

eltrombopag, 25mg, 50mg, 75mg film-coated tablets (Revolade®) SMC No. (919/13)

GlaxoSmithKline

08 November 2013

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

ADVICE: following a full submission

eltrombopag (Revolade®) is accepted for use within NHS Scotland.

Indication under review: In adult patients with chronic hepatitis C virus infection, for the treatment of thrombocytopenia, where the degree of thrombocytopenia is the main factor preventing the initiation or limiting the ability to maintain optimal interferon-based therapy.

Two double-blind, randomised, controlled studies in patients with chronic hepatitis C virus infection and thrombocytopenia demonstrated significantly higher sustained viral response rates in patients who continued treatment with eltrombopag during interferon-based antiviral therapy than in those patients whose eltrombopag treatment was discontinued on initiation of antiviral therapy.

This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of eltrombopag. This SMC advice is contingent upon the continuing availability of the Patient Access Scheme in NHS Scotland or a list price that is equivalent or lower.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

In adult patients with chronic hepatitis C virus infection, for the treatment of thrombocytopenia, where the degree of thrombocytopenia is the main factor preventing the initiation or limiting the ability to maintain optimal interferon-based therapy.¹

Dosing Information

Eltrombopag dosing requirements must be individualised based on the patient's platelet counts. The objective of treatment with eltrombopag should not be to normalise platelet counts but to achieve the minimum level of platelet counts needed to initiate antiviral therapy, in adherence to clinical practice recommendations. During antiviral therapy, the aim of treatment should be to keep platelet counts at a level which prevents the risk of bleeding complications, normally around 50 to 75 x 10⁹/L. Platelet counts above 75 x 10⁹/L should be avoided. The lowest dose of eltrombopag needed to achieve the targets should be used. Dose adjustments are based upon the platelet count response. In most patients, measurable elevations in platelet counts take one to two weeks.

Eltrombopag should be initiated at a dose of 25mg once daily and the dose should be adjusted in 25mg increments every two weeks as necessary to achieve the target platelet count required to initiate antiviral therapy and up to a maximum of 100mg once daily. Platelet counts should be monitored every week prior to starting antiviral therapy. On initiation of antiviral therapy the platelet count may fall, so immediate eltrombopag dose adjustments should be avoided. During antiviral therapy, the dose of eltrombopag should be adjusted as necessary (platelet levels around 50 to 75 x 10⁹/L) to avoid dose reductions of peginterferon due to decreasing platelet counts that may put patients at risk of bleeding.

Eltrombopag should be discontinued if the required platelet level to initiate antiviral therapy is not achieved after two weeks of treatment at a dose of 100mg daily. Treatment should also be terminated when antiviral therapy is discontinued unless otherwise justified. Excessive platelet count responses or important liver test abnormalities also necessitate discontinuation.

Eltrombopag treatment should be initiated and remain under the supervision of a physician who is experienced in the management of chronic hepatitis C and its complications.¹

Product availability date

24 September 2013

Summary of evidence on comparative efficacy

Hepatitis C is a viral disease of the liver. Anti-viral therapy is the mainstay of treatment for this disease. A minimum platelet count is recommended for the initiation and maintenance of anti-viral therapy therefore when thrombocytopenia occurs it can present a significant difficulty in treating patients effectively. Eltrombopag is an orally administered, non-peptide thrombopoietin receptor agonist which activates megakaryocyte proliferation and differentiation in bone marrow progenitor cells resulting in increased platelet counts. Eltrombopag has previously been accepted for chronic immune (idiopathic) thrombocytopenic purpura. This submission is for an

extension to the marketing authorisation to include adults with chronic hepatitis C virus infection, for the treatment of thrombocytopenia, where the degree of thrombocytopenia is the main factor preventing the initiation or limiting the ability to maintain optimal interferon-based therapy.

