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**Eltrombopag for the treatment of chronic idiopathic (immune) thrombocytopenic  
purpura (ITP): A NICE Single Technology Appraisal**

**Authors:** <sup>1</sup>Dwayne Boyers  
<sup>2</sup>Xueli Jia  
<sup>2</sup>David Jenkinson  
<sup>2</sup>Graham Mowatt

<sup>1</sup>Health Economics Research Unit  
Institute of Applied Health Sciences  
University of Aberdeen

<sup>2</sup>Health Services Research Unit  
Institute of Applied Health Sciences  
University of Aberdeen

**Correspondence to:** Dwayne Boyers  
Health Economics Research Unit  
University of Aberdeen  
Foresterhill  
Aberdeen AB25 2ZD  
Tel: 0044 1224558984  
Fax: 0044 1224550926  
Email: [d.boyers@abdn.ac.uk](mailto:d.boyers@abdn.ac.uk)

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## Eltrombopag for ITP: A Single Technology Appraisal

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Further acknowledgements and contributions are detailed in the evidence review group report.

The views and opinions expressed therein are those of the authors and do not necessarily reflect those of NICE or the department of health.

### **Competing interests:**

Dwayne Boyers completed an internship (3 month student placement, Dublin, Ireland) with GlaxoSmithKline as part of an MSc in Economics degree from the National University of Ireland, Galway, during which time he completed a minor dissertation on the supply and reimbursement of medicines in Ireland. As part of the programme between NUI Galway and GlaxoSmithKline, he received a small stipend to cover living expenses while on placement in Dublin in 2009. The remaining authors have no further conflicts of interest.

**Abstract:**

***Background:***

The National Institute for Health and Clinical Excellence (NICE) invited the manufacturer of eltrombopag (GlaxoSmithKline) to submit evidence for the clinical and cost-effectiveness of this drug for the treatment of patients with chronic immune or idiopathic thrombocytopenic purpura (ITP), as part of the their Single Technology Appraisal (STA) process. The Aberdeen technology assessment review (TAR) group, commissioned to act as the Evidence Review Group (ERG) critically reviewed and supplemented the submitted evidence. This paper describes the company submission, the ERG review and NICE's subsequent decisions.

***Objective:***

To summarize the independent review of the clinical and cost-effectiveness evidence relating to eltrombopag for the treatment of ITP as conducted by the ERG together with NICE's subsequent final assessment decision (FAD).

***Methods:***

The ERG critically appraised the submitted clinical and cost-effectiveness evidence submitted by the manufacturer, independently searched for relevant literature, conducted a critical appraisal of the submitted economic models and explored the impact of altering some of the key model assumptions as well as combining relevant sensitivity analyses.

***Results:***

Three trials were used to inform the safety and efficacy aspects of this submission; however, one high quality randomised controlled trial (RAISE study) was the principal

source of evidence and was used to inform the economic model. Eltrombopag had greater odds of achieving the primary outcome of a platelet count between  $50 \times 10^9/L$  and  $400 \times 10^9/L$  during the six month treatment period than placebo, 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 duration of response was 10.9 weeks for eltrombopag (splenectomised 6 and non splenectomised 13.4) compared with 0 for placebo. Eltrombopag patients required less rescue medication and had lower odds of bleeding events for both the splenectomised and non splenectomised patients.

For a watch and rescue strategy of care, the comparator was placebo and the ERG found that substantial reductions in the cost of eltrombopag are needed before the incremental cost per QALY is less than £30,000. There was significant uncertainty, with the ICER reported varying from £33,561 to £103,500 per QALY (splenectomised) and £39,657 to £150,245 per QALY (non-splenectomised). All costs were reported in UK pounds sterling, year 2008. Other than bleeding, no adverse events were modelled. In relation to the long term treatment model, the ERG questioned the robustness of the use of non-randomised non-comparative data. The base case results restricting the time horizon to 2 years and prescribing eltrombopag as second line treatment post rituximab were found to be favourable towards eltrombopag. As rituximab is not a licensed treatment for ITP, the ERG were concerned that its inclusion may not be reflective of clinical practice. None of the treatment sequences resulted in an ICER approaching the recommended threshold of £30,000 per QALY gained.

