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

This guidance was developed using the single technology appraisal process
Eltrombopag for the treatment of chronic immune (idiopathic) thrombocytopenic purpura

Ordering information

You can download the following documents from www.nice.org.uk/guidance/TA205

- The NICE guidance (this document).
- A quick reference guide – the recommendations.
- ‘Understanding NICE guidance’ – a summary for patients and carers.
- Details of all the evidence that was looked at and other background information.

For printed copies of the quick reference guide or ‘Understanding NICE guidance’, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk and quote:

- N2340 (quick reference guide)
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1 Guidance

1.1 Eltrombopag is not recommended within its marketing authorisation for the treatment of chronic immune (idiopathic) thrombocytopenic purpura:

- in splenectomised adults whose condition is refractory to other treatments (for example, corticosteroids, immunoglobulins) or
- as second-line treatment in non-splenectomised adults where surgery is contraindicated.

1.2 People currently receiving eltrombopag for the treatment of chronic immune (idiopathic) thrombocytopenic purpura should have the option to continue treatment until they and their clinician consider it appropriate to stop.

2 The technology

2.1 Eltrombopag (Revolade, GlaxoSmithKline) increases platelet production through activation of the thrombopoietin receptor. By stimulating platelet production, it helps to reduce bleeding.

Eltrombopag has a UK marketing authorisation for the treatment of adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) in splenectomised patients whose condition is refractory to other treatments (such as corticosteroids and immunoglobulins) and as a second-line treatment for adult non-splenectomised patients where surgery is contraindicated.

2.2 Eltrombopag is for oral administration. The summary of product characteristics (SPC) states that the recommended initial dosage is 50 mg once daily. If, after 2–3 weeks of initial therapy, platelet counts are below the clinically targeted levels (50 × 10^9 per litre), the dosage may be increased to a maximum of 75 mg once daily. Treatment should be discontinued if the platelet count does not
increase sufficiently to avoid clinically important bleeding after 4 weeks of therapy at a dosage of 75 mg once daily. For full details of dosage and administration, see the SPC.

2.3 The SPC reports that the most common adverse effects associated with eltrombopag include pharyngitis, diarrhoea, nausea, vomiting, alopecia, rash and musculoskeletal pain. For full details of adverse effects and contraindications, see the SPC.

2.4 The manufacturer’s submission states that the price per 50 mg tablet is £55. Eltrombopag is available in 28-tablet packs containing 25 mg tablets (£770) or 50 mg tablets (£1540). The cost per patient will vary with dose adjustment and treatment duration, as described in section 2.2. For full details, see the SPC. Costs may vary in different settings because of negotiated procurement discounts.

3 The manufacturer’s submission

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

3.1 ITP is an autoimmune disease of variable natural history characterised by a reduction in platelet production and, in some people, an increase in platelet destruction. In a blood test, a normal platelet count is between 150 and 400 × 10⁹ per litre. Low platelet counts (below 30 × 10⁹ per litre) can result in bleeding, which varies from World Health Organization (WHO) grade 1 (petechiae), grade 2 (mild blood loss), grade 3 (gross blood loss) to grade 4 (debilitating blood loss). Management of ITP includes monitoring platelet counts and the associated bleeding. The aim of pharmaceutical treatment for ITP is to reduce bleeding and minimise the adverse effects of treatment. Many people do not require active treatment but, when it is indicated, significant benefits usually occur with the use of steroids, intravenous
immunoglobulin, splenectomy and, where clinically appropriate, 
anti-D immunoglobulin. In addition, non-selective 
immunosuppressants can help people with ITP.

