

PUBLIC SUMMARY DOCUMENT

Product: Eltrombopag olamine, tablets, 25 mg and 50 mg, Revolade®

Sponsor: GlaxoSmithKline Australia Pty Ltd

Date of PBAC Consideration: November 2010

1. Purpose of Application

The submission sought a Section 100 (Highly Specialised Drugs Program) Authority Required listing for adult patients with chronic immune (idiopathic) thrombocytopenia purpura (ITP).

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

This drug had not previously been considered by the PBAC.

3. Registration Status

Eltrombopag olamine was TGA registered on 2 July 2010 for the treatment of adult patients with chronic ITP who have an inadequate response or are intolerant to corticosteroids and immunoglobulins.

4. Listing Requested and PBAC's View

Section 100 (*program not specified*)

Authority required

Initiation

For initial treatment, as the sole PBS-subsidised thrombopoietin receptor agonist (TRA), of an adult patient with chronic ITP who is:

- Splenectomised and:
 - who has an inadequate response to splenectomy, OR
 - who requires additional chronic intervention to maintain a response post splenectomy where the intervention is associated with unacceptable toxicity; OR
- Non splenectomised and who has had an inadequate response to, or is intolerant to, both corticosteroids and immunoglobulins, and in whom splenectomy is contraindicated.

NOTE:

Inadequate response is defined as a persistent platelet count of:

- less than or equal to 20,000/microlitre or
- 20,000 – 30,000/microlitre where the patient is experiencing bleeding or has a history of bleeding in this platelet range.

Continuation

For continuing treatment of an adult patient with chronic ITP who has displayed a sustained platelet response or a significant reduction in bleeding events during the first six (6) months of treatment.

NOTE:

A sustained platelet response is defined as a platelet count greater than or equal to 50,000/microlitre on at least four occasions; or a platelet count greater than 30,000/microlitre AND a doubling of baseline platelet count, on at least four occasions.

The PBAC noted that the sponsor, in its Pre-Sub-Committee response, agreed that the restriction for eltrombopag should be consistent with that recommended for romiplostim and considered this to be appropriate.

5. Clinical Place for the Proposed Therapy

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 platelet count to a safe level while minimising treatment-related toxicity. 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. Splenectomy is recommended as second-line therapy.

The submission proposed eltrombopag as an alternative to romiplostim for patients where splenectomy has failed or is contraindicated and where patients are unresponsive/intolerant to corticosteroids and IVIg therapy.

6. Comparator

The submission nominated romiplostim as the comparator. This was accepted by the PBAC.

7. Clinical Trials

The submission presented one randomised trial comparing eltrombopag 25-75 mg, administered orally once a day, with placebo (both given in addition to standard care) in both splenectomised and non-splenectomised adult patients with chronic ITP (RAISE); and two randomised trials comparing romiplostim (weekly injection titrated to effect) with placebo (both given in addition to standard care), the first in splenectomised patients with chronic ITP (Kuter 2008S), and the second in non-splenectomised patients with chronic ITP (Kuter 2008NS).

Details of the published trials are presented in the following table.

Trials and associated reports presented in the submission

Trial ID/First Author	Protocol title/Publication title	Publication citation
RAISE Cheng G, et al (2010)	Eltrombopag for management of chronic immune thrombocytopenia (RAISE): a 6-month, randomised, phase 3 study.	<i>Lancet</i> 2010; Early Online Publication, 24 August 2010 doi:10.1016/S0140-6736(10)60959-2

Trial ID/First Author	Protocol title/Publication title	Publication citation
George JN, et al.	Improved quality of life for romiplostim-treated patients with chronic immune thrombocytopenic purpura: results from two randomized, placebo-controlled trials.	<i>British Journal of Haematology</i> 2008; 144:409-415
George JN, et al.	Abstract 1314	<i>Blood</i> 2007; 110
Gernsheimer TB, et al.	Abstract 2	<i>Blood</i> 2007; 110
Jamali F, et al.	Romiplostim for the treatment of chronic immune (idiopathic) thrombocytopenic purpura.	<i>Oncology</i> 2009; 23:704-9.
Kuter DJ, et al. (2008)	Effect of romiplostim in patients with chronic immune thrombocytopenic purpura: a double-blind randomised controlled trial.	<i>Lancet</i> 2008; 371:395-403
Kuter DJ, et al. (2007)	Abstract 565	<i>Blood</i> 2007; 110
Lyons R, et al.	Abstract 1300	<i>Blood</i> 2007; 110
Pullarkat V, et al. (2007)	Abstract 1304	<i>Blood</i> 2007; 110
Pullarkat VA, et al. (2009)	Quantifying the reduction in immunoglobulin use over time in patients with immune mediated thrombocytopenic purpura receiving romiplostim (AMG531).	<i>American Journal of Hematology</i> 2009; 84:538-40.

