Eltrombopag for the treatment of chronic idiopathic (immune) thrombocytopenic purpura (ITP)

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Discussion of ERG reports is invited. Visit the HTA website correspondence forum (www.hta.ac.uk/correspond).

Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical effectiveness and cost-effectiveness of eltrombopag for the treatment of adults with chronic idiopathic (immune) thrombocytopenic purpura (ITP), based on a review of the manufacturer's submission (MS) to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal process. ITP is an autoimmune disorder by which antibodies are formed against platelets with annual incidence rates in the UK/USA ranging from 1.13 to 6.62 cases per 100,000 adults. Eltrombopag increases the production of platelets at a rate that outpaces their destruction by the immune system, and has a UK marketing authorisation both for the treatment of adult ITP in splenectomised patients who are refractory to other treatments and as a second-line treatment for adult non-splenectomised patients for whom surgery is contraindicated. Both splenectomised and non-splenectomised patient groups were considered in the analysis. Two economic models were presented, one for a watch-and-rescue treatment scenario and the second for the long-term treatment of patients with more severe ITP. The submission's evidence was sourced from the relatively high-quality RAISE [RAndomized placebo-controlled Idiopathic thrombocytopenic purpura (ITP) Study with Eltrombopag] randomised controlled trial. The study indicated a statistically significant difference in favour of eltrombopag compared with placebo in the odds of achieving the primary outcome of a platelet count of between 50 and 400×10^9/l during the 6-month treatment period (odds ratio 8.2, 99% confidence interval 3.6 to 18.7). In the eltrombopag group, 50/83 (60%) non-splenectomised patients and 18/49 (37%) splenectomised patients achieved this outcome. Median duration of response for all patients was 10.9 weeks (splenectomised patients 6 weeks and non-splenectomised patients 13.4 weeks). Patients treated with eltrombopag required less rescue medication and had lower odds of bleeding events than placebo-treated subjects in both patient groups. In the watch-and-rescue economic model, the ERG found that substantial reductions in the cost of eltrombopag are needed for the incremental cost-effectiveness ratio (ICER) to fall below £30,000. Further analyses found that the ICER varied from £33,561 to £103,500 per quality-adjusted life-year (QALY) (splenectomised) and from £39,657 to £150,245 per QALY (non-splenectomised). Other than bleeding, no adverse events were modelled. In relation to the long-term treatment model, the ERG found that using non-randomised non-comparative data may result in biased estimates of unknown magnitude and direction. None of the treatment sequences resulted in an ICER approaching the recommended threshold of £30,000. The base-case results, using a 2-year time horizon and prescribing eltrombopag as second-line treatment post rituximab, were found to be favourable towards eltrombopag. In conclusion, based on the MS and additional ERG work, eltrombopag appears to be a safe treatment for ITP (although long-term follow-up studies are awaited) and has short-term efficacy. However, there is no robust evidence on long-term efficacy or cost-effectiveness of eltrombopag, and there is a lack of robust direct evidence on the effectiveness and cost-effectiveness of eltrombopag compared with other relevant comparators. NICE did not recommend eltrombopag for the treatment of chronic ITP within its marketing authorisation for splenectomised or non-splenectomised patients.

Introduction

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of the responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, where most of the relevant evidence lies with one manufacturer or sponsor. Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG), an external organisation independent of NICE. This paper presents a summary of the ERG report for the STA entitled *Eltrombopag for the treatment of chronic idiopathic (immune) thrombocytopenic purpura (ITP)*.

Description of the underlying health problem

Idiopathic (immune) thrombocytopenic purpura (ITP) is a condition in which autoantibodies are formed against platelets, leading to increased clearance from the circulation. When the rate of destruction exceeds production, the platelet count will fall, which may lead to a reduced ability for blood to clot. ITP may present as bleeding and/or bruising or be asymptomatic and picked up on blood counts taken for other reasons. The incidence rates quoted for adult ITP in the UK/USA range from 1.13[1] to 6.62[2] cases per 100,000 adults per year. Traditionally, the only licensed medical treatments for ITP were steroids, intravenous immunoglobulin (IVIG) and anti-D immunoglobulin, although anti-D immunoglobulin has now been withdrawn as a treatment for ITP from the European market by the manufacturer owing to safety concerns. Other treatments include splenectomy (a surgical treatment), cyclophosphamide, vinca alkaloids, danazol, azathioprine, ciclosporin, rituximab, mycophenolate mofetil, dapsone, alemtuzumab, autologous stem cell transplantation, interferon and combination chemotherapy. Recently, thrombopoietin analogues (romiplostim and eltrombopag), which increase platelet production, have been licensed for treatment of ITP.

