

# Romiplostim for the treatment of chronic immune thrombocytopenia

Technology appraisal guidance

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## Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the [Yellow Card Scheme](#).

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Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should [assess and reduce the environmental impact of implementing NICE recommendations](#) wherever possible.

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# 1 Guidance

1.1 Romiplostim is recommended as an option for treating chronic immune thrombocytopenia in adults, only if:

- their condition is refractory to standard active treatments and rescue therapies or
- they have severe disease and a high risk of bleeding that needs frequent courses of rescue therapies.

Romiplostim is recommended only if the company makes it available with the discount agreed in the patient access scheme.

1.2 These recommendations are not intended to affect treatment with romiplostim that was started in the NHS before this guidance was published. People having treatment outside these recommendations may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

## 2 The technology

- 2.1 Romiplostim (Nplate, Amgen) is a protein that mimics the action of thrombopoietin by acting as an agonist at thrombopoietin receptors. It stimulates the differentiation and proliferation of bone marrow cells responsible for producing platelets (megakaryocytes), thereby increasing platelet production and platelet counts (concentrations). Immune thrombocytopenia (ITP) is an autoimmune bleeding disorder characterised by increased platelet destruction and, in some cases, inadequate platelet production. The disorder can result in low platelet counts and bleeding. Chronic ITP is defined as that which lasts longer than 12 months. Clinicians in the UK treat people with ITP as needed with 'rescue therapies' (corticosteroids, intravenous immunoglobulins and platelet infusions) and thereafter, as needed, with 'active treatments' (rituximab, immunosuppressive agents including azathioprine, mycophenolate mofetil and ciclosporin, danazol, dapsone, and cytotoxic agents including cyclophosphamide and vinca alkaloids). Romiplostim has a marketing authorisation 'for chronic immune (idiopathic) thrombocytopenic purpura (ITP) patients 1 year of age and older who are refractory to other treatments (e.g. corticosteroids, immunoglobulins)'.
- 2.2 The summary of product characteristics (SPC) states that the recommended initial dose of romiplostim is 1 microgram/kg of actual body weight, administered once weekly as a subcutaneous injection. The dose may be increased by increments of 1 microgram/kg until a platelet count equal to or above  $50 \times 10^9$  platelets per litre of blood is reached. A maximum dose of 10 micrograms/kg once weekly should not be exceeded. Platelet counts should be measured weekly until a stable count equal to or above  $50 \times 10^9$  platelets per litre is observed for at least 4 weeks without adjusting the dose. Thereafter, platelet counts should be measured monthly. Treatment with romiplostim should be stopped if the platelet count does not increase sufficiently to avoid clinically significant bleeding after 4 weeks of romiplostim therapy at the highest weekly dose of 10 micrograms/kg. Romiplostim should also be stopped if a peripheral blood smear indicates increased bone marrow reticulin as well as if a loss of efficacy is observed. For full details of dose and administration, see the SPC.

- 2.3 The SPC lists special warnings and precautions for the use of romiplostim, including: recurrence of thrombocytopenia and bleeding after stopping treatment; increased bone marrow reticulin; thrombotic and/or thromboembolic complications (described by the SPC as a 'theoretical risk' from platelet counts above the reference range); and loss of response (which could result from immunogenicity or increased bone marrow reticulin). The SPC lists headache as a 'very common' undesirable effect. For full details of side effects and contraindications, see the SPC.
- 2.4 The SPC states that romiplostim is supplied in both 500 microgram and 250 microgram vials. However, only 250 microgram vials are available in the UK. Romiplostim costs £1.93 per microgram, so a 250 microgram vial costs £482 (excluding VAT; 'British national formulary' [BNF] edition 60). The cost of treatment varies depending on the patient's weight and the dosing regimen. The cost will also be affected by any waste that results from discarding any unused drug from the single use of a 250 microgram vial. The SPC states that romiplostim is a sterile but unpreserved product and therefore is intended for single use only. The annual cost of romiplostim treatment for a person weighing 80 kg would be £8020 at a dose of 1 microgram/kg weekly and £80,204 at a dose of 10 micrograms/kg weekly (assuming no waste). The manufacturer of romiplostim (Amgen) has agreed a patient access scheme with the Department of Health which makes romiplostim available with a discount on the 250 microgram vial. The size of the discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS. The manufacturer has agreed that the patient access scheme will remain in place until any review of this NICE technology appraisal guidance is published.

### 3 The manufacturer's submission

The Appraisal Committee ([appendix A](#)) considered evidence submitted by the manufacturer of romiplostim and a review of this submission by the Evidence Review Group (ERG; [appendix B](#)).

#### Clinical effectiveness

- 3.1 The manufacturer's submission compared romiplostim in addition to standard care with standard care alone for patients with ITP who had undergone splenectomy and, separately, for patients with ITP who had not undergone splenectomy. Evidence was obtained from two double-blind placebo-controlled randomised controlled trials (RCTs) of romiplostim in addition to standard care (defined as prednisone, azathioprine and danazol) compared with standard care alone. One RCT enrolled patients with ITP who had undergone splenectomy (42 patients were assigned to romiplostim and 21 to placebo). The other RCT enrolled patients with ITP who had not undergone splenectomy, but who did not necessarily have a contraindication to splenectomy (41 patients were assigned to romiplostim and 21 to placebo).
- 3.2 In both RCTs, patients with ITP (defined as the mean of three platelet counts being below or equal to  $30 \times 10^9$  per litre, with none of the three counts being above  $35 \times 10^9$  per litre) whose condition was refractory to at least one previous treatment were randomised to romiplostim plus standard care or to standard care alone (placebo) for 24 weeks. The mean platelet count at baseline in the trials was  $18 \times 10^9$  per litre in the non-splenectomised group and  $15 \times 10^9$  per litre in the splenectomised group. Romiplostim was given weekly. Platelet counts were monitored and the dose of romiplostim was adjusted to achieve and maintain a platelet count of between  $50 \times 10^9$  and  $200 \times 10^9$  per litre. Investigators could increase the dose by 2 micrograms/kg each week (for platelet counts of  $10 \times 10^9$  per litre or below) or every 2 weeks (after 2 consecutive weeks of platelet counts between  $10 \times 10^9$  and  $50 \times 10^9$  per litre). The dose remained stable for platelet counts above  $50 \times 10^9$  per litre. If a patient's platelet count reached  $50 \times 10^9$  per litre or more

and subsequently fell, the maintenance dose could be increased by 1 microgram/kg each week (if the platelet count fell to  $10 \times 10^9$  per litre or below) or by 1 microgram/kg every 2 weeks (if the platelet count fell to between  $10 \times 10^9$  and  $50 \times 10^9$  per litre for 2 consecutive weeks). The maximum dose permitted in the trial was 15 micrograms/kg, which exceeds the maximum dose of 10 micrograms/kg recommended in the SPC.

