

# Romiplostim and eltrombopag for idiopathic thrombocytopenic purpura: predicted versus actual analysis

## Drug utilisation sub-committee (DUSC)

*June 2015*

### **Abstract**

#### ***Purpose***

To examine the utilisation of the thrombopoietin receptor agonists (TRAs), romiplostim and eltrombopag, for idiopathic thrombocytopenic purpura (ITP). The Pharmaceutical Benefits Advisory Committee (PBAC) requested review of these agents once data for three years of use were available.

#### ***Date of listing on PBS***

- Romiplostim – 1 April 2011.
- Eltrombopag – 1 November 2011.

#### ***Data Source / methodology***

Authority approvals data and prescription data from the Department of Human Services (DHS). Data were extracted from the date of listing (April 2011) to the most currently available data (December 2014). Prescription data was based on the date of supply.

#### ***Key Findings***

- The total of 303 patients supplied with TRA therapy in the first year of listing (April 2011 to March 2012) was ■% less than projected (■ patients). The actual total number of patients was more than predicted in the third year of listing (506 vs. ■, respectively).
- The financial estimates for eltrombopag were sensitive to the proportional use of its maximal dose (75 mg). The actual mean daily dose for continuers (54 mg) was similar to the predicted average doses of 58 mg for splenectomised and 56 mg for non-splenectomised patients. The actual mean daily dose for initiators (45 mg) was lower than the predicted doses.
- The majority of patients remained on TRA treatment for more than a year (mean duration of 1.1 years for romiplostim and 1.5 years for eltrombopag).

- Of the 147 patients initiating on PBS subsidised TRA therapy during the first year of listing (April 2011 to March 2012), 60 patients (41%) switched from their initial therapy. Sixty eight of the 147 patients initiating in Year 1 were grandfathered. The mean time on TRA therapy was slightly longer for patients who switched treatment (1.5 years) or who were grandfathered (1.4 years) compared to all initiators (1.3 years).
- The PBS and RPBS (R/PBS) actual expenditure on TRA therapy has been significantly less than predicted during the first three years of listing.

## Purpose

To examine the utilisation of the thrombopoietin receptor agonists (TRAs), romiplostim and eltrombopag, for idiopathic thrombocytopenic purpura (ITP). The Pharmaceutical Benefits Advisory Committee (PBAC) requested review of these agents once data for three years of use were available.

## Background

### Pharmacology

Thrombopoietin is involved in platelet production. Romiplostim and eltrombopag are thrombopoietin receptor agonists which act to increase platelet production.

Romiplostim is an Fc-peptide fusion protein that signals and activates intracellular transcriptional pathways via the thrombopoietin receptor.

Eltrombopag interacts with the transmembrane domain of the thrombopoietin receptor to initiate signalling cascades similar but not identical to that of endogenous thrombopoietin.

### Therapeutic Goods Administration (TGA) approved indications

Romiplostim is indicated for treatment of thrombocytopenia in adult patients with chronic immune (idiopathic) thrombocytopenic purpura: (1) who are non-splenectomised and have had an inadequate response, or are intolerant, to corticosteroids and immunoglobulins; and (2) who are splenectomised and have had an inadequate response to splenectomy.

Eltrombopag is indicated for the treatment of adult patients with chronic immune (idiopathic) thrombocytopenic purpura who have had an inadequate response or are intolerant to corticosteroids and immunoglobulins.

### Dosage and administration

Table 1 summarises the dosage and administration for romiplostim and eltrombopag.

**Table 1: Dosage and administration of medicines used to treat idiopathic thrombocytopenic purpura**

Brand name and sponsor	Product	Dose and frequency of administration
Nplate (Amgen Australia Pty Limited)	Romiplostim	Romiplostim is administered weekly as a subcutaneous injection with dose adjustments based upon the platelet count response.  The initial dose for romiplostim is 1 microgram/kg, based on actual body weight.  The weekly dose of romiplostim is adjusted by increments of 1 microgram/kg until the patient achieves a platelet count $\geq 50 \times 10^9/L$ , but $\leq 200 \times 10^9/L$ . The platelet count is assessed weekly until a stable platelet count ( $\geq 50 \times 10^9/L$ for at least 4 weeks without dose adjustment) has been achieved.

Brand name and sponsor	Product	Dose and frequency of administration
Revolade (Novartis Pharmaceuticals Australia Pty Limited)	Eltrombopag	<p>The maximum weekly dose should not exceed of 10 microgram/kg.</p> <p>Eltrombopag is administered orally. Dosing regimens are individualised based on the patient's platelet counts.</p> <p>The recommended starting dose of REVOLADE is 50 mg once daily.</p> <p>For patients of East Asian ancestry (e.g. Chinese Japanese, Taiwanese, Korean or Thai), REVOLADE should be initiated at a reduced dose of 25 mg once daily.</p> <p>After initiating REVOLADE, the dose is adjusted to achieve and maintain a platelet count <math>\geq 50,000/\mu\text{l}</math> as necessary to reduce the risk for bleeding. The maximum daily dose is 75 mg.</p>

Source: Product Information for romiplostim and eltrombopag.

The current Product Information (PI) and Consumer Medicine Information (CMI) are available from [the TGA \(Product Information\)](#) and [the TGA \(Consumer Medicines Information\)](#).

## Clinical situation

Chronic ITP is a long-term autoimmune disorder characterised by persistently low platelet counts (thrombocytopenia) and cutaneous and mucosal bleeding. Bleeding can range from mild (bruising and purpura) to severe (intracranial or gastrointestinal haemorrhage) and can sometimes result in death. The major therapeutic goal for ITP is to increase the platelet count to a safe level while minimising treatment-related toxicity (American Society of Haematology Guidelines, 2011).

The majority of patients with chronic ITP only need watching and occasional intervention with steroids. First-line treatment typically involves corticosteroids for asymptomatic patients with low platelet counts or with mild bleeding symptoms, and high-dose corticosteroids, intravenous immunoglobulin (IVIg) and/or platelet transfusions for patients with clinically significant bleeding (American Society of Haematology Guidelines, 2011). Splenectomy is recommended as second-line therapy (American Society of Haematology Guidelines, 2011). Splenectomy is historically the most effective treatment for recurrent ITP severe enough to warrant intervention.

Those contraindicated or refractory to splenectomy may revisit high dose steroids and IVIg or take a range of other drugs that are not specifically indicated for ITP such as azathioprine, rituximab, anti-D, danazol and cyclophosphamide. Romiplostim and eltrombopag provide an alternative to these less frequently used drugs for those patients that are refractory to steroids, IVIg and splenectomy.

## PBS listing details

Romiplostim and eltrombopag are Section 100 (S100) Authority Required listings.

The listing details for romiplostim and eltrombopag as at March 2015 are summarised in Tables 2 and 3, respectively.

**Table 2: PBS listings of romiplostim (as at 1 March 2015)**

Item	Name, form & strength, pack size	Max. qty. Packs / Units	Rpts	DPMQ	Brand name and manufacturer
9696H (Public)	Romiplostim 250 microgram injection, 1 x 250 microgram vial	1/1	0	\$977.50	Nplate (Amgen Australia Pty Limited)
9697J (Private)	Romiplostim 250 microgram injection, 1 x 250 microgram vial	1/1	0	\$1,023.36	Nplate (Amgen Australia Pty Limited)
9698K (Public)	Romiplostim 500 microgram injection, 1 x 500 microgram vial	1/1	0	\$1,955.00	Nplate (Amgen Australia Pty Limited)
9699L (Private)	Romiplostim 500 microgram injection, 1 x 500 microgram vial	1/1	0	\$2,001.76	Nplate (Amgen Australia Pty Limited)

Source: Accessed on 3 March 2015 from the [PBS website](#).

As the romiplostim dose is based on weight and platelet count (see Table 1), the prescriber requests the appropriate quantity and number of repeats at the time of the authority application. DHS will authorise a maximum of:

- one treatment at a dose of 1mcg/kg and up to 1 repeat , for the first prescription;
- one treatment and up to one repeat in the remaining dose titration period;
- once the dose has been stable for 4 weeks, up to 4 treatments and up to 4 repeats (within the first 24 weeks of treatment); and
- up to 4 treatments and up to 5 repeats for continuing treatment in responders.