### ***Conclusions:***

Eltrombopag appears to be a safe treatment for ITP (although long-term follow-up studies are awaited) and has short term efficacy. However, NICE found based on the evidence submitted and reviewed that there was no robust evidence on long-term efficacy or cost-effectiveness of eltrombopag and a lack of direct evidence for eltrombopag tested against other relevant comparators.

## **1. Introduction:**

The National Institute for Health and Clinical Excellence (NICE) is an independent organisation whose responsibilities include providing national guidance to the NHS in England and Wales on the use of selected new and established health technologies. One aspect of this is the Single Technology Appraisal (STA) process, which is specifically designed for the appraisal of a single health technology, with a single indication, where most of the relevant evidence lies with one manufacturer or sponsor.<sup>1</sup> Typically, it is used for new pharmaceutical products recently launched. The evidence for an STA is principally derived from a submission by the manufacturer/sponsor of the technology, which should be based on a specification developed by NICE. A report reviewing this evidence submission is then produced by an external organisation independent of NICE: the evidence review group (ERG).

The NICE appraisal committee then considers the submissions from the manufacturer or sponsor and the ERG alongside testimony from experts and other stakeholders to formulate preliminary guidance. All stakeholders have an opportunity to comment on this preliminary guidance, after which the NICE appraisal committee meet again to produce the final guidance (Final Appraisal Determination; FAD). This paper presents a summary of the ERG report for the STA of eltrombopag for chronic immune of idiopathic thrombocytopenic purpura (ITP) and the subsequent development of NICE guidance for the use of this drug.

Full details of all the relevant appraisal documents (including the appraisal scope, ERG report, manufacturer and consultee submissions, ACD, FAD, and comments on each of these) can be found on the NICE website.<sup>2</sup>

## **2. The Decision Problem:**

ITP is a condition where auto-antibodies are formed against platelets leading to increased clearance from the circulation. Where 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

range from 1.13<sup>3</sup> to 6.6 per 100,000/year.<sup>4</sup> Table I outlines the common treatments for ITP, as well as those under appraisal in this STA.

**Table I: Common treatments for ITP**

Treatments considered by appraisal	Other treatments*
Rituximab (not licenced for ITP)	Splenectomy (surgical treatment)
Thrombopoietin analogues: Romiplostim and Eltrombopag (under appraisal by NICE)	cyclophosphamide
Intavenous Immunoglobulin (IVIg)	vinca alkaloids
Anti –D immunoglobulin (withdrawn in Europe over safety concerns)	danazol
	azathioprine
	ciclosporin
	mycophenolate mofetil
	dapsone
	alemtuzumab
	autologous stem cell transplantation
	interferon
	combination chemotherapy

*\* It is assumed that these treatments will have been tried alone or in combination prior to prescribing treatments in column 1*

*ITP = immune or idiopathic thrombocytopenic purpura; NICE = National Institute for health and Clinical Excellence.*

Eltrombopag increases 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 Limited, 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.

The manufacturer presented evidence on the clinical and cost-effectiveness of eltrombopag accompanied by two de-novo economic evaluations for two distinct patient groups. This appraisal considers the use of eltrombopag for patients treated under a “Watch and Rescue” programme (the majority of patients) and also for those with serious “long-term” ITP.

NICE developed a scope for the assessment of eltrombopag, which specified that the clinical and cost-effectiveness of this drug should be established, within its licensed indication relative to comparators (romiplostim, IVIg, anti D and rituximab). It was assumed that patients would all have been pre-treated with steroids.

### **3. The independent ERG review:**

The manufacturer (GlaxoSmithKline Limited) provided a submission to NICE on the use of eltrombopag (within the context of the licensed indication) in adults with chronic immune of idiopathic thrombocytopenic purpura (ITP) for two identified scenarios. The ERG report comprised a critical review of this evidence, incorporating three aims:

- Assess whether the manufacturer's submission conformed to the methodological guidelines issued by NICE;
- Assess whether the manufacturer's interpretation and analysis of the evidence were appropriate;
- Indicate the presence of other sources of evidence or alternative interpretations of the evidence that could help to inform NICE guidance.

The ERG modified the manufacturer's search strategy to identify additional studies not identified in the manufacturer's submission; examined the impact of altering some of the key model assumptions; conducted additional analyses and sought a number of points of clarification from the manufacturer, the results of which were incorporated into the review of the evidence. The manufacturer submitted an addendum and revised economic model following the identification of a factual error in the model. The discussion in this paper focuses on the amended economic model unless otherwise stated.