The evidence for use in this indication is from a pooled analysis of two similar phase III double-blind randomised controlled studies (ENABLE 1 and 2) investigating the efficacy and safety of eltrombopag in adults with chronic hepatitis C virus (HCV) infection and thrombocytopenia.^{1,2,3} The studies comprised an initial phase in which all patients received open label eltrombopag to boost platelets to target levels ($\geq 90 \times 10^9/L$ for ENABLE 1 and $\geq 100 \times 10^9/L$ for ENABLE 2). Patients who achieved the target platelet count entered the double-blind, placebo-controlled, randomised phase and received antiviral treatment with peginterferon alfa-2a 180 micrograms once weekly plus ribavirin 800mg to 1,200mg/day (ENABLE 1), or peginterferon alfa-2b 1.5 microgram/kg once weekly plus ribavirin 800mg to 1,400mg/day (ENABLE 2) for 24 weeks (HCV genotype 2 or 3) or 48 weeks (HCV genotype 1, 4 or 6).¹ Patients were included if they were appropriate candidates for peginterferon and ribavirin antiviral therapy, had platelet counts $< 75 \times 10^9/L$, haemoglobin $> 11.0g/dL$ (men) or $> 10.0g/dL$ (women), absolute neutrophil count $> 750/mm^3$ and no history of infections associated with neutropenia, and creatinine clearance $> 50mL/minute$.

In the initial phase, all patients received once daily oral eltrombopag 25mg for two weeks, increased, if the target platelet count was not achieved, to 50mg daily for up to two weeks, then to 75mg daily for up to two weeks and to 100mg daily for up to three weeks. All patients who achieved target platelet counts entered the randomised, double-blind phase and were assigned, in a 2:1 ratio, to continue treatment with eltrombopag (at the open label phase effective dose) or to receive placebo (withdrawal of eltrombopag) for 24 or 48 weeks according to the duration of antiviral treatment. Randomisation was stratified by platelet count ($< 50 \times 10^9/L$ and ≥ 50 to $< 75 \times 10^9/L$), screening HCV RNA ($< 800,000$ IU/mL and $\geq 800,000$ IU/mL), and HCV genotype (genotype 2/3, and genotype 1/4/6).^{1,2,3}

The primary efficacy endpoint was sustained viral response (SVR) defined as the percentage of patients with no detectable HCV RNA at 24 weeks after completion of the planned treatment period in the intention to treat population which included all randomised patients.¹ In the individual ENABLE studies and in the pooled analysis, significantly higher proportions of patients in the eltrombopag group achieved an SVR compared with the placebo group.¹

Table 1 Sustained viral response in ENABLE 1 and ENABLE 2 (references 1,4)

	Pooled Data		ENABLE 1		ENABLE 2	
Number of patients who achieved target platelet counts	95% (1439/1520)		95% (680/715)		94% (759/805)	
	Eltrombopag	Placebo	Eltrombopag	Placebo	Eltrombopag	Placebo
Number of patients entering Antiviral Treatment Phase (ITT population)	956	485	450	232	506	253
Overall SVR (ITT) *	21%	13%	23%	14%	19%	13%
Genotype 2 or 3	35%	25%	35%	24%	34%	25%
Genotype 1, 4 or 6	15%	8%	18%	10%	13%	7%

SVR=sustained viral response; ITT=intention to treat *p<0.05

Treatment benefit was observed for all pre-specified subgroups: baseline (for open label phase) platelet counts $<50 \times 10^9/L$ versus $>50 \times 10^9/L$, viral load ($<800,000$ IU/mL versus $\geq 800,000$ IU/mL) and genotype (2 or 3 versus 1 or 4 or 6).¹

Significantly fewer patients receiving eltrombopag than placebo discontinued antiviral therapy early (45% versus 60%). A greater proportion of patients in the eltrombopag group compared with placebo did not require antiviral dose reduction (45% versus 27%). Treatment with eltrombopag delayed and reduced the number of peginterferon dose reductions.¹

Other data were also assessed but remain commercially confidential.*

Summary of evidence on comparative safety

During the double-blind, randomised phase of the pivotal studies, patients in the eltrombopag group received higher doses of peginterferon and remained on study drug for longer than those in the placebo group. The safety profile mainly reflected the toxicity of peginterferon and ribavirin. During the double-blind phase, serious adverse events were reported in 20% (189/955) of eltrombopag patients and in 15% (72/484) of placebo patients. Treatment-related adverse events were reported in 91% (873/955) of eltrombopag patients and in 91% (442/484) of placebo patients.⁷ Thromboembolic events were reported in 4.0% (38/955) of eltrombopag patients and in 1.2% (6/484) of placebo patients and portal vein thrombosis was the most common of these events in both treatment groups.¹

During the double-blind phase the most frequent serious adverse event in both treatment groups was malignant hepatic neoplasm: 4.2% (40/955) versus 3.1% (15/484) in the eltrombopag versus placebo groups. Fatal adverse events occurred in 3.0% (29/955) of eltrombopag patients versus 2.0% (10/484) of placebo patients.⁷

