

6.9 ELTROMBOPAG Tablets, 25 mg and 50 mg; Revolade®; GlaxoSmithKline Pty Ltd.

1 Purpose of Application

- 1.1 The minor submission requested to amend continuation restriction of eltrombopag for the treatment of severe chronic immune idiopathic thrombocytopenic purpura (iCTP) in adult patients to allow switching of treatment between eltrombopag and romiplostim in patients whose disease is stable.

2 Requested listing

- 2.1 The submission seeks the following changes to the existing restriction:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
ELTROMBOPAG			Revolade	GK
eltrombopag 25 mg tablet, 28	-	-		
eltrombopag 50 mg tablet, 28				

Public and private hospital authority required **Continuing therapy or re-initiation after a break in therapy**

First period of PBS-subsidised continuing treatment or re-initiation of interrupted PBS-subsidised treatment, as the sole PBS-subsidised thrombopoietin receptor agonist (TRA), of severe thrombocytopenia in an adult patient with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who has displayed a sustained platelet response to treatment with eltrombopag **or romiplostim** during the initial period of PBS-subsidised treatment.

For the purposes of this restriction, a sustained platelet response is defined as:

- (a) use of rescue medication (corticosteroids or immunoglobulins) on no more than one occasion during the initial period of PBS-subsidised eltrombopag,

AND either of the following:

- (b) a platelet count greater than or equal to 50,000 million per L on at least four (4) occasions, each at least one week apart;

OR

- (c) a platelet count greater than 30,000 million per L and which is double the baseline (pre-treatment) platelet count on at least four (4) occasions, each at least one week apart.

Applications for the first period of continuing PBS-subsidised treatment or re-initiation of interrupted treatment must be made in writing and must include:

- (1) a completed authority prescription form, and
- (2) a completed Idiopathic Thrombocytopenic Purpura Continuing PBS Authority Application - Supporting Information Form [may be downloaded from the Medicare Australia website (www.medicareaustralia.gov.au)], and
- (3) copies of the platelet count pathology reports (unless previously provided for patients re-initiating therapy).

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The most recent platelet count must be no more than one month old at the time of application.

A maximum of 24 weeks of treatment with eltrombopag will be authorised under this criterion.

Where fewer than 5 repeats are initially requested with the authority prescription, authority approvals for sufficient repeats to complete a maximum of 24 weeks of treatment may be made by telephone

Public and private hospital authority required **Second and subsequent applications for continuing therapy**

Continuing treatment, as the sole PBS-subsidised thrombopoietin receptor agonist (TRA), of severe thrombocytopenia in an adult patient with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who has previously received PBS-subsidised therapy with eltrombopag **or romiplostim** and who continues to display a response to treatment with eltrombopag **or romiplostim**.

For the purposes of this restriction, a continuing response to treatment with eltrombopag **or romiplostim** is defined as:

- (a) use of rescue medication (corticosteroids or immunoglobulins) on no more than one occasion during the most recent 24 week period of PBS-subsidised treatment with eltrombopag,

AND either of the following:

- (b) a platelet count greater than or equal to 50,000 million per L

OR

- (c) a platelet count greater than 30,000 million per L and which is double the baseline platelet count.

Platelet counts must be no more than 1 month old at the time of application.

Authority applications for second and subsequent periods of continuing therapy may be made by telephone by contacting Medicare Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday)

For more detail on PBAC's view, see Section 4 "Quality use of medicines" and 5 "PBAC outcome".

