Public Summary Document

Product: Eltrombopag tablets, 25 mg, 50 mg, 75 mg and 100 mg (as olamine), Revolade®
Sponsor: GlaxoSmithKline Australia Pty Ltd
Date of PBAC Consideration: July 2013

1. Purpose of Application

The submission sought listing of eltrombopag for adult patients with chronic hepatic C virus (HCV) infection for the treatment of thrombocytopenia:
1) to enable the initiation of interferon based therapy; and
2) to maintain interferon based therapy.

The submission was lodged under TGA/PBAC Parallel Process. At the time of PBAC consideration, the Clinical Evaluation Report and TGA Delegate's Overview were available.

The PBAC noted the sponsor's advice in its pre-PBAC response that due to the issues identified via the regulatory process, it was no longer requesting listing of the 100 mg tablet on the PBS.

2. Background

Eltrombopag had not previously been considered by the PBAC for the requested indication.

At the November 2010 meeting, the PBAC rejected a submission for eltrombopag 25 mg and 50 mg on the basis of uncertain clinical effectiveness in comparison with romiplostim for treatment of chronic immune (idiopathic) thrombocytopenia purpura (ITP).

In March 2011, the PBAC recommended listing eltrombopag 25 mg and 50 mg tablets on the basis of acceptable cost effectiveness at a revised price for patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) to the same population as romiplostim. Listing was effective on 1st of November 2011.

3. Registration Status

Eltrombopag was TGA registered on 16 July 2010for the treatment of adult patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who have had an inadequate response or are intolerant to corticosteroids and immunoglobulins.

Eltrombopag was TGA registered on 5 September 2013 for the extended indication:

- treatment of thrombocytopenia in patients with chronic hepatitis C to allow initiation and maintenance of interferon-based therapy.

4. Listing Requested and PBAC's View

Section 100 Highly Specialised Drugs Program
Private Hospital Authority required
Public Hospital Authority required

Initial treatment

For the treatment of thrombocytopenia prior to initiation of interferon-based therapy, in adult patients with documented chronic hepatitis C virus (HCV) infection (repeatedly anti-HCV positive and HCV RNA positive) who have a baseline platelet count <75,000/µL, and who are otherwise eligible candidates for interferon-based therapy.

Note:
A maximum of 8 weeks of therapy will be authorised under this criterion.
Patients who fail to demonstrate a response to eltrombopag under the initial restriction will not be eligible to receive further PBS subsidised treatment with eltrombopag.

Continuing treatment

For the continuing treatment of adult patients with chronic HCV infection during interferon-based therapy who have achieved a platelet response enabling initiation of full-dose interferon-based therapy during the initial treatment period.

For the purpose of this restriction, a platelet response enabling initiation of full-dose interferon-based therapy is defined as:

a) A platelet count greater than or equal to 90,000/µL for use with pegylated interferon alpha-2a
b) A platelet count greater than or equal to 100,000/µL for use with pegylated interferon alpha-2b

Note:
A maximum of 48 weeks of therapy will be authorised under this criterion. Authority approvals may be made by telephone by contacting Medicare Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday)

The submission requested listing on a cost-effectiveness basis versus no treatment, claiming that eltrombopag followed by eltrombopag plus antiviral therapy (AVT) is superior in terms of comparative effectiveness and inferior in terms of comparative safety to no treatment.

The PBAC considered that there was potential for eltrombopag to be used outside of the requested restriction in patients:

- who have failed to achieve platelets greater than 90,000/µL following enabling treatment as guidelines suggest AVT treatment should be initiated with platelets greater than 75,000/µL;
- who develop thrombocytopenia during treatment with AVT (a known side effect of AVT) where it may be used:
  - prophylactically to prevent thrombocytopenia; or
  - as a treatment for thrombocytopenia that has developed during AVT to prevent the need for a dose reduction in AVT.

