NICE National Institute for Health and Care Excellence

NICE guidance

Eltrombopag for treating 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.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

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.

Contents

This guidance replaces TA205.

1 Guidance

1.1 Eltrombopag 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.

  Eltrombopag is recommended only if the company provides it with the discount agreed in the patient access scheme.

1.2 These recommendations are not intended to affect treatment with eltrombopag 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 Eltrombopag (Revolade, GlaxoSmithKline) increases platelet production by activating the thrombopoietin receptor, thereby stimulating platelet production and reducing bleeding. Eltrombopag has a UK marketing authorisation for the treatment of 'chronic immune (idiopathic) thrombocytopenic purpura (ITP) patients aged 1 year and above who are refractory to other treatments (e.g. corticosteroids, immunoglobulins)'.

2.2 Eltrombopag is taken orally. The summary of product characteristics states that the recommended starting dose is 50 mg once daily but that patients of East Asian ancestry should start eltrombopag at a reduced dose of 25 mg once daily. It recommends that patients should take eltrombopag at least 4 hours before or after antacids, dairy products (or other calcium-containing food products) or mineral supplements containing polyvalent cations (for example, iron, calcium, magnesium, aluminium, selenium and zinc). If, after initial therapy, platelet counts are below the target level (50×10^9 per litre), the dosage may be increased to a maximum of 75 mg once daily. Treatment should be stopped if the platelet count does not increase sufficiently to avoid clinically significant bleeding after 4 weeks of therapy at a dosage of 75 mg once daily. The summary of product characteristics stipulates that eltrombopag treatment should remain under the supervision of a physician who is experienced in the treatment of haematological diseases. For full details of dosage and administration, see the summary of product characteristics.

2.3 The summary of product characteristics lists the following adverse reactions for eltrombopag as being common (1 or more patient in every 100 and fewer than 1 patient in every 10) or very common (1 or more patient in every 10): psychiatric disorders (insomnia), nervous system disorders (headache and paraesthesia), eye disorders (cataract and dry eye), gastrointestinal disorders (nausea, diarrhoea, constipation and upper abdominal pain), hepatobiliary disorders (increased alanine aminotransferase, increased aspartate aminotransferase, increased blood bilirubin and hyperbilirubinaemia, and abnormal hepatic function), skin and subcutaneous tissue disorders (rash, pruritus and alopecia),

musculoskeletal and connective tissue disorders (arthralgia, myalgia, muscle spasm and bone pain), and general disorders (fatigue and peripheral oedema). For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.4 The 'British national formulary' (BNF; edition 64) states that the net price of a 28-tablet pack of 25 mg eltrombopag is £770 (a single 25 mg dose costs £27.50). The net price of a 28-tablet pack of 50 mg eltrombopag is £1540 (a single 50 mg dose costs £55). The cost per patient will vary with dose adjustment and treatment duration. The manufacturer indicated that the average daily cost of eltrombopag (based on the mean dose of eltrombopag in the EXTEND study of 51.3 mg per day) is £56.43. The manufacturer of eltrombopag (GlaxoSmithKline) has agreed a patient access scheme with the Department of Health that makes eltrombopag available with a discount. 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.

3 The manufacturer's submission

The Appraisal Committee (section 9) considered evidence submitted by the manufacturer of eltrombopag and a review of this submission by the Evidence Review Group (ERG; section 10).

3.1 The manufacturer compared eltrombopag within a standard care pathway with the standard care pathway alone, and separately with romiplostim plus standard care. Standard care was defined as a pathway of care without eltrombopag or romiplostim, that is, without thrombopoietin receptor agonists (non-thrombopoietin receptor agonist pathway). It consisted of a sequence of rituximab, azathioprine, mycophenolate mofetil, ciclosporin, dapsone, danazol, cyclophosphamide, vincristine and vinblastine. The manufacturer evaluated the clinical and cost effectiveness of eltrombopag for 2 groups: patients who had had a splenectomy and patients who had not had a splenectomy.

Clinical effectiveness

3.2 The manufacturer presented clinical evidence from 3 randomised controlled trials (RCTs), TRA 100773A, TRA 100773B and RAISE, all of which were placebo-controlled, and from an extension study (EXTEND) that followed patients who had previously participated in the RCTs. The key clinical evidence was obtained from RAISE. The manufacturer also presented a meta-analysis of the results of the 3 eltrombopag RCTs (TRA 100773A, and TRA 100773B and RAISE), and 2 indirect comparisons, 1 between eltrombopag and romiplostim, and the other between eltrombopag and standard care.

3.3 RAISE was a phase III multicentre RCT (including 9 UK centres) that evaluated the efficacy and safety of eltrombopag plus standard care compared with placebo plus standard care in adults with a platelet count of less than 30×10^9 per litre. RAISE was a 6-month study that followed patients for up to 4 weeks after treatment had been stopped, then at 3 and 6 months. Investigators randomised 197 patients to eltrombopag

(n=135) or placebo (n=62), and stratified randomisation by baseline platelet counts (15×10^9 per litre or less, and more than 15×10^9 per litre), whether or not a patient had had a splenectomy, and whether or not patients were taking medication for immune thrombocytopenia (ITP) at baseline. Approximately 30% of patients had ITP that was refractory to, or had relapsed after, splenectomy. Patients randomised to either treatment group received standard care (that is, treatment with corticosteroids, non-selective immunosuppressants and rescue medication) as needed, plus either 50 mg eltrombopag or placebo, and investigators adjusted the dose of eltrombopag based on individual platelet counts. Over the 6-month study period, the mean dose of eltrombopag was 54.7 mg per person per day. At the end of the study, 69% of patients randomised to the placebo group and 55% of those randomised to the eltrombopag group had received concomitant ITP medication.

3.4 The primary outcome in the RAISE trial was the odds of achieving a platelet count of $50–400\times10^9$ per litre at any point during the 6-month study period. Secondary outcomes included use of rescue treatment (defined as a composite of a newly prescribed ITP medication, an increased dose of a concomitant ITP medication, a platelet transfusion or a splenectomy), incidence and severity of bleeding, and health-related quality of life.

3.5 In RAISE, the odds ratio reflecting a response during the 6-month study period (primary outcome) was 8.2 (99% confidence interval [CI] 3.59 to 18.73; $p<0.001$). At the end of the study, 52% of patients receiving eltrombopag and 17% of those receiving placebo had platelet counts of $50–400\times10^9$ per litre. Once treatment was stopped, the proportions of patients with target platelet counts in the eltrombopag and placebo groups converged, reaching 20% for eltrombopag and 14% for placebo after 4 weeks. The manufacturer reported that the response to eltrombopag did not depend on whether or not the patient had had a splenectomy (p value for interaction was 0.562).

3.6 The manufacturer carried out a post hoc analysis of platelet response in RAISE, that is, an analysis of how long during the study patients maintained platelet counts of $50–400\times10^9$ per litre. The manufacturer

categorised platelet response into 'sustained' platelet response, when a patient had a platelet count of 50–400×10^9 per litre for at least 6 of the last 8 weeks of treatment; 'transient' platelet response, when a patient had a platelet response for 4 or more consecutive weeks during the treatment period; and 'overall' platelet response, when a patient had either a sustained or a transient response. The manufacturer performed the analysis on the intention-to-treat population and on the subset of patients treated with study medication for 6 months or more (that is, including patients who continued taking eltrombopag after the study ended). In both groups, a higher proportion of patients receiving eltrombopag had 'sustained' and 'overall' platelet responses than patients receiving placebo, irrespective of whether or not they had had a splenectomy.

3.7 The manufacturer reported results for secondary outcomes in the RAISE trial. Fewer patients randomised to eltrombopag needed protocol-defined rescue treatments than those randomised to placebo (18% and 40% respectively). Among the safety population, the odds of experiencing bleeding (World Health Organization [WHO] grades 1–4) during the study period were 76% lower among patients who took at least 1 dose of eltrombopag than in those who took at least 1 dose of placebo (odds ratio [OR] 0.24; p<0.001; CI not given). At the end of the study, 57% of patients receiving placebo had experienced a grade 1–4 WHO bleed (any type of bleeding) compared with 27% of those receiving eltrombopag (OR 0.25; p>0.001; CI not given). However, a grade 2-4 WHO bleed (clinically significant bleeding) did not differ between treatment groups (13% and 10% in the placebo and eltrombopag groups respectively). The manufacturer also performed an analysis of the risk of bleeding at least once at any point during the study, and stratified this analysis by whether or not the patient had had a splenectomy. It found that patients randomised to eltrombopag were statistically significantly less likely to have clinically significant bleeding than those randomised to placebo (33% for eltrombopag and 53% for placebo; OR 0.30; p>0.001); the results of the analysis were also statistically significantly different in favour of eltrombopag for patients who had or had not had a splenectomy.

3.8 The manufacturer reported treatment-related adverse reactions for

48 patients (36%) in the eltrombopag group and 18 patients (30%) in the placebo group. The most common adverse reactions experienced by patients receiving eltrombopag were headache (30%), diarrhoea (13%), nausea (12%), nasopharyngitis (10%), upper respiratory tract infection (10%) and fatigue (10%). The manufacturer also reported 2 thromboembolic events in the eltrombopag group and none in the placebo group. A post hoc analysis of patients treated with concomitant medication showed a reduction in corticosteroid-related adverse reactions (including dyspepsia, peripheral oedema and hyperglycaemia) in the eltrombopag group.