- 3.3 No studies were found that compared romiplostim with a specified sequence of active treatments or rescue therapies for the treatment of ITP. Concurrent active treatments or rescue therapies for ITP in trials were given at the investigators' discretion. Six non-RCTs investigating the safety of romiplostim and one open-label extension study of the phase III RCTs were reported in the manufacturer's submission. In the latter, patients treated with romiplostim or placebo who had completed the phase III study and other clinical studies, and whose platelet counts had fallen below  $50 \times 10^9$  per litre after stopping romiplostim or placebo, were eligible to enrol in the study and to receive open-label romiplostim. Data from patients going into this extension study were used to calculate time to failure for romiplostim, as this could not be calculated from the phase III studies alone because the interventions ended after 24 weeks.
- 3.4 The primary endpoint for the two RCTs was the incidence of a durable platelet response, defined as a platelet count of at least  $50 \times 10^9$  per litre in at least six weekly assessments in the last 8 weeks of treatment without the use of rescue therapies. Rescue therapies included corticosteroids (oral or intravenous), intravenous immunoglobulin (IVIg) and intravenous anti-D immunoglobulin. Other outcomes were: incidence of an overall platelet response (either a durable or a transient platelet response, where a transient response is defined as a platelet count of at least  $50 \times 10^9$  per litre in at least four weekly assessments during weeks 2 to 25 of treatment, with no weekly response eligible within 8 weeks of the use of rescue therapies, 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 therapies; mortality; adverse events; and health-related quality of life. The primary and secondary outcomes were analysed prospectively. Time to failure (that is, time to stopping romiplostim) and bleeding events were analysed



retrospectively.

- 3.5 In the RCT of splenectomised patients, 16 of 42 patients (38.1%) in the romiplostim group and none of 21 patients in the placebo group had a durable platelet response. Thirty-three patients (78.6%) in the romiplostim group had an overall platelet response. The median time to the first platelet response was 3 weeks. No patients in the placebo group had an overall platelet response. The mean number of weeks with a platelet count equal to or above  $50 \times 10^9$  per litre (in a study period of 24 weeks) was 12.3 weeks for the romiplostim group and 0.2 weeks for the placebo group ( $p < 0.0001$ ). Eleven patients (26.2%) in the romiplostim group and twelve patients (57.1%) in the placebo group received rescue therapies during the treatment period (odds ratio 0.3; 95% confidence interval [CI] 0.1 to 0.8;  $p = 0.02$ ). There were no deaths in the romiplostim group. Three patients in the placebo group died; the causes of death were pneumonia (after the end of the study), pulmonary embolism and cerebral haemorrhage.
- 3.6 The manufacturer's submission stated that in the RCT of non-splenectomised patients, 25 of 41 patients (61.0%) in the romiplostim group and one of 21 patients (4.8%) in the placebo group had a durable platelet response (odds ratio 24.5; 95% CI 3.3 to 179.2;  $p < 0.0001$ ). Thirty-six patients (87.8%) in the romiplostim group and three patients (14.3%) in the placebo group had an overall platelet response (odds ratio 34.7; 95% CI 7.8 to 155.4;  $p < 0.0001$ ). The median time to the first platelet response was 2 weeks. The mean number of weeks with a platelet count equal to or above  $50 \times 10^9$  per litre (in a study period of 24 weeks) was 15.2 weeks for the romiplostim group and 1.3 weeks for the placebo group ( $p < 0.0001$ ). Seven patients (17.1%) in the romiplostim group and 13 patients (61.9%) in the placebo group received rescue therapies during the treatment period. One patient in the romiplostim group and no patients in the placebo group died. The cause of death was intracranial haemorrhage 2 weeks after stopping romiplostim. All patients included in both RCTs received at least one dose of either romiplostim or placebo. One non-splenectomised patient randomly assigned to placebo received three doses of romiplostim in error and was included in the safety analysis as a patient given romiplostim and in the efficacy analysis as a patient randomised to placebo.

- 3.7 The manufacturer's submission reported results for bleeding events, adverse events and health-related quality-of-life outcomes pooled from the two RCTs. These showed that 45 of 84 patients (54%) in the combined romiplostim groups (a revised figure of 48 of 84 [57%] was given in the Evidence Review Group [ERG] report using data provided by the manufacturer following a request for clarification) and 25 of 41 patients (61%) in the combined placebo groups experienced at least one bleeding event of any severity. A serious bleeding event, as defined by the regulatory protocol (which includes, but may not be limited to, any event that: is fatal, is life threatening [puts the person at immediate risk of death], needs in-patient hospitalisation or prolongation of existing hospitalisation, or is a persistent or significant disability or incapacity), was reported for 5 of 84 patients (6%) in the combined romiplostim groups and 4 of 41 patients (10%) in the combined placebo groups. Bleeding of grade 3 or above (rated as severe, life threatening or fatal) occurred in 6 of 84 patients (7%) in the combined romiplostim groups and 5 of 41 patients (12%) in the combined placebo groups. Bleeding events of grade 2 or above (rated as moderate, severe, life threatening or fatal) occurred in 13 of 84 patients (15%) in the combined romiplostim groups and 14 of 41 patients (34%) in the combined placebo groups.
- 3.8 Data on safety were derived from combined results from the two RCTs and seven case series, which included dose-finding studies, an open-label extension study (that included patients from other romiplostim studies), a study of patients with severe refractory ITP and a bone marrow morphology substudy. Both the incidence and event rates adjusted for study duration for all adverse events that occurred during treatment were calculated. Safety data were submitted as academic-in-confidence information by the manufacturer.
- 3.9 Data on health-related quality of life from the two phase III RCTs included data from EuroQol 5-D (EQ-5D) and from the ITP Patient Assessment Questionnaire, which is a disease-specific instrument comprising 10 scales. Statistically significant differences between health-related quality of life were not reported in the manufacturer's original submission. In a revised submission, the manufacturer provided a linear regression analysis of combined EQ-5D data from both RCTs, which showed statistically significant differences favouring romiplostim compared with

placebo in the mean change in EQ-5D score. Combined data from both RCTs for the change from baseline using the ITP Patient Assessment Questionnaire indicated a statistically significantly greater ( $p < 0.05$ ) improvement in the 'Symptoms', 'Bother', 'Social Activity' and 'Women's Reproductive Health' scales in the romiplostim group than the placebo group for splenectomised patients. For non-splenectomised patients, those in the romiplostim group had a statistically significantly greater improvement in the 'Activity' scale than those in the placebo group.

- 3.10 The manufacturer did not identify any RCTs on the effectiveness of comparator treatments used in standard care for ITP compared with romiplostim, as defined in the scope of this appraisal. These included corticosteroids, IVIg, rituximab, immunosuppressive agents (azathioprine, mycophenolate mofetil and ciclosporin), anti-D immunoglobulin and splenectomy for non-splenectomised patients, and corticosteroids, IVIg, rituximab and immunosuppressive agents for splenectomised patients. The manufacturer assessed clinical guidelines, systematic reviews, trials and observational studies for evidence on the effectiveness of comparator treatments and found mostly case series. The manufacturer combined data on efficacy from different studies that examined the same treatment by a method described in the manufacturer's submission as 'taking a weighted average, weighting by sample size'. The number of studies combined in this way varied by treatment.

## Cost effectiveness

### Original economic model

- 3.11 The manufacturer submitted an original economic model and, after consultation on the first appraisal consultation document (ACD), a revised model. The manufacturer's original cohort-type economic model used a lifetime horizon and assessed the impact of romiplostim separately for patients with ITP who had undergone splenectomy and those who had not. The model assumed that all patients started with a platelet count below  $50 \times 10^9$  per litre. Romiplostim was compared with standard care in a model structure in which patients initially either enter 'watch and rescue' (treated as necessary with intravenous

immunoglobulin, anti-D immunoglobulin [non-splenectomised patients] or intravenous corticosteroids) or are treated with romiplostim followed by 'watch and rescue'. In the model, patients move through a care pathway consisting of active treatments and 'watch and rescue'. When a patient becomes refractory to an active treatment they receive 'watch and rescue'. The active treatments modelled in the remainder of the care pathway were rituximab, immunosuppressive agents (azathioprine, mycophenolate mofetil, ciclosporin), danazol, dapsone and cytotoxic agents (such as cyclophosphamide and vinca alkaloids).