5. Clinical Place for the Proposed Therapy

Eltrombopag is intended for use as a supportive therapy in patients with thrombocytopenia to increase platelet counts to a level which enables the initiation of an interferon based AVT in patients who are otherwise candidates for AVT; and continuation treatment to subsequently maintain platelet counts throughout AVT.

The PBAC noted the submission's claim that "eltrombopag plays a unique role in the treatment of chronic HCV infection, by enabling patients with platelet counts less than 75,000/µL who would otherwise be excluded from accessing combination pegylated interferon (peginterferon) alpha and ribavirin, to access this treatment following a successful course of eltrombopag." However, the PBAC noted that AVT is currently initiated in patients with thrombocytopenia, and that the thresholds for introducing treatment in clinical practice are somewhat arbitrary.

The PBAC noted the submission's claim that eltrombopag assists those patients receiving AVT to receive the recommended dose and optimise outcomes. The PBAC accepted that trial data from ENABLE and other HCV trials show that thrombocytopenia can be dose limiting; that eltrombopag does increase platelet counts in HCV patients on AVT and that early viral response (EVR) and sustained viral response (SVR) are higher if AVT dosing is maintained.

The PBAC noted that thrombocytopenia is relatively common in HCV patients with cirrhosis and that this was a patient group with a high need for AVT.

The PBAC accepted that there would be patients in whom eltrombopag will enable effective AVT that otherwise could not be delivered safely. However the PBAC considered that this group of patients needed to be more clearly defined, to allow the determination of incremental benefit and incremental cost.

6. Comparator

The submission nominated standard medical management (i.e. no treatment) as the main comparator.

The PBAC considered that no treatment was the appropriate comparator during initial 'enabling' treatment, but was not the likely comparator for patients receiving maintenance treatment.

The PBAC considered that given eltrombopag is intended as an enabling therapy to be used before initiation with AVT and as a maintaining therapy during AVT (under the proposed restriction), the appropriate comparator is best defined as a treatment algorithm, inclusive of enabling and maintaining phases:

- The nomination of placebo for no treatment is appropriate during enabling treatment based on the rationale that there are currently no supportive therapies available to increase platelet levels.
- For maintaining treatment, when eltrombopag is considered as part of a treatment regimen with AVT, placebo for no treatment is not the only comparator. Whilst there are some patients with very severe thrombocytopenia who would never be considered for treatment with AVT, some patients may still be treated as clinicians and patients recognise that it is important to treat HCV, and that the risk/benefit balance around thrombocytopenia is not "black and white". Expert advice sought during the evaluation suggested that in practice, patients with platelets as low as 50,000/µL may still be treated with AVT, and the Australian Therapeutic Guidelines state "despite product information, it is common to allow platelets to

drop to 30,000/µL, providing the patient is asymptomatic, has no other risk factors for bleeding and is carefully monitored before dose reducing pegylated interferon-alfa".

The PBAC agreed that given prescribers may allow platelets to fall to 30,000/µL before reducing the dose of interferon therapy, it is not inconceivable that prescribers could initiate interferon therapy at levels lower than 75,000/µL. The PBAC also considered that given (i) the importance of achieving an SVR, (ii) the lack of alternative treatments and (iii) the small window of opportunity for treatment of patients with advanced disease before it progresses to decompensating disease, that clinicians would opt to treat (either at full or reduced doses) despite thrombocytopenia.

The PBAC therefore considered that the appropriate comparator should be a mix of no treatment and AVT with Australian dose-modification, unless use is restricted to patients with a platelet count of less than 30,000/µL.

Prior to consideration of the evidence presented in the submission, the PBAC considered the appropriateness of considering an application for a drug that delivers no direct benefits, but rather relies on indirect benefits from the treatment it enables, within the usual PBAC framework. The PBAC considered that the certainty of health benefits, and not whether they are accrued directly or indirectly, was the primary issue.

The Committee concluded that it was appropriate to consider the submission for eltrombopag within the usual PBAC framework and that it was important to accurately determine what the actual benefits of treatment are, and to ensure the costs and benefits of all treatments are captured.

