PUBLIC SUMMARY DOCUMENT
Product: ROMIPLOSTIM, powder for injection, 165 micrograms, 375 micrograms and 625 micrograms, Nplate®
Sponsor: Amgen Australia Pty Ltd
Date of PBAC Consideration: March 2010

1. Purpose of Application:

To submission sought a Section 100 (Highly Specialised Drugs Program) listing for initial and continuing treatment of thrombocytopenia in adult patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who meet certain criteria.

Highly Specialised Drugs are medicines for the treatment of chronic conditions, which, because of their clinical use or other special features, are restricted to supply to public and private hospitals having access to appropriate specialist facilities.

2. Background:

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.

3. Registration Status:

Romiplostim 375 micrograms and 625 micrograms were TGA registered on 8 August 2008 for the indication:

> For the treatment of thrombocytopaenia in adult patients with chronic immune (idiopathic) thrombocytopaenic purpura (ITP)
> - who are non-splenectomised and have had an inadequate response, or are intolerant, to both corticosteroids and immunoglobulins;
> - who are splenectomised and have had an inadequate response to splenectomy.

At the time of consideration, the 165 microgram vial of romiplostim had not been approved by the TGA.

4. Listing Requested and PBAC's View:

Section 100 (Highly Specialised Drugs)
Private hospital authority required
Initiation:
For the treatment of thrombocytopenia in adult patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who fulfil one of the following criteria:

a) Splenectomised patients who:
- (i) Have had an inadequate response to splenectomy OR
- (ii) Are requiring additional chronic intervention to maintain response post splenectomy where the intervention is associated with unacceptable toxicity OR

b) Non splenectomised patients who have had an inadequate response or are intolerant to both corticosteroid therapy and immunoglobulin therapy and in whom splenectomy is contraindicated for medical reasons.

Inadequate response is defined as a persistent platelet count of:

- $\leq 20 \times 10^9$/L or
- $20 – 30 \times 10^9$/L where the patient is experiencing bleeding or has a history of bleeding in this platelet range.

Continuation:
Patients should continue treatment if they display a sustained platelet response and have not required more than one occasion of IVIg use during the first episode of treatment.
A sustained platelet response is defined as:

- A weekly platelet count $\geq 50 \times 10^9$/L on at least four (4) occasions; or
- A platelet count $> 30 \times 10^9$/L AND a doubling of baseline platelet count, on at least four (4) occasions.

Assessment of response following the first episode of treatment would occur 24-28 weeks after initiation of therapy.

NOTE:
The following information relates to prescriptions based on the criteria described in Initiation criteria a) ii) above. Where steroids are used to maintain a response post splenectomy, patients may be eligible for PBS-subsidised treatment where doses are ≥ 10 mg/day as this dose is associated with long term toxicity.

The PBAC agreed that, subject to minor amendment, the requested restriction was clinically applicable and assisted in targeting to the most severe and needy patients who had failed or could not undergo splenectomy. The sponsor's proposal in the Pre-PBAC Response concerning the dose and duration of corticosteroid therapy was considered to be reasonable, although the PBAC did also note the variability in current practice reflected in clinician feedback. The PBAC also considered it reasonable for the restriction to cater for patients who have a break in therapy.

5. Clinical place for the Proposed Therapy:

Chronic immune (idiopathic) thrombocytopenic purpura (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 platelet count to a safe level while minimising treatment-related toxicity.

Romiplostim is a peptibody that stimulates platelet production for long-term treatment of adult chronic ITP patients.

6. Comparator:

The submission nominated placebo as the comparator. The PBAC considered this was appropriate for non-splenectomised patients given the new requested restriction.

7. Clinical Trials

The re-submission re-presented the same two key direct randomised trials as the original submission, comparing romiplostim with placebo (both given in addition to standard care), in patients with chronic immune thrombocytopenia purpura (ITP). One trial assessed non-splenectomised patients, while the other trial was conducted in splenectomised patients. Both of the key direct randomised trials are reported in Kuter et al 2008. The re-submission also presented new supplementary trial data in non-splenectomised patients (as reported in Rummel et al 2009). Additional safety data from the long term extension study of romiplostim were also presented.

