TAR 421a – Daratumumab for people with multiple myeloma who have had one prior line of treatment (update)

Date analysis update: September 2024

1. Executive Summary

This report provides an updated evaluation of daratumumab for people with multiple myeloma who require a second line treatment (see Technology Assessment Report (TAR) 421 (Objective ID A1555232) for details). The assessment incorporates recent clinical advice and reflects changes in the treatment paradigm in New Zealand. It outlines the methods for assessment and estimated likely cost-effectiveness range of daratumumab with pomalidomide and dexamethasone (DPd) for people with MM who have had one prior line of treatment, and its budgetary impact.

The Cancer Treatments Advisory Committee (CTAC) has recommended the use of daratumumab in combination with pomalidomide and dexamethasone (DPd), rather than with bortezomib (DVd), aligning with updated treatment protocols.

The primary clinical evidence for daratumumab is derived from the APOLLO trial, a randomized controlled study. This trial demonstrated that the combination of daratumumab, pomalidomide, and dexamethasone extended median overall survival by approximately 10.7 months; however, this difference was not statistically significant.

It is important to note that over half of the participants in the APOLLO trial had received two or more prior lines of treatment, making them more heavily pretreated than the target population for this assessment. There is currently no head-to-head comparative data for patients with only one prior line of treatment, which represents a key limitation.

The MM-014 trial, a recent phase 2 single-arm study, included a population in which nearly two-thirds of patients had received only one prior line of treatment, and included a subgroup analysis of patients with only one prior line of treatment. Although not randomized, this trial is considered more representative of the New Zealand clinical setting.

An indirect comparison was conducted using data from the MM-014 trial to compare daratumumab with pomalidomide and dexamethasone (DPd ± bortezomib) against pomalidomide and dexamethasone alone (Pd ± bortezomib). The indirect comparison included only individuals with one line of prior therapy in the MM-014 trial. The modelled overall survival gain for those treated with (DPd ± bortezomib) compared to (Pd ± bortezomib) was estimated at 23.3 months.

It is arguable that this may be an optimistic assumption, as it more than doubles the non-statistically significant survival gain observed in the APOLLO trial and lacks direct comparative evidence in the relevant treatment setting. Pharmac's health economic guidelines emphasize that lower-quality evidence necessitates the use of conservative

assumptions. The current appraisal may not fully align with this standard. Any future update to the model should critically assess the assumption of clinical benefit made in this analysis, especially if more robust evidence becomes available.

Despite these methodological concerns, the results of the economic appraisal—presented below—demonstrate that the supplier's current pricing remains the dominant factor influencing cost-effectiveness.

Gains in health-related quality of life were attributed to improvements in progression-free survival. In the model, the PFS gain between treatment arms was 12 months compared with 4.5 months in the APOLLO trial. Again this improvement may be considered optimistic.

Overall cost-effectiveness was estimated at s 9(2)(b)(ii), s 9(2)(i) QALYs per million invested, and the five-year undiscounted cost to the CPB is s 9(2)(b)(ii), s 9(2)(j) and s 9(2)(b)(ii), s 9(2)(j) to the health sector overall.

2. Proposal Overview

2.1. Background to update

Daratumumab treatment for individuals with one prior line (1PL) of therapy was first ranked on the options for investment list (OFI) in December 2021. This assessment had daratumumab used in combination with bortezomib and dexamethasone, based on the proposal application and proposed special authority criteria by CTAC in July 2021. The proposal for daratumumab with bortezomib and dexamethasone has subsequently been re-ranked several times due to price changes or modelling adjustments.

In July 2024, Pharmac made the decision to fund lenalidomide for untreated multiple myeloma regardless of eligibility for stem cell transplant, and pomalidomide for second or later line treatment of MM. The funding of these proposals changed the treatment paradigm for people with MM.

Further advice was sought from the Cancer Treatments Advisory Committee (CTAC) in July 2024 about the impact of this change on the paradigm and population, intervention, comparator and outcomes (PICO) associated with the daratumumab assessment. Based on this advice, the model for daratumumab was updated, as described in this report.

