eltrombopag, 25mg and 50mg film-coated tablets (Revolade®)

No. (625/10)

GlaxoSmithKline UK

09 July 2010

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 NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

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

Indication under review: Eltrombopag is indicated for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) splenectomised patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins). Eltrombopag may be considered as second-line treatment for adult non-splenectomised patients where surgery is contraindicated.

SMC restriction: in both the splenectomised and non-splenectomised patient populations, restricted to use in patients with severe symptomatic ITP or a high risk of bleeding.

Eltrombopag has been shown to be significantly more effective than placebo in raising and maintaining platelet counts at (or above) a minimum target level in previously treated patients with ITP.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

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Dosing information

Eltrombopag dosing requirements must be individualised based on the patient's platelet counts. The recommended starting dose of eltrombopag is 50 mg once daily. For patients of East Asian ancestry, eltrombopag should be initiated at a reduced dose of 25 mg once daily. After initiating eltrombopag, the dose should be adjusted, up to a maximum of 75mg daily, to achieve and maintain a platelet count ≥ 50 x 10^9/L as necessary to reduce the risk for bleeding.

Eltrombopag treatment should remain under the supervision of a physician who is experienced in the treatment of haematological diseases.

Product availability date

19 April 2010

Eltrombopag was designated an orphan medicine by the European Medicines Agency (EMA) in August 2007.

Summary of evidence on comparative efficacy

Eltrombopag is an orally administered, small molecule, non-peptide thrombopoietin receptor agonist which binds to the thrombopoietin receptor on the surface of platelets, megakaryocytes and megakaryocyte precursor cells. The drug activates megakaryocyte proliferation and differentiation in bone marrow progenitor cells, similar to the effects observed with endogenous thrombopoietin. Platelet counts are increased as a result of eltrombopag therapy. It has been designated an orphan medicine for the treatment of ITP in the European Union.

In a randomized, double-blind, placebo-controlled, phase III study, 197 adult (≥ 18 years) patients with previously treated chronic ITP and platelet counts ≤ 30 x 10^9/L were randomized in a 2:1 ratio to eltrombopag or placebo. They were stratified by splenectomy status, use of concomitant ITP medication at baseline, and baseline platelet count ≤15 or > 15 x 10^9/L. Patients were initiated on treatment with either eltrombopag 50mg or matching placebo once daily and followed specific instructions for dosing modifications based upon their individual platelet count response. Treatment was for 6 months. Patients could continue on maintenance ITP medication (e.g. corticosteroids, azathioprine, danazol, cyclosporine A or mycophenolate mofetil) during the study period.

The primary endpoint was the odds of achieving a platelet count ≥50 x 10^9/L and ≤400 x 10^9/L during the 6-month treatment period, for patients receiving eltrombopag relative to placebo.

The patient response profiles during the 6-month treatment period were compared between treatments using a repeated measures model for binary data adjusted for the randomisation stratification variables. The odds of responding over the 6-month treatment period were

significantly greater in eltrombopag than in placebo-treated patients; odds ratio (OR) 8.2, 99% confidence interval (CI): 3.6 to 18.7. Fifty-four percent of the eltrombopag-treated patients and 13% of placebo-treated patients achieved this level of response after six weeks of treatment. A similar platelet response was maintained throughout the study, with 52% and 16% of patients responding at the end of the six-month treatment period in the eltrombopag and placebo group respectively. This response was observed regardless of splenectomy status, baseline platelet count and baseline use of ITP medications.