No trials directly comparing eltrombopag with romiplostim were identified.

There was concern regarding the exchangeability of the trials, arising from differences in the patient populations and the conduct of the trials. Some of the key differences between the RAISE and Kuter studies are presented in the table below.

Differences between RAISE and Kuter trials

	RAISE Eltrombopag	Kuter 2008 Romiplostim
% Placebo group achieving platelet response	6.5%	2.4%
Median duration of ITP (yr)	1.6 (E)/2.3 (P)	2.5 (R)/2.5 (P)
% With ≥ 3 prior treatments	56%(E)/52%(P)	65%(R)/60%(P)
Proportion receiving rescue treatment	38%(E)/63%(P)	22%(R)/60%(P)

E = Eltrombopag; R = Romiplostim; P = Placebo

For PBAC's view of the trials, see Recommendation and Reasons.

8. Results of Trials

The submission presented the results of an indirect comparison of eltrombopag and romiplostim, with placebo as the common comparator. As none of the predefined

outcomes of the trials were comparable, a post hoc analysis of durable platelet response and overall platelet response (the primary and main secondary outcomes of the romiplostim trials) was performed in the intention-to-treat (ITT) population of the RAISE trial. As randomisation in the RAISE trial was stratified by splenectomy status, the submission also presented separate post hoc analyses for the splenectomised and non-splenectomised subgroups.

The submission did not define the non-inferiority margin for the comparison.

The surrogate outcomes used in the indirect comparison defined a treatment response in terms of the proportion of patients with platelet counts above an arbitrary platelet count threshold of $50 \times 10^9/L$. The submission acknowledged that platelet count was an imperfect measure of bleeding risk because the relationship between the two is not linear. Therefore, changes in these 'surrogate' outcomes were not necessarily predictive of the magnitude of the comparative treatment effect in terms of clinically relevant outcomes, such as clinically important bleeding and mortality. The submission acknowledged that the relationship between the surrogates and patient relevant outcomes is difficult, but argued that "romiplostim was approved for listing based largely on these surrogate outcomes." Further, the submission noted that outcomes 'any' and 'clinically meaningful bleeding' were significantly reduced in eltrombopag patients in the RAISE study, but that these outcomes could not be used in the indirect comparison as the romiplostim studies included bleeding outcomes only as adverse events.

The submission claimed that, based on the results of the indirect comparison, it can be concluded that eltrombopag and romiplostim provide similar rates of durable platelet response in the target PBS population of adults with chronic refractory ITP. The PBAC considered that this conclusion was not adequately supported by the evidence. *See Recommendations and Reasons.*

The most common adverse events in the RAISE trial and the romiplostim trials included headache, diarrhoea, nausea, nasopharyngitis, fatigue and upper respiratory tract infection. The submission stated that, while differences in reporting methods made it difficult to draw any meaningful conclusions about the relative safety of eltrombopag and romiplostim, their safety profiles are at least comparable, and eltrombopag may result in fewer adverse events than romiplostim.

The PBAC considered that differences in the base-line risks of the trial populations and in the reporting of adverse events between the trials made it difficult to reliably assess the comparative safety of eltrombopag and romiplostim. *See Recommendation and Reasons.*

9. Clinical Claim

The submission claimed eltrombopag to be non-inferior to romiplostim in terms of both comparative effectiveness and comparative safety. The PBAC did not accept this claim. *See Recommendation and Reasons.*

10. Economic Analysis

The submission presented a cost minimisation analysis. On the basis of the trial data, the submission estimated that eltrombopag 55.2 mg/day and romiplostim 276.2 mcg/week are equi-effective.

11. Estimated PBS Usage and Financial Implications

The financial savings per year to the PBS estimated by the submission were less than \$10 million in Year 5. The submission's estimate was uncertain, and relied on estimated cost savings from substitution for romiplostim.

12. Recommendation and Reasons

The PBAC noted that the sponsor, in its Pre-Sub-Committee response, agreed that the restriction for eltrombopag should be consistent with that recommended for romiplostim and agreed that this is appropriate.

The submission's nomination of romiplostim as the appropriate comparator was accepted.