2.2. Special Authority Criteria

The proposal was reviewed by CTAC in July 2024 (see record) subsequent to the funding of lenalidomide and pomalidomide. They recommended that daratumumab be listed within the context of treatment of malignancy, subject to the following Special Authority criteria:

Initial application - (Relapsed/refractory multiple myeloma) from any relevant practitioner. Approvals valid for 12 months for applications meeting the following criteria:

All of the following:

1. Patient has relapsed or refractory multiple myeloma with progressive disease; and
2. Patient has received one prior line of therapy for multiple myeloma; and
3. Patient has not received prior funded daratumumab.

Renewal application – (Relapsed/refractory multiple myeloma) from any relevant practitioner. Approvals valid for 6 months where there is no evidence of disease progression.

The key change from the special authority criteria recommended in July 2021 is that daratumumab is not required to be taken with bortezomib.

2.3. PICO

The updated PICO agreed by CTAC in July 2024 is shown in the table below. The key change to this PICO table is that instead of individuals receiving daratumumab in combination with bortezomib and dexamethasone (DVd), individuals would receive triplet therapy with pomalidomide and dexamethasone (DPd), and would be able to receive bortezomib re-treatment on progression.

Table 1. Population, intervention, comparator and outcomes of proposal

Population	People with relapsed or refractory multiple myeloma disease after one prior line of therapy
Intervention	Daratumumab with **pomalidomide** and dexamethasone (DPd) (+/- bortezomib) *Subsequent treatment:* Bortezomib retreatment
Comparator(s) (NZ context)	Pomalidomide with dexamethasone (Pd) (+/- bortezomib) *Subsequent treatment:* Bortezomib retreatment
Outcome(s)	Longer PFS and OS
Table definitions: **P**opulation: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup) **I**ntervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation). **C**omparator: Details the therapy(s) that the patient population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation). **O**utcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.	

2.4. Quadruple therapy

CTAC considered (see record exert below) that people with relapsed/refractory MM would be treated with a quadruple therapy of daratumumab + pomalidomide + bortezomib + dexamethasone if they were fit enough.

"The Committee considered it possible that quadruple therapy could be used in younger fit people who have experienced disease relapse following first-line treatment, as the second line is the last efficacious line of treatment available in New Zealand, and clinicians may wish to trial all possible options in this line for people who could tolerate it."

3. Pharmac Cost-Utility Analysis

3.1. Model overview

The cost-utility model structure was adapted from previous modelling by Pharmac.

The core model and intervention arm was based on a model of daratumumab with bortezomib and dexamethasone (DVd), which was previously outlined in TAR 421 (Objective ID A1555232). The model structure was simplified to represent only a single population, compared to the original model which modelled those who were transplant eligible, ineligible but tolerant of bortezomib, and ineligible with intolerance to bortezomib, separately. These distinctions defined eligibility for lenalidomide at 2L and 3L.

This was no longer considered necessary as with the funding of pomalidomide and lenalidomide for multiple myeloma, the treatment paradigms in the intervention and comparator arms of the model are identical from second line onwards. This assessment adopted a three-state model structure (PFS – in which people receive DPd in the intervention arm and PVd or Pd in the comparator arm depending on their tolerance of bortezomib, progressed disease and death).

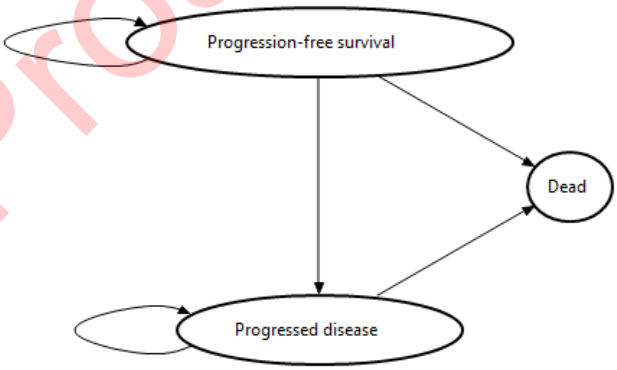

Figure 1. State transition diagram for model

The comparator arm treatment-specific costs and transition probabilities were sourced and adapted from previous models for pomalidomide plus dexamethasone +/- bortezomib, which are outlined in TARs 460 (Objective ID: A1542082) and 504 (Objective ID: A1675001).

