUS VIAL 1800 MG	1800 mg	8	\$7,041.49 published price \$ [REDACTED] effective price	DARZALEX®, Janssen Cilag Pty Ltd

Category/Program:	Section 100 – Highly Specialised Drugs Program (Public/Private Hospital)
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)
Restriction:	Authority Required – Telephone, Electronic
Clinical criteria:	<ul style="list-style-type: none"> • The condition must be confirmed by a histological diagnosis, AND • The treatment must be in combination with bortezomib and dexamethasone, AND • Patient must have progressive disease after only one prior therapy (i.e. use must be as second-line drug therapy; use as third-line drug therapy or beyond is not PBS-subsidised), AND • Patient must not be receiving concomitant PBS-subsidised carfilzomib, thalidomide or its analogues, AND • Patient must not have previously received this drug for this condition, OR • If the patient is currently receiving the intravenous form of this drug for this condition, the patient can switch to receive the subcutaneous form of this drug for this condition.

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Name, Restriction, Manner of administration and form	Max. Amt	No. of Rpts	Dispensed Price for Max. Amt	Proprietary Name and Manufacturer
CONTINUING TREATMENT (WEEKS 10 TO 24) DARATUMUMAB SUBCUTANEOUS VIAL 1800 MG	1800 mg	4	\$7,041.49 published price \$ [REDACTED] effective price	DARZALEX®, Janssen Cilag Pty Ltd

Category/Program:	Section 100 – Highly Specialised Drugs Program (Public/Private Hospital)
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)
Restriction:	Authority Required – Telephone, Electronic
Clinical criteria:	<ul style="list-style-type: none"> • Patient must have previously received PBS-subsidised treatment with this drug for this condition, AND • The treatment must be in combination with bortezomib and dexamethasone, AND • Patient must not have developed disease progression while receiving treatment with this drug for this condition, AND • Patient must not be receiving concomitant PBS-subsidised carfilzomib, thalidomide or its analogues, AND • If the patient is currently receiving the intravenous form of this drug for this condition, the patient can switch to receive the subcutaneous form of this drug for this condition.

Name, Restriction, Manner of administration and form	Max. Amt	No. of Rpts	Dispensed Price for Max. Amt	Proprietary Name and Manufacturer
CONTINUING TREATMENT (WEEKS 25 ONWARDS) DARATUMUMAB SUBCUTANEOUS VIAL 1800 MG	1800 mg	5	\$7,041.49 published price \$ [REDACTED] effective price	DARZALEX®, Janssen Cilag Pty Ltd

Category/Program:	Section 100 – Highly Specialised Drugs Program (Public/Private Hospital)
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)
Restriction:	Authority Required – Telephone, Electronic
Clinical criteria:	<ul style="list-style-type: none"> • Patient must have previously received PBS-subsidised treatment with this drug for this condition, AND • Patient must not have developed disease progression while receiving treatment with this drug for this condition, AND • Patient must not be receiving concomitant PBS-subsidised bortezomib, carfilzomib or thalidomide or its analogues, AND • If the patient is currently receiving the intravenous form of this drug for this condition, the patient can switch to receive the subcutaneous form of this drug for this condition

Source: Table 1.6, pp.22-23 of the submission.

- 3.1 The submission proposed a Special Pricing Arrangement (SPA) with a rebate of [REDACTED]% for daratumumab SC under a Section 100 (Highly Specialised Drugs Program) listing. In its pre-PBAC Response the sponsor reiterated that the Highly Specialised Drugs Program is the most appropriate place for daratumumab SC on the PBS, on the basis that this formulation was a ready-to-use formulation that does not require reconstitution or require any specialised equipment or preparation outside of the standard practice for preparing drugs for parenteral use.

- 3.2 The PBAC recalled that, when considering the SC forms of rituximab (November 2014) and trastuzumab (July 2015), for which IV forms of these agents were listed on the PBS under the Section 100 (Efficient Funding of Chemotherapy), it had recommended a dual listing for the SC forms under the General Schedule and the Section 100 (Efficient Funding of Chemotherapy – Related Benefits). The PBAC could not see any differences in the circumstances of listing SC daratumumab to those which led to the listing of SC rituximab and SC trastuzumab in two separate sections of the PBS Schedule. Therefore, for consistency, the PBAC considered that the listing of the SC form of daratumumab should follow the examples of SC rituximab and SC trastuzumab.
- 3.3 The proposed PBS restriction of SC DBd was for use as a second-line MM treatment. This was consistent with the PBS restriction for IV DBd; however, was inconsistent with the COLUMBA trial which formed the basis of the clinical claim, in which patients received daratumumab SC monotherapy after receiving at least three prior lines of therapy. However, the TGA Delegate’s Overview concluded that the data “supported the use of daratumumab SC in all the indications for which IV administration is currently approved”. The submission concluded that the results from the COLUMBA trial are applicable for daratumumab when used in combination and in other MM indications.
- 3.4 The pre-PBAC response clarified that for a patient whose body weight is less than 112.5 kg, switching from daratumumab IV, 16 mg/kg (total dose = 1,800 mg) to the 1,800 mg SC formulation would not be considered an overdose. The pre-PBAC response stated that this was based on a subgroup analysis of the COLUMBA trial which demonstrated acceptable tolerability and safety in lower weight patients. This was also confirmed in the TGA’s Clinical Evaluator response which stated that the various exposure-response analyses did not indicate lower efficacy in high body weight patients or increased toxicity in low bodyweight patients as a result of the daratumumab SC flat-dosing. It was noted in the Product Information that in refractory/relapsed myeloma, when given in combination with bortezomib and dexamethasone, the dosing schedule for the SC form is the same as that for the IV form, meaning that the number of repeats for the existing IV form could be transcribed over into the SC form listing.