Eltrombopag is designed to increase the production of platelets at a rate that outpaces their destruction by the immune system. On 3 August 2007, orphan designation (EU/3/07/467) was granted by the European Commission to GlaxoSmithKline Research & Development Ltd, London, UK, for eltrombopag olamine for the treatment of adult ITP. Eltrombopag is indicated for the treatment of adult ITP when at least one other prior treatment has failed.

Scope of the evidence review group report

The manufacturer's submission (MS) assessed the clinical effectiveness and cost-effectiveness of eltrombopag for the treatment of chronic ITP in adult patients who had, prior to treatment, a baseline platelet count of $< 30 \times 10^9$/l. They were considered to have responded to treatment when the platelet count reached 50×10^9/l. Two patient populations were considered: splenectomised patients who were refractory to other treatments and non-splenectomised patients who had inadequate response to first-line treatment and for whom splenectomy was contraindicated.

The data used to assess the safety and efficacy of eltrombopag came from three randomised controlled trials (RCTs): TRA100773A,[3] TRA100773B[4] and TRA102537 RAISE [RAndomized placebo-controlled Idiopathic thrombocytopenic purpura (ITP) Study with Eltrombopag].[5]

The manufacturer submitted two separate economic evaluations. The first considered the addition of eltrombopag to a 'watch-and-rescue' strategy and compared this with a watch-and-rescue strategy with the use of placebo. The second considered the use of eltrombopag as part of a treatment sequence provided for those patients needing longer-term continuous care who had tried, and failed, to respond to a number of treatment options. These patients were heavily pretreated and represented a smaller number of patients with more severe ITP.

Both models were constructed using Microsoft EXCEL (Microsoft Corporation, Redwood, WA, USA), and for both models two patient populations were modelled (splenectomised and non-splenectomised). The watch-and-rescue model mirrored the trial-based comparison of eltrombopag with placebo using data from the RAISE trial.[5] The longer-term care model was a cohort-type model ($n = 25$) in which a Markov model was used to compare strategies in which eltrombopag was used as part of a sequence of treatments. The analysis also compared treatment sequences with eltrombopag versus the same sequences without eltrombopag. The principal source of the clinical effectiveness data for eltrombopag used to inform this model was the RAISE trial.[5] Pooled data from the RAISE[5] and EXTEND (Eltrombopag Extended Dosing study) trials were also used. The EXTEND trial is an extension study (case series) that is due to be completed in June 2012.

Methods

The ERG report comprised a critical review of the evidence for the clinical evidence and cost-effectiveness of the technology based upon the MS to NICE as part of the STA process.[6]

Following submission of the manufacturer's report, the ERG:

- requested clarification from the manufacturer on a number of issues, mainly regarding clinical effectiveness and cost-effectiveness aspects together with requests for more detailed information to be provided in other areas
- assessed the clinical effectiveness section of the MS for its methodological quality and accuracy
- undertook independent searches for eltrombopag and the clinical effectiveness of the comparators
- performed additional sensitivity analyses on the manufacturer's indirect comparison between eltrombopag and romiplostim
- performed an array of additional sensitivity analyses on each of the economic models with a particular focus on multivariate sensitivity analysis.

Results

Summary of submitted clinical evidence

Evidence in relation to the efficacy of eltrombopag came principally from the RAISE study (*Table 1*).[5] This was a 6-month phase III RCT, with 197 participants randomised 2 : 1 to eltrombopag plus standard care or placebo plus standard care. Of the 197 participants, 71 (36%) had undergone a splenectomy. Additional supporting evidence came from two 6-week RCTs comparing eltrombopag with placebo. TRA100773A[3] was a phase II dose-finding study involving 118 participants, and TRA100773B[4] was a phase III RCT involving 114 participants.

