

Lenalidomide for myelodysplastic syndrome: predicted versus actual analysis

Drug utilisation sub-committee (DUSC)

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Abstract

Purpose

To compare the predicted and actual utilisation of lenalidomide for myelodysplastic syndrome (MDS) since it was PBS listed for this indication in October 2013. To list any key uncertainties identified by the PBAC during evaluation of the submission and explore what information about these can be determined from studies of current utilisation or information from key stakeholders.

Current PBS restriction for MDS

Listed under the s100 Highly Specialised Drug (HSD) Authority Required PBS program for treatment of transfusion-dependent, low risk or intermediate stage (low risk/INT-1), deletion 5q MDS. Details of the full restriction are attached in Appendix A.

Prescribers need to provide information specified in the restriction in writing to the Department of Human Services (DHS) to commence treatment (establish eligibility) and to continue treatment (establish response to treatment has occurred within 16 weeks of treatment). Once the first continuation is approved prescribers obtain subsequent prior approval for continuation by telephone.

Data Sources

Data to assess utilisation was obtained from the Department of Human Services (DHS) PBS prescription claims database and the DHS authority approvals database.

Key Findings

- The actual prescription utilisation was much less than predicted due both to a lower than predicted number of patients treated and lower than predicted prescriptions per patient per year.
- The reason for the number of patients treated being less than predicted is not clear.
 - The proportion of eligible patients could have been an overestimate. This report notes that the prevalence was incorrectly calculated in the estimates considered

by the PBAC. When corrected during this analysis, the eligible patient numbers were slightly less. The estimate of the proportion of MDS patients that are low risk/INT-1 was based on a small study and clinical information which may not accurately reflect the overall Australian experience.

- Lower than expected uptake rate may be a result of patient and prescriber experience of intolerance and adverse events or achievement of less than expected benefit in a larger number of patients with transfusion dependent MDS in practice.
- The submission overestimated the number of prescriptions per patient per year. This was due to a “part cycle correction” not being applied to each year which allows for patients to commence treatment during the year.
- This analysis found that the number of prescriptions per patient **overall** was slightly more than expected, but these were spread over a longer period than expected and included breaks in treatment.
- The proportion of use of the 5 mg capsules (32.7%) was higher than predicted (██████). This result is consistent with PBAC’s concern that adverse events and dose reduction would be greater than predicted.
- The predicted cost savings from reduction of deferasirox use were not realised.

Background

Clinical situation

The myelodysplastic syndromes are a group of disorders of haematopoiesis (formation of blood cellular components), which include refractory anaemia, chronic myelomonocytic leukaemia, acute myeloid leukaemia (AML) and a specific subtype characterised by the presence of a deletion of the 5q chromosome. The 5q deletion subtype is typically associated with a better prognosis for survival and freedom from progression to AML than occurs in patients without a 5q deletion.

The incidence of MDS is highest among older persons, with the median age of diagnosis being in the range of 65 to 70 years. There are currently no curative options available for most patients with MDS although a small percentage of younger and fitter patients may achieve long-term disease control through allogeneic transplantation. Almost all patients with MDS will receive background supportive therapy consisting of red blood cell (RBC) and platelet transfusions, antibiotics, growth factor support and iron chelating therapy. Additional active therapies, such as chemotherapy, will be used in patients at higher risk of transforming to leukaemia. The PBAC noted that iron chelation therapy was overused in this condition and provided limited benefits in patients with short life expectancy.

Lenalidomide provides an alternative treatment option to best supportive care for people with the 5q deletion who are unable or not suitable to be treated with active chemotherapy/stem cell transplantation.

Pharmacology

Lenalidomide inhibits proliferation of certain haematopoietic tumour cells (including multiple myeloma [MM] plasma tumour cells and those with deletions of chromosome 5), enhances T cell- and Natural Killer (NK) cell-mediated immunity and increases the number of NK T cells, inhibits production of pro-inflammatory cytokines (e.g. TNF- α and IL-6) by monocytes, inhibits angiogenesis by blocking the migration and adhesion of endothelial cells and the formation of microvessels, and augments foetal haemoglobin production by CD34+ haematopoietic stem cells (sourced from the Product information available on the ARTG website).

Therapeutic Goods Administration (TGA) approved indications and other PBS restrictions

Lenalidomide (Revlimid[®]) is approved by the TGA for:

- Newly diagnosed multiple myeloma in patients who are ineligible for autologous stem cell transplantation. Subsidised on the PBS (25 mg item codes 11055W, 11041D; 15 mg item codes 11042E, 11062F; 10 mg item codes 11064H, 11063G; 5 mg item codes 11029L, 11036W). The PBS restriction also specifies that treatment is in combination

with dexamethasone and that treatment is discontinued in patients with progressive disease.

- In patients who have received one prior therapy and have progressed multiple myeloma disease (20 December 2007). Lenalidomide is administered in combination with dexamethasone. Subsidised on the PBS (25 mg 9645P, 9644N; 15 mg 5785L, 9644N; 10 mg 5784K, 9643M; 5 mg 5783J, 9642L). The PBS restriction also specifies that patients are not eligible for stem cell transplant and treatment is discontinued in patients with progressive disease.
- Patients with relapsed or refractory mantle cell lymphoma.
- Transfusion dependent anaemia due to low or intermediate-1 risk myelodysplastic syndrome associated with deletion 5q cytogenetic abnormality (15 April 2010).

Lenalidomide is a category X (high risk) poison. All patients, prescribers and dispensing pharmacists are required to be registered on the i-access® program provided by Celgene Pty Ltd.

Dosage and administration

10 mg orally once daily on days 1 to 21 of a 28 day repeating cycle.

Treatment interruption and subsequent return to therapy at a lower dose are required for a range of commonly occurring grade 3 or 4 adverse events. These include neutropenia, thrombocytopenia (haematologic toxicity was reported in 80% patients in clinical trials) thromboembolism, abnormal liver function tests, tumour flare reaction, severe dermatological reactions. Dose reduction is required if renal function is reduced. Lenalidomide has been used in older patients in clinical trials.

Relevant aspects of consideration by the PBAC (abridged)

The following details are extracted from the March 2013 PBAC Minutes, the Pre-PBAC Response from Celgene Pty Ltd, re-submission section E spreadsheet and main body.

Comparative clinical effectiveness

The PBAC considered that lenalidomide treatment resulted in a statistically significant increase in transfusion independence in people with low risk or INT-1 MDS after 6 months of treatment. These patients progressed to AML at a slower rate. The trial results did not support increased overall survival but the PBAC considered an increase in overall survival was likely.

The main trial considered by the PBAC was a randomised phase 3 trial of 205 patients comparing lenalidomide to best supportive care. The primary outcome was the proportion of patients who had no transfusions of red blood cells in 6 months and an increase of haemoglobin of 1 g/dL in 12 months. This was statistically significant for the lenalidomide arm (NNT: 2.0 95%CI 1.5, 3).

The economic analysis relied on a secondary trial effect measure – transfusion independence for ≥ 56 days. This was considered clinically meaningful by the International

Working Group for Myelodysplastic Syndrome (NNT 1.9; 95%CI 1.4, 2.7). This result was recorded after 8 weeks' duration of the trial.

Overall survival and reduction in the time to transform MDS to AML was measured in a continuation phase of the original trial. Overall survival results could not be clearly attributed to treatment with lenalidomide as the study protocol allowed crossover; i.e. study patients who did not receive lenalidomide in the initial allocation of treatments were able to cross over to the lenalidomide treatment arm after 16 weeks of treatment if they required a transfusion during the initial 16 weeks.

Quality of life was measured using the health related quality of life measure (HRQoL). There was considerable loss to follow-up after the first measurement at 24 weeks making it difficult to draw conclusions about quality of life gains.

Cost effectiveness

PBAC found that the decision analytic model in the submission favoured lenalidomide. The key inputs to the model were:

- Proportion of people achieving transfusion independence \geq 56 days.
- Cost of lenalidomide compared to current best supportive care.

The PBAC recommended lenalidomide on the basis of the proposed reduction in the cost of treatment which reduced the ICER/QALY to between \$15,000 - \$45,000 per QALY gained.

The key uncertainties that remained were:

- The source of utility measures. The base case used utilities sourced from Szende et al (2010) which the ESC considered favoured lenalidomide. An alternative source of utilities, Buckstein, resulted in an ICER of \$44,000 per QALY gained. The PBAC accepted that this could not be further resolved.
- The proportion of 5 mg and 10 mg doses used in the model. The health economic model and the financial estimates assumed each patient received [REDACTED]% 5 mg capsules and [REDACTED]% 10 mg capsules over the course of treatment.
- The duration of treatment per patient. The base case model used [REDACTED] cycles per patient.
- Risk of continuation in patients with minor erythroid response to lenalidomide

For further details refer to the March 2013 PBAC Public Summary Document.

Approach taken to estimate utilisation

Following is a summary of key assumptions that were used in the submission's financial estimates (March 2013 PBAC).

Incidence rate for MDS was sourced from the Australian Institute of Health and Welfare (AIHW). The proportion of MDS patients that were intermediate and low risk stages and 12 month mortality for each stage were sourced from Hui et al (2008) which reported South Australian data for MDS. The proportion of patients on 5 mg ([REDACTED]%) and 10 mg

(████%) was from Celgene marketing data. The proportion of patients with deletion 5q MDS was based on advice from PBAC July 2011. The source of the percentage of patients who were transfusion dependence of █████% was a clinician survey undertaken by the sponsor.