The two trials presented in the submission had been published at the time of submission, as follows:

Trial ID/First author	Protocol title/ Publication title	Publication citation
Direct randomised trials		
Kuter D et al (2008)	Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: a double-blind randomised controlled trial.	Kuter D et al, The Lancet 2008;371 (9610): 395-403
Supplementary randomised trial		
Rummel M et al (2009)	Efficacy and safety of romiplostim versus medical standard of care as chronic therapy for nonsplenectomized patients with immune thrombocytopenia (ITP).	Rummel M et al, Abstract for European Haematology Association 2009

There was uncertainty, acknowledged by the sponsor, about the applicability of the supplementary randomised trial data to the population for whom PBS listing was sought as the present requested listing restricts to those patients who are either already splenectomised or who have a significant medical contraindication to splenectomy.

8. Results of Trials

The re-submission presented the results of post hoc analyses for the high-risk subgroup of patients from each trial who are more representative of those for whom PBS listing is sought; namely, those who have received at least two prior ITP therapies and who had a baseline platelet count of less than 20×10^9/L, or a platelet count of $20\text{-}30\times10^9$/L with current or prior bleeding.

The objective of treatment was to prevent symptomatic bleeding by increasing platelet count and/or improving function. It was accepted that romiplostim increased platelet count, although there was wide variability in the response (see the interquartile ranges below). However, the data about the effect of romiplostim on symptomatic bleeding was reported in the trials but not used as the basis of the submission. The submission's cost-effectiveness analysis was based entirely on a transformation of a surrogate (platelet response) into a clinically relevant endpoint (bleeding events).

The median platelet count at every weekly study visit for splenectomised (A) and non-splenectomised (B) patients is shown in the following figure, taken from Kuter et al 2008:

