Analysis of medicines to treat multiple myeloma

**Drug utilisation sub-committee (DUSC)**

***September 2017***

## Abstract

### Purpose

At its June 2017 meeting, DUSC requested a review of medicines to treat multiple myeloma supplied through the Pharmaceutical Benefits Scheme (PBS) and Repatriation Pharmaceutical Benefits Scheme (RPBS). A predicted versus actual analysis for pomalidomide was also undertaken.

### Date of listing on the Pharmaceutical Benefits Scheme (PBS)

| **Drug** | **Abridged restriction** | **Date** |
| --- | --- | --- |
| Thalidomide | Relapsed or refractory multiple myeloma. | 1 February 2006 |
| Bortezomib | As monotherapy or in combination with a corticosteroid for multiple myeloma after at least 1 prior therapy (except thalidomide). | 1 November 2007 |
| Thalidomide | Multiple myeloma. | 1 September 2009 |
| Lenalidomide | As monotherapy or in combination with dexamethasone for multiple myeloma after at least 1 prior therapy.  | 1 November 2009 |
| Bortezomib | Newly diagnosed patients with symptomatic multiple myeloma. | 1 October 2012 |
| Pomalidomide | In combination with dexamethasone for multiple myeloma after prior treatment failure with bortezomib and treatment failure with lenalidomide. | 1 August 2015 |
| Lenalidomide | In combination with dexamethasone for newly diagnosed patients with multiple myeloma. | 1 February 2017 |

See [**the PBS website**](http://www.pbs.gov.au/pbs/home) for full details of the restrictions.

### Data Source / Methodology

The prescription dispensing data were extracted from the Department of Human Services (DHS) prescription database. This contained non-identifying patient level PBS & RPBS (R/PBS) data for the time period 1 July 2013 to 31 December 2016. The medicines to treat multiple myeloma (MM) that were included in the analysis were thalidomide, bortezomib, lenalidomide and pomalidomide.

Data extracted from DHS was used to determine the date of death of patients. Data was supplied for patients who died in the time period 1 July 2013 and 31 December 2016.

R/PBS data were used to determine:

1) the prevalent and incident populations treated with the PBS listed medicines for multiple myeloma

2) clinical pathways of use of medicines for multiple myeloma, including first, second and third line treatment.

3) the duration of treatment with medicines for multiple myeloma

4) the extent of co-prescribing of two or more medicines for multiple myeloma.

5) the consistency of use of PBS subsidised medicines for multiple myeloma with the recommendations in Australian guidelines ([1](#_ENREF_1)) and the PBS restrictions.

### Key Findings

* Overall, 9,445 people received 204,947 dispensings for the medicines listed for multiple myeloma in the period 1 July 2013 to 31 December 2016. The number of people receiving treatment rose from 9.4 per 100,000 in July 2013 to 11.8 per 100,000 in December 2016.
* 1,826 people initiated therapy with the medicines listed for multiple myeloma in 2016, with most initiating bortezomib. Their median age was 70 years. This is consistent with AIHW (2013) estimates of incidence of approximately 1,600 persons per year.
* 61% of people treated for multiple myeloma received one therapy only in the period 2014-2016, with two-thirds of these receiving therapy with bortezomib only, a quarter receiving thalidomide only, and the remaining receiving therapy with lenalidomide only. Where people did require a second therapy, the most common pathways were from bortezomib to thalidomide, and thalidomide to lenalidomide.
* For patients eligible for stem cell transplant who initiated therapy in 2014, the median duration of the first episode on bortezomib was 3 months; it was 3.5 months for other bortezomib; it was 5 months for thalidomide and 9.5 months for lenalidomide.
* Analysis on cumulative duration of all episodes on any medicine showed a median duration of 282 days (95% CI 269-293). Analysis on cumulative duration of all breaks (gaps) in medicine coverage showed a median duration of 29 days (95% CI 21-39). The majority of the people survived the two year follow-up (Figure 9); overall 11% died within the follow-up period.
* There was very little co-prescribing. Only 1% of all 9,445 people with a multiple myeloma medicine between 1 July 2013 and 31 December 2016 had concurrent use of two medicines listed for multiple myeloma for a whole month at some point of time.
* Utilisation was mostly consistent with guideline recommendations and PBS restrictions. The use found outside the recommendations was for pomalidomide which was first or second line therapy in 1% of people, and for lenalidomide as first line therapy. The analysis showed that lenalidomide accounted for 6% of first line medicine use when assessed across the 2014 to 2016 cohort, and up to 12% when assessed in the 2014 cohort alone.

# Background

Multiple myeloma (MM) is a plasma cell malignancy. Approximately 1,600 new cases are diagnosed in Australian each year ([2](#_ENREF_2)). Multiple myeloma mostly affects older people with median age at diagnosis of 65-70 years ([3](#_ENREF_3)). Although there is no cure for MM, survival outcomes have improved because of various treatment options.

Medicines for the treatment of multiple myeloma were reviewed by DUSC at its meeting in October 2013. The analysis included thalidomide, lenalidomide and bortezomib. Since the 2013 review, there have been new medicines and different lines of therapy introduced to the PBS.

Within this context, analysis of the use of medicines for multiple myeloma through the PBS/RPBS was undertaken.

## Pharmacology

The mechanism of action of thalidomide has not been confirmed. Its effect in myeloma is thought to be due to inhibition of myeloma cell growth and survival, anti-angiogenesis, suppression of the production of tumour necrosis factor-α , inhibition of selected cell surface adhesion molecules that assist leukocyte migration, shifts in the ratio of CD4+ lymphocytes (helper T cells) to CD8+ lymphocytes (cytotoxic T cells), and effects on interleukins (IL) and interferon-γ.

Lenalidomide and pomalidomide are analogues of thalidomide. Additionally, pomalidomide inhibits the proliferation of, and synergised with dexamethasone to induce apoptosis of, lenalidomide-resistant multiple myeloma cell lines.

Bortezomib is a reversible inhibitor of the activity of the 26S proteasome in mammalian cells. The inhibition of 26S proteasome prevents targeted proteolysis, affecting cell signalling cascades and leading to cell death.

Source: [TGA Product Information](https://www.tga.gov.au/product-information-pi) for thalidomide5, lenalidomide6, pomalidomide7 and bortezomib8.

## Therapeutic Goods Administration (TGA) approved indications

**Thalidomide** has the following indications for multiple myeloma

* In combination with melphalan and prednisone for treatment of untreated patients aged ≥ 65 years or ineligible for high dose chemotherapy.
* In combination with dexamethasone as induction therapy prior to high dose chemotherapy with autologous stem cell rescue in previously untreated patients.
* As monotherapy after the failure of standard therapies.

Thalidomide is also indicated for erythema nodosum leprosum (a complication of leprosy).

**Lenalidomide** has the following indications for multiple myeloma

* Treatment of newly diagnosed multiple myeloma patients who are ineligible for autologous stem cell transplantation.
* In combination with dexamethasone for treatment of patients whose disease has progressed after one therapy.

Lenalidomide is also indicated for myelodysplastic syndromes and mantle cell lymphoma.

**Pomalidomide** in combination with dexamethasone, is indicated for the treatment of patients with relapsed and refractory multiple myeloma who have:

* received at least two prior treatment regimes, including both lenalidomide and bortezomib, and
* have demonstrated progression on the last therapy.

Thalidomide, lenalidomide and pomalidomide all have boxed warnings about birth defects if taken during pregnancy and advising against pregnancy until four weeks after ceasing the medicine.

**Bortezomib** has the following indications for multiple myeloma

* Treatment of previously untreated multiple myeloma in patients who are not candidates for high dose chemotherapy in combination with melphalan and prednisone.
* As part of combination therapy, for induction therapy prior to high dose chemotherapy with autologous stem cell rescue for patients under 65 years of age with previously untreated multiple myeloma.
* Treatment of multiple myeloma in patients who have received at least one prior therapy, and who have progressive disease

Bortezomib is also indicated for mantle cell lymphoma in combination with rituximab, cyclophosphamide, doxorubicin and prednisone.

Further details are available in the Product Information (PI) and Consumer Medicine Information (CMI) available from [the TGA (Product Information)](http://tga.gov.au/hp/information-medicines-pi.htm) and [the TGA (Consumer Medicines Information)](http://www.tga.gov.au/consumers/information-medicines-cmi.htm).

## Dosage and administration

The dosage and administration details presented below were extracted from the Product Information documents, for thalidomide, bortezomib, lenalidomide and pomalidomide, and the PBS website.

Table 1: Dosage and administration of medicines for multiple myeloma

| Medicine | Dose and frequency of administration  | PBS restriction (selected information relating to combination use, for further information refer to the current PBS schedule and the ‘PBS listing details’ section in this report) |
| --- | --- | --- |
| BORTEZOMIB (powder for injection) 1mg, 3mg, 3.5mg | Dose: 1.3g/m2 of body surface area (BSA). For intravenous or subcutaneous use only.**Patients with untreated Multiple Myeloma eligible for autologous stem cell transplant (ASCT)*** Bortezomib in combination with **thalidomide and dexamethasone** (for induction therapy): Bortezomib administered on days 1, 4, 8 and 11 of a 21-day cycle, for 3 cycles. Thalidomide given at 100mg orally on days 1-14 of the first cycle, and given at 200mg orally per day for every day of cycles 2 and 3.
* In combination with **dexamethasone only:** Administered on days 1 , 4, 8 and 11 of a 21-day cycle, for 4 cycles

**Patients with untreated Multiple Myeloma not eligible for ASCT*** In combination with melphalan and prednisone: Administered in nine 6-week treatment cycles. In cycles 1-4, administered twice weekly (days 1, 4, 8, 11, 22, 25, 29 and 32). In cycles 5-9, administered once weekly (days 1, 8, 22 and 29).

**Relapsed/Refractory Multiple Myeloma*** Administered on days 1, 4, 8 and 11 of a 21 day cycle. Patients with a confirmed response should receive 2 additional cycles, responding patients who do not achieve complete remission receive 8 cycles.
* Extended therapy (cycle 8 onwards): Days 1, 8, 15, and 22 followed by a 13 day rest period (days 23-35).