3 Background

- 3.1 Eltrombopag is TGA registered for the treatment of adult patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who have inadequate response or are intolerant to corticosteroids and immunoglobulins.
- 3.2 At its March 2011 meeting, the PBAC recommended listing of eltrombopag on the basis of acceptable cost-effectiveness at a revised price (less effective and less expensive with romiplostim) for patients with cITP, restricted to the same population as romiplostim.
- 3.3 The PBAC recommended that patients must achieve a satisfactory response with one or other of eltrombopag or romiplostim within a 24 week period, during which time switching is to be allowed. This allows flexibility for prescribers and patients to establish the most suitable treatment for each individual within this period. Patients who fail treatment either with eltrombopag or romiplostim after the initial 24 week period will not be eligible for further PBS-subsidised therapy with either of the drugs, unless the PBAC is presented with evidence of effectiveness and cost effectiveness in this situation

- 3.4 The current initial restriction for eltrombopag and romiplostim includes a NOTE that allows patients to trial either eltrombopag and/or romiplostim within the 24 weeks treatment period. Patients who fail to demonstrate a response to treatment with either eltrombopag and/or romiplostim under the initial restriction will not be eligible to receive further PBS-subsidised treatment with either of these drugs.

For more detail on PBAC’s view, see Section 5 “PBAC outcome”

4 Consideration of the evidence

Sponsor hearing

- 4.1 There was no hearing for this item as it was a minor submission.

Consumer comments

- 4.2 The PBAC noted that there were no consumer comments. The sponsor of romiplostim submitted a comment through the public access portal.

Clinical trials

- 4.3 The minor submission presented the following clinical studies:

Supportive studies presented in the re-submission

Trial ID	Protocol title/ Publication title	Publication citation
Eltrombopag studies		
GSK Study 113922	A Retrospective Observational and a Patient Survey: Outcomes Comparison of Chronic Immune Thrombocytopenia (ITP) patients switched to Eltrombopag and Romiplostim	2012
Khellaf, M et al	A Retrospective pilot evaluation of switching thrombopoietic receptor-agonists in immune thrombocytopenia	Haematologica. 2013 Jun;98(6):881-7.

Source: Compiled during evaluation

- 4.4 The submission proposed to modify the restriction for continuation of eltrombopag and romiplostim to allow continuation of treatment with eltrombopag in patients whose disease is stable and responding to treatment with romiplostim or vice versa based on retrospective observational studies GSK Study 113922 and Khellaf et al (2013) where one of the primary outcomes is patient preference as a reason for switching between TRA treatments.
- 4.5 The submission included a brief overview of the efficacy outcomes reported in Study 113922 (n= 280) following medication switch in the patient groups relevant to this submission. This relevant subgroup appeared to be patients who switched from romiplostim to eltrombopag and indicated that their preference was a reason for requesting the switch (n=42) and patients who switched from eltrombopag to romiplostim and indicated that their preference was a reason for requesting the switch (n=44).

Comparative effectiveness and harms

- 4.6 The submission stated that in Study 113922 no significant differences were found between eltrombopag and romiplostim treatment cohorts in the effectiveness and side effects domain scores on the Treatment Satisfaction Questionnaire for Medication (TSQM) in patients who switched to either the eltrombopag or romiplostim treatment. In addition, no hospitalisations, emergency department visits, or splenectomies were observed in either the eltrombopag or romiplostim treatment groups following the medication switch. The submission also stated that this was further supported by the Khellaf et al (2013) study.

Clinical claim

- 4.7 The submission claimed that in terms of clinical efficacy, no difference was observed between eltrombopag and romiplostim.

Economic analysis

- 4.8 As a minor submission, there was no economic comparison presented.

Estimated PBS usage & financial implications

- 4.9 The minor submission estimated a net save to the PBS of less than \$10 million in Year 5 of listing, with a total net save to the PBS of less than \$10 million over the first 5 years of listing. This is summarised in the table below with the expected patient numbers.

Net cost of drug to the PBS/RPBS	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients to switch to eltrombopag					
Change in number of patients treated with eltrombopag	■	■	■	■	■
Total cost for PBS/RPBS of increased use of eltrombopag					
Total cost @ DPMQ	■	■	■	■	■
Total Co-payments	■	\$■	■	■	■
Total cost to PBS/RPBS	■	■	■	■	■
Total cost for decreased use of romiplostim					
Total cost @ DPMQ	■	■	■	■	■
Total Co-payments	■	■	■	■	■
Total cost to PBS/RPBS	■	■	■	■	■
Overall Net Cost to PBS/RPBS					
Overall Net Cost to PBS/RPBS	■	■	■	■	■

Source: Minor submission p17 and Section E of submission (excel workbook)

The redacted table above shows that at Year 5, the estimated change in number of patients treated with eltrombopag will be less than 10,000.