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

4 Population and disease

- 4.1 MM is a cytogenetically heterogeneous clonal plasma cell proliferative disorder characterised by an abnormal serum and/or urine immunoglobulin. As MM progresses and patients relapse following initial treatment, the presence of subclonal populations of malignant plasma cells becomes increasingly prevalent. Typical clinical features include: bone disease (and bone loss) with skeletal pain, impaired renal function, anaemia, fatigue, hypercalcaemia, recurrent and/or persistent bacterial infection,

and/or hyperviscosity of the blood (paragraph 4.1, Daratumumab, Public Summary Document, November 2017).

- 4.2 Daratumumab SC is a monoclonal antibody with ATC classification L01XC24.
- 4.3 The submission proposed the addition of the 1,800 mg daratumumab SC flat dosing for second line MM. The PBAC considered this was reasonable.

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

5 Comparator

- 5.1 The submission nominated daratumumab 16 mg/kg IV infusion as the main comparator. The submission noted that daratumumab SC is expected to replace the PBS listed IV form of daratumumab, given they are the same active medicine for the same PBS-subsidised population. This was appropriate.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (38), health care professionals (1) and organisations (3) via the Consumer Comments facility on the PBS website. Both the individual comments and the advice received from the Myeloma Australia, Myeloma Australia's Medical and Scientific Advisory Group and the Leukaemia Foundation highlighted the quality of life and convenience benefits that a five-minute SC injection of daratumumab would provide for patients over the current multi-hour IV administration requirements.

Clinical trial

- 6.3 The submission was based on one head-to-head trial (COLUMBA, N=522) comparing daratumumab SC monotherapy to daratumumab IV monotherapy.
- 6.4 The table below provides details of the trial presented in the submission.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/Publication title	Publication citation
COLUMBA	A Phase 3 Randomised, Multicentre Study of Subcutaneous versus Intravenous Administration of Daratumumab in Subjects with Relapsed or Refractory Multiple Myeloma. Primary analysis Clinical Study Report	8 January 2019
	A Phase 3 Randomised, Multicentre Study of Subcutaneous versus Intravenous Administration of Daratumumab in Subjects with Relapsed or Refractory Multiple Myeloma. Synoptic Clinical Study Report (6-month update)	8 July 2019
	Mateos MV, et al. (2020). Subcutaneous versus intravenous daratumumab in patients with relapsed or refractory multiple myeloma (COLUMBA): a multicentre, open-label, non-inferiority, randomised, phase 3 trial.	Lancet Haematology 2020; 7(5):e370-e380

Source: Table 2.5, p.31 of the submission.

6.5 The key features of the direct randomised trial are summarised in Table 3.

6.6 The dosing schedule of the SC and IV daratumumab monotherapy in the COLUMBA trial (weekly for Cycles 1 and 2, every two weeks for Cycles 3 to 6 and every four weeks from Cycle 7; 23 prescriptions per year) differed to the proposed PBS listing of SC DBd and the current PBS listing of IV DBd (weekly for Cycles 1 to 3; every three weeks for Cycles 4 to 8 and every four weeks from Cycle 9; 21 prescriptions per year).

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes
Daratumumab SC vs. Daratumumab IV					
COLUMBA	522	R, OL, MC, median follow-up 13.73 months	Low	RRMM	Maximum C _{trough} , ORR, PFS, OS

Source: Table 2.7, Table 2.11, Table 2.15, Table 2.16 of the submission

MC = multicentre; OL = open label; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; R = randomised; RRMM = relapsed and/or refractory multiple myeloma.

Comparative effectiveness

6.7 The non-inferiority of daratumumab SC relative to daratumumab IV for C_{trough} was defined using a non-inferiority margin of at least 80% of the ratio of geometric mean (GM) of maximum C_{trough}. Non-inferiority of daratumumab SC to daratumumab IV based on maximum C_{trough} was declared if the lower bound of the 90% confidence interval (CI) for the ratio of the GMs was at least 80%.