Table 2. Summary of the TARs describing how each treatment regimen is modelled

Treatment regimen	TAR section
DPd scenario based on trial data	TAR 421a, Section 2.2.1
DPd scenario based on DVd observational data	TAR 421a, Sections 2.2.3 and 2.2.4
PVd	TAR 460, Section 3.3
Pd	TAR 504, Section 3.5.1.2

Specific changes to these previous models are outlined below.

3.2. Transformation and Extrapolation of Clinical Evidence

Changes made to the clinical parameters in the intervention arm of the model were based on evidence from the MM-015 trial (see section 3.2.1) in the base case. Scenario analyses were also undertaken as described below, representing:

- greater efficacy in the intervention arm if people with relapsed/refractory MM benefited from quadruple therapy (DPd with bortezomib) (see section 3.2.2)
- lesser efficacy in the intervention arm based on observational evidence of lower PFS and OS with DVd triplet therapy than reported in the CASTOR phase 3 trial (see sections **Error! Reference source not found.** and **Error! Reference source not found.**)

These changes are described in the following subsections.

3.2.1 Trial evidence of DPd (Base case)

The progression free survival (PFS) and overall survival (OS) of people with relapsed/refractory MM treated with DPd was modelled based on the evidence in the MM-014 trial. The MM-014 trial is a recent phase 2 trial (Bahlis et al. Leuk Lymphoma. 2022;63:1407-1417, Bahlis et al. Clin Lymphoma Myeloma Leuk. 2024;24:852-862) which reported the efficacy of DPd in people with relapsed/refractory MM, who had received prior treatment with lenalidomide. 62.5% of the trial population were individuals with only one prior line (1PL). A subgroup analysis in the 1PL group was also reported.

This trial evidence was chosen as it most closely matched the New Zealand population proposed for treatment, who are also a population with one prior line of treatment, and are expected to have been pre-treated with lenalidomide. Evidence from the APOLLO trial (Dimopoulos et al. Lancet Oncol. 2021;22:801-812), which is the key trial comparing

a DPd regimen to Pd, was from a patient population who had mostly had two or three previous lines of treatment, and therefore would likely underestimate survival with DPd in second line. It was considered that the benefit would also favour the intervention more than in the NZ context, as the comparator in NZ for the majority of patients is PVd rather than Pd, which is estimated to be a more efficacious regimen.

The median PFS was not reached in the 1PL subgroup, and 31 months in the intention to treat (ITT) population, of MM-014. The median OS in the 1PL group was 57 months. The Kaplan-Meier curves for PFS and OS in the 1PL subgroup are shown in figures 1 and 2 below. These curves were digitised and fitted with four parametric survival curves (Weibull, log-logistic, log-normal and exponential). The fit of each of these curves was assessed using the R-squared statistic and visual inspection. The Weibull and log-normal curves were used to extrapolate PFS and OS respectively, given that these had the highest R-squared statistics of the curves tested.