**Table 3: PBS listings of eltrombopag (as at 1 March 2015)**

Item	Name, form & strength, pack size	Max. qty. Packs / Units	Rpts	DPMQ	Brand name and manufacturer
5825N (Public)	Eltrombopag 25 mg tablet, 28	1/28	5	\$1,512.00	Revolade (Novartis Pharmaceuticals Australia Pty Limited)
5827Q (Private)	Eltrombopag 25 mg tablet, 28	1/28	5	\$1,558.76	Revolade (Novartis Pharmaceuticals Australia Pty Limited)
5826P (Public)	Eltrombopag 50 mg tablet, 28	1/28	5	\$3,024.00	Revolade (Novartis Pharmaceuticals Australia Pty Limited)
5828R (Private)	Eltrombopag 50 mg tablet, 28	1/28	5	\$3,070.76	Revolade (Novartis Pharmaceuticals Australia Pty Limited)

Source: Accessed on 3 March 2015 from the [PBS website](#)

### ***Restriction (Abridged)***

Romiplostim and eltrombopag are S100 Authority Required listings for the treatment of severe, chronic thrombocytopenic purpura in:

- (1) splenectomised patients who have failed, or are intolerant to, prior corticosteroid and immunoglobulin therapy; and
- (2) non-splenectomised patients who have failed or who are intolerant to corticosteroid therapy (at a dose equivalent to 0.5-2 mg/kg/day of prednisone for at least 4-6 weeks) and who have failed or who are intolerant to immunoglobulin therapy and in whom splenectomy is contraindicated for medical reasons.

The restrictions are for initial treatment, the first period of continuing treatment and subsequent continuing treatment. There is also a grandfathering restriction for those patients who initiated TRA therapy before the PBS listing of romiplostim and eltrombopag. For grandfathered patients to receive subsidised treatment, they must demonstrate that the criteria for initial treatment was met at the time they commenced on romiplostim or eltrombopag.

A written authority must be made for the initial prescription and one repeat may be requested. A written authority is also required for the first period of continuing treatment or for the re-initiation of interrupted treatment. Authority applications can be made by telephone during the initial period of dose titration and for subsequent courses of continuing treatment after the first period of continuing treatment.

To receive a first course of continuing treatment, or to restart interrupted treatment, patients must satisfy the following continuation criteria:

- the completion of an initial course of treatment with PBS subsidised romiplostim or eltrombopag; and
- the demonstration of a sustained platelet response defined as:
  - the use of rescue medication up to one time during initial treatment, and
  - a platelet count that is either:
    - greater than or equal to  $50 \times 10^9/L$  on at least four occasions, each at least one week apart, or:
    - more than  $30 \times 10^9/L$  which is double the pre-treatment baseline platelet count on at least four occasions, each at least one week apart.

During initial treatment, patients can trial either romiplostim and/or eltrombopag. Patients who switch therapy and fail to respond are not permitted to receive further PBS subsidised treatment with these drugs.

The full version of the restriction for romiplostim is available from the [PBS website](#).

The full version of the restriction for eltrombopag is available from the [PBS website](#).

#### ***Date of listing on PBS***

- Romiplostim – 1 April 2011.
- Eltrombopag – 1 November 2011.

### **Relevant aspects of PBAC consideration**

#### ***Romiplostim***

At the July 2009 meeting, the PBAC rejected a submission to list romiplostim for the initial and continuing treatment of adult patients with chronic immune (idiopathic) thrombocytopenic purpura who meet certain criteria because of the uncertain place in treatment for romiplostim, uncertain clinical benefit and uncertain and unacceptable cost-effectiveness (Public Summary Document, Romiplostim, July 2009). The Committee considered that the target patient groups for treatment with romiplostim included:

- those who have failed therapy with steroids or immunoglobulins, and the majority of these patients would be post splenectomy, or patients requiring high dose steroids to maintain post splenectomy responses; and
- patients with a contraindication to splenectomy who are refractory to therapy with steroids or immunoglobulins.

The PBAC noted that most chronic severe ITP patients will have had, or been considered for, splenectomy (Public Summary Document, Romiplostim, July 2009). The Committee further noted that a main reason for non-elderly patients not having splenectomy was the availability of alternative drug therapy, such as romiplostim, and considered that it was uncertain whether patients with less severe disease should receive TRA therapy as the long term safety of these drugs was not established (Public Summary Document, Romiplostim, July 2009). The Committee considered that it would be difficult to define contraindication to splenectomy and this would need to be managed through a risk sharing arrangement.

For further details refer to the [Public Summary Document](#) from the July 2009 PBAC meeting.

Romiplostim was recommended by PBAC in March 2010 to treat adult patients with chronic immune (idiopathic) thrombocytopenia (ITP) who met certain criteria. This was in the context of a high clinical need in a subgroup of ITP patients. For the previous submission considered in July 2009, the Committee had determined that the nominated comparator of placebo was relevant to patients who had failed splenectomy or where splenectomy was medically contraindicated. This was because the submission had not considered splenectomy as a comparator and there was an absence of data to justify the use of romiplostim instead of splenectomy (Public Summary Document, romiplostim, March 2010). While romiplostim was noted to be less effective in splenectomised patients, PBAC considered that this patient group had the highest unmet clinical need. PBAC raised concerns about inappropriate use, particularly in non-splenectomised patients.

For further details refer to the [Public Summary Document](#) from the March 2010 PBAC meeting.

The cost-effectiveness for romiplostim presented in the March 2010 submission was based on average extractable volumes. The TGA recommended a change to the label, specifying minimum rather than average extractable volumes for romiplostim and the sponsor made a further submission to the July 2010 PBAC which presented a new cost-effectiveness analysis based on the minimum extractable volumes. The submission also sought to amend the restrictions that were recommended in March 2010 (Public Summary Document, romiplostim, July 2010).

The PBAC considered that the revised cost-effectiveness for splenectomised and non-splenectomised patients was acceptable given the high clinical need for this treatment. The proposed amendments to the restriction were not accepted. The previous recommendation to list romiplostim under Section 100 (Highly Specialised Drug) Public and Private Hospital Authority Required for treatment of adult patients with chronic immune (idiopathic) thrombocytopenia purpura (ITP) who meet certain criteria was confirmed on the basis of high but acceptable cost-effectiveness ratios.

For further details refer to the [Public Summary Document](#) from the July 2010 PBAC meeting.

### ***Eltrombopag***

The PBAC rejected the November 2010 submission for eltrombopag due to uncertain clinical effectiveness in comparison with romiplostim (Public Summary Document, eltrombopag, November 2010). An indirect comparison of eltrombopag and romiplostim was presented with placebo as the common comparator. PBAC considered that the patient populations of the included trials (RAISE for eltrombopag and the Kuter 2008 splenectomised and non-splenectomised trials for romiplostim) were not representative of patients for whom PBS listing was sought (i.e. high risk ITP). The Committee was also concerned about the exchangeability of the RAISE and Kuter trials as RAISE appeared to have milder ITP compared to the romiplostim (Kuter) trials. Further, a non-inferiority

margin was not defined. As such, there was considerable uncertainty in the results from the indirect comparison, and the width of the confidence intervals indicated that this comparison was not adequately powered to test for non-inferiority between eltrombopag and romiplostim (Public Summary Document, eltrombopag, November 2010). There was a lack of long-term comparative safety data between the two TRA agents and the PBAC considered that it was possible that eltrombopag was less effective than romiplostim in non-splenectomised patients.

For further details refer to the [Public Summary Document](#) from the November 2010 PBAC meeting.

Eltrombopag was subsequently recommended in March 2011 and it was restricted to the same population as romiplostim. The cost-effectiveness was considered to be acceptable at a revised price accounting for eltrombopag being less effective than romiplostim (Public Summary Document, eltrombopag, March 2011). The PBAC recommended that switching between romiplostim and eltrombopag should be allowed within a 24 week period and that patients must achieve a response within this time in order to receive further PBS subsidised TRA therapy.

For further details refer to the [Public Summary Document](#) from the March 2011 PBAC meeting.

At its November 2014 meeting the PBAC rejected a minor submission seeking to amend the continuation restriction to allow switching of TRA therapy for patients whose disease was stable. The sponsor argued that patients may incorrectly dose romiplostim if they have difficulty in self-administering the subcutaneous injection. As such, the sponsor considered that allowing switching from romiplostim to eltrombopag in continuing patients may avoid unintentional side effects in users of romiplostim (Public Summary Document, eltrombopag, November 2014). PBAC was concerned about the possibility of retreatment with eltrombopag after failure to respond to this drug during initial treatment. It was also unclear to the Committee what the impact of switching therapy for reasons other than failure would be on clinical outcomes and the financial risks of the proposed amendment were considered to be unknown. The submission's claim of cost savings was only considered to be relevant if there was no change in the overall use of TRA therapy.

PBAC considered that allowing switching in stable patients could grow the market as these patients could cease injectable romiplostim and opt to take oral eltrombopag rather than having a trial off therapy. The Committee noted that some of these of patients may only need episodic TRA therapy.