3.9 The RAISE trial assessed health-related quality of life at baseline, and at 6, 14 and 26 weeks using the SF-36 instrument, which consists of 8 subdomains and 2 component summary scores (representing physical and mental health). In addition, investigators used subscales of the Functional Assessment of Chronic Illness Therapy for Patients with Thrombocytopenia (FACIT-Th) and Functional Assessment of Chronic Illness Therapy (FACIT) instruments. The manufacturer reported that patients receiving eltrombopag improved more from baseline to week 26 across most of the SF-36 domains for health and wellbeing than those receiving placebo. There were statistically significant differences between treatment groups in the change from baseline in the component summaries for physical role, vitality, emotional role and mental health.

3.10 The manufacturer did a meta-analysis of TRA 100773A, TRA 100773B and RAISE to establish whether treatment with eltrombopag improved platelet counts compared with placebo. It reported the odds ratios for attaining a platelet count of 50×10^9 per litre or more 6 weeks after the beginning of the study. In this analysis, eltrombopag was associated with higher odds of responding to treatment compared with placebo, with an odds ratio from a fixed effects model of 8.23 (95% CI 4.68 to 14.48) and an odds ratio from a random effects model of 8.16 (95% CI 4.63 to 14.37); there was little evidence of statistical heterogeneity.

3.11 Because there were no head-to-head trials comparing eltrombopag with romiplostim, the manufacturer performed an indirect comparison between the 2 treatments. A systematic review by the manufacturer identified 2 RCTs comparing romiplostim with placebo (both reported in

Kuter et al. 2008), which the manufacturer used to compare eltrombopag with romiplostim for efficacy and rates of clinically significant bleeding. Both RCTs evaluated the safety and efficacy of romiplostim in patients with ITP; 1 enrolled 63 patients who had had a splenectomy, and the other enrolled 62 patients who had not. In both studies, patients had platelet counts of 30×10^9 per litre or less and ITP that was refractory to at least 1 previous treatment. Patients were randomised to either romiplostim plus standard care, or standard care alone, and they received treatment for 6 months. The primary outcome in both studies was the proportion of patients with a durable platelet response (defined as a platelet count of 50×10^9 per litre or more in 6 or more weekly assessments in the last 8 weeks of treatment), and who did not need rescue medication. The manufacturer combined the results of the 2 studies using standard meta-analytic techniques and then treated them as a single trial to do the indirect comparison.

3.12 The manufacturer used the Bucher method in its indirect comparison between eltrombopag (data from RAISE) and romiplostim (data from the 2 Kuter et al. 2008 trials), using placebo as a common comparator. It performed the comparison for the whole population, and separately for patients who had or had not had a splenectomy. The manufacturer considered 2 main outcome measures: platelet response and clinically significant bleeding. The end points for platelet response differed between the eltrombopag and romiplostim trials. In Kuter et al., the primary outcome was the proportion of patients with platelet counts of 50×10^9 per litre or more in 6 or more weekly assessments during the last 8 weeks of treatment without using rescue medication (durable platelet response), which the manufacturer equated to 'sustained response' as defined in the post hoc analyses of RAISE (section 3.6). The manufacturer further defined an 'overall response' as having either a durable response or a transient response. There were also differences in the definitions of bleeding between the eltrombopag and romiplostim trials: in RAISE, data on bleeding were collected using the WHO bleeding scale and the Common Terminology Criteria for Adverse Events (CTCAE) scale, whereas in Kuter et al., they were collected using an unnamed scale.

3.13 The manufacturer performed separate analyses for durable response and

overall response. The results of the indirect comparison were framed so that odds ratios of more than 1.00 favoured eltrombopag. When eltrombopag was compared with romiplostim, the odds ratio for attaining a durable response was 0.32 (95% CI 0.03 to 3.14) and that for attaining an overall response was 0.22 (95% CI 0.05 to 1.02). For people who had had a splenectomy, the odds ratios were 0.50 (95% CI 0.01 to 17.3) for durable response and 0.09 (95% CI 0.00 to 2.52) for overall response; for people who had not had a splenectomy, the odds ratios were 0.41 (95% CI 0.04 to 4.80) and 0.34 (95% CI 0.06 to 2.14) for durable response and overall response respectively.

3.14 The indirect comparison of rates of bleeding showed that the point estimates favoured eltrombopag in some analyses and romiplostim in others, with no statistically significant differences between the 2 treatments. When eltrombopag was compared with romiplostim, the odds ratio of a clinically significant bleed was 0.60 (95% CI 0.08 to 4.29), and that of a moderate or clinically significant bleed was 1.63 (95% CI 0.4.6 to 5.80).

3.15 The manufacturer highlighted that the indirect comparison showed no statistically significant differences between eltrombopag and romiplostim, and suggested that the differences between individual studies should be acknowledged when interpreting the results. The manufacturer indicated that patients differed between RAISE and the 2 Kuter et al. (2008) trials in terms of duration of ITP, previous use of ITP medications, use of concomitant medication, and whether or not patients had had a splenectomy. It also indicated that the design of the trials was different for timing of platelet count assessments, timeframes in which patients were allowed to reduce concomitant ITP medications, definitions of response and definitions of 'period of rescue medication'. The manufacturer pointed out that 2 published clinical guidelines, the 'International consensus report on the investigation and management of primary immune thrombocytopenia' (Provan et al. 2010) and 'The American Society of Haematology 2011 evidence-based practice guideline for immune thrombocytopenia' (Neunert et al. 2011), do not favour 1 treatment over the other. The manufacturer concluded that its indirect comparison between eltrombopag and romiplostim did not provide evidence of clinical superiority for 1 treatment over the other. In

absence of evidence to the contrary, the manufacturer concluded that eltrombopag and romiplostim have 'equal efficacy' and applied this assumption to the cost-effectiveness analysis.

3.16 The manufacturer presented an indirect comparison between eltrombopag and standard care alone (excluding eltrombopag and romiplostim). In this, the manufacturer restricted the treatments used in standard care to those included in the international consensus report (that is, intravenous immunoglobulin G, anti-D, rituximab, corticosteroids, vinca alkaloids, mycophenolate mofetil, ciclosporin, cyclophosphamide, danazol and dapsone). The manufacturer's systematic review of treatments used in standard care identified 113 studies (including 20 RCTs). However, the manufacturer altered its inclusion criteria after performing the search, which resulted in the exclusion of most of the identified studies. The manufacturer combined results from 37 studies, including 6 RCTs, to calculate weighted averages of response rate, time to response and duration of response for each drug used within the standard care pathway. The manufacturer pooled data regardless of the definition of response, and calculated the efficacy of each intervention using a simple average. The manufacturer highlighted that the results of the weighted averages for each of the included treatments were obtained mainly from non-randomised, highly heterogeneous, older trials; however, it acknowledged that the results largely reflected the response rates outlined in the international consensus report (Provan et al. 2010) and in Romiplostim for the treatment of chronic immune thrombocytopenia (NICE technology appraisal guidance 221).

Cost effectiveness

3.17 The manufacturer developed a de novo economic model to assess the cost effectiveness of eltrombopag in 2 populations of chronic ITP:

- adults who have not had a splenectomy

- adults who have had a splenectomy, but whose condition is refractory to previous treatments.

  The manufacturer assumed that patients who have not had a splenectomy reflect those for whom splenectomy is contraindicated.

3.18 The cost-effectiveness model developed by the manufacturer is a state-transition Markov cohort model with a 4-week cycle length. The model simulates patients with chronic ITP receiving eltrombopag plus standard care, romiplostim plus standard care, or standard care alone. The manufacturer assumed that all patients entering the model have ITP that is refractory to first-line treatment with corticosteroids or immunoglobulins and, if rituximab is considered an appropriate treatment option, patients will have already received it. For patients starting a treatment, the model permits their platelet count to reach 50×10^9 per litre or more (equal to a response) in the first, second, third or fourth cycle, depending on the time to response associated with each treatment. When the platelet count reaches 50×10^9 per litre, patients have a treatment-specific probability of losing the response in each cycle, and of receiving rescue therapy when bleeding occurs or a patient is deemed at high risk of bleeding. If the platelet count does not reach 50×10^9 per litre or patients lose their response, they stop treatment but may receive rescue therapy (intravenous immunoglobulin, anti-D and corticosteroids), which may result in a temporary platelet response lasting for 1 cycle. During each cycle, a proportion of patients who experience a bleed or whose platelet count does not respond 'exit' the 'non-responder' state and move on to other treatments further down the treatment sequence. Rates of rescue treatment, rates of non-severe bleeds treated in the outpatient setting, and rates of severe bleeds treated in the inpatient setting were lower in patients whose condition responds than in those whose condition does not. Patients in the model who are less likely to bleed are less likely to die.

3.19 The economic evaluation compared 3 treatment sequences: a pathway reflecting standard care without a thrombopoietin agonist (sequence 'a': azathioprine, mycophenolate mofetil, ciclosporin, danazol, dapsone, cyclophosphamide, vinblastine and vincristine), a pathway of eltrombopag with standard care (eltrombopag followed by sequence 'a'), and a pathway of romiplostim with standard care (romiplostim followed

by sequence 'a'). The sequence of treatments used as standard care reflects that used by the manufacturer of romiplostim in NICE technology appraisal guidance 221, except that rituximab is removed from the sequence for the base-case analysis in the current submission. This is because, as the manufacturer explained, UK local guidance suggests that clinicians offer rituximab to patients before eltrombopag or romiplostim. The manufacturer discounted costs and benefits at an annual 3.5% rate.