#### **3.1 Clinical evidence:**

The principal evidence on efficacy came from the RAISE study.<sup>5</sup> This was a six-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 six-week RCTs comparing eltrombopag with placebo. TRA100773A<sup>6</sup> was a phase II dose finding study involving 118 participants and TRA100773B<sup>7</sup> was a phase III RCT involving 114 participants.

### **3.1.1 Efficacy:**

In the RAISE<sup>5</sup> study, eltrombopag had statistically significantly greater odds of achieving the primary outcome of a platelet count between 50 and 400 x 10<sup>9</sup>/l during the 6 month treatment period. Of the patients treated with eltrombopag, those who had not received a splenectomy had longer response times. Furthermore, eltrombopag patients required less rescue medication and had a greater proportion of patients reducing or discontinuing concomitant ITP medication compared with placebo. Odds ratios and confidence intervals indicating statistical significance or otherwise are presented overall and for each patient group in table II.

In a meta-analysis of the TRA100773A<sup>6</sup>, TRA100773B<sup>7</sup> and RAISE<sup>5</sup> studies for the outcome of a platelet count 50 to 400 x 10<sup>9</sup>/l at day 43, eltrombopag had statistically significant greater odds of platelet response compared with placebo for all patients (OR 8.39, 95% CI: 4.77 to 14.75); non-splenectomised (OR 9.17, 95% CI: 4.52 to 18.60) and splenectomised (OR 7.20, 95% CI: 2.82 to 18.35).

### **3.1.2 Safety:**

Safety of the intervention was assessed in terms of bleeding data from RAISE<sup>5</sup> trial respondents. The odds of any bleeding (WHO grade 1-4) events were lower in all patients treated with eltrombopag compared with placebo. The OR was statistically significant for non-splenectomised patients but was not significant for the splenectomised patient group. The odds of clinically significant bleeding (WHO grades 2-4) were also lower in the eltrombopag group. Odds ratios and confidence intervals presented by the manufacturer are summarised in table II. The risk of liver function disturbances were greater for eltrombopag, however no cases of bone marrow fibrosis, photo-, cardio- or renal- toxicity occurred during the intervention.



**Table II. Summary of the results from the RAISE study**

Outcome measure	All participants**	Splenectomized**	Non-splenectomized**
Odds of achieving a platelet count between 50 and 400× 10 <sup>9</sup> /L over 6 month treatment period	ELT 52%, PL 17% OR 8.2 (99% CI 3.6, 18.7)	ELT 37%, PL 15%	ELT 60%, PL 18%
Durable response – median cumulative wks of response	ELT 10.9, PL 0	ELT 6, PL 0	ELT 13.4, PL 0
Need for rescue medication during the intervention	ELT 25/135 (18%) PL 25/62 (40%)* OR 0.33 (95% CI 0.16, 0.64)	ELT 11/50 (22.0%) PL 10/21 (47.6%) OR 0.33 (95% CI 0.11, 1.02)	ELT 14/85 (16.5%) PL 15/41 (36.6%) OR 0.34 (95% CI 0.14, 0.79)
Reduction in dose/frequency of concomitant ITP medications taken at baseline	ELT 37/63 (59%) PL 10/31 (32%)*	ELT 12/27 (44.4%) PL 5/13 (38.5%) OR 1.29 (95% CI 0.33, 5.04)	ELT 25/36 (69.4%) PL 5/18 (27.8%) OR 5.87 (95% CI 1.67, 20.59)
Odds of any bleeding (WHO grade 1–4)	ELT 106/135 (79%) PL 56/60 (93%) OR 0.24 (95% CI 0.16, 0.38)	ELT 41/50 (82%) PL 18/20 (90%) OR 0.87 (95% CI 0.12, 6.07)	ELT 65/85 (76%) PL 38/40 (95%) OR 0.10 (95% CI 0.02, 0.53)
Odds of clinically significant bleeding (WHO grade 2–4)	ELT 44/135 (33%) PL 32/60 (53%) OR 0.35 (95% CI 0.19, 0.64)	ELT 19 (38%) PL 14 (70%) OR 0.27 (95% CI 0.08, 0.95)	ELT 25 (29%) PL 18 (45%) OR 0.31 (95% CI 0.11, 0.83)

ELT = eltrombopag; ITP = immune or idiopathic thrombocytopenic purpura; OR = odds ratio; PL = placebo; \*  $p \leq 0.001$  between treatment arms.