For further details refer to the [Public Summary Document](#) from the November 2014 PBAC meeting.

## **Approach taken to estimate utilisation**

An epidemiological approach was used to estimate the eligible population for romiplostim and eltrombopag. Following is a description of the stepwise method that was used to derive the eligible population, the patient numbers at each step are summarised in Table 4.

Consistent with the PBAC recommendation, the forward estimates are based on the prevalent population in the first year of listing and the incident population in the subsequent years of listing.

The size of the adult Australian population was based on projections provided by the Australian Bureau of Statistics (ABS, 2008). The prevalence of ITP was assumed to be [REDACTED] per 100,000 persons based on the mid-range of estimates from [REDACTED]. An incidence estimate of [REDACTED] per 100,000 persons was used based on a review of the literature conducted for the July 2009 submission for romiplostim which reported a range of [REDACTED] per 100,000 persons. The proportion of chronic ITP patients were estimated to be [REDACTED]% based on a retrospective review (Australian ITP Chart Audit) of patients with chronic ITP ([REDACTED]%) and a survey of Australian haematologists ([REDACTED]%) which were conducted for the July 2009 submission for romiplostim. The proportion of patients with severe ITP was estimated to be [REDACTED]% based on the results of the Australian ITP Chart Audit. Of these, [REDACTED]% were assumed to be splenectomised.

Based on the [REDACTED], it was assumed that [REDACTED]% of patients would not respond to first-line therapy. The proportion of patients who were refractory to splenectomy was estimated to be [REDACTED]% from [REDACTED].

Using the results from a commissioned clinician survey for the romiplostim submission ([REDACTED]), it was assumed that [REDACTED]% of the non-splenectomy population require a splenectomy but have a medical contraindication for surgery.

Table 4 presents the stepped analysis to predict the eligible incident population for a TRA.

**Table 4: Summary of the modelled eligible patient population**

	2011	2012	2013	2014	2015
Relevant Australian population (ABS series B,18 years and older)	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Prevalence of the disease	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Incidence of the disease	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Population with ITP	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
percentage with chronic ITP (thrombocytopenia persist longer 6 mths)	[REDACTED]%	[REDACTED]%	[REDACTED]%	[REDACTED]%	[REDACTED]%
No. of pts chronic ITP	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
% chronic ITP with platelet count < 30 (severe ITP)	[REDACTED]%	[REDACTED]%	[REDACTED]%	[REDACTED]%	[REDACTED]%
<b>No of patients with chronic severe ITP</b>	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
% not responding to 1st line steroids and fail IVIg	[REDACTED]%	[REDACTED]%	[REDACTED]%	[REDACTED]%	[REDACTED]%
No of pts refractory to steroids and IVIg	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

	2011	2012	2013	2014	2015
% splenectomised	█%	█%	█%	█%	█%
No. pts splenectomised for ITP	█	█	█	█	█
% refractory to splenectomy	█%	█%	█%	█%	█%
<b>No of eligible patients post splenectomy</b>	█	█	█	█	█
% severe refractory contraindicated to splenectomy	█%	█%	█%	█%	█%
<b>Pts eligible without splenectomy</b>	█	█	█	█	█
<b>Total no. patients initiating PBS TRA</b>	█	█	█	█	█

The expected uptake of thrombopoietin receptor agonists was assumed to be █% of patients in the first year, increasing to █% over the first five years of the listing. The uptake rates were assumed to be high due to the lack of alternative treatments.

Based on the overall response in the non-splenectomy sub group in █ it was assumed that █% of initiating non-splenectomised patients would only receive six months of treatment with either romiplostim or eltrombopag. For post-splenectomy patients initiating on romiplostim or eltrombopag, █% were estimated to receive 6 months of treatment from the overall response observed in █. The patient estimates for the first year of listing factor in initiating grandfathered patients.

The 'all cause' withdrawal rate of █% from an open label extension study (█) was used as the assumption for discontinuation at 12 months for both the non-splenectomised and post-splenectomised patient groups.

In the first year of listing, it was predicted that the market share split between romiplostim and eltrombopag would be █%:█%. For the subsequent years of listing, these agents were assumed to have █ share of the market.

A summary of the projected treated splenectomised and non-splenectomised populations are presented in Table 5.

**Table 5: Summary of the projected treated splenectomised and non-splenectomised populations**

	Year 1	Year 2	Year 3
<b>Splenectomised patients</b>			
Eligible splenectomised patients			
Uptake rate for splenectomised patients	%	%	%
<b>Treated incident population with splenectomy</b>			
<b>Non-splenectomised patients</b>			
Eligible non-splenectomised patients			
Uptake rate for non-splenectomised patients	%	%	%
<b>Treated non-splenectomised incident population</b>			

Source: Modelled estimates agreed with sponsors.

Using the average doses from the RAISE trial, 24% of non-splenectomy patients and 32% of post-splenectomy patients were assumed to require the maximum dose of eltrombopag (75 mg). To project the expenditure for eltrombopag, an average cost was estimated by adding 24% or 32% of the DPMQ for 25 mg for non-splenectomised and post-splenectomised patients, respectively, to the DPMQ for the 50 mg strength.

The total expenditure for eltrombopag was calculated as the product of the average cost by the number of patients by the number of scripts for the relevant patient group.

## Previous reviews by DUSC

This was the first review of romiplostim and eltrombopag.

## Methods

All analyses were undertaken using SAS Enterprise Guide version 5.1.

The modelled estimates were obtained from the financial estimates model which was agreed with the sponsors of romiplostim and eltrombopag. Part-year adjustments were applied to the estimates to align the figures with the listing date in order to compare them with the actual figures.

Data were extracted from the Department of Human Services Authority Approvals database for the period from the first date of listing (1 April 2011) to 31 December 2014 based on the date authority approval was given. The approvals data was used to identify grandfathered patients and patients on their first period of continuing treatment and to derive approved doses for romiplostim and eltrombopag.

The average daily dose of eltrombopag was calculated as the maximum amount approved divided by 28 (number of tablets per pack). The average weekly dose of romiplostim was derived as the maximum amount approved divided by the authorised quantity.

PBS/RPBS prescription data for romiplostim and eltrombopag were extracted from the Department of Human Services Prescription database for the period from the first date of listing (April 2011) to December 2014 inclusive, based on the date that the prescription was supplied. The data differs from that available from the DHS (Medicare) PBS statistics

website which is based on the date of processing and is only for subsidised R/PBS prescriptions.<sup>1</sup> Patient counts are based on de-identified unique patient identification numbers (PINs) from the prescription data.

Length of treatment analyses were based on patients who initiated TRA therapy during the first year of listing (1 April 2011 to 31 March 2012). The median time to re-supply for TRA therapy was 27 days. It was assumed that a patient had discontinued therapy if there was no re-supply within a period of three times the median time to re-supply (i.e. 81 days). A patient was assumed to be continuing treatment if the time from their last supply was less than 81 days from the data cut-off date (31 December 2014) and they were censored from the treatment duration analyses. The assumption for discontinuation of TRA therapy was tested in a sensitivity analysis by extending the time from 81 to 160 days. In addition to the analysis of all initiating patients, separate analyses were undertaken for: (1) patients who switched from the TRA agent that they initiated on to assess if TRA therapy is potentially prolonged by allowing the use of alternative therapy; and (2) grandfathered patients who initiated TRA therapy in the first year of listing. Histograms of the treatment time distribution for all initiators, initiators who switched and grandfathered patients were constructed using SAS with the bin set at 6 months.

Persistence to treatment was also examined through constructing Kaplan-Meier plots of the duration of therapy for the all initiating, switching and grandfathered patient groups. The number of patients at risk at the end of each year was determined to derive discontinuation rates for romiplostim compared to eltrombopag in the all initiating patient group. The potential impact of switching treatment and the receipt of prior treatment as a grandfathered patient on the overall time on treatment was also assessed.

## Results

### Analysis of drug utilisation

#### *Patient numbers*

Comparisons of the predicted versus actual number of patients for the first three years of listing since romiplostim first listed on 1 April 2011 are presented in Table 6. The same time periods are used for assessing the utilisation of eltrombopag (listed from 1 November 2011) as this allows a predicted versus actual comparison of the total market, consistent with the epidemiological basis of the estimates.

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<sup>1</sup> PBS statistics. Australian Government Department of Human Services Medicare. Canberra. Available from the [Department of Human Services website](#).