3.20 The manufacturer submitted 3 separate economic evaluations: a base case, an 'alternative' evaluation and a scenario analysis. In the base case, the manufacturer applied a set of assumptions it deemed most relevant to the decision problem, using NICE technology appraisal guidance 221 as its main source of data and assumptions. The only parameters in the base-case model that the manufacturer sourced from the RAISE and EXTEND trials were the thrombopoietin receptor agonist response rates and the thrombopoietin receptor agonist time on treatment. The alternative evaluation applied data from RAISE and EXTEND, along with clinical evidence retrieved from the manufacturer's systematic review for this appraisal. In the scenario analysis, the manufacturer applied all the assumptions and model inputs used in the economic evaluation for romiplostim in NICE technology appraisal guidance 221 (including those that were not used in the base case) to try to replicate as closely as possible the analysis in that technology appraisal.

3.21 In the base case and alternative evaluation, the manufacturer assumed that the response rate (attaining a platelet count of 50–400×10^9 per litre at any time during the 6-month study period) for eltrombopag was the same as that observed in the RAISE trial. It also assumed that, if a patient had a platelet response at any time during the 6-month period, the patient maintained the platelet response while on treatment and had a probability of bleeding and death as if the platelet count had remained elevated. Both the base case and alternative evaluation assumed complete clinical equivalence between eltrombopag and romiplostim, and so a patient in the model taking eltrombopag had the same rate of platelet response as a patient taking romiplostim. The manufacturer assumed that the effectiveness of the 2 treatments was the same because its indirect comparison had not shown that the treatments were

different (section 3.15). However, the manufacturer performed sensitivity analyses to test the possibility that romiplostim was more effective than eltrombopag by applying the odds ratio for overall response from its indirect comparison between eltrombopag and romiplostim (0.22).

3.22 For treatments considered to be standard care, the manufacturer took response rates for the base case from NICE technology appraisal guidance 221, in which the response rates were calculated from a systematic review that the manufacturer of romiplostim had done. In the alternative evaluation, the manufacturer estimated a response rate for each treatment from its indirect comparison between eltrombopag and treatments comprising standard care (section 3.16).

3.23 In the base case and alternative evaluation, time to platelet response for eltrombopag was 15 days (standard error 3.75 days), as observed in RAISE. For romiplostim, the time to response was assumed to be 28 days (standard error 7 days), based on the Kuter et al. (2008) trials. For treatments comprising standard care, time to response from NICE technology appraisal guidance 221 was used in the base case and, for the alternative evaluation, it was obtained from the manufacturer's indirect comparison between eltrombopag and standard care (section 3.16).

3.24 Because the manufacturer assumed that eltrombopag and romiplostim were equally effective, it also assumed that time on treatment was the same for eltrombopag and romiplostim. To extrapolate time on treatment over a lifetime horizon, the manufacturer modelled time on treatment as a survival variable using patient-level data on treatment discontinuation from RAISE and EXTEND, and carried out a parametric analysis. The manufacturer found that, among patients whose condition responded to treatment, those who had had a splenectomy spent less time on eltrombopag than those who had not.

3.25 For the time on treatment for therapies included in standard care, the manufacturer took values from NICE technology appraisal guidance 221 for its base case, and from the indirect comparison between eltrombopag and standard care (section 3.16) for its alternative evaluation. The manufacturer assumed that time on treatment for

standard therapy followed an exponential distribution.

3.26 The manufacturer assumed that the risk of bleeding in the model is a function of platelet response irrespective of treatment, so patients with platelet counts of 50×10^9 per litre or more were at risk of non-severe bleeds (treated as an outpatient), and patients with platelet counts of less than 50×10^9 per litre had a risk of severe (needing inpatient care) or non-severe bleeds. For its base case, the manufacturer applied the rates of bleeding previously used in NICE technology appraisal guidance 221 for romiplostim. For patients who did not have a platelet response, the rate of severe bleeds applied in the base-case model was 4.3% per month. For its alternative evaluation, the manufacturer used the rate of severe bleeds from RAISE and EXTEND (0.8% per month). The manufacturer assumed that patients whose condition is refractory to all previous treatments are twice as likely to bleed as patients whose condition does not respond to treatment but who are between treatments. The manufacturer took this assumption from NICE technology appraisal guidance 221.

3.27 The manufacturer modelled mortality from chronic ITP as a function of severe bleeds in the base case and alternative evaluation. For each bleed for which a patient needed to be hospitalised, the manufacturer applied a mortality rate from Danese et al. (2009), and assumed that this rate doubles for patients whose condition is refractory to all previous treatments. The manufacturer considered that patients would need to be hospitalised for the following categories of bleeds: gastrointestinal haemorrhage, intracranial haemorrhage and haemorrhage resulting from a 'coagulation disorder'.

3.28 For the base case, the modelling assumed that only patients with platelet counts of less than 50×10^9 per litre receive rescue medication, the types and rates of which were used in NICE technology appraisal guidance 221. The rate of rescue therapy for patients who had had a splenectomy was 68% and, for patients who had not had splenectomy, it was 33%. Rescue medications included intravenous immunoglobulin, anti-D and corticosteroids, and the proportions in which patients received these medications in the model were based on a survey of 169 UK haematologists that the manufacturer of romiplostim did for NICE

technology appraisal guidance 221. To estimate the rate of rescue for patients with platelet counts above and below 50×10^9 per litre for its alternative evaluation, the manufacturer used data from RAISE and EXTEND limited to countries with healthcare resources comparable to the UK.

3.29 Adverse events in the model were considered as either severe or 'other'. In the base case and alternative evaluation, the manufacturer assumed that the rates of adverse events for eltrombopag and romiplostim were equivalent and used the rates from NICE technology appraisal guidance 221. The manufacturer estimated adverse event rates for treatments included in standard care from the same technology appraisal.

3.30 Although RAISE and EXTEND collected health-related quality-of-life data, the manufacturer chose to use utility data for the base case and alternative evaluation from a study it had identified (Szende et al. 2010). This study developed 6 ITP-related health states that investigators had evaluated using the time trade-off method in 359 members of the UK general public.

3.31 The manufacturer did not identify any resource-use studies relevant to the UK from its systematic review of the literature. Therefore, it used unpublished data to estimate costs including the costs of acquisition and administration of the intervention and comparators, and the costs of the rescue medication, as well as the costs of monitoring. The manufacturer took the list prices of the different drugs from the 'British national formulary' (BNF) edition 63 and applied the patient access schemes for eltrombopag and romiplostim. It calculated the average doses of eltrombopag from RAISE and, after the 6-month study period, it estimated a stable dose from the EXTEND study. For romiplostim, the manufacturer calculated the average doses from Kuter et al. (2008) and assumed that the dose on which a patient is likely to remain (the stable dose) equals the last dose used in the trials (last dose carried forward). Dosages of drugs other than romiplostim and eltrombopag were taken from Provan et al. (2010), the international consensus report, or NICE technology appraisal guidance 221. Eltrombopag and other oral treatments did not have administration costs. Because romiplostim is injected subcutaneously, it can be administered at home or in hospital;

the manufacturer assumed that costs were incurred only when the drug was administered in hospital. The cost of bleeds covered drug costs, hospitalisation and follow-up. The manufacturer assumed that all patients, regardless of treatment, needed monitoring by a haematologist and 2 laboratory tests every 4 weeks.

3.32 In the manufacturer's base-case analysis, eltrombopag dominated romiplostim (that is, was more effective and less costly) for patients who had or had not had a splenectomy. For the comparison of eltrombopag with standard care, eltrombopag dominated standard care for patients who had had a splenectomy, and its incremental cost-effectiveness ratio (ICER) for patients who had not had a splenectomy was £15,105 per quality-adjusted life year (QALY) gained.

3.33 The manufacturer carried out a wide range of sensitivity analyses on the base case, varying 1 parameter at a time. It did not perform one-way sensitivity analyses on the results of the alternative evaluation or the scenario analysis.

- For patients who had had a splenectomy, eltrombopag dominated the standard care pathway in all analyses explored. In comparison with romiplostim, eltrombopag dominated in all analyses except when the model incorporated the odds ratio for overall response between eltrombopag and romiplostim from the manufacturer's indirect comparison (0.22, section 3.13). In this scenario, romiplostim gave 0.56 additional QALYs compared with eltrombopag, but at an additional cost of £95,649; the resulting ICER for eltrombopag compared with romiplostim was £171,156 saved per QALY lost (that is, eltrombopag was less effective but also less expensive than romiplostim).

- For patients who had not had a splenectomy, the ICER for eltrombopag compared with standard care remained below £33,000 per QALY gained in all scenarios except when a 6-month time horizon was used, in which case the ICER for eltrombopag compared with standard care was £74,250 per QALY gained. For the comparison of eltrombopag with romiplostim, eltrombopag dominated romiplostim in all sensitivity analyses, except when the odds ratio for overall response from the indirect comparison was used to estimate the relative efficacy of eltrombopag and romiplostim (OR 0.22, section 3.13). In this scenario, romiplostim offered 0.46 additional QALYs compared with eltrombopag, but at an additional cost of £51,416. This gave an ICER for eltrombopag compared with romiplostim of £110,983 saved per QALY lost.