- 4.10 The estimated PBS usage was based on a survey of 30 haematologists in Australia. The survey reported that 13% of adult cITP patients would be switched from eltrombopag to romiplostim (mainly due to compliance and frequency of administration) and 24% of adult cITP patients would be switched from romiplostim to eltrombopag (mainly due to convenience of an oral route of administration), having a net result of 11% switch from romiplostim to eltrombopag. The cost to the PBS/RPBS associated with the proposed change in PBS listing was calculated based on the estimate for the increased number of patients being treated with eltrombopag following the proposed change in PBS listing, DPMQ (Published Price) for eltrombopag and average patient co-payment. The cost offset to the PBS/RPBS was calculated based on the decreased number of patients being treated with romiplostim following the proposed change in PBS listing, DPMQ (Published Price) for romiplostim and average patient co-payment. The submission also claimed in the sensitivity analysis that the net savings are slightly higher when the effective price of each drug was used, with a total net save of less than \$10 million per year in 5 Years.

Quality use of medicines

- 4.11 The minor submission stated the proposed changes to continuing treatment will allow continuation of treatment with eltrombopag in patients whose disease is stable and responding to treatment with romiplostim which may assist in improving QUM by reducing unintentional adverse events from incorrect dosing of romiplostim in patients who find it difficult to self-administer their treatment by subcutaneous injection. The Secretariat overview noted that it was unclear how quality use of medicine would be achieved for patients who did not respond to eltrombopag but did respond to romiplostim during the initial treatment period, and then expressed a preference to revert to eltrombopag on the basis of patient preference/convenience. The Pre-PBAC Response stated it was not suggesting that patients who have previously failed treatment with eltrombopag prior to successful treatment with romiplostim revert to treatment with eltrombopag for reasons of patient preference, and strongly doubts that this would occur in clinical practice. The sponsor suggested the inclusion of more explicit switching criteria, such as “Patients may not be re-prescribed a TRA to which they have failed to experience a satisfactory response during initial treatment.” The PBAC expressed that it was intent of the Committee that there should not be retreatment with a drug that a patient had failed previously. The PBAC noted the suggested restriction addition by the sponsor, but considered that it was unclear how such criteria could be managed administratively.

For more detail on PBAC’s view, see Section 5 “PBAC outcome”

5 PBAC Outcome

- 5.1 The PBAC rejected the submission to amend the continuation restriction of eltrombopag for the treatment of severe chronic idiopathic thrombocytopenic purpura (iCTP) in adult patients to allow switching of treatment between eltrombopag and romiplostim beyond the initial 24 week treatment in patients whose disease is stable.

The PBAC considered that the clinical impact for patients who wish to switch treatment for reasons other than treatment failure is unclear and the cost-effectiveness in this patient group and financial risk to government are unknown.