**Table 6: Predicted vs Actual utilisation – Patient numbers**

Patient group	Comparison	Year 1	Year 2	Year 3
		Apr11 to Mar12	Apr12 to Mar13	Apr13 to Mar14
Total patients	Predicted	■	■	■
	Actual	303	412	506
	% of Predicted	■%	■%	■%
Initiating patients	Predicted	■	■	■
	Actual	150	145	154
	% of Predicted	■%	■%	■%
Prevalent patients	Predicted	■	■	■
	Actual	153	267	352
	% of Predicted	■%	■%	■%
<b>Romiplostim</b>				
Initiating patients	Predicted	■	■	■
	Actual	122	63	64
	% of Predicted	■%	■%	■%
Prevalent patients	Predicted	■	■	■
	Actual	124	156	186
	% of Predicted	■%	■%	■%
<b>Eltrombopag</b>				
Initiating patients	Predicted	■	■	■
	Actual	28	82	90
	% of Predicted	■	■	■
Prevalent patients	Predicted	■	■	■
	Actual	29	111	166
	% of Predicted	■	■	■

Source: Department of Human Services (DHS) Prescription database data accessed 23 March 2015, based on date of prescription supply.

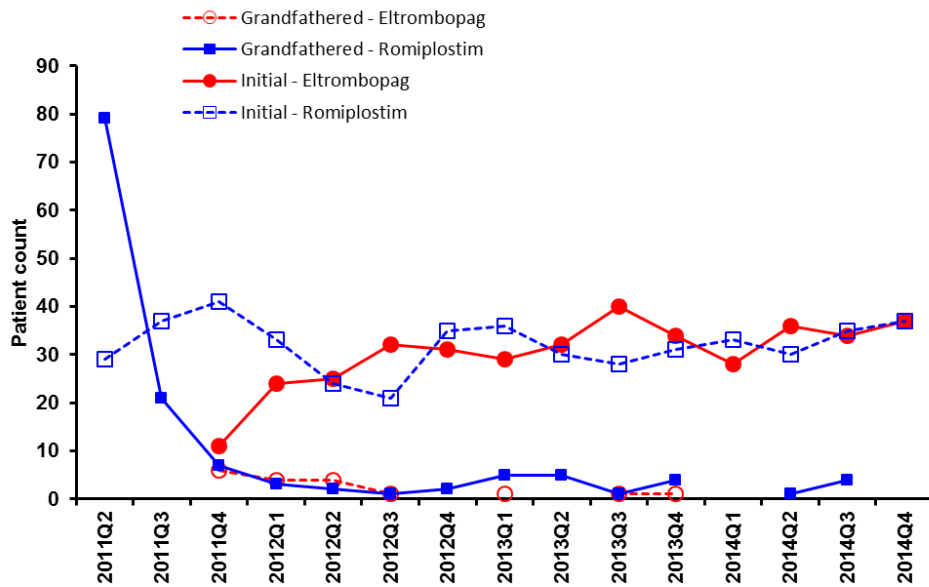
For comparison with actual data, part-year corrections are applied to the predicted data to adjust for the listing date.

'Initiating patients' includes those patients who received an authority approval for grandfathered or initial treatment.

In the first year of listing, the actual number of patients initiating on romiplostim and eltrombopag was less than predicted. In Years 2 and 3 the actual number of incident and prevalent patients accessing TRA therapy has been more than predicted (Table 6). In Years

2 and 3, there was a large underestimate of the number of initiating patients for both romiplostim and eltrombopag (Table 6). In Year 3, the total number of prevalent patients was underestimated by [REDACTED].

Forty-six per cent of patients initiating TRA therapy in the first year of listing were grandfathered patients. The number of patients receiving approvals for grandfathered and initial treatment is shown in Figure 1.



**Figure 1: Number of approvals for initial treatment with romiplostim or eltrombopag for new and grandfathered patients by quarter**

Source: Authority Approvals database, DHS, extracted April 2015 (actual)

**Utilisation by drug form and strength**

In modelling the financial estimates, the projected number of vials for romiplostim was derived. By the third year of listing, the predicted vs. actual total vial use was similar (a variance of less than 10%). In the preceding years, the expected utilisation was overestimated by a factor of around one third.

The mean actual weekly dose of romiplostim was 358 micrograms for patients receiving their first course of treatment (Table 7). Grandfathered patients had a higher weekly mean dose of 405 micrograms (Table 7). Patients on their first course of continuing treatment and subsequent courses of continuing treatment received higher mean doses than new incident patients (399 micrograms and 400 micrograms, respectively, Table 7).

**Table 7: Average weekly dose of romiplostim for grandfathered, initiating and continuing patients**

Patient group	Mean (micrograms)	Median (micrograms)	Min (micrograms)	Max (micrograms)
Grandfathered	405.7	500	250	1000
Initial	358.6	250	250	1750
First continuing treatment	399.1	500	250	1250
Second and subsequent continuing treatment	400.2	500	250	1250

Source: Authority Approvals database, DHS, extracted April 2015.

Includes the maximum amount of drug approved (based on the approved quantity and strength) for all patients receiving romiplostim since its listing from 1 April 2011.

The actual mean daily dose of eltrombopag was higher in patients receiving their first period of continuing treatment (54.3 mg) and subsequent continuing treatment (54.6 mg) than initiating patients (44.8 mg), (Table 8). Patients grandfathered to eltrombopag received the highest mean daily dose (55.0 mg, Table 8).

**Table 8: Average daily dose of eltrombopag for grandfathered, initiating and continuing patients**

Patient group	Mean (mg)	Median (mg)	Min (mg)	Max (mg)
Grandfathered	55.0	50	25	75
Initial	44.8	50	25	150
First continuing treatment	54.3	50	25	125
Second and subsequent continuing treatment	54.6	50	25	150

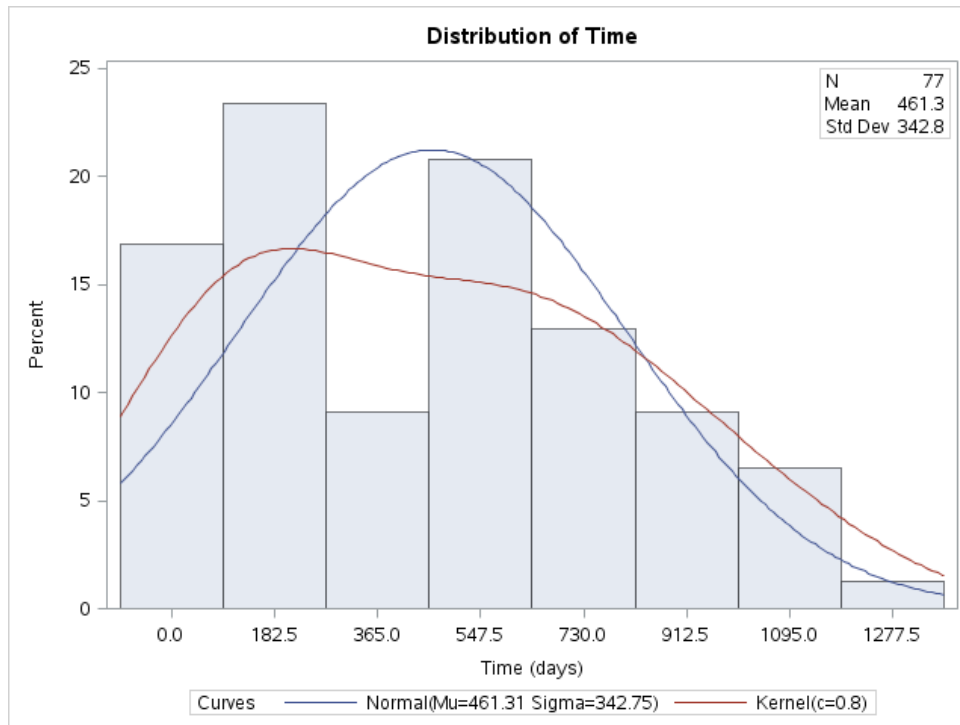
Source: Authority Approvals database, DHS, extracted April 2015.

Includes the maximum amount of drug approved (based on the approved quantity and strength) for all patients receiving eltrombopag since its listing from 1 November 2011.

### ***Length of treatment analysis***

In its consideration of the July 2009 submission for romiplostim the PBAC noted that there was a lack of data on the long-term efficacy of TRA therapy. The efficacy data from placebo-controlled trials included in the July 2009 submission (Study 105 and Study 212) only related to a 24-week period. As such, an analysis of the length of treatment on romiplostim and eltrombopag was undertaken to assess the durability of these therapies in practice. Time to discontinuation of treatment was examined for patients who initiated romiplostim or eltrombopag in the first year of listing (between 1 April 2011 and 31 March 2012). Patients were assumed to be continuing on treatment if their date of last supply was within three times the median time to re-supply (81 days) from the specified end-date (31 December 2014). The median re-supply time for all patients was 27 days. Patients categorised as continuing were censored from the treatment length analyses.