Prior to initiating a new cycle of therapy: • Platelet count should be ≥70 x 109 /L and the ANC should be ≥ 1.0 x 109 /L • Non-haematological toxicities should have resolved to Grade 1 or baseline. | **First line*** Must be in combination with chemotherapy, and not receiving PBS subsidised thalidomide, lenalidomide or pomalidomide.

**Second line** **and subsequent*** Must be as monotherapy or in combination with a corticosteroid and/or cyclophosphamide.
* Must not be receiving PBS subsidised lenalidomide or pomalidomide.
 |
| THALIDOMIDE (capsules)50mg, 100mg | **Patients with Untreated Multiple Myeloma*** In combination with Melphalan and Prednisone: Give at a starting dose of 200 mg orally per day (for > 75 years 100mg) for a maximum of 12 cycles of 6 weeks.
* In combination with Dexamethasone (for induction therapy): Given at a starting dose of 200 mg orally per day (for > 75 years 100mg) for 4 cycles of 4 weeks.
* In combination with bortezomib and dexamethasone (for induction therapy): See bortezomib administration.

**After Failure of Standard Therapies** * Monotherapy: Given at a starting dose on 200 mg orally daily (for elderly 50mg) and increased by 100 mg at weekly intervals to a maximum dose of 400 mg daily according to tolerance and toxicity.

Depending on tolerance and observed toxicity, lower maintenance doses can be used. The required total duration of treatment should be individually determined for each patient depending on tolerability and disease progression. | For treatment of multiple myeloma. |
| LENALIDOMIDE (capsules)5mg, 10mg, 15mg, 20mg, 25mg | **Newly Diagnosed Multiple Myeloma in Patients Not Eligible for ASCT** * In combination with dexamethasone: Given at a starting dose of 25 mg orally once daily on days 1-21 of repeated 28- day cycles.

**Previously treated**  **Multiple Myeloma*** In combination with dexamethasone: Given at a starting dose of 25 mg orally once daily on Days 1-21 of repeated 28- day cycles.

Treatment should be continued until disease progression or unacceptable toxicity. Dose reductions are recommended to manage Grade 3 or 4 neutropenia or thrombocytopenia, or other Grade 3 or 4 toxicities judged to be related to lenalidomide. | **Initial treatment*** Must be in combination with dexamethasone
* Must not be receiving PBS subsidised bortezomib

Second line and subsequent* Must be as monotherapy or in combination with dexamethasone
* Must not be receiving PBS subsidised bortezomib
 |
| POMALIDOMIDE (capsules)3mg, 4mg |  **Relapsed/Refractory Multiple Myeloma*** In combination with dexamethasone: Given at a starting dose of 4 mg orally daily on Days 1-21 of repeated 28-day cycles until disease progression.

To initiate a cycle of pomalidomide, the platelet count must be ≥ 50 x 109/L and the neutrophil count must be ≥ 1.0 x 109 /L. | **Third line and subsequent therapy*** Must be in combination with dexamethasone.

Must not be receiving PBS subsidised thalidomide, lenalidomide or pomalidomide. |

Source: [TGA Product Information](https://www.tga.gov.au/product-information-pi) and the [PBS website](http://www.pbs.gov.au/pbs/home).

Further details are available in the Product Information (PI) and Consumer Medicine Information (CMI) available from [the TGA (Product Information)](http://tga.gov.au/hp/information-medicines-pi.htm) and [the TGA (Consumer Medicines Information)](http://www.tga.gov.au/consumers/information-medicines-cmi.htm).

## Clinical situation – Australian Guidelines

The Clinical Practice Guideline: Multiple Myeloma (1) (the Australian Guidelines) developed by the Medical Scientific Advisory Group to the Myeloma Foundation of Australia, provides recommendations on a number of administration and treatment options. There are combination therapies recommended in the Guidelines that are not included the Product Information of the medicines, and are not allowable under the current PBS restrictions. In addition, the Guidelines also recommend once weekly intravenous or subcutaneous administration of bortezomib to improve tolerability.

Since the previous DUSC review of multiple myeloma medicines in 2013, the criteria for diagnosis of symptomatic myeloma has changed to include biomarkers of malignancy. The following description of treatment practices is based on the Australian Guidelines(1).

Initial treatment of multiple myeloma is dependent on the patient’s eligibility for high dose chemotherapy (HDC) and autologous stem cell transplant (AuSCT). For patients less than 65 years of age, or between 65-70 years of age with a good performance status and organ reserve, standard treatment is HDC and AuSCT.

### Patients eligible for AuSCT

*Initial therapy*

Patients receive 3-6 cycles of induction therapy prior to AuSCT. Induction regimes may be proteasome inhibitor based (bortezomib), immunomodulatory drug based (thalidomide or lenalidomide), combination (bortezomib with thalidomide/lenalidomide), or chemotherapy based. These regimens include dexamethasone +/- cyclophosphamide. The incorporation of proteasome inhibitors and/or immunomodulatory drugs as part of induction therapy is considered standard of care. Three-drug combinations are preferred to two-drug combinations. Combination induction therapy was not recommended in the 2013 Guidelines considered in the previous DUSC review.

The choice of induction therapy is dependent on a patient’s age and co-morbidities, as well as local availability and access to medicines. In Australia, only bortezomib and thalidomide, but not lenalidomide, are PBS listed for induction therapy for patients who are eligible for AuSCT. The PBS does not allow the concurrent use of bortezomib and thalidomide or lenalidomide.

Induction therapy is followed by mobilisation and harvesting of the patient’s stem cells, high dose chemotherapy and transplantation of stem cells. AuSCT is not curative.

*Maintenance therapy post AuSCT*

Consolidation therapy (a short treatment course after AuSCT that improves depth of response) is not routinely recommended in Australia.

Maintenance therapy with thalidomide with or without corticosteroids is recommended for 12 months following AuSCT. Lenalidomide may also be used as maintenance therapy, but it is not subsidised on the PBS for this use.

### Patients ineligible for AuSCT

*Initial therapy*

Patients ineligible for AuSCT will generally receive pharmacological treatment. Currently accepted standard of care is continuous lenalidomide in combination with dexamethasone, or bortezomib in combination with melphalan (or cyclophosphamide) and prednisolone. A weekly or subcutaneous schedule of bortezomib is recommended. Thalidomide in combination with melphalan and prednisolone should only be used if bortezomib and lenalidomide are contraindicated. For unfit elderly patients, bortezomib in combination with dexamethasone should be considered. Bortezomib in combination with a corticosteroid, *without* melphalan (or cyclophosphamide), is only PBS subsidised in patients with severe acute renal failure in this setting.

*Maintenance therapy*

The benefit of maintenance therapy is most evident for lenalidomide in combination with dexamethasone. However, this lacks firm data if the patient is initially treated with a thalidomide or bortezomib based induction regime. Lenalidomide is not registered or reimbursed for this indication. The benefits of thalidomide or bortezomib based maintenance therapy is unclear.

### Relapsed/refractory multiple myeloma

There is no single standard treatment for patients with relapsed/refractory multiple myeloma. In Australia, the main treatment options are immunomodulatory drugs (including thalidomide, lenalidomide and pomalidomide), bortezomib, alkylating agents, anthracyclines and corticosteroids. These are administered alone, or in various combinations and sequences. Selected patients may undergo HDT with AuSCT.

The choice of treatment depends on prior treatment, response to prior treatment, co-morbidities and general health.

### Emerging novel therapeutics

There are a number of emerging novel therapeutics for the treatment of multiple myeloma, including second generation proteasome inhibitors (carfilzomib and ixazomib), monoclonal antibodies (daratumumab and elotuzumab), and histone deacetyclase inhibitors (panabinostat). These medicines have recently been approved by the Food and Drug Administration (FDA) for relapsed/refractory multiple myeloma.

The PBAC (July 2017) recommended carfilzomib for listing for the treatment of in relapsed or refractory multiple myeloma. Carfilzomib has yet to list on the PBS.

## PBS listing details (as at 1 August 2017)

The R/PBS listings for thalidomide, bortezomib, lenalidomide and pomalidomide are summarised in Table 2. Further details about all current R/PBS listings as at August 2017 are provided in Attachment 1.

Thalidomide has S100 private Authority Required and S100 Authority Required (STREAMLINED) listings.

### Restrictions (abridged versions)

**Thalidomide**

Thalidomide has a Section 100 (Highly Specialised Drugs) listing for ‘multiple myeloma’. The S100 HSD Private listing is Authority Required, the S100 HSD Public listing is Authority Required (STREAMLINED). Patients receiving thalidomide under the PBS listing must be registered in the sponsor’s i-access risk management program which aims to avoid embryo-foetal exposure to the drug.

Thalidomide was first listed from 1 February 2006 for relapsed or refractory multiple myeloma. The listing changed to the treatment of ‘multiple myeloma’ from 1 September 2009.

Table 2: Overview of R/PBS listings multiple myeloma medicines

| **First line** | **Second line and subsequent** | **Third and subsequent lines of therapy** |
| --- | --- | --- |
| **Bortezomib*** eligible for high-dose chemotherapy and autologous stem cell transplant (4732C, 7275X)
* ineligible for high dose chemotherapy (initial 4403R, 7238Y and continuing 4429D, 7274W)
* severe acute renal failure (initial 4403R, 7238Y and continuing 4429D, 7274W)
 | **Bortezomib** (treatment of progressive disease)* initial [4 cycles], continuing [4 cycles] 4706Q, 7268M, continuing 4712B, 7269N [additional 3 cycles]
 | **Bortezomib** (retreatment of progressive disease)* initial [4 cycles], continuing [4 cycles] 4713C, 7271Q, continuing [additional 3 cycles] 4725Q, 7272R
 |
| **Lenalidomide** (newly diagnosed)* ineligible for primary stem cell transplant (initial and continuing)

11055W, 11042E, 11063G, 11036W, 11041D, 11062F, 11064H, 11029L | **Lenalidomide** (relapsed/refractory)* initial and continuing

9645P, 9644N, 9643M, 9642L, 5786M, 5785L, 5784K, 5783J | **Lenalidomide** * initial and continuing(same item codes as relapsed refractory)
 |
| **Thalidomide*** multiple myeloma

6469L, 9566L, 9667T, 9684Q | **Thalidomide*** multiple myeloma

(same item codes as 1st line) | **Thalidomide*** multiple myeloma

(same item codes as 1st line) |
|  |  | **Pomalidomide*** must have experienced treatment failure to both bortezomib AND lenalidomide.
 |

For details of the current PBS listing refer to the [PBS website](http://www.pbs.gov.au/pbs/home).