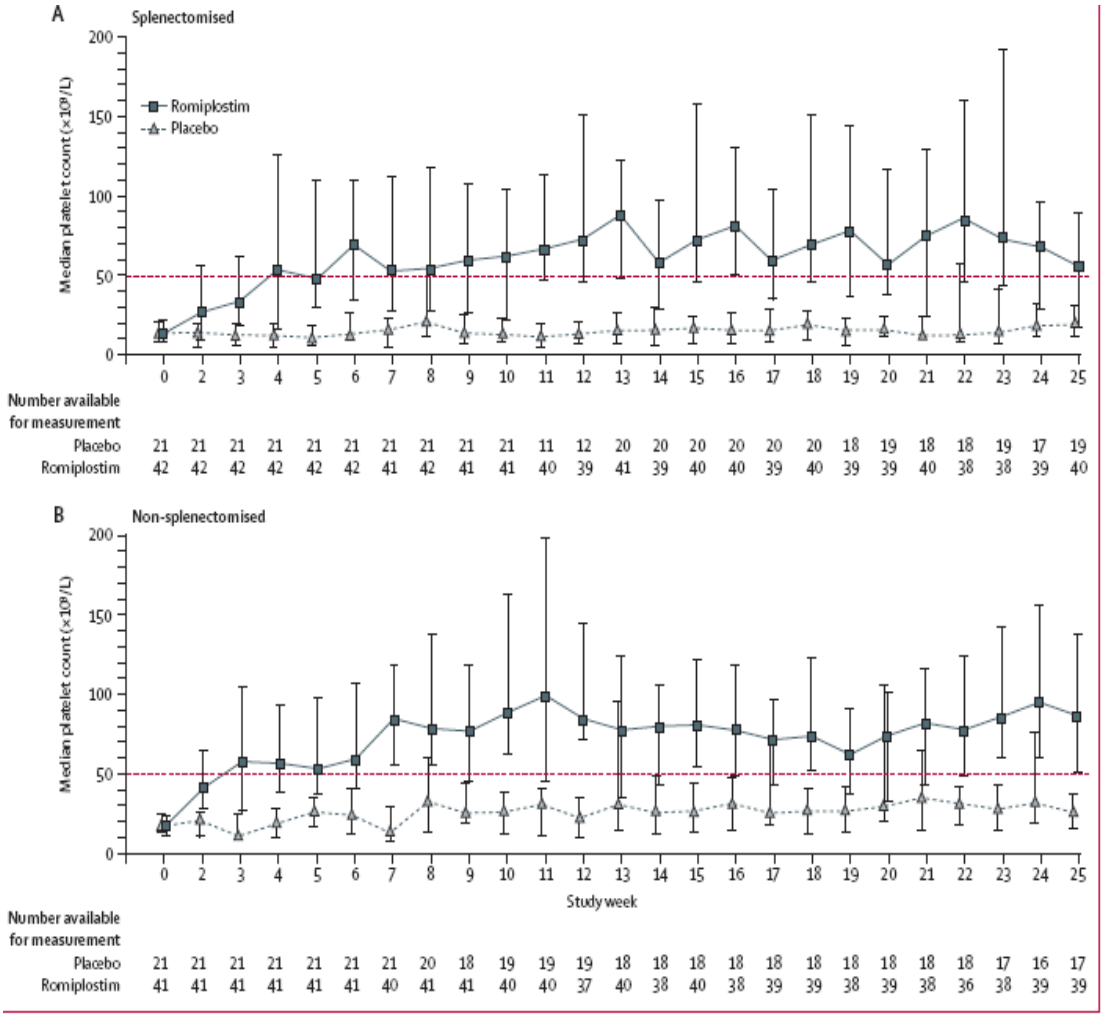

Figure 3: Median platelet count at every weekly study visit for splenectomised (A) and non-splenectomised (B) patients
Data includes all patients, even those who received rescue drugs. Error bars indicate the range from the first to third quartiles. Dashed line indicates platelet count of 50x10⁹/L.

Kuter et al 2008 reported that patients given romiplostim achieved platelet counts of $50x10^{(9)}$/L or more on a mean of 13.8 (SE 0.9) weeks (mean 12.3 [1.2] weeks in the splenectomised group versus 15.2 [1.2] weeks in non-splenectomised group) compared with 0.8 (0.4) weeks for those given placebo (0.2 [0.1] weeks versus 1.3 [0.8] weeks).

The adverse events occurring in 10 % of the patients in Kuter et al 2008 reproduced in the figure below did not show a clear signal that romiplostim reduces the bleeding event rates:

	Placebo (n=41)	Romiplostim (n=84)
Headache	13 (32%)	29 (35%)
Fatigue	12 (29%)	28 (33%)
Epistaxis	10 (24%)	27 (32%)
Arthralgia	8 (20%)	22 (26%)
Contusion	10 (24%)	21 (25%)
Petechiae	9 (22%)	14 (17%)
Diarrhoea	6 (15%)	14 (17%)
Upper respiratory tract infection	5 (12%)	14 (17%)
Dizziness	0	14 (17%)
Insomnia	3 (7%)	13 (16%)
Myalgia	1 (2%)	12 (14%)
Back pain	4 (10%)	11 (13%)
Nausea	4 (10%)	11 (13%)
Pain in extremity	2 (5%)	11 (13%)
Cough	7 (17%)	10 (12%)
Anxiety	5 (12%)	9 (11%)
Gingival bleeding	5 (12%)	9 (11%)
Abdominal pain	0	9 (11%)
Nasopharyngitis	7 (17%)	7 (8%)
Ecchymosis	6 (15%)	6 (7%)

*Because no statistically significant difference between splenectomised and non-splenectomised patients was recorded, the results for this analysis were pooled.

Table 3: **Adverse events occurring in at least 10% of patients in either treatment group***

The submission in support of the effectiveness of romiplostim in reducing bleeding events, presented a post hoc analysis of bleeding events from the pooled safety data from the two key direct randomised trials and trial 131 (Rummel M, EHA 2009, abstract 1059). As the two key direct randomised trials recruited non-splenectomised patients who did not necessarily have a contraindication to splenectomy, the majority of subjects in this post hoc pooled analysis were not representative of the PBS population for whom listing was requested in the re-submission.

The two key trials presented used platelet response, a surrogate outcome, rather than a clinically relevant outcome, such as symptomatic bleeding or mortality.

The PBAC noted as previously that there was a degree of uncertainty about quantification of the effectiveness of romiplostim in reducing clinically important bleeding, despite evidence that romiplostim treatment results in a significant increase in the platelet count. The tabulation of adverse events occurring in at least 10 % of patients in either treatment group (Kuter et al, 2008) did not reveal any difference in bleeding. However, the PBAC considered that because the reporting of these events were based on proportions of patients ever experiencing bleeding during the trial, rather than number of bleeding events, any benefit of romiplostim in prevention of bleeding could not be detected. There was also uncertainty in interpreting the difference in the trials with respect to severity of bleeding using the post hoc analysis of bleeding related events from the pooled safety

data from the two key direct randomised trials and trial 131 (Rummel M, EHA 2009, abstract 1059). Most patients were non-splenectomised and did not necessarily have a contraindication to splenectomy (as noted above). In addition, the high rate of use of intravenous immunoglobulin (IVIg) use and other rescue medication was considered likely to have reduced the number of bleeding events in the placebo arm of the trials. Furthermore, it is biologically plausible that an increase in platelets will result in a lowered risk of bleeding. The PBAC thus acknowledged that the totality of the evidence suggests it is reasonable to conclude that romiplostim reduces severe bleeding events, in patients at high risk for bleeding.

