

## **PUBLIC SUMMARY DOCUMENT**

**Product:** Eltrombopag, tablets, 25 mg and 50 mg, (as olamine), Revolade®

**Sponsor:** GlaxoSmithKline Australia Pty Ltd

**Date of PBAC Consideration:** March 2011

### **1. Purpose of Application**

To request a Section 100 (Highly Specialised Drug) Public and Private Hospital Authority Required listing for adult patients with severe chronic immune (idiopathic) thrombocytopenic 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**

At the November 2010 meeting, the PBAC rejected a submission for eltrombopag on the basis of uncertain clinical effectiveness in comparison with romiplostim.

The PBAC considered that the patient populations of the trials presented 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.

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, is uncertain.

A copy of the Public Summary Document from that meeting is available from:

<http://www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-eltrombopag-olamine-nov10>

### **Registration Status**

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

### **4. Listing Requested and PBAC's View**

#### Section 100 Public and Private Hospital Authority Required

Note: Eltrombopag is not PBS-subsidised as an alternative to splenectomy

Any queries concerning the arrangements to prescribe eltrombopag may be directed to Medicare Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m EST Monday to Friday).

Written applications for authority to prescribe eltrombopag should be forwarded to:

Medicare Australia

Prior Written Approval of Specialised Drugs

Reply Paid 9826

GPO Box 9826

HOBART TAS 7001

Further prescribing information is on the Medicare Australia website at [www.medicareaustralia.gov.au](http://www.medicareaustralia.gov.au)

Public and private hospital authority required

Initial (new patients)

Initial treatment, as the sole PBS-subsidised thrombopoietin receptor agonist (TRA), of severe thrombocytopenia in an adult patient with severe chronic immune (idiopathic) thrombocytopenic purpura (ITP) who is:

Splenectomised and:

- a. Has had an inadequate response to, or is intolerant to, corticosteroid therapy post splenectomy; and
- b. Has had an inadequate response to, or is intolerant to, immunoglobulin therapy post splenectomy;

OR

Not splenectomised and

- c. Has had an inadequate response to, or is intolerant to, corticosteroid therapy at a dose equivalent to 0.5-2 mg/kg/day of prednisolone for at least 4-6 weeks; and
- d. Has had an inadequate response to, or is intolerant to, immunoglobulin therapy; and
- e. In whom splenectomy is contraindicated for medical reasons.

The following criteria indicate failure to achieve an adequate response and must be demonstrated in all patients at the time of initial application

a platelet count of  $\leq 20 \times 10^9/L$ .

OR

a platelet count of  $20-30 \times 10^9/L$  where the patient is experiencing significant bleeding in this platelet range.

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

1. a completed authority prescription form,
2. a signed patient acknowledgement,
3. a completed Eltrombopag PBS Authority Application – Supporting Information form [may be downloaded from the Medicare Australia website ([www.medicareaustralia.gov.au](http://www.medicareaustralia.gov.au)) ],
4. a copy of a full blood count pathology report supporting the diagnosis of ITP, and
5. where the application is sought on the basis of a medical contraindication to surgery, a signed and dated letter from the clinician making this assessment which includes the date upon which the patient was assessed for surgery and the clinical grounds upon which surgery is contraindicated.

The full blood count must be no more than 1 month old at the time of application.

Public and private hospital authority required

Initial (grandfather patients)

Initial PBS-subsidised treatment, as the sole PBS-subsidised thrombopoietin receptor agonist (TRA), of severe thrombocytopenia in an adult patient with severe chronic immune (idiopathic) thrombocytopenic purpura (ITP) who was receiving treatment with eltrombopag prior to [listing date] and in whom the criteria for initial treatment can be demonstrated to have been met at the time eltrombopag was commenced:

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

1. a completed authority prescription form,
2. a signed patient acknowledgement,
3. a completed Eltrombopag PBS Authority Application – Supporting Information Form [may be downloaded from the Medicare Australia website ([www.medicareaustralia.gov.au](http://www.medicareaustralia.gov.au))],
4. where the application is sought on the basis of a medical contraindication to surgery, a signed and dated letter from the clinician making this assessment which includes the date upon which the patient was assessed for surgery and the clinical grounds upon which surgery is contraindicated.

For patients whose dose of eltrombopag has been stable for at least 4 weeks at the time of the initial application for PBS-subsidy, the medical practitioner should request a sufficient number of tablets of appropriate strength based on the patient's response to initial therapy to provide 4 weeks treatment. Up to a maximum of 5 repeats may be authorised.

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.