**Lenalidomide**

Lenalidomide has a S100 (Highly Specialised Drugs) Authority Required listing for treatment:

* in combination with dexamethasone of patients with newly diagnosed multiple myeloma who are ineligible for primary stem cell transplant; and
* relapsed or refractory multiple myeloma in patients in whom thalidomide therapy has failed or in whom there is severe intolerance/toxicity to thalidomide.

The following is an abridged version of the PBS restrictions for lenalidomide. For the full copy of the restriction, including definitions of progressive disease, treatment failure and severe intolerance, refer to the [PBS website](http://www.pbs.gov.au).

**Newly diagnosed multiple myeloma (listed from 1 February 2017)**

For initial PBS-subsidised treatment - all conditions must be met:

* the condition must be newly diagnosed,
* the condition must be confirmed by a histological diagnosis,
* patient must be ineligible for primary stem cell transplantation,
* patient must not be receiving PBS subsidised bortezomib for this condition,
* the treatment must be in combination with dexamethasone.

**Relapsed or refractory multiple myeloma (listed from 1 November 2009)**

For initial PBS-subsidised treatment - all conditions must be met:

* The condition must be confirmed by a histological diagnosis,
* the treatment must be as monotherapy or given in combination with dexamethasone,
* patient must have progressive disease after at least one prior therapy,
* patient must have undergone or be ineligible for a primary stem cell transplant,
* patient must have experienced treatment failure after a trial of at least four (4) weeks of thalidomide at a dose of at least 100 mg daily or have failed to achieve at least a minimal response after eight (8) or more weeks of thalidomide-based therapy for progressive disease,
* the patient must not be receiving concomitant PBS-subsidised bortezomib.

For continuing PBS-subsidised treatment – all conditions must be met:

* patient must have previously received an authority prescription for lenalidomide,
* patient must not have progressive disease,
* the treatment must be as monotherapy or the treatment must be in combination with dexamethasone.

**Bortezomib**

Bortezomib has numerous Authority Required PBS listings for multiple myeloma through the Efficient Funding of Chemotherapy Program.

The following is an abridged version of the restrictions. All authority applications must be made in writing. For the full copy of the restriction, including definitions of progressive disease, treatment failure, and sever intolerance, refer to the current PBS schedule.

**Multiple myeloma** - **Treatment of progressive disease (listed from 1 November 2007)**

The restrictions where amended on 1 March 2011 to allow for re-treatment of progressive disease.

Initial treatment (4706Q, 7268M cycles 1-4 and 5-8) – all conditions must be met:

* the condition must be confirmed by a histological diagnosis,
* the treatment must be as monotherapy; or in combination with a corticosteroid and/or cyclophosphamide,
* patient must have progressive disease after at least one prior therapy,
* patient must have undergone or be ineligible for a primary stem cell transplant,
* patient must have experienced treatment failure after a trial of at least four weeks of thalidomide at a dose of at least 100 mg daily or have failed to achieve at least a minimal response after eight (8) or more weeks of thalidomide-based therapy for progressive disease,
* the patient must not be receiving PBS subsidised lenalidomide.

To qualify for cycles 5-8, patients are required to have at least a partial response after cycle 4.

Continuing treatment (4712B, 7269N cycles 9-11) – all conditions must be met:

* the patient must have previously received 8 treatment cycles of bortezomib for progressive disease,
* have demonstrated at the completion of cycle 8 at least a partial response to bortezomib,
* must not have received 2 treatment cycles after first achieving a confirmed complete response,
* must not have a gap of more than 10 months between initial application and completion of 8 cycles,
* the treatment must be as monotherapy or in combination with a corticosteroid and/or cyclophosphamide.

**Multiple myeloma** – **Retreatment of progressive disease (listed from 1 March 2011)**

Initial treatment (4713C, 7271Q cycles 1-4 and 5-8) – all conditions must be met:

* the treatment must be as monotherapy or in combination with a corticosteroid and/or cyclophosphamide,
* the patient must have progressive disease,
* the patient must have been previously been treated with PBS-subsidised bortezomib and have experienced at least a partial response to the most recent course,
* the patient must not be receiving PBS subsidised lenalidomide or pomalidomide.

To qualify for cycles 5-8, patients must demonstrate at least a partial response after cycle 4.

Continuing retreatment (4725Q, 7272R cycles 9-11) – all conditions must be met:

* the treatment must be as monotherapy or in combination with a corticosteroid and/or cyclophosphamide,
* the patient must have previously received 8 treatment cycles of bortezomib in the current treatment course,
* the patient must have demonstrated at the completion of cycle 8 at least a partial response to bortezomib,
* the patient must not have received 2 treatment cycles after first achieving a confirmed compete response,
* the patient must not have a gap of more than 10 months between an initial application and completion of 8 cycles.

**Symptomatic multiple myeloma** (listed from 1 October 2012)

Initial treatment (cycles 1-4; 4403R, 7238Y) – all conditions must be met:

* in newly diagnosed patients ineligible for high dose chemotherapy,
* the treatment must be given in combination with a corticosteroid and melphalan or cyclophosphamide,
* the patient must not be receiving PBS subsidised thalidomide, lenalidomide or pomalidomide,
* the patient must not receive more than 4 cycles of treatment with bortezomib under this restriction.

OR

In newly diagnosed patients with severe acute renal failure (who require dialysis or are at high risk of requiring dialysis):

* the treatment must be given in combination with a corticosteroid and/or cyclophosphamide,
* the patient must not be receiving PBS subsidised thalidomide, lenalidomide or pomalidomide,
* the patient must not receive more than 4 cycles of treatment with bortezomib under this restriction.

Continuing treatment (cycles 5-10; 4429D, 7274W) – all conditions must be met:

* the patient must have received an initial authority prescription and be ineligible for high dose chemotherapy,
* the patient must not have progressive disease at the time of the application,
* the patient must not have achieved a best confirmed response to bortezomib at the time of application,
* the patient must not be receiving PBS subsidised thalidomide, lenalidomide or pomalidomide,
* the patient must be used in combination with a corticosteroid and melphalan or cyclophosphamide,
* the patient must not receive more than 5 cycles of treatment with bortezomib under this restriction.

OR

If the patient has received an initial authority prescription and has severe acute renal failure:

* the patient must have demonstrated at least a partial response at the completion of cycle 4,
* the treatment is to be used in combination with a corticosteroid and/or cyclophosphamide,
* the patient must not be receiving PBS subsidised thalidomide, lenalidomide or pomalidomide,
* the patient must not receive more than 5 cycles of treatment with bortezomib under this restriction.

For this first line symptomatic multiple myeloma listing, cycles 1-4 of both renal failure and ineligible for high dose chemotherapy restrictions are in the single item code. Likewise for cycles 5-10 both restrictions are also in a single continuing restriction.

**Symptomatic multiple myeloma – induction treatment** (listed from 1 October 2012)

Induction treatment (cycles 1-4; 4732C, 7275X) – all conditions must be met:

* the patient must be newly diagnosed,
* the patient must be eligible for high dose chemotherapy and autologous stem cell transplantation,
* the treatment is must be given in combination with chemotherapy,
* the patient must not be receiving PBS subsidised thalidomide, lenalidomide or pomalidomide,
* the patient must not receive more than 4 cycles of treatment with bortezomib under this restriction.

**Pomalidomide**

Pomalidomide has a S100 (Highly Specialised Drugs) Authority Required listing for the treatment of patients with multiple myeloma who have previously received and failed treatment with lenalidomide and bortezomib. Pomalidomide was listed on the PBS on 1 August 2015.

The following is an abridged version of the restrictions. For full information on the restrictions, refer to the [PBS website](http://www.pbs.gov.au/).

Initial treatment – all conditions must be met:

* the treatment must be in combination with dexamethasone,
* the patient must have undergone or be ineligible for a primary stem cell transplant,
* the patient must have experienced treatment failure with lenalidomide and bortezomib,
* the patient must not be receiving concomitant PBS-subsidised thalidomide, lenalidomide or bortezomib.

To qualify for continuing treatment, patients must have previously been issued an authority for this drug.

### Date of listing on PBS

Table 3 summarises the first date that thalidomide, bortezomib, lenalidomide and pomalidomide were listed for each of their multiple myeloma indications.

Table 3: Date if listing on the PBS

| **Drug** | **Abridged restriction** | **Date** |
| --- | --- | --- |
| Thalidomide | Relapsed or refractory multiple myeloma. | 1 February 2006 |
| Bortezomib | As monotherapy or in combination with a corticosteroid, of multiple myeloma after at least 1 prior therapy (except thalidomide). | 1 November 2007 |
| Thalidomide | Multiple myeloma. | 1 September 2009 |
| Lenalidomide | As monotherapy or in combination with dexamethasone for multiple myeloma after at least 1 prior therapy. | 1 November 2009 |
| Bortezomib | Newly diagnosed patient with symptomatic multiple myeloma. | 1 October 2012 |
| Pomalidomide | In combination with dexamethasone for multiple myeloma after prior treatment failure with bortezomib and treatment failure with lenalidomide. | 1 August 2015 |
| Lenalidomide | In combination with dexamethasone for newly diagnosed patients with multiple myeloma. | 1 February 2017 |

### Changes to listing

From 1 September 2009, the S100 listing for thalidomide was extended to include the treatment of a patient newly diagnosed with multiple myeloma.

The listing for bortezomib was expanded to include re-treatment in March 2011 and newly diagnosed multiple myeloma in October 2012.