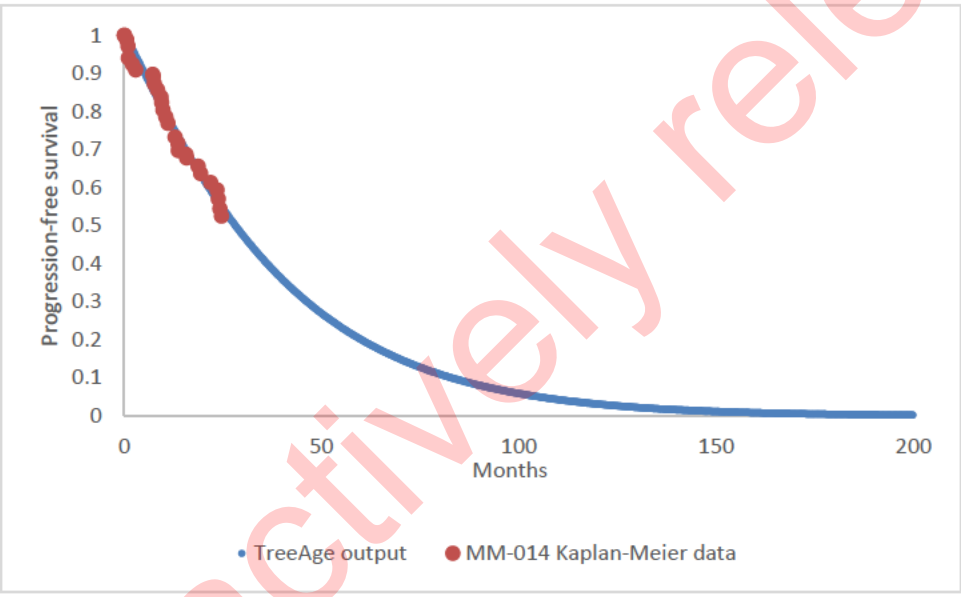

Figure 2. Progression free survival in people with relapsed/refractory MM with one prior line of treatment in the MM-014 trial (shown in red), and extrapolated in the TreeAge model (shown in blue)

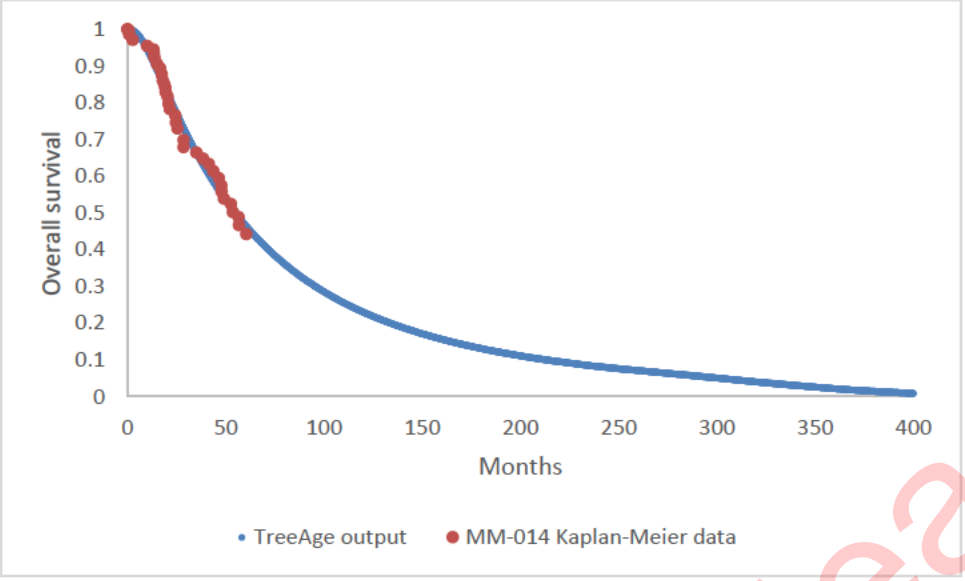

Figure 3. Overall survival in people with relapsed/refractory MM with one prior line of treatment in the MM-014 trial (shown in red), and extrapolated in the TreeAge model (shown in blue)

3.2.2 Quadruple daratumumab + pomalidomide + bortezomib + dexamethasone (DPd + bortezomib) treatment

Clinical advice Pharmac received suggested that clinicians may treat people with relapsed/refractory MM with DPd + bortezomib if the individual is well enough to receive this quadruple therapy (see section 2.4). No evidence supporting the addition of bortezomib to the daratumumab, pomalidomide, and dexamethasone (DPd) triplet regimen was identified in the application, through clinical advice, or via an unstructured search of the literature (Google Scholar).

It was considered whether the incremental benefit of daratumumab added to the PVd regimen could be approximated by the incremental benefit of daratumumab added to Pd in the APOLLO trial or Vd in the CASTOR trial. However using the incremental benefit from APOLLO was considered inappropriate for the same reason it was considered inappropriate to model DPd; the patients are more heavily pre-treated than the population being modelled.