3.2 The manufacturer’s submission compared adding eltrombopag to 
current standard ‘watch and rescue’ management (in which people 
received ongoing treatment with immunosuppressants and, when 
necessary, rescue treatments for bleeding with anti-D 
immunoglobulin or intravenous immunoglobulin) with watch and 
rescue management alone. In a separate analysis, eltrombopag 
was considered as part of a long-term treatment sequence with 
romiplostim, intravenous immunoglobulin, rituximab and anti-D 
immunoglobulin. The population included people with chronic ITP 
(defined in the manufacturer’s submission as persisting for more 
than 6 months) who had previously undergone, or had 
contraindications to, surgery to remove their spleen, and whose 
condition was refractory to other treatments such as corticosteroids 
and immunoglobulins. Only people who had a baseline platelet 
count of less than $30 \times 10^9$ per litre were considered. Outcomes 
were platelet count, response rate, duration of response, need for 
rescue treatments, use of concurrent treatments, reduction in 
symptoms, mortality and health-related quality of life. In the 
economic evaluation the incremental cost per quality-adjusted life 
year (QALY) gained was presented. In the base case, a 26-week 
time horizon was used in the evaluation of eltrombopag added to 
standard watch and rescue management, and a 2-year time 
horizon was used in the evaluation of eltrombopag as part of the 
long-term treatment sequence. Costs were considered from the 
NHS and personal social services (PSS) perspective.

Clinical effectiveness

3.3 The key clinical evidence in the manufacturer’s submission was a 
6-month phase III randomised controlled trial (RCT; RAISE 
[TRA102537]) that evaluated the efficacy, safety and tolerability of
eltrombopag added to standard care in adults with a platelet count of less than $30 \times 10^9$ per litre. RAISE was a double-blind multicentre study (recruiting nine people from the UK) that randomised 197 people to eltrombopag plus standard care ($n = 135$) or placebo plus standard care ($n = 62$). Randomisation was stratified by baseline platelet counts (less than or equal to $15 \times 10^9$ per litre and greater than $15 \times 10^9$ per litre), splenectomy status and use of ITP medication at baseline. Approximately 30% of people had ITP that was refractory to, or had relapsed after, splenectomy. All participants had prior exposure to at least one ITP medication: 89% had taken corticosteroids, 41% had received intravenous immunoglobulin, 21% had exposure to rituximab and about 50% had had three or more previous ITP medications. Platelet counts were less than $15 \times 10^9$ per litre in 50% of the people who entered the study.

3.4 Standard care consisted of treatment with steroids, non-selective immunosuppressants and rescue medication as required. People in the eltrombopag group received an initial dosage of 50 mg eltrombopag daily. The dose was increased to maintain a target platelet count of between 50 and $400 \times 10^9$ per litre. Over the 6-month study period the mean dosage of eltrombopag was 54.7 mg per person per day. At the end of the study, 69% of people randomised to the placebo group and 55% of those in the eltrombopag group had received concomitant medication for ITP.

3.5 The primary outcome in the RAISE trial was the odds of achieving a platelet count of between 50 and $400 \times 10^9$ per litre during the 6-month treatment period. Secondary outcomes included use of rescue treatment, incidence of bleeding and health-related quality of life. Health-related quality of life was assessed using the SF-36 questionnaire version 2, Functional Assessment of Chronic Illness Therapy for Patients with Thrombocytopenia (FACT-Th) and
3.6 The manufacturer reported the results for the whole population and separately according to splenectomy status. The overall odds of achieving a platelet count of between 50 and $400 \times 10^9$ per litre over the 6-month treatment period (primary outcome) were eight times greater in the eltrombopag group than in placebo group (odds ratio 8.2; 99% confidence interval [CI] 3.6 to 18.7, $p < 0.001$). People in the eltrombopag group also needed fewer protocol-defined rescue treatments (high-dose corticosteroids, platelet transfusion or intravenous immunoglobulin) than people in the placebo group (18% versus 40%, CI not given, $p = 0.001$). The odds of any bleeding event (WHO grades 1–4) were 76% lower in the eltrombopag group compared with the placebo group ($p < 0.001$, CI not given), and the odds of clinically significant bleeding (defined in the manufacturer’s submission as WHO grades 2–4) were 65% lower in the eltrombopag group ($p < 0.001$, CI not given). There was no significant difference between the eltrombopag and placebo groups in the low incidence of WHO grade 3 and 4 bleeding events. The main reduction in bleeding with eltrombopag was in grade 2 bleeding.