- 5.2 The submission stated that a small group of patients who may be 'grandfathered' on romiplostim therapy, who are responding to treatment may benefit from the opportunity to change to treatment with eltrombopag due to the oral route of administration. If the switch to eltrombopag does not elicit an adequate response, a patient may not meet the current criteria to return to use romiplostim. The PBAC considered that the restriction should allow resumption of previously effective therapy.
- 5.3 The PBAC recalled its March 2011 meeting, where it recommended listing of eltrombopag on the basis of acceptable cost-effectiveness at a revised price (less effective and less expensive compared with romiplostim). The PBAC recommended switching between eltrombopag and romiplostim within a 24 week period to allow flexibility for prescribers and patients to establish the most suitable treatment for each individual within this period. In making its recommendation the PBAC noted that patients who fail treatment after this 24 week period, regardless of whether exposed to romiplostim, eltrombopag or both, will not be eligible for further PBS-subsidised therapy with either of the drugs, unless the PBAC is presented with evidence of effectiveness and cost effectiveness in this situation. The PBAC considered that if the proposed switching in this submission (for reasons other than treatment failure) is allowed beyond the initial 24 week period, it will be potentially difficult to manage administratively if patients are allowed to be treated with the drug that originally failed in initiation period.
- 5.4 The PBAC considered that further modifications would be required in the restrictions for eltrombopag than the proposed addition "or romiplostim" in the continuing criteria (and visa versa for the restriction of romiplostim) to allow patients to consider to switch treatments for reasons other than treatment failure.
- 5.5 The PBAC noted that the claim of unmet need for switching beyond the 24 week initial period was based on the retrospective observational studies GSK Study 113922 and Khellaf et al (2013) where one of the primary outcomes was patient preference as a reason for switching between TRA treatments. The PBAC considered that it was unclear whether the studies presented were relevant to the Australian setting where patients have a choice at initiation and an option to switch during the first 24 weeks of therapy. The PBAC also noted that neither study recorded why a person was on either romiplostim or eltrombopag prior to switching, and that switching for treatment failure (which is not currently allowed under PBS due to major uncertainty with respect to efficacy and cost-effectiveness) was common.
- 5.6 The PBAC noted that submission presented the efficacy outcomes in subgroups of 42-44 patients who switched therapy for preference. It was not possible to assess the safety and durability of response data for these patients in the Study 113922. The PBAC noted that the study by Khellaf (2013) stated eight (17%) romiplostim responders asked to switch to eltrombopag mainly because they considered oral intake easier for them. No difference in terms of efficacy was observed for any 8 patients after switching.

- 5.7 The PBAC noted that while no differences in efficacy domains were reported by patients in the observational studies, some changes in convenience and satisfaction were observed. The PBAC also noted the clinical study report stated ‘In this study, ITP patients treated with eltrombopag reported statistically higher scores on convenience, overall treatment satisfaction, energy and emotional well-being compared with patients receiving romiplostim; however, whether these differences are clinically meaningful is not known’.
- 5.8 The PBAC noted that the submission claimed that no difference was observed between eltrombopag and romiplostim in terms of clinical efficacy. The PBAC considered that this claim could not be verified in the relevant population of patients switching for preference, beyond 24 weeks.
- 5.9 The PBAC noted that there were no consumer comments for this submission. In any future application, the committee would value the opinion of patients and the Haematology Society of Australia & New Zealand about the value of switching treatments beyond 24 weeks of treatment and the extent of patient preference for switching.
- 5.10 The PBAC considered that allowing switching could grow the market, with stable patients who could safely cease an injectable medicine opting to swap to an oral medicine, rather than simply having a trial off therapy. The PBAC noted that patients with very severe ITP would likely never cease therapy, but a significant proportion of patients who benefit from TRA may only need episodic therapy. The PBAC noted that the current arrangements allow discontinuation and recommencement if a patient relapses off therapy.
- 5.11 The PBAC considered that the claim of cost savings would only be true if use of TRA overall does not increase. The PBAC noted that DUSC will review utilisation of eltrombopag and romiplostim when dispensing data for three years are available. The PBAC considered that the appropriate time to re-assess both the clinical need for patients to be able to switch as proposed in the submission and the associated financial risk to Government will be following the DUSC analysis. The PBAC considered a major submission would be required to assess the cost-effectiveness of the use of TRAs as proposed in this submission.
- 5.12 The PBAC noted that this submission is not eligible for an Independent Review because the requested change to PBS-listed drug was not for an additional indication.

Outcome:

Rejected

6 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

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PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

7 Sponsor's Comment

The sponsor is disappointed with the outcome and will consider its position regarding any future course of action.