Table 1: Summary of the predicted patients, packs and financial cost of listing lenalidomide.

	Year 1 (Oct 2013 to Sept 2014)	Year 2 (Oct 2014 to Sept 2015)	Year 3 (Oct 2015 to Sept 2016)	Year 4 (Oct 2016 to Sept 2017)
MDS incident patients (total)	████	████	████	████
Low risk	████	████	████	████
INT-1	████	████	████	████
MDS prevalent patients*	████	████	████	████
Low risk	████	████	████	████
INT-1	████	████	████	████
Number eligible**	████	████	████	████
Uptake rate***	████	████	████	████
Number treated	████	████	████	████
Packs 5 mg****	████	████	████	████
Pack 10 mg*****	████	████	████	████
Total government expenditure (net copayment, published price)	████	████	████	████
Number of non-responders	████	████	████	████
Total government expenditure (net copayment and non-responders)	████	████	████	████
Reduction in deferasirox	████	████	████	████
Additional gCSF PBS drug costs *****	████	████	████	████
Additional gCSF hospital costs	████	████	████	████
Additional gCSF total costs	████	████	████	████

Source: March 2013 submission section E spreadsheet, corrected for price negotiation post PBAC recommendation.

gCSF = granulocyte colony-stimulating factor

INT-1 = intermediate stage

*Prevalent patients were calculated by incident patients from the previous year x survival % for each stage at 12 months (Hui, 2008) – █████% who transform to high risk (PBAC 2011 ratified minutes)

** Prevalent patients in low risk and INT-1 stages with 5q deletion (████%) and transfusion dependent (████%)

*** uptake of treatment proposed by Celgene

**** █████% patients taking █████ packs to provide █████ treatment cycles. *This appears to be an error in the estimates as there is no stated reason why patients take 5 mg daily for 28 days rather than the treatment cycle in the PI which stated 21 days of 28 day cycle.*

***** █████% patients taking █████ packs to provide █████ treatment cycles

***** 60% patients expected to have Grade 3 or 4 neutropenia requiring gCSF treatment.

The prices were adjusted in this analysis to allow for the published price agreed with Celgene after the PBAC recommendation to list. The PBAC made the recommendation on the basis of the effective price proposed by Celgene. The effective price is commercial-in-confidence. Celgene and the Commonwealth have a deed of agreement that provides for the Department of Health to invoice Celgene for the difference between the expenditure based on the published and effective price per quarter.

The submissions considered by PBAC in March 2011, July 2011 and March 2013 were not reviewed by DUSC.

The following is extracted from the PBAC Minutes March 2013.

The PBAC considered that a remaining uncertainty in the [health economic] model, the accuracy of the proportion of 5 mg and 10 mg tablets used per patient and the duration of treatment, would be best addressed through calculation of the estimates of likely use in a risk sharing arrangement between the Commonwealth and the sponsor.

The PBAC accepted the net cost to the Government provided in the pre-PBAC response reflected the most likely estimate of use in Australia. The patients enrolled in the clinical trial reflected the PBS-eligible population but [the PBAC was] concerned that there was a risk of broader use, particularly where patients did not cease therapy when non-responsive (non-response as measured in the clinical trial). The committee noted that inclusion of non-responders and use of PBS listed medicines to manage adverse drug events in the estimates model was appropriate.

In considering the total cost, the PBAC recommended that the Commonwealth and sponsor have a risk sharing arrangement to manage the possibility of additional costs to those provided in the submission (outlined in the pre-PBAC response). The PBAC considered that there were three particular areas of concern; the possibility of people with other MDS being included in treatment, uncertainty about the proportion of 5 mg and 10 mg packs, and about the proportion of non-responders who continue therapy.

The PBAC asked that the DUSC include analysis of the duration of therapy per patient and the proportion of use of the different strength packs in any review of utilisation post listing.

PBS listing details (as at August 2017)

The treatment must be limited to a maximum duration of 16 weeks, AND patients must be classified as Low risk or Intermediate-1 according to the International Prognostic Scoring System (IPSS), AND patients must have a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities, AND patients must be red blood cell transfusion dependent.

Details of the full restriction are attached in Appendix A. There have been no changes to the restriction wording since listing on 1 October 2013.

Table 2: Listing Details

Name Form & Strength	Max Qty	No of Rpts	Original Dispensed Price Current Dispensed Price ¹ (current effective price) ²				Proprietary Name and Manufacturer	
			Public hospitals	Item	Private hospitals	Item		
Lenalidomide								
Hard Capsules 5 mg	21	3	\$5,392.38 \$5,122.76	2799H	\$5,439.01 \$5,169.91	2798G	Revlimid®	Celgene
Hard Capsules 10 mg	21	3	\$5,643.33 \$5,361.16	2802L	\$5,689.96 \$5,408.31	2796E		

1. Original Published and Effective prices were reduced by 5% following application of Government pricing policy in 1 April 2017. This is the only change in price since listing.

2. A proposal for a Special Pricing Arrangement was included in the submission and approved by the government post recommendation. The 5 mg and 10 mg capsules have a [REDACTED]% and [REDACTED]% rebate respectively applied to the PBS expenditure.

Analysis

The following assumptions were tested in the utilisation analysis:

- The number of patients who received treatment each year (prevalent and incident)
- The number and type of prescriptions (5 mg or 10 mg) supplied per patient
- The duration of lenalidomide therapy per patient for MDS
- A comparison of the predicted number of patients, packs supplied and financial expenditure for lenalidomide (net of copayment and using the PBS schedule published unit cost)
- Change in quantities and cost of desferasirox and gCSF in patients receiving prescriptions for lenalidomide for MDS.

Methods

PBS prescription data for lenalidomide from 1 November 2009 (the date of first listing of lenalidomide on the PBS) to 31 March 2017 were extracted from the DHS prescription database based on the date of dispensing. The date of processing of PBS prescriptions may differ from the date of dispensing. Consequently there may be differences in data reported by date of dispensing or processing (such as that available publicly available from DHS Medicare website).

PBS prescription data were used to determine the number of prescriptions supplied and the PBS expenditure. These data were also used to count the number of patients, both incident (new to treatment) and prevalent (number treated in each time period, i.e. year or quarter).

The main analysis relates to utilisation since lenalidomide was listed for the MDS indication (1 October 2013). Data prior to this was used as part of the analysis to determine the "Patient Classification" in the "Indication sequence and patient classification" section.

Prescriptions from public hospitals are not all available at the patient level prior to July 2013. This has a small impact on the prescription history for patients that was used in this analysis. More details regarding this issue are in Appendix B.

There is a possibility that PBS item numbers assigned to MDS may have been used for non-MDS patients, and vice versa. Additional information on this is detailed in section 3. As this misclassification could have an effect on the patient-level analyses a second dataset was developed to minimise the effect of misclassification in these analyses (see below).

This analysis used the Kaplan Meier (aka Product-Limit) method to determine the length of treatment for patients on lenalidomide for MDS. Two ways of measuring length of treatment were undertaken. One excluded any breaks in treatment and the other did not. A break in treatment was defined as a gap of more than 3 x median time to resupply between supplies, which was an estimated break in treatment of at least 2 x median time to resupply. A patient was deemed to be continuing treatment (classified as censored in the Product-Limit method) at the end of the data period (ie. the end of March 2017) if their last prescription is within 3 x median time to resupply of this end date. Otherwise the patient was deemed to have ceased treatment with the treatment coverage end date being the supply date of their last prescription plus a median time to resupply.

In the "Estimated Dose" section the estimated dose was calculated at the patient level and is equal to the total mass of lenalidomide supplied to a patient summed across all their prescriptions, divided by their total length of treatment (excluding breaks).

There were two different sets of data used in the analyses.

1. The utilisation dataset includes all the prescription information for lenalidomide PBS items indicated for MDS (see Listing Details section above and Table 3 below). Refer to sections 1 and 2 of the results
2. The patient cohort described as "Considered to be patients with MDS" (Cohort MDS) contains lenalidomide prescription data for all patients considered to definitely have MDS. Refer to section 3 of the results.

Results

1. Utilisation analyses

1.1 Prescription Utilisation

The PBS items included in this analysis were all MDS indication specific items (see Table 3) and the analysis uses dataset 1.