- 3.12 The manufacturer built seven health states into the model. The manufacturer conducted a utility survey with the primary objective of directly measuring health utility values for these ITP health states as perceived by members of the public in the UK. Respondents were presented with descriptions of each ITP health state, and utility values for five of the seven health states were derived using the time trade-off method. The utility values for these five health states were: 0.863 for platelet count above  $50 \times 10^9$  per litre and no bleed; 0.734 for platelet count above  $50 \times 10^9$  per litre and outpatient bleed; 0.841 for platelet count below  $50 \times 10^9$  per litre and no bleed; 0.732 for platelet count below  $50 \times 10^9$  per litre and outpatient bleed; 0.038 for platelet count below  $50 \times 10^9$  per litre and intracranial haemorrhage. For the remaining two health states included in the model (low platelet count with gastrointestinal bleed and low platelet count with other bleeding events requiring hospitalisation) the manufacturer used a utility value of 0.54 taken from the literature.
- 3.13 The manufacturer divided use of resources and costs into 4-week cycles. Costs of treatment included those of the romiplostim vials, laboratory testing to check blood counts every cycle (four tests), physician appointments (two sessions), and other drugs. Costs of management of bleeds included those for minor bleeds treated in an outpatient setting, intracranial haemorrhage, gastrointestinal bleeds and other bleeds requiring hospitalisation.
- 3.14 Other costs for drugs used in treatment and in managing bleeds were taken from the BNF (edition 55) and NHS reference costs.

- 3.15 The manufacturer's base-case analyses using the original economic model gave incremental cost-effectiveness ratios (ICERs) 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 and with a target platelet count of  $50 \times 10^9$  per litre. These ICERs reflected new inputs added to the model at the request of the ERG during the clarification step.
- 3.16 Sensitivity analyses performed by the manufacturer using the original economic model, in response to a request for clarification from the ERG, included the effects of: changes in drug costs to account for vial wastage in practice; the use of EQ-5D data available from the RCTs for serious adverse events; the cost of a bone marrow assessment needed when the condition no longer responds to romiplostim; and the cost of blood film tests (which are needed before treatment with romiplostim can begin).
- 3.17 The manufacturer, in response to a request for clarification from the ERG, also performed a sensitivity analysis in which it assumed a target platelet count of  $30 \times 10^9$  per litre (instead of  $50 \times 10^9$  per litre). This gave ICERs of £14,840 per QALY gained for non-splenectomised patients and £14,655 per QALY gained for splenectomised patients using romiplostim as a first-option treatment compared with 'watch and rescue'.
- 3.18 The manufacturer estimated that the probability that romiplostim would be cost effective using a target platelet count of  $50 \times 10^9$  per litre at different acceptability threshold levels of £10,000, £20,000 and £30,000 per QALY gained was 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).
- 3.19 The ERG noted that limited evidence was available for romiplostim and potential comparators for the treatment of patients with chronic ITP, and particularly for long-term outcomes. The ERG also considered that the evidence for comparators did not distinguish between patients who had not undergone splenectomy and splenectomised patients. The ERG was

particularly concerned about the methods the manufacturer had used to estimate the efficacy of romiplostim and the comparators, while acknowledging that using formal methods may also have been inappropriate. The ERG was not presented with further evidence that would have significantly altered the results presented in the manufacturer's original submission.

- 3.20 The ERG performed explorative sensitivity analyses using the manufacturer's original economic model. The one-way sensitivity analysis that had the most effect on the ICER was that in which the cost of romiplostim was adjusted to account for wastage from single-use vials that would occur in practice. On changing the number of vials from 0.93 to 1 for non-splenectomised patients, the ICER increased from £14,633 to £21,214 per QALY gained. For splenectomised patients, a change in the number of vials from 1.4 to 2 increased the ICER from £15,595 to £91,406 per QALY gained. The ERG carried out multivariate analyses which combined sensitivity analyses conducted by the ERG with those provided by the manufacturer. When patients entered the model on active treatment (rituximab) in the comparator arm (rather than 'watch and rescue') the ERG reported ICERs that increased from £14,633 to £21,674 per QALY gained for non-splenectomised patients and from £15,595 to £29,771 per QALY gained for splenectomised patients. When patients entered the model on active treatment (with rituximab) and the cost of romiplostim was adjusted to account for wastage, the ICER increased from £16,633 to £28,556 per QALY gained for non-splenectomised patients and from £15,595 to £109,802 per QALY gained for splenectomised patients. In a multivariate analysis that incorporated EQ-5D data from the RCTs rather than the utility values originally provided by the manufacturer, the cost of romiplostim adjusted to account for wastage, a 50% reduction in serious adverse events and the cost of bone marrow tests and blood film assessments, the ICERs increased from £14,633 to £37,290 per QALY gained for non-splenectomised patients and from £15,595 to £131,017 per QALY gained for splenectomised patients.

## Revised economic model

- 3.21 After consultation on the first ACD, the manufacturer provided revised



analyses of the cost effectiveness of romiplostim that addressed a number of the key issues that were raised by the Committee in the first ACD.

- 3.22 In the manufacturer's revised base-case analysis, it was assumed that 59% of patients in the comparator group start on rituximab and the remaining 41% start on another active treatment in the pathway (that is, immunosuppressive agents, dapsone, danazol and cytotoxic agents). Once an active treatment fails, and before the next active treatment is used, the model assumes that a patient enters a period of 'watch and rescue'.
- 3.23 The manufacturer took into account potential vial wastage of romiplostim and the fact that patients in the trials received doses that were higher than the maximum dose recommended in the SPC of 10 micrograms/kg. The manufacturer stated that six of the 42 patients in the trial of splenectomised patients were given more than 10 micrograms/kg romiplostim, and one of these showed a response to treatment. In the trial of non-splenectomised patients, two of the 41 patients received more than 10 micrograms/kg romiplostim, one of whom showed a response to treatment. In the cost-effectiveness analyses, the manufacturer provided two base-case scenario analyses: a 'conservative' scenario and a 'realistic' scenario. In both scenarios, all patients who received more than 10 micrograms/kg romiplostim were modelled as 'non-responders'. In the conservative scenario, the costs of continuing treatment at doses above 10 micrograms/kg were included in the model. In the realistic scenario, romiplostim costs were capped at 10 micrograms/kg.
- 3.24 The manufacturer pooled two sources of utility data: the individual patient level EQ-5D utility values from the two RCTs, and individual person level utility values from the time trade-off study (see section 3.12). The two resulting utility values that differed from the manufacturer's original utility values (based on the time trade-off study) were 0.835 for patients with a platelet count above  $50 \times 10^9$  per litre and no bleed, and 0.800 for patients with a platelet count below  $50 \times 10^9$  per litre and no bleed.

