NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Romiplostim for the treatment of chronic idiopathic (immune) thrombocytopenic purpura

Pre-meeting briefing

This briefing presents major issues arising from the manufacturer's submission (MS), Evidence Review Group (ERG) report and statements made by consultees and their nominated clinical specialists and patient experts. Please note that although condensed summary information is included for ease of reference, this briefing should be read in conjunction with the full supporting documents.

The manufacturer was asked to provide clarification of data used in the submission and of how evidence was identified, selected and analysed.

The manufacturer re-ran the economic model for a range of scenarios, including: revised assumptions on vial wastage, rates of adverse events, costs of testing and assessment associated with treatment, target platelet count of treatment, and correction of some errors within the model.

The manufacturer also revised the anticipated acquisition cost of romiplostim and submitted an updated economic model and results.

Indicative licensed indication

The EMEA Committee for Medicinal Products for Human Use (CHMP) positive opinion for romiplostim (Nplate, Amgen)[1] states the following: 'Nplate is indicated for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) splenectomised patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins). Nplate may be considered as second line treatment for adult non-splenectomised patients where surgery is contraindicated.'

[1] Committee for Medicinal Products for Human Use, 20 Nov 2008

Key issues for consideration

Clinical effectiveness

- A target platelet count of 50 × 109 per litre was considered in the evidence base and the manufacturer's base case. Should a specific target platelet count be considered?
  - Is the 'hypothetical scenario' for a target platelet count of 30 × 109 per litre and the results generated credible?

- Which comparator strategy best reflects current clinical practice in the UK:
  - 'watch and rescue' with use of IV corticosteroids, intravenous immunoglobulin, anti-D immunoglobulin as needed (non-splenectomised patients only) as needed **or**
  - an active treatment strategy with initial use of rituximab?

- Does the Committee consider that the evidence presented in the manufacturer's submission is applicable to the proposed licensed indication and the appraisal decision problem?
  - Are both the evidence from trials of romiplostim and comparator treatments and the survey of UK clinicians applicable to current UK practice?
  - Is further, specific definition required with respect to:
    - ◊ splenectomised patients who are refractory to other treatments
    - ◊ non-splenectomised patients where surgery is contraindicated?

- Does the Committee consider that the assumptions made about the similarity of effectiveness of romiplostim for both splenectomised and non-splenectomised patients are appropriate?

Cost effectiveness

- The economic model assumed no vial wastage and the availability of a range of vial sizes, including a [redacted]microgram vial. In practice, it is likely that there will be some wastage from each vial. Does the Committee

consider how to take into account results using the [redacted]microgram vials even though this size is not currently available?

- Noting the sensitivity analyses provided by the manufacturer in the original submission, those revised in the clarification and those additionally considered by the ERG:
  - Which values for the parameters explored in univariate sensitivity analyses are plausible?
  - Are the results of ERG's multivariate sensitivity analyses plausible?

1 Decision problem

1.1 Decision problem approach in the manufacturer's submission

Population	Adults with idiopathic (immune) thrombocytopenic purpura (ITP) with a platelet count of below 30×10^9 per litre. Assessing the following subgroups of ITP patients: • Non-splenectomised patients as second-line treatment after an inadequate response to initial corticosteroid treatment and where splenectomy is contraindicated. • Patients refractory to splenectomy.
Intervention	Romiplostim administered once weekly as a subcutaneous injection. • Initial dose of romiplostim of 1 microgram/kg based on actual body weight. • Weekly dose should be increased by increments of 1 microgram/kg until the patient achieves a platelet count above 50×10^9 per litre.
Comparators	• Corticosteroids • Watchful waiting ['watch and rescue'] with intravenous ['human normal'] immunoglobulin (intravenous Ig) • Watchful waiting with anti-D [Rh_0] immunoglobulin (anti-D Ig) as needed (non-splenectomised patients only) • Rituximab • Immunosuppressive agents (azathioprine, mycophenolate mofetil, ciclosporin) • Danazol • Dapsone • Cytotoxic agents (such as cyclophosphamide, vinca alkaloids) The manufacturer stated that the treatment pathway was based on existing guidelines for ITP, reviews, and a survey of clinicians experienced in the management of ITP.
Outcomes	• Durable or long-term response and/or duration of response • Overall response (patients with any platelet response) • Time to platelet response • Reduction in need for rescue medications or chronic therapies • Bleeding • Adverse effects of treatment • Mortality • Health-related quality of life (HRQoL)