6.8 The non-inferiority of daratumumab SC relative to daratumumab IV for overall response rate (ORR) was defined using 60% retention of the lower bound of the 95% CI from the SIRIUS study (Lonial, et al. 2016)¹. The SIRIUS study enrolled 106 patients with RRMM who had received at least three prior therapies and who were treated with daratumumab IV 16 mg/kg and an ORR of 29.2% (95% CI: 20.8%, 38.9%) was

¹ Lonial S, et al. (2016), 'Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial', Lancet, 387 (10027), [https://doi.org/10.1016/S2352-3026\(20\)30081-8](https://doi.org/10.1016/S2352-3026(20)30081-8)

observed. Non-inferiority was declared if the lower bound of the two-sided 95% CI of the relative risk was > 60%.

- 6.9 Table 4 presents the results of maximum C_{trough} concentration in COLUMBA. At the 6-month update (13.7 months follow-up) the geometric mean ratio for maximum C_{trough} was 110.30% (95% CI: 98.08%, 124.05%), and the lower bound of the 95% CI (98.08%) was greater than the pre-specified non-inferiority margin of 80%.

Table 4: Results of maximum C_{trough} concentration (µg/mL, cycle 3, day 1 pre-dose) (PK-evaluable) in COLUMBA

	Daratumumab SC		Daratumumab IV		Ratio (95% CI)
	N, mean (SD)	Geometric mean ^a	N, mean (SD)	Geometric mean ^a	
Primary analysis ^b	149, 593 (306)	499	146, 522 (226)	463	107.93% (95.74%, 121.67%)
6-month update ^c	157, 611 (318)	514	150, 525 (227)	466	110.30% (98.08%, 124.05%)

Source: Table 2.17, p.47 of the submission, Table 13, p.52 COLUMBA Primary analysis CSR of Attachment 6 of the submission

CI = confidence interval; IV = intravenous; PK = pharmacokinetic; SC = subcutaneous; SD = standard deviation

^a Maximum C_{trough} concentration data were natural log (ln) transformed prior to the calculation of geometric mean, the ratio of geometric mean and its 90% confidence interval, and then transformed back to the linear scale.

^b Primary analysis with median 7.5 month follow-up

^c 6-month update analysis with median 13.7 month follow-up

- 6.10 Table 5 presents the results of ORR. At the 6-month update, the lower bound of the 95% CI of the estimated RR of ORR was 0.90 that was greater than the pre-specified non-inferiority margin of 0.60.

Table 5: Results of ORR in ITT population in COLUMBA

	Daratumumab SC n/N (%; 95% CI)	Daratumumab IV n/N (%; 95% CI)	Relative risk (95% CI), p-value ^a
Primary analysis^b			
ORR (sCR+CR+VGPR+PR)	108/263 (41.1%; 35.1%, 47.3%)	96/259 (37.1%; 31.2%, 43.3%)	1.11 (0.89, 1.37), p<0.001
CR or better (sCR+CR)	5/263 (1.9%; 0.6%, 4.4%)	7/259 (2.7%; 1.1%, 5.5%)	NR
VGPR or better (sCR+CR+VGPR)	50/263 (19.0%; 14.5%, 24.3%)	44/259 (17.0%; 12.6%, 22.1%)	NR
6-month update^c			
ORR (sCR+CR+VGPR+PR)	114/263 (43.3%; 37.3%, 49.6%)	102/259 (39.4%; 33.4%, 45.6%)	1.10 (0.90, 1.35), p<0.0001
CR or better (sCR+CR)	8/263 (3.0%; 1.3%, 5.9%)	12/259 (4.6%; 2.4%, 8.0%)	NR
VGPR or better (sCR+CR+VGPR)	57/263 (21.7%; 16.8%, 27.1%)	54/259 (20.8%; 16.1%, 26.3%)	NR

Source: Table 2.19, p.50 of the submission, Table 16, p.62 COLUMBA Primary analysis CSR of Attachment 6 of the submission

CI = confidence interval; CR=complete response; n = number of participants with event; IV=intravenous; N = total participants in group, NR = not reported; PR=partial response; RR=relative risk, SC=subcutaneous; sCR=Stringent complete response, VGPR=very good partial response;

Bold indicates statistically significant results.

^a Farrington-Manning estimates of the relative risk of daratumumab SC over daratumumab IV and associated CI and the p-value is from Farrington-Manning test for the non-inferiority hypothesis that daratumumab SC retains at least 60% of ORR in Dara IV.

^b Primary analysis with median 7.5 month follow-up

^c 6-month update analysis with median 13.7 month follow-up

- 6.11 Table 6 presents the results of PFS and OS.