The Committee noted that the submission presented one randomised trial comparing eltrombopag 25-75 mg, administered orally once a day, with placebo (both given in addition to standard care) in both splenectomised and non-splenectomised adult patients with chronic ITP (RAISE); and two randomised trials comparing romiplostim (weekly injection titrated to effect) with placebo (both given in addition to standard care), the first in splenectomised patients with chronic ITP (Kuter 2008S), and the second in non-splenectomised patients with chronic ITP (Kuter 2008NS). The PBAC considered that the patient populations of these trials were not representative of the more restricted high-risk subgroup of chronic ITP patients for whom PBS listing was sought. In addition, the indirect comparison was based on post-hoc analyses of the RAISE study. However, the PBAC acknowledged that, currently, these are the only available data and that the recommendation to list romiplostim had been made on the basis of the Kuter trials.

Further, as none of the predefined outcomes of the trials were comparable, a post hoc analysis of durable platelet response and overall platelet response (the primary and main secondary outcomes of the romiplostim trials) was performed in the intention-to-treat (ITT) population of the RAISE trial. As randomisation in the RAISE trial was stratified by splenectomy status, the submission also presented separate post hoc analyses for the splenectomised and non-splenectomised subgroups. The PBAC considered that there were considerable concerns regarding the exchangeability of the trials, arising from differences in the patient populations and the conduct of the trials. On this basis, the appropriateness of an indirect determination of the comparative treatment effect for eltrombopag and romiplostim, using these trials, was uncertain.

There was a higher placebo response, lower median duration of ITP, lower proportion of patients with greater than or equal to 3 prior treatments and a higher proportion of patients receiving rescue medication in the eltrombopag trial. Overall the PBAC considered it likely that the patients in the RAISE trial had milder ITP than the patients in the Kuter trials.

The submission claimed that, based on the results of the indirect comparison, it could be concluded that eltrombopag and romiplostim provide similar rates of durable platelet response in the target PBS population of adults with chronic refractory ITP. This conclusion was not adequately supported by the evidence. The point estimates of the comparative treatment effect all favoured romiplostim. Additionally, non-inferiority margins were not defined for the comparison. Further, in particular, due to the low event rates in the placebo arms of the trials, and also the substantial potential for confounding,

the results of the indirect comparison of eltrombopag and romiplostim were subject to considerable uncertainty. In addition, the width of the confidence intervals indicated that the indirect comparison was not adequately powered for statistical testing of non-inferiority, especially in the patient subgroups in which patient numbers were small (splenectomised/non-splenectomised). These factors resulted in considerable uncertainty around any conclusions drawn from this comparison regarding the relative efficacy of eltrombopag and romiplostim.

The PBAC also considered that differences in the base-line risks of the trial populations and in the reporting of adverse events between the trials made it difficult to reliably assess the comparative safety of eltrombopag and romiplostim. This was clearly illustrated by the differences in reporting in both active and placebo arms in reporting of epistaxis (5% vs. 10%, and 32% vs. 24%, respectively) and petechiae (2% vs. 2% and 17% vs. 22%, respectively). These results also suggested that romiplostim may be more effective than eltrombopag in reducing bleeding events.

The PBAC considered that there was insufficient evidence to draw any reliable conclusions regarding the comparative safety of eltrombopag and romiplostim in patients with chronic ITP. In particular, there were no comparative safety data on the long-term use of these treatments. However, it was considered possible that eltrombopag is less effective than romiplostim, and that the case for non-inferiority had not been made.

The submission presented a cost minimisation analysis. The PBAC noted that the equi-effective doses proposed by the submission were based on the ITT populations of the trials and not the high risk sub-groups

The PBAC noted that the submission's estimate of the equi-effective doses remained highly uncertain on the following grounds:

- There are four distinct patient groups in the requested listing: splenectomised initiating patients, non-splenectomised initiating patients, splenectomised continuing patients, and non-splenectomised continuing patients. Doses, and therefore equi-effective doses, varied between these patient subgroups.
- Using the mean dose to determine the total cost of romiplostim was not accurate, as it was the distribution of doses in the splenectomised and non-splenectomised populations that determine the number and size of vials used and, therefore, the extent of wastage as a result of partially used vials.
- The cost-minimisation analysis was incomplete as it only considered the drug costs of eltrombopag and its comparator, ignoring possible differences in the utilisation of other relevant resources. The March 2010 Public Summary Document for romiplostim noted the uncertainty relating 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 PBAC noted that the Pre-PBAC response reported that use of rescue medication was similar between the two drugs. However, given that it is likely that in the eltrombopag trial, patients were less severely affected than those in the romiplostim trials, this comparison was not considered useful.

The PBAC therefore rejected that submission on the basis of uncertain clinical

effectiveness in comparison with romiplostim.

Recommendation

Reject

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 recognises the difficulties involved in the clinical comparison considered and is working with the PBAC to find a solution which will enable eltrombopag to be made more accessible to patients with chronic refractory ITP as soon as possible.