The SPC for eltrombopag notes an increased risk for adverse events, including potentially fatal hepatic decompensation and thromboembolic events in thrombocytopenic HCV patients with advanced chronic liver disease, during treatment with eltrombopag in combination with interferon-based therapy.¹

Summary of clinical effectiveness issues

The causes of thrombocytopenia in patients with chronic HCV infection are thought to be multifactorial. It appears to be more prevalent in patients with cirrhosis and is a known adverse effect of antiviral treatment with peginterferon and ribavirin.⁸ Eltrombopag is the first medicine to be licensed for this indication. The relevant comparator is current standard of care where patients with a low platelet count receive no antiviral treatment or receive reduced doses. The platelet count threshold for withholding antiviral treatment may vary among clinicians. The recommended threshold for initiation of peginterferon alfa is 90 to 100 x 10⁹/L, however clinical experts consulted by SMC have advised that they may use a threshold of 50 x 10⁹/L or lower.

The pivotal studies evaluated the effect of concurrent treatment with eltrombopag and antiviral drugs in patients with adequate platelet counts at treatment initiation. A total of 5.2% (79/1,520) of patients who received open-label eltrombopag did not achieve study target platelet counts (above 90-100 x 10⁹/L) and did not enter the randomisation phase. The study population mainly consisted of patients with compensated cirrhotic HCV, and most (64%) were genotype 1. Almost one third of patients had been treated with prior HCV therapies, mainly peginterferon plus ribavirin. The proportions of patients with platelet counts <20, <50 and ≥50 x 10⁹/L on entering the open label phase were 0.8 %, 28 % and 72 %, respectively. Data from the pivotal studies demonstrated significantly higher SVR rates in patients who continued treatment with eltrombopag during interferon-based antiviral therapy than in those whose eltrombopag treatment was discontinued on reaching study target platelet levels.¹ SVR is a surrogate, but clinically relevant, outcome although it is indirectly related to eltrombopag. SVR is generally associated with resolution of liver disease in patients without cirrhosis; however, in the cirrhotic population under review, patients remain at risk of life-threatening complications, especially hepatocellular carcinoma, which may occur even after the eradication of viral infection.⁹

The main limitation of the data from the ENABLE studies is that the comparator arms do not reflect clinical practice as these patients received eltrombopag prior to initiating antiviral treatment. In pooled analysis, the proportion of patients that achieved SVR in the comparator groups was 13%. In clinical practice it would be expected that these patients would either not be treated at all with antiviral drugs or would receive reduced doses leading to a lower SVR rate.

The pivotal studies, which have been published in abstract form only, have other limitations. The method of dose adjustment of eltrombopag/matched placebo may have led to investigators being unblinded to randomised treatments. Furthermore there are differences between the use of eltrombopag in the ENABLE studies and its proposed licensed use with respect to target platelet levels. Clinical experts consulted by SMC have indicated that, in practice, eltrombopag is likely to be used to maintain platelet target ranges much lower than in the pivotal studies: 50-75 x 10⁹/L rather than 90-200 x 10⁹/L.¹ The SPC states that platelet counts above 75 x 10⁹/L should be avoided. Clinical experts have also advised that eltrombopag may not be prescribed for the full duration of antiviral therapy. Finally, the antiviral treatment regimen for genotype 1

patients in the pivotal studies does not reflect current recommendations to consider triple therapy including a protease inhibitor, (boceprevir or telaprevir).¹¹ Therefore, the safety and efficacy of eltrombopag has not been established when used with current antiviral treatment strategies for genotype 1 HCV.¹

The use of eltrombopag in the population under review is associated with increased toxicity, including potentially fatal hepatic decompensation and thromboembolic events (portal vein thrombosis is a known risk). Treatment benefits are considered to be modest but current practice is that these patients would either receive no, or suboptimal antiviral therapy. Eltrombopag can provide an option enabling a small number of hepatitis C patients with thrombocytopenia to receive anti-viral therapy who would otherwise not have been able. Eltrombopag should only be prescribed by physicians experienced in the management of advanced chronic HCV, and only when the risks of thrombocytopenia or withholding antiviral therapy necessitate intervention.¹

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis comparing eltrombopag plus antiviral therapy to standard of care (SoC) (suboptimal or no antiviral therapy) for the treatment of patients with thrombocytopenia and chronic HCV. Antiviral therapy consisted of peginterferon in combination with ribavirin. The economic model was based on a lifetime time horizon, and was built from an NHS perspective.