Secondary outcomes included concurrent use of other ITP medications, requirement for rescue medications (a composite of new ITP medication, increased dose of concomitant ITP medication from baseline, platelet transfusion and splenectomy) and the risk of bleeding symptoms. At baseline 47% (63/135) and 50% (31/62) of patients in the eltrombopag and placebo groups respectively were on concurrent ITP medication. At least one concomitant ITP medication was reduced or discontinued in 59% (37/63) versus 32% (10/31) of patients respectively. Significantly fewer eltrombopag-treated patients required protocol-defined rescue treatment (18% [24/135]) compared to placebo-treated patients (40% [25/62]). Bleeding symptoms (including clinically significant bleeding events) during treatment with eltrombopag were significantly reduced compared with placebo. Grade 1 to 4 bleeding was reported in 79% of the patients receiving eltrombopag versus 93% receiving placebo. Grade 2 to 4 bleeding was reported in 33% of the patients receiving eltrombopag versus 53% receiving placebo. At each time point in both treatment groups, more than half of the bleeding observed was grade 1 bleeding. Throughout the treatment period, clinically significant bleeding occurred infrequently, generally in <25% of subjects in the placebo group and in <15% of subjects in the eltrombopag group.

Subject-reported outcome assessment, including health-related quality of life (HRQoL), symptomatology and health status, were analysed, using the Short Form-36, version 2 (SF-36v2), to determine if there was change from baseline and differences between the treatment groups. Patients in the eltrombopag group compared to those in the placebo group had significantly greater improvements in the domains of physical role, vitality, emotional role, and mental health component summary, as well as in the activities and concerns associated with thrombocytopenia.

A further phase III randomised double-blind placebo-controlled study, in 119 adults ≥ 18 years with previously treated chronic ITP and platelet counts ≤ 30 x 10^9/L, assigned patients in a 2:1 ratio to receive eltrombopag 50mg or placebo once daily for up to six weeks. Randomisation was stratified as in the previous study. The eltrombopag dose could be increased to 75mg after three weeks in patients whose platelet counts were less than 50 x 10^9/L. Treatment was discontinued when platelet counts exceeded 200 x 10^9/L. Patients could continue on maintenance ITP medication as in the previous study.

The primary outcome was the proportion of responders, defined as patients who achieved platelet counts ≥ 50 x 10^9/L at day 43 of treatment. Fifty-nine percent (43/73) of eltrombopag patients and 16% (6/37) of placebo patients achieved a response (OR 9.61 [95% CI: 3.31 to 27.86]). Patients responded to eltrombopag irrespective of the use of concomitant ITP drugs, splenectomy status, or baseline platelet count ≤ 15 x 10^9/L. There was also a statistically significant decrease in bleeding at any point during the treatment period for patients treated with eltrombopag compared to placebo (OR=0.49, 95% [CI=0.26 to 0.89]).

Health-related quality of life was analysed with the acute recall version of the SF-36v2 questionnaire, which was completed by every patient at screening and on completion of the study. Mean scores were similar at baseline and at the end of the study and health-related quality of life was comparable between responders and non-responders.

Summary of evidence on comparative safety

In the above studies, the overall incidence of serious adverse effects (AEs) and AEs leading to withdrawal was similar in the both groups. Nausea and vomiting were the only two AEs that commonly occurred in more patients in the eltrombopag group than in the placebo group.

Other more serious adverse effects associated with eltrombopag include liver dysfunction, thromboembolic events, cataracts and development or progression of reticulin deposits in the bone marrow. There are also concerns that thrombocytopenia recurs on cessation of treatment.

Summary of clinical effectiveness issues

The studies provide evidence of significantly improved platelet counts with eltrombopag compared to placebo in patients unresponsive to at least one first-line therapy. In addition, the European Medicines Agency noted that an association between eltrombopag and reduced bleeding has been consistently observed in secondary analyses of both phase III studies, although the effect is essentially driven by mild to moderate cutaneous bleeding.

Clinical experts in NHS Scotland indicated that the approach to treatment has become more conservative over time and that initiation of treatment for ITP is based on clinical symptoms and whether an invasive procedure is planned, in addition to platelet count. Experts suggest that a platelet count of 20 to 30 x 10^9/L alone would not necessarily result in treatment being initiated. Therefore the patient population in the pivotal studies (who were required to have a platelet count of ≤ 30 x10^9/L alone) may not be representative of Scottish patients likely to be considered for treatment with eltrombopag in clinical practice.