7. Clinical Trials

The submission was based on two randomised trials comparing eltrombopag to placebo: ENABLE 1 and ENABLE 2, in adult patients with chronic HCV associated thrombocytopenia.

The ENABLE trials were Phase III, randomised, placebo-controlled studies that evaluated the efficacy and safety of eltrombopag to raise and maintain platelet counts in patients with chronic hepatitis C and low platelet counts. The trial included an open-label, pre-antiviral treatment phase in which all patients received eltrombopag. Upon achievement of specified platelet thresholds, patients were randomised to treatment with eltrombopag or placebo, both in combination with AVT. Thus, no evidence was presented in the submission to inform the comparative efficacy and safety of eltrombopag versus placebo in the initial treatment phase. However, expert advice suggests that spontaneous resolution of thrombocytopenia is not likely. Following open-label eltrombopag, patients who achieved the required platelet levels were randomised to eltrombopag + AVT or placebo + AVT maintenance treatments.

The table below details the published trials presented in the submission:

Trial ID/ First author	Protocol title/ Publication title	Publication citation
ENABLE 1 (TPL103922)	Clinical Study Report: Randomised, placebo-	09-March-2012

	controlled, multicentre study to assess the efficacy and safety of eltrombopag in thrombocytopenic subjects with hepatitis C virus (HCV) who are otherwise eligible to initiate antiviral therapy (peginterferon alpha-2a plus ribavirin) Afdhal et al. (2011) Final results of ENABLE 1, a phase 3, multicentre study of eltrombopag as adjunct for antiviral therapy of hepatitis C virus-related chronic liver disease associated with thrombocytopenia	*Hepatology*, 2011: 54;SUPPL. 1 (1427A-1428A)
ENABLE 2 (TPL108390)	Clinical Study Report: Randomised, placebo-controlled, multicentre study to assess the efficacy and safety of eltrombopag in thrombocytopenic subjects with hepatitis C virus (HCV) who are otherwise eligible to initiate antiviral therapy (peginterferon alpha-2b plus ribavirin) Dusheiko et al. (2012) Final results of ENABLE 2, a phase 3, multicentre study of eltrombopag and peginterferon alpha-2b treatment in patients with hepatitis C and thrombocytopenia.	09-April-2012 *Hepatology*, 2012: 56;SUPPL. 2(S27)
TPL102357	Clinical Study Report: A double-blind, randomised, placebo-controlled, multi-centre, dose-ranging, parallel group, phase II study to assess efficacy, safety/tolerability, and pharmacokinetics of a thrombopoietin receptor agonist, SB-497115-GR (eltrombopag), when administered as 30, 50, and 75 mg once daily for 16 weeks in subjects with chronic hepatitis C-related thrombocytopenia who are potential candidates for antiviral treatment with pegylated interferon and ribavirin. McHutchison et al. (2007) Eltrombopag for thrombocytopenia in patients with cirrhosis associated with hepatitis C	31-October-2007 NEJM, 2007: 357; 22 (2227-2236)

Thus, the submission did not provide any clinical trial evidence to inform the comparative efficacy and safety of the proposed treatment algorithm (eltrombopag enabling therapy followed by eltrombopag + AVT) versus 1) the treatment algorithm nominated as the comparator (placebo for no treatment), or 2) another likely treatment algorithm of no treatment followed by full or reduced dosing of AVT.

The PBAC agreed that the treatment population from the ENABLE trials were not completely generalisable to the PBAC population given the exclusion criteria (non-responders to prior interferon-based therapy for reasons other than thrombocytopenia), and bias in favour of therapy.

8. Results of Trials

The PBAC noted that eltrombopag has no intrinsic antiviral activity; rather it acts to stimulate platelet production to enable initiation and maintenance of full-dose AVT.