Efficacy

In the RAISE study,[5] there was a statistically significant difference in favour of eltrombopag compared with placebo in the odds of achieving the primary outcome of a platelet count of between 50 and 400×10^9/l during the 6-month treatment period [odds ratio (OR) 8.2, 99% confidence interval (CI) 3.6 to 18.7]. In the eltrombopag group, 50/83 (60%) of non-splenectomised patients and 18/49 (37%) of splenectomised patients achieved this outcome. The median cumulative weeks of response were 10.9 for eltrombopag (splenectomised patients 6 weeks, non-splenectomised patients 13.4 weeks) compared with none for placebo. Patients treated with eltrombopag were less likely to require rescue treatment than those treated with placebo [25/135 (19%) vs 25/62 (40%)]. The OR between eltrombopag and placebo was

TABLE 1 Summary of the results from the RAISE study[5]

Outcome measure	All participants	Splenectomised	Non-splenectomised
Odds of achieving a platelet count of between 50 and 400×10⁹/l over the 6-month treatment period	OR 8.2 (99% CI 3.6 to 18.7)	Elt 37%, Pla 15%	Elt 60%, Pla 18%
Durable response – median cumulative weeks of response	Elt 10.9, Pla 0	Elt 6, Pla 0	Elt 13.4, Pla 0
Need for rescue medication during the intervention	Elt 25/135 (18%), Pla 25/62 (40%), $p<0.001$	Elt 11/50 (22.0%), Pla 10/21 (47.6%) – OR 0.33 (95% CI 0.11 to 1.02)	Elt 14/85 (16.5%), Pla 15/41 (36.6%) – OR 0.34 (95% CI 0.14 to 0.79)
Reduction in dose/frequency of concomitant ITP medications taken at baseline	Elt 18%, Pla 40%, $p=0.001$	Elt 12/27 (44.4%), Pla 5/13 (38.5%) – OR 1.29 (95% CI 0.33 to 5.04)	Elt 25/36 (69.4%), Pla 5/18 (27.8%) – OR 5.87 (95% CI 1.67 to 20.59)
Odds of any bleeding (WHO grades 1–4)	Elt vs Pla 0.24 (76% lower), $p<0.001$	Elt 41 (82%), Pla 18 (90%) – OR 0.87 (95% CI 0.12 to 6.07)	Elt 65 (76%), Pla 38 (95%) – OR 0.10 (95% CI 0.02 to 0.53)
Odds of clinically significant bleeding (WHO grades 2–4)	Elt vs Pla 0.35 (65% lower), $p<0.001$	Elt 19 (38%), Pla 14 (70%) – OR 0.27 (95% CI 0.08 to 0.95)	Elt 25 (29%), Pla 18 (45%) – OR 0.31 (95% CI 0.11 to 0.83)

CI, confidence interval; Elt, eltrombopag; ITP, idiopathic (immune) thrombocytopenic purpura; OR, odds ratio; Pla, placebo; WHO, World Health Organization.

statistically significant for non-splenectomised (OR 0.34, 95% CI 0.14 to 0.79) but not for splenectomised (OR 0.33, 95% CI 0.11 to 1.02) patients (OR for overall group was not reported). Thirty-seven out of 63 (59%) patients treated with eltrombopag reduced or discontinued concomitant ITP medication compared with 10/31 (32%) of patients receiving placebo (p-value not reported). The OR was statistically significant for non-splenectomised (OR 5.87, 95% CI 1.67 to 20.59) but not splenectomised (OR 1.29, 95% CI 0.33 to 5.04) patients (OR for overall group was not reported).

In a meta-analysis of the TRA100773A, TRA100773B and RAISE[5] studies for the outcome of a platelet count of 50–400×10⁹/l at day 43, eltrombopag was associated with statistically significantly greater odds of platelet response than placebo for all patients [OR (fixed) 8.39, 95% CI 4.77 to 14.75]. Splitting the data by splenectomy status, eltrombopag was associated with statistically significantly greater odds of platelet response than placebo for both non-splenectomised (OR 9.17, 95% CI 4.52 to 18.60) and splenectomised (OR 7.20, 95% CI 2.82 to 18.35) patients.