Table 3: PBS items which are only indicated for the treatment of MDS

Drug	Description	PBS Item	Setting
lenalidomide	Capsule 5 mg 21	2798G	HSD Private
		2799H	HSD Public Hospital
	Capsule 10 mg 21	2796E	HSD Private
		2802L	HSD Public Hospital

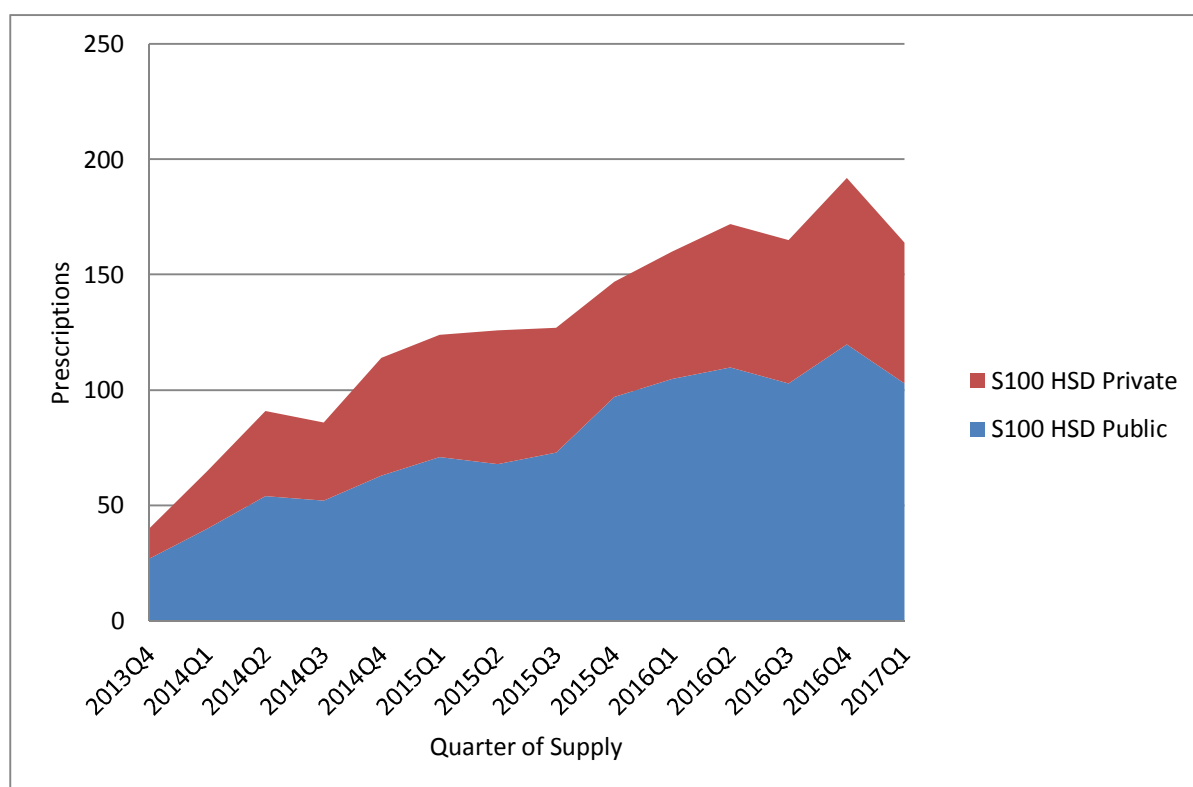


Figure 1: PBS/RPBS Prescriptions of lenalidomide for MDS item numbers by setting.

Source: DHS prescription claims database (accessed 13 June 2017).

Figure 1 shows the utilisation of lenalidomide for MDS is increasing and is yet to stabilise. The treatment setting was more commonly in public hospital outpatient clinics.

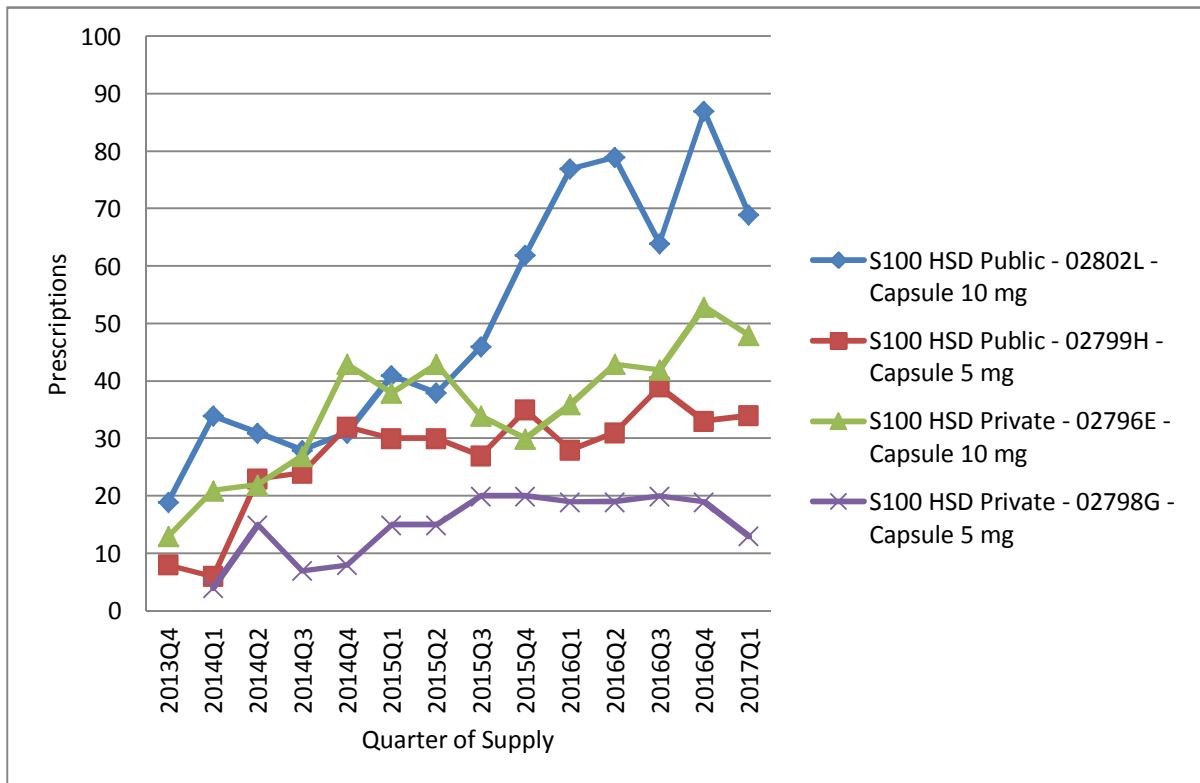


Figure 2: PBS/RPBS Prescriptions of lenalidomide for MDS item numbers by setting and strength.

Source: DHS prescription claims database (accessed 13 June 2017).

Figure 2 shows Figure 1 broken down by capsule strength. The 10 mg capsule has a greater proportion of use than 5 mg. Refer to analysis of predicted and actual for additional information on the proportions of use of 5 mg and 10 mg strengths (section 2).

1.2 Initiating and prevalent patient counts

This analysis uses dataset 1. Prescription data contains the unique identification number for each patient (PIN). The PINs for all prescriptions supplied for PBS items numbers allocated to MDS were extracted. Incident patients were defined as having no supplies of a PBS prescription for lenalidomide for MDS from 1 October 2013 to the date of the first prescription supply. Prevalent patients were the count of all unique PINs receiving a PBS prescriptions for supply of any item number for MDS in each period (i.e. by 3 months of supply in Figure 3).

The potential for some misclassification of patients to MDS rather than multiple myeloma was investigated later in this report. Refer to section 3.

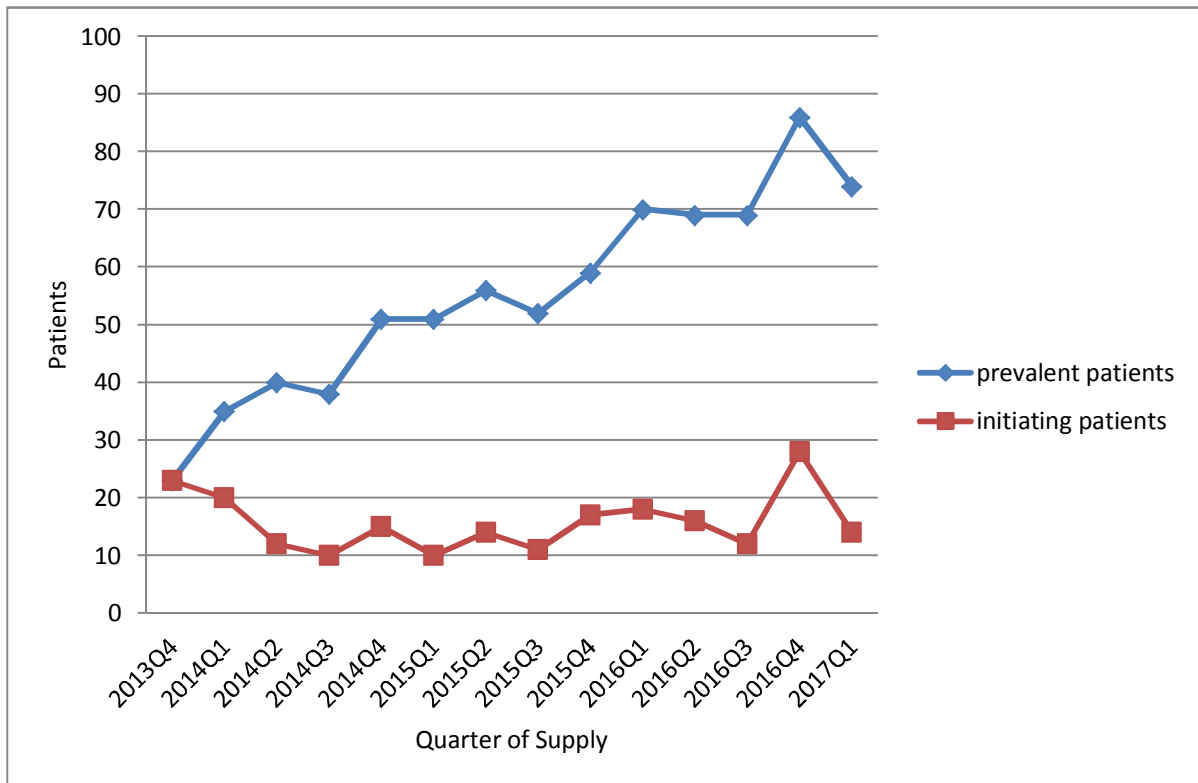


Figure 3: Number of patients initiating and prevalent to lenalidomide for MDS.