Figure 2 presents a histogram of time on treatment for non-censored patients initiating on romiplostim or eltrombopag. The treatment time was not normally distributed (Kolmogorov-Smirnov statistic  $D=0.131$ ,  $p < 0.01$ ) but positively skewed relative to the fitted normal curve (shown in blue). The kernel density estimates (shown in red) were also skewed to the right. These distributions reflect that the majority of patients (over 75%) received more than a year's treatment with TRA therapy with a mean treatment time of 461 days (1.3 years).



**Figure 2: Histogram of time on treatment for all patients initiating on TRA therapy in the first year of listing (Apr 2011 to Mar 2012)**

Blue line = Normal curve fitted to the histogram. Red line = Fitted kernel density estimates.

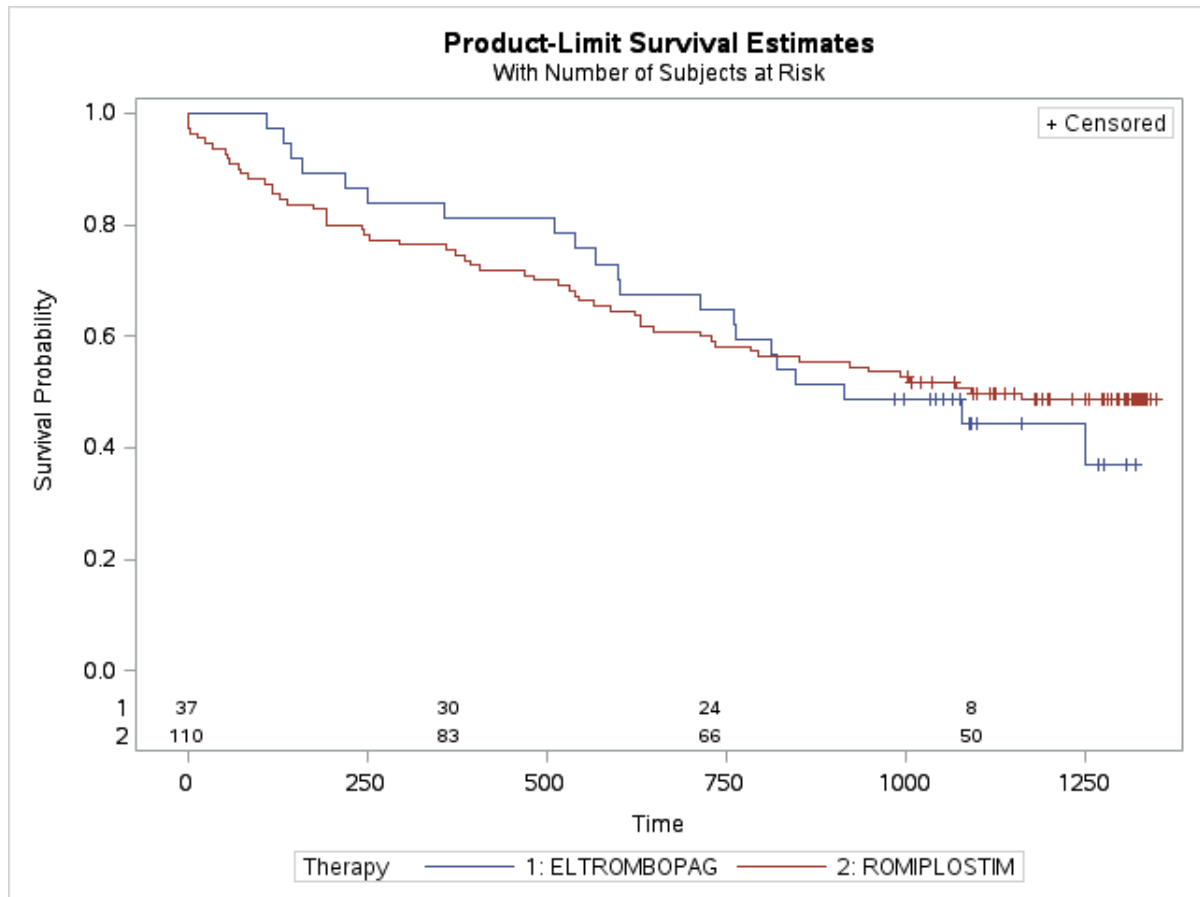
Note: The depressed histogram bar at 365 days and associated drop in the kernel density estimates indicates that this lower frequency at 365 days is not an artefact of sampling variation or binning.

Source: PBS Supplied Prescriptions Database, DHS, extracted March 2015 (actual)

The assumption for discontinuation of TRA therapy was tested in a sensitivity analysis by extending the time from 81 to 160 days. An additional three patients were censored and there was only a minor impact to the mean time on treatment (1.2 years compared to 1.3 years).

The persistence on romiplostim and eltrombopag is depicted in the Kaplan-Meier curve shown in Figure 3. The mean time on treatment was 403 days (1.1 years) for romiplostim and 545 days (1.5 years) for eltrombopag. Referring to the number of at risk patients displayed at the bottom of Figure 3, by the end of the first year 25% of patients had discontinued romiplostim. At the end of the second and third year the proportions of discontinuing patients were 40% and 55%. As eltrombopag listed on a later date to romiplostim there are less patients ( $n=37$ ) in the initial cohort. The discontinuation rates for

eltrombopag were similar to romiplostim at the end of year 1 and 2 (19% and 35%, respectively) but higher at the end of year 3 (78%) due to the small sample size.



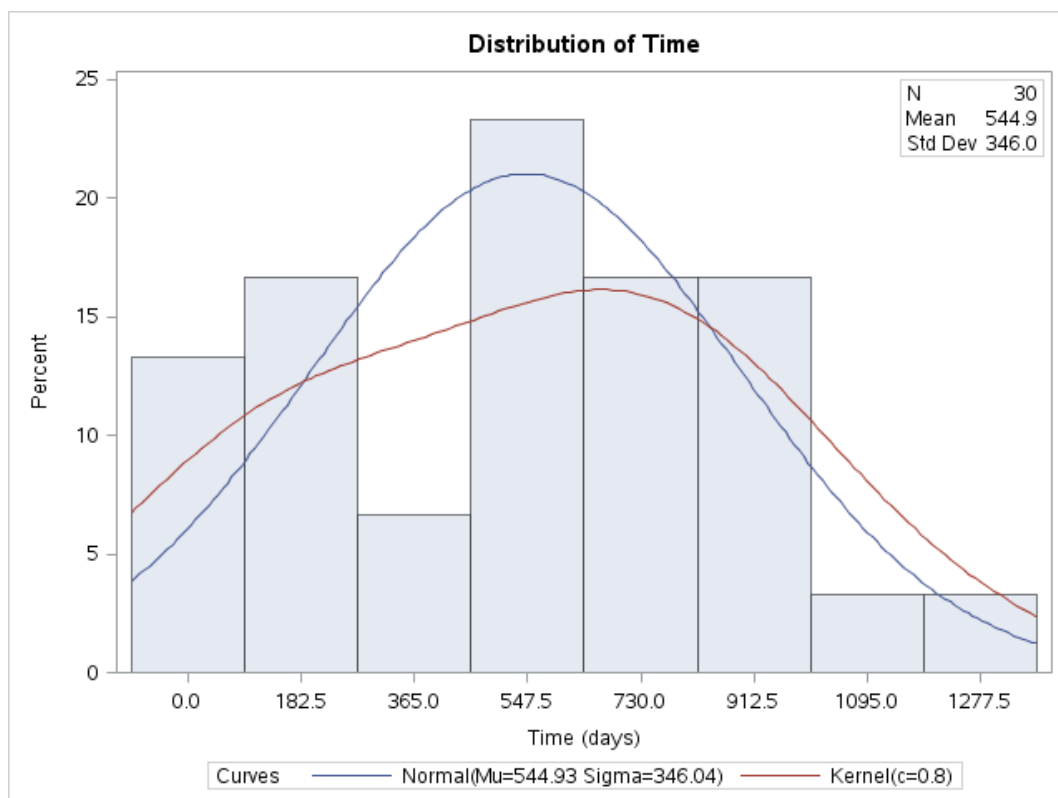
**Figure 3: Kaplan-Meier curves and the number of patients at risk at the beginning of each year for romiplostim and eltrombopag**

Source: PBS Supplied Prescriptions Database, DHS, extracted March 2015 (actual)

Patients are permitted to switch between romiplostim and eltrombopag during the first 24 weeks of treatment. A further analysis was conducted on patients initiating treatment in the first year of listing who switched therapy to assess if switching had an impact on the time to discontinuation from treatment. Sixty of the 147 patients initiating TRA therapy in the first listing year switched their therapy<sup>2</sup>. Thirty five patients switched from eltrombopag to romiplostim and 25 patients initiating on romiplostim changed to eltrombopag. A histogram of the time on TRA therapy for switching patients is presented in Figure 4. Patients identified as continuers<sup>3</sup> (n=30) were excluded from this analysis.