Table 6: Summary of survival outcomes in COLUMBA (6-month update)

	Daratumumab SC	Daratumumab IV	HR (95% CI)
Progression-free survival			
Patients with event, n/N (%)	180/263 (68.4%)	180/259 (69.5%)	-
Median PFS, months (95% CI)	5.62 (4.70, 7.49)	6.08 (4.73, 7.43)	1.00 (0.81, 1.23)
Overall survival			
Patients with event, n/N (%)	74/263 (28.1%)	77/259 (29.7%)	-
Median OS, months (95% CI)	NE	NE (17.02, NE)	0.91 (0.66, 1.25)

Source: Table 2.20, p.52 and Table 2.21, p.53 of the submission.

HR = hazard ratio; IV = intravenous; n = number of participants reporting data; N = total participants in group; NE= not evaluable; PFS = progression free survival; OS = overall survival; SC = subcutaneous.

Comparative harms

6.12 Presented below is a summary of key adverse events in COLUMBA.

Table 7: Summary of key adverse events in COLUMBA

Trial ID	Daratumumab SC	Daratumumab IV	OR (95% CI)
6 month update, n/N (%)			
Any TEAE	233/260 (89.6%)	237/258 (91.9%)	0.76 (0.42, 1.39)
TEAE leading to treatment discontinuation	19/260 (7.3%)	22/258 (8.5%)	0.85 (0.45, 1.60)
Grade 3 or 4 TEAEs	127/260 (48.8%)	134/258 (51.9%)	0.88 (0.63, 1.25)
IRRs	33/260 (12.7%)	89/258 (34.5%)	0.28 (0.18, 0.44) ^a , p<0.0001

Source: Table 2.28, p.61, Table 2.30, p.62, Table 2.33, p.65 of the submission and calculated during the evaluation.

CI = confidence interval; IRR = infusion related reaction; n = number of participants reporting data; N = total participants in group; NR = not reported; OR = odds ratio; TEAE = treatment emergent adverse event.

Note: ^a Stratified Cochran-Mantel-Haenszel estimate of the common odds ratio of daratumumab SC over daratumumab IV is used. The stratification factors include body weight at baseline (≤ 65 kg, 66 kg to 85 kg, > 85 kg), number of prior lines of therapy (≤ 4 prior lines versus > 4 prior lines), and type of myeloma (IgG versus non-IgG).

Benefits/harms

6.13 A benefits/harms analysis was not presented as the clinical claim is of non-inferiority.

Clinical claim

6.14 The submission described the 1,800 mg flat dosing regimen of daratumumab SC monotherapy as non-inferior in terms of effectiveness compared to the 16 mg/kg weight-based regimen of daratumumab IV monotherapy. The ESC considered that this claim was adequately supported.

6.15 The submission described the 1,800 mg flat dosing regimen of daratumumab SC monotherapy as non-inferior in terms of safety compared to the 16 mg/kg weight-based regimen of daratumumab IV monotherapy. The ESC considered that this claim was adequately supported.

6.16 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.

6.17 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

Economic analysis

- 6.18 A cost-minimisation analysis was presented. This was consistent with the clinical evidence.
- 6.19 The equi-effective doses estimated by the submission were:
 1,800 mg daratumumab SC = 1,200 mg daratumumab IV
- 6.20 The submission estimated the equi-effective dose of daratumumab IV as 1,200 mg using the mean weight (77.69 kg, n=478) and mean dose intensity (93.36%, n=243) of daratumumab IV reported in the CASTOR trial. The submission estimated an efficient vial combination of 3 x 400mg vials. This was also the mean dose of DBd per infusion applied in the July 2020 model. The submission justified the use of the CASTOR trial as the basis of the estimation of the equi-effective dose as the CASTOR population more closely represented the proposed PBS population than the COLUMBA population. A sensitivity analysis conducted during the evaluation based on the mean weight (74.14 kg) and mean dose intensity (96.8%) reported in the COLUMBA trial, resulted in an average dose of daratumumab IV of 1,148 mg, and an efficient vial combination of 3 x 400 mg vials. The ESC considered that the submission’s estimation of the equi-effective daratumumab IV dose, based on the CASTOR trial, was appropriate.
- 6.21 Table 8 presents the results of the cost-minimisation analysis. The ESC considered that the estimation of the cost-minimisation analysis was reasonable, although there were differences in the net cost to the Government due to the lower mark-ups and fees applied to the daratumumab SC formulation listing Section 100 (Highly Specialised Drugs) compared with daratumumab IV listing Section 100 (Efficient Funding of Chemotherapy). The PBAC noted that the mark-ups and fees applied to the SC formulation would differ if listed on the General Schedule and Section 100 (Efficient Funding of Chemotherapy – Related Benefits).