3.7 In the splenectomised subgroup (approximately one third of the trial population), 37% of people in the eltrombopag group and 15% of people in the placebo group achieved a platelet count of between 50 and $400 \times 10^9$ per litre (statistical analysis not presented). Eltrombopag was also associated with a statistically non-significant reduction in the use of rescue treatments (22% in the eltrombopag group received rescue medication compared with 47.6% in the placebo group) and in the number of bleeding events (82% of people in the eltrombopag group had a WHO grade 1–4 bleeding event compared with 90% in the placebo group, odds ratio 0.87; 95% CI 0.12 to 6.07). A significantly lower percentage of people in
the eltrombopag group had clinically significant bleeding (38% versus 70% in the placebo group, odds ratio 0.27; 95% CI 0.08 to 0.95, p = 0.041). This was statistically significant. There was no significant difference between the eltrombopag and placebo groups in the low incidence of WHO grade 3 and 4 bleeding events.

3.8 In the non-splenectomised subgroup (approximately two thirds of the trial population), 60% of people in the eltrombopag group and 18% of people in the placebo group achieved a platelet count of between 50 and 400 × 10⁹ per litre (statistical analysis not presented). Fewer people in the eltrombopag group required rescue medication than those taking placebo (16.5% versus 36.6%, odds ratio 0.34; 95% CI 0.14 to 0.79, p = 0.013). There was a statistically significant reduction in the odds of any bleeding event (WHO grades 1–4) with eltrombopag compared with placebo (76% versus 95%, odds ratio 0.10; 95% CI 0.02 to 0.53, p = 0.007). There was also a statistically significant reduction in clinically significant bleeding (WHO grades 2–4) with eltrombopag compared with placebo (29% versus 45%, odds ratio 0.31; 95% CI 0.11 to 0.83, p = 0.020). There was no significant difference between the eltrombopag and placebo groups in the low incidence of WHO grade 3 and 4 bleeding events.

3.9 The manufacturer reported changes in health-related quality of life using the SF-36. Eltrombopag was associated with statistically significant improvements in four domains (physical role, vitality, emotional role and mental health summary). Changes were not significant in six domains (physical functioning, body pain, general health, social functioning, mental health and physical health summary). Statistical analyses were not presented by splenectomy status.

3.10 Treatment-related adverse events were reported for 48 people (36%) in the eltrombopag group compared with 18 people (30%) in the placebo group (statistical comparisons were not presented).
The most common adverse events in the eltrombopag group were headache (30%), diarrhoea (13%), nausea (12%), nasopharyngitis (10%), upper respiratory tract infection (10%) and fatigue (10%).

The manufacturer’s submission stated that hepatobiliary laboratory abnormalities of potential clinical significance were more common in the eltrombopag group than in the placebo group (13% versus 7%). Two thromboembolic events were reported in the eltrombopag group in people with at least one risk factor for developing thromboembolism compared with no events in the placebo group.

3.11 The manufacturer presented a meta-analysis of the results of three placebo-controlled RCTs (RAISE [TRA102537], TRA100773A and TRA100773B). Eltrombopag was associated with a greater likelihood of platelet response in splenectomised people compared with placebo (odds ratio [Mantel–Haenszel fixed effect] 7.20; 95% CI 2.82 to 18.35, odds ratio [inverse variance with random effects] 7.20; 95% CI 2.82 to 18.33, both p < 0.0001) and non-splenectomised people (odds ratio [Mantel–Haenszel fixed effect] 9.17; 95% CI 4.52 to 18.60, odds ratio [inverse variance with random effects] 8.80; 95% CI 4.30 to 18.00, both p < 0.00001).

3.12 The manufacturer also presented an indirect comparison of eltrombopag with romiplostim, using placebo as a common comparison group. This comparison reported a statistically significant difference in favour of romiplostim for overall response at 6 months for all people (odds ratio 0.17; 95% CI 0.03 to 0.82, no p values given) and non-significant differences in favour of romiplostim for overall response at 6 months when data were analysed separately by splenectomy status (odds ratio 0.05; 95% CI 0 to 1.43 in the splenectomised group; odds ratio 0.29; 95% CI 0.04 to 1.95 in the non-splenectomised group, no p values given).

The manufacturer emphasised that there were differences between the populations enrolled in the romiplostim and eltrombopag trials and that overall response had not been a prespecified outcome in
the eltrombopag trial. The manufacturer argued that, for these reasons as well as the inherently exploratory nature of indirect comparisons, these results were subject to significant uncertainty.