3.34 The manufacturer carried out probabilistic sensitivity analyses to summarise the uncertainty in the base-case ICER. This showed that, for patients who had had a splenectomy, there was a 65% probability of eltrombopag being cost effective if the maximum acceptable ICER was £20,000 per QALY gained, and a 70% probability of it being cost effective if the maximum acceptable ICER was £30,000 per QALY gained. For patients who had not had a splenectomy, there was a 54% probability of eltrombopag being cost effective if the maximum acceptable ICER was £20,000 per QALY gained, and a 63% probability of it being cost effective if the maximum acceptable ICER was £30,000 per QALY gained.

3.35 In the manufacturer's alternative evaluation, eltrombopag dominated romiplostim in the analyses for patients who had or had not had a splenectomy. When eltrombopag was compared with standard care, the ICER for eltrombopag was £61,337 per QALY gained for patients who had had a splenectomy and £95,536 per QALY gained for patients who had not had a splenectomy.

3.36 The manufacturer presented a scenario analysis to replicate the analysis for NICE technology appraisal guidance 221. In this, the manufacturer:

- assumed that eltrombopag and romiplostim are administered before rituximab in the treatment pathway
- assumed that time on treatment followed an exponential distribution (instead of a log-normal distribution for the base case)

- remodelled the response rates for eltrombopag and romiplostim to exclude patients whose condition responded to unlicensed doses
- calibrated rescue rates to produce rates when the treatment pathway is set to exclude maintenance treatments
- based utility values on pooled EQ-5D and vignette utility data as per NICE technology appraisal guidance 221
- estimated the number of vials of romiplostim needed from NICE technology appraisal guidance 221
- set administration costs to £262 per cycle for all treatments and assumed that romiplostim did not incur further costs of administration.

3.37 In the scenario analysis, eltrombopag dominated both romiplostim and standard care for all patients.

Evidence Review Group critique and exploratory analyses

3.38 The ERG stated that the manufacturer identified all relevant studies comparing eltrombopag with placebo and presented a suitable meta-analysis. It also considered that the literature review carried out by the manufacturer to estimate the efficacy of standard care was reasonable.

3.39 For the indirect comparison of eltrombopag with romiplostim, the manufacturer used a Mantel-Haenszel fixed-effect approach to combine the results of the 2 Kuter et al. (2008) trials and then used the Bucher method. The ERG expressed the following concerns about this methodology:

- Heterogeneity exists between the 2 Kuter et al. trials, and pooling their results may have introduced bias.
- Although differences exist between RAISE and the 2 Kuter et al. trials (section 3.15), the ERG felt that it was reasonable that the manufacturer had proceeded with the indirect comparison, but advised caution with respect to the results.

- Because the manufacturer had presented the indirect comparison stratified by splenectomy status, the analyses did not preserve randomisation in RAISE, and the ERG considered them to be observational analyses.

3.40 The ERG performed an exploratory indirect comparison between eltrombopag and romiplostim for the outcomes of durable and overall response, and for clinically significant and moderate bleeds using a Bayesian network meta-analysis to account for the heterogeneity between the 2 Kuter et al. (2008) studies. For durable response and bleeding, the ERG found similar results to those of the manufacturer. For overall response, the manufacturer had found no statistically significant difference between treatments (OR 0.22; 95% CI 0.05 to 1.02), but the ERG found a statistically significant difference in favour of romiplostim (OR 0.15; 95% credible interval 0.02 to 0.84).

3.41 For the indirect comparison of eltrombopag with standard care, the ERG expressed concerns about the methodological rigor of the manufacturer's approach. Because the manufacturer excluded studies from the systematic review after the review had been performed, and had pooled response estimates using a simple weighted average regardless of the definition of response, the ERG considered that bias may exist. The ERG recommended caution when considering the results of this indirect comparison.

3.42 The ERG noted that a major weakness in the base-case analysis was that the manufacturer chose not to use data from the eltrombopag RCTs or from its systematic review of the literature, and instead opted to populate the base-case model with estimates from NICE technology appraisal guidance 221 for romiplostim. Because of this, the ERG considered the alternative evaluation to be more appropriate.

3.43 The ERG had concerns about the manufacturer's assumption that eltrombopag and romiplostim are equally effective, given the uncertainty around the results of the indirect comparison between eltrombopag and romiplostim (section 3.15).

3.44 The ERG noted that the manufacturer did not address the optimal positioning of eltrombopag and romiplostim within the treatment sequence in the model. The manufacturer assumed that eltrombopag

and romiplostim followed after rituximab, but preceded other drugs used in standard care. In addition, the ERG pointed out that there is uncertainty about the optimal place of eltrombopag and romiplostim if one is assumed to be more effective than the other. The ERG stated that the manufacturer should have explored additional sequences of treatment.

3.45 The ERG had concerns about the manufacturer's assumption that 'response' and 'platelet response' are the same. The ERG noted that, in RAISE, only 60–80% of patients whose condition responded to eltrombopag had a sustained platelet response of more than 50×10^9 per litre. Because platelet counts drive bleeding rates and mortality in the model, the ERG stated that the manufacturer's assumption would improve the ICERs for eltrombopag and romiplostim.

3.46 The manufacturer averaged eltrombopag and romiplostim doses from the relevant trials across patients whose condition had responded and those whose condition had not. The ERG noted that, in the Kuter et al. (2008) trials, the median dose of romiplostim in patients whose condition had responded was 40–60% lower than that across the trial as a whole. The ERG stated that eltrombopag and romiplostim doses should be response-specific.

3.47 To model utility, the ERG considered that the manufacturer, in its cost-effectiveness analysis, should have used the SF-6D health-related quality-of-life data collected from the RAISE and EXTEND trials, which are derived from a validated generic instrument.

3.48 The ERG questioned the manufacturer's assumption that the rate of severe bleeding doubles for patients whose ITP is refractory to all previous treatments, noting that these rates were high.

3.49 The ERG undertook exploratory sensitivity analyses, varying 1 parameter at a time, on both the base case and alternative evaluation; these included the following:

- Applying the overall response rates from the manufacturer's indirect comparison (60% for eltrombopag and 94% for romiplostim for people who had had a splenectomy [OR 0.09], and 72% for eltrombopag and 88% for romiplostim for people who had not had a splenectomy [OR 0.34]).
  - In the comparison of eltrombopag with romiplostim, eltrombopag was associated with both fewer QALYs and lower costs than romiplostim. For the base-case analysis, the ICERs suggested savings of £174,503 per QALY lost for people who had had a splenectomy when using eltrombopag instead of romiplostim. The ERG did not explicitly report ICERs for people who had not had a splenectomy from its analyses on the base case, nor did it report the ICERs for any of the subpopulations from its analyses on the alternative evaluation.
  - In the comparison of eltrombopag with standard care, the ERG reported costs and QALYs for the base-case analysis only for people who had not had a splenectomy, and for the alternative evaluation both for people who had or had not had a splenectomy. In the base-case analysis, eltrombopag dominated standard care for people who had had a splenectomy. For those who had not had a splenectomy, the ICER for eltrombopag compared with standard care was £15,843 per QALY gained. In the alternative evaluation, the ICERs for eltrombopag compared with standard care were £73,335 and £108,336 per QALY gained for people who had and had not had a splenectomy respectively.
- Applying the SF-6D utility data collected from RAISE and EXTEND.
  - In the comparison of eltrombopag with romiplostim, the ERG found that eltrombopag dominated romiplostim for both the base case and alternative evaluation, irrespective of whether or not the person had had a splenectomy.
  - For the comparison of eltrombopag with standard care in the base-case analysis, eltrombopag was dominant for people who had had a splenectomy, and gave an ICER of £18,489 per QALY gained for people who had not had a splenectomy. When the ERG applied the utility values to the alternative evaluation, eltrombopag was associated with ICERs of £90,753 and £133,508 per QALY gained for people who had and had not had a splenectomy respectively.

- Reducing modelled doses of romiplostim by 40% for people who had had a splenectomy and 60% for people who had not had a splenectomy.
    - In the comparison of eltrombopag with romiplostim, the ERG found that, despite the lower cost of romiplostim, eltrombopag dominated romiplostim in both the base case and alternative evaluation, irrespective of whether or not people had had a splenectomy.

3.50 In response to comments received during consultation on the first appraisal consultation document, the ERG carried out additional exploratory sensitivity analyses on the alternative evaluation, varying 1 parameter at a time, and then varying multiple parameters simultaneously. The ERG stated that, in its opinion, the alternative parameter inputs used in these analyses did not necessarily reflect the most reasonable assumptions. For the following parameters, the ERG:

- **a.** applied the odds ratio of 0.22 for overall response from the manufacturer's indirect comparison between eltrombopag and romiplostim (section 3.13). The resulting overall response rates were 60% for eltrombopag and 87% for romiplostim for patients who had had a splenectomy, and 72% for eltrombopag and 92% for romiplostim for patients who had not had a splenectomy
- **b.** applied the SF-6D utility data collected from RAISE
- **c.** removed anti-D treatment from the rescue therapies for patients who had not had a splenectomy
- **d.** applied the odds ratio of 0.15 for overall response from the ERG's indirect comparison between eltrombopag and romiplostim, for which the ERG had used a Bayesian approach (section 3.40). The resulting overall response rates were 60% for eltrombopag and 91% for romiplostim for patients who had had a splenectomy, and 72% for eltrombopag and 94% for romiplostim for patients who had not had a splenectomy
- **e.** applied a dose of romiplostim of 1.54 vials for patients who had had a splenectomy and 1.10 vials for patients who had not had a splenectomy, as calculated by the manufacturer of romiplostim
- **f.** applied a cost per administration of romiplostim equal to £11.50, as suggested by the manufacturer of romiplostim

- **g.** applied the above-listed sensitivity analyses b and c simultaneously
- **h.** applied the above-listed sensitivity analyses b, c and d simultaneously
- **i.** applied the above-listed sensitivity analyses b, c, d and e simultaneously
- **j.** applied the above-listed sensitivity analyses b, c, d, e and f simultaneously.