\*\* Where odds ratios and / or confidence intervals are not reported in the table, this is because they were not reported in the appraisal documentation.

### **3.1.3 Indirect comparison between eltrombopag and romiplostim:**

There was no direct RCT evidence comparing eltrombopag with any of the relevant comparators specified in the NICE scope. The manufacturer of eltrombopag conducted an indirect comparison and meta analysis between EPAG (RAISE study<sup>5</sup>) and Romiplostim<sup>8</sup> (2 RCT's). Such an indirect comparison and meta analysis was not possible with any of the other comparators, as romiplostim was the only comparator to report placebo controlled RCTs for this disease.

Romiplostim had a greater 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 odds ratio favored 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\*<sup>1</sup>.

### **3.1.4 Critique of clinical evidence and interpretation:**

The manufacturer identified 20 RCTs and 93 non-randomised comparative studies or case series in the systematic review reporting on eltrombopag or comparator treatments. Of these, 36 reporting comparator treatments included children or adolescents (< 18 years old).

No attempt was made to statistically describe or quantitatively synthesise data on comparator treatments. Instead, evidence from one or two primary studies / reviews was used for each comparator treatment in the economic model. The manufacturer stated that the evidence chosen for the economic model was the best available. However, the ERG identified the American Society of Hematology (ASH) guideline<sup>9</sup> and a high quality systematic review<sup>10</sup> where more reliable evidence on IVIg and anti-D was reported. The use of such data would not have materially affected the conclusions of the economic evaluation.

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\* Durable response was defined as a weekly platelet count  $\geq 50 \times 10^9/l$  during six or more weeks of the last eight weeks of treatment excluding those who received rescue medication at any time during the study, while overall response was durable plus transient response (four or more weekly responses  $\geq 50 \times 10^9/l$  during the study without a platelet response from week 2 to 25).

In terms of the representativeness of the study participants in the eltrombopag trials, only 3/109 (2.8%), 10/114 (8.8%), and 9/197 (4.7%) were from the UK in trials TRA100773A<sup>6</sup>, TRA100773B<sup>7</sup> and RAISE<sup>5</sup> respectively. It is unclear whether the participants in the eltrombopag trials were representative of UK chronic ITP patients. In addition, the decision problem specified that one group of patients considered should be non-splenectomised patients for whom splenectomy is contraindicated. The manufacturer made an assumption that all non-splenectomised patients were contraindicated to having a splenectomy. However, patients who were in the non-splenectomised group, may have been suitable for having a splenectomy, therefore the manufacturer's assumptions do not fully address the decision problem in this scenario.

Intention To Treat (ITT) analysis was not used in TRA100773A<sup>6</sup> and B<sup>7</sup> as the manufacturer stated. A small number of randomised patients (8/109 [7.3%] in TRA100773A<sup>6</sup>, 2/102 [2.0%] in TRA100773B<sup>7</sup>) were excluded from the statistical analysis. Any degree of exclusion following randomisation may break the balance of the baseline patient characteristics achieved by randomisation.

Large proportions of participants withdrew or were lost to follow-up in the trials, ranging from 7% to 21% across treatment groups. In TRA100773A<sup>6</sup> and B<sup>7</sup> there were more such participants in the placebo groups and in the RAISE<sup>5</sup> trial there were more in the eltrombopag group. As such participants were counted as non-responders (platelet count), the results for platelet response might have favoured eltrombopag in studies TRA100773A<sup>6</sup> and B<sup>7</sup>, and placebo in the RAISE<sup>5</sup> study.