CASTOR was also considered inappropriate to model the incremental benefit of daratumumab due to changes in the NZ treatment setting since DVd was modelled. Specifically, prior to lenalidomide and pomalidomide being funded in 2024, a bortezomib based triplet regimen (bortezomib, cyclophosphamide and dexamethasone, (CyBorD)) was the first line treatment option, with retreatment offered in second line. Retreatment with bortezomib is not considered especially effective.

Today, patients are offered lenalidomide in first line (with bortezomib and dexamethasone, RVd), and pomalidomide (with bortezomib and dexamethasone) in

second line. First line treatment with RVd is already considered to extend overall survival, and PVd in second line offers the patient a new agent compared to their first line treatment. For these reasons, the above method of estimating the incremental benefit of DPd + bortezomib was not used.

Therefore, in the base case, no additional benefit is modelled for those who may have this quadruple therapy compared to daratumumab triplet therapy, and quadruple therapy is modelled using the MM-014 trial data.

A scenario was tested, where a proportion of people with relapsed/refractory MM were assumed to have increased efficacy due to the addition of bortezomib. Two approaches were identified to approximate this:

1. The number who received quadruple therapy was assumed to be equal to the number of individuals who would have been transplant eligible in their first line of treatment. This was chosen as a proxy value for the number of people who would be “relatively fit” (per clinical advice). The proportion of people with relapsed/refractory MM (29%) who are estimated to be transplant eligible is previously detailed in TAR 421.
2. Pharmac staff noted an observational cohort study (Han et al. Cancer Med. 2024;13:e7232) for which only two of 24 patients receiving DPd therapy also received bortezomib as part of their treatment regimen. This would correspond to 8.3% of people using quadruple therapy.

A sensitivity analysis was run with the higher proportion (29%) receiving quadruple therapy, to test the materiality of the assumption. In the scenario analysis, the probabilities of progression and death for those receiving quadruple therapy were adjusted downwards with a multiplier of 0.95. The CUA results were not sensitive to this, and therefore it was not explored further.

3.3. Health-Related Quality of Life

The utility values included in the analysis have been previously described in TAR 421.

Previous modelling of DVd by Pharmac had included a treatment benefit to HRQoL for those treated with DVd compared to the cyclophosphamide plus bortezomib plus dexamethasone (CyBorD) (see TAR 421). This was included in the absence of evidence, as a treatment benefit was modelled for carfilzomib, and it was assumed a similar benefit would be present for DVd over CyBorD.

A study investigating the health-related quality of life of patients in the APOLLO trial (Terpos et al. Am J Hematol. 2022;97:481-490) suggested no statistically significant changes from baseline in patients' HRQoL when daratumumab was added to Pd. Despite the APOLLO trial being in a population who are further progressed than the

population of this proposal, this evidence was considered more relevant than the carfilzomib evidence the prior assumption was based upon.

Therefore, no HRQoL benefit specific to one treatment or the other for any given health state was modelled in the base case. However, a HRQoL benefit is still captured indirectly for patients receiving daratumumab, as they are modelled to remain in the progression-free survival state for longer—an average of 12 months, compared to 4.5 months in the APOLLO trial. Since HRQoL is higher in the PFS state than in the progressed disease (PD) state, this extended time in PFS contributes to an overall increase in quality-adjusted life years.

A scenario analysis was undertaken to test the impact of including a HRQoL benefit within given health state for individuals treated with the intervention. The values used in this scenario are described in TAR 421.

3.4. Costs

Most of the costs used in this analysis have been previously described in TAR 421 and TAR 460. Any changes made are described in the sections below.

3.4.1 Pharmaceutical cost

The cost of daratumumab, pomalidomide and bortezomib where they are part of the DPd +/- bortezomib regimen is outlined in Table 3below. The dosing regimen for DPd is based on the APOLLO trial (Dimopoulos et al, 2021). This dosing is slightly more frequent than the regimen previously modelled for DVd (based on the CASTOR trial) as from the ninth week of treatment, dosing is every two weeks in APOLLO, compared to every three weeks in CASTOR. This results in the average cost per cycle being slightly higher than the previously modelled DVd regimen.

In absence of a published DPd + bortezomib regimen, the dosing for bortezomib in combination with both daratumumab and pomalidomide with dexamethasone, was assumed to be equal to that of the CASTOR trial. Bortezomib is costed for only the proportion of patients who were considered likely to be well enough to be treated with quadruple therapy (29%, see section 3.2.2).