Economic evaluation	Cost–utility analysis results as incremental cost per quality-adjusted life year (QALY) Time horizon: lifetime Perspective: NHS and Personal Social Services

1.2 Evidence Review Group comments

1.2.1 Population

The Evidence Review Group (ERG) identified that specification of the population in the manufacturer's decision problem differed from that in the proposed licensed indication stated in the CHMP positive opinion for romiplostim. The positive opinion specifies that romiplostim is indicated for ITP in 'splenectomised patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins). Nplate may be considered as second line treatment for adult non-splenectomised patients where surgery is contraindicated.'

The manufacturer clarified the epidemiological data for ITP and estimated that in England and Wales there may be 2669 people for whom romiplostim would be indicated (according to the proposed licensed indication).

1.2.2 Comparators

The ERG noted that only corticosteroids, intravenous Ig and anti-D Ig have a marketing authorisation for the treatment of ITP, but acknowledged that the comparators presented were consistent with those included in existing clinical guidelines and identified in the manufacturer's clinician survey. The ERG also acknowledged that although splenectomy may be an option for people with ITP whose condition does not respond to drug-based treatments, the proposed indication for non-splenectomised patients is limited to those with a contraindication to this surgery. It was agreed that splenectomy is not, therefore, a comparator.

The ERG noted that alemtuzumab (as included in the British Committee for Standards in Haematology guidelines and reported in the clinician survey as a treatment for ITP) and eltrombopag were not included in the decision problem.

2 Clinical effectiveness evidence

2.1 Clinical effectiveness in the manufacturer's submission

The manufacturer's submission compared romiplostim in addition to standard care with standard care alone for people with chronic ITP. Two populations were considered: people who had undergone splenectomy and, separately, those who had a contraindication to splenectomy.

Evidence on the efficacy of romiplostim was derived from two randomised placebo-controlled trials. One trial enrolled only people with ITP who had undergone splenectomy and the other recruited only non-splenectomised people with ITP, though this did not appear to be restricted to people with a contraindication to splenectomy. Safety data on romiplostim were taken from the two randomised controlled trials (RCTs) and from seven case series. The efficacy and safety of comparators was assessed using evidence from a literature search for existing guidelines, reviews and primary studies. No meta-analysis or indirect comparison was conducted.

2.1.1 Romiplostim

The submission reported the results of a literature review which included two placebo-controlled trials: one enrolled 63 patients who had undergone splenectomy, and the other enrolled 62 patients who had not. In both studies patients with ITP (mean of three platelet counts equal to or below 30×10^9 per litre, with none above 35×10^9 per litre) refractory to at least one previous treatment were randomised to either romiplostim plus standard care or standard care alone for 24 weeks. Concurrent or rescue medications were used at the investigators' discretion. Seven non-RCTs of romiplostim were reported in the manufacturer's submission. These included one open-label

extension study of the two included RCTs and six non-RCTs. No studies compared romiplostim with pre-specified treatment pathways.

The studies considered for efficacy data included:

- Study 20030105: a double-blind RCT including splenectomised patients (42 patients assigned to romiplostim, 21 to placebo).
- Study 20030212: a double-blind RCT including non-splenectomised patients (41 patients assigned to romiplostim, 21 to placebo).

It was acknowledged in the submission that the results could be confounded owing to platelet counts being known to clinicians and patients; this would indicate whether the patient was receiving treatment or placebo. The manufacturer suggested that platelet count is an objective measure and therefore less prone to bias, but acknowledged that outcomes with more subjective components (such as quality-of-life outcomes or use of rescue treatments) could have been influenced.

The two completed RCTs of romiplostim reported the following results:

- The primary endpoint was the incidence of durable response (a platelet count of at least 50×10^9 per litre in six or more weekly assessments in the last 8 weeks of treatment without use of rescue medication).
- Overall response (durable or transient platelet response, where a transient response was a platelet count of at least 50×10^9 per litre in four or more weekly assessments during weeks 2 to 25 of treatment, with no weekly response eligible within 8 weeks after rescue medication use and in the absence of a durable response).
- Time to platelet response (Kaplan–Meier estimated time to first platelet response).
- Duration of platelet response.
- Use of rescue treatments.
- Mortality.
- Adverse events.

- Health-related quality of life.