The manufacturer used an inappropriate method (Mantel-Haenszel fixed effect meta-analysis) to combine the two romiplostim trials.<sup>8</sup> In most meta-analyses an important issue is whether the populations used in the different trials are homogeneous. In this case it is clear that the two populations being meta-analysed are heterogeneous: one considered splenectomised patients and the other considered non-splenectomised patients. In addition, as there were more participants who did not complete the treatment (withdrew or were lost to follow-up) in the eltrombopag trial than in the romiplostim trials, assuming such participants were non-responders (worst case scenario) might bias the results in favour of romiplostim. The ERG undertook a further indirect comparison analysis in which all such participants were classed as

responders (best scenario). Estimates were derived from a logistic regression model. 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, although the difference remained non-significant (OR 1.04, 95% CI: 0.32 to 3.44). These indirect comparison data were not explored in the economic model.

### **3.2 Cost-effectiveness evidence:**

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

The “watch and rescue” model compared eltrombopag plus standard care with standard care alone. This model was based on the double blind RAISE<sup>5</sup> RCT. The proportion of people who would receive eltrombopag in practice to treat ITP was determined from an internal GlaxoSmithKline study. The main comparator for analysis in the economic evidence is placebo. The incremental cost per QALYs for the base case analyses for splenectomised and non-splenectomised patients were £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 “long term treatment” 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 [which was considered only for those who were contra-indicated to splenectomy] 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 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 of the non-dominated sequences. No other sequences had an incremental cost per QALY approaching £30,000. Treatment sequences including eltrombopag dominated the same sequences without eltrombopag

when patients had received prior treatment with rituximab. Deterministic sensitivity analysis varied the response rate used in the model and the model time horizon as well as other uni-variant analyses. These did not greatly change the results.

### **3.2.1 Critique of cost-effectiveness evidence and interpretation:**

#### ***Watch and Rescue model:***

The RAISE trial used to populate the economic model was of high quality. However, within the model, benefits were allowed to accrue over a patient's life time but costs for this period were only assumed to occur over 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.

Modelling assumptions were made based on both published data and clinical expert opinion. It was not always clear how expert opinion was used to value parameters in the model and further which experts contributed to which issues or if the assumptions were representative of a UK ITP population. It was assumed that all patients in the non-splenectomised group were contra-indicated to having a splenectomy. This may not be a true reflection of all non-splenectomised patients in reality.

The ERG believed that the manufacturer failed to adequately describe the impact of combined uncertainty in parameter values within the model. The model is sensitive to the rate of mortality and discount rate used, however multi-variant sensitivity analyses were not undertaken. Plausible changes to certain combinations of assumptions conducted by the ERG lead to substantial increases or decreases in the reported incremental cost per QALY for both patient groups. None of the sensitivity analyses conducted either by the manufacturer or the ERG bring the ICER below £30,000 / QALY (Table III).

**Table III Exploratory sensitivity analyses for splenectomised and non splenectomised patients (watch and rescue model)**

	Incremental cost per QALY*	
	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 200010 – lower bound	131,841	150,245
8. Annual Risk of fatal bleed Cohen 200010 – upper bound	55,778	64,882
9. Combining 2,3,4,6 & 7 (Worst Case Scenario)	231,195	193,293
10. Combining 5 & 8 (Best Case Scenario)	33,561	39,657

QALY: Quality Adjusted Life Year

\*ICER refers to the economic watch and rescue model, comparing eltrombopag with placebo

In addition, the manufacturer did not indicate the price at which eltrombopag would be cost-effective. ERG analysis found that the price of eltrombopag would need to be substantially below the anticipated market price for eltrombopag to be considered cost-effective at typical thresholds that society might be willing to pay for a QALY gain.

***Long-term model:***

Expert opinion was used throughout the model to inform the choice of model structure and parameter values. As these assumptions represented judgements made by the manufacturer and their advisors their basis can be questioned as alternative assumptions might have been made.

There is likely to be considerable uncertainty surrounding the manufacturer’s estimates of incidence rates, proportions of patients receiving eltrombopag treatment and the

proportion of patients requiring long-term care. Sensitivity analysis illustrates that changes in the assumptions used can lead to considerable variation in cost with little variation in QALYs gained in each treatment sequence.

Specifically, in relation to the model structure, the ERG noted that rituximab was the first line of treatment presented on the cost-effectiveness frontier. However, rituximab is not licensed in the UK for the treatment of ITP patients and so may not be clinically relevant. Further, the inclusion of anti-D as a comparator may have been inappropriate as the drug recently lost its UK market authorisation.