In February 2017, the listing of lenalidomide was expanded to treat newly diagnosed multiple myeloma in combination with dexamethasone.

Current PBS listing details are available from the [PBS website](file:///%5C%5Ccentral.health%5CDFSGroupData%5CSites%5CCO1%5CCO%5CPBD%5CPEB%5CEVAL%5CDUSC%5CDUSC%20Documents%5CPredicted%20vs%20actual%20usage%5Cpbs.gov.au).

The current PBS listing details are available from the [PBS website](http://www.pbs.gov.au/pbs/home).

## Relevant aspects of consideration by the Pharmaceutical Benefits Advisory Committee (PBAC)

### Thalidomide

At the March 2005 meeting, the PBAC recommended the listing of thalidomide 50mg for relapsed or refractory multiple myeloma on the basis of a high, but acceptable cost-effectiveness ratio compared with a weighted average of a mixture of salvage treatments. The listing was effective from 1 February 2006. At the March 2009 meeting, the PBAC recommended an extension to the listing of thalidomide to include a patient newly diagnosed (first-line setting) on the basis of acceptable cost-effectiveness at the current rather than the requested price. The PBAC acknowledged that thalidomide is effective in all stages of multiple myeloma and that its use is limited by cumulative toxicity. The PBAC noted that if thalidomide is PBS-subsided in first-line therapy, then there would be less use of thalidomide in second and subsequent lines. Patient would have a ceiling with respect to total lifetime exposure due to cumulative toxicity or to the expiry of clinical benefit.

The listing became effective on 1 September 2009. The 100 mg strength of thalidomide was available on the PBS from 1 November 2010.

For further details refer to the [Public Summary Document for the March 2009 PBAC meeting](http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2009-03/pbac-psd-thalidomide-march09).

### Lenalidomide

At its November 2008 meeting the PBAC recommended the listing of lenalidomide for the treatment of patients with relapsed or refractory multiple myeloma in whom thalidomide therapy has failed or in whom there is severe intolerance/toxicity to thalidomide. Listing was recommended on a cost minimisation basis with bortezomib with the equi-effective doses to be based on 6 cycles of bortezomib. Listing took effect on 1 November 2009. For further details refer to the [Public Summary Document for the March 2008 PBAC meeting](http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2008-03/pbac-psd-lenalidomide-mar08).

At its March 2013 meeting, the PBAC rejected a request to amend the current lenalidomide listings to remove the requirement for prior treatment with thalidomide in multiple myeloma patients with progressive disease on the basis of insufficient clinical evidence to support the claim of superior effectiveness in comparison to thalidomide. For further details refer to the [Public Summary Document for the March 2013 PBAC meeting](http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2013-03/lenalidomide).

At its March 2014 meeting, the PBAC considered a request to amend the current lenalidomide listing that requires prior treatment failure with thalidomide, to wording that requires prior treatment failure with thalidomide or bortezomib in patients with multiple myeloma (MM).The PBAC rejected this submission on the basis of an absence of the relevant economic comparison of lenalidomide to re-treatment with bortezomib or treatment with thalidomide. For further details refer to the summary of the [PBAC outcomes for the March 2014 PBAC meeting](http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/pbac-outcomes/pbac-recommendations-march-2014).

At its November 2015 meeting, the PBAC deferred making a recommendation for a submission to list lenalidomide in combination with dexamethasone (Rd), as first line therapy for patients who are newly diagnosed with multiple myeloma. This was due to the nominated comparators, the inclusion of favourable assumptions to Rd in the presented model and a highly uncertain and high ICER for the requested treatment setting. However, PBAC acknowledged the high clinical need for oral therapies in the treatment of multiple myeloma. For further details refer to the [Public Summary Document for the November 2015 PBAC meeting](http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2015-11/lenalidomide-revlimid-psd-11-2015).

At its March 2016 meeting, PBAC considered a new price offered by the sponsor, for lenalidomide as a first line therapy in the treatment of patients with newly diagnosed symptomatic multiple myeloma (NDMM) who are ineligible for stem cell transplant. The PBAC recommended the listing of lenalidomide, in combination with dexamethasone for the indication, under Section 100 (Highly Specialised Drugs). This was on the basis of acceptable cost effectiveness over thalidomide plus melphalan plus prednisone (or prednisolone) (MPT).

The PBAC also noted recent correspondence from clinical stakeholders regarding re-use of lenalidomide upon disease progression. The PBAC advised that the PBS restriction should permit retreatment with lenalidomide following disease progression, in patients who had discontinued earlier when the disease was controlled. The PBAC also considered that once lenalidomide is listed for first line use in patients with multiple myeloma who are ineligible for stem cell transplant, that changes to the bortezomib restriction should be enacted to enable use of bortezomib in patients with progressive disease after initial therapy with lenalidomide or thalidomide. For further details refer to the [Public Summary Document for the March 2016 PBAC meeting](http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2016-03/files/lenalidomide-psd-march-2016.pdf).

At its March 2016 meeting, the PBAC also considered a separate submission to amend the wording in the current listing of pomalidomide and lenalidomide. The submission included a request to change the lenalidomide restriction, to enable re-treatment with lenalidomide after a “treatment holiday”. The PBAC recalled views previously expressed by the Myeloma Foundation and Haematology Society of Australia and New Zealand (HSANZ) in support of such a change, and considered it would be reasonable to make the following changes:

* That the listing allow for re-use of lenalidomide in patients who have not previously failed lenalidomide treatment, since there are situations where it may be clinically appropriate to allow patients to take a ‘drug holiday’ and then recommence treatment.
* That the need to try thalidomide treatment prior to accessing lenalidomide, upon relapsing after bortezomib treatment be removed.

The PBAC considered that these changes to the lenalidomide would address some of the concerns for clinicians and patients being treated for multiple myeloma, where lenalidomide had been discontinued for reasons other than failure of the medicine.

The outcome of this consideration for pomalidomide is discussed further below in this section under ‘Pomalidomide’.

For further details refer to the [Public Summary Document for the March 2016 PBAC meeting](http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2016-03/files/pomalidomide-psd-march-2016.pdf).

### Bortezomib

Progressive disease

Bortezomib was first recommended for listing at the July 2007 PBAC meeting for the treatment of patients with refractory multiple myeloma on the basis of acceptable cost-effectiveness when compared to a mixture of salvage treatments and where the extent of substitution from mini-allogeneic transplants is zero. The PBAC recommended no more than 11 cycles of treatment be authorised, and where a confirmed complete response was achieved, no more than two additional cycles administered beyond a confirmation. Listing was effective from 1 November 2007. For further details refer to the [Public Summary Document for the July 2017 PBAC meeting](http://www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-bortezomib-july07).

Initial treatment (symptomatic multiple myeloma)

At the July 2009 PBAC meeting, the PBAC recommended the listing of bortezomib for first line treatment for patients with multiple myeloma not eligible for high dose chemotherapy in combination with melphalan or cyclophosphamide and corticosteroids. The sponsor had sought to demonstrate that bortezomib was superior to thalidomide however the indirect comparison presented was considered not conclusive by the PBAC. As a result, the PBAC recommended listing on the basis of cost-minimisation with thalidomide. For further details refer to the [Public Summary Document for the July 2009 PBAC meeting](http://www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-Bortezomib-jul09.).

Bortezomib for first line use was again considered at the March 2010 PBAC meeting. The PBAC did not consider superiority of bortezomib in comparison to thalidomide was demonstrated. The PBAC advised that the cost-minimisation recommendation from the July 2009 meeting therefore should be maintained. For further details refer to the summary of the [PBAC outcomes for the March 2010 PBAC meeting](http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2010-03/pbac-psd-bortezomib-mar10).

At the March 2011 PBAC meeting, the PBAC considered the use of first line bortezomib in patients with renal failure. The PBAC acknowledged that there was a high clinical need in this patient group and deferred the submission pending further discussion with clinicians and the sponsor regarding use in this patient group. At the July 2011 PBAC meeting, the PBAC recommended the listing of bortezomib for first line use in newly diagnosed multiple myeloma patients with acute renal failure or who were at a high risk of requiring dialysis. The recommendation was made on the basis of acceptable cost-effectiveness in patients with a high clinical need and in whom the currently available treatment (thalidomide) was of uncertain efficacy.

At the March 2012 PBAC meeting, the committee recommended the listing of bortezomib as a part of induction therapy in newly diagnoses multiple myeloma patients eligible for high dose chemotherapy and stem cell transplantation. The PBAC considered bortezomib to be non-inferior to thalidomide and the listing was on a cost-minimisation basis. For further details refer to the summary of the [PBAC outcomes for the March 2012 PBAC meeting](http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2012-03/bortezomib).

The three listings for first line use came into effect on 1 October 2012.

At its March 2016 meeting, the PBAC recommended the listing of a new strength of bortezomib, 3mg vial, for the same indications as the existing 1mg and 3.5mg vials. For further details refer to the summary of the [PBAC outcomes for the March 2016 PBAC meeting](http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2016-03/files/bortezomib-psd-march-2016.pdf). The 3mg strength became available on the PBS on 1 October 2016 for all indications.

At the March 2016 meeting, the PBAC also recommended lenalidomide for first line therapy in patients with multiple myeloma who are ineligible for stem cell transplant. The PBAC also considered that once lenalidomide is listed for first line use in patients who are ineligible for stem cell transplant, that changes to the bortezomib restriction should be enacted to enable use of bortezomib in patients with progressive disease after initial therapy with lenalidomide or thalidomide. For further details refer to the summary of the [PBAC outcomes for the March 2016 PBAC meeting](http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2016-03/files/lenalidomide-psd-march-2016.pdf).