**Cost effectiveness**

3.13 The manufacturer submitted two analyses that modelled different treatment strategies. The manufacturer stated that these were current clinical practice for two different populations with chronic ITP. The watch and rescue model compared the cost effectiveness of eltrombopag plus standard care for 6 months with standard care alone. Standard care was defined as ongoing treatment with immunosuppressants and, when necessary, rescue treatments for bleeding with anti-D immunoglobulin or intravenous immunoglobulin. An economic evaluation of long-term continuous treatment was presented for people whose platelet counts did not respond to watch and rescue management. This analysis modelled the cost effectiveness of eltrombopag as part of a sequence of ITP treatments for people with persistent bleeding. The manufacturer noted that the watch and rescue model represented the most common treatment strategy in the UK for chronic ITP.

**Watch and rescue model**

3.14 The watch and rescue model used effectiveness data from the RAISE trial to estimate the cost effectiveness of adding eltrombopag to standard care for 6 months. People entered the model with platelet counts of less than $30 \times 10^9$ per litre. The model had a time horizon of 26 weeks and assumed no further benefits or attenuation of response after the end of treatment.

3.15 The main RAISE effectiveness parameter was the difference in the relative risk of clinically significant bleeding (WHO grades 2–4) in the eltrombopag group compared with the placebo group. This parameter was used as a proxy for modelling the mortality benefit.
of eltrombopag plus standard care compared with standard care alone.

3.16 The manufacturer’s model extrapolated the mortality benefit associated with eltrombopag (in the RAISE trial) for the lifetime of the cohort. To estimate the number of years of benefit, the mean life expectancy of people in the RAISE trial, adjusted for the annual background rate of mortality in the ITP population, was calculated. In the absence of a published mortality rate in this population, the manufacturer identified a non-age-adjusted annualised risk of a fatal bleeding event of 2.76% from a literature search for use as a proxy.

3.17 QALYs gained in the manufacturer’s model reflected two components: the improvement in quality of life generated as a result of the treatment administered, and the utility gained from a reduced risk of death and bleeding. The improvement in quality of life while on treatment (eltrombopag or placebo) was measured through pooled SF-36 data taken from the RAISE trial and an open-label extension study (EXTEND). The scores were translated to SF-6D preference-based utility scores. QALYs gained from a reduced risk of death and bleeding were estimated using a baseline utility value from the RAISE trial for each year of life after treatment until average UK life expectancy and discounted at 3.5%.

3.18 Resource use in the model included the active treatment, concomitant and rescue medications, and resources required to treat bleeding events. The mean dosage of eltrombopag was taken from the RAISE trial (54.7 mg per person per day) based on the acquisition cost of £55 per 50 mg tablet. Use of concomitant and rescue medications was also taken from the RAISE trial. Resource consumption associated with bleeding events was estimated by clinical specialists using two methods, which the manufacturer described as ‘micro’ and ‘macro’ costing approaches. For micro costing, clinical specialists estimated a percentage of resource
consumption associated with each bleeding event for GP visits required, hospital outpatient consultation, accident and emergency visits and cost per day of hospitalisation. The macro costing approach used clinical opinion to provide analogous disease areas for which national NHS reference cost information was available (for example, grade 3 bleeding events were assumed to cost the same as a gastrointestinal bleed). The manufacturer’s base case used the macro costing approach.

3.19 In the manufacturer’s base case, the incremental cost-effectiveness ratios (ICERs) ranged from £77,496 per QALY gained for splenectomised people to £90,471 per QALY gained for non-splenectomised people. Subgroup analysis for all people with ITP (not presented separately by splenectomy status) reported ICERs of £96,749 per QALY gained for people with a baseline platelet count of less than $15 \times 10^9$ per litre and £72,331 per QALY gained for people receiving concomitant medication at baseline. The ICER for a subgroup of people with clinically severe ITP (baseline platelet count of less than $15 \times 10^9$ per litre and a higher mortality risk of 4.03%) was £66,880 per QALY gained.