<sup>2</sup> The figure of 147 initiating patients excludes a small number of patients who received an authority approval for initial treatment and initial grandfathered treatment. It therefore differs to the 150 initial patients reported in Table 6.

<sup>3</sup> Continuers were defined as having a date of last supply within three times the median time to re-supply (27 days) from the specified end-date (31 December 2014).



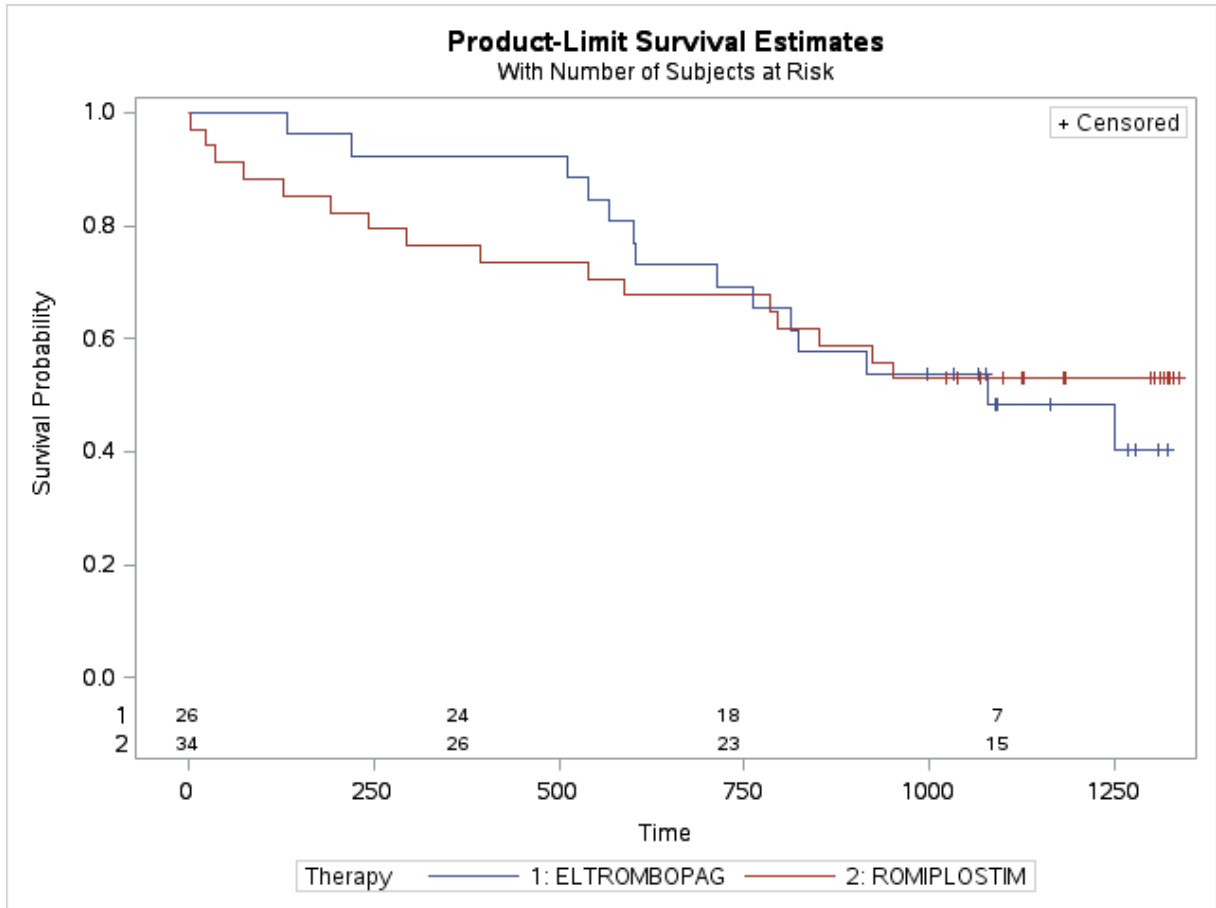
**Figure 4: Histogram of time on treatment for patients initiating on TRA therapy in the first year of listing (Apr 2011 to Mar 2012) who switched their treatment**

Blue line = Normal curve fitted to the histogram. Red line = Fitted kernel density estimates.

Source: PBS Supplied Prescriptions Database, DHS, extracted March 2015 (actual)

Compared to all initiators, patients who switched treatment had a slightly longer mean time on TRA therapy (1.5 years (544 days) vs. 1.3 years (461 days), Figures 2 and 4). Patients switching from eltrombopag to romiplostim (n=14) had a longer mean time on treatment than patients who switched from romiplostim (n=16), (1.9 years vs. 1.2 years, respectively).

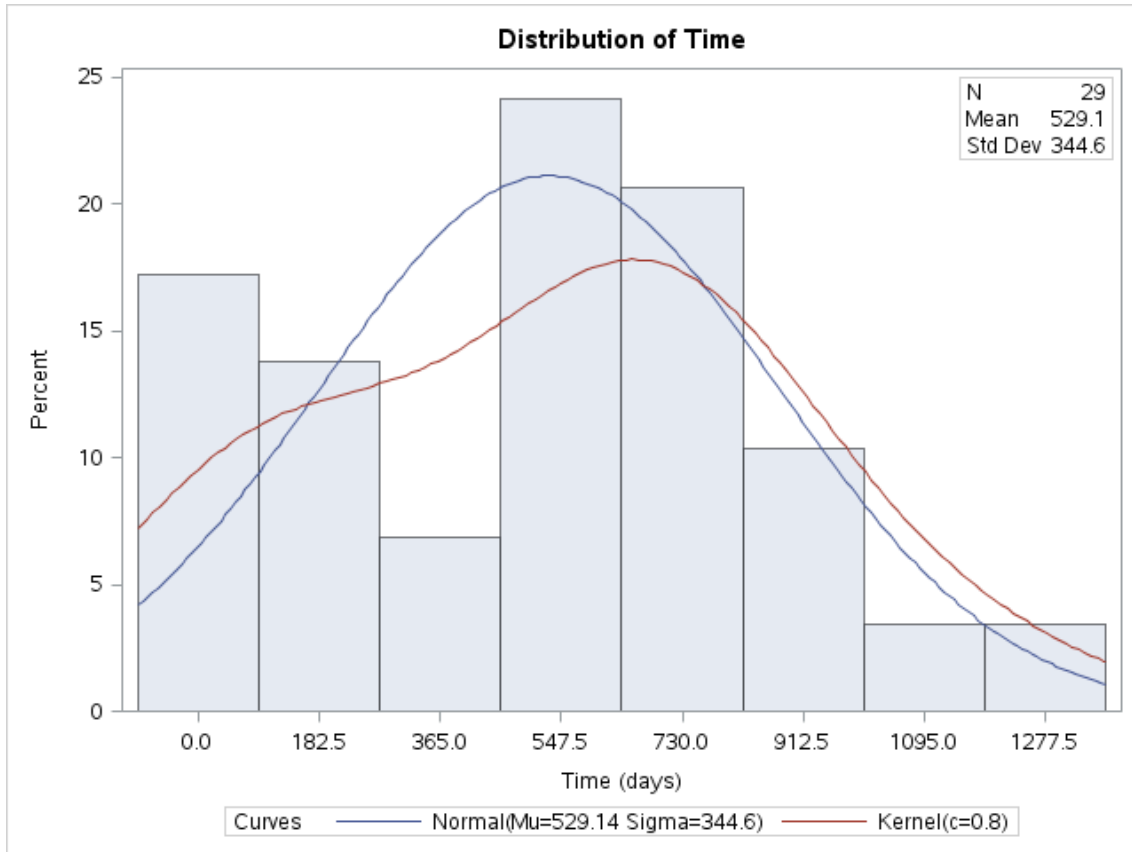
Referring to the at risk numbers shown in the Kaplan-Meier curves for switching patients in Figure 5, by the end of the first year a larger proportion of patients who switched from romiplostim discontinued TRA therapy compared to those who switched from eltrombopag to romiplostim (24% vs. 8%, respectively). By the end of the second year, the discontinuation rates were similar regardless of which TRA agent that patients switched from (31% for patients switching from eltrombopag vs. 32% for patients switching from romiplostim). Only a few patients remained on therapy at three years.