The ERG found that, when varying 1 parameter at a time, eltrombopag dominated romiplostim (that is, gave the same QALYs as romiplostim but at a lower cost) for patients who had or had not had a splenectomy in all analyses, except when the odds ratio of 0.22 or 0.15 was applied for overall response. In these instances, eltrombopag was associated with fewer QALYs and lower costs compared with romiplostim; when the ERG applied the odds ratio of 0.22, the corresponding ICERs suggested savings of £689,084 and £372,782 per QALY lost for patients who had and had not had a splenectomy respectively; when the odds ratio of 0.15 was applied, the ICERs were savings of £638,042 and £350,685 per QALY lost for patients who had and had not had a splenectomy respectively. The ERG estimated from the analyses in which it varied multiple parameters simultaneously that eltrombopag compared with romiplostim was associated with savings per QALY lost greater than £250,000 in all analyses, irrespective of whether or not the patient had had a splenectomy. The ICER from the sensitivity analysis in which all parameters were varied simultaneously (sensitivity analysis j) was £388,799 saved per QALY lost for patients who had had a splenectomy and £270,694 saved per QALY lost for patients who had not had a splenectomy.

3.51 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 eltrombopag, having considered evidence on the nature of chronic immune thrombocytopenia (ITP) and the value placed on the benefits of eltrombopag 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 discussed the nature of the condition with patient experts and clinical specialists, and heard that chronic ITP impacts on quality of life by affecting both the physical and emotional wellbeing of people with the condition. The Committee heard from clinical specialists that the signs and symptoms associated with chronic ITP vary; some people may not have any signs or symptoms, while others may have fatigue and bruise easily. It also heard from patient experts that chronic ITP may cause a patient to worry about the risk of bleeding because significant bleeding would normally cause a person to seek medical care, receive rescue treatment and possibly be hospitalised. The Committee recognised that anxiety related to bleeding may affect work or leisure activities, and, in extreme situations, causes people to become housebound. The Committee heard that family members may also worry on behalf of their relatives about the complications that may result from low platelet counts. The Committee noted that adequate treatment could psychologically benefit people with chronic ITP and their families by reducing anxiety and enabling them to lead more normal lives. The Committee agreed that these benefits may not be fully captured in the calculation of the quality-adjusted life year (QALY).

4.3 The Committee discussed the clinical management of chronic ITP. The clinical specialists explained that managing ITP depends on individual circumstances, and the specialists could not define a single treatment pathway as routine practice. The Committee understood that, although clinicians tend to offer active treatment to patients with low platelet counts or before surgery, treatment would not normally be determined solely on the platelet count. The Committee heard that splenectomy would be considered as first-line, second-line or subsequent-line

treatment, and that approximately two-thirds of patients can expect remission after splenectomy. The Committee was aware that splenectomy might be contraindicated in patients at greater risk of bleeding, but that laparoscopic procedures for splenectomy have lowered the risk of bleeding.

4.4 The Committee heard from patient experts about the perceived benefits of eltrombopag for patients with chronic ITP. It understood that the adverse reactions of most standard treatments for chronic ITP (such as those associated with corticosteroid use) limit both the use and duration of treatment, and that thrombopoietin receptor agonists (eltrombopag and romiplostim) had a different mode of action and a better adverse reaction profile than these standard treatments. It also understood that eltrombopag, as a daily oral treatment, would represent significant value for some patients with chronic ITP, while other patients would prefer romiplostim administered weekly by subcutaneous injections. The Committee heard from patient experts that some patients take a tablet of eltrombopag only once every 3 days rather than daily. The Committee noted that the summary of product characteristics states potential interactions of eltrombopag with dairy or calcium-containing products. The patient experts felt that, given the severity of ITP and the alternative treatment options available, few patients would have difficulties adhering to eltrombopag's dosage regimen because most would take it before bedtime to minimise the impact of dairy or calcium-containing foods on absorption. The Committee recognised that an oral treatment would add value for patients who have an aversion to needles.

4.5 The Committee considered the place of eltrombopag in the treatment pathway for people with chronic ITP and discussed the appropriate comparators, noting the licensed indications for eltrombopag. The Committee heard from the clinical specialists that there are few treatment options licensed for people with chronic ITP, and the specialists' view was that eltrombopag represents an effective approach. The Committee heard from clinical specialists that they are likely to offer eltrombopag to people whose condition is refractory to rituximab, or who are intolerant of rituximab, although rituximab is not licensed for the treatment of chronic ITP.

4.6 The Committee discussed the manufacturer's decision problem, noting that the manufacturer compared a pathway of eltrombopag plus standard care with a pathway of standard care alone, and separately with a pathway of romiplostim plus standard care. In all 3 pathways, the manufacturer defined standard care as sequential use of rituximab, azathioprine, mycophenolate mofetil, ciclosporin, dapsone, danazol, cyclophosphamide, vincristine and vinblastine. The Committee considered the relevance of the 2 comparator pathways (that is, the pathway of standard care alone, and the pathway of romiplostim plus standard care) in relation to the population in the RAISE trial. The Committee was aware that, since the publication of NICE technology appraisal guidance 221, romiplostim had been introduced into standard care in the NHS in England and Wales, and it was aware that the clinical specialists had indicated that eltrombopag was likely to be used in the same position as romiplostim in the treatment pathway. The Committee noted that the RAISE trial had included all patients with chronic ITP with a low platelet count for whom other treatments had failed, and not only those with severe chronic ITP who are at high risk of bleeding and need frequent courses of rescue therapy (that is, the population for which romiplostim is recommended in NICE technology appraisal guidance 221). The Committee agreed that comparing eltrombopag with the pathway including romiplostim plus standard care would be appropriate only for the same population for which romiplostim is recommended in NICE technology appraisal guidance 221. It also agreed that, for the population in the RAISE trial for which romiplostim is not recommended in NICE technology appraisal guidance 221 (that is, patients who did not have severe disease and a high risk of bleeding), comparing eltrombopag with the pathway of standard care alone would be appropriate. The Committee therefore concluded that both comparator pathways described in the manufacturer's decision problem were appropriate, but for 2 different populations.

Clinical effectiveness

4.7 The Committee considered the evidence on the clinical effectiveness of eltrombopag, noting that the evidence was derived mainly from the RAISE trial. It noted that the available evidence showed that, for people with chronic ITP for whom other treatments had failed, eltrombopag was

clinically effective when compared with placebo in attaining the target platelet count and reducing the need for rescue therapy.

4.8 The Committee discussed the safety and tolerability of eltrombopag and noted that the adverse reactions other than bleeding were similar between people who took eltrombopag or placebo in the RAISE trial. The Committee noted the lack of long-term safety data for both eltrombopag and romiplostim; however, it acknowledged that both treatments had better safety profiles than most standard treatments for chronic ITP.

4.9 The Committee discussed whether the manufacturer's indirect comparison between eltrombopag and romiplostim was appropriate. The Committee was aware that both the manufacturer and the Evidence Review Group (ERG) had advised caution when interpreting the results of the indirect comparison because of differences in baseline patient characteristics between RAISE and the 2 Kuter et al. (2008) trials for: duration of ITP, the proportion of patients who had received more than 3 prior ITP therapies, and the proportion of patients receiving concomitant ITP medication at baseline. The Committee discussed the sources of heterogeneity between the trials, and heard from the clinical specialists that the romiplostim trials were conducted before the eltrombopag trials; the Committee recognised that this may have caused more patients with severe chronic ITP to be enrolled into the earlier romiplostim trials. The Committee agreed that the differences between the RAISE trial and the 2 Kuter et al. trials may have introduced bias in the indirect comparison, but it concluded that it would be appropriate to perform an indirect comparison between the 2 treatments.

4.10 The Committee considered the manufacturer's indirect comparison and the ERG's exploratory analysis between eltrombopag and romiplostim, noting the different statistical approaches used to estimate the results. The Committee noted that, for the outcomes durable response and overall response, the manufacturer's indirect comparison gave odds ratios lower than 1 (favouring romiplostim), but the confidence intervals around those odds ratios suggested that the differences between eltrombopag and romiplostim were not statistically significant; for example, the odds ratio for overall response was 0.22 (in favour of romiplostim) with an upper limit of the 95% confidence interval of 1.02.

The Committee understood that the statistical approach used by the manufacturer did not account for the heterogeneity between the 2 Kuter et al. (2008) trials, whereas the ERG's exploratory indirect comparison, which used a Bayesian approach, treated the Kuter et al. trials separately. The Committee noted that, for overall response, the ERG's indirect comparison suggested a statistically significant difference in favour of romiplostim (odds ratio 0.15). For durable response, the Committee noted that the ERG found non-significant differences similar to those found by the manufacturer. The Committee was aware that the ERG's results depended on the degree of heterogeneity it assumed. The Committee agreed that the point estimates in both the manufacturer's and the ERG's analyses were associated with considerable uncertainty.