***Pomalidomide***

At its July 2014 meeting, PBAC considered an application to seek a Section 100 (Highly Specialised Drugs) listing for pomalidomide for treatment of patients with multiple myeloma who have previously received and failed, or are intolerant to, treatment with lenalidomide and bortezomib. The PBAC rejected the submission on the basis that cost-effectiveness had not been demonstrated. However, the PBAC acknowledged that there may be a clinical place for the drug in patients who have failed bortezomib and lenalidomide. The PBAC stated the following in regards to the proposed restriction: that a definition of failure of treatment, in line with that of the entry criteria of the MM- 003 trial, is included in the restriction. i.e. “Treatment failure is defined as confirmed progressive disease during treatment or within 6 months of discontinuing treatment”. For further details refer to the summary of the [PBAC outcomes for the July 2017 PBAC meeting](http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2014-07/pomalidomide-psd-07-2014).

At its November 2014 meeting, the PBAC considered a re-submission proposing a re-specified base case and revised inputs to the economic model following the July 2014 PBAC consideration. The PBAC recommended the listing of pomalidomide for the treatment of multiple myeloma under the Section 100 Highly Specialised Drugs Program (HSDP). For further details refer to the summary of the [PBAC outcomes for the November 2014 PBAC meeting](http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2014-07/pomalidomide-psd-07-2014). This listing became available on the PBS on 1 August 2015.

At its March 2016 meeting, the PBAC considered a submission to amend the wording in the listing pomalidomide and lenalidomide. The submission requested to amend the restriction for pomalidomide to change the definition of treatment failure of bortezomib and lenalidomide, and amend the listing to include patients who have ‘experienced severe intolerance or toxicity to bortezomib (or lenalidomide), unresponsive to clinically appropriate dose adjustment’. The PBAC rejected the application to change the restriction for pomalidomide. The PBAC considered that the issue was not whether pomalidomide is effective in these populations, but whether pomalidomide is cost-effective against the additional comparators that would apply in those circumstances (for example re-use of lenalidomide or bortezomib with adjusted scheduling). For further details refer to the summary of the [PBAC outcomes for the March 2016 PBAC meeting](http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2016-03/files/pomalidomide-psd-march-2016.pdf). This listing became available on the PBS on 1 August 2015.

At its March 2017 meeting, the PBAC rejected at submission to amend the current wording to the restriction of pomalidomide to include the treatment of patients who have experienced severe intolerance or toxicity to lenalidomide and/or bortezomib for relapsed/refractory multiple myeloma. The PBAC also noted that the safety of pomalidomide in patients previously experiencing a severe toxicity when treated with lenalidomide was uncertain, as were the utilisation estimates. For further details refer to the summary of the [PBAC outcomes for the March 2017 PBAC meeting](http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2017-03/pomalidomide-psd-march-2017).

***Carfilzomib***

The PBAC (November 2016) did not recommend the listing of carfilzomib for the treatment of relapsed or refractory multiple myeloma in combination with dexamethasone (Cd) or in combination with lenalidomide and dexamethasone (CLd) on the basis of high and uncertain incremental cost-effectiveness ratios (ICERs). The PBAC considered the role of CLd versus Cd in clinical practice was unclear and noted clinical data comparing these two regimens are not available. The PBAC considered the modelled overall survival gains with carfilzomib to be uncertain because the data from the clinical trials were immature and the differences were not statistically significant. The PBAC noted a number of assumptions in the economic model which favoured carfilzomib and hence considered that the base case ICERs were likely to be substantially underestimated. For further details refer to the summary of the [PBAC outcomes for the November 2016 PBAC meeting](http://www.pbs.gov.au/pbs/industry/listing/elements/pbac-meetings/psd/2016-11/carfilzomib-psd-november-2016).

In July 2017, the PBAC recommended the listing of carfilzomib for use in combination with dexamethasone (Cd) in patients with relapsed or refractory multiple myeloma. The resubmission requested listing of Cd only.

## Approach taken to estimate utilisation for the predicted versus actual analysis of pomalidomide

**Committee-in-confidence**

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**End committee-in-confidence**

## Previous reviews by the DUSC

Medicines for the treatment of multiple myeloma were reviewed by DUSC at its meeting in October 2013. The analysis included thalidomide, lenalidomide and bortezomib. The review found a general trend of higher than expected utilisation of multiple myeloma medicines. DUSC considered that this was likely due to an improving life expectancy of multiple myeloma patients, allowing them to access multiple lines of treatment. DUSC was of the view that risk share arrangements are vital for this therapeutic area to manage Government expenditure and considered that the findings of the report should inform future risk sharing agreements.

DUSC noted that the future use of new multiple myeloma medicines could be underestimated if older epidemiological data, that has not captured improving survival, is used to develop the estimates of use. DUSC suggested that PBAC consider this in assessing any future submissions and requested that the report be provided to PBAC. Since the 2013 review, there have been new medicines and different lines of therapy introduced to the PBS.

The Outcome Statement for the October 2013 DUSC meeting is available on the [PBS website](http://www.pbs.gov.au/industry/listing/elements/dusc-meetings/dos/dusc-dos-oct-2013.pdf).

# Methods

The medicines included in the analysis are summarised in Table 4.

Table 4: Medicines included in the analysis

| **Drug**  | **ATC code** | **Category** | **Indication for MM as recommended by Australian guidelines (**[**1**](#_ENREF_1)**) and the PBS restrictions** |
| --- | --- | --- | --- |
| Thalidomide | L04AX02 | Immuno-modulator | 1st; 2nd; 3rd line therapy.(Item codes do not specify line of therapy) |
| Bortezomib | L01XX32 | Proteasome inhibitor | 1st; 2nd; 3rd line therapy;PBS item codes used:4732C, 7275X 🡪 1st line in those eligible for autologous stem cell transplantation4403R, 7238Y 🡪 1st line initial treatment in newly diagnosed with severe acute renal failure or ineligible for high dose chemotherapy (max 4 cycles)4429D, 7274W 🡪 1st line continuing therapy in those with severe acute renal failure or ineligible for high dose chemotherapy, who responded to initial therapy (max 5 cycles)4706Q, 7268M, 🡪 2nd line initial treatment for progressive disease4712B, 7269N🡪 2nd line continuing treatment for progressive disease4713C, 7271Q,🡪 3rd line initial retreatment of progressive disease4725Q, 7272R 🡪 3rd line continuing retreatment of progressive disease |
| Lenalidomide | L04AX04 | Immuno-modulator | 2nd or subsequent line therapy; (Listed as 1st line therapy from 1 Feb 2017 only which was outside period of analysis); PBS item codes used: 9645P, 9644N, 9643M, 9642L, 5786M, 5785L, 5784K, 5783J |
| Pomalidomide | L04AX06 | Second generation immune-modulator | 3rd line after two or more prior therapies failed including with bortezomib and lenalidomide; (first listed August 2015) |

Note: Lenalidomide is also indicated for myelodysplastic syndrome (MDS). People who initiated lenalidomide where the first prescription had a PBS code indicating myelodysplastic syndrome were excluded. People who initiated lenalidomide where the first prescription was for a PBS code indicating multiple myeloma (MM) were included. Seventy three people had their initial prescription indicating MM with a subsequent prescription for MDS. Less than 5% of all lenalidomide prescriptions for these 73 people were dispensed under the PBS code for myelodysplastic syndrome (MDS). MDS prescriptions were not included in the analysis.

The prescription dispensing data were extracted from the Department of Human Services (DHS) prescription database. This contained non-identifying patient level R/PBS data for the time period 1 July 2013 to 31 December 2016.

From 1 July 2013 there was complete prescription data capture for Highly Specialised Drugs (HSD) prescriptions dispensed by public and private hospital pharmacies. Prior to 1 July 2013, most HSD prescriptions supplied through public hospitals were processed through the DHS Offline processing system, for which only aggregated data was available, i.e. the number of packs supplied and the cost per quarter. As such, data was extracted from 1 July 2013 as the data for the S100 listings (i.e. thalidomide, lenalidomide and pomalidomide) was likely to be incomplete prior to this time for patient level analysis.

Data extracted from DHS was used to determine the date of death of patients. Data was supplied for patients who died in the time period 1 July 2013 and 31 December 2016.

PBS/RPBS pharmacy claims data were used to determine:

**1) The prevalent and incident populations treated with the PBS listed medicines for multiple myeloma**

* 1. To determine the prevalent population treated with PBS listed medicines for multiple myeloma, the number of persons dispensed at least one of the available medicines was identified in each month from 1 Jul 2013 to 31 Dec 2016. ABS population estimates of the number of people at 30 June 2013 to 30 June 2016 ([4](#_ENREF_4)) were used to calculate the monthly prevalence per 100,000 Australian residents.
	2. The monthly number of individuals who initiated (first occurrence of any of the four medicines) a medicine for multiple myeloma in each month for the period 1 Jan 2014 to 30 Jun 2016 was reported (the period from 1 Jul 2013 to 31 Dec 2013 was excluded to ascertain true initiation). ABS population estimates of the number of people at 30 June 2013 to 30 Jun 2016 ([4](#_ENREF_4)) were used to calculate the population rates per 100,000 Australian residents. The age distribution of initiators was also determined.

Annual incidence and prevalence numbers are reported as are monthly rates per 100,000 population.

**2) Clinical pathways of use of medicines for multiple myeloma, including first, second and third line treatment.**

Patient level data were utilised to determine the treatment paths of individual patients from initiation of their first medicine for multiple myeloma between 2014 and 2016 (after no dispensing in the previous 6 months) to end of study (31 December 2016). The results were aggregated to present patterns of clinical pathways for treatment from first line to last line treatment, including and excluding gaps in therapy (a gap in refill for the current medicine of three times the length of the estimated prescription duration). The estimated prescription duration for each medicine was based on dosing protocols, which is every 28 days for thalidomide, lenalidomide and pomalidomide, and 1 week for bortezomib. The time period for repeat dispensings in the data was analysed which confirmed those estimates reflect the time period within which 50% of patients return for the specific medicines.

A sensitivity analysis was undertaken which was limited to patients who initiated their first medicine for multiple myeloma in 2014. These patients were followed until the end of the study (31 December 2016). (See Appendix for the sensitivity analysis).

**3) The duration of treatment with medicines for multiple myeloma.**

A cohort study was conducted to investigate duration of treatment in people who initiated a medicine for multiple myeloma in the calendar year 2014 (after no dispensing for such a medicine in the previous 6 months). The initiators were followed for 24 months.