The table below presents the results for the proportion of patients patients achieving the platelet thresholds required to initiate AVT in the open-label, 'enabling' phase of the ENABLE studies. The PBAC noted the results of the open label phase demonstrate that eltrombopag increases platelet counts into the range for initiation of peginterferon suggested in the relevant Product Information documents for more than 95% of patients.

Response to eltrombopag (open label phase, safety population), n/N (%)

	ENABLE 1	ENABLE 2	Pooled
Achieved platelet threshold[a]	691/715 (96.64%)	773/805 (96.02%)	1464/1520 (96.32%)
Initiated antiviral therapy	680/715 (95.10%)	759/805 (94.29%)	1439/1520 (94.67%)

[a] 90,000/μL - ENABLE 1 (peginterferon α-2a); 100,000/μL - ENABLE 2 (peginterferon α-2b)

The table below presents the results for the proportions of patients achieving EVR and SVR in the ENABLE trials. The PBAC noted the results demonstrate that a statistically significantly greater proportion of patients randomised to continue eltrombopag treatment + AVT achieved SVR compared to those treated with placebo + AVT.

Summary of the results for EVR and SVR in the ENABLE trials

	Placebo n/N (%)	Eltrombopag n/N (%)
Achieved EVR		
ENABLE 1	115/232 (49.57%)	297/450 (66.00%)
ENABLE 2	103/253 (40.71%)	313/506 (61.86%)
Pooled		
Achieved SVR		
ENABLE 1	33/232 (14.22%)	104/450 (23.11%)
ENABLE 2	32/253 (12.65%)	97/506 (19.17%)
Pooled		

Abbreviations: RD=risk difference; NNT=number needed to treat (calculated as 1/RD); RR=relative risk; CI=confidence interval.

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The PBAC considered that the protocol-mandated adjustments to AVT based on platelet count levels nominated in the product information for each peginterferon confound full understanding of the incremental benefit attributable to eltrombopag per se. For example, the protocols required permanent cessation of AVT after one week of significant thrombocytopenia (defined variably across protocols according to whether the patient was treated in the USA or elsewhere and which peginterferon alpha type was used) while off AVT. This caveat is particularly relevant in the Australian context where AVT is commenced at lower platelet counts than in the trials, and doses may only be adjusted if platelets are less than 30,000/μ/L. The net effect of the protocol-mandated adjustments to AVT therapy and cessation at levels of platelet counts above that applied in some Australian practice, it is likely to be an over-estimation of the incremental benefit.

The PBAC noted that the results summarised above were not used in the economic model. Key transition probabilities in the eltrombopag arm of the modelled economic evaluation were derived from post-hoc analyses of the ENABLE trials. These included proportions of patients achieving:

1) a platelet response during enabling treatment;
2) early viral response; and
3) subsequently achieving sustained viral response.

The response rates of patients in the no treatment arm of the model were informed by data from the literature.

With regard to comparative harms, during the open label phase, the most commonly reported adverse events (pooled across ENABLE 1 and ENABLE 2) were headache, fatigue, nausea , diarrhoea and insomnia.

During the double blind maintaining phase of the ENABLE trials, the most common events reported in the pooled AVT + placebo, and AVT + eltrombopag arms included anaemia, neutropenia , fatigue, pyrexia, headache, influenza-like illness, nausea, asthenia and thrombocytopenia . The submission noted that these events are most commonly associated with AVT. Given the nominated comparator was no treatment (in the maintenance phase), the PBAC considered the safety comparison between AVT + placebo and AVT + eltrombopag was not informative as the effects of AVT would have cancelled out.

Fatal adverse events were reported by participants randomised to eltrombopag and participants randomised to the placebo arm within 30 days post AVT. The most common causes of death were consistent with cirrhotic HCV: hepatic failure, variceal bleeding, ascites, GI bleeding and infections.