Table 8: Results of the cost-minimisation analysis

	Daratumumab SC	Daratumumab IV
Route of administration	Subcutaneous	Intravenous
Dosing schedule	Administered weekly for the first 3 cycles (each cycle is 3 weeks in duration), every three weeks from cycles 4 to 8 (each cycle is 3 weeks in duration) and then once every 4 weeks from cycle 9 onwards (each cycle is 4 weeks in duration) until disease progression or treatment-limiting toxicity).	
Cost minimisation as per submission		
Published AEMP per vial	N/A	\$2,336.76 per 400 mg vial
Effective AEMP per vial	N/A	\$ [REDACTED] per 400 mg vial
Equi-effective doses	1,800 mg vial	1,200 mg as 3 x 400 mg vials
Published AEMP	\$7,010.28	\$7,010.28
Effective AEMP	\$ [REDACTED]	\$ [REDACTED]
Other costs (e.g. MBS)	None applied	None applied
Net effective DPMQ (weighted) ^a	\$ [REDACTED]	\$ [REDACTED]
Difference in net effective DPMQ		-\$ [REDACTED]

Source: Table 3.2 of the submission, sheet '3c.Impact – proposed (eff) in Excel spreadsheet 'Daratumumab SC utilisation cost model', Attachment 13 of the submission and calculated during the evaluation.

AEMP = approved ex-manufacturer price; DPMQ = dispensed price for maximum quantity; IV = intravenous; N/A = not applicable, SC = subcutaneous

Note: ^aPublic and private split is 34.63% and 65.37%, respectively.

Drug cost/patient/year

Table 9: Drug cost per patient for daratumumab SC and daratumumab IV

	Daratumumab SC		Daratumumab IV	
	Trial dose and duration ^a	CMA ^b	Trial dose and duration ^a	CMA ^b
Dosing schedule	Once weekly (Cycles 1 and 2), every 2 weeks (Cycles 3–6), and then every 4 weeks until progressive disease or toxicity.	Once weekly (Cycles 1-3, 3-week cycles), every 3 weeks (Cycles 4-8, 3 week cycles), and then every 4 weeks until disease progression or toxicity	Once weekly (Cycles 1 and 2), every 2 weeks (Cycles 3–6), and then every 4 weeks until progressive disease or toxicity.	Once weekly (Cycles 1-3, 3-week cycles), every 3 weeks (Cycles 4-8, 3 week cycles), and then every 4 weeks until disease progression or toxicity
Mean dose	1,800 mg	1,800 mg	1,200 mg	1,200 mg
Mean duration	6.7 months	NR	6.9 months	NR
Median duration	5.5 months	NR	6.0 months	NR
Cost/patient/cycle	Cycle 1-2: \$ [REDACTED] Cycle 3-6: \$ [REDACTED] Cycle 7+: \$ [REDACTED]	Cycle 1-3: \$ [REDACTED] Cycle 4-8: \$ [REDACTED] Cycle 9+: \$ [REDACTED]	Cycle 1-2: \$ [REDACTED] Cycle 3-6: \$ [REDACTED] Cycle 7+: \$ [REDACTED]	Cycle 1-3: \$ [REDACTED] Cycle 4-8: \$ [REDACTED] Cycle 9+: \$ [REDACTED]
Cost/patient/year	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]

Source: Table 2.12 of the submission and calculated during the evaluation.

^a Assuming 23 prescriptions per year (2 initial cycles (8 scripts in Cycle 1-2) and 10 continuing cycles (8 scripts in Cycle 3-6 and 7 scripts in Cycle 7 to 13) in COLUMBA.

^b Assuming 21 prescriptions per year (3 initial cycles (9 scripts in Cycle 1-3) and 10 continuing cycles (5 scripts in Cycle 4-8 and 7 scripts in Cycle 9-14).

CMA = cost-minimisation analysis; IV = intravenous; NR = not reported; SC = subcutaneous.

6.22 The annual cost of daratumumab SC is \$ [REDACTED] per patient, based on the proposed DPMQ of \$ [REDACTED] and 21 prescriptions per year (3 initial cycles (9 prescriptions in Cycle 1-3) and 10 continuing cycles (5 prescriptions in Cycle 4-8 and 7 prescriptions in Cycle 9-14)).

Estimated PBS usage & financial implications

6.23 DUSC did not consider this submission. The submission used a market share approach to derive the utilisation estimates.

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Table 10: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Number of doses total	DBd IV utilisation cost model based on Alternative case 2 in the DBd IV July 2020 PBAC submission post-recommendation negotiations of the RSA (Attachment 14)	This scenario was considered to best represent the current situation in July 2020 (paragraph 5.21, daratumumab, PSD, July 2020).
Uptake rate	Year 1: 45%, Year 2: 60%, Year 3-Yr 6: 70% Assumption	It is likely that the uptake of daratumumab SC will be higher than assumed by the submission.
Scripts dispensed	Number of prescriptions equated to number of doses of daratumumab.	-
Daratumumab subcutaneous	Published: \$7,010.28 (public), \$7,058.02 (private), \$█ (weighted) Effective: \$█ (public), \$█ (private), \$█ (weighted)	The proposed SPA for daratumumab SC is a █% rebate.
Daratumumab intravenous 100mg/400 mg	Published: \$7,096.06 (public), \$7,234.83 (private), \$█ (weighted) Effective: \$█ (public), \$█ (private), \$█ (weighted) Daratumumab IV PB11a form, 1,200 mg (3*400 mg vials)	The SPA for daratumumab IV is a █% rebate. The difference between the SPA percentage rebate for daratumumab IV and daratumumab SC is a result of differences in the mark-up fees.