3.20 At the time of the submission, the price of eltrombopag had not been confirmed and therefore the manufacturer presented deterministic sensitivity analyses around the acquisition cost of eltrombopag (£50 to £60 per 50 mg). Further deterministic sensitivity analyses were presented around the costing approach used (macro or micro), the relative risk of bleeding (changing the assumption of relative risk of a fatal bleed at WHO grades 2–4 to WHO grades 1–4), and the utility values adopted (based on the upper and lower bounds of the 95% confidence intervals at each assessment point). Sensitivity analysis was also carried out to demonstrate the impact of varying the annual rate of fatal bleeding on the ICER. The highest ICER reported was £99,441 per QALY gained, which resulted from changing the price of eltrombopag to
£60 for the non-splenectomised population. The lowest ICER reported was £69,301 per QALY gained, which resulted from changing the price of eltrombopag to £50 for the splenectomised population.

Evidence Review Group comments (watch and rescue model)

3.21 The ERG noted that the evidence from the RAISE trial showed that eltrombopag was statistically significantly more efficacious than placebo for all outcomes except the need for rescue medication and the reduction in concomitant medications in splenectomised people. The ERG noted, however, that the trial included people who did not have a medical contraindication to splenectomy, which is not consistent with the marketing authorisation for eltrombopag.

3.22 The ERG was concerned that the simplicity of the model structure, which assumed that differences between treatments arise primarily because of death and bleeding events and did not include other outcomes such as adverse events, would potentially affect cost and outcomes. The ERG noted that there was no direct comparison with other active comparator treatments.

3.23 The ERG considered the key assumptions in the model and questioned the use of clinically significant bleeds (WHO grades 2–4) as a proxy for differences in mortality rates, because they included mild blood loss (grade 2), which is unlikely to be fatal. The ERG also noted that the RAISE trial only reported a reduction in grade 1 and 2 bleeding with eltrombopag compared with placebo, and similar rates of grade 3 and 4 bleeds. Therefore, by using a mortality estimate that equates to bleeding at WHO grades 2–4, the manufacturer’s base-case model calculated a differential mortality risk between the two groups based primarily on grade 2 bleeds. The ERG noted that the manufacturer’s sensitivity analysis used a wider range of WHO bleeding grades (1–4) and not a narrower range of more serious bleeds (WHO grades 3 and 4) as a proxy for mortality rates.
3.24 The ERG conducted a multivariate exploratory analysis using the manufacturer’s model, which varied the discount rate and the annual rate of fatal bleeds. The ERG reported a wide range of ICERs of between £33,561 and £231,195 per QALY gained for splenectomised people and between £39,657 and £193,293 per QALY gained for non-splenectomised people. The ERG concluded that the model was most sensitive to the cost of eltrombopag, the costing approach adopted (macro or micro), the risk of fatal bleeds, the WHO grade of bleed applied and the discount rate used.

Long-term continuous treatment model

3.25 The long-term continuous treatment model submitted by the manufacturer used a Markov structure to assess the cost effectiveness of eltrombopag as part of a long-term treatment sequence for a hypothetical cohort of 25 people with severe chronic ITP. Severe chronic ITP was described by the manufacturer as a platelet count of less than $30 \times 10^9$ per litre combined with persistent bleeding that had not previously responded to conventional treatment with non-selective immunosuppressants or splenectomy (if not contraindicated).

3.26 The model analysed the cost effectiveness of eltrombopag as part of a treatment sequence with rituximab, intravenous immunoglobulin, anti-D immunoglobulin and romiplostim. As there is no standard treatment sequence, the manufacturer modelled all possible treatment sequences. The treatment sequence for non-splenectomised people required intravenous immunoglobulin to be used before anti-D immunoglobulin.

3.27 People entered the model with a platelet count of less than $30 \times 10^9$ per litre and with ITP that had responded inadequately to previous treatment. During each treatment in the sequence people were assessed to determine ITP response and bleeding events. People with ITP that had an inadequate response to treatment were switched to the next treatment in the sequence. Health effects
and values were measured according to the proportion of people who entered each of the four possible health states: controlled platelet count (greater than $50 \times 10^9$ per litre) with or without a significant bleed, or uncontrolled platelet count with or without a significant bleed. A utility value, cost and risk of bleeding were attached to each of these health states. The total costs and utility values were then combined and weighted by the time spent in each state. The model had a cycle length of 4 weeks and a 2-year time horizon.