- 3.25 The manufacturer included the costs of bone marrow tests and blood film assessments associated with treatment with romiplostim in the revised analyses. The manufacturer also accounted for reductions in the number of blood counts and patient visits to clinicians.
- 3.26 The manufacturer submitted a patient access scheme, which is a discount on the 250 microgram vial of romiplostim, and provided four cost-effectiveness analyses: for the use of the 250 microgram vial with and without the patient access scheme, and for the use of a 100 microgram vial with and without the patient access scheme. This document only details the results for the use of the 250 microgram vial with the patient access scheme.
- 3.27 The manufacturer's revised base-case ICERs for the non-splenectomised group, incorporating all of the above assumptions and the patient access scheme, were £24,795 and £28,278 per QALY gained for the realistic scenario and the conservative scenario respectively. The ICERs for the splenectomised group were £4615 and £16,530 per QALY gained for the realistic scenario and the conservative scenario respectively.
- 3.28 The ERG reviewed the manufacturer's revised base-case analysis, and noted that uncertainty remained about which active treatment best reflects UK clinical practice. The ERG highlighted that the manufacturer's model describes a defined sequence of treatments, and questioned whether it was reasonable to exclude some treatments in the comparator arm. The ERG performed analyses using the manufacturer's revised base-case model and noted that a patient who enters the comparator arm of the model spends most time on 'watch and rescue' rather than on any other treatment. The ERG noted that any change in the model structure that reduces the amount of time a patient spends in 'watch and rescue' would increase the ICERs for romiplostim.
- 3.29 The ERG expressed concerns about the methods by which the manufacturer calculated the utility values in its revised base-case analysis. The ERG noted that the manufacturer simply aggregated the two utility measures, without considering whether it was appropriate to combine data from two different tools and two different samples. The ERG questioned whether the EQ-5D data derived directly from the trials



might provide the best estimates of utility values.

- 3.30 The ERG reviewed the approach taken by the manufacturer to account for patients who received doses of romiplostim above the maximum dose stated in the SPC. The ERG noted that patients lost to follow-up in the trials may not have had the same outcomes as patients not lost to follow-up, which could affect the calculation of time to failure. Censored patients were defined as 'lost to follow-up' in the evaluation of time to failure for romiplostim, and were those who had a last observed visit that was not recorded as a withdrawal in the open-label extension study. The ERG expressed further concerns about the assumption that romiplostim extends life, and about the generalisability and applicability of the trial results to a typical NHS population of patients with ITP. The ERG identified no additional evidence that would reduce this uncertainty.
- 3.31 The ERG conducted an exploratory analysis using the manufacturer's 'realistic' scenario, to test the impact of a 10% increase in the average number of 250 microgram vials of romiplostim used. For splenectomised patients the ICER rose from £4615 to £20,340 per QALY gained, and for non-splenectomised patients the ICER rose from £24,795 to £34,410 per QALY gained. The ERG also noted that if there was lower usage of romiplostim in NHS clinical practice than is reflected in the values included in the manufacturer's model the ICERs for romiplostim would decrease.
- 3.32 The ERG explored the impact of reducing the duration of the response to romiplostim in the model by 10%, 20% and 30%. When this was reduced by 30%, the ICER rose from £4615 to £6138 per QALY gained for splenectomised patients, and from £24,795 to £25,363 per QALY gained for non-splenectomised patients.
- 3.33 The ERG conducted one-way sensitivity analyses by varying individual parameters in the revised base-case model to check the impact on the ICERs. These changes included increasing the use of comparator treatments by 25%; increasing the response time for comparators by 50%; increasing response rates for comparators by 25%; reducing the use of rescue therapies to 80% of the base case in both the comparator and romiplostim arms; using alternative utility values; and assuming a

'worst case scenario' in which all patients who were censored in the open-label extension study were assumed to have no longer responded to romiplostim and were treated as withdrawals. The change in the use of rescue therapies had the greatest impact, increasing the ICERs from £24,795 to £35,248 per QALY gained for non-splenectomised patients and from £4615 to £32,190 per QALY gained for splenectomised patients. The ERG noted that when all patients who were censored in the open-label extension study were assumed to have no longer responded to romiplostim and were treated as withdrawals, the ICERs rose from £24,795 to £31,601 per QALY gained for non-splenectomised patients and from £4615 to £18,647 per QALY gained for splenectomised patients.

- 3.34 The ERG performed a multi-way sensitivity analysis to show the impact on the ICERs of the cumulative effects of varying all individual parameters explored in the one-way sensitivity analyses (see section 3.33). The ICER for splenectomised patients rose from £4615 to £64,646 per QALY gained, and that for non-splenectomised patients rose from £24,795 to £55,470 per QALY gained.
- 3.35 Full details of all the evidence are in the [manufacturer's submission and the ERG report](#).

## 4 Consideration of the evidence

- 4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of romiplostim, having considered evidence on the nature of chronic ITP and the value placed on the benefits of romiplostim by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.
- 4.2 The Committee considered the nature of the condition, and noted evidence submitted and presented by the patient experts and clinical specialists on the clinical signs and symptoms associated with chronic ITP. The Committee heard that the signs and symptoms associated with low platelet counts vary, and that bleeding and bruising can have a considerable impact on the daily activities of people with chronic ITP, may attract a social stigma associated with the appearance of bruises, and can limit lifestyle choices. The Committee heard that many people with ITP experience fatigue, but that there is no clear relationship between fatigue and platelet count or haemoglobin concentration. The Committee understood that anxiety about the risk of bleeding can affect a person's quality of life and the ability to work, travel and/or undertake leisure activities. The Committee understood from patient experts that a bleed could result in a person seeking medical care to receive rescue therapies, and if the bleeding was severe the person could need hospitalisation.
- 4.3 The Committee discussed the clinical management of chronic ITP. It noted that the pathway of care for chronic ITP varies depending on the person's circumstances, and that no single standard treatment pathway is used in routine practice. The Committee heard from the clinical specialists that, in the UK, first-line treatment for chronic ITP is considered to be corticosteroids (or intravenous immunoglobulin for people for whom corticosteroids are contraindicated), also referred to as rescue therapy. The clinical specialists estimated that approximately 30% of people would enter remission after such first-line treatment. The Committee heard from the clinical specialists that, for chronic ITP that does not respond to rescue therapy, active treatments are considered as second-line treatment including rituximab, immunosuppressive agents

(azathioprine, mycophenolate mofetil, ciclosporin), danazol, dapsone, and cytotoxic agents (cyclophosphamide, vinca alkaloids). The clinical specialists explained that clinicians increasingly prescribe rituximab as the first choice of active treatment (for approximately 50–60% of patients who need active treatment), and this leads to remission in approximately 50% of people treated. However, the clinical specialists noted that these people will, in general, eventually relapse and need further treatment. The clinical specialists also stated that azathioprine would be used for people whose condition is refractory to rituximab or who are intolerant of rituximab, but that cyclophosphamide and ciclosporin were considered too toxic, and that people do not tolerate vinca alkaloids and danazol well and were considered unlikely to benefit from them. The Committee understood that people receiving active treatments for ITP would need monitoring and would still be likely to need rescue therapies from time to time.