4.11 The Committee considered the relative effectiveness of eltrombopag and romiplostim in light of the manufacturer's indirect comparison and the ERG's exploratory analysis. It noted that the manufacturer interpreted the effectiveness of the 2 drugs as the same (that is, not different) on the basis that its indirect comparison did not show a statistically significant difference between them. The Committee heard from the clinical specialists that, while it is difficult to know whether 1 treatment is superior to the other, the use of eltrombopag and romiplostim in clinical practice is broadly interchangeable. The Committee accepted that the manufacturer's indirect comparison may have underestimated the clinical effectiveness of romiplostim given that the romiplostim trials preceded those for eltrombopag, and so the clinical trials for romiplostim may have enrolled patients whose condition was relatively more severe. The Committee noted that more patients in the romiplostim trials had received multiple previous therapies, which suggests that they better reflected patients whose condition had not responded than those in the eltrombopag trials. The Committee agreed that the available evidence suggested that romiplostim was likely to be more effective than eltrombopag rather than equally effective, and so it did not agree with the manufacturer's assumption used for the modelling that the treatments were equally effective. The Committee concluded that the most plausible odds ratio for overall response for eltrombopag compared with romiplostim would be less than 1.00 but, given the uncertainty around the point estimates obtained from the indirect comparison, it could not determine the likely value of this ratio.

4.12 The Committee considered the clinical effectiveness of eltrombopag compared with the pathway of standard care alone. The Committee understood that there was no direct evidence comparing eltrombopag with standard care, and so discussed the manufacturer's indirect comparison (section 3.16). The Committee noted that the evidence for treatments used in standard care was derived mainly from non-randomised, highly heterogeneous trials. It also noted that the manufacturer had altered its inclusion criteria after performing the literature review, and pooled response estimates using a simple weighted average of treatment groups. The Committee agreed that the indirect comparison lacked methodological rigor, and concluded that the results of the indirect comparison were not sufficiently robust to compare eltrombopag with the pathway of standard care alone.

Cost effectiveness

4.13 The Committee considered the manufacturer's cost-effectiveness analyses, and the ERG's critique of the analyses. The Committee agreed that, of the 3 economic evaluations (the base case, the alternative evaluation and the scenario analysis), the alternative evaluation represented the most valid analysis because the modelling applied data derived directly from the pivotal trials of eltrombopag and the manufacturer's own systematic review.

4.14 The Committee considered the cost effectiveness of eltrombopag compared with the pathway of standard care alone in the alternative evaluation, that is, for people with ITP for whom romiplostim is not recommended. It noted that the manufacturer had estimated response rates and time on treatment for drugs used in standard care from its indirect comparison of treatments used in standard care (section 3.22), and used the estimates in the alternative evaluation. The Committee, however, agreed that the indirect comparison lacked methodological rigor (section 4.12), and that there was no sufficiently robust cost-effectiveness evidence to make a recommendation for eltrombopag compared with the pathway of standard care alone. The Committee concluded that it could not recommend eltrombopag for patients who do not have severe disease and a high risk of bleeding.

4.15 The Committee then considered the cost effectiveness of eltrombopag compared with the pathway of standard care plus romiplostim in the alternative evaluation. It noted that the results of this comparison would apply only to people with severe chronic ITP and a persistent high risk of bleeding (that is, people for whom romiplostim is recommended in NICE technology appraisal guidance 221 for romiplostim). The Committee considered the sensitivity analyses in which romiplostim was more effective than eltrombopag, and noted that neither the manufacturer nor the ERG had provided incremental cost-effectiveness ratios (ICERs) for eltrombopag compared with romiplostim. However, from the costs and QALYs presented by the ERG from its exploratory sensitivity analyses on the alternative evaluation (section 3.49), the Committee initially estimated that the ICERs would be more than £400,000 saved per QALY lost for patients who had or had not had a splenectomy. The Committee noted that a comment received during consultation on the first appraisal consultation document indicated that it would be more appropriate to include in the sensitivity analyses the odds ratio for overall response of 0.15 estimated from the ERG's indirect comparison (section 3.40). The Committee heard from the ERG that, in response to this comment, it had carried out sensitivity analyses within the alternative evaluation, varying the parameter for overall response rate in the model (section 3.50). The Committee noted that, when the ERG applied an odds ratio of 0.22 to derive overall response rates, the ICERs for eltrombopag compared with romiplostim were savings of £689,000 and £373,000 per QALY lost for patients who had and had not had a splenectomy respectively; when the ERG applied an odds ratio of 0.15, these ICERs decreased to £638,000 and £351,000 per QALY lost respectively. The Committee was aware that the clinical specialists felt that eltrombopag and romiplostim were broadly interchangeable (section 4.11), and it concluded that, if the odds ratio for overall response moved towards 1.0 (as implied by the clinical specialists' willingness to substitute 1 treatment for another), the ICERs would further increase leading to further savings per QALY lost.

4.16 The Committee noted that the ERG questioned the source of the data on health-related quality of life used in the manufacturer's model because the manufacturer did not use the SF-36 health-related quality-of-life data collected from RAISE and EXTEND that it had mapped on to the SF-6D. The Committee noted that the manufacturer applied the SF-6D

utility data in a sensitivity analysis within the base case, but not within the alternative evaluation favoured by the Committee. The Committee noted comments received during consultation on the second appraisal consultation document suggesting that it would be more appropriate to use, in sensitivity analyses within the alternative evaluation, EQ-5D utility data obtained either from mapping SF-36 data on to the EQ-5D or from other studies from the literature identified by the manufacturer (such as Szende et al. 2010). The Committee heard that mathematical algorithms exist to map from SF-36 (used in RAISE and EXTEND) on to EQ-5D, and that, because no single algorithm is considered more valid than others, the EQ-5D data obtained from using a particular algorithm would be associated with further uncertainty. It also heard from the ERG that the Szende et al. study used by the manufacturer in its base-case analysis did not report EQ-5D utility values. The Committee was aware that the reference case outlined in NICE's Guide to the methods of technology appraisal states that EQ-5D is the preferred measure of health-related quality of life in adults. However, in the absence of EQ-5D data, the Committee concluded that, of the utility data available, the SF-6D data provided by the manufacturer were the most appropriate to use within the alternative evaluation.

4.17 The Committee discussed the ERG's concern about the dosing of romiplostim in the analyses (section 3.46). It noted that the doses of romiplostim used in the manufacturer's model did not depend on whether or not the patient's condition had responded, whereas in the Kuter et al. (2008) trials, the median dose of romiplostim in patients whose condition had responded was 40–60% lower than that across the trial as a whole. The Committee noted a comment received during consultation on the second appraisal consultation document suggesting to set the dose of eltrombopag after 24 weeks of treatment equal to the average dose from week 12 to week 23 in the RAISE trial (which was 7–12% higher than the originally modelled doses) to link the doses of eltrombopag with the modelled response rates from RAISE. The Committee discussed the impact of this suggestion on the cost effectiveness of eltrombopag compared with romiplostim, and heard from the ERG that the proposed dosing for eltrombopag would only minimally affect the relative cost effectiveness of the 2 treatments. In addition, the Committee was aware that patient experts indicated that some patients take a tablet of

eltrombopag only once every 3 days rather than daily (section 4.4), which implies that the dose of eltrombopag in clinical practice might in fact be lower than that observed in the RAISE trial. The Committee concluded that it was appropriate to use a median dose of romiplostim that is 40–60% lower than that used in the Kuter et al. trials and that the dose of eltrombopag used in the model was appropriate.

4.18 The Committee noted that comments received during consultation on the first appraisal consultation document raised concerns about some of the parameters used in the model, namely that the duration of treatment for romiplostim is longer than that for eltrombopag; that doses of romiplostim should be calculated in line with the approach used for NICE technology appraisal guidance 221 (that is, 1.54 vials for patients who had had a splenectomy and 1.10 vials for patients who had not had a splenectomy); that time to response for eltrombopag should be equal to that for romiplostim; that an in-hospital cost of £11.75 per administration for romiplostim should be used; and that anti-D should be excluded as a rescue therapy for patients who had not had a splenectomy.

4.19 The Committee considered these comments as follows:

- With regard to duration of treatment, the Committee heard from the ERG that the curves used to determine time on treatment within the model are specific to patients whose condition responded to eltrombopag; and, even if response rates differ between eltrombopag and romiplostim, it may still be reasonable to assume that duration of treatment is similar for both drugs. The ERG explained that the assumption of equal duration of treatment does not rely on the assumption of equal response rates and that, in the absence of other robust evidence, it was acceptable to assume equal time on treatment. The Committee concluded that no sensitivity analyses varying the duration of treatment parameter were needed.

- With regard to time to response, the Committee heard from the ERG that, in the model, for both eltrombopag and romiplostim, all patients receive 1 full 4-week cycle of treatment, at the end of which patients whose condition does not respond stop treatment. The ERG indicated that the assumption about time to response does not affect the relative costs and QALYs associated with eltrombopag and romiplostim in the model. The Committee accepted that the ICERs were not sensitive to the assumptions underlying time to response, and concluded that it did not need to consider those assumptions further.

- With regard to the cost of administering romiplostim, the Committee noted that the model included an average in-hospital cost of £204.81 per administration. The Committee was aware that the manufacturer of eltrombopag assumed that patients receive romiplostim in hospital for the first 4 weeks, and that 72% self-administer thereafter. Although the Committee agreed that the cost of administering romiplostim used in the model was likely to be an overestimate, it considered the alternative cost of £11.75, as suggested in the comments received during consultation on the first appraisal consultation document, to be too low.