Figure 3 shows that the number of patients initiating lenalidomide has been relatively constant since 2014 Q2 (except for 2016 Q4). The number of prevalent patients has increased steadily since listing in October 2013. Using this dataset between 10 and 28 patients per quarter commence treatment with lenalidomide for MDS. The number of prevalent patients continues to rise (refer to Table 4 for actual numbers) indicating that patients are likely to remain on treatment. Refer to Figure 5 for additional analysis of duration of treatment.

2. Analysis of predicted versus actual utilisation

This analysis compares the predicted and actual use of lenalidomide for MDS. The predicted use was extracted from section E of the submission considered by PBAC in March 2013 (refer to Table 1) The PBS items included in this analysis of actual utilisation were all MDS indication specific items (see Table 3).

Table 4: Predicted vs Actual analysis

		Year1	Year 2	Year 3
		Oct13 to Sep14	Oct14 to Sep15	Oct15 to Sep16
Prevalent patients (PBS & RPBS)	Predicted (P)	█	█	█
	Actual (A)	65	86	108
	% Difference (A-P)/P	█	█	█
Prescriptions / packs* for 5 mg capsules	Predicted (P)	█	█	█
	Actual (A)	87	177	211
	% Difference (A-P)/P	█	█	█
Prescriptions / packs for 10 mg capsules	Predicted (P)	█	█	█
	Actual (A)	195	314	433
	% Difference (A-P)/P	█	█	█
Prescriptions / packs Total	Predicted (P)	█	█	█
	Actual (A)	282	491	644
	% Difference (A-P)/P	█	█	█
Prescriptions per patient	Predicted (P)	█	█	█
	Actual (A)	4.3	5.7	6.0
	% Difference (A-P)/P	█	█	█
R/PBS expenditure (published)	Predicted (P)	█	█	█
	Actual (A)	\$1,556,001	\$2,735,616	\$3,523,073
	% Difference (A-P)/P	█	█	█

Notes: R/PBS = PBS & Repatriation PBS combined

* Predicted values are in packs and actuals are in prescriptions and these units are equivalent in this instance.

Table 4 shows that utilisation has been much lower than predicted. This is due approximately equally to a lower than predicted number of patients and a lower than predicted number of prescriptions per patient per year. During the preparation of this report it was noted that the calculation of the number of prescriptions per patient assumed that every patient had █ prescriptions (█ cycles) of treatment every year. This does not allow patients to commence or cease treatment part way through the year (often referred to as a part cycle correction) and is likely to have the greatest effect in the first few years of listing i.e. until the market reaches stable equilibrium. This assumption of utilisation (█ cycles per patient per year) was not consistent with the amount of lenalidomide per patient in the health economic model which assumed █ cycles in total per patient, not every year they are alive.

The PBAC expressed concern about the uncertainty in the proportional use of the 5 mg and 10 mg packs. The PBAC noted a greater use of the 5 mg strength is consistent with the product information. This reports that 80% of patients in the clinical trial considered by PBAC had grade 3 or 4 haematologic toxicity which may require a short break from therapy and reintroduction of lenalidomide using the 5 mg strength (refer to TGA information above).

The submission assumed in the health economic model and its estimates of utilisation that ████% of patients would take ████ packs of the 5 mg capsule and ████% of patients would take ████ packs of the 10 mg capsule in a year. These assumptions translated to the percentage of 5 mg and 10 mg prescriptions supplied being ████% and ████%, respectively. The actual proportions in Year 3 were 32.7% and 67.2%, respectively. Thus the proportion of 5 mg supply was more than predicted. This is consistent with the concerns expressed by the PBAC that the proportion of 5 mg use was underestimated in the submission. This analysis did not re-run the economic model to determine if this difference would have a substantial effect on the ICER.

3. Patient-level duration of therapy

Indication sequence and patient classification issues

Applications for eligibility to prescribe lenalidomide for multiple myeloma and MDS are provided in writing to DHS. For each original prescription, patients can receive up to three repeats to be supplied for the three subsequent cycles (a 16 week period in total). The original authority prescription is endorsed by DHS with the relevant item number and the first supply is cross checked against the authorities database at the time the prescription is submitted to DHS for claiming. Therefore a cohort of patients identified using first original prescriptions specifically for MDS was assumed to be the least likely to have misclassification bias. It was still possible for a small number of original and repeat prescriptions to be entered in the pharmacy claim database with an inaccurate item number. This possibility was considered and the extent and possible effect of misclassification was explored.

Construction of dataset 2 containing patients with MDS and minimal misclassification

In order to identify an 'as accurate as possible' cohort of patients with MDS with a full medication history for lenalidomide, all PBS supplied prescriptions from the DHS pharmacy claim database for lenalidomide (1 November 2009 to 31 March 2017) were extracted.

Patients were classified as being likely to have MDS or multiple myeloma (MM) based on the indication sequence of original prescriptions in relation to the MDS indication listing date of 1 October 2013. That is, if a patient's first original prescription after 1 October 2013 was indicated for MDS and they did not receive a MM indicated original prescription prior to 1 October 2013, then it was considered that the patient is being treated for MDS (Cohort MDS - 141 patients). Otherwise the patient was considered to be treated for multiple myeloma (Cohort MM - 5,079 patients).

Table 5 shows indication sequences for all lenalidomide original prescriptions (i.e. including all PBS item codes) and subsequent patient classifications.

Table 5: Original prescription indication sequence

Patient classification	Original prescription indication sequence	Patients	% Patients
Considered to be patients with MDS (Cohort MDS)	All original prescriptions were indicated for MDS	137	2.6%
	First original prescription was post 1 October 2013 and indicated for MDS, but patients also had at least one MM original after this.	4	0.1%
	Sub-total	141	2.7%
Considered to be patients with multiple myeloma (Cohort MM).	First original prescription post 1 October 2013 was indicated for MDS, but patient also had at least one MM original prior to 1 October 2013. Not clear if MDS post 1 October entry was an error.	4	0.1%
	All original prescriptions were indicated for multiple myeloma PBS item numbers	5,012	96.0%
	Patients whose first original authority prescription was for MM after 1 October 2013 but at least one subsequent original authority prescription was for MDS. Later originals could have been for either indication.	63	1.2%
	Sub-total	5,079	97.3%
Total		5,220	100.0%

The total number of patients in the previous analyses (sections 1 & 2), which only had regard to MDS indicated prescriptions (both originals and repeats), was 220. This means that 220 – 141 = 79 patients that were included in the previous analysis were possibly misclassified as MDS. For the purpose of analysis of utilisation, these patients did not have a complete prescription history for lenalidomide as all MM item number prescription supplies were not included for these 79 patients.

The subsequent analyses in this report were designed to compare parameters assumed in the submissions with an estimate of the parameters observed in practice (e.g. length of treatment, average dose, time to resupply, number prescriptions per patient). This parameter estimation is most accurate if based on a cohort of patients in which there was a high degree of confidence that they were MDS patients and that they had their full lenalidomide prescription history; even if some prescriptions were misclassified as being for an MM patient (4 patients).

Note that the number of patients in the category “First original prescription post 1 October 2013 was indicated for MDS, but patient also had at least one MM original prior to 1 October 2013” would be an underestimate as public hospital HSD data was incomplete prior to July 2013 in the patient level DHS prescription database used for this analysis. This limitation does not impact the PBS item codes indicated for MDS, as these were listed in October 2013, but it does impact the MM item codes. See Appendix B for more details of

this issue. It means that some of the 141 patients classified as MDS patients in Table 5 may have been classified as multiple myeloma patients if the patient level data was complete. However, this was considered relatively unlikely as the patient level data was complete from July 2013.