- 4.4 The Committee understood that people who have certain treatments (intravenous immunoglobulin, corticosteroids and immunosuppressive agents) over long periods of time will experience adverse effects that can lead to chronic conditions, including infections, diabetes mellitus, an increased risk of gastrointestinal bleeds, and hypertension. The Committee heard that some people may need knee or hip replacements as a result of the side effects of long-term use of corticosteroids. The Committee understood from comments made by consultees and commentators in response to the first ACD that the consequences of treatment with alkylating agents (such as cyclophosphamide and vinca alkaloids) can include malignancies and fertility problems.
- 4.5 The Committee discussed when a person with chronic ITP would receive treatment and heard from the clinical specialists that a person's platelet count alone does not determine whether or not he or she receives treatment, and that clinicians take into account the person's symptoms (such as fatigue) and risk of bleeding. Overall, the Committee understood from the clinical specialists that the lower a person's platelet count, the more likely a clinician is to offer treatment, but that treatment is not usually offered unless absolutely necessary because of the side effects of many of the current treatments. Active treatments are more likely to be considered for people with severe symptoms or who are at high risk

of bleeding, and in particular when rescue therapies are failing to produce satisfactory platelet counts or relief of symptoms. The Committee heard that people with a platelet count of between  $20 \times 10^9$  and  $30 \times 10^9$  per litre would rarely be offered an active treatment in the UK unless they had a significant bleed. The clinical specialists and patient experts informed the Committee that in clinical practice a platelet count of between  $10 \times 10^9$  and  $20 \times 10^9$  per litre would be the level at which clinicians would be likely to begin active treatment. A separate group of people who may be considered for active treatments at higher platelet counts would be those, for example, who needed aspirin therapy for cardiovascular disease. For people without severe symptoms and who are not perceived to be at high risk of bleeding, the preferred approach would be a strategy of 'watch and rescue' (with 'rescue' intervention dictated by the frequency of bleeding episodes) rather than an active treatment. The Committee heard from the clinical specialists that only people who are classed as having severe ITP would receive an active treatment, and this accounts for approximately 5–10% of people with chronic ITP. The Committee concluded that, in UK clinical practice, treatment for people with chronic ITP is dictated by the severity of symptoms, in particular bleeding.

- 4.6 The Committee discussed the place of romiplostim in the pathway of care for people with chronic ITP, and considered the appropriate comparators. It noted that the licensed indication for romiplostim for people who have undergone splenectomy is restricted to people who are refractory to other treatments such as corticosteroids and immunoglobulin, and also that romiplostim may be considered as a second-line treatment for people with a contraindication to splenectomy. The Committee understood that there are few treatments licensed for the treatment of chronic ITP. The Committee heard from the clinical specialists that the place of romiplostim in clinical practice would be for people whose condition is refractory to rituximab, or who are intolerant of rituximab.
- 4.7 The Committee considered the evidence presented by the manufacturer on the clinical effectiveness of romiplostim compared with placebo and standard care. It was mindful that the evidence was mainly derived from two small placebo-controlled RCTs. The Committee noted that

romiplostim significantly improved platelet count (the response measure used in the trials) and reduced the frequency of bleeding – particularly the occurrence of moderate and severe bleeding episodes. However, the Committee was mindful that these two RCTs did not provide clear evidence about the relative effectiveness of romiplostim compared with the active comparator treatments listed in the scope for the appraisal. The Committee noted that the manufacturer took a pragmatic rather than a systematic approach when collecting evidence for comparator treatments because of heterogeneity among studies of the comparators and because many of the comparators do not have a marketing authorisation for the treatment of ITP. The Committee also noted that data related to certain outcomes, such as the time to failure and the mean response time for romiplostim, had been generated by the manufacturer from a non-comparative open-label study. The Committee acknowledged comments received from consultees and commentators in response to consultation on the first ACD that highlighted the difficulty of conducting comparative trials with romiplostim, mainly because ITP is a rare and heterogeneous disease. The Committee heard from the clinical specialists that the population in the trials had the most severe ITP, which is estimated as representing 1–4% of people with chronic ITP, and were at high risk of bleeding and therefore needed high levels of rescue therapies throughout the trial. The Committee was aware of the limitations of the evidence on clinical effectiveness provided by the small RCTs, but considered that the available data demonstrated that romiplostim was clinically effective in people with severe ITP who are at high risk of bleeding and need repeated and frequent courses of rescue therapies.

- 4.8 The Committee then discussed the adverse effects associated with romiplostim. It noted that very few patients treated with romiplostim in the trials experienced adverse effects, including bleeding. The Committee heard from the clinical specialists that romiplostim may have benefits over other active treatments because it produces a sustained platelet response during treatment, it can be continued for a longer time than other active treatments, it can be used in a wider population, and because adverse effects limit both the use and duration of other active treatments. The Committee noted from comments received from consultees and commentators in response to consultation on the first

ACD that romiplostim has a different mode of action from current treatments for chronic ITP. The clinical specialists stated that romiplostim represents a 'step-change' for the treatment of ITP, in that it does not have immunosuppressive properties. The Committee also considered comments from consultees and commentators in response to consultation on the second ACD about setting a stopping rule for romiplostim, but noted that the modelling of the cost effectiveness for romiplostim did not include analyses addressing stopping. The Committee was also aware that the SPC specifies conditions under which to stop treatment with romiplostim. The Committee concluded that romiplostim has a novel mechanism of action (as a thrombopoietin receptor agonist) and a good adverse-effect profile, particularly in comparison with currently available treatments.

4.9 The Committee next considered the revised economic model submitted by the manufacturer that included the patient access scheme. The Committee agreed with the new approach taken by the manufacturer, wherein the comparator arm of the model started with active treatments instead of 'watch and rescue' and the costs of bone marrow tests and blood film assessment were included in the cost of treatment with romiplostim. The Committee noted that it would have been preferable to see romiplostim modelled after rituximab, which is where the clinical specialists currently position romiplostim in the treatment pathway for ITP, but recognised that this was not the case at the time of the consultation on the first ACD. The Committee considered the ERG's comments on the manufacturer's revised base-case analysis that included the patient access scheme, and noted that the ERG considered the approaches taken by the manufacturer in the revised analyses to being generally reasonable.

4.10 The Committee considered the ICERs in the manufacturer's revised base-case analysis that included the patient access scheme. For non-splenectomised patients the ICERs were £24,800 and £28,300 per QALY gained for the realistic and conservative scenarios respectively. For splenectomised patients the ICERs were £4620 and £16,500 per QALY gained for the realistic and conservative scenarios respectively.

4.11 The Committee noted that the median dose of romiplostim used in the



RCTs was 3 micrograms/kg for splenectomised patients and 2 micrograms/kg for non-splenectomised patients, and heard from the clinical specialists that these doses reflect clinical practice. The Committee discussed the number of vials used in the realistic and conservative scenarios presented by the manufacturer. It heard from the clinical specialists that although they would not use doses as high as those given in the trials, there may be some instances where the entire contents of a vial of romiplostim would be used, rather than wasting some, and so the dose may occasionally exceed the maximum dose specified in the SPC. Therefore the Committee concluded that the most plausible scenario would be somewhere between the realistic and conservative scenarios modelled by the manufacturer.