- With regard to the use of anti-D as a rescue therapy, the Committee agreed that it would be appropriate to exclude it from the model.

4.20 The Committee noted the comment received during consultation on the second appraisal consultation document, which suggested that it would be more appropriate to model higher rates of bleed and rescue therapy from the Kuter et al. (2008) trial to reflect the severely affected population for which romiplostim is recommended. The Committee recognised that rates of bleeding and use of rescue therapies are important parameters in the model. It noted that both rates were higher in the romiplostim trials (Kuter et al.) than in the eltrombopag trials (RAISE and EXTEND). It heard from the ERG that the SF-6D utility data (favoured by the Committee, section 4.16) for bleeding events were aligned with the definition of bleeds in RAISE, but not with the definition in the Kuter et al. trials. The Committee was aware that neither the manufacturer nor the ERG applied the bleed and rescue rates from Kuter et al. in sensitivity analyses within the alternative evaluation favoured by the Committee. The Committee noted that there was no information available on bleeding and rescue rates in clinical practice, but it heard from the ERG that including the higher rates from Kuter et al. would not

lower the cost effectiveness of eltrombopag compared with romiplostim below £30,000 saved per QALY lost. It accepted that, if the higher rates of bleeds and rescue therapy from Kuter et al. were more pertinent to the population with severe ITP for which romiplostim is recommended and for which eltrombopag was being considered, this would have an impact on the ICERs in favour of romiplostim, but it would be extremely unlikely to affect the relative cost effectiveness of eltrombopag and romiplostim to a degree where the Committee would change its recommendations. The Committee concluded that it did not need to consider further sensitivity analyses incorporating the higher bleed and rescue rates from the Kuter et al. trials.

4.21 The Committee discussed the most plausible ICERs for eltrombopag compared with romiplostim. The Committee noted that the ERG did not initially report ICERs for eltrombopag compared with romiplostim from its exploratory sensitivity analyses within the alternative evaluation. It was also aware that no ICERs were available that incorporated all the parameter inputs favoured by the Committee within a single analysis. Therefore, the Committee considered the additional sensitivity analyses carried out by the ERG in response to comments on the first appraisal consultation document (section 4.18). The Committee agreed that romiplostim is likely to be more clinically effective than eltrombopag; that it was appropriate to use the SF-6D utility data collected from RAISE and EXTEND, a lower romiplostim dose and a lower administration cost for romiplostim, and to exclude anti-D. The Committee considered the analysis that mirrored this, and noted that the resulting ICERs for eltrombopag compared with romiplostim were £389,000 saved per QALY lost for patients who had had a splenectomy and £271,000 saved per QALY lost for patients who had not had a splenectomy. The Committee acknowledged that these ICERs are associated with considerable uncertainty. It accepted that the ICERs would be higher (in favour of eltrombopag) when accounting for a romiplostim administration cost in hospital of more than £11.50, or if romiplostim relative to eltrombopag was less effective (that is, if the odds ratio for overall response was greater than the 0.15 used in the ERG's analyses). The Committee also accepted that the ICER would be lower (in favour of romiplostim) if the rates of bleeding and rescue therapy in clinical practice were higher than those applied in the cost-effectiveness analysis. The Committee

accepted that there was a degree of uncertainty surrounding the ICER for eltrombopag compared with romiplostim. However, it was satisfied that, based on the evidence it had seen and the comments received during consultation on 2 appraisal consultation documents, eltrombopag can be considered a cost-effective use of NHS resources. The Committee noted that, in situations in which an ICER is derived from a technology that is less effective and less costly than its comparator, the commonly assumed decision rule of accepting ICERs below a given threshold is reversed, and so the higher the ICER, the more cost effective a treatment becomes. The Committee concluded that eltrombopag should be recommended as specified in its marketing authorisation (that is, in adults who have had a splenectomy and whose condition is refractory to other treatments, or as a second-line treatment in adults who have not had a splenectomy because surgery is contraindicated) as an option for treating adults with chronic ITP, but 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, and the manufacturer provides eltrombopag with the discount agreed in the patient access scheme.

4.22 The Committee noted that comments received in response to consultation on the appraisal consultation documents suggested that a specialist haematologist should supervise treatment with eltrombopag. The Committee agreed that, because the summary of product characteristics stipulates that eltrombopag treatment should remain under the supervision of a physician who is experienced in the treatment of haematological diseases (section 2.2), it did not need to repeat this in its recommendations.

4.23 The Committee was aware of comments received in response to the consultation on the appraisal consultation documents expressing concerns about the wording of the preliminary recommendation for eltrombopag, which, unlike the recommendation for romiplostim in NICE technology appraisal guidance 221, included reference to whether a person had or had not had a splenectomy. While the Committee appreciated the concerns raised, it was aware that the wording of the marketing authorisations for eltrombopag and romiplostim stipulates that both of these treatments should only be used if a person has had a

splenectomy or has not had a splenectomy because such surgery is contraindicated. The Committee acknowledged that NICE cannot recommend a treatment outside its marketing authorisation, and agreed that the wording of the recommendation in section 1 should reflect the wording of the marketing authorisation for eltrombopag.

4.24 The Committee discussed the limited published data on the long-term safety and effectiveness for both eltrombopag and romiplostim (sections 4.8 and 4.11), and on observed rates of bleeding and rescue therapy in clinical practice (section 4.20). The Committee considered that the collection of more data on the clinical effectiveness of both eltrombopag and romiplostim would be useful for future appraisals of treatments for chronic ITP because it would enable a more robust estimate of the clinical and cost effectiveness of the treatments. Given the difficulties of conducting randomised controlled trials and in generalising their results to clinical practice, the Committee supported generating and analysing observational data including, but not limited to, the existing UK ITP Registry, which collects data on the long-term outcomes of patients treated with eltrombopag and romiplostim.

4.25 The Committee discussed the differences in the wording of the guidance developed in this appraisal and the wording in the recommendations for romiplostim in NICE technology appraisal guidance 221, the latter of which were developed some time ago. The Committee concluded that it is necessary to ensure clarity around the fact that the recommendations for eltrombopag and romiplostim are for exactly the same patient population.

Summary of Appraisal Committee's key conclusions

TA293	Appraisal title: Eltrombopag for treating chronic immune thrombocytopenia (review of technology appraisal 205)	Section
Key conclusion		

Eltrombopag is recommended as an option for treating adults with chronic immune thrombocytopenia, 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. Eltrombopag is recommended only if the company provides it with the discount agreed in the patient access scheme.		1.1
For people with severe chronic ITP who are at high risk of bleeding and need frequent courses of rescue therapy (that is, the population for which romiplostim is recommended in NICE technology appraisal guidance 221), the Committee agreed that eltrombopag was less effective and less costly than romiplostim. The analysis that mirrored the Committee's preferred assumptions gave ICERs of more than £250,000 saved per QALY lost. The Committee noted that, in this situation, the higher the ICER, the more cost effective a treatment becomes. The Committee therefore concluded that eltrombopag can be considered a cost-effective use of NHS resources in this population.		4.6, 4.20
The Committee agreed that there was no sufficiently robust cost-effectiveness evidence to make a recommendation for eltrombopag compared with the pathway of standard care alone. Therefore, it concluded that it could not recommend eltrombopag for patients who do not have severe disease and a high risk of bleeding (that is, the population for which romiplostim is not recommended in NICE technology appraisal guidance 221).		4.12, 4.14
Current practice		
Clinical need of patients, including the availability of alternative treatments	The clinical specialists indicated that the signs and symptoms associated with chronic ITP vary. Chronic ITP may cause a patient to worry about the risk of bleeding, which may affect the ability of patients with chronic ITP to lead a normal life. The Committee recognised that adequate treatment could psychologically benefit people with chronic ITP and their families by reducing anxiety and enabling them to lead more normal lives.	4.2

	The Committee heard from the clinical specialists that there are few treatment options licensed for people with chronic ITP.	4.5
The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The Committee understood that eltrombopag had a better adverse reaction profile than most standard treatments.	4.4
	The Committee understood that a daily oral treatment would represent significant value for some patients with chronic ITP.	4.4
What is the position of the treatment in the pathway of care for the condition?	The Committee heard from clinical specialists that they are likely to offer eltrombopag to people whose condition is refractory to rituximab, or who are intolerant of rituximab.	4.5
Adverse reactions	The Committee understood that the adverse reactions of most standard treatments for chronic ITP (such as those associated with corticosteroid use) limit both the use and duration of treatment, and that eltrombopag had a better adverse reaction profile than those standard treatments.	4.4
	The Committee noted the lack of long-term safety data for both eltrombopag and romiplostim; however, it acknowledged that both treatments had better safety profiles than most standard treatments for chronic ITP.	4.8
Evidence for clinical effectiveness		