3.1 Time to resupply and length of treatment for Cohort MDS patients

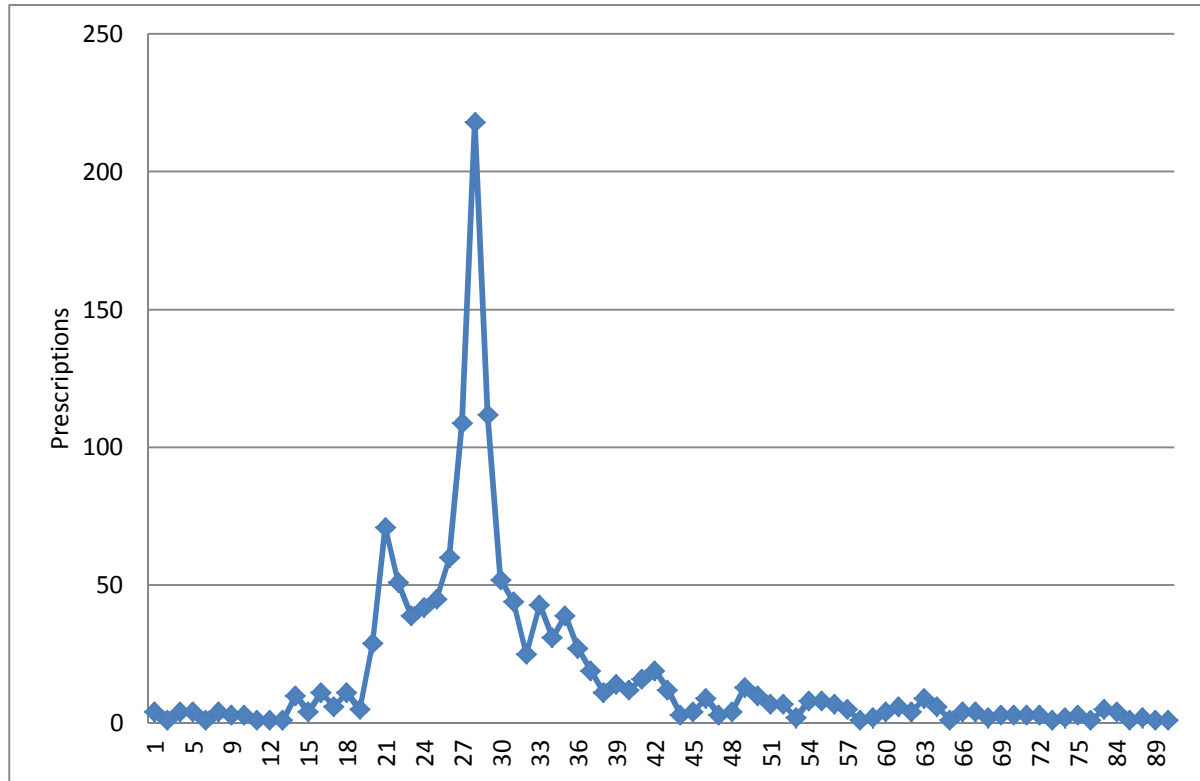


Figure 4: Number of days to prescription re-supply for Cohort MDS patients.

Note: does not include prescriptions with no re-supply and re-supply > 90 days.

Figure 4 shows that the most common (mode) time for resupply was 28 days (which was also the median time for resupply). Next most common was 21 days. This bimodal distribution is likely due to there being 21 capsules in each pack which is designed for 21 days of treatment in a 28 days cycle (i.e. 7 days without treatment). Lenalidomide is a s100 HSD and supplied by the hospital rather than a local pharmacy. The reason for 21 days could be related to convenience for patients who were attending a clinic at the hospital.

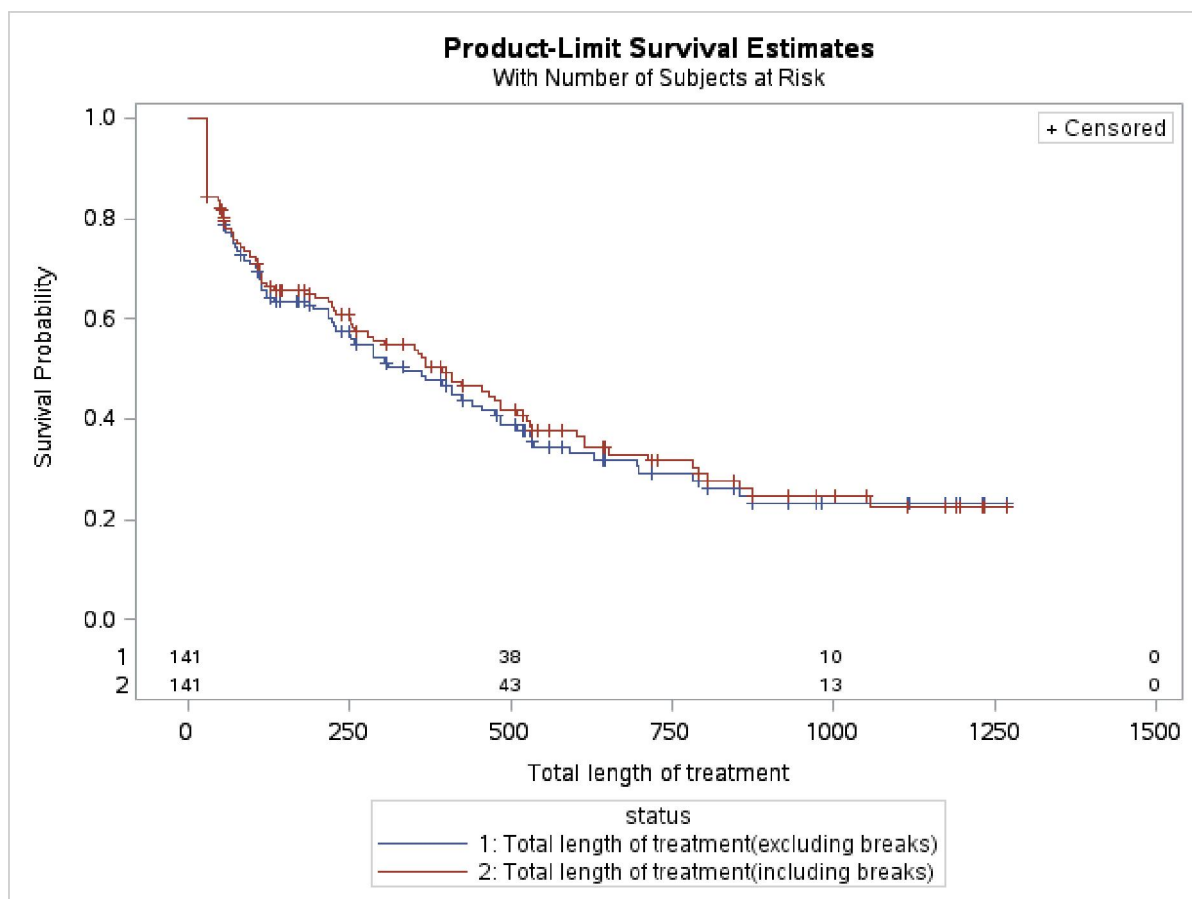


Figure 5: Length of treatment (days) with lenalidomide for Cohort MDS patients (n=141)

Figure 5 shows the Kaplan Meier estimates of length of treatment using two measures.

Total length of treatment (excluding breaks) is the time that patients received supplies of medicine not counting the time that patients did not have medicine supplied (i.e. were having a break between episodes of treatment).

A break is defined as a gap of more than 3 x median time to resupply (i.e. $3 \times 28 = 84$ days) between supplies, which is an estimated break in treatment of at least 2 x median time to resupply (i.e. 2×28 days = 56 days). The product information states that patients can suspend treatment and recommence at a reduced dosed if there is severe toxicity. This analysis assumed that a break of 56 days was longer than temporary suspension to manage toxicity.

Total length of treatment (including breaks) is the time that patients received supplies of medicine and counts the additional time that patients were not receiving supply of medicine between episodes of treatment.

These analyses both allow patients to stop treatment (i.e. no more supplies of medicine) or be censored (i.e. deemed to be continuing treatment at the end of the data period). See Method section above for more details.

The median lengths of treatment (excluding breaks) was 334 days (11.0 months). The median length of treatment (including breaks) was 395 days (13.0 months). The total observation period of the study was 42 months.

The submission assumed that patients would on average have █ cycles of treatment which would take █ supplies of medication and last approximately █ months (if there were no breaks in treatment). The actual length of treatment figures are a little longer than this, 11.0 months of treatment if breaks are excluded and 13 months of treatment in they are included.

3.2 Estimated Dose for Cohort MDS patients

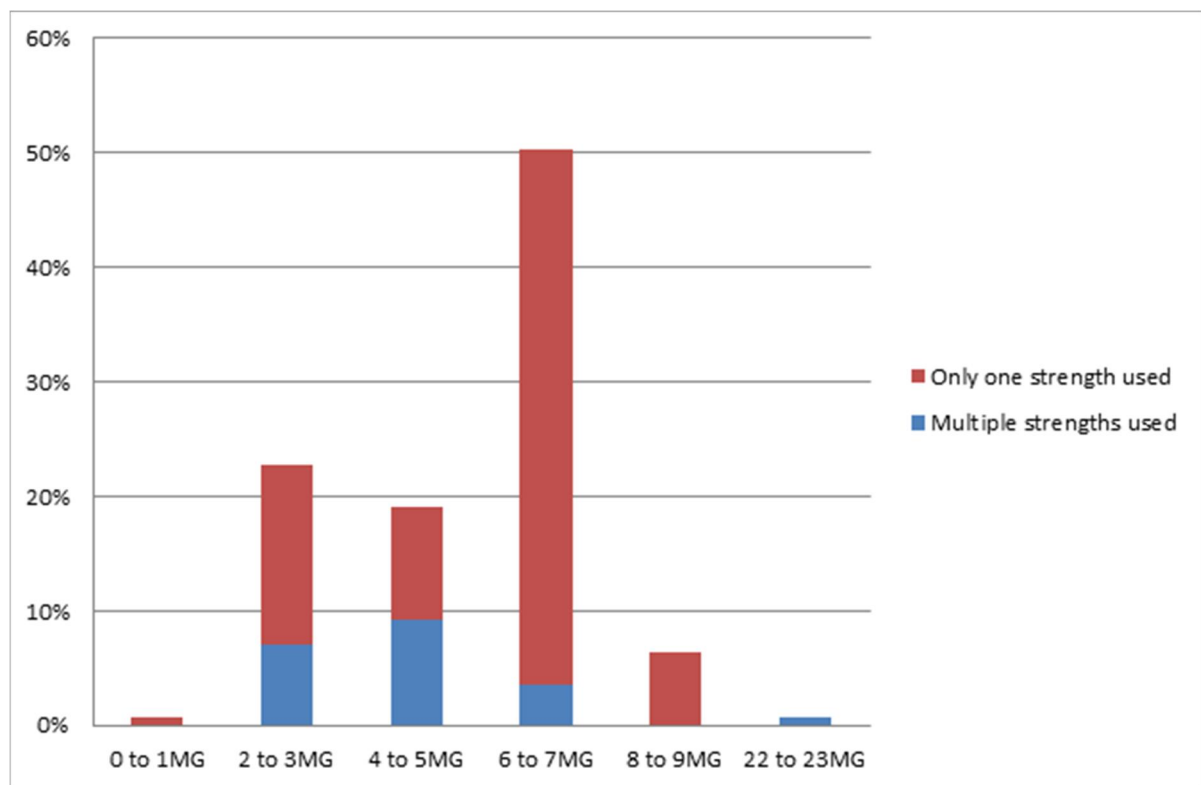


Figure 6: Estimated dose (mg/day) distribution for lenalidomide for Cohort MDS patients by the number of strengths used.