Safety

The odds of any bleeding [World Health Organization (WHO) grades 1–4] during 6-month eltrombopag treatment were 76% lower in the eltrombopag group than in the placebo group ($p<0.001$). The OR was statistically significant for non-splenectomised (OR 0.10, 95% CI 0.02 to 0.53) but not for splenectomised (OR 0.87, 95% CI 0.12 to 6.07) patients. The odds of clinically significant bleeding (WHO grades 2–4) were 65% lower in the eltrombopag group ($p<0.001$). The OR was statistically significant for both non-splenectomised (OR 0.31, 95% CI 0.11 to 0.83) and splenectomised (OR 0.27, 95% CI 0.08 to 0.95) patients. ORs were not reported for the overall group for either any or clinically significant bleeding.

During the 6-month treatment period, eltrombopag and placebo had similar risks for any adverse event (118/135, 87% vs 56/61, 92%), any serious adverse event (15/135, 11% vs 11/61, 18%), adverse events related to study medication (48/135, 36% vs 18/61, 30%) and adverse events leading to withdrawal (12/135, 9% vs 4/61, 7%). Types of adverse events appeared to be similar between the eltrombopag and placebo groups.

The risk of liver function disturbances was higher for eltrombopag (8% during 6-week treatment and 13% during 6-month treatment) than for placebo (3% during 6-week treatment and 8% during 6-month treatment). No cases of bone marrow fibrosis, phototoxicity, cardiotoxicity or renal toxicity occurred during the intervention.

Indirect comparison between eltrombopag and romiplostim

An indirect comparison was possible only between eltrombopag (RAISE study[5]) and romiplostim (two RCTs[7]), as no RCTs reporting any of the other treatments used placebo as a comparator.

There was a statistically significant difference in favour of romiplostim for overall response for all patients (OR 0.17, 95% CI 0.03 to 0.82). When the patients were split by splenectomy status, the point estimates of the OR favoured romiplostim but they were not statistically significant. For durable response, there was no statistically significant difference between eltrombopag and romiplostim, either for all patients (OR 0.26, 95% CI 0.03 to 2.62) or separately by splenectomy status. *Durable response* was defined as a weekly platelet count of $\geq 50 \times 10^9$/l during ≥ 6 weeks of the last 8 weeks of treatment, excluding those who received rescue medication at any time during the study, whereas *overall response* was durable plus transient response (four or more weekly responses of $\geq 50 \times 10^9$/l during the study without a platelet response from weeks 2 to 25).

In the manufacturer's analysis, all participants who did not complete treatment were classed as non-responders (worst scenario). The ERG undertook further analysis in which all such participants were classed as responders (best scenario). In this further analysis the results for overall response (all patients) remained statistically significant in favour of romiplostim (OR 0.26, 95% CI 0.07 to 0.97), while the point estimate for durable response (all patients) changed to favour eltrombopag rather than romiplostim, although the difference remained non-significant (OR 1.04, 95% CI 0.32 to 3.44).

Comparator treatments

No attempt was made to statistically or narratively synthesise data on the effectiveness of comparators. The manufacturer stated that best available evidence was used to generate values for the long-term economic model. However, alternative evidence could have been used for IVIG [American Society for Haematology (ASH) guideline[8] and a Health Technology Assessment review[9]] and for anti-D immunoglobulin (ASH guideline[8]).

Summary of submitted cost-effectiveness evidence

The manufacturer submitted two economic evaluations and models analysing the cost-effectiveness of eltrombopag for the treatment of adult ITP.

Watch-and-rescue model

The watch-and-rescue model compares eltrombopag plus standard care with standard care. The model was based on the double-blind RAISE RCT,[5] with uptake rates of the drug determined from an internal GlaxoSmithKline study.

The incremental cost per quality-adjusted life-year (QALY) for the base-case analyses for splenectomised and non-splenectomised patients was £78,253 and £90,471, respectively. Sensitivity analyses varying the risk of death, target platelet counts and use of concomitant medications did not reduce the incremental cost per QALY greatly. A probabilistic analysis showed that there was little or no chance of eltrombopag being cost-effective at a threshold of £30,000 per QALY. Substantial reductions in the price of eltrombopag would be required to obtain a cost per QALY of £30,000.