- 4.12 The Committee noted that in clinical practice it would be rare for clinicians to use doses of romiplostim that were aimed at obtaining a platelet count above  $50 \times 10^9$  per litre (as was the case in the trials). Therefore, in practice, aiming for a lower target platelet count would mean less frequent use of romiplostim, and lower doses of romiplostim when it is used. The Committee noted that, in the ERG's exploratory analyses, the ICERs were sensitive to a change in the number of vials used, and concluded that romiplostim would be more cost effective if less romiplostim was used in clinical practice than was assumed in the model.
- 4.13 The Committee considered the estimates of the effectiveness of the comparators assumed in the model, and heard from the clinical specialists that these estimates seemed reasonable and reflected clinical practice. The Committee noted that the model did not sufficiently account for long-term adverse effects of some of the comparators. The Committee concluded that had the model incorporated these adverse effects, the ICERs of romiplostim would have been lower.
- 4.14 The Committee noted that the submitted model assumed that treatment with romiplostim extended the life of people with chronic ITP by 2.92 and 2.03 years for the non-splenectomised and splenectomised groups respectively. The Committee noted that the survival advantage associated with romiplostim resulted from avoiding severe life-threatening bleeds. The Committee understood from the comments of



consultees and commentators that observational evidence supported the association between low platelet counts and an increased risk of dying. The Committee heard from the clinical specialists that this assumption was plausible, and that an additional mortality benefit could result from reducing the number of deaths associated with the long-term adverse effects of the comparator treatments. The Committee concluded that although there were no robust data supporting the ability of romiplostim to reduce the risk of dying compared with standard care in people with chronic ITP, this possibility was plausible.

- 4.15 The Committee noted the ERG's concern that if it was assumed that romiplostim was no longer effective in the patients who were lost to follow-up during the trial period, the ICERs increased markedly. The Committee heard from the manufacturer that of the 31 patients who withdrew during the open-label extension study, only two patients (6%) withdrew because they did not respond to romiplostim. The Committee concluded that the patients who were lost to follow-up were neither more nor less likely to have stopped responding to romiplostim than patients who were not lost to follow-up.
- 4.16 The Committee noted that the use of intravenous immunoglobulin in 'watch and rescue' care was a major driver of costs in the comparator arm. The Committee noted that the manufacturer had used data from the clinical trials to model the costs and use of resources by assuming that a certain proportion of patients would need rescue therapies during each monthly cycle in the model. The Committee noted that in the ERG's one-way sensitivity analyses, the use of rescue therapies had the greatest impact on the ICER. When the use of rescue therapies was reduced to 80% of the base case in both the comparator and romiplostim arms, the ICER for romiplostim for the realistic scenario increased from £4620 to £32,200 per QALY gained for the splenectomised patients, and from £24,800 to £35,200 per QALY gained for the non-splenectomised patients. The Committee heard from the clinical specialists that the use of rescue therapies was higher in the RCTs than in UK clinical practice on average. This reflected the disease severity of the patients in the RCTs and was consistent with 'severe refractory ITP'. The clinical specialists agreed with the ERG's estimates of time spent on each treatment in the model and stated that people with severe refractory ITP could potentially

be on 'watch and rescue' for 18 out of 20 years, and receive rescue treatment as frequently as in the romiplostim RCTs (that is, on 'watch' for 4 months and on rescue treatment for 8 months in each year). The Committee concluded that the majority of people with chronic ITP would not receive rescue therapies as frequently as this, and that the manufacturer's revised base-case ICERs would be relevant only for the treatment of patients at the very severe end of the spectrum of ITP. However, the Committee noted that there remained some uncertainty over the manufacturer's revised base-case ICERs, because even a small reduction of the amount of rescue treatments would increase the ICERs.

- 4.17 The Committee considered the comments received from consultees and commentators in response to consultation on the second ACD. The consultees and commentators requested that the Committee clarify the terms 'specialist in haematology' and 'standard active treatments', and define the dosages of unlicensed treatments. In response to the first point, the Committee recommended that the wording be changed to 'haematologist'. The Committee believed that a haematologist would have a good understanding of what is meant by standard active treatments for chronic ITP, and of dosages. The Committee did not agree that recommending an arrangement of shared care with general practitioners, as proposed by one commentator, was appropriate at this time. Consultees and commentators also requested that a registry is set up to collect data on the use of romiplostim, in order to monitor adverse events, and to audit the implementation of this guidance on romiplostim. The Committee was aware of the UK ITP registry and supported the collection of data on treatment with romiplostim. The Committee furthermore concluded that these data would be useful for any future appraisal of romiplostim for the treatment of chronic ITP.
- 4.18 The Committee agreed that a starting point for the most plausible ICERs would lie between the ICERs for the manufacturer's realistic and conservative scenarios, and may be slightly higher to account for any small reduction in the amount of rescue therapy seen in clinical practice compared with the romiplostim RCTs. Therefore the Committee concluded that the ICERs would be under £20,000 per QALY gained for the treatment of splenectomised patients, and around £30,000 per QALY gained for the treatment of non-splenectomised patients. In addition, the

Committee concluded that two factors would reduce these ICERs: the potentially lower use of romiplostim in clinical practice when clinicians aim for target platelet counts lower than those in the romiplostim RCTs, and the fact that the model excluded the long-term adverse effects of the comparator treatments. The Committee was also aware that since the publication of the second ACD, the marketing authorisation of romiplostim had changed such that the platelet count at which the dose of romiplostim can be reduced had been lowered. The Committee appreciated that this would be likely to reduce the ICERs for romiplostim. Therefore the Committee concluded that romiplostim is recommended as a cost-effective use of NHS resources for the treatment of adults with chronic ITP 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, and if the manufacturer makes romiplostim available with the discount agreed as part of the patient access scheme. The Committee heard from clinical specialists that approximately 1–4% of the UK population with chronic ITP would be eligible for treatment with romiplostim using these criteria. Because these people have severe ITP, the Committee concluded that only a haematologist should start and supervise treatment with romiplostim.

- 4.19 The Committee considered whether its recommendations raised any equality issues for people with chronic ITP. The Committee was aware that certain religious groups would not consent to the use of blood products, and also that ITP might affect pre-menopausal women more than men. It also understood that romiplostim might reduce the burden of hospital admission for long hours to receive intravenous immunoglobulin, especially for people for whom it is difficult to travel to a hospital. The Committee noted that no specific representations had been made for these groups of people. The Committee concluded that its recommendations do account for the individual needs of people to receive romiplostim, and do not make it more difficult for any particular group to access treatment with romiplostim compared with any other group.

## Summary of the Appraisal Committee's key

## conclusions

TA221	Appraisal title: Romiplostim for the treatment of chronic immune thrombocytopenia	Section
<b>Key conclusion</b>		
<p>Romiplostim is recommended as an option for treating chronic immune thrombocytopenia in adults, only if:</p> <ul style="list-style-type: none"> <li>• their condition is refractory to standard active treatments and rescue therapies or</li> <li>• they have severe disease and a high risk of bleeding that needs frequent courses of rescue therapies.</li> </ul> <p>Romiplostim is recommended only if the company makes it available with the discount agreed in the patient access scheme.</p> <p>This is because treatment with romiplostim has been shown to be cost effective only for patients with severe refractory ITP.</p>		1.1
<b>Current practice</b>		
Clinical need of patients, including the availability of alternative treatments	The Committee noted that the pathway of care for ITP varies depending on the person's circumstances, and that no single standard treatment pathway is used in routine practice. The clinical specialists stated that clinicians increasingly prescribe rituximab as the first choice of active treatment; that azathioprine would be used for people whose condition is refractory to rituximab or who are intolerant of rituximab; that cyclophosphamide and ciclosporin were considered too toxic; and that people do not tolerate vinca alkaloids and danazol well and were considered unlikely to benefit from them.	4.3
	The Committee heard from the clinical specialists that only people who are classed as having severe ITP would receive an active treatment, and this accounts for approximately 5–10% of people with chronic ITP.	4.5