The pivotal studies of eltrombopag were only of six weeks and six months duration so long term data on safety and efficacy are lacking.

Recent guidelines advise that physicians are required to make individual judgements on the choice of second-line treatment of ITP based on bleeding history, co-morbidities, patient expectations and compliance. Several second-line options are available but in the studies submitted eltrombopag has been compared only to placebo, therefore, its effectiveness in relation to other second-line options is not known.

Currently, there are two thrombopoietin receptor agonists licensed for use in the UK. The other commercially available thrombopoietin receptor agonist, romiplostim, must be administered once weekly as a subcutaneous injection. The dose is based on body weight, necessitating the use of a dose calculator. An orally administered treatment may be more acceptable to the patient. Liver function monitoring is required with eltrombopag treatment but not with romiplostim.

As only placebo-controlled studies are available, an indirect comparison to romiplostim was included in the company's submission using data on the odds of achieving a durable and overall response with eltrombopag and romiplostim. The manufacturer concluded that eltrombopag and romiplostim had comparable efficacy. However, the results indicated that romiplostim was likely to be the superior treatment in terms of overall response.

There were limitations with the indirect comparison including the methodology used, the differing designs of the studies, differences in concurrent ITP medication use and different pre-defined primary efficacy outcomes in the studies. In addition:

The Bucher method was used which limits the number of trials that can be included in the analysis as this method requires the trials to have a common comparator, which in this case was placebo.

- A number of trials were identified in the literature search but only six had a common comparator. This resulted in a number of potentially relevant studies being excluded due to the method of indirect comparison chosen. If a mixed treatment comparison had been conducted it may have been possible to include more trials and control for the differences between the trials, such as splenectomy status and study design.

Summary of comparative health economic evidence

The manufacturer presented a cost-utility analysis comparing eltrombopag with romiplostim for the treatment of patients with ITP. The analysis was conducted separately for splenectomised patients refractory to other treatments and for previously treated patients contraindicated for splenectomy and whose ITP is not adequately controlled. Clinical data on bleeding events were used in the model based on the mean number of bleeds per patient from the eltrombopag pivotal trial and on safety data from the SMC Detailed Advice Document (DAD) for the romiplostim arm. Using these data the manufacturer estimated a relative risk of clinically significant bleeding in the eltrombopag arm of 0.38 for splenectomised patients and 0.46 for non-splenectomised patients. In the romiplostim arm the relative risk of clinically significant bleeding was estimated to be 0.60 regardless of splenectomy status. The analysis was conducted over a 26-week time horizon, however the manufacturer also stated that the outcomes observed and the costs incurred would continue as no disease progression or regression was assumed. Resource use included in the model related to the treatment of bleeding events and was based on expert opinion. Quality of life data were collected in the eltrombopag clinical trial using the SF-36 which was converted to utility values using a recognised method. The utility gain associated with romiplostim was then estimated to be less than the eltrombopag utility gain due to the assumed higher bleeding rates in the romiplostim arm of the model.

In the base case analysis the manufacturer estimated that treatment with eltrombopag would dominate romiplostim. In the splenectomised population the manufacturer estimated savings of £12,641 and a Quality-Adjusted Life Year (QALY) gain of 0.039. In the non-splenectomised population the savings were estimated to be £2,094 and a QALY gain of 0.028.

Whilst a number of second-line treatment options are currently available for these patients, including romiplostim, the comparator appears to be reasonable on the basis that romiplostim would be the treatment most likely to be replaced in practice. The manufacturer suggested that eltrombopag be considered alongside romiplostim as a treatment option for use in patients with severe symptomatic ITP or in patients with a high risk of bleeding in line with the SMC restriction for romiplostim.

Rather than using the primary outcome of platelet response, the clinical data used in the model were derived from secondary outcome measures of mean number of bleeds per patient from the eltrombopag study, and on safety data quoted in the SMC DAD for the romiplostim arm of the model.