The ERG conducted additional sensitivity analyses around the source of cost data for managing bleeds, discount rate and the annual risk of bleeding. Only by combining these changes into an optimistic multivariate sensitivity analysis did the incremental cost per QALY begin to approach £30,000. Sensitivity analyses conducted by the manufacturer and by the ERG are presented in *Table 2*.

Long-term care model

This model referred to a smaller patient group with more severe ITP and aimed to assess the most cost-effective sequence of treatments [rituximab, romiplostim, IVIG, anti-D immunoglobulin (which was considered only for those in whom splenectomy was contraindicated) and eltrombopag] for the treatment of chronic adult ITP. Given the input parameters used, the model was very similar for the two patient groups.

The analyses conducted by the manufacturer assumed that patients would always be offered an active treatment and it was found that a treatment sequence of rituximab, eltrombopag, romiplostim and IVIG was the least costly but least effective of the non-dominated sequences. No other sequences had an incremental cost per QALY approaching £30,000. The manufacturer reported that treatment sequences including eltrombopag dominated the same sequences without eltrombopag when patients had received prior treatment with rituximab. The manufacturer's deterministic sensitivity analysis varied the response rate used in the model and the model time horizon. These did not greatly change the results.

The ERG's further univariate analyses (varying the discount rate, changing response rates of eltrombopag, allowing romiplostim to respond over a 12-week period and varying the assumption of a fatal bleeding event between 0% and 100%) did not greatly alter the results. Plausible combinations of changes could change which treatment sequence was least costly but least effective, but, again, no other sequence had an incremental cost-effectiveness ratio (ICER) approaching £30,000. The ERG also conducted a further exploratory sensitivity analysis by introducing a standard-care sequence in which patients received only rescue medication. This treatment sequence was the least effective but least costly sequence. No other treatment sequence was associated with an ICER < £50,000.

TABLE 2 Exploratory sensitivity analyses for splenectomised and non-splenectomised patients (watch-and-rescue model)

	Incremental cost per QALY (£)	
Scenario	Splenectomised	Non-splenectomised
1. Baseline results	77,496	90,471
2. Typo correction	78,253	90,471
3. Micro cost	83,284	91,175
4. All bleeding events	100,350	89,850
5. 0% discount rate	47,712	55,622
6. 6% discount rate	103,500	118,847
7. Annual risk of fatal bleed (Cohen,[10] lower bound)	131,841	150,245
8. Annual risk of fatal bleed (Cohen,[10] upper bound)	55,778	64,882
9. Combining scenarios 2, 3, 4, 6 and 7 (worst-case scenario)	231,195	193,293
10. Combining scenarios 5 and 8 (best-case scenario)	33,561	39,657

QALY, quality-adjusted life-year.

Commentary on robustness of submitted evidence

The overall quality of the RCTs used to support the watch-and-rescue model appears reasonable. However, within the model, benefits were allowed to accrue over a patient's lifetime, but costs for this period were assumed to occur over only the 26-week trial period, with no extrapolation to a longer time horizon. This is likely to introduce a bias in favour of eltrombopag in the analysis.

Only indirect evidence relating to relatively short follow-up was available for use in the long-term model, and the use of these data introduces a bias of unknown direction and magnitude. Owing to the lack of other suitable data, two different measures of utilities were used (the Short Form questionnaire-6 dimensions and the European Quality of Life-5 Dimensions). Furthermore, apart from bleeding, no other utility decrements (e.g. for other adverse events) were included in either of the economic models. Information on other parameters for both models can be questioned, but even when assumptions were varied the incremental costs per QALYs remained well above £30,000.

Conclusions

Overall, the key issues for a decision-maker to note are as follows.

Effectiveness

Key issues

- Eltrombopag appears to be a safe treatment for ITP, although long-term follow-up studies are awaited.
- Eltrombopag has short-term efficacy for the treatment of ITP.
- There is no robust evidence on long-term efficacy of eltrombopag.
- Eltrombopag appears to be less effective in achieving an overall response rate than romiplostim in a 6-month intervention period.
- There is no robust direct evidence on the effectiveness of eltrombopag compared with other relevant comparators.