The age and gender of those who initiated each medicine were reported as means and frequencies. Differences in age and gender by medicine were compared using student’s T test for age and Chi squared test for gender. Results with a p value <0.05 were considered significantly different.

Kaplan Meier survival analysis was conducted to estimate the duration of the first episode with the index medicine. The study end point was time to discontinuation of the index medicine. Discontinuation was defined as either cessation (a gap in refill for the index medicine of three times the length of the estimated prescription duration) or a switch to a therapy not including the index medicine (switches from one strength to another of the same medicine were regarded as continuing therapy with that medicine). The estimated prescription duration for each medicine was based on dosing protocols, which is every 28 days for thalidomide, lenalidomide and pomalidomide, and 1 week for bortezomib. Persons were followed up until cessation, switching to therapy not including the index medicine, or for 24 months post index prescription. Those who ceased or switched therapy before the end of the 24 months are reported as “event” persons, while those who died or continued therapy with the index medicine at 24 months are reported as “censored” persons. Results were stratified by the type of index medicine provided.

Additional analysis allowing for switches from one medicine to another medicine for multiple myeloma to be considered as continuation of initial therapy were conducted to estimate the length of first episode on any PBS-listed multiple myeloma medicine.

The cumulative duration of all episodes on any medicine was also estimated as well as the cumulative duration of all breaks (gaps) in medicine coverage that could be considered treatment holidays or discontinuation due to sustained remission of the disease.

**4) The extent of co-prescribing of two or more PBS subsidised medicines for multiple myeloma.**

Monthly rates of people who received dispensings for one, two, three or four different medicines for multiple myeloma in a given month were reported as a proportion of the total number of people with at least one dispensing for any medicine in a given month. A conservative estimate of sufficient supply was used where a person had to be using both medicines for the whole month and reported the proportion of people based on that definition of co-prescribing.

**5) The consistency of use of PBS subsidised medicines for multiple myeloma with the recommendations in Australian guidelines (**[**1**](#_ENREF_1)**) and the PBS restrictions.**

The patterns of use of the multiple myeloma listed medicines were compared against guideline recommendations and PBS restrictions specified in Table 4. This was undertaken for the primary analysis and the sensitivity analysis (See Appendix for sensitivity analysis).

# Results

## Analysis of drug utilisation

### Overall utilisation

**1) The prevalent and incident population treated with the PBS listed medicines for multiple myeloma**

Overall, there were 9,445 distinct people who received 204,947 dispensings for the listed medicines for multiple myeloma in the period 1 July 2013 to 31 December 2016.

Table 5 summarises the number of incident and prevalent patients by calendar year.

**Table 5: Number of incident and prevalent patients by calendar year and by drug**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **2014** | **2015** | **2016** |
| **Number of incident patients** |
| Total patients for all drugs | 2,083 | 1,971 | 1,826 |
| By drug: |   |   |   |
| BORTEZOMIB | 1,260 | 1,395 | 1,365 |
| LENALIDOMIDE | 202 | 124 | 84 |
| POMALIDOMIDE | - | 10 | 6 |
| THALIDOMIDE | 621 | 442 | 371 |
| **Number of prevalent patients** |
| Total patients for all drugs | 4,797 | 5,176 | 5,546 |
| By drug: |   |   |   |
| BORTEZOMIB | 2,366 | 2,704 | 2,788 |
| LENALIDOMIDE | 1,470 | 1,701 | 1,945 |
| POMALIDOMIDE | - | 190 | 424 |
| THALIDOMIDE | 1,950 | 1,932 | 1,906 |

Source: DHS prescriptions database. The figures are based on the date of supply.

Figure 1 presents the monthly prevalence rate per 100,000 Australian residents and shows an increase in the number of people receiving treatment, from 9.4 per 100,000 in July 2013 to 11.8 per 100,000 in December 2016.

**Figure 1: Prevalence rate per 100,000 Australian residents dispensed at least one medicine for multiple myeloma in a given month.**

Figure 2 shows the prevalence rates by medicine. The use of bortezomib increased from 10 to 12 people per 100,000 Australians, followed by similar rate of use for thalidomide and lenalidomide (8 per 100,000 people in 2016). Pomalidomide was listed for multiple myeloma in August 2015.

**Figure 2: Annual prevalence rates per 100,000 people receiving at least one dispensing for the specific medicine in a given year.**

Note: 2013 was excluded as data only for 6 months was available.

Figure 3 presents the monthly incidence rate per 100,000 Australian residents and shows that less than one in 100,000 people initiated a medicine for multiple myeloma in a given month.

**Figure 3: Incidence rate per 100,000 Australian residents who initiated at least one medicine for multiple myeloma in a given month.**

Figure 4 shows the incidence rates by medicine. There were 1,826 distinct initiators in 2016, with a median age of 70 years. Bortezomib was initiated in 6 out of 100,000 Australians in 2016, compared to 2 people who initiated thalidomide, and very low numbers of initiators of lenalidomide or pomalidomide in 2016.

Figure 4: Annual incidence rates per 100,000 people by type of multiple myeloma medicine.

Note: 2013 was excluded as data only for 6 months was available.

Figure 5 presents the age distribution of the initiators, with 21% of all initiators across the study period being of age 65 to 70 years.

Figure 5: Initiation of medicine for multiple myeloma by age.

### Patient level analysis

**2) Clinical pathways of use of multiple myeloma medicines, including first, second and third line treatment.**

The clinical pathways were analysed for 5,880 people who initiated one of the listed medicines for multiple myeloma (after no dispensing in the previous 6 months was investigated) between 2014 and 2016. Their clinical pathways from initiation to 31 December 2016 are presented in Figures 6 and 7. A sensitivity analysis was undertaken for those who initiated in 2014 only, which is included in the appendix. Figure 6 reports all different (distinct) regimens in order of occurrence (i.e. if the same regimen was found again later in time it would have been reported just once). Overall, 61% received one therapy only, with 42% having bortezomib only, 14% thalidomide only, and 5% lenalidomide only.

**Figure 6: Common pathways of multiple myeloma treatment (pathways for > 0.5% of all patients are presented in the graph).**

Legend: “🡪” denotes transition from one therapy to another

“+” denotes concurrent use of medicines

Borte = bortezomib

Thali = thalidomide

Lenal = lenalidomide

Pomal = pomalidomide

Figure 7 presents the clinical pathways in more detail, starting from the first to the last regimen of treatment, including the same regimens separated by gaps in therapy (i.e., when the same regimen is presented one after another that implies that there was a break in therapy).

**Figure 7: Common pathways of multiple myeloma treatment (pathways for > 0.5% of all patients are presented).**

Legend: “🡪” denotes transition from one therapy to another.

“+” denotes concurrent use of medicines

Borte = bortezomib

Thali = thalidomide

Lenal = lenalidomide

Pomal = pomalidomide

**3) The duration of treatment with medicines for multiple myeloma**

There were 2,320 people who initiated a multiple myeloma medicine in 2014. The initiators were followed for 24 months. The age and gender of these initiators are shown in Table 6. People who were initiated on bortezomib for stem cell transplantation were significantly younger than those who were initiated on bortezomib listed for non-stem cell use (Student’s t-test, p<0.0001), as well as those who were initiated on thalidomide or lenalidomide (p<0.0001). The mean age did not differ between bortezomib for non-stem cell transplant use, thalidomide and lenalidomide initiators (Student’s t-test, p=0.916). The ratio of women to men was similar between the groups (Chi-square test, p=0.755) with more men than women in all of the groups.

Table 6: Age and gender of 2014 initiators

|  | **Bortezomib for stem cell transplantation****(N=410)** | **Bortezomib for other indication (N=923)** | **Thalidomide****(N=710)** | **Lenalidomide****(N=277)** |
| --- | --- | --- | --- | --- |
| Mean age (SD) | 59.3 (SD=8.4) | 70.9 (SD=9.9) | 70.8 (SD=11.2) | 70.6 (SD=10.5) |
| Female | 39% | 40% | 42% | 41% |
| Male | 61% | 60% | 58% | 59% |

Results from the Kaplan Meier survival analysis showed that the median time to discontinuation of the first episode on the index medicine was around 4 months (Figure 8).



**Figure 8: Kaplan-Meier estimate for time to treatment discontinuation of the first episode with multiple myeloma medicine.**

Model summary for Figure 8:

| No of subjects | Event | Censored | Percent Censored | Median duration |
| --- | --- | --- | --- | --- |
| 2320 | 2184 | 138 | 6% | 111 days(95% CI 105-113) |

The majority of people survived the two year follow-up (Figure 9); overall 11% died within the follow-up period.

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**Figure 9: Kaplan-Meier estimate for overall survival from initiation of multiple myeloma medicine to end of follow-up.**

Stratification by the type of the index medicine showed that 18% started on bortezomib for stem cell transplant (median duration of the first treatment episode was 3 months), another 40% who were not indicated for stem cell transplant started on bortezomib (median duration of 3.5 months), 30% stated on thalidomide (median duration of 5 months) and 12% started on lenalidomide (median duration of 9.5 months) (Figure 10). Lenalidomide is restricted as second line therapy. We had a 6 month period in which we determined initiation, and while we can’t rule out that some of the lenalidomide use may be second line therapy after a gap in therapy of six months (180 days) or more, median gaps in therapy were less than 30 days and average gaps in treatment during this study were 110 days. Thus, it is likely that most of the lenalidomide use reflects first line use outside of PBS restrictions.

There were no initiators on pomalidomide in 2014 as the product was listed for multiple myeloma in August 2015. Variations in the time to discontinuation by the type of medicine initiated should be interpreted cautiously. There were some as differences in the population profile by the type of medicine initiated, with bortezomib initiators being slightly younger and including more men, however, the time to discontinuation is not adjusted for aged and gender differences.