The re-submission presented updated non-comparative toxicity data from the long-term romiplostim extension study. Adverse events (AEs), reported in 184/215 (86 %) patients, were generally mild-moderate in severity; most common were headache (34 %), contusion (32 %), and fatigue (31 %). Serious adverse events were reported in 29 % (62/215) of patients. Serious AEs reported in three or more patients each were thrombocytopenia (10/215, 7 %), increased bone marrow reticulin (5/215, 3.5 %), and congestive cardiac failure (3/215, 2.1 %). Deaths occurred in 4 (2 %) patients; none were treatment related.

The PBAC considered that the long-term safety of romiplostim had not been adequately established, especially in regard to the incidence and potential consequences of bone marrow reticulin formation.

9. Claim

The re-submission claimed romiplostim as superior in terms of comparative effectiveness to placebo, but associated with a higher incidence of mild to moderate drug-related adverse events.

10. Economic Analysis

An updated modelled economic evaluation was presented. The economic evaluation was altered to reflect the changes to the requested restriction in terms of the proposed PBS population. In addition, the results of the post hoc analysis of bleeding-related episodes and IVIg use events were incorporated into the model.

The model reanalysed the post-hoc bleeding-related episodes (BREs) and the subsequent effect of this on the probability of bleeding and hospitalisation, and the rate of IVIg use. This re-analysis of BREs increased the incremental effectiveness of romiplostim versus placebo. As these results were derived from the post hoc re-analysis of the non-validated post hoc outcome of BREs, their validity was uncertain.

Restricting the proposed PBS population to high-risk chronic ITP patients greatly reduced the incremental cost-effectiveness ratio (ICER) for non-splenectomised patients. However, the effect on the ICER for the post-splenectomy patients was not as pronounced Additional sensitivity analyses related to the effect on the incremental cost-effectiveness ratio of the rate of IVIg use were undertaken.

The PBAC was concerned that the use of IVIg in the model, while consistent with the trial may not be consistent with Australian clinical practice, hence the cost-effectiveness of romiplostim in Australia may be less favourable than calculated by the submission on the basis of the main trial.

The method of calculating the probabilities of IVIg use was unchanged from the initial March 2009 submission - the probabilities of IVIg being used to treat outpatient-managed bleeding events were calculated for the model based on IVIg usage rates from the randomised clinical trials (RCTs). This was done by a calibration exercise – the model inputs, probabilities of IVIg use, were manually adjusted until the model, when run for 6 months or a year, gave IVIg usage outputs that matched usage rates from the RCTs.

The model used 5.4 IVIg treatments per patient per year. However, the sponsor's own Australian data, showed that IVIg use in those who have failed splenectomy is usually restricted to one use, with only 36 % of patients receiving more than two such treatments and none more than five treatments.

Sensitivity Analyses

As the sponsor did not supply the details of the calibration, it was not possible to calculate the probability for specific rates of IVIg use in the placebo arm. Sensitivity analyses were preformed by assuming that the probability of IVIg use in the placebo arm is 1, 2 or 3 times the probability for the romiplostim arm (first 6 months).

With the data available, although it was possible to estimate how a lower rate of IVIg use in the placebo arm would affect the incremental cost, it was not possible to estimate the effect of lowering IVIg use (and potential increased risk of bleeding events) on health outcomes and thus incremental quality adjusted life years (QALYs).

The submission and the presenter at the PBAC hearing for this application argued that it was reasonable to base the rate of IVIg use in the model on that used in the trials. The PBAC noted concerns that data from a practice survey provided by the sponsor suggested that the 5.4 IVIg treatments per annum for the placebo arm in the model was not realistic in the Australian setting. However, PBAC also noted its solicited correspondence from the Australian Red Cross Blood Service which confirmed the existence and size of 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. In view of this information, in conjunction with the information presented, the PBAC considered that romiplostim represents a cost-effective treatment for the proposed groups of patients at an incremental cost effectiveness ratio (ICER) in the range of $45,000 to $75,000 per QALY for post-splenectomy patients and possibly dominant for non-splenectomy patients.

11. Estimated PBS Usage and Financial Implications:

The submission estimated a financial cost per year to the PBS in the range of $10 to 30 million in Year 5. This was compared with a range of $30 to 60 million in the original submission. This decrease was mainly due to the decrease in the number of eligible chronic ITP patients as a result of the narrower restriction in the requested PBS listing for the non-splenectomised subgroup.