The estimated dose was the total mass of lenalidomide supplied to a patient summed across all their prescriptions, divided by their total length of treatment (excluding breaks). The length of treatment estimates relies on the analysis in the previous section 3.1.

The median and mean doses were 6.7 and 6.0 mg/day respectively. The most common dose (mode) was 7.5 mg/day, which was consistent with the recommended starting dose of 10 mg/day taken for 21 days in a 28 day cycle.

The March 2013 submission predicted the average dose would be █ mg/day, which is only slightly more than the actual estimated dose of 6.0 mg/day .

The number of strengths used (i.e. one or multiple) does not have regard to the timing of the supply. Thus if a patient was initiated on 10 mg capsules and then later was down titrated to 5 mg capsules then this would be classified as “Multiple strengths used.” A patient who was supplied both the 5 and 10 mg capsules at the same time would also have the “Multiple strengths used” classification.

3.3 Prescriptions per patient

The March 2013 submission contained assumptions about the number of packs per year per patient (i.e. █% of patients would take █ packs of the 5 mg capsule and █% of patients would take 9 packs of the 10 mg capsule in a year. There were no explicit assumptions about patients taking both strengths). These assumptions were incorrectly applied to each prevalent patient in each year after listing, whereas they should have been applied to the year after initiation of each patient and then the patients allowed to initiate evenly throughout the post listing years.

The number of prescriptions per patient in the 24 months after initiation was calculated (Figure 7) for cohort MDS patients (n=141) that initiated from October 2013 to the end of March 2015 (n=74) to allow for 24 months of follow-up for each patient. Figure 8 shows the distribution by strength for the same cohort.

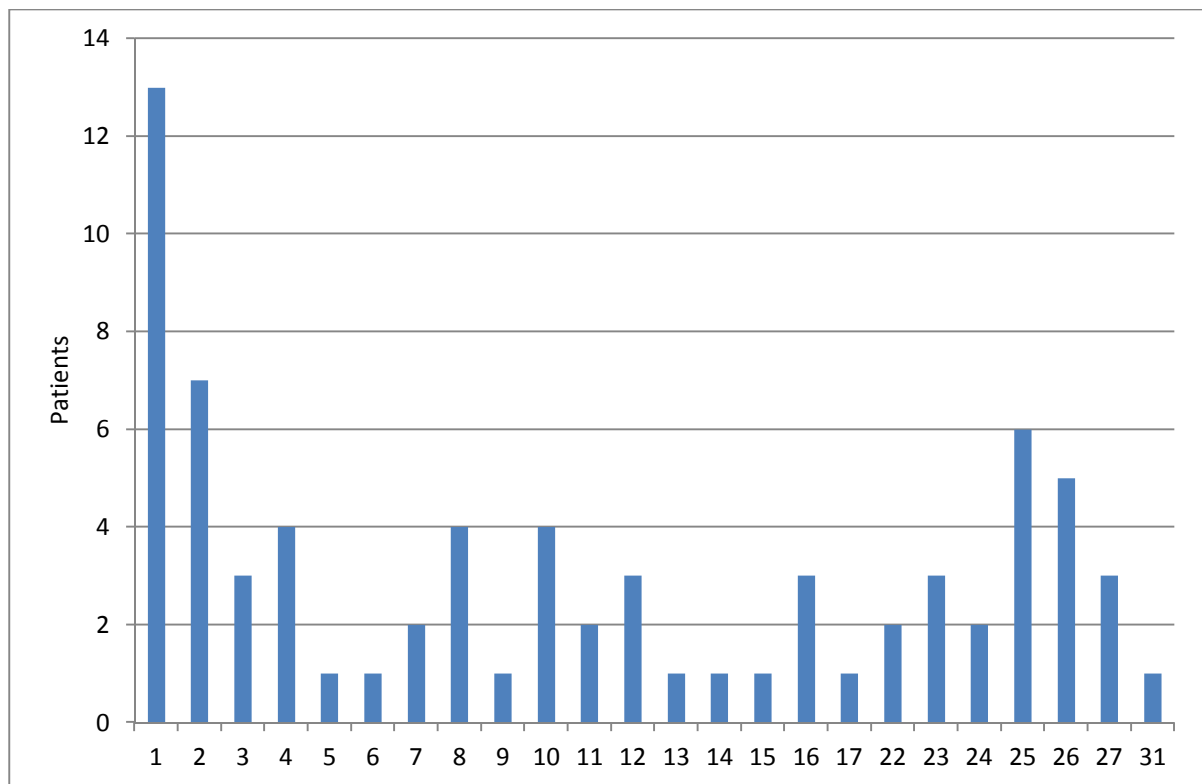


Figure 7: Distribution of the number of lenalidomide prescriptions per patient in 24 months post initiation.

Figure 7 shows that the discontinuation rate (i.e. rate of no further supply of lenalidomide) after the first prescription supplied was 13 / 74 = 17.6%. This is lower than the non-responder rate of █% assumed in the March 2013 submission, where it is assumed that

non-responders will discontinue treatment. If non-response (including patients intolerant to treatment) is defined as a patient not receiving a second original script, then there were 25 such patients (calculated separately) in this cohort giving a rate of 33.8% non-responders who discontinued treatment.

PBAC was concerned that some non-responders may not discontinue treatment. It is not possible to detect these patients using this analysis. However it can be said that the combined non-response plus intolerance rate was at least 33.8% (including 17.6% who did not have more than one supply) which was greater than that non-response rate assumed in the submission (i.e. ███%).

The median and mean number of prescriptions per patient was 10 and 11.8, respectively. Figure 7 shows this was made up of approximately 3 groups. The non-responders (including patients intolerant to treatment) who had from 1 to 4 prescriptions (the standard number of repeats is 3), the patients that were still continuing after 24 months (these are probably the patients with 22 to 31 prescriptions) and the rest which had stopped after a course of treatment.

The mean number of 11.8 prescriptions per patient was more than the ███ treatments assumed in the submission.

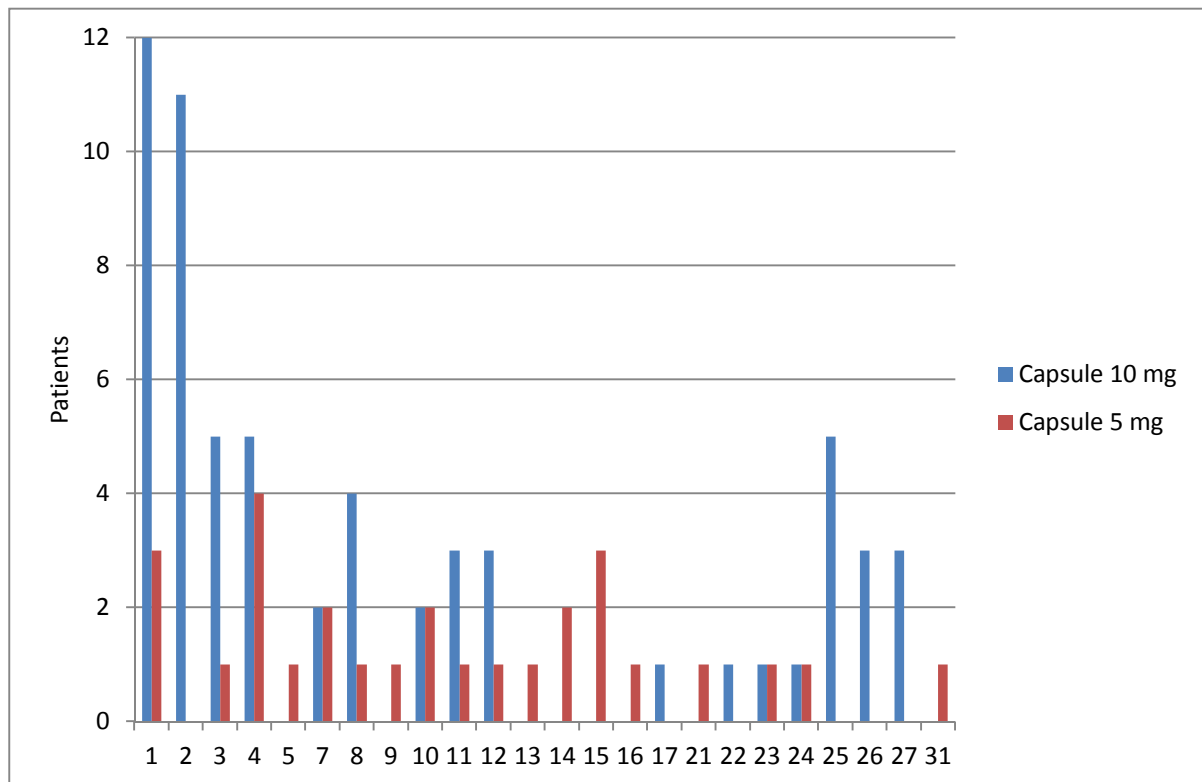


Figure 8: Distribution of the number of lenalidomide prescriptions per patient by strength in 24 months post initiation

The median and mean number of prescriptions per patient was 10 and 10.8 respectively for 5 mg and 4 and 9.3 respectively for 10 mg. There is a large difference in the median and

mean for the 10 mg capsule because the distribution is bimodal. The submission assumed an average of [redacted] prescriptions for the 10 mg capsule in a course of treatment and this is close the actual average of 9.3.