For adverse events and health-related quality of life, the manufacturer's submission reported pooled results from both studies.

Results for splenectomised patients

Efficacy results for study 20030105 (splenectomised patients) as reported in the manufacturer's submission were as follows:

- For the primary endpoint, no one in the placebo group (n =21) and 16 patients (38.1%) in the romiplostim group experienced a durable platelet response.
- No one in the placebo group and 33 patients (78.6%) in the romiplostim group achieved an overall platelet response.
- The Kaplan–Meier estimated median time to the first platelet response was 3.0 weeks.
- The mean period with a platelet response was 0.2 weeks for placebo and 12.3 weeks for romiplostim (difference 12.1 weeks; 95% confidence interval [CI] 8.7 to 15.6 weeks; $p < 0.0001$).
- A total of 12 patients (57.1%) in the placebo group and 11 people (26.2%) in the romiplostim group received rescue medication during the treatment period (odds ratio 0.278; 95% CI 0.094 to 0.822; $p = 0.0175$). The placebo group had 80 occurrences of rescue medication use to prevent and/or treat bleeding (0.17 per subject weeks [where subject weeks reflects total time in treatment]) while the romiplostim group had 63 occurrences (0.06 per subject weeks).
- Three patients in the placebo group died; the causes of death were pneumonia (after the end of study), pulmonary embolism and cerebral haemorrhage. There were no deaths in the romiplostim group.

Results for non-splenectomised patients

Efficacy results for study 20030212 (non-splenectomised patients) as reported in the manufacturer's submission were as follows:

- For the primary endpoint, one patient (4.8%) in the placebo group and 25 patients (61.0%) in the romiplostim group achieved a durable platelet response (odds ratio 24.45; 95% CI 3.34 to 179.18; p < 0.0001).
- Three patients (14.3%) in the placebo group and 36 patients (87.7%) in the romiplostim group achieved an overall platelet response (odds ratio 34.74; 95% CI 7.77 to 155.38; p < 0.0001).
- The Kaplan–Meier estimated median time to the first platelet response was 2.0 weeks.
- The mean period with a platelet response was 1.3 weeks for placebo and 15.2 weeks for romiplostim (difference 13.9 weeks; 95% CI 10.5 to 17.4 weeks; p < 0.0001).
- In total, [redacted] patients ([redacted]%) in the placebo group [redacted] patients ([redacted]%) in the romiplostim group received rescue medication during the treatment period (odds ratio [redacted]; 95% CI [redacted] to [redacted]; p = [redacted]).
- No patients in the placebo group and one patient in the romiplostim group died. The cause of death was intracranial haemorrhage 2 weeks after discontinuation of romiplostim.

Pooled results for adverse events (including bleeding events) and health-related quality–of-life outcomes reported in the manufacturer's submission were derived from a post-hoc analysis (conducted in response to the NICE scope for the appraisal) of data from the RCTs. Pooled results for the efficacy outcome 'time to failure' were also reported (table 6.4.2 [page 56] of the manufacturer's submission and section 4.3.1 [page 27] of the ERG report).

Based on the two RCTs, [redacted]% ([redacted]) of the combined romiplostim groups and [redacted]% ([redacted]) of the combined placebo groups experienced at least one bleeding event of any severity. A serious bleeding event, as defined by the regulatory protocol, was reported for [redacted]% ([redacted]) of the combined romiplostim

groups and [redacted]% ([redacted]) of the combined placebo groups. Bleeding of grade 3 severity or greater occurred in [redacted]% ([redacted]) of the combined romiplostim group and [redacted]% ([redacted]) of the combined placebo group. Bleeding events of grade 2 (moderate) severity or greater occurred in [redacted]% ([redacted]) of the romiplostim group and [redacted]% ([redacted]) of the placebo group.

Safety data were derived from combined results from the two RCTs and seven case series, which included dose-finding studies (20000137A, 20000137B, 20010218, 20050162), an open-label extension study (20030213; which included patients from other romiplostim studies), a study of patients with severe refractory ITP (20040209) and a bone marrow morphology sub-study (20050123). Details are given in the manufacturer submission, section 6.7.1 (pages 73-75). Bone marrow abnormality consistent with increased bone marrow reticulin was reported for 6 romiplostim-treated patients (3%, n = 204); no such abnormalities where reported for the placebo-only group.