The PBAC noted that there was considerable uncertainty about the predicted utilisation estimates for romiplostim and there was also concern about inappropriate use, particularly in patients who have not undergone splenectomy.

12. Recommendation and Reasons:

The PBAC recommended listing as a pharmaceutical benefit 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, on the basis of a high but acceptable cost effectiveness ratio, in the context of a high clinical need in a small subgroup of ITP patients. In a previous submission, PBAC had determined that cost-effectiveness comparison with placebo was only appropriate in ITP patients who had failed splenectomy or in whom splenectomy was medically contraindicated, as the sponsor had not considered splenectomy as a comparator, nor provided data to justify the use of romiplostim in preference to splenectomy. Although less effective, and therefore less cost-effective, in splenectomised patients, the PBAC noted that it was this patient group who have the highest unmet clinical need.

The PBAC agreed that, subject to minor amendment, the requested restriction was clinically applicable and assisted in targeting to the most severe and needy patients who had failed or could not undergo splenectomy. The proposal by the sponsor concerning the dose and duration of corticosteroid therapy was considered to be reasonable, although the PBAC did also note the variability in current practice reflected in clinician feedback. The PBAC also considered it reasonable for the restriction to cater for patients who have a break in therapy.

The PBAC noted that the re-submission presented new supplementary trial data in non-splenectomised patients. There was uncertainty, acknowledged by the sponsor, about the applicability of the supplementary trial data to the population for whom PBS listing is sought as the present requested listing restricts to those patients who are either already splenectomised or who have a significant medical contraindication to splenectomy.

The PBAC noted as previously that there was a degree of uncertainty about quantitation of the effectiveness of romiplostim in reducing clinically important bleeding, despite evidence that romiplostim treatment results in a significant increase in the platelet count. The tabulation of adverse events occurring in at least 10 % of patients in either treatment group (Kuter et al, 2008) did not reveal any difference in bleeding. However, the PBAC considered that this may have been a misrepresentation, as these events were based on proportions of patients ever experiencing bleeding during the trial, rather than number of bleeding events, and therefore any benefit of romiplostim in prevention of bleeding could not be detected. There was also uncertainty in interpreting the difference in the trials with respect to severity of bleeding using the post hoc analysis of bleeding related events from the pooled safety data from the two key direct randomised trials and new supplementary trial data (Rummel M, EHA 2009, abstract 1059). Most patients were non-splenectomised and did not necessarily have a contraindication to splenectomy (as noted above). In addition, the high rate of use of intravenous immunoglobulin (IVIg) use and other rescue medication was considered likely to have reduced the number of bleeding events in the placebo arm of the trials. Furthermore, it is biologically plausible that an increase in platelets will result in a lowered risk of bleeding. The PBAC thus acknowledged that the totality of the evidence suggests it is reasonable to conclude that romiplostim reduces severe bleeding events, in patients at high risk for bleeding.

The remaining uncertainty related to the rate of IVIg use, as reduction in IVIg use represented the major cost offset in the model, without which cost-effectiveness could not be demonstrated. The submission and the presenter at the PBAC hearing for this

application argued that it was reasonable to base the rate in the model on that used in the trials. PBAC noted concerns that data from a practice survey provided by the sponsor suggested that the 5.4 IVIg treatments per annum for the placebo arm in the model was not realistic in the Australian setting. However, PBAC also noted its solicited correspondence from the Australian Red Cross Blood Service which confirmed the existence and size of 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. In view of this information, in conjunction with information presented, the PBAC considered that romiplostim represents a cost-effective treatment for the proposed groups of patients at an incremental cost effectiveness ratio (ICER) in the range of $45,000 to $75,000 per QALY for post-splenectomy patients and possibly dominant for non-splenectomy patients.

The PBAC noted that there was considerable uncertainty about the predicted utilisation estimates for romiplostim and there was also concern about inappropriate use, particularly in patients who have not undergone splenectomy. The PBAC considered that evidence that use in a larger group of patients with less severe ITP is both clinically necessary and cost effective should be presented before romiplostim is subsidised for this group.

Recommendation:
ROMIPLOSTIM, powder for injection, 165 micrograms, 375 micrograms and 625 micrograms

Restriction:	Section 100 listing (Highly Specialised Drug) Public and Private hospital authority required Restriction to be finalised
Pack size:	1

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

The sponsor had no comment.