**Figure 5: Kaplan-Meier curves and the number of patients at risk at the beginning of each year for romiplostim and eltrombopag for patients who switched therapy**

Source: PBS Supplied Prescriptions Database, DHS, extracted March 2015 (actual)

Grandfathered patients had a longer mean time on treatment compared to all initiating patients (1.4 years (529 days) vs. 1.3 years (461 days), Figures 2 and 6).

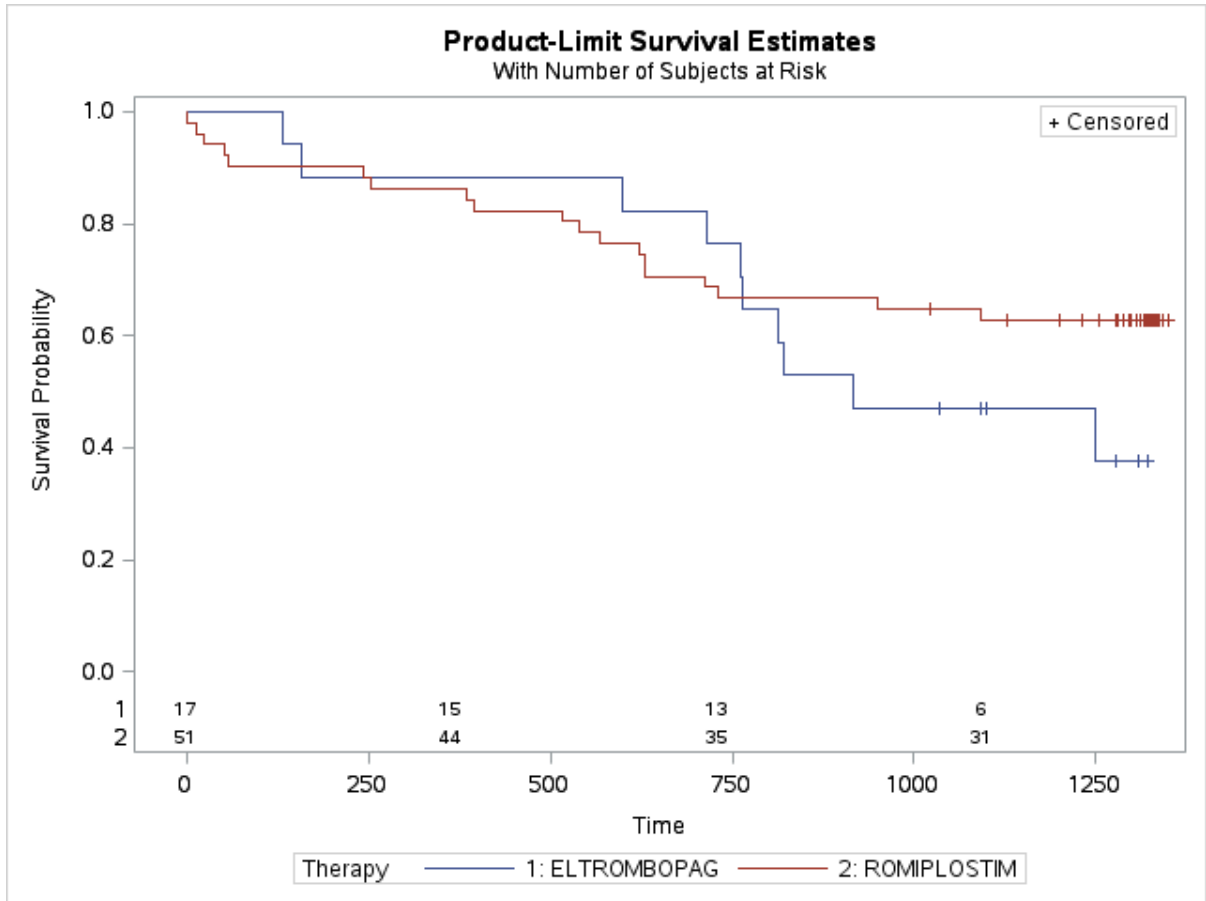


**Figure 6: Histogram of time on treatment for patients grandfathered to TRA therapy in the first year of listing (Apr 2011 to Mar 2012).**

Blue line = Normal curve fitted to the histogram. Red line = Fitted kernel density estimates.

Source: PBS Supplied Prescriptions Database, DHS, extracted April 2015 (actual)

A relatively high proportion of patients grandfathered to romiplostim remained on their treatment with 61% of patients still receiving treatment at three years (Figure 7). Of the 17 grandfathered patients supplied with eltrombopag in the first year of listing, only four had discontinued after two years (Figure 7).



**Figure 7: Kaplan-Meier curves and the number of grandfathered patients at risk at the beginning of each year for romiplostim and eltrombopag**

Source: PBS Supplied Prescriptions Database, DHS, extracted March 2015 (actual)

## Analysis of expenditure

Table 9 presents a comparison of the predicted versus actual expenditure for romiplostim and eltrombopag based on their published prices.

**Table 9: Predicted vs Actual R/PBS expenditure**

		Year 1 Apr11 to Mar12	Year 2 Apr12 to Mar13	Year 3 Apr13 to Mar14
Overall expenditure	Predicted	\$ ██████████	\$ ██████████	\$ ██████████
	Actual	\$7,736,105	\$10,450,742	\$14,344,158

Note: All figures are based on published prices and are net of patient co-payments. Some medicines have special pricing arrangements and government expenditure may be less than presented. The predicted estimates were agreed between the Sponsors and the Department post PBAC recommendation to list. Part-year corrections have been applied to account for the listing date to allow a comparison to the actual figures.

The actual figures were sourced from the Department of Human Services PBS Prescriptions Database accessed in March 2015. These figures are based on the date of prescription supply.

## Discussion

The PBS and RPBS (R/PBS) actual expenditure on TRA therapy has been significantly less than predicted during the first three years of listing. The DUSC considered that expenditure on TRAs could potentially exceed the predicted expenditure over the remaining forward estimates period given the higher than expected growth in the treated population.

The total of 303 patients supplied with TRA therapy in the first year of listing (April 2011 to March 2012) was ██████% less than projected (█████ patients). The DUSC noted the response from the Haematology Society of Australia and New Zealand (HSANZ) and the Australasian Society of Thrombosis and Haemostasis (ASTH) which stated that the lower than anticipated uptake in Year 1 could indicate caution in the prescribing the new TRA therapies due to their associations with thrombotic complications and myelofibrosis. The actual total number of patients was more than predicted in the third year of listing (506 vs. ██████, respectively). The DUSC considered that the higher than expected number of patients could indicate that the availability of TRA therapy is diverting patients from splenectomy. The DUSC noted that the proportion of non-splenectomised patients receiving an approval for romiplostim had risen over the first three years of listing, as shown in the following table.

	Year 1	Year 2	Year 3
Proportion of non-splenectomised patients receiving an initial or grandfathered application for romiplostim	46%	68%	76%
Number of patients receiving an initial or grandfathered application for romiplostim	154	53	45
Number of non-splenectomised patients receiving an initial or grandfathered application for romiplostim	71	36	34

Source: Department of Human Services, 4 May 2015.

Patients who have a medical contraindication to splenectomy, or are refractory to splenectomy, are eligible to receive second-line TRA therapy. Based on a literature review of case series from ██████████ reported a response rate to splenectomy of ██████%, thus it was assumed for the modelled estimates that ██████% of patients would be refractory to splenectomy. This assumption appears to be reasonable as it is consistent with more recent analyses of response rates to splenectomy. For example, Vianelli et al. (2013) conducted a retrospective analysis of 233 ITP patients who underwent splenectomy with a minimum ten year follow up period. They reported that a long-term stable response was achieved in 60% of patients. A requirement for the initiation on TRA therapy is the demonstration of failure or intolerance to prior corticosteroid or immunoglobulin therapy. To predict the eligible population it was assumed that ██████% of patients would fail prior therapy based on the ██████████. The response rates to prior therapy can be highly variable, for instance they can range from between 50-80% for dexamethasone or be as low as 23% for methylprednisolone (Provan et al., 2010). Given this variation, it is possible that the number of incident patients was under predicted by underestimating the failure rate on prior therapy. The DUSC noted that reporting from the National Blood Authority (NBA) indicates that the use of immunoglobulin therapy for idiopathic thrombocytopenic purpura (ITP) has been declining since the financial year that the TRA agents were first listed, as shown in the following table.

	2011-12	2012-13	2013-14
Total number of ITP patients	3,039	941	878

Source: National Blood Authority, 'Report on the Issue and Use of Immunoglobulin (Ig)', Annual Reports for the 2011-12, 2012-13 and 2013-14 financial years.