The linear regression analysis of combined data from the two RCTs presented in the revised manufacturer's submission identified statistically significant differences (favouring romiplostim over placebo) in the mean change in EQ-5D score between the romiplostim and placebo groups (see manufacturer's response to clarification point B2; table 12). Statistically significant differences were not, however, identified by the regression method used in the original submission. Combined data from the two RCTs for change from baseline in the ITP-Patient Assessment Questionnaire (a disease-specific HRQoL instrument which comprises 10 scales) indicated that splenectomised patients in the romiplostim group had a statistically significantly greater ($p < 0.05$) improvement in the 'Symptoms', 'Bother', 'Social Activity' and 'Women's Reproductive Health' scales compared with placebo, while in non-splenectomised patients the romiplostim group had a statistically significant improvement in the 'Activity' scale.

2.1.2 Comparators

In the absence of studies comparing romiplostim with specified treatments, the manufacturer used a 'pragmatic' approach to identifying and selecting evidence on comparators. This resulted in a variety of study designs being assessed for the different treatments used in standard care. These included clinical guidelines, systematic reviews and observational as well as comparative studies. No meta-analysis was conducted. Efficacy data for different treatments were not compared using any statistical model (such as formal indirect or mixed treatment comparisons). Instead, efficacy data from different studies, but examining the same treatment, were combined by a method described in the submission as 'taking a weighted average, weighting by sample size'. The number of studies that were combined varied for different interventions: for example, 12 case series were pooled for initial response to intravenous Ig, but only one case series was used for initial response to azathioprine (non-splenectomised patients).

Efficacy data reported in the submission for initial response rate ranged from approximately 45% (46% for anti-D Ig and 45% for danazol in non-splenectomised patients and 44% for mycophenolate mofetil in splenectomised patients) to 80% (for intravenous Ig in unspecified ITP patients). Table 12 in section 4.3.1 (pages 48–49) of the ERG report lists comparator efficacy data.

Rates of severe adverse events and any other adverse events respectively were: for corticosteroids, 3% and 70%; for intravenous Ig, 2% (range 1–4%) and 0%; for anti-D, 3% and 0%; for rituximab, 3% and 0%; for danazol, 16% and 35%; for dapsone, 11% (range 3–27%) and 24%; for immunosuppressants (azathioprine, mycophenolate mofetil, ciclosporin), 15% (range 11–30%) and 12 to 36%; and for cytotoxic agents 21% and 30% (cyclophosphamide, vinca alkaloids).

2.2 Evidence Review Group comments

The ERG noted that limited evidence was available on the treatment of people with chronic ITP, including romiplostim and potential comparators, and particularly for long-term outcomes. The identification and selection of evidence in the manufacturer's submission may not have been systematic, and populations considered in the evidence did not fully match that specified in the decision problem or, in some cases, were poorly defined. It was likely that there was considerable heterogeneity among the evidence considered, and no adjustment for potential confounders was attempted. The ERG also noted that for comparators, evidence on non-splenectomised and splenectomised patients was commonly not distinguished.

A key concern was the methods used for estimating efficacy data for romiplostim and comparators. Data from the two romiplostim RCTs were not used for estimating comparative efficacy within the model; rather, each arm of the studies was used separately, with the control arms of the RCTs contributing little. Furthermore, data from various studies were combined with simple aggregation. The ERG report summarises the difficulties with this approach (section 5.2.2), stating, 'Effectively, indirect comparisons were made between absolute treatment effectiveness data without any explicit consideration of potential effect modifiers. The method used can not be characterised as being robust, it is therefore difficult to state with any degree of certainty how effective the treatments are.'

The ERG acknowledged that pooling using formal methods may have also been inappropriate, and for small number of studies may have produced similar estimates of efficacy and safety. It was also noted that underlying data abstraction was accurate and no evidence on romiplostim had been excluded. The ERG did not identify any additional evidence that would significantly alter the results presented in the manufacturer's submission. The ERG critique of the manufacturer's evidence synthesis is in section 4.1.7 of the ERG report (pages 19–23).

2.3 Statements from professional/patient groups and nominated experts

Patient experts described the impact of ITP, the value of controlling platelet count, limitations of current therapy and their views of romiplostim.

The patient experts indicated that people with low platelet counts fear that they will experience a major bleed, and that the condition impacts on daily activities and complicates dental and surgical procedures. Specifically, heavy menstrual periods were described as debilitating, and a stigma associated with exposing ITP-related bruises was cited.