3.28 The effectiveness inputs for each of the ITP treatments were taken from publications identified by the manufacturer. The effectiveness of eltrombopag and romiplostim came from the RAISE trial for eltrombopag and two 6-month RCTs for romiplostim. Evidence for intravenous immunoglobulin was taken from two short RCTs; case series evidence was used for rituximab and anti-D immunoglobulin.

3.29 Utility data for controlled or uncontrolled platelet counts were based on pooled data from the RAISE trial and an open-label extension study with people recruited from eltrombopag trials (EXTEND), and mapped to SF-6D. The model incorporated a utility decrement for bleeding events (defined as WHO grades 3 and 4), which were identified from the literature and measured using EQ-5D.

3.30 Resource use in the model included: medication, the cost of treating a bleeding event, consultation costs incurred with a treatment switch, and the cost of a monthly liver function test. Resource use was estimated from a range of secondary sources (such as reference costs and the ‘British national formulary’ [BNF], 58th edition). Event rates from the RAISE trial were used to inform resource use.

3.31 The manufacturer acknowledged a number of key assumptions in the model, in particular that populations in the 26-week RAISE trial and comparator studies were appropriate for an evaluation of
eltrombopag used as a long-term continuous treatment for severe chronic ITP. Further assumptions included: people with a persistently low platelet count (less than $50 \times 10^9$ per litre) were at a higher risk of bleeding; there was no loss of response (attenuation) throughout the duration of the model; the risk of a WHO grade 3 or 4 bleed was independent of ITP treatment; and adverse events were considered to be equal across all treatments and excluded from the model.

3.32 The manufacturer presented the cost per QALY gained for all possible treatment sequences on a cost-effectiveness plane; however, the incremental results were presented only for the four most cost-effective treatment sequences on the plane. The most cost-effective (lead) treatment sequence was rituximab, followed by eltrombopag, then romiplostim, then intravenous immunoglobulin (and anti-D immunoglobulin as an additional final treatment in the sequence for non-splenectomised people). The manufacturer compared this sequence with the same sequence without eltrombopag. The sequence containing eltrombopag was more efficacious and incurred less cost than the sequence without eltrombopag (that is, it was dominant). The manufacturer also demonstrated that the remaining three most cost-effective sequences on the cost-effectiveness plane were dominant over the same sequences without eltrombopag. The manufacturer presented an incremental analysis that used the lead treatment sequence as the baseline and presented the incremental costs and QALYs gained for the other three sequences, all containing eltrombopag. These analyses showed that there was very little difference between sequences in the incremental QALYs gained (for example, 1.4284 compared with 1.4286), yet differences in incremental costs were substantial (£18,527 compared with £21,133).
3.33 Sensitivity analysis for the four most cost-effective sequences in the manufacturer’s base case (all containing eltrombopag) was conducted using a platelet response level of $30 \times 10^9$ per litre instead of $50 \times 10^9$ per litre and the time horizon (lifetime [50 years] instead of 2 years). At the time of the submission the price of eltrombopag was unconfirmed and so sensitivity analysis was carried out for a lower price of £50 per 50 mg and an upper price of £60 per 50 mg, instead of £55 per 50 mg as in the base case. ICERs ranged from £6 million to more than £545 million per QALY gained for the non-splenectomised population and from £6 million to more than £200 million per QALY gained for the splenectomised population. These large ICERs were based on incremental QALYs ranging from 1.428 to 15.694 and incremental costs ranging from £18,527 to £469,238 in the splenectomised population, and incremental QALYs ranging from 1.43 to 15.821 and incremental costs ranging from £17,587 to £386,796 in the non-splenectomised population. The manufacturer concluded that the model was largely cost driven.

Evidence Review Group comments (long-term continuous treatment model)

3.34 The ERG considered that the evidence used for comparator effectiveness was highly selective. It acknowledged the lack of evidence base but highlighted that non-randomised and non-comparative data had been used without quality assessment. In addition, statistical analysis of the relative effectiveness of comparator treatments had been conducted only for romiplostim.