Only indirect evidence relating to a short follow up was available and the use of such data in the long term model created bias of unknown magnitude and direction. Utility values reflected two components, namely the utility gained from reduced risk of death / bleeding and the improvement in quality of life generated as a result of the treatment administered. One single utility measure was not available to measure both components, therefore due to a lack of data, two measures of utility were used (EQ-5D to measure treatment related improvement in quality of life and SF-6D to measure reduced risk of bleeding<sup>11</sup>). It was unclear how comparable these methods were for ITP patients.<sup>12,13</sup> More importantly, however, was the issue that the manufacturer did not incorporate utility decrement due to adverse events associated with eltrombopag or any of the comparator treatments in the model. The only utility decrement measured was in relation to bleeding events. The direction of the bias this introduced was unclear but it was quite plausible that it was against eltrombopag.

Results of one way deterministic sensitivity analyses for both patient groups appeared robust. However, various combinations of plausible variation were explored further by the ERG in multi-variant analyses. It was found that the results were influenced and were most sensitive to changes in: time horizon, response rate & response target value. A platelet response rate of  $>30 \times 10^9/L$  combined with 50 years' time horizon favoured romiplostim over eltrombopag as the most cost-effective treatment option post rituximab. These results applied to both patient groups; however none of the analyses of any treatment sequences brought the ICER below £30,000 per QALY gained.

The manufacturer did not present adequate probabilistic sensitivity analyses and Cost Effectiveness Acceptability Curves (CEACs) were not reported. The ERG presented CEACs based on the net benefit statistic, the results of which corroborated those of the multi-way deterministic analyses.

While the limitations of the submission are outlined, it is also acknowledged that there was a real paucity of data for eltrombopag and its comparators available in the public domain and the ERG agreed that the data used to inform the manufacturer's model was generally the best available at the time of this appraisal.

### **3.3 Conclusions of the ERG report:**

Overall, the key issues identified by the erg were as follows:

While Eltrombopag appeared to be a safe treatment with short term efficacy for ITP, there was no robust long-term efficacy or safety data.

There was no robust direct evidence on the effectiveness of eltrombopag compared with other relevant comparators. However, eltrombopag appeared to be less effective in achieving an overall response rate than romiplostim in a 6-month intervention period.

The representativeness of the RAISE<sup>5</sup> trial to the UK ITP population was uncertain, as were the estimates of incidence, prevalence and potential numbers of patients requiring long term treatment with eltrombopag.

Substantial reductions in the cost of eltrombopag are needed before the incremental cost per QALY would fall below £30,000 for either watch and rescue or long term care. There was large variation in the ICERs presented surrounded by large confidence intervals.

Using non-randomised non-comparative data in the long term model may have resulted in biased estimates. The magnitude and direction of these biases was uncertain. Extending the model to a 50 year time horizon for a lower target response value favoured a sequence involving romiplostim in treatment post rituximab; however the relevance of rituximab's inclusion as first line treatment was questionable and likely favoured the comparator drugs.



#### **4. Key Methodological Issues:**

The ICER presented by the manufacturer was well above the £30,000 per QALY threshold as recommended by NICE to be considered as potentially cost-effective. The ERG considered the key methodological issues of this review to be the uncertainty surrounding the point estimate of the ICER as presented in the “watch and rescue” model. Probabilistic analyses were not conducted by the manufacturer and no joint uncertainty was modeled. The ERG found that there was wide variation in the results depending on model parameter inputs and it was thus almost impossible to detect the true value for either the splenectomised or non-splenectomised group. Further, in relation to the long term model presented, it was unclear how best to model the potential sequences. Including rituximab (an unlicensed product) may have been inappropriate and underestimated the use of eltrombopag in both splenectomised and non-splenectomised patient groups. One final methodological issue was the combination of utility estimates from both the SF-6D and EQ-5D. It is unclear how these can be combined and projecting values based on algorithms can create noise in the estimates and increase uncertainty in the parameters. It would have been superior for all utility values to come from the same source. At the time of modeling, the EXTEND trial had not been completed and long term data were incomplete. The EXTEND trial is an open-label, dose-adjustment, extension study to evaluate the safety and efficacy of eltrombopag over a longer time horizon. Patients who have previously been enrolled in an eltrombopag trial were eligible for inclusion and it is anticipated that the trial will be concluded by July 2014. It is arguable that projective parametric modeling beyond the trial follow up may have been incomplete. This was further evidenced by the fact that benefits of treating with eltrombopag in the watch and rescue model were extrapolated over a life time, however associated costs with treatment on the placebo arm were not. It would have been better for the manufacturer to have explored a method of extrapolation exploring both cost and QALY implications. This was explored by the ERG and found to create a bias in favour of eltrombopag.