Current individual treatment options were described as lacking efficacy for all people with ITP, being unpredictable and producing unwanted effects (including complications in the long term). Some treatments require infusion, which is disruptive to normal activities. High doses of steroids may be used and it was highlighted that splenectomy is irreversible, carried a risk of adverse effects and may not be effective.

Patient experts did not expect that romiplostim would 'change the course of the condition', but valued the option of another therapy, the potential to maintain platelet count while reducing need for other treatments, and the possibility that romiplostim could be self-administered outside hospital.

3 Cost effectiveness

3.1 Cost effectiveness in the manufacturer's submission

The UK list price for romiplostim anticipated by the manufacturer is 192.8p per microgram[2] and the anticipated price for vials of [redacted], 250 micrograms and 500 micrograms were stated to be £[redacted], £482.00 and £964.00, respectively.

[2] Based on the US price of [redacted].

The manufacturer submitted a cohort-type model in which patients were modelled separately depending on whether or not they had undergone splenectomy. It was assumed that all started with a platelet count below 50×10^9 per litre. The cost effectiveness of romiplostim was compared with standard care in a structure where modelled patients initially enter 'watch and rescue' standard care (treated as necessary with intravenous Ig, anti-D Ig [non-splectomised patients] or intravenous corticosteroids) or are treated initially with romiplostim followed by 'watch and rescue' care. In the model patients move through the care pathway, consisting of active therapies and 'watch and rescue' care. When a patient becomes refractory to an active treatment they move back to 'watch and rescue' care. The active treatments modelled in the remainder of the care pathway were rituximab, immunosuppressives (azathioprine, mycophenolate mofetil, ciclosporin), danazol, dapsone and cytotoxic agents (such as cyclophosphamide and vinca alkaloids).

Seven health states were used in the model. Five of them were identified and utility values derived from time trade off in research conducted on a general population sample which was commissioned by Amgen. These were as follows: sufficient platelets (above 50×10^9 per litre) and no bleed (utility [redacted], standard deviation [SD] 0.15); sufficient platelets with minor bleed treated as an outpatient (utility [redacted], SD [redacted]); low platelets (below 50×10^9 per litre) and no bleed (utility [redacted], SD [redacted]); low platelets and minor (outpatient) bleed (utility [redacted], SD [redacted]); low platelets and intracranial haemorrhage (utility [redacted], SD [redacted]). For the remaining two health states included in the model – low platelets with gastrointestinal bleed and low platelets with other bleeding events requiring hospitalisation – utilities were extracted from the literature; these were estimated at a value 0.54 for both health states[3].

[3] Source: Regier DA, Sunderji R, Lynd LD, et al (2006) Cost-effectiveness of self-managed versus physician-managed oral anticoagulation therapy. *CMAJ* 174(13):1847-52

Resource use and costs were divided into the following:

- Cost of treatment per 4-week cycle for splenectomised and non-splenectomised patients, including the costs of the romiplostim vials, testing (four tests), physician appointments (two sessions), and other drugs.
- Cost of management of bleeds, including minor bleeds treated in an outpatient setting, gastrointestinal bleeds and other bleeds requiring hospitalisation, and intracranial haemorrhage.

Overall (revised) costs for romiplostim were as follows:

- £2922.64 for splenectomised patients, based on an average body weight of 83.7 kg and a mean dose of 388 micrograms; patients use on average [redacted] of the [redacted] vials (or 1.38 of the 250 microgram vials).
- £2055.04 for non-splenectomised patients – mean dose of 242 micrograms; patients use on average 0.93 of the 250 microgram vials.

These costs assume the availability of both the 250 microgram and [redacted] vials. The manufacturer stated that drug remaining in any vials would be discarded and therefore the cost of whole numbers of vials required for one patient was applied in the model (but see ERG comment below). Other costs for drugs used in treatment and managing bleeds were taken from the British National Formulary and NHS reference costs. These are given in table 7.4 of the manufacturer's submission (pages 138–139). All costs and benefits were discounted at a rate of 3.5%.

The manufacturer's economic evaluation was revised following requests for clarification. This included a range of sensitivity analyses, including use of EQ-5D data available from RCTs, utility values for serious adverse effects, the cost of a bone marrow assessment required when response to the drug is lost, costs for a blood film test before treatment, reduced numbers of blood counts and clinic visits, and counting of physician visits. Key inputs were also

revised and results presented. This included an update to the anticipated acquisition cost of romiplostim (revised costs are quoted above) and analysis assuming a target platelet count of 30×10^9 per litre (modelled by increasing the response estimates).