It was assumed that eltrombopag was superior to romiplostim using this crude comparison of bleeding events, but there is no robust evidence to support this assumption as a formal indirect comparison based on this outcome was not conducted. However, sensitivity analysis was provided which assumed no difference in efficacy between eltrombopag and romiplostim. This showed that eltrombopag would be associated with savings of £12k in the splenectomised population and £2k in the non-splenectomised population including differences in drug costs alone. Additionally, threshold analysis was provided to show that the relative risk of bleeding events would have to fall substantially from the base case values before eltrombopag would no longer be considered cost-effective.

While there were some weaknesses in the clinical evidence used to drive the economic analysis, the economic case was considered to be demonstrated as eltrombopag would offer an additional treatment option with the benefit of oral administration and, given the orphan status of the drug, greater uncertainty in the economic analysis could be accepted by SMC.

Summary of patient and public involvement

A Patient Interest Group Submission was received from the ITP Support Association.

Additional information: guidelines and protocols

Guidelines for the investigation and management of idiopathic thrombocytopenic purpura in adults, children and in pregnancy was published in 2003 by the British Committee for Standards in Haematology. It predates the availability of eltrombopag and other thrombopoietin receptor agonists. The guideline states that there is no indication for treatment in adults in whom there are no signs and symptoms and platelets are greater than $30x10^9$/L. Oral corticosteroids and intravenous immunoglobulin are recommended as first-line treatments but the recommendations for second-line therapy and treatment of refractory patients are less clear. In these patients treatment should be tailored to suit the individual.

An international consensus report on the investigation and management of primary immune thrombocytopenia was published in 2010 and makes similar recommendations to the 2003 guideline regarding first line therapy. It discusses thrombopoietin agonists as a possible option for second-line therapy. However, several options are recommended and therapy should be selected on an individual patient basis.

Additional information: comparators

Romiplostim is the only other thrombopoietin receptor agonist licensed in the UK.

Cost of relevant comparators

Drug	Dose regimen	Cost per year (£)
Eltrombopag	**25 to 75mg daily orally**	**10,010 to 30030**
Romiplostim	1 microgram/kg to 10 microgram/kg/week subcutaneously	25,064 – 75,192

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 28 April 2010. Doses for romiplostin calculated using 70kg weight and assuming single use of 250 microgram vials. Romiplostim dose of 3 microgram/kg was the median dose used in splenectomised patients.

Additional information: budget impact

The manufacturer presented two estimates of the net drug budget impact based on a low and high rate of prevalence of ITP. Assuming the lower prevalence rate, the manufacturer estimated there would be net savings of £237k in year 1 (24 patients) rising to £1.2m in year 5 (120 patients). With the higher prevalence rate the manufacturer estimated there would be net savings of £589k in year 1 (60 patients) rising to £2.9m in year 5 (299 patients). A 10% market share was assumed in year 1 rising to 50% in year 5. Feedback from experts indicates that these figures are likely to overestimate the patient population that will be treated with eltrombopag.

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.

This assessment is based on data submitted by the applicant company up to and including 21 June 2010.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. 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.

The undernoted references were supplied with the submission.

GlaxoSmithKline group. A randomized, double-blind, placebo-controlled phase III study to evaluate the efficacy, safety and tolerability of eltrombopag olamine (SB-497115-GR), a thrombopoietin receptor agonist, administered for 6 months as oral tablets once daily in adult subjects with previously treated chronic idiopathic thrombocytopenic purpura (ITP). RAISE. RAndomized placebo-controlled ITP Study with Eltrombopag. Data on file. (2009).

The European Medicines Agency (EMEA) European Public Assessment Report. Eltrombopag (Revolade®). EMEA H-C-001110. http://www.ema.europa.eu

Bussel J, Provan A, Shamsi T, et al. Effect of eltrombopag on platelet counts and bleeding during treatment of chronic idiopathic thrombocytopenic purpura : a randomised, double-blind, placebo-controlled trial. Lancet 2009; 373: 641-48.

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