The DUSC noted AIHW National Hospital Morbidity Database figures which showed a fall in the number of procedures for splenectomy between 2011-12 and 2012-13 (800 vs. 749, respectively). The DUSC noted that in addition to the treatment of ITP there were other factors which would influence this trend, such as splenectomy arising from trauma.

The number of continuing patients has exceeded the estimates from a higher than expected number of patients initiating on TRA therapy (Table 6). The assumed discontinuation rates for patients commencing on the first period of continuing treatment (█████% for non-splenectomised based on ██████████ and ██████% for splenectomised based on ██████████) appear reasonable. For patients initiating TRA therapy in the first year of listing, 78% went on to receive a first course of continuing treatment. The assumption for the annual discontinuation rate ██████% was significantly less than the actual annual discontinuation rates for both romiplostim and eltrombopag. Of the 147 patients initiating TRA therapy in the first year of listing, 55% commencing on romiplostim and 78% starting on eltrombopag had discontinued by the third year of listing (Figure 3). Overall, 61% of patients had discontinued after three years of TRA therapy (Figure 3).

The mean daily dose of eltrombopag for continuers was 54 mg. The DUSC considered that the eltrombopag dosing figures indicate that clinicians are treating to target for this agent.

For all patients initiating TRA therapy in the first year of listing (n=147), the mean time on therapy was 1.3 years. For this analysis, patients were assumed to have discontinued therapy if the date of their last supply of a TRA medicine was greater than 81 days from the specified analysis end date (31 December 2014). That is, three times longer than the median time to re-supply (27 days). It is possible that some patients may have had interrupted treatment for a period longer than 81 days before resuming therapy. A sensitivity analysis was undertaken which doubled the assumption for discontinuation (i.e. an increase from 81 to 160 days). This was found to have a minimal impact on the results with an additional three patients censored and a slight reduction in the mean time on treatment (1.2 years compared to 1.3 years).

Of the 147 patients initiating on PBS subsidised TRA therapy during the first year of listing (April 2011 to March 2012), 60 patients (41%) switched from their initial therapy. The mean time on TRA therapy was slightly longer for patients who switched therapy (1.5 years) or who were grandfathered (1.4 years) compared to all initiators (1.3 years). Gonzalez-Porras et al. (2015) reported that response can be well maintained in patients after switching from romiplostim to eltrombopag. However, while the majority of participants in this trial had chronic ITP (86%) and the proportion of non-splenectomised patients is similar to that expected for the PBS population (around 60%), patients had a longer time on romiplostim (median 12 months) prior to switching than the PBS population and one-third of patients had received prior rituximab. The DUSC noted that there was only a marginal difference between the time on treatment for patients who switched therapy compared to all patients initiating on TRA therapy. A large proportion (46%) of initiating patients in Year 1 were grandfathered. To examine if treatment experienced grandfathered patients may have biased the length of treatment results, their time on treatment was analysed separately (see Figures 6 and 7). Compared to all initiators the mean time on treatment for grandfathered patients was similar (1.4 years (529 days) vs. 1.3 years (461 days), Figures 2 and 6). As such, the inclusion of grandfathered patients in the cohort of initiating patients does not appear to bias the length of treatment results.

## **DUSC Consideration**

The DUSC noted that splenectomy has been the established second-line treatment in adults with ITP unresponsive to initial corticosteroid therapy. The DUSC observed the recommendation in current guidelines to defer splenectomy for at least one year after the time of ITP diagnosis as a large proportion of patients enter remission during that time. The DUSC noted that around two thirds of patients achieve normal platelet counts post-splenectomy with no additional therapy required and most of the remainder have an improvement in platelet counts.

The DUSC noted the advice from the Haematology Society of Australia and New Zealand (HSANZ) and the Australasian Society of Thrombosis and Haemostasis (ASTH) that there are emerging risks associated with splenectomy which may impact on its acceptability to physicians and patients, including malignancy, a greater risk of venous thromboembolism and sepsis. The DUSC considered that the introduction of TRA therapy may have altered practice to divert patients from splenectomy. The DUSC noted that over the first three

years of listing, there was an increasing trend towards patients initiating on romiplostim being non-splenectomised. The DUSC observed that under the current restrictions there are no set guidelines to establish eligibility for a TRA on the basis of a medical contraindication to surgery. The supporting documentation required is in the form of a letter from the clinician making the assessment stating the clinical reasons why surgery is contraindicated. The DUSC considered that the PBAC may wish to seek advice from clinicians on the guidelines and criteria which are used to establish contraindication to splenectomy.

Another way that the introduction of TRA therapy may have altered practice is the reduction in use of other immunotherapies such as rituximab. As rituximab is not PBS subsidised for chronic ITP, such use would be through public hospitals or private supply, the utilisation of which cannot be assessed from the PBS prescriptions data.

The DUSC noted that the mean time on treatment of 1.3 years for all initiating patients was lower than expected based on clinical trial data. The DUSC considered that the provision in the restriction to allow treatment breaks and re-initiation without the need to requalify encourages appropriate use of the TRAs. The HSA NZ and ASTH advised that clinicians may attempt to wean or withdraw therapy once durable complete remission is achieved. Furthermore, experienced clinicians may accept a lower range of platelet counts also minimising patient exposure and thus overall utilisation of TRAs.

The DUSC recalled the November 2014 submission for eltrombopag which sought to amend the restriction to allow switching of TRA therapy beyond 24 weeks. The DUSC noted the PBAC's concerns that allowing switching in stable patients might prolong TRA therapy unnecessarily. Patients on romiplostim who may only need episodic therapy could instead take oral eltrombopag rather than having a trial off therapy. However, the DUSC observed that the mean time on TRA therapy was similar for all initiating patients compared to those who switched their therapy. The DUSC noted the response from the HSA NZ and ASTH that, in addition to an inadequate response or loss of response, switching occurs for several other reasons. For romiplostim, patients can experience intolerance or discomfort with injected therapy and may lack the competency to self-administer subcutaneous injections. Patients may prefer the convenience of less frequent romiplostim injections rather than taking daily oral eltrombopag. Patients may also experience difficulty in adhering to the dietary requirements for eltrombopag (exclusion of concomitant ingestion of divalent cations).

The DUSC noted the request from HSA NZ and the ASTH to extend the eligibility for continuing TRA therapy to patients with a platelet count of  $< 10 \times 10^9/L$  before commencement who achieve a post platelet count of  $20-30 \times 10^9/L$ . Presently, continuing therapy is only available if the platelet count is greater than  $30 \times 10^9/L$  and if this is double the baseline (pre-treatment) platelet count. The DUSC referred this request to the PBAC for consideration.

Based on annual reporting from the NBA there appears to have been a significant diversion away from immunoglobulin therapy in adult ITP patients over the last three financial years

to 2013-14. The DUSC considered that this could partly reflect a tightening in the criteria to access intravenous immunoglobulin (IVIg).

## **DUSC actions**

DUSC referred the report to the PBAC to consider:

- A request from the Haematology Society of Australia and New Zealand (HSANZ) and the Australasian Society of Thrombosis and Haemostasis (ASTH) to extend the eligibility for continuing TRA therapy for patients who do not qualify for ongoing PBS supply based on platelet count alone.
- Whether clinical advice should be sought on the criteria for establishing suitability for splenectomy. The DUSC noted that the supporting documentation currently required is in the form of a letter from the clinician stating the clinical reasons why surgery is contraindicated. A checkbox of criteria for establishing contraindication to splenectomy on the authority application form could be an alternate method that would reduce administrative burden for clinicians and improve data collection.

## **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.

## **Sponsor's comment**

Amgen Australia Pty Limited:

In relation to the statement that use “could potentially exceed the predicted expenditure over the remaining forward estimates”, Amgen would like to emphasise that the expenditure on TRAs is significantly less than expected (largely due to discontinuation rates being significantly higher than expected and a total duration of therapy much lower than anticipated). With regard to the increase in proportion of non-splenectomised years, this intervention was rarely conducted at the time of listing and remains so today. It is important to note that when the actual patient numbers are considered, the number of non-splenectomised patients initiated to romiplostim therapy is in decline.

Finally, the listing of romiplostim was granted on the grounds that there were a “group of patients with severe ITP who were receiving at least 4 IVIg treatments per annum, and averaging at least 5.4 treatments per annum” (romiplostim PSD March 2010). The current restriction was targeted at these patients and the NBA data demonstrating the significant reduction in IVIg use over the period which TRA therapy has been PBS listed supports that the intended population is being reached.

Novartis Pharmaceuticals Australia 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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