Authority approval will not be given for doses higher than 75 mg per day.

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 severe 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 TRA therapy,

AND either of the following

a platelet count  $\geq 50 \times 10^9/L$  on at least four (4) occasions, each at least one week apart;

OR

a platelet count  $> 30 \times 10^9/L$  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,
2. a completed Eltrombopag PBS Authority Application – Supporting Information form [may be downloaded from the Medicare Australia website ([www.medicareaustralia.gov.au](http://www.medicareaustralia.gov.au)) ],
3. copies of the platelet count pathology reports (unless previously provided for patients re-initiating therapy).

The most recent platelet count must be no more than 1 month old at the time of application.

The medical practitioner should request sufficient number of tablets of appropriate strength based on the patient's response to initial therapy to provide 4 weeks treatment. Up to a maximum of 5 repeats may be authorised.

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.

Authority approval will not be given for doses higher than 75 mg per day.

#### 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 severe 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.

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

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

AND either of the following

a platelet count  $\geq 50 \times 10^9/L$ ;

OR

a platelet count  $> 30 \times 10^9/L$  and which is double the baseline platelet count.

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

*For PBAC's view, see Recommendation and Reasons.*

## **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 previously accepted by the PBAC.

## **7. Clinical Trials**

No new clinical data were presented in this submission compared to the November 2010 submission. See November 2010 Public Summary Document (PSD) for details.

## **8. Summary of Submission**

The submission provided the following to address the PBAC's concerns from the November 2010 meeting:

- Clarification of the proposed indication for eltrombopag;
- Additional information regarding the most likely therapeutic relativity between eltrombopag and romiplostim;
- A new price for eltrombopag;
- Updated estimates of the financial impact to government of listing eltrombopag at the reduced price; and
- Details of a proposed company-supported ITP registry project.

### Cost offsets with Reductions in IVIg Use

The submission presented an indirect comparison of IVIg use based on reported rates in the ITT populations.

The submission stated that although the point estimates generally favour romiplostim, the confidence intervals are wide and do not exclude the possibility of 'no difference' between treatments. Factors which might bias the comparison of reductions in IVIg use in favour of romiplostim include differences in patient populations, the clinical setting and protocol restrictions on allowable rescue medications.

### Comparative Safety

The submission re-presented the same data from the original submission but stated that in the eltrombopag trial, unlike the romiplostim trial, bleeding events were assessed as efficacy outcomes and the definition of an adverse event specifically excluded 'the disease/disorder being studied or expected progression, signs or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.' Therefore, the extent of minor bleeding events captured in the eltrombopag trial are likely to be significantly reduced, which will bias the results of the indirect comparison in favour of romiplostim. The submission also claimed that rates of important non-bleeding events were similar among patients taking the two drugs. However, the PBAC noted that there are also lower rates of fatigue, arthralgia and contusion in the entire eltrombopag trial population.

### Equi-effective Doses of Eltrombopag and Romiplostim

The submission presented further analyses of the mean, median and range of doses by patient category (ie splenectomised and non-splenectomised patients who meet initiation and continuation criteria) from the RAISE study.

The submission did not present a revised estimate of the equi-effective doses. The November 2010 submission estimated the equi-effective doses as eltrombopag 55.2 mg/day and romiplostim 276.2 mcg/day.

The submission stated that the sponsor would support an independent international disease database for newly diagnosed adult patients with primary ITP and provided details of how this might be implemented.

#### **9. Estimated PBS Usage and Financial Implications**

The submission presented revised estimates of the net cost to the PBS and government health budgets, incorporating the revised price for eltrombopag, revised (lower) market share assumptions and an IVIg cost offset analysis.

The November 2010 submission estimated net PBS savings per year to be less than \$10 million in Year 5.

The submission stated that, as previously shown in the original submission, the revised financial analysis showed that listing eltrombopag on the PBS as an alternative to romiplostim is expected to result in significant cost savings to the PBS and government health budgets.

*For PBAC's view, see Recommendation and Reasons.*

#### **12. Recommendation and Reasons**

The PBAC recommended listing on the basis of acceptable cost effectiveness at the revised price (less effective and less expensive compared with romiplostim) for patients with chronic immune (idiopathic) thrombocytopenia purpura (ITP), restricted to the same population as romiplostim. The PBAC acknowledged that the data may suggest that eltrombopag is similar in safety and efficacy to romiplostim in the post-splenectomy population, but this is not the case in the non-splenectomised group.