A further issue of uncertainty was how the manufacturer compared eltrombopag and romiplostim from their meta-analysis. This was explored for the second appraisal committee meeting, but was not found to alter the conclusions, however, there were

inconsistencies in the methods of reaching a relative risk value for both romiplostim and eltrombopag.

The key issue for a decision maker in terms of methodology is whether or not these economic uncertainties outweigh any patient gain from taking the drug.

## **5. NICE Guidance:**

The Final Appraisal Determination (FAD) was published by NICE in September 2010 and did not recommend eltrombopag for the treatment of chronic ITP in patients who were splenectomised or for patients who were not-splenectomised and assumed contraindicated to having a splenectomy. The committee did not deem the recommendation of eltrombopag appropriate in either a “watch and rescue” care setting or for long term care of more serious ITP patients to be a cost-effective use of scarce NHS resources.

### **5.1 Consideration of the evidence:**

The appraisal committee considered all of the available evidence submitted by the manufacturer and critiqued by the ERG together with additional sensitivity analyses presented by the ERG. The committee further took into account submissions from patient representatives and clinical experts in the field, noting the increased risk of bleeding associated with ITP as well as the significant impact on patient’s daily living. The impact of adverse side effects to some of the current ITP treatments especially steroids and the potential place for eltrombopag in treatment pathways for both watch and rescue patients and long-term patients were considered. The appraisal committee also took into account the effective use of scarce NHS resources.

#### **5.1.1 Clinical Evidence:**

The committee noted the small number of patients in the RAISE trial from the UK and questioned the trial’s representativeness. However, they accepted clinical opinion that these participants would be broadly reflective of patients undergoing treatment in England and Wales. The short term use of eltrombopag as in the RAISE trial was not

found to be clinically relevant as treatment would not likely stop at 26 weeks in practice. Therefore, the RAISE trial was deemed not sufficiently representative of the likely clinical management of these patients. For this reason, together with a lack of follow up data, the RAISE trial data were not deemed appropriate for the long term treatment scenario either.

The committee noted the increased odds of achieving target platelet count on eltrombopag as well as reduced risk of minor bleeds. They noted however, that the risk of serious bleeds was non-significantly different between the placebo and eltrombopag arms of the trial. In terms of adverse events, there was no data comparing eltrombopag with comparators, however adverse events between the eltrombopag and placebo arms were not different. ERG and manufacturer indirect comparisons showed a greater overall response for eltrombopag compared to romiplostim, however, as pointed out by the manufacturer, there were great uncertainties surrounding this estimate.

### **5.1.2 Cost-effectiveness evidence:**

While the committee found the model structure to be sound, it was concerned with the level of uncertainty surrounding key parameters used in the model. Further in relation to this, it was concluded that the model time frame was not sufficiently long enough to capture the full costs and benefits associated with eltrombopag or standard care. Due to great levels of uncertainty in parameters and in the ICER produced by the model under various one way and multi way sensitivity analyses (considered by both manufacturer and ERG), the committee concluded that the model was not able to provide a precise estimate of the ICER. Some of the initial concerns were addressed by the manufacturer in a re-submitted model, and was corrected by the ERG, showing a range of ICERs above those usually accepted by NICE. The committee also addressed concerns that it had not considered the relatively low aggregate impact on NHS budget, however pointed out that this is beyond their remit and overall budgetary impact should not form the basis of their guidance decision.

Therefore, due to uncertainty in the ICERs, lack of predictive power of the model and the associated large costs for little QALY gain, the committee concluded that the use of

eltrombopag in a watch and rescue setting was not a cost-effective use of NHS resources and no exceptional circumstances would exist where this would be the case.