Patients with chronic HCV require a suitably high platelet level in order to receive antiviral therapy. Eltrombopag does not treat HCV directly, but facilitates the administration of antiviral therapy by raising patients' platelet counts. Within the economic evaluation, the comparator of SoC is deemed to be appropriate since there is no currently licensed or unlicensed medication used in current clinical practice to treat thrombocytopenia in chronic HCV. The model included both a short term and long term component. The short term model comprised two subsections, the enabling phase and the maintenance phase. In the enabling phase, patients were modelled to receive eltrombopag or SoC with the intention of increasing platelet count to a level suitable for starting antiviral therapy. In the maintenance phase, having raised platelet levels, the aim was to maintain the platelet levels during antiviral therapy for a period up to 48 weeks, with SVR assessed 24 weeks after cessation of antiviral therapy. In the long term model, the longer term consequences of chronic HCV were taken into account.

Many of the data estimates used in the economic model were derived from the pooled results of the pivotal studies. The results for the eltrombopag treatment arm were used to model eltrombopag treatment in the economic model. However, for the comparator arm, the company chose to adjust the data from the pooled pivotal studies before including it in the economic model. This was because patients received eltrombopag prior to antiviral therapy. Therefore, SoC patients were more likely to achieve SVR than in usual practice. To calculate this adjustment, the submitting company combined the data from the pivotal studies with data from the literature to try to reflect more accurately the SoC outcomes in current clinical practice.

Quality of life data according to disease severity were drawn from the data collected during the pivotal studies. Quality of life was measured at five specific points from baseline up until the final 24-week post treatment point. The SF-36 questionnaire was used, with the results mapped

to the preference based measure the SF-6 Dimensions (SF-6D). Long-term quality of life values were taken from the literature.

Resource use included the cost of eltrombopag, the costs of antiviral treatment (intermittent where appropriate), and the costs associated with the longer term health states; for example, stages of fibrosis moving towards decompensated cirrhosis, ascites, liver cancer, liver transplantation, and death.

A Patient Access Scheme (PAS) has been submitted by the company and assessed by the Patient Access Scheme Assessment Group as acceptable for implementation in NHS Scotland. The submitted PAS offers a discount on the list price of the medicine. The result with the PAS was a cost per QALY of £22,760 based on an added lifetime cost of £11,320 and a QALY gain of 0.50.

There are a number of uncertainties surrounding the analysis.

- The company chose to adapt the data from the placebo-controlled arms of the pivotal studies in order that the SoC arm in their economic model more accurately reflected clinical. This has been built into the model by using data from the literature to estimate a relative risk of SVR for the SoC arm of 7%. However, there is concern that the company has applied the relative risk to the wrong arm of the pooled pivotal studies i.e. it would have been more appropriate for the relative risk to have been applied to the intervention arm than to the comparator arm. To address this issue, the company subsequently provided a more conservative sensitivity analysis using an estimated SoC SVR rate of 10.6% which resulted in a cost per QALY of £29,945 with the PAS.
- A further uncertainty is that the patients in the pivotal studies were required to have platelet levels of 90 or 100 x 10⁹/L in order to be eligible for antiviral therapy. However, SMC clinical experts have indicated that in current clinical practice, antiviral therapy may be initiated at much lower platelet levels ranging from 25 to 50 x 10⁹/L. As such, the pivotal studies may not accurately represent current treatment in Scotland, which increases uncertainty with the economic evaluation.

Despite these issues, the economic case has been demonstrated.

Other data were also assessed but remain commercially confidential.*

Summary of patient and public involvement

A Patient Interest Group Submission was received from the Hepatitis C Trust.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published a national clinical guideline 133 Management of Hepatitis C, in July 2013. It recommends that all patients with chronic HCV infection should be considered for antiviral therapy with peginterferon and weight-based ribavirin and that patients infected with HCV genotype 1 should be considered for triple therapy with the addition of a protease inhibitor.¹¹

EASL published EASL Clinical Practice Guidelines: Management of hepatitis C virus infection, in 2011. It states that “patients with compensated cirrhosis must be treated in the absence of contra-indications, in order to prevent the complications of chronic HCV infection that occur exclusively in this group in the short- to mid-term. Indeed, large cohort studies and meta-analyses have shown that an SVR in patients with advanced fibrosis is associated with a significant decreased incidence of clinical decompensation and hepatocellular carcinoma. However, the SVR rates with peginterferon and ribavirin are lower in patients with advanced fibrosis or cirrhosis than in patients with mild to moderate fibrosis. Thus, it may also be justified to wait for the approval of triple therapies with protease inhibitors (genotype 1) if their local availability is anticipated within a few months. Assiduous monitoring and management of side-effects is required in this group of patients, who are generally older and have a lower tolerance than patients with less advanced liver disease. Due to portal hypertension and hypersplenism, leucocyte and platelet counts at baseline may be low in cirrhotic patients. Haematological side effects are more frequent in cirrhotic than in non-cirrhotic patients, and may contraindicate therapy. Irrespective of the achievement of an SVR, patients with cirrhosis should undergo regular surveillance for the occurrence of HCC and for portal hypertension, as the risk of complications is decreased but not abolished when HCV infection has been eradicated.”⁹