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**Figure 10: Kaplan-Meier estimate for time to treatment discontinuation of the first episode by type of the index multiple myeloma medicine.**

Model summary for Figure 10:

| Index medicine | No of subjects | Event | Censored | Percent Censored | Median duration(95%CI) |
| --- | --- | --- | --- | --- | --- |
| Bortezomib (stem cell) | 410 | 408 | 2 | 0.5% | 86 days (84-89) |
| Bortezomib (other) | 923 | 911 | 12 | 1% | 105 days (98-112) |
| Thalidomide | 710 | 665 | 45 | 6% | 149 days (137-167) |
| Lenalidomide | 277 | 198 | 79 | 29% | 287 days (227-400) |

Overall survival stratified by the type of index medicine showed no differences between the groups with the majority of people surviving the two years follow-up (Figure 11); The death rate was lowest for bortezomib stem cell initiators (4%) compared to 12%-14% for the remaining index medicines.

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**Figure 11: Kaplan-Meier estimate for overall survival from initiation of multiple myeloma medicine to end of follow-up, by type of the index medicine.**

Sensitivity analysis when switches from one to another medicine for multiple myeloma were considered as continuation of initial therapy showed median duration of 127 days (95% CI 119-134) (Figure 12).

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**Figure 12: Kaplan-Meier estimate for time to treatment discontinuation of the first episode with multiple myeloma medicines when switches from one to another medicine were allowed.**

Analysis on cumulative duration of all episodes on any medicine showed a median duration of 436 days (95% CI 408-468) (Figure 13).

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**Figure 13. Kaplan-Meier estimate for cumulative duration of all episodes on any medicine for multiple myeloma (including gaps between treatment episodes)**

Analysis on cumulative duration of all breaks (gaps) in medicine coverage between therapies showed a median duration of 29 days (95% CI 21-39) (Figure 14). The average gap duration was 110 days.



**Figure 14: Kaplan-Meier estimate for cumulative duration of all breaks (gaps) in medicine coverage.**

**4) The extent of co-prescribing of two or more medicines for multiple myeloma.**

The proportion of people who had dispensings for two or three different medicines for multiple myeloma in the same month was very low (Figure 15). Only 1% of all 9,445 people with a multiple myeloma medicine between 1 July 2013 and 31 December 2016 had concurrent use of two medicines for a whole month at some point of time. Overall, only 6 people had lenalidomide co-dispensed with thalidomide (4 people) or bortezomib (2 people) for a whole month.

Figure 15: Monotherapy and concurrent use of medicines for multiple myeloma.

**5) The consistency of use of PBS subsidised medicines for multiple myeloma with the recommendations in Australian guidelines (**[**1**](#_ENREF_1)**) and the PBS restrictions**

The pathways of use presented in Figure 6 were aggregated to determine first, second and third line regimens. Figure 16 shows the first line regimens for those 5,880 people who initiated a multiple myeloma medicine after no dispensing in the previous six months. Bortezomib was dispensed for two-thirds of all people, followed by thalidomide (24%) and lenalidomide (7%) as first line therapy. Lenalidomide was restricted as second or subsequent line therapy in our study period, while pomalidomide was restricted as 3rd line therapy – thus, their use is highlighted in red as outside recommendations.

Of those who initiated bortezomib as first line therapy (N=4,018), 33% started it according to restrictions for newly diagnosed patients eligible for stem cell transplantation (PBS codes 4732C and 7275X); 53% initiated it according to restrictions for newly diagnosed patients with severe acute renal failure and newly diagnosed patients who are ineligible for high dose chemotherapy (PBS codes 4403R and 7238Y); the rest received second (11%) or third line (3%) therapy codes for bortezomib.

Figure 16: Choice of medicine as first line therapy.

Note:

Legend: “+” denotes concurrent use of medicines

Borte = bortezomib

Thali = thalidomide

Figure 17 shows that 38% of people needed a second line therapy, with thalidomide and lenalidomide being the most commonly used medicines (20% and 9% respectively). Pomalidomide is not recommended as second line and the results confirm very low use (<1%).

Figure 17: Choice of medicine as second line therapy.

Note:

Legend: “+” denotes concurrent use of medicines

Borte = bortezomib

Thali = thalidomide

Lenal = lenalidomide

Figure 18 presents what was the first line regimen before the administration of the second line.

Figure 18: Type of second line therapy and the preceding first line.

Note:

Legend: “+” denotes concurrent use of medicines

Borte = bortezomib

Thali = thalidomide

Lenal = lenalidomide

Pomal = pomalidomide

Figure 19 shows that only 16% of people received a third line therapy. Lenalidomide accounted for almost half of third line therapy after trialling bortezomib and thalidomide (Figure 20). Pomalidomide which is recommended as third line was used in only 1% of people (Figure 19) mostly after trialling bortezomib and lenalidomide (Figure 20). However, it should be noted, pomalidomide was only available for a short time period during the data analysis.

Overall, pomalidomide was used as first or second line therapy in 0.9% of people, and lenalidomide was used as first line therapy in 7% of people, which was not consistent with guideline recommendations.

Figure 19: Choice of medicine as third line therapy.

Note:

Legend: “+” denotes concurrent use of medicines

Borte = bortezomib

Thali = thalidomide

Lenal = lenalidomide

Pomal = pomalidomide

Figure 20: Type of third line therapy and the preceding regimens

Note:

Legend: “+” denotes concurrent use of medicines

Borte = bortezomib

Thali = thalidomide

Lenal = lenalidomide

Pomal = pomalidomide

## Analysis of expenditure

Table 7 presents the benefits paid for thalidomide, bortezomib, lenalidomide and pomalidomide between 2014 and 2016.

**Table 7: Expenditure on thalidomide, bortezomib, lenalidomide and pomalidomide by calendar year and by drug**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **2014** | **2015** | **2016** |
| Total expenditure on all drugs | $131,652,463 | $151,730,622 | $178,573,413 |
| Expenditure by drug: |
| BORTEZOMIB | $57,407,538 | $65,109,862 | $64,877,227 |
| LENALIDOMIDE | $65,638,112 | $73,270,764 | $85,753,503 |
| POMALIDOMIDE | - | $5,586,725 | $20,930,922 |
| THALIDOMIDE | $8,606,814 | $7,763,271 | $7,011,761 |

Source: DHS prescriptions database. Figures are based on the date of supply.

Note: The figures presented here are based on the published list prices. Special pricing arrangements apply for some listings. As such, the actual government expenditure on these medicines may be less than shown.

## Analysis of actual versus predicted utilisation for pomalidomide

The predicted versus actual use of pomalidomide is presented in Table 8.

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The predicted and actual figures are presented as year to date to June 2017.

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Table 8: Predicted vs. actual utilisation for pomalidomide

|  | **Year 1****Aug2015-Jul2016** | **Year 2****Aug2016-Jun2017 YTD2** |
| --- | --- | --- |
| **Eligible population (number of patients):**- Predicted (n)- Actual (n)1- Actual vs. predicted (n, %) | xxxxx1,378xxxxxxx | xxxxx1,607 (YTD) |
| **Number of patients treated with pomalidomide:**- Predicted (n)- Actual (n)- Actual vs. predicted (n, %) | xxxx365xxxxx | xxxxxx429 (YTD) |
| **Total cost of pomalidomide3:**- Predicted (n)- Actual (n)- Actual vs. predicted (n, %) | xxxxxxx$16,372,766xxxxxxx | Xxxxxxxx$22,596,805 (YTD) |

Note:

The figures are based on the date of supply. Xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx A special pricing arrangement applies to this medicine and its actual cost to the Commonwealth may differ.

1 Patients who received a supply of bortezomib and lenalidomide (as per the restriction criteria for pomalidomide).

2 Year 2 presents year to date predicted and actual figures as a complete data for a full year to July 2017 was not available at the time of the analysis.

3 Excluding patient co-payments.

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# Discussion

A total of 1,826 (eight in 100,000) Australians initiated therapy with medicine for multiple myeloma in 2016, which is similar to AIHW (2013) estimates of incidence for the disease. The median age of those initiators was 70 years, similar to the median age observed over the past three decades ([3](#_ENREF_3)) .

According to the Australian guidelines ([1](#_ENREF_1)) , both thalidomide and bortezomib are indicated for multiple myeloma as first, second or third line therapy. The medicine utilisation analysis showed that bortezomib was the medicine most commonly initiated as first line therapy followed by thalidomide, while thalidomide was the most common second line therapy. Both medicines were rarely used for the first time as the third line therapy. Use of bortezomib and thalidomide was consistent with the guideline recommendations.

Lenalidomide was indicated as second line and subsequent therapy during the study period. Lenalidomide was subsequently recommended as a first line therapy in the Australian guidelines(1) and listed on the PBS for first line therapy in January 2017. The use of lenalidomide outside the recommendations during the study period was as first line therapy. The analysis showed that lenalidomide accounted for 6% of first line medicine use when assessed across the 2014 to 2016 cohort, and up to 12% of first line use when assessed in the 2014 cohort alone.

Pomalidomide is only indicated as third line therapy in patients who have experienced treatment failure with bortezomib and lenalidomide. Use of pomalidomide was generally consistent with the guideline recommendation, with only 1% of patients’ dispensed pomalidomide as either first or second line therapy.

The analysis showed that approximately 61% of patients were treated with one therapy only, with two-thirds receiving therapy with bortezomib only, a quarter with thalidomide only, and the rest with lenalidomide only. The remaining 39% of patients were treated with sequential regimens involving more than one medicine, ‘bortezomib and then thalidomide’ being the most common pathway. Coadministration rather than sequential use of therapies was rare (less than 1%).

About a third of patients do not respond to first-line therapy, and relapse occurs eventually in nearly all patients with an initial response ([1](#_ENREF_1)). Following the first-line therapy, subsequent management is dependent upon the choice of previous therapy, duration of response and the physical status of patients([1](#_ENREF_1)). Patients who did not respond to the first-line therapy, or had a relapse, would have accounted for the vast number of different clinical pathways of multiple myeloma treatment. It should be noted, however, that the analysis was limited to two years of follow up. The analysis showed that the majority of patients were still alive at the end of follow-up, thus the time period for assessing subsequent therapies may have been insufficient.