For the 5 mg capsule the submission assumed an average of [redacted] prescriptions in a course of treatment. This is slightly more than actual average of 10.8 prescriptions

Note that this “by strength” analysis does not have regard to whether or not a patient had more than one strength, each strength is analysed independently.

3.4 Reduction in deferasirox and increase in granulocyte colony-stimulating factor (gCSF) medication costs

The March 2013 submission assumed cost savings through reduction in deferasirox use and additional costs due to an increase in gCSF use. To test this assumption, the deferasirox and gCSF (ATC = L03AA; filgrastim, lenograstim, lipegfilgrastim, pegfilgrastim) use for Cohort MDS (n=141) was extracted from the DHS pharmacy claim prescription database.

All these drugs have an HSD listing and so the previously mentioned data limitation in the patient level PBS data (see Appendix B) is again relevant to this analysis. The patient level data is complete from July 2013, so it is not possible to compare PBS expenditure on these drugs for the MDS patient cohort in the full year prior to listing (October 2012 to September 2013) with the years after listing, because the year prior to listing is incomplete. Thus an alternative approach was taken, where for each patient the expenditure in the 12 months prior and post initiation was compared for the Cohort MDS patients that initiated lenalidomide from July 2014 to the end of March 2016 (n=74). All these patients have complete 12 month history pre and post initiation. Only 19 of these 74 patients had either deferasirox or gCSF supplied in the 12 months pre or post initiation to lenalidomide. These supplies are summarised in Table 6.

Table 6: Expenditure on deferasirox and gCSF drugs pre and post initiation to lenalidomide for Cohort MDS patients that initiated from July 2014 to the end of March 2016

Drug	Deferasirox	Filgrastim
12 months prior to lenalidomide initiation (A)	\$139,121	\$29,319
12 months post lenalidomide initiation (B)	\$99,123	\$42,085
Difference (B-A)	-\$39,998	\$12,766
Average difference per patient (n=74)	-\$541	\$173

The only gCSF drug supplied to these patients was filgrastim. Table 6 shows the average patient saving in a year for deferasirox was \$541 and the average additional cost for filgrastim was \$173. Overall there was a \$541 - \$173 = \$368 savings per patient in the first year after listing for these two drugs.

The March 2013 submission predicted (Table 1) that in Year 1 there would be an expenditure saving of [redacted] for [redacted] treated patients (\$ [redacted] per patient) for deferasirox and an additional expenditure of [redacted] (\$ [redacted] per patient) for gCSF drugs .

Overall there was predicted to be \$ [REDACTED] in savings per patient. These predictions are much larger than the actual expenditure per patient and so the expected savings were not realised.

Risk Sharing Arrangement

Commercial-in-Confidence

[REDACTED]

[REDACTED]

End of Commercial-in-Confidence

Discussion

The actual prescription utilisation was much less than predicted due to both the number of patients treated and prescriptions per patient being less than predicted.

Number of treated patients

It is not possible to determine a specific reason for the number of treated patients being much less than predicted. The number of predicted incident MDS patients in Year 1 (Oct 2013 to Sept 2014) was 1,161 patients based on AIHW incident rate data from 2006. This was reasonably accurate as the most recent data from the AIHW indicates that there were 1,307 MDS patients diagnosed in 2013.¹

The submission estimated that [REDACTED] of incident MDS patients would be low risk or INT-1 risk (based on Hui et al (2008)² which reported South Australian data for MDS) and so eligible under the PBS restriction. It is possible that this percentage was an overestimate for the population of MDS patients in Australia.

¹ 2017 Australian Cancer Incidence and Mortality (ACIM) book for Myelodysplastic syndromes (ICD-10 code D46)

² Hui, C. H., N. Horvath, et al. (2008). "Outcome of patients with myelodysplastic syndromes - experience from a single institution in South Australia." *Intern Med J*: 1-5.

The other possible areas of overestimation in the number of treated patients were the incorrect method of converting incident to prevalent patients, the percentage estimated to have the 5q deletion (■■%), the percentage that were transfusion dependant (■■%) and the uptake rate (■■% in Year 1 to ■■% in Year 4). There is minimal evidence to indicate which of these factors contributed to the overestimate of treated patients.

Section 3.3 showed that the combined non-response plus intolerance discontinuation rate was 33.8% (based on the number of patients that did not have a 2nd original prescription). PBAC was concerned that not all non-responders might cease treatment. If this has occurred then the combined non-response plus intolerance discontinuation rate is at least 33.8%, because some of the non-responders were not detected by this analysis. This relatively high rate of non-response and intolerance may have led to lower than expected uptake of this treatment by prescribers. Prescribers may view lenalidomide as beneficial for a smaller group of patients with MDS than expected.

The submission predicted that that the percentage of 5 mg and 10 mg prescriptions supplied would be ■■% and ■■%, respectively. The actual proportions in Year 3 were 32.7% and 67.2%, respectively. Thus the proportion of 5 mg supply was more than predicted. This may be evidence that adverse events and subsequent dose reduction were greater than expected. This also may have contributed to a lower than expected uptake rate by prescribers.

Prescriptions per patients

During the preparation of this report it was noted that the calculation of the number of prescriptions per patient assumed that every patient had ■■ prescriptions (■■ cycles) of treatment in every year they were predicted to be alive. This does not allow patients to commence or cease treatment part way through the year (often referred to as a part cycle correction) and is likely to have the greatest effect in the first few years of listing i.e. until the market reaches stable equilibrium. The health economic model assumed ■■ cycles (where each cycle would require one prescription) per patient in total, not in every year alive.

The analysis in Section 3.3 of this report, which looked at the number of prescriptions per patient since initiation to lenalidomide (with a 24 month follow-up for each patient), found that the average number of prescriptions per patient was 11.8 and so was more than that assumed in the economic model (■■ cycles). However the average of 11.8 prescriptions took 2 years to achieve and both Figures 5 and 7 show that a reasonable proportion of patients are still on treatment after 24 months. This means that even though patients are getting more prescriptions per patient in total than assumed by the economic model, they are receiving them over a longer period than assumed in the model. This is partly due to some patients having breaks in treatment. The length of treatment analysis in Section 3.1 estimated that there was a 2 month difference between the median length of treatment excluding breaks (i.e. 11.0 months) and the length of treatment including breaks (i.e. 13 months). The reason for long breaks in therapy is not clear.

Cost offsets

The submission predicted a saving of \$ [REDACTED] per patient for reduced use of deferasirox and the actual saving was \$541 per patient on average. Also an additional cost of \$774 per patient was predicted for gCSF drugs and the actual additional cost was \$ [REDACTED] per patient. One reason for these large differences is that only 19 of the 74 patients that were part of the analysis (see Section 3.4) had supplies of either deferasirox or gCSF supplied in the 12 months pre or post initiation to lenalidomide. Thus the large number of patients with no utilisation decreased the saving or cost per patient averaged over all 74 patients.

The submission assumption was that [REDACTED]% of lenalidomide treated patients would be transfusion dependant and [REDACTED]% of these would be treated with deferasirox. This means [REDACTED]% of patients were expected to be treated with deferasirox after treatment with lenalidomide. Of the 74 patients in the actual analysis, 9 patients had treatment with deferasirox in the year after initiating lenalidomide. This is [REDACTED]% which is less than predicted.

In regard to gCSF, the submission assumed that [REDACTED]% patients would have Grade 3 or 4 neutropenia requiring gCSF treatment. Of the 74 patients in the actual analysis, 6 patients had treatment with a gCSF (i.e. filgrastim) in the year after initiating lenalidomide. This is [REDACTED]% which is less than predicted.

DUSC consideration

The written requirements for the authority required restrictions were effective in targeting eligible patients and DUSC considered it was unlikely that other patients were accessing treatment.

In considering the assumptions for eligible patients DUSC noted that MDS is a disease with a large proportion of older fragile patients who frequently had other severe comorbidities and are not suitable for investigations to confirm cytogenetic diagnosis of MDS. These factors limit the appropriateness of commencing treatment with lenalidomide given the toxicity of this medicine.

The assumption of [REDACTED]% with the 5q deletion was poorly substantiated and possibly not correct. The estimates ranged from [REDACTED]%.

In considering the number of prescriptions per patient DUSC noted that the assumptions in the model were considerably different to those in the pivotal clinical trial. In List et al (2006)³ adjustment of lenalidomide dose was required in 84% of patients. At week 24 of the study 32% of patients were receiving 10 mg, 44% receiving 5 mg daily and 24% 5 mg every other day. The trial dosing results were much closer to that seen in practice in Australia.

³ List A, Dewald G, Bennett J et al. New England Journal of Medicine 2006 (355, October 5)1456-1465, 2006

Breaks in therapy are likely to be associated with toxicity and management of adverse events. Given the older age group and presence of co-morbidities occurrence of severe adverse events necessitating cessation of treatment for a period of time are highly probable.