3.35 The ERG was concerned that the manufacturer had not explored the effect of using the indirect evidence comparing romiplostim with eltrombopag, which resulted in a favourable result for romiplostim (see section 3.12) in the model. It noted that the results of the model were inconsistent with the indirect evidence because the
treatment sequences placed eltrombopag before romiplostim, suggesting that it was a more effective treatment.

3.36 The ERG conducted exploratory analyses based on the time horizon which demonstrated that romiplostim was a more cost-effective treatment than eltrombopag if a lifetime (50-year) horizon was used. In addition, the length of time for assessing a response to romiplostim was 8 weeks in the manufacturer’s model, whereas a higher response rate was seen at 12 weeks. Therefore, the clinical benefit of romiplostim might be underestimated.

Additional evidence submitted by the manufacturer during consultation

3.37 Following consultation on the appraisal consultation document (ACD), the manufacturer submitted new clinical evidence and revised cost-effectiveness models. Recalculated overall response results from RAISE were presented, clarifying the response status of participants who had required rescue medication during the treatment period. As the differences from the original analysis were minor, the manufacturer did not repeat the indirect comparison with romiplostim that was based on this outcome (see section 3.12).

3.38 The manufacturer submitted an updated version of the watch and rescue model containing revisions addressing concerns raised by the Committee at the first Committee meeting. The Committee was concerned that the original model may have overestimated QALY gain by assuming constant utility values in projected life years, in spite of evidence from population norms showing utility values reducing with age. The manufacturer stated that it had addressed this criticism by adopting age-specific utility values that were proportional to population norms. The Committee had also expressed reservations about the projection of survival using normal average life expectancy, with no adjustment for excess mortality in the population with ITP. The manufacturer agreed that this was likely to result in an overestimate of QALYs gained and adjusted the model to predict lower life expectancy. In addition, the
manufacturer’s revised model corrected minor typographical errors identified by the ERG in their report. The revised base-case results combining these amendments suggested that, compared with standard watch and rescue management alone for splenectomised people, eltrombopag produces health gains of 0.096 QALYs per 26-week treatment period at an additional cost of £9,571, equating to an ICER of £99,543 per QALY gained. For non-splenectomised people, a gain of 0.090 QALYs at an additional cost of £10,038 was estimated, producing an ICER of £111,989 per QALY gained.

3.39 The manufacturer also submitted a new cost-effectiveness analysis comparing eltrombopag with romiplostim, using the revised watch and rescue model. In order to estimate the effectiveness of romiplostim, bleeding rates were taken from safety data reported in the submission to the Scottish Medicines Consortium for romiplostim. The relative risk of experiencing a clinically significant bleeding event with romiplostim compared with placebo was used as a proxy for expected mortality reduction, in the same way that survival benefit for eltrombopag was projected (see section 3.15). A similar approach was used to estimate the QALY gain with romiplostim during the modelled 26-week treatment period, so the amount of additional utility assigned to romiplostim was proportional to its effect in reducing bleeding events. The manufacturer’s new base-case analysis suggested that eltrombopag could be expected to dominate romiplostim (that is, be less expensive and more effective) in both splenectomised and non-splenectomised populations. A series of sensitivity analyses were presented, in each of which eltrombopag dominated romiplostim. The manufacturer also provided a scenario analysis in which the efficacy of the two products was assumed to be identical. In this analysis, it was estimated that eltrombopag offers cost savings of £12,389 in the splenectomised population and £2063 in the non-splenectomised population over a 26-week treatment period.
3.40 The ERG reviewed the additional clinical-effectiveness evidence submitted by the manufacturer during consultation. It repeated the indirect comparison of overall response rates with eltrombopag and romiplostim, concluding that the revised data had little impact on results. The comparison using all participants remained statistically significant in favour of romiplostim and the direction of effect for the splenectomised and non-splenectomised subgroups remained in favour of romiplostim without being statistically significant. A difference was observed in a sensitivity analysis in which all participants who had dropped out of the trial were assumed to have had ITP that responded to treatment: when all participants were considered together, the effect favouring romiplostim became non-significant in this analysis.