Source: Table 4.1 and Table 4.2 of the submission.

DBd = daratumumab, bortezomib and dexamethasone; IV = intravenous; RSA = risk share arrangement; SC = subcutaneous; SPA = special pricing arrangement.

6.24 The estimated use and financial implications are presented below.

Table 11: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of scripts dispensed ^a	█ ¹	█ ²	█ ²	█ ²	█ ³	█ ³
Estimated financial implications of daratumumab SC						
Cost to PBS/RPBS less copayments	\$█ ⁴	\$█ ⁶	\$█ ⁷	\$█ ⁸	\$█ ⁹	\$█ ¹¹
Estimated financial implications for daratumumab IV						
Cost to PBS/RPBS less copayments	-\$█ ⁴	-\$█ ⁶	-\$█ ⁸	-\$█ ⁹	-\$█ ¹⁰	-\$█ ¹¹
Net financial implications						
Net cost to PBS/RPBS	-\$█ ⁵	-\$█ ⁵	-\$█ ⁵	-\$█ ⁵	-\$█ ⁵	-\$█ ⁵

Source: Table 4.3, Table 4.8, Table 4.10 of the submission.

^a Assuming 21 scripts per year (3 initial cycles (9 scripts in Cycle 1-3) and 10 continuing cycles (5 scripts in Cycle 4-8 and 7 scripts in Cycle 9-14) as estimated by the submission.

IV = intravenous; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme; SC = subcutaneous

The redacted values correspond to the following ranges:

¹ 5,000 to < 10,000

² 10,000 to < 20,000

³ 20,000 to < 30,000

⁴ \$20 million to < \$30 million

⁵ \$0 to < \$10 million

⁶ \$40 million to < \$50 million

⁷ \$50 million to < \$60 million

⁸ \$60 million to < \$70 million

⁹ \$70 million to < \$80 million

¹⁰ \$80 million to < \$90 million

¹¹ \$90 million to < \$100 million

- 6.25 As per the submission, if daratumumab SC was listed as a Section 100 (Highly Specialised Drugs Program), the total cost to the PBS/RPBS of listing daratumumab SC was estimated to be a cost saving of \$0 to < \$10 million in Year 6, and a total cost saving of \$10 million to < \$20 million over the first 6 years of listing. The estimated net cost saving to the PBS/RPBS was due to differences in dispensing fees and mark-ups between the Highly Specialised Drugs Program and Efficient Funding of Chemotherapy.

Quality Use of Medicines

- 6.26 The submission provided materials to be distributed to healthcare professionals and patients.

Financial Management – Risk Sharing Arrangements

- 6.27 The submission requested that daratumumab SC join the agreed daratumumab IV RSA and did not propose any changes to the subsidisation caps or rebates. The submission estimated that the per patient cost of daratumumab SC was lower than the per patient cost of daratumumab IV due to differences in fees and mark-ups between the Section 100 (Highly Specialised Drugs Program) and the Section 100 (Efficient Funding of Chemotherapy). Therefore, if daratumumab SC is listed as a Section 100 (Highly Specialised Drugs Program), maintaining the subsidisation caps at the existing level would allow for an increase in the number of doses supplied under the cap.
- 6.28 The pre-PBAC Response reiterated the submission's argument it was reasonable to maintain the current RSA caps for daratumumab, as it would allow additional patients to be treated and as the new SC form offers tangible advantages over the IV formulation given the simpler preparation and administration requirements.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the dual General Schedule and Section 100 (Efficient Funding of Chemotherapy – Related Benefits), Authority Required listings of a flat 1,800 mg subcutaneously (SC) delivered form of daratumumab for all indications for which the intravenous (IV) form of daratumumab is currently listed. The PBAC advised the listing of the SC form should be on a cost minimisation basis with the IV formulation of daratumumab.
- 7.2 In making this recommendation, the PBAC agreed with the consumer comments that the SC form of daratumumab offered additional quality of life and convenience benefits over the IV form.
- 7.3 The PBAC advised the equi-effective doses, based on the mean weight and dose intensity of the IV formulation reported in the CASTOR trial were:

1,800 mg daratumumab SC = 1,200 mg daratumumab IV

- 7.4 The PBAC considered the nominated comparator of IV daratumumab was appropriate.
- 7.5 The PBAC noted the clinical evidence presented which compared daratumumab SC monotherapy with daratumumab IV monotherapy (COLUMBA trial). The PBAC considered the clinical evidence supported a conclusion that the 1,800 mg flat dose SC formulation of daratumumab was non-inferior in terms of comparative efficacy and safety compared to the weight-based IV formulation of daratumumab. The PBAC also noted the TGA Delegate's Overview which concluded that the data from the COLUMBA trial supported the use of daratumumab SC in all the indications for which the IV administration is currently approved, including its combination use indications, which form the basis of the current PBS listings for daratumumab.
- 7.6 The PBAC considered the cost minimisation analysis presented in the submission was reasonable, noting that dispensed price of the SC formulation would vary from that of the IV formulation due to differences in the mark-ups between the different schedules.
- 7.7 The PBAC considered that although there would be minor differences due to the differences in mark-ups between the schedules, daratumumab SC would essentially be cost neutral compared to the current IV listing.
- 7.8 The PBAC considered that it would be reasonable for daratumumab SC to join the existing RSA caps at the current levels established for the IV form as the existing RSA structure [REDACTED]
- 7.9 Regarding the proposed restriction, the PBAC considered the listing for daratumumab SC should mirror that of the current IV listing (albeit in the listed schedules) and permit:
- switching between the IV formulation and the SC formulation; and
 - a grandfather restriction to allow for patients entering a planned product familiarisation program to transition to PBS subsidised therapy. The PBAC noted the sponsor stated that the grandfather restriction would be required for three months only and considered that this was reasonable.
- 7.10 The PBAC advised, under *Section 101 (4AACD) of the National Health Act*, that the SC and IV forms of daratumumab should not be considered equivalent for the purposes of substitution, given the differences in dosing, preparation and administration requirements.
- 7.11 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because the SC form of daratumumab is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over its IV form, and not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009 for Pricing Pathway A were not met.

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

Outcome:

Recommended

8 Recommended listing

8.1 Add new medicinal product pack (new form) as follows:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No.of Rpts	Available brands
DARATUMUMAB					
daratumumab 1.8 g/15 mL injection, 15 mL vial	New (EFC – Related Ben.) New (Gen. Sch)	1	1	8	Darzalex SC
Restriction Summary / Treatment of Concept [New 1]					
Category / Program: <input checked="" type="checkbox"/> Section 100 –Efficient Funding of Chemotherapy– Related Benefits (Code CT) <input checked="" type="checkbox"/> General Schedule (Code GE)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Restriction type: <input checked="" type="checkbox"/> Authority Required – (telephone/online PBS Authorities system)					
Administrative Advice: This drug is not PBS-subsidised for use in patients with multiple myeloma who have received two or more 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.					
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.					
Administrative Advice: No increase in the maximum number of repeats may be authorised.					
Administrative Advice: Special Pricing Arrangements apply.					
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 only one prior therapy (i.e. use must be as second-line drug therapy; use as third-line drug therapy or beyond is not PBS-subsidised)					
AND					
Clinical criteria:					
Patient must not be receiving concomitant PBS-subsidised carfilzomib, thalidomide or its analogues					
AND					
Treatment criteria:					

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	Patient must be undergoing treatment with this drug in one of the following situations: (i) for the first time, (ii) changing the drug's form (intravenous/subcutaneous) within the first 9 weeks of treatment
	Prescribing 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 in 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).
	Prescribing Instructions: Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M protein.
	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.
	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.

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
DARATUMUMAB					
daratumumab 1.8 g/15 mL injection, 15 mL vial	New (EFC – Related Ben.) New (Gen.Sch)	1	1	4	Darzalex SC

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Restriction Summary 11076 / Treatment of Concept [2] 11076 (current as at 1 July 2021 for PBS item codes 12220E & 12225K)	
Category / Program: <input checked="" type="checkbox"/> Section 100 –Efficient Funding of Chemotherapy– Related Benefits (Code CT) <input checked="" type="checkbox"/> General Schedule (Code GE)	
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners	
Restriction type: <input checked="" type="checkbox"/> Authority Required – (telephone/online PBS Authorities system)	
	Administrative Advice: This drug is not PBS-subsidised for use in patients with multiple myeloma who have received two or more 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.
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.
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 this drug for this condition	
AND	
Clinical criteria:	
The treatment must be in combination with bortezomib and dexamethasone	
AND	
Clinical criteria:	
Patient must not have developed disease progression while receiving treatment with this drug for this condition	
AND	
Clinical criteria:	
Patient must not be receiving concomitant PBS-subsidised carfilzomib, thalidomide or its analogues	
Prescribing 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 in 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).	
Prescribing Instructions: Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M protein.	