Overall there are a smaller number of responders than anticipated in the submission.

It may take several years for the proportion of people with MDS who respond to treatment to increase to predicted levels. Therefore peak prevalence has not been achieved. This has implications for continuing the risk sharing arrangements past the current 5 years.

DUSC noted the breaks in therapy. DUSC questioned if cost effectiveness is adversely affected in patients who require breaks in therapy. The cost effectiveness was also affected by extent of use of 5 mg doses and this may need to be reviewed. DUSC also considered that the breaks in therapy may be a quality use of medicines issue as breaks could be associated with additional toxicity in a large number of patients.

DUSC actions

- The report, Sponsor response, and DUSC minutes were referred to the PBAC noting.

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

Celgene Pty Limited: The sponsor has 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.

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Appendix A: PBS Restriction

Lenalidomide (Revlimid®) in Myelodysplastic syndrome

Treatment Phase: Initial treatment

Clinical criteria:

- The treatment must be limited to a maximum duration of 16 weeks,

AND

- Patient must be classified as Low risk or Intermediate-1 according to the International Prognostic Scoring System (IPSS),

AND

- Patient must have a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities,

AND

- Patient must be red blood cell transfusion dependent.

•

Classification of a patient as Low risk requires a score of 0 on the IPSS, achieved with the following combination: less than 5% marrow blasts with good karyotypic status (normal, -Y alone, -5q alone, -20q alone), and 0/1 cytopenias.

Classification of a patient as Intermediate-1 requires a score of 0.5 to 1 on the IPSS, achieved with the following possible combinations:

1. 5%-10% marrow blasts with good karyotypic status (normal, -Y alone, -5q alone, -20q alone), and 0/1 cytopenias; OR
2. less than 5% marrow blasts with intermediate karyotypic status (other abnormalities), and 0/1 cytopenias; OR
3. less than 5% marrow blasts with good karyotypic status (normal, -Y alone, -5q alone, -20q alone), and 2/3 cytopenias; OR
4. less than 5% marrow blasts with intermediate karyotypic status (other abnormalities), and 2/3 cytopenias; OR
5. 5%-10% marrow blasts with intermediate karyotypic status (other abnormalities), and 0/1 cytopenias; OR
6. 5%-10% marrow blasts with good karyotypic status (normal, -Y alone, -5q alone, -20q alone), and 2/3 cytopenias; OR
7. less than 5% marrow blasts with poor karyotypic status (complex, greater than 3 abnormalities), and 0/1 cytopenias.

Classification of a patient as red blood cell transfusion dependent requires that:

- (i) the patient has been transfused within the last 8 weeks; and
- (ii) the patient has received at least 8 units of red blood cell in the last 6 months prior to commencing PBS-subsidised therapy with lenalidomide; and would be expected to continue this requirement without lenalidomide treatment.

Patients receiving lenalidomide under the PBS listing must be registered in the i-access risk management program.

Treatment Phase: Continuing treatment

Clinical criteria:

- Patient must be classified as Low risk or Intermediate-1 according to the International Prognostic Scoring System (IPSS),

AND

- Patient must have a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities,

AND

- Patient must have received PBS-subsidised initial therapy with lenalidomide for myelodysplastic syndrome,

AND

- Patient must have achieved and maintained transfusion independence; or least a 50% reduction in red blood cell unit transfusion requirements compared with the four month period prior to commencing initial PBS-subsidised therapy with lenalidomide,

AND

- Patient must not have progressive disease.

The following evidence of response must be provided at each application:

- (i) a haemoglobin level taken within the last 4 weeks; and
- (ii) the date of the last transfusion; and
- (iii) a statement of the number of units of red cells transfused in the 4 months immediately preceding this application; and
- (iv) a statement confirming that the patient has not progressed to acute myeloid leukaemia

Information to Prescribers about the operation of the restriction

The authority application must be made in writing and must include:

- (a) a completed authority prescription form; and
- (b) a completed Myelodysplastic Syndrome Lenalidomide Authority Application - Supporting Information Form; and
- (c) a copy of the bone marrow biopsy report demonstrating that the patient has myelodysplastic syndrome; and
- (d) a copy of the full blood examination report; and
- (e) a copy of the pathology report detailing the cytogenetics demonstrating Low risk or Intermediate-1 disease according to the IPSS (note: using Fluorescence in Situ Hybridization (FISH) to demonstrate MDS -5q is acceptable); and
- (f) details of transfusion requirements including: (i) the date of most recent transfusion and the number of red blood cell units transfused; and (ii) the total number of red cell units transfused in the 4 and 6 months preceding the date of this application; and
- (g) a signed patient acknowledgement form.

The first authority application for continuing supply must be made in writing. Subsequent authority applications for continuing supply may be made by telephone.

Applications for authority to prescribe initial treatment with lenalidomide should be in writing and forwarded to:

Department of Human Services
Complex Drugs
Reply Paid 9826
HOBART TAS 7001

Subsequent authority applications for continuing treatment may be made by telephone to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

Note. This restriction has been abbreviated. Some administrative information has been removed. Refer to the schedule on pbs.gov.au for additional information.

Source: pbs.gov.au extracted 1 August 2017

Appendix B: Details of HSD data issue

Figure A.1 below shows an estimate of the amount of missing patient level data in the DHS prescription database for lenalidomide

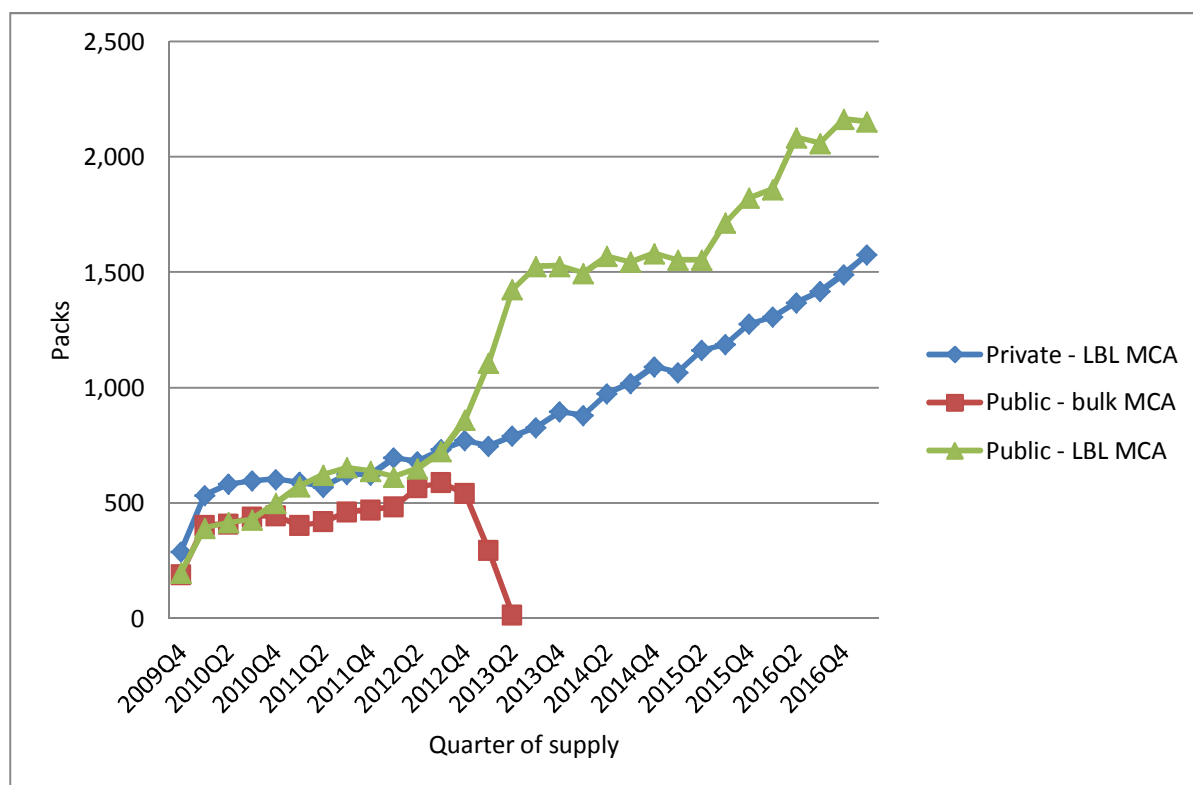


Figure B.1: Combined HSD data, lenalidomide packs for multiple non-MDS (ie. multiple myeloma) PBS items. Source: DUSC HSD database, Note: MCA = Medicare Australia (now DHS), LBL = Line by line (i.e. patient level data), bulk = aggregated data (ie. not patient level).

The “Public – bulk MCA” plot is the number of packs missing from the DHS patient level data. It is slightly less than the number of Public Hospital supplied packs in the DHS patient level data (ie. “Public – LBL MCA”). The utilisation measure in the “bulk MCA” source is packs and it is not possible to convert this to prescriptions. However it is possible to convert the prescriptions in the “LBL MCA” source to packs, so that utilisation can be combined and compared across the sources. The missing non-MDS prescriptions in the patient level data will have led to the non-MDS containing sequences in Table 5 being underestimated.

This means that some of the 141 patients classified as MDS patients in Table 5 may have been classified as multiple myeloma patients if the patient level data was complete. However, this was considered relatively unlikely as the patient level data was complete from July 2013.