Revision of the originally submitted base-case analysis resulted in an incremental cost-effectiveness ratio (ICER) of £14,633 per quality-adjusted life year (QALY) gained for non-splenectomised patients, and £15,595 per QALY gained for splenectomised patients, when using romiplostim as a first option treatment compared with 'watch and rescue' standard care (see table 1).

Table 1 Cost-effectiveness results (manufacturer's revised analysis) for treatment with romiplostim compared to 'watch and rescue' (standard) care using a target platelet count of 50×10^9 per litre and a romiplostim acquisition cost of 192.8p per microgram

Treatment	Costs (£)	QALYs	Marginal costs	Marginal QALYs	ICER per QALY
Non-splenectomised					
Standard care	408,203	10.76	£23,955	1.64	£14,633
Standard care plus romiplostim	432,158	12.40			
Splenectomised					
Standard care	611,641	11.70	£17,586	1.13	£15,595
Standard care plus romiplostim	629,228	12.83			

QALY, quality-adjusted life year.

Further revision of the base-case analysis to give a target platelet count of 30×10^9 per litre resulted in an ICER of £14,840 per QALY gained for non-splenectomised patients and an ICER of £14,655 per QALY gained for splenectomised patients using romiplostim as a first option treatment compared with 'watch and rescue' standard care (table 2).

Table 2 Cost-effectiveness results (manufacturer's revised analysis) for treatment with romiplostim compared to 'watch and rescue' (standard) care using a target platelet count of 30 × 10^9 per litre and a romiplostim acquisition cost of 192.8p per microgram

Treatment	Costs (£)	QALYs	Marginal costs	Marginal QALYs	ICER per QALY
Non-splenectomised					
Standard care	409,037	10.94	£23,911	1.61	£14,840
Standard care plus romiplostim	432,948	12.55			
Splenectomised					
Standard care	616,915	11.98	£16,447	1.12	£14,655
Standard care plus romiplostim	633,362	13.10			

QALY, quality-adjusted life year.

Probabilistic sensitivity analysis was undertaken and revised results were presented in the manufacturer's clarification response. Distributions for the sensitivity analysis were taken either from the literature or from trial data. Distributions for the effectiveness comparators were estimated because only low-quality data were available. Cost-effectiveness acceptability curves (CEACs) were derived from the revised probabilistic sensitivity analysis. The probability that romiplostim is cost effective at different acceptability threshold levels of £10,000, £20,000 and £30,000 per QALY gained was estimated to be 10%, 60% and 81% respectively for non-splenectomised patients (mean ICER £14,633 per QALY gained) and 25%, 55% and 77% respectively for splenectomised patients (mean ICER £15,595 per QALY gained).

3.2 Evidence Review Group comments

The ERG noted that sensitivity analyses using single parameters had only a small effect on the cost effectiveness of romiplostim compared with the result of the manufacturer's base case, but commented that the omission of multivariate analyses was a major weakness of the submission.

Although the manufacturer stated in the text of their submission that the use of full vials of romiplostim was modelled, the ERG stated that this was not the case in the model submitted and that the results were based upon the costs of fractions of a vial and so the model assumed no wastage.

Explorative sensitivity analyses were performed by the ERG using the manufacturer's revised model. These included multivariate analysis which combined sensitivity analyses conducted by the ERG with those provided by the manufacturer. Parameters varied in the ERG analyses included number of vials of romiplostim used and whether patients enter the comparator arm on 'watch and rescue' care or on active care (that is, a treatment regimen comprising use of rituximab at outset rather than 'watch and rescue').

The ERG identified that larger changes in the ICER resulted from the multivariate than from the univariate sensitivity analysis. Where patients entered the model on an active therapy (rituximab) in the comparator arm (rather than 'watch and rescue') the ERG reported an ICER of £21,674 per QALY gained for non-splenectomised patients and £29,771 per QALY gained for splenectomised patients. The ERG's multivariate sensitivity analyses, combined with the additional assumption that 'watch and rescue' is not the first-line treatment, increased the ICERs to £37,290 per QALY gained for non-splenectomised patients and £131,017 per QALY gained for splenectomised patients. The results of the ERG's sensitivity analysis are presented in appendix B, tables 3 and 4.