Table 3. Pharmaceutical cost of DPd

	Daratumumab	Pomalidomide	Bortezomib
Form, strength and pack size	1800mg vial	21 x 4mg tablets	3.5mg vial
Net price per pack	s 9(2)(b)(ii), s 9(2)(j)	$284.71[2]	$74.93
Regimen[4]	1800 mg subcutaneously weekly during cycles[3] 1 and 2, every 2 weeks during cycles 3–6, and every 4 weeks thereafter	4 mg, once daily on days 1–21	1.3mg/m2, 4 times per 21 day cycle for 8 cycles

1. s 9(2)(b)(ii), s 9(2)(j)
2. Pharmac schedule
3. Cycles are 28 days.
4. Per APOLLO trial

The duration of treatment modelled for DPd is described below.

3.4.1.1 Duration of treatment of daratumumab

The time on treatment (ToT) of daratumumab in the 1PL subgroup of the MM-014 trial was not reported. Instead, ToT was estimated based on the ratio of median ToT and median PFS in the ITT population. This method was used in the absence of treatment discontinuation curves. The median ToT for the ITT population was 15.2 months (Bahlis et al., 2024) and the median PFS was 23.7 months (Bahlis et al., 2022), resulting in a ratio of 0.64 (15.2/23.7). It was assumed that the ToT in the 1PL subgroup was 61% of the mean time spent in PFS also.

In MM-014, the treatment durations of pomalidomide and daratumumab were very similar, at 15.7 months and 15.2 months respectively, therefore pomalidomide was modelled to have the same duration as daratumumab in the DPd regimen.

It was considered that there remained some uncertainty around this ratio of ToT:PFS. It was noted that the ratio in the APOLLO study ITT population (a phase 3 trial of DPd vs Pd in previously treated MM, Dimopoulos et al. Lancet Oncol 2021;22:801-12) was significantly higher, at 93% (median ToT = 11.5 months and median PFS = 12.4 months). This ratio was used as a scenario in the sensitivity analysis.

3.5. Cost-Effectiveness Results

The incremental cost was estimated at s 9(2)(b)(ii), s 9(2)(j) with a QALY gain of 0.85. The cost-utility is estimated to be s 9(2)(j), s 9(2)(b)(ii) QALYs per $1m (or cost per QALY of s 9(2)(j), s 9(2)(b)(ii)). This is shown in Table 4.

Table 4. Cost-Effectiveness Results

	Intervention	Status Quo	Incremental
QALYs	3.51	2.66	0.85
Cost	s 9(2)(b)(ii), s 9(2)(j)		
QALYs per $1m			s 9(2)(b)(ii), s 9(2)(j)

3.5.1 Sensitivity Analysis

A range of one-way sensitivities were run. Results of sensitivity analyses are displayed in the table below

Table 5. Sensitivity Analysis

Input/Scenario Tested	**Base-Case Value**	**Alternate value**	**QALYs per $m**
Base Case	-	-	s 9(2)(j), s 9(2)(b)(ii)
One-way sensitivities			
No individuals treated with quadruple intervention treatment (DPd + bortezomib)	29%	8.3%%	
Individuals treated with quadruple therapy have an additional efficacy benefit (see section 3.2.2)	-	-	
Individuals treated with the intervention receive a treatment benefit to HRQoL. HRQoL in PFS health state equal to:	0.714	0.741	
Treatment duration to PFS ratio based on APOLLO trial	0.64	0.93	

The likely range is defined by a scenario using a variation in the treatment duration to PFS ratio, and a scenario where there is a HRQoL benefit for patients treated with the intervention. This is shown in the table below.