Watch-and-rescue model

Key issues

- Substantial reductions in the cost of eltrombopag are needed before the incremental cost per QALY is < £30,000.
- If the chance of dying from a bleeding event increases towards the upper boundary considered by the manufacturer, and the price of eltrombopag is reduced, then it is plausible that the cost per QALY could be reduced to < £30,000.
- Other than bleeding, no adverse events were modelled. The bias this causes is unknown.

Long-term treatment model

Key issues

- Using non-randomised non-comparative data may result in biased estimates. The magnitude and direction of these biases is uncertain.
- The inclusion of standard care in the model allows one to begin to think about how cost-effective any of the treatment sequences are. No sequence results in an ICER approaching the recommended threshold of £30,000.
- Restricting the time horizon to 2 years results in a treatment sequence in which eltrombopag given after rituximab is most likely to be cost-effective. A 50-year time horizon favours a sequence involving romiplostim in treatment post rituximab.

- Many assumptions are used to estimate the target patient population and the numbers of patients who will require long-term treatments. It is unclear how applicable these are.

Furthermore, the representativeness of participants in the eltrombopag trials of the UK population of patients with chronic ITP is uncertain, as are the estimates of incidence and prevalence given in the MS.

Summary of NICE guidance issued as a result of the STA

The final appraisal determination was published by NICE in September 2010 and final guidance published in October 2010.[11] NICE did not recommend eltrombopag within its marketing authorisation for the treatment of chronic ITP in splenectomised adults whose condition is refractory to other treatments (e.g. corticosteroids, immunoglobulins) or as second-line treatment in non-splenectomised adults where surgery is contraindicated.

Key references

1. Neylon AJ, Saunders PW, Howard MR, Proctor SJ, Taylor PR, Northern Region Haematology Group. Clinically significant newly presenting autoimmune thrombocytopenic purpura in adults: a prospective study of a population-based cohort of 245 patients. *Br J Haematol* 2003;**122**:966–74.
2. George JN, El-Harake MA, Aster RH. Thrombocytopenia due to enhanced platelet destruction by immunologic mechanisms. In Beutler E, Lichtman MA, Coller BS, Kipps TJ, editors. *Williams haematology*. New York, NY: McGraw-Hill; 1995. pp. 1315–55.
3. Bussel JB, Cheng G, Saleh MN, Psaila B, Kovaleva L, Meddeb B, *et al.* Eltrombopag for the treatment of chronic idiopathic thrombocytopenic purpura. *N Engl J Med* 2007;**357**:2237–47.
4. Bussel JB, Provan D, Shamsi T, Cheng G, Psaila B, Kovaleva L, *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**:641–8.
5. Cheng G, Saleh MN, Bussel JB, Marcher C, Vasey S, Mayer B, *et al.* Oral eltrombopag for the long-term treatment of patients with chronic idiopathic thrombocytopenic purpura: results of a phase III, double-blind, placebo-controlled study (RAISE). *Blood* 2008;**112**:abstract 400.
6. National Institute for Health and Clinical Excellence (NICE). *Guide to the Single Technology Appraisal (STA) process.* 2009. URL: www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf (accessed February 2010).
7. Kuter DJ, Bussel JB, Lyons RM, Pullarkat V, Gernsheimer TB, Senecal FM, *et al.* Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: a double-blind randomised controlled trial. *Lancet* 2008;**371**:395–403.
8. George JN, Woolf SH, Raskob GE, Wasser JS, Aledort LM, Ballem PJ, *et al.* Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Haematology. *Blood* 1996;**88**:3–40.
9. Chen S, Pi D, Ansari M, Puil M, Desjardins B, Banks R, *et al. Polyclonal intravenous immunoglobulin in patients with immune thrombocytopenic purpura: clinical systematic review. Technology report number 108.* 2008. URL: www.cadth.ca/index.php/en/publication/809 (accessed February 2010).

10. Cohen YC, Djulbegovic B, Shamai-Lubovitz O, Mozes B. The bleeding risk and natural history of idiopathic thrombocytopenic purpura in patients with persistent low platelet counts. *Arch Intern Med* 2000;**160**:1630–8.

11. National Institute for Health and Clinical Excellence. *Thrombocytopenic purpura – eltrombopag*. 2010. URL: www.nice.org.uk/nicemedia/live/13250/51269/51269.pdf (accessed January 2011).