In relation to the long term model, the committee (based on expert opinion) felt that the manufacturer sequence of treatments was not the most likely in practice as they did not feel an unlicensed treatment (rituximab) would be given before a licensed one (e.g. eltrombopag). A treatment sequence where the lead treatment was eltrombopag would not likely be cost-effective. Further, as romiplostim was likely associated with a greater response rate, it was clinically implausible that romiplostim would not be prescribed before eltrombopag. Variations in treatment sequences lead to huge increases in ICERs reported and the committee was concerned with this uncertainty. As romiplostim was under consideration at the time of appraisal, rituximab was an unlicensed treatment and IVIg and anti-D were not likely long term treatments, this potentially left only eltrombopag which was shown in the watch and rescue model not to be a cost-effective use of NHS resources. The committee concluded that the long term continuous model did not provide a basis on which to appraise the cost-effectiveness of eltrombopag and that the comparators and sequences of treatment were not plausible in clinical practice. They further felt that the eltrombopag treatment effect was based on trial evidence from a population that was much broader than the patient group under consideration.

Since development of this guidance, a second NICE appraisal committee has found romiplostim to offer a cost-effective use of NHS resources. The guidance was developed as part of technology appraisal TA221 and recommended the use of romiplostim for chronic ITP in patients whose condition is refractory to standard active treatments and rescue therapies or who have severe disease and a high risk of bleeding that needs frequent courses of rescue therapies. The recommendation stands on condition that the manufacturer makes romiplostim available at a discount agreed as part of a Patient Access Scheme (PAS) submission to NICE.

### **6. Conclusion:**

The main evidence reported for this STA process came from a single randomised placebo controlled trial (RAISE trial)<sup>5</sup> and is typical of novel treatments for diseases

such as ITP. Two other trials<sup>6,7</sup> supplemented the evidence from the RAISE study<sup>5</sup> and indicate that eltrombopag appears to be a safe and effective treatment for ITP; however the modeling provided fails to demonstrate a robust case for cost-effectiveness. ICERs are very large and associated with considerable uncertainty. Assumptions surrounding the applicability of the trial and economic models to clinical practice were questionable and therefore eltrombopag was not deemed to be a cost-effective use of NHS resources for the treatment of chronic ITP. There is a lack of evidence comparing eltrombopag with other comparator treatments and there is a need for a high quality trial comparing all the main comparators. Alternatively, a fully integrated high quality economic modeling process of the comparators (especially romiplostim and eltrombopag) would be appropriate in determining the most effective and cost-effective treatment for this condition.

*References*

- 1 **Guide to the Single Technology Appraisal (STA) process [document on the Internet].** London: National Institute for Health and Clinical Excellence; 2009 [accessed January 2011]. URL: <http://www.nice.org.uk/media/42D/B3/STAGuideLrFinal.pdf>.
- 2 **Thrombocytopenic purpura - eltrombopag [webpage on the Internet].** London: National Institute for Health and Clinical Excellence; 2010 [accessed January 2011]. URL: <http://guidance.nice.org.uk/TA/Wave17/14>.
- 3 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.
- 4 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 Hematology.* New York: McGraw-Hill; 1995. p. 1315-1355.
- 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 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.
- 7 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.
- 8 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.
- 9 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 Hematology. *Blood* 1996;88:3-40.
- 10 Chen S, Pi,D, Ansari,M, Puil,M, Desjardins,B, Banks,R. *Polyclonal intravenous immunoglobulin in patients with immune thrombocytopenic purpura: clinical systematic review. Technology report number 108. [document on the Internet].* Ottawa: Canadian Agency for Drugs and Technologies in

- Health; 2008 [accessed January 2011]. Available from: URL: <http://www.cadth.ca/index.php/en/publication/809>.**
- 11 Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. *J Health Econ* 2002;21:271-92.**
  - 12 Bruneneberg D, Joore,MA, Boonen,A, Nelemans,P, Kuijpers,P, Honig,A et al. *Comparing SF-6D & EQ-5d: Data from 4 Patient Populations [conference abstrct on the Internet]. iHEA 6th World Congress, Copenhagen, July 2007; 2007 [accessed January 2011]. Available from: URL: [http://papers.ssrn.com/sol3/papers.cfm?abstract\\_id=992656](http://papers.ssrn.com/sol3/papers.cfm?abstract_id=992656).***
  - 13 Seymour J, McNamme P, Scott A, Tinelli M. Shedding new light onto the ceiling and floor? A quantile regression approach to compare EQ-5D and SF-6D responses. *Health Econ* 2009;19:683-96.**