From the ENABLE trials, the submission identified ‘any thromboembolic events’ and ‘cataracts’ as the main adverse events expected to have an impact on cost. These adverse events were identified as they showed a difference of at least 2% between groups in the ENABLE trials (favouring placebo). The identification of adverse events for the modelled evaluation is not appropriate given all reported adverse events for both AVT and eltrombopag are likely to be higher than no treatment (the nominated comparator).

The PBAC noted that the ELEVATE study, a randomised, double-blind, placebo-controlled, multinational study to evaluate the safety and efficacy of eltrombopag to reduce the need for platelet transfusion in thrombocytopenic subjects with chronic liver disease undergoing

elective invasive procedures, was terminated, following the identification of an imbalance of thrombosis of the portal venous system in the patients treated with eltrombopag versus matching placebo. Six patients (4%) in the eltrombopag group and one (1%) in the placebo group experienced a thrombotic event of the portal venous system. Five of the six patients treated with eltrombopag experienced the portal venous thrombosis at platelet counts above 200,000/μL. The PBAC noted that this information had been available on the US FDA's website since 12 May 2010.

9. Clinical Claim

The submission described eltrombopag followed by eltrombopag + AVT as superior in terms of comparative effectiveness and inferior in terms of comparative safety over no treatment. The PBAC noted that this comparison was not presented in the submission.

Based on the results of the ENABLE trials which provided comparative evidence of eltrombopag + AVT versus placebo + AVT and demonstrated that a statistically significantly greater proportion of patients achieved an SVR, the PBAC considered the submission's claim was reasonable on the basis that eltrombopag + AVT is superior to AVT which is superior to no treatment in terms of effectiveness and eltrombopag + AVT is inferior to AVT which is inferior to no treatment in terms safety.

However, because of the caveat arising from protocol-mandated reductions and cessation of AVT based on platelet count thresholds nominated in peginterferon product information, the PBAC considered that the magnitude of benefit in effectiveness in Australian practice was likely to be lower than that observed in the clinical trials.

10. Economic Analysis

The submission presented a modelled economic evaluation cost-utility analysis (CUA) based on the claim of superior efficacy and inferior safety.

The modelled economic evaluation was separated into two parts:

- A short-term decision tree (enabling and maintaining phases); and
- A long-term Markov model

The decision tree was the short-term (1.5 years) model after which patients were deemed to have achieved SVR or not and were entered into the long-term Markov model. Patients entered the model at 52 years of age. Patients were stratified by baseline liver disease and post-AVT liver disease based on evidence that SVR rates may be different in these groups and progression through the Markov model was determined by baseline liver disease. The time horizon of the model was 30 years

The incremental cost/QALY gained was in the range of $45,000 - $75,000.

The base case results did not reflect the recent change in treatment of patients with genotype 1 HCV on the PBS, namely the availability of the protease inhibitors boceprevir and telaprevir for use in combination with AVT. The results of a scenario analysis giving the adjusted ICERs for patients with genotype 1 HCV both with and without protease inhibitors were presented in the submission. The PBAC considered this analysis particularly relevant as

going forward, use of protease inhibitors will be the new standard of care for these patients. However, the PBAC agreed that the results were uncertain as the analysis assumes that all patients in the model have genotype 1 HCV, rather than applying the adjusted treatment effect to only the proportion of patients with genotype 1 HCV in the ENABLE trials.

The PBAC noted that other univariate sensitivity analyses presented in the submission showed the ICER not to vary greatly with the assumptions. However, no multivariate analyses combining the effect of uncertainty from all these parameters were conducted. The PBAC considered that there was considerable potential for uncertainty with the model. Further, the PBAC noted that the model did not incorporate wastage into the costs of eltrombopag. The PBAC considered there was significant potential for wastage, which would impact on both the cost-effectiveness and financial estimates. The cost of drug assumed a full course of treatment (enabling 3.7 weeks and maintenance 48 weeks) at the average dose in the trial exactly matched to the proposed packs and strengths of eltrombopag. The average dose and variation in doses in the PBS population may be different to the trials as patients may require different packs and strengths, requiring dose modification over time and may discontinue treatment.