	The Committee heard from the clinical specialists that, in the UK, first-line treatment for chronic ITP is considered to be corticosteroids (or intravenous immunoglobulin for people for whom corticosteroids are contraindicated), also referred to as rescue therapy.	4.3
<b>The technology</b>		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	<p>The Committee noted that very few patients treated with romiplostim in the trials experienced adverse effects, including bleeding. The Committee heard from the clinical specialists that romiplostim may have benefits over other active treatments because it produces a sustained platelet response during treatment, it can be continued for a longer time than other active treatments, it can be used in a wider population, and adverse effects limit both the use and duration of other active treatments.</p> <p>The clinical specialists stated that romiplostim represents a 'step-change' for the treatment of ITP, in that it does not have immunosuppressive properties.</p>	4.8
What is the position of the treatment in the pathway of care for the condition?	Clinical specialists stated that the place of romiplostim in clinical practice would be for people whose condition is refractory to rituximab, or who are intolerant of rituximab.	4.6
Adverse events	The Committee noted that very few patients treated with romiplostim in the trials experienced adverse effects, including bleeding. The Committee concluded that romiplostim has a novel mechanism of action (as a thrombopoietin receptor agonist) and a good adverse-effect profile, particularly in comparison with currently available treatments.	4.8
<b>Evidence for clinical effectiveness</b>		

Availability, nature and quality of evidence	The Committee was mindful that the evidence was mainly derived from two small placebo-controlled RCTs and a non-comparative open-label study.	4.7
Relevance to general clinical practice in the NHS	The Committee considered that the available data demonstrated that romiplostim was clinically effective in people with severe ITP who are at high risk of bleeding and need repeated and frequent courses of rescue therapies.	4.7
Uncertainties generated by the evidence	The Committee was mindful that the two RCTs did not provide clear evidence about the relative effectiveness of romiplostim compared with the active comparator treatments listed in the scope for the appraisal. The Committee noted that the manufacturer took a pragmatic rather than a systematic approach when collecting evidence for comparator treatments because of heterogeneity among studies of the comparators. The Committee also noted that data related to certain outcomes, such as the time to treatment failure and the mean response time for romiplostim, had been generated by the manufacturer from a non-comparative open-label study.	4.7
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	No subgroups based on differential effectiveness were identified.	N/A
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee was aware of the limitations of the evidence on clinical effectiveness provided by the small RCTs, but considered that the available data demonstrated that romiplostim was clinically effective in people with severe ITP at high risk of bleeding who need repeated and frequent courses of rescue therapies.	4.7

Evidence for cost effectiveness		
Availability and nature of evidence	<p>The manufacturer's economic model assumed that all patients started with a platelet count below <math>50 \times 10^9</math> per litre.</p> <p>Romiplostim was compared with standard care in a model structure in which patients in the romiplostim group start treatment with romiplostim, while 59% of patients in the comparator group start on rituximab and the remaining 41% start on another active treatment in the pathway: immunosuppressive agents (azathioprine, mycophenolate mofetil, ciclosporin), danazol, dapsone and cytotoxic agents (such as cyclophosphamide and vinca alkaloids). Once an active treatment fails, and before the next active treatment is used, patients enter a period of 'watch and rescue' (treated as necessary with intravenous immunoglobulin, anti-D immunoglobulin [non-splenectomised patients] or intravenous corticosteroids). Modelled patients then move through a care pathway consisting of active treatments and 'watch and rescue'.</p>	3.11, 3.22
Uncertainties and plausibility of assumptions and inputs in the economic model	<p>The Committee agreed with the new approach taken by the manufacturer, wherein the comparator arm of the model started with active treatments instead of 'watch and rescue'. The Committee noted that it would have been preferable to see romiplostim modelled after rituximab, which is where the clinical specialists currently position romiplostim in the treatment pathway for ITP, but recognised that this was not the case at the time of the consultation on the first ACD.</p>	4.9



	The Committee noted that in clinical practice it would be rare for clinicians to use doses of romiplostim that were aimed at obtaining a platelet count above $50 \times 10^9$ per litre (as was the case in the trials). Therefore, in practice, aiming for a lower target platelet count would mean less frequent use of romiplostim, and lower doses of romiplostim when it is used. The Committee noted that, in the ERG's exploratory analyses, the ICERs were sensitive to a change in the number of vials used, and concluded that romiplostim would be more cost effective if less romiplostim was used in clinical practice than was assumed in the model.	4.12
	The Committee heard from the clinical specialists that the estimates of the effectiveness of the comparators assumed in the model seemed reasonable and reflected clinical practice.	4.13
	The Committee noted that the model did not sufficiently account for the long-term adverse effects of some of the comparators. The Committee concluded that had the model incorporated these adverse effects, the ICERs for romiplostim would be lower.	4.13
	The Committee noted that the submitted model assumed that treatment with romiplostim extended the life of people with chronic ITP by 2–3 years, and that this survival advantage resulted from avoiding severe life-threatening bleeds. The Committee heard from the clinical specialists that this assumption was plausible, and that an additional mortality benefit could result from reducing the number of deaths associated with the long-term adverse effects of the comparator treatments.	4.14
Incorporation of health-related quality-of-life benefits and utility values	The manufacturer pooled two sources of utility data: the individual patient level EQ-5D utility values from the two RCTs, and individual person level utility values from the time trade-off study.	3.24



	The ERG expressed concerns about the methods by which the manufacturer calculated the utility values in its revised base-case analysis. The ERG noted that the manufacturer simply aggregated the two utility measures, without considering whether it was appropriate to combine data from two different tools and two different samples. The ERG questioned whether the EQ-5D data derived directly from the trials might provide the best estimates of utility values.	3.29
Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The Committee noted that the model did not sufficiently account for long-term adverse effects of some of the comparators. The Committee concluded that had the model incorporated these adverse effects, the ICERs for romiplostim would be lower.	4.13
Are there specific groups of people for whom the technology is particularly cost effective?	The Committee concluded that the manufacturer's revised base-case ICERs would be relevant only for the treatment of patients at the very severe end of the spectrum of ITP.	4.16
What are the key drivers of cost effectiveness?	The Committee noted that the use of rescue therapies, in particular intravenous immunoglobulin in 'watch and rescue', had the greatest impact on the ICER.	4.16

Most likely cost-effectiveness estimate (given as an ICER)	The Committee agreed that a starting point for the most plausible ICERs would lie between the ICERs for the manufacturer's realistic and conservative scenarios, and may be slightly higher to account for any small reduction in the amount of rescue therapy seen in clinical practice compared with the romiplostim RCTs. Therefore the Committee concluded that the ICERs would be under £20,000 per QALY gained for the treatment of splenectomised patients, and around £30,000 per QALY gained for the treatment of non-splenectomised patients. In addition, the Committee concluded that two factors would reduce these ICERs: the potentially lower use of romiplostim in clinical practice when clinicians aim for target platelet counts lower than those in the romiplostim RCTs, and the fact that the model excluded the long-term adverse effects of the comparator treatments.	4.18
<b>Additional factors taken into account</b>		
Patient access schemes (PPRS)	The manufacturer submitted a patient access scheme. The scheme is a discount on the 250 microgram vial of romiplostim. The size of the discount is commercial in confidence.	2.4
End-of-life considerations	Not applicable.	–

Equalities considerations and social value judgements	<p>The Committee considered whether its recommendations raised any equality issues for people with chronic ITP. The Committee was aware that certain religious groups would not consent to the use of blood products, and also that ITP might affect pre-menopausal women more than men. It also understood that romiplostim might reduce the burden of hospital admission for long hours to receive intravenous immunoglobulin, especially for people for whom it is difficult to travel to a hospital. The Committee noted that no specific representations had been made for these groups of people. The Committee concluded that its recommendations do account for the individual needs of people to receive romiplostim, and do not make it more difficult for any particular group to access treatment with romiplostim compared with any other group.</p>	4.19
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## 5 Implementation

- 5.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- 5.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.
- 5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has chronic immune thrombocytopenia and the doctor responsible for their care thinks that romiplostim is the right treatment, it should be available for use, in line with NICE's recommendations.