For persons who initiated therapy in 2014, the median duration of the first episode on bortezomib for stem cell transplant was 3 months; it was 3.5 months for other bortezomib; it was 5 months for thalidomide and 9.5 months for lenalidomide. Variations in the time to discontinuation by the type of medicine initiated should be interpreted cautiously. The PBS restrictions for bortezomib stem cell only allows for 4 treatment cycles. The other first line bortezomib restrictions allow for more cycles. The use of bortezomib in patients indicated for stem cell transplant may have been longer than 4 cycles, however, it cannot be determined from the data whether it is being used incorrectly, or whether there may be some mixing of items and some use includes patients with multiple myeloma not indicated for stem cell transplant. There were also some differences in the population profile by the type of medicine initiated, with bortezomib initiators who were indicated for stem cell transplant being slightly younger, however, the time to discontinuation is not adjusted for aged and gender differences. We used estimated prescription durations based on dosing protocols. This was one week for bortezomib, which results in a break of three weeks between dispensings being considered cessation. By comparison, 28 day prescription durations were used for thalidomide and lenalidomide, with a gap of 84 days between dispensings being defined as cessation. Finally, bortezomib is an injectable formulation while the other preparations are oral which may also have influenced duration. The extent of influence of these different factors on duration could not be determined from the data available.

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The listing of lenalidomide from 1 February 2017 for use in combination with dexamethasone for newly diagnosed patients with multiple myeloma may change the future patterns of treatment for multiple myeloma.

# Acknowledgement

Prepared by the Quality use of Medicines and Pharmacy Research Centre in conjunction with the DUSC Secretariat.

# DUSC consideration

Since the previous DUSC review of multiple myeloma medicines in 2013, the criteria for diagnosis of symptomatic myeloma had changed to include biomarkers of malignancy. New clinical practice guidelines were released by the Medical Scientific Advisory Group to the Myeloma Foundation of Australia in 2017. As the analysis period ended in December 2016, DUSC noted that changes to the guidelines are not reflected in the current utilisation analysis but may have an impact on the future utilisation of multiple myeloma medicines.

A total of 1,826 (eight in 100,000) Australians initiated therapy with medicine for multiple myeloma in 2016. DUSC noted that the number of initiators in 2016 was similar to the Australian Institute of Health and Welfare (AIHW) estimate of the incidence of multiple myeloma of 1,600 persons in 2013. DUSC further noted that there had only been a modest increase in the prevalence rate for the treated population over time. The monthly prevalence rate ranged from 9.4 per 100,000 in July 2013 to 11.8 per 100,000 in December 2016 (see Figure 1). DUSC considered that the increase in prevalence was likely due to an improving life expectancy of multiple myeloma patients. DUSC noted that as a result of improved survival, some patients would be living longer with the burden of side effects from treatment, such as peripheral neuropathy. DUSC considered that this may have implications for the cost of other drugs to manage these side effects.

DUSC noted that the use of multiple myeloma medicines was mostly consistent with the restriction criteria. There were very few cases identified of potential coadministration of the therapies (less than 1%). DUSC noted that the method used to identify coadministration was conservative which required patients to be on more than one medicine for a whole month. DUSC considered that for the purposes of the review, this approach was reasonable. DUSC further considered that there was a potential for bortezomib and lenalidomide to be used in combination in clinical practice which may not be identified from the PBS data because one of the drugs could be supplied via a clinical trial or other mechanism. The use of lenalidomide outside the recommendations during the study period was as first line therapy. The analysis showed that lenalidomide accounted for 6% of first line medicine use when assessed across 2014 to 2016. DUSC noted that lenalidomide was now listed for first-line use since February 2017. Pomalidomide is only indicated as third line therapy in patients who have experienced treatment failure with bortezomib and lenalidomide. DUSC noted that less than 1% of patients were dispensed pomalidomide as either first or second line therapy.

A cohort study was conducted to investigate the duration of treatment in people who initiated a medicine for multiple myeloma in the calendar year 2014 (after no dispensing for such a medicine in the previous 6 months). The initiators were followed for 24 months. DUSC noted that the median duration for all episodes of any multiple myeloma medicine was 282 days (or 436 days including gaps between treatment episodes). DUSC considered that the analysis of time on treatment was limited by being based on a relatively short follow-up period of two years. DUSC further noted that only 11% of patients had died over the two year analysis period.

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# DUSC actions

DUSC requested that the report be provided to the PBAC.

DUSC considered that a further review after two years’ time would be informative to examine whether: the utilisation of multiple myeloma medicines had been impacted by the release of revised clinical guidelines in 2017; and the change to the listing of lenalidomide from February 2017 for first line use.

# Context for analysis

The DUSC is a Sub Committee of the Pharmaceutical Benefits Advisory Committee (PBAC). The DUSC assesses estimates on projected usage and financial cost of medicines.

The DUSC also analyses data on actual use of medicines, including the utilisation of PBS listed medicines, and provides advice to the PBAC on these matters. This may include outlining how the current utilisation of PBS medicines compares with the use as recommended by the PBAC.

The DUSC operates in accordance with the quality use of medicines objective of the National Medicines Policy and considers that the DUSC utilisation analyses will assist consumers and health professionals to better understand the costs, benefits and risks of medicines.

The utilisation analysis report was provided to the pharmaceutical sponsors of each drug and comments on the report were provided to DUSC prior to its consideration of the analysis.

# Sponsors’ comments

The sponsors had no comment.

# Disclaimer

The information provided in this report does not constitute medical advice and is not intended to take the place of professional medical advice or care. It is not intended to define what constitutes reasonable, appropriate or best care for any individual for any given health issue. The information should not be used as a substitute for the judgement and skill of a medical practitioner.

The Department of Health (DoH) has made all reasonable efforts to ensure that information provided in this report is accurate. The information provided in this report was up-to-date when it was considered by the Drug Utilisation Sub-committee of the Pharmaceutical Benefits Advisory Committee. The context for that information may have changed since publication.

To the extent provided by law, DoH makes no warranties or representations as to accuracy or completeness of information contained in this report.

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# Appendix: Sensitivity Analysis

**2014 initiators cohort: clinical pathways of use of multiple myeloma medicines, including first, second and third line treatment.**

There were 2,320 people who initiated one of the listed medicines for multiple myeloma (after no dispensing in the previous 6 months was investigated) in 2014. Their clinical pathways from initiation to 31 December 2016 are presented in Figures A.1 and A.2. Figure A.1 reports all different (distinct) regimens in order of occurrence (i.e. if the same regimen was found again later in time it would have been reported just once). Overall, 48% received one therapy only, with 52% having bortezomib only, 31% thalidomide only, and 17% lenalidomide only.

**Figure A.1: Common pathways of multiple myeloma treatment (pathways for > 0.5% of all patients are presented in the graph).**

Legend: “🡪” denotes transition from one therapy to another.

“+” denotes concurrent use of medicines

Borte = bortezomib

Thali = thalidomide

Lenal = lenalidomide

Pomal = pomalidomide

Figure A.2 presents the clinical pathways in more details, starting from the first to the last regimen of treatment, including the same regimes separated by gaps in therapy (i.e., when the same regimen is presented one after another that implies that there was a break in therapy).

**Figure A.2: Common pathways of multiple myeloma treatment (pathways for > 0.5% of all patients are presented).**

Legend: “🡪” denotes transition from one therapy to another.

“+” denotes concurrent use of medicines

Borte = bortezomib

Thali = thalidomide

Lenal = lenalidomide

Pomal = pomalidomide

**2014 initiators cohort: the consistency of use of PBS subsidised medicines for multiple myeloma with the recommendations in Australian guidelines (**[**1**](#_ENREF_1)**) and the PBS restrictions**

The pathways of use presented in Figure A.1 were aggregated to determine first, second and third line regimens. Figure A.3 shows the first line regimens for those 2,320 people who initiated a multiple myeloma medicine after no dispensing in the previous six months. Bortezomib was dispensed for 58% of all people, followed by thalidomide (31%) and lenalidomide (12%) as first line therapy. Lenalidomide was restricted as second or subsequent line therapy in our study period– thus, its use is highlighted in red as outside recommendations.

Of those who initiated bortezomib as first line therapy (N=1333), 31% started it according to restrictions for newly diagnosed patients eligible for stem cell transplantation (PBS codes 4732C and 7275X); 50% initiated it according to restrictions for newly diagnosed patients with severe acute renal failure (PBS codes 4403R and 7238Y); the rest received second or third line therapy codes for bortezomib.

Figure A.3 Choice of medicine as first line therapy.

Figure A.4 shows that 52% of people needed a second line therapy, with thalidomide and lenalidomide being the most commonly used medicines (23% and 14% respectively). Pomalidomide is not recommended as second line and the results confirm very low use (<1.5%).

Figure A.4 Choice of medicine as second line therapy.

Legend: “+” denotes concurrent use of medicines

Borte = bortezomib

Thali = thalidomide

Lenal = lenalidomide

Figure A.5 presents what was the first line regimen before the administration of the second line.

Figure A.5: Type of second line therapy and the preceding first line.

Legend: “+” denotes concurrent use of medicines

Borte = bortezomib

Thali = thalidomide

Lenal = lenalidomide

Figure A.6 shows that only 24% of people received a third line therapy. Lenalidomide accounted for almost half of third line therapy after trialling bortezomib and thalidomide (Figure A.7). Pomalidomide which is recommended as third line was used in only 2% of people (Figure A.6) mostly after trialling bortezomib and lenalidomide (Figure A.7). However, it should be noted, pomalidomide was only available for a short time period during the data analysis.

Overall, pomalidomide was used as second line therapy in 1.3% of people, and lenalidomide was used as first line therapy in 12% of people, which was not consistent with guideline recommendations.

Figure A.6 Choice of medicine as third line therapy.

Legend: “+” denotes concurrent use of medicines

Borte = bortezomib

Thali = thalidomide

Lenal = lenalidomide

Pomal = pomalidomide

**Figure A.7 Type of third line therapy and the preceding regimens**

Legend: “+” denotes concurrent use of medicines

Borte = bortezomib

Thali = thalidomide

Lenal = lenalidomide

Pomal = pomalidomide