With respect to the restriction, 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 will allow flexibility for prescribers and patients to establish the most suitable treatment for each individual within this period. 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 noted that use of IVIG may increase with the use of eltrombopag compared with romiplostim.

The PBAC recommended that eltrombopag is not suitable for inclusion in the PBS medicines for prescribing by nurse practitioners.

#### ***Recommendation:***

ELTROMBOPAG, tablets, 25 mg and 50 mg, (as olamine)

Restriction: Section 100 Public and Private Hospital Authority Required (Highly Specialised Drug)

Note:

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Written applications for authority to prescribe eltrombopag should be forwarded to:

Medicare Australia  
Prior Written Approval of Specialised Drugs  
Reply Paid 9826  
GPO Box 9826  
HOBART TAS 7001

Further prescribing information is on the Medicare Australia website at [www.medicareaustralia.gov.au](http://www.medicareaustralia.gov.au).

Authority Required

Initial (new patients)

Initial treatment, as the sole PBS-subsidised thrombopoietin receptor agonist (TRA), of severe thrombocytopenia in an adult patient with severe chronic immune (idiopathic) thrombocytopenic purpura (ITP) who is:

(1) Splenectomised and:

(a) has had an inadequate response to, or is intolerant to, corticosteroid therapy post splenectomy; and

(b) has had an inadequate response to, or is intolerant to, immunoglobulin therapy post splenectomy;

OR

(2) Not splenectomised and:

(a) has had an inadequate response, or is intolerant to, corticosteroid therapy at a dose equivalent to 0.5-2 mg/kg/day of prednisone for at least 4-6 weeks; and

(b) has had an inadequate response, or is intolerant to, immunoglobulin therapy; and

(c) in whom splenectomy is contraindicated for medical reasons.

The following criteria indicate failure to achieve an adequate response and must be demonstrated in all patients at the time of initial application:

(a) a platelet count of less than or equal to 20,000 million per L;

OR

(b) a platelet count of 20-30,000 million per L, where the patient is experiencing significant bleeding or has a history of significant bleeding in this platelet range.

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

(1) a completed authority prescription form,

(2) a signed patient acknowledgement,

(3) a completed Idiopathic Thrombocytopenic Purpura Initial PBS Authority Application - Supporting Information Form [may be downloaded from the Medicare Australia website ([www.medicareaustralia.gov.au](http://www.medicareaustralia.gov.au))],

(4) a copy of a full blood count pathology report supporting the diagnosis of ITP, and

(5) where the application is sought on the basis of a medical contraindication to surgery, a signed and dated letter from the clinician making this assessment which includes the date upon which the patient was assessed for surgery and the clinical grounds upon which surgery is contraindicated.

The full blood count must be no more than 1 month old at the time of application.

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

Note:

Patients will be able to trial either eltrombopag and/or romiplostim within the initial 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.

No applications for increased repeats will be authorised.

MQ: 28

Rpts: 5

Authority Required

Initial (grandfather patients)

Initial treatment, as the sole PBS-subsidised thrombopoietin receptor agonist (TRA), of severe thrombocytopenia in an adult patient with severe chronic immune (idiopathic) thrombocytopenic purpura (ITP) who was receiving treatment with eltrombopag prior to [listing date] and in whom the criteria for initial treatment can be demonstrated to have been met at the time eltrombopag was commenced.

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

- (1) a completed authority prescription form,
- (2) a signed patient acknowledgement,
- (3) a completed Idiopathic Thrombocytopenic Purpura Initial PBS Authority Application - Supporting Information Form [may be downloaded from the Medicare Australia website ([www.medicareaustralia.gov.au](http://www.medicareaustralia.gov.au))], and
- (4) where the application is sought on the basis of a medical contraindication to surgery, a signed and dated letter from the clinician making this assessment which includes the date upon which the patient was assessed for surgery and the clinical grounds upon which surgery is contraindicated.

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

Note:

No applications for increased repeats will be authorised.

MQ: 28

Rpts: 5

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 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](http://www.medicareaustralia.gov.au))], and
- (3) copies of the platelet count pathology reports (unless previously provided for patients re-initiating therapy).

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.

Note:

No applications for increased repeats will be authorised.

MQ: 28

Rpts: 5

#### 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 and who continues to display a response to treatment with eltrombopag.

For the purposes of this restriction, a continuing response to treatment with eltrombopag 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).

Note:

No applications for increased repeats will be authorised.

MQ: 28

Rpts: 5

### **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 is satisfied with the PBAC decision. This decision will allow for consideration of the future listing of Eltrombopag for use in adult patients with severe chronic ITP as an important alternative medicine.