Availability, nature and quality of evidence	The evidence on the clinical effectiveness of eltrombopag was derived mainly from the RAISE trial.	4.7
	In the manufacturer's indirect comparison between eltrombopag and romiplostim, the Committee agreed that heterogeneity exists between RAISE and the 2 Kuter et al. (2008) trials, which may have introduced bias in the indirect comparison. However, the Committee concluded that it would be appropriate to perform an indirect comparison between both treatments.	4.9, 4.10
Relevance to general clinical practice in the NHS	No specific Committee considerations on the relevance to general clinical practice in the NHS.	
Uncertainties generated by the evidence	The Committee heard from the clinical specialists that the romiplostim trials were conducted before the eltrombopag trials; the Committee recognised that this may have caused more patients with severe chronic ITP to be enrolled into the earlier romiplostim trials. The Committee also heard that the use of eltrombopag and romiplostim in clinical practice is broadly interchangeable.	4.9, 4.11
	The Committee noted that the different statistical approaches used to perform an indirect comparison between eltrombopag and romiplostim gave an odds ratio for overall response that was statistically significantly in favour of romiplostim in the ERG's analysis but not in the manufacturer's. The Committee understood that the statistical approach used by the manufacturer did not account for heterogeneity between the 2 Kuter et al. (2008) trials, and that the ERG's results depended on the degree of heterogeneity it assumed. The Committee agreed that the point estimates in both the manufacturer's and the ERG's analyses were associated with considerable uncertainty.	4.10

	The Committee agreed that the manufacturer's indirect comparison between eltrombopag and the pathway of standard care alone was not sufficiently robust to compare eltrombopag with the pathway of standard care alone.	4.12
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	Not applicable.	
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The available evidence showed that eltrombopag was clinically effective when compared with placebo.	4.7
	The odds ratio for overall response from the manufacturer's indirect comparison between eltrombopag and romiplostim was 0.22, and that from the ERG's indirect comparison was 0.15. Only the latter was statistically significant.	4.10
	The Committee concluded that the most plausible odds ratio for overall response for eltrombopag compared with romiplostim would be less than 1.00 but, given the uncertainty around the point estimates obtained from the indirect comparison, it could not determine the likely value of this ratio.	4.11
	For the comparison of eltrombopag with the pathway of standard care alone, the Committee concluded that the results of the indirect comparison between the 2 pathways of care were not sufficiently robust to estimate a relative effect size.	4.12
Evidence for cost effectiveness		
Availability and nature of evidence	The manufacturer presented 3 economic analyses: a base case, an alternative evaluation and a scenario analysis. In all 3 analyses, the manufacturer compared eltrombopag with a pathway of standard care alone, and separately with a pathway of romiplostim plus standard care.	4.6

	The Committee agreed that the alternative evaluation represented the most valid analysis because the modelling applied data derived directly from the pivotal trials of eltrombopag and the manufacturer's own systematic review.	4.13
Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee considered that there was no sufficiently robust cost-effectiveness evidence to make a recommendation for eltrombopag compared with the pathway of standard care alone because the model incorporated data based on the manufacturer's indirect comparison of treatments used in standard care that, in the Committee's opinion, lacked methodological rigor.	4.14, 4.15, 4.17
	The Committee agreed that romiplostim is likely to be more clinically effective than eltrombopag, that it was appropriate to use the SF-6D utility data collected from RAISE and EXTEND, a lower romiplostim dose and a lower administration cost for romiplostim, and to exclude anti-D. The Committee acknowledged that the ICERs, even those reflecting its favoured parameters and assumptions, are associated with considerable uncertainty.	4.16, 4.19, 4.21
	The Committee noted that there was no information available on bleeding and rescue rates observed in clinical practice. It accepted that, if these rates are higher than those applied in the model, this would have an impact on the ICERs in favour of romiplostim, but it would be extremely unlikely to affect the relative cost effectiveness of eltrombopag and romiplostim to a degree where the Committee would change its recommendations.	4.20

Incorporation of health-related quality-of-life benefits and utility values 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 manufacturer did not use the health-related quality-of-life data collected from RAISE and EXTEND. The Committee concluded that, of the utility data available, the SF-6D data provided by the manufacturer were the most appropriate to use within the alternative evaluation.	4.16
	The Committee considered that the EQ-5D data obtained from using a particular mapping algorithm would be associated with further uncertainty and, in the absence of other EQ-5D data, the Committee concluded that the SF-6D data provided by the manufacturer were the most appropriate to use within the alternative evaluation.	4.16
	The Committee noted that adequate treatment could psychologically benefit people with chronic ITP and their families by reducing anxiety and enabling them to lead more normal lives. The Committee agreed that these benefits may not be fully captured in the calculation of the QALY.	4.2
Are there specific groups of people for whom the technology is particularly cost effective?	The Committee considered the cost effectiveness of eltrombopag compared with the pathway of standard care plus romiplostim in the alternative evaluation. It noted that the results of this comparison would apply only to people with severe chronic ITP and a persistent high risk of bleeding (that is, people for whom romiplostim is recommended in NICE technology appraisal guidance 221 for romiplostim).	4.15
What are the key drivers of cost effectiveness?	The key driver of cost effectiveness is the relative effect size of eltrombopag and romiplostim. The Committee did not agree with the manufacturer's assumption that eltrombopag and romiplostim were equally effective, and so considered the sensitivity analyses in which romiplostim was more effective than eltrombopag.	4.15

Most likely cost-effectiveness estimate (given as an ICER)	The Committee considered the analysis that mirrored its preferred assumptions and parameters. It noted that the resulting ICERs for eltrombopag compared with romiplostim were £389,000 saved per QALY lost for patients who had had a splenectomy and £271,000 saved per QALY lost for patients who had not had a splenectomy.	4.21
Additional factors taken into account		
Patient access schemes (PPRS)	The manufacturer of eltrombopag has agreed a patient access scheme with the Department of Health that makes eltrombopag available with a discount. The size of the discount is commercial in confidence.	2.4
End-of-life considerations	Not applicable.	
Equalities considerations and social value judgements	During consultation on the second appraisal consultation document a consultee highlighted under the heading 'Unlawful discrimination or groups who will be disadvantaged?' that the 'draft guidance puts doctors in an indefensible position and lays the NHS wide open to a legal class action by patients that are forced into a surgical procedure [splenectomy] that may not be relevant to, or in fact resolve, their ITP.' This comment does not highlight any unlawful discrimination or groups of patients with ITP that could be disadvantaged. The wording of the marketing authorisation for eltrombopag stipulates that eltrombopag should only be used if a person has had a splenectomy or has not had a splenectomy because such surgery is contraindicated. The regulatory agency has stated that the benefit-harm balance for eltrombopag could not be considered favourable for patients for whom a splenectomy remained a therapeutic option. NICE has to give recommendations in line with the marketing authorisation.	

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 paragraph above. This means that, if a patient has chronic immune thrombocytopenia and the doctor responsible for their care thinks that eltrombopag is the right treatment, it should be available for use, in line with NICE's recommendations.

6 Recommendations for further research

6.1 The Committee recommends that research should be carried out to directly compare eltrombopag with non-thrombopoietin receptor agonist treatments routinely used in UK clinical practice.

6.2 The Committee recommends research generating and analysing observational data including, but not limited to, the existing UK ITP Registry, which collects data on the long-term outcomes of patients treated with eltrombopag and romiplostim.

7 Appraisal Committee members and NICE project team

7.1 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 4 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)
Consultant Physician, Addenbrooke's Hospital

Professor Ken Stein (Vice Chair)
Professor of Public Health, Peninsula Technology Assessment Group (PenTAG), University of Exeter

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 Peter Barry

Consultant in Paediatric Intensive Care, Leicester Royal Infirmary

Professor John Cairns
Professor of Health Economics Public Health and Policy, London School of Hygiene and Tropical Medicine

David Chandler
Lay Member

Mark Chapman
Health Economics and Market Access Manager, Medtronic UK

Professor Fergus Gleeson
Consultant Radiologist, Churchill Hospital, Oxford

Professor Daniel Hochhauser
Consultant in Medical Oncology

Dr Neil Iosson
General Practitioner

Anne Joshua
Associate Director of Pharmacy, NHS Direct

Terence Lewis
Lay member

Professor Ruairidh Milne
Director of Strategy and Development and Director for Public Health Research at the National Institute for Health Research (NIHR) Evaluation, Trials and Studies Coordinating Centre at the University of Southampton

Dr Rubin Minhas
General Practitioner and Clinical Director, BMJ Evidence Centre

Dr Elizabeth Murray
Reader in Primary Care, University College London

Dr Peter Norrie
Principal Lecturer in Nursing, DeMontfort University

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

Dr John Pounsford
Consultant Physician, Frenchay Hospital, Bristol

Dr Danielle Preedy
Lay member

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

Roderick Smith
Finance Director, West Kent Primary Care Trust

Cliff Snelling
Lay Member

Marta Soares
Research Fellow, Centre for Health Economics, University of York

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

Dr Nerys Woolacott
Senior Research Fellow, Centre for Health Economics, University of York

7.2 NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Ahmed Elsada

Technical Lead

Nicola Hay
Technical Adviser

Jeremy Powell
Project Manager

8 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by Aberdeen Health Technology Assessment Group:

- Cummins E, Fielding S, Scott N et al. Eltrombopag for the treatment of chronic immune thrombocytopenic purpura (ITP): A Single Technology Appraisal (October 2012)

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:

- GlaxoSmithKline

II. Professional/specialist and patient/carer groups:

- British Blood Transfusion Society
- 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
- NHS North Yorkshire and York

- Welsh Government

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

- Amgen
- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- Roche

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 eltrombopag by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Nichola Cooper, Consultant haematologist, Hammersmith 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
- Chris Allen nominated by the ITP Support Association – patient expert
- Shirley Watson, nominated by the ITP Support Association – patient expert

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

- GlaxoSmithKline

Update information

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

April 2017: The company changed from GlaxoSmithKline to Novartis. Contact details for the patient access scheme updated.

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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