The PBAC agreed that there were a range of issues with the model which may have a moderate effect on the reported cost-effectiveness, favouring eltrombopag, including:

- A comparison of transition probabilities and utilities applied for a range of hepatitis C cost-effectiveness models indicated that the transition probabilities used in the eltrombopag model were higher than those used in other models, providing greater scope for benefit from treatment;
- The small, but potentially real increased short-term mortality effect of eltrombopag is not represented;
- Costs of eltrombopag are based on the average dose in the clinical trial and are exactly matched to proposed packs and strengths of eltrombopag for a full course of treatment (3.7 weeks + 48 weeks). This assumption does not include any allowance for wastage: for example if there are frequent dose changes, if there is a large variability in dose requirements in the PBS population or if patients stop and start treatment.

Overall, the PBAC considered the base case ICER of between $45,000 – $75,000 to be a likely underestimate and uncertain.

The PBAC considered that it was difficult to determine what the appropriate ICER range for the type of health benefit associated with eltrombopag should be, given there is no immediate benefit, benefits are gained over a long time horizon, utility gains are extrapolated (and so are associated with greater uncertainty), and the need to consider opportunity costs of immediate versus deferred benefits.

11. Estimated PBS Usage and Financial Implications

The submission estimated a net cost per year to the PBS /RPBS of less than $10 million in Year 5.

The PBAC agreed that there is a potential for the number of eligible patients to be greater than the estimate in the submission:

- Uncertainties in the assumptions used, particularly the proportion of thrombocytopenic patients considered awaiting new treatment, which appears to be an underestimate given eltrombopag would enable future AVT;
- If eltrombopag is used in those who have failed previous eltrombopag enabling treatment but remain eligible for AVT;
- If eltrombopag is intended for use in patients who fail their first course of AVT but remain eligible for a second course of AVT.

The PBAC also considered that the submission's estimate of cost to Government was likely to be an underestimate. In addition to the concern regarding eligible patient numbers, the PBAC noted that the submission only considered additional costs from toxicity for eltrombopag + AVT over AVT alone, and did not consider the costs of treating toxicity from AVT versus no AVT.

12. Recommendation and Reasons

The PBAC rejected the submission to extend the PBS-listing of eltrombopag due to an unreliable ICER, which was inadequately supported by the clinical evidence provided in the submission. The PBAC considered there was uncertainty associated with the clinical place of eltrombopag, an inappropriate comparator, uncertainty about the magnitude of the incremental benefit from use of eltrombopag, and, problems associated with the economic evaluation.

With regard to the clinical place of eltrombopag, the PBAC accepted that there was a patient population in whom eltrombopag will enable effective AVT that could not otherwise be delivered safely. The Committee noted that the platelet level thresholds for introducing AVT vary and are somewhat arbitrary in Australian clinical practice. Given this AVT is currently being initiated in patients with thrombocytopenia.

The PBAC also noted that the clinical management of HCV is rapidly evolving, and the future place of interferon-based therapies in the treatment algorithm of HCV is not known.

The PBAC considered that the patient population in whom eltrombopag treatment is clinically indicated needs to be more clearly defined so that the clinical and cost-effectiveness of treatment in this population can be determined.

The PBAC did not accept 'no treatment' as the appropriate comparator. Rather, the Committee considered the appropriate comparator for the requested population to be a mix of no treatment and AVT with Australian dose modification.

The PBAC considered there were significant issues with the economic evaluation, and that the resultant base case ICER was both uncertain and a likely underestimate.

The PBAC considered the submission's estimates of usage and cost to Government were also uncertain and likely to be underestimated.

The PBAC advised that any future resubmission for eltrombopag for this indication would need to be a major submission.

Outcome
Rejected

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

GlaxoSmithKline is committed to working closely with the PBAC to address the Committee's outstanding issues of interest to ensure that eltrombopag is made available on the PBS for patients with HCV-associated thrombocytopenia at the earliest opportunity.