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MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
DARATUMUMAB					
daratumumab 1.8 g/15 mL injection, 15 mL vial	New (EFC – Related Ben.) New (Gen. Sch)	1	1	5	Darzalex SC
Restriction Summary 11075 / Treatment of Concept 11075					
Category / Program: <input checked="" type="checkbox"/> Section 100 –Efficient Funding of Chemotherapy– Related Benefits (Code CT) <input checked="" type="checkbox"/> General Schedule (Code GE)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Restriction type: <input checked="" type="checkbox"/> Authority Required – (telephone/online PBS Authorities system)					
Administrative Advice: This drug is not PBS-subsidised for use in patients with multiple myeloma who have received two or more 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.					
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.					
Administrative Advice: No increase in the maximum number of repeats may be authorised.					
Administrative Advice: Special Pricing Arrangements apply.					
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)					
Clinical criteria: Patient must have previously received PBS-subsidised treatment with this drug for this condition					
AND					
Clinical criteria: Patient must not have developed disease progression while receiving treatment with this drug for this condition					
AND					
Clinical criteria: Patient must not be receiving concomitant PBS-subsidised bortezomib, carfilzomib or thalidomide or its analogues					
Prescribing 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 in 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).					
Prescribing Instructions: Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M protein.					

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MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
DARATUMUMAB					
daratumumab 1.8 g/15 mL injection, 15 mL vial	New (EFC – Related Ben.) New (General Sch.)	1	1	7	Darzalex SC
Restriction Summary [New GF1] / Treatment of Concept [New GF2]					
Category / Program: <input checked="" type="checkbox"/> Section 100 –Efficient Funding of Chemotherapy– Related Benefits (Code CT) <input checked="" type="checkbox"/> General Schedule (Code GE)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Restriction type: <input checked="" type="checkbox"/> Authority Required – (telephone/online PBS Authorities system)					
Administrative Advice: This drug is not PBS-subsidised for use in patients with multiple myeloma who have received two or more 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.					
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.					
Administrative Advice: Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria.					
Administrative Advice: This grandfather restriction will cease to operate from 3 months after the date specified in the clinical criteria.					
Administrative Advice: No increase in the maximum number of repeats may be authorised.					
Administrative Advice: Special Pricing Arrangements apply.					
Indication: Relapsed and/or refractory multiple myeloma					
Treatment Phase: Transitioning from non-PBS to PBS-subsidised supply – 'grandfather' arrangements					
Clinical criteria:					
Patient must have been on treatment with this drug in the subcutaneous form for this condition prior to [insert listing date here]					
AND					
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					
Clinical criteria:					
Patient must not have developed disease progression while receiving treatment with this drug for this condition					
AND					
Clinical criteria:					
Patient must not be receiving concomitant PBS-subsidised bortezomib, carfilzomib or thalidomide or its analogues					
Prescribing Instructions: Progressive disease is defined as at least 1 of the following:					

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	<p>(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 in 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).</p>
	<p>Prescribing Instructions: Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M protein.</p>
	<p>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.</p>
	<p>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.</p>

Flow on changes to the existing intravenously administered daratumumab restrictions to permit switching between IV and SC forms (only required in the 'Initial treatment' listing) are as follows:

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MEDICINAL PRODUCT Form	PBS item code	Max. Amount	No. of Rpts
DARATUMUMAB Injection	12228N (Public) 12230Q (Private)	1920 mg	8
Available brands			
Darzalex (daratumumab 100 mg/5 mL injection, 5 mL vial)			
Darzalex (daratumumab 400 mg/20 mL injection, 20 mL vial)			
Edit Restriction Summary / Treatment of Concept: 11142 to form New 1 as above (current as at 1 July 2021)			
Category / Program: Section 100 (Efficient Funding of Chemotherapy) (Public/Private hospitals)			
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners			
Restriction type: <input checked="" type="checkbox"/> Authority Required – (telephone/online PBS Authorities system)			
Administrative Advice: This drug is not PBS-subsidised for use in patients with multiple myeloma who have received two or more 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.			
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.			
Administrative Advice: No increase in the maximum number of repeats may be authorised.			
Administrative Advice: Special Pricing Arrangements apply.			
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 only one prior therapy (i.e. use must be as second-line drug therapy; use as third-line drug therapy or beyond is not PBS-subsidised)			
AND			
Clinical criteria:			
Patient must not be receiving concomitant PBS-subsidised carfilzomib, thalidomide or its analogues			
AND			
Clinical criteria:			
Patient must not have previously received this drug for this condition			
Treatment criteria:			
Patient must be undergoing treatment with this drug in one of the following situations: (i) for the first time for this PBS indication, (ii) changing the drug's form (intravenous/subcutaneous) within the first 9 weeks of treatment			
Prescribing 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 in 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).
	<p>Prescribing Instructions: Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M protein.</p>
	<p>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.</p>
	<p>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.</p>

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

9 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.

10 Sponsor's Comment

The sponsor had no comment.