The ERG further commented that some 'plausible' changes in the parameters in the manufacturer's submission could reduce the ICER for romiplostim below the results reported in the submission, but that these had not been modelled. The ERG also noted that the direction (whether favouring romiplostim or comparators) and magnitude of these uncertainties were not assessed in the evidence presented – this was probably because of current limitations in the evidence base relating to the treatment of people with ITP.

The ERG investigated threshold values for changes in marginal costs and marginal QALYs which would produce an ICER of £30,000 per QALY gained. The ERG stated that for the alternative assumption that 'watch and rescue' was not the initial treatment for those not receiving romiplostim, the magnitude of changes to marginal costs and marginal QALYs required to give ICERs of above £30,000 per QALY were 'relatively modest'.

Noting the potential drivers of the cost effectiveness of romiplostim identified by the sensitivity analyses and the uncertainties discussed above, the ERG suggested a range of key questions for the decision maker based on these parameters (ERG Report, section 7.2 [page 102]).

4 Authors

Ruaraidh Hill, Helen Chung and Janet Robertson, with input from the Lead Team (Mark Chakravarty, Peter Barry).

Appendix A: Sources of evidence considered in the preparation of the premeeting briefing

A The evidence review group (ERG) report for this appraisal was prepared by Aberdeen Health Technology Assessment Group:

- Mowatt G, Boachie C, Crowther M et al., Romiplostim for the treatment of chronic immune or idiopathic thrombocytopenic purpura (ITP): a single technology appraisal, December 2008.

B Submissions or statements from the following organisations:

I Manufacturer/sponsor

- Amgen

II Professional/specialist, patient/carer and other groups:

- ITP Support Association
- Mr Derek Elston, patient expert
- Mrs Jeanette Atkinson, patient expert
- Dr John Grainger, Consultant Paediatric Haematologist, CMMCNHS Trust (endorsed ITP Support Association statement; no separate statement provided)

Appendix B: Supporting information

Revised cost-effectiveness results: ERG's exploratory sensitivity analyses

Table 3 Splenectomised patient group

Scenario	ICER (£ per QALY gained)	
	Watch and rescue is initial comparator intervention (as adopted by manufacturer)	Rituximab is initial comparator intervention (ERG analysis using manufacturer's model)
Base case	**15,595**	29,771
1. Use of EQ-5D data from RCTs	17,580	33,558
2. Change in number of vials (from 1.38 to 2.0)	91,406	109,802
3. Serious adverse events +50%	15,580	21,687
4. Serious adverse events −50%	15,608	29,796
5. Cost of bone marrow test included	15,639	29,817
6. Cost of blood assessment included	22,068	26,154
7. Reducing frequency of physician visits	15,642	29,803
8. Combining 1–2 and 4–7	110,352	131,017
9. Response rate for romiplostim (worst case for censoring)	17,501	106,703
10. Response rate for romiplostim (best case for censoring)	15,367	24,669
11. Combining 8 and 9	106,515	233,106
12. Romiplostim effectiveness reduced to 0.25 of base case	17,245	446,204
13. Romiplostim effectiveness reduced to 0.75 of base case	15,808	39,268

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Table 4 Non-splenectomised patient group

Scenario	ICER (£ per QALY gained)	
	Watch and rescue is initial comparator intervention (as adopted by manufacturer)	Rituximab is initial comparator intervention (ERG analysis using manufacturer's model)
Base case	**14,633**	21,674
1. Use of EQ-5D data from RCTs	16,503	24,426
2. Change in number of vials (from 0.93 to 1.0)	21,214	28,556
3. Serious adverse events +50%	14,623	21,658
4. Serious adverse events −50%	14,641	29,741
5. Cost of bone marrow test included	14,663	21,706
6. Cost of blood assessment included	19,230	36,131
7. Reducing frequency of physician visits	14,669	21,701
8. Combining 1–2 and 4–7	29,179	37,290
9. Response rate for romiplostim (worst case for censoring)	16,258	57,593
10. Response rate for romiplostim (best case for censoring)	14,152	18,776
11. Combining 8 and 9	29,934	76,728
12. Romiplostim effectiveness reduced to 0.25 of base case	16,354	165,129
13. Romiplostim effectiveness reduced to 0.75 of base case	14,884	26,439