Table 6. Summary of the Likely Cost-utility Range

Input/Scenario Tested	Incremental Cost	Incremental QALY	QALYs per $m
Individuals treated with the intervention receive a treatment benefit to HRQoL	s 9(2)(b)(ii), s 9(2)(j)	0.93	s 9(2)(b)(ii), s 9(2)(j)
Treatment duration to PFS ratio based on APOLLO trial		0.85	

3.5.2 Summary of Overall Cost-Effectiveness

As outlined above, the base-case cost utility, in QALY per $1m, i s 9(2)(b)(ii), s 9(2)(j) Considering the results of the sensitivity analysis, the likely range is estimated to be s 9(2)(b)(ii), s 9(2)(j) his range captures uncertainty in what the likely treatment duration would be, and whether a treatment HRQoL benefit exists.

4. Budget Impact Analysis

4.1. Patient numbers

The estimated patient numbers for people with MM with 1PL of treatment have been detailed previously in TAR 504 (Objective ID: A1675001).

4.1.1 Data from the Australian Pharmaceutical Benefits Scheme (PBS)

Data from the Australian Pharmaceutical Benefits Scheme (PBS) was also considered to inform this assumption.

PBS data for patients initiating Daratumumab as second-line therapy for multiple myeloma for 2024[1] :

- 244 in-hospital IV dispensing's (codes: 12228N, 12230Q)
- 7,700 subcutaneous dispensing's (codes: 12683M, 12746W)

These codes specifically capture initial treatment during weeks 1 to 9, administered once weekly.

Assuming subcutaneous patients received an average of 8 dispensing's (to account for early discontinuation and some completing initiation in 2025), this suggests approximately 963 patients initiated subcutaneous Daratumumab in 2024.

In-hospital IV use appears minimal, with the volume suggesting fewer than 10 patients.

[1] Note Australia funded daratumumab for multiple myeloma in January 2021. https://www.health.gov.au/ministers/the-hon-greg-hunt-mp/media/pbs-listings-bring-greater-hope-in-fight-against-multiple-myeloma-and-severe-psoriasis

Using a straight population-based extrapolation[2], this would imply an incident population of approximately 185 patients in New Zealand initiating Daratumumab for MM in its fourth year of funding.

Our estimate of 285 incident cases might therefore be considered conservative. We have estimated a higher figure because the MM patient population in NZ is highly engaged and connected to health professions so we would expect a high uptake rate.

Initial data on uptake of pomalidomide in relapsed/refractory MM would also indicate a higher uptake than is suggested by this approach based on PBS data. Special authority dispensing data[3] show that 255 patients have been dispensed pomalidomide for relapsed/refractory MM in nine months, which could indicate an uptake of approximately 340 patients (255*(12/9)) over 12 months. Pomalidomide is indicated for any relapsed/refractory MM, not just those seeking 2L treatment, so we would expect this estimate to be higher than for daratumumab in the first year. Nonetheless, the data suggest that uptake for this population could be higher than what is seen in Australia.

For this reason, Pharmac have retained the previous estimate of patient numbers, seen in Table 8 below.

4.2. Results

The budget impact is uncertain due to uncertainty in time on treatment (ToT) for daratumumab. In order to be conservative, Pharmac has used the upper estimate of the ToT to PFS ratio that was used in the CUA (ie. a ratio that indicates that individuals are on treatment for 93% of the time that they are in the PFS health state).

The budget impact (five-year net present value (NPV)) to the Combined Pharmaceutical Budget (CPB) is estimated to be s 9(2)(b)(ii), s 9(2)(j) with a cost in the first 12 months of s 9(2)(b)(ii), s 9(2)(j) This is outlined in

Table 7 below. The budget impact (five-year NPV) to the wider health system (pharmaceutical costs and other costs to the sector) is estimated to be s 9(2)(b)(ii), s 9(2)(j) All costs are discounted at a rate of 8%.

[2] Considering the Australian general population is just over five times that of the New Zealand general population.
[3] Qlik data, August 2024- April 2025, Patients with initial approvals for pomalidomide. Data accessed: 11 June 2025.

Table 7. Net Budget Impact to health system

	Year 1	Year 2	Year 3	Year 4	Year 5	5-Year NPV
Number of patients initiating treatment	268	273	279	285	291	-
Total patient years on treatment	220	387	514	609	682	
Net Cost to Pharmaceutical Budget	s 9(2)(b)(ii), s 9(2)(j)					
Net Cost to Other Health System Budgets						
Net Cost to Health System						