Both guidelines predate the licensing of eltrombopag for the indication currently under review.

Additional information: comparators

There is no active comparator. Current practice is that this patient population would receive either no, or suboptimal, antiviral therapy.

Cost of relevant comparators

Drug	Dose Regimen	Cost per course (£)
Eltrombopag	25 to 75 mg orally once daily	3,850 to 30,030

Costs from online British National Formulary on 30.08.13. Duration of antiviral treatment is 24 to 48 weeks depending on genotype. Costs were calculated for a treatment duration range of 20 to 54 weeks. The lower limit of treatment duration reflects initiation of eltrombopag only after occurrence of platelet reduction during ongoing treatment with antiviral treatment (arbitrary time point taken to be four weeks after start of antiviral treatment) and continuing till the end of a 24 week antiviral treatment period. The upper limit of treatment duration reflects initiation of eltrombopag six weeks prior to starting antiviral

therapy and continuing till the end of a 48 week antiviral treatment period. It includes a titration period of two weeks at 25mg dose and two weeks at 50mg dose.

Additional information: budget impact

The submitting company provided two estimates of budget impact based on the total eligible population and a subgroup.

Total population ($\leq 75 \times 10^9/L$)

Without PAS

The submitting company estimated the population eligible for treatment to be 138 in year 1 through to year 5, with an estimated uptake rate of 70% in year 1 through to year 5. The gross impact on the medicines budget was estimated to be £570k in each year. As no drugs were assumed to be displaced, no net budget impact was presented.

Subgroup ($\leq 50 \times 10^9/L$)

Without PAS

The submitting company estimated the population eligible for treatment to be 74 in year 1 through to year 5, with an estimated uptake rate of 70% in year 1 through to year 5. The gross impact on the medicines budget was estimated to be £307k in each year. As no drugs were assumed to be displaced, no net budget impact was presented.

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. GlaxoSmithKline. Revolade Summary of Product Characteristics. 2013.
2. Clinicaltrials.gov NCT00516321
3. Clinicaltrials.gov NCT00529568
4. GlaxoSmithKline. Integrated Summary of Efficacy for Eltrombopag. 2013.
5. GlaxoSmithKline. Eltrombopag to initiate and maintain interferon antiviral treatment to benefit subjects with hepatitis C related liver disease (ENABLE 1) Clinical study report. 2012.
6. GlaxoSmithKline. Eltrombopag to initiate and maintain interferon antiviral treatment to benefit subjects with hepatitis C related liver disease (ENABLE 2) Clinical study report. 2012.
7. GlaxoSmithKline. Integrated summary of safety for SB497115, eltrombopag, for treatment of thrombocytopenic subjects with hepatitis C virus (HCV) infection. 2012.
8. Prevalence of thrombocytopenia among patients with chronic hepatitis C: a systematic review Louie KS, Micallef JM, Pimenta JM, Forssen UM Journal of Viral Hepatitis 2011, 18: 1-7
9. European Association for the Study of the Liver (EASL) published EASL Clinical Practice Guidelines: Management of hepatitis C virus infection in 2011
10. Shiffman ML, Ghany MG, Morgan TR et al. Impact of reducing peginterferon alfa-2a and ribavirin dose during retreatment in patients with chronic hepatitis C. Gastroenterology 2007 132 (1):103-12.
11. Scottish Intercollegiate Guidelines Network (SIGN) National clinical guideline 133 Management of Hepatitis C 2013.
12. Giannini EG, Marengo S, Fazio V et al. Peripheral blood cytopaenia limiting initiation of treatment in chronic hepatitis C patients otherwise eligible for antiviral therapy. Liver Int 2012 32 (7):1113-9.

This assessment is based on data submitted by the applicant company up to and including 22 October 2013.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*

http://www.scottishmedicines.org.uk/About_SMC/Policy_Statements/Policy_Statements

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group

(PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.