# Appendix A: Appraisal Committee members and NICE project team

## A Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are four Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

### **Dr Amanda Adler (Chair from 2010)**

Consultant Physician, Addenbrooke's Hospital, Cambridge

### **Professor Keith Abrams**

Professor of Medical Statistics, University of Leicester

### **Dr Ray Armstrong**

Consultant Rheumatologist, Southampton General Hospital

### **Dr Jeff Aronson**

Reader in Clinical Pharmacology, University Department of Primary Health Care, University of Oxford

### **Dr Darren Ashcroft**

Reader in Medicines Usage and Safety, School of Pharmacy and Pharmaceutical Sciences,

University of Manchester

**Professor David Barnett (Chair, 2009)**

Professor of Clinical Pharmacology, University of Leicester

**Dr Peter Barry**

Consultant in Paediatric Intensive Care, Leicester Royal Infirmary

**Professor John Cairns**

Public Health and Policy, London School of Hygiene and Tropical Medicine

**Dr Mark Chakravarty**

External Relations Director Pharmaceuticals & Personal Health, Oral Care Europe

**Dr Martin Duerden**

Medical Director, Conwy Local Health Board

**Professor Fergus Gleeson**

Consultant Radiologist, Churchill Hospital, Oxford

**Eleanor Grey**

Lay member

**Dr Neil Losson**

General Practitioner

**Dr Rosa Legood**

Lecturer, London School of Hygiene and Tropical Medicine

**Terence Lewis**

Lay member

**Professor Gary McVeigh**

Professor of Cardiovascular Medicine, Queen's University, Belfast

**Professor Ruairidh Milne**

Senior Lecturer in Public Health, National Coordinating Centre for Health Technology Assessment

**Dr Neil Milner**

General Practitioner, Tramways Medical Centre, Sheffield

**Dr Rubin Minhas**

General Practitioner and Clinical Director, BMJ Evidence Centre

**Dr Peter Norrie**

Principal Lecturer in Nursing, DeMontfort University

**Professor Stephen Palmer**

Senior Research Fellow, Centre for Health Economics, University of York

**Dr Sanjeev Patel**

Consultant Physician & Senior Lecturer in Rheumatology, St Helier University Hospital

**Dr John Pounsford**

Consultant Physician, Frenchay Hospital, Bristol

**Dr Stephen Saltissi**

Consultant Cardiologist, Royal Liverpool University Hospital

**Dr Casey Quinn**

Lecturer in Health Economics, Division of Primary Care, University of Nottingham

**Dr John Rodriguez**

Assistant Director of Public Health, NHS Eastern and Coastal Kent

**Alun Roebuck**

Consultant Nurse in Critical and Acute Care, United Lincolnshire NHS Trust

**Dr Florian Alexander Ruths**

Consultant Psychiatrist & Cognitive Therapist, Maudsley Hospital, London

**Navin Sewak**

Primary Care Pharmacist, NHS Hammersmith and Fulham

**Dr Lindsay Smith**

General Practitioner, East Somerset Research Consortium

**Roderick Smith**

Finance Director, West Kent Primary Care Trust

**Cliff Snelling**

Lay member

**Professor Ken Stein (Vice Chair)**

Professor of Public Health, Peninsula Technology Assessment Group (PenTAG), University of Exeter

**Professor Andrew Stevens**

Professor of Public Health, Department of Public Health and Epidemiology, University of Birmingham

**Dr Rod Taylor**

Associate Professor in Health Services Research, Peninsula Medical School, Universities of Exeter and Plymouth

**Nathalie Verin**

Health Economics Manager, Boston Scientific UK and Ireland

**Mr Colin Watts**

Consultant Neurosurgeon, Addenbrooke's Hospital, Cambridge

**Tom Wilson**

Director of Contracts and Information Management and Technology, Milton Keynes Primary Care Trust

## **B NICE project team**

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

**João Vieira, Dr Ruairidh Hill and Panagiota Vrouchou**

Technical Leads

**Joanna Richardson and Helen Chung**



Technical Advisers

**Jeremy Powell**

Project Manager

## Appendix B: Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by the 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. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

### I) Manufacturer/sponsor

- Amgen

### II) Professional/specialist and patient/carers groups

- British Committee for Standards in Haematology
- British Society for Haematology
- ITP Support Association
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians

### III) Other consultees

- Department of Health

- Eastern and Coastal Kent Teaching Primary Care Trust
- Welsh Assembly Government

IV) Commentator organisations (did not provide written evidence and without the right of appeal)

- Actavis UK
- Baxter BioScience
- Bio Products Laboratory
- CSL Behring
- Department of Health, Social Services and Public Safety for Northern Ireland
- Focus Pharmaceuticals
- GlaxoSmithKline UK
- NHS Quality Improvement Scotland
- Pharmacia

C. The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on romiplostim for the treatment of chronic immune thrombocytopenia by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Paula Bolton-Maggs, Consultant Haematologist, Manchester Royal Infirmary, nominated by the Royal College of Pathologists and the British Committee for Standards in Haematology – clinical specialist
- Dr Nichola Cooper, Consultant Haematologist, Hammersmith Hospital, nominated by the ITP Support Association – clinical specialist
- Dr John Grainger, Consultant Paediatric Haematologist, Royal Manchester Children's Hospital, nominated by the ITP Support Association – clinical specialist
- Dr Jennie Wimperis, Consultant Haematologist, Norfolk and Norwich University Hospital, nominated by the ITP Support Association – clinical specialist

- Mrs Shirley Watson, Chief Executive, ITP Support Association, nominated by the ITP Support Association – patient expert
- Mr Derek Elston, nominated by the ITP Support Association – patient expert

D. Representatives from the following manufacturer/sponsor attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Amgen

## Update information

**October 2018:** The recommendations and section 2 were updated because the marketing authorisation for romiplostim now includes people who have not had a splenectomy.

**May 2014:** The recommendation wording has been updated in line with NICE's existing wording conventions and the wording used in [NICE technology appraisal guidance 293: Eltrombopag for treating chronic immune thrombocytopenia \(review of technology appraisal 205\)](#).

### Minor changes since publication

**January 2023:** The title of this guidance was updated and the term 'immune (idiopathic) thrombocytopenic purpura' was changed to 'immune thrombocytopenia' throughout.

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## Accreditation