3.41 The ERG reviewed the manufacturer's revised model. It noted that, in contradiction of the manufacturer's consultation comments, the results presented failed to take account of utility values reducing with age. The ERG corrected the model to reflect the intended amendment. Corrected ICERs of £104,139 per QALY gained for splenectomised people and £116,800 per QALY gained for non-splenectomised people were generated.

3.42 The ERG reviewed the manufacturer's new cost-effectiveness analysis comparing eltrombopag with romiplostim. It noted that the effectiveness of romiplostim had been estimated using per-patient bleeding event data. The ERG commented that this was inconsistent with the calculated effectiveness of eltrombopag, which relied on per-incident bleeding event rates. To investigate the effects of this imbalance, the ERG changed the model to use per-patient data for both technologies. The results indicated that the QALY difference between eltrombopag and romiplostim could be very much smaller than in the manufacturer's base case. However, because eltrombopag remained very slightly more effective (with 0.0003 additional QALYs gained in each population) and
substantially less expensive than romiplostim, eltrombopag continued to dominate romiplostim.

3.43 The ERG also noted that the predominant reason for romiplostim being much more costly than eltrombopag, especially in the splenectomised subgroup, was that the model assumed more than one 250-microgram vial of medication would be required for most people taking romiplostim. The ERG agreed that this was an appropriate reflection of the average number of vials used in the key trials of romiplostim. However, the ERG also noted that a smaller vial of romiplostim may soon become available, which would reduce wastage of excess medication. To investigate the effects of this, the ERG undertook a further analysis of the model assuming that a 100-microgram vial of romiplostim was available. This analysis resulted in a reduced difference in estimated costs between the two technologies. Nevertheless, eltrombopag remained less expensive than romiplostim and thus continued to dominate romiplostim.

3.44 Full details of all the evidence are in the manufacturer’s submission and the ERG report, which are available from www.nice.org.uk/guidance/TA205

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 (idiopathic) thrombocytopenic purpura and the value placed on the benefits of eltrombopag by people with the condition, those who represent them, and clinical specialists. It considered comments received at consultation on the appraisal consultation document. It also took into account the effective use of NHS resources.
4.2 The Committee considered the evidence presented by the patient experts and clinical specialists on the clinical signs and symptoms associated with chronic ITP, and noted that the risk of bleeding associated with low platelet counts was variable. It noted that bleeding and bruising can have considerable impact on the daily activities of people with chronic ITP. Bleeding could prevent or delay surgery and limit lifestyle choices, and bruising may result in social stigma. Spontaneous bleeding is an important but rare cause of premature death in people with ITP. The Committee heard that anxiety about the risk of bleeding can also affect quality of life and a person’s ability to travel and take part in leisure activities.

4.3 The Committee heard from the patient experts that current licensed treatments for chronic ITP, especially steroids, have adverse effects which frequently need further treatment and affect quality of life. It noted that people with ITP are often anxious to avoid surgery to remove their spleen because of the risk of contracting a hospital-acquired infection and the increased risk of infection following spleen removal, which requires life-long daily treatment. The Committee also heard from clinical specialists that there are few medical contraindications to surgery as the procedure is now routinely performed as a minimally invasive operation.

4.4 The Committee understood that options for treatment of chronic ITP are limited when conventional treatments fail to reduce the risk of bleeding. In particular, it heard from the clinical specialists that they were mindful that rituximab does not have a marketing authorisation for the treatment of chronic ITP and may be associated with adverse effects, and that long-term safety data are currently not available for people with ITP treated with rituximab. Treatment with rituximab is further complicated because the correct dosage for treatment is not known. The Committee noted that although intravenous immunoglobulin is routinely used in severe chronic ITP, there is a reluctance to use it because of limited
supplies and the inconvenience to the person of being admitted to hospital. The Committee therefore understood that the use of intravenous immunoglobulin was restricted to people with acute symptoms as a rescue medication and would not be considered for the long-term management of ITP. It heard that the marketing authorisation for anti-D immunoglobulin had been withdrawn. The Committee understood from the clinical specialists that the licensed drug romiplostim (currently undergoing NICE appraisal) is generally considered to be clinically efficacious, although long-term data are not available. The clinical specialists also informed the Committee of their preference to use licensed treatments before unlicensed options.

4.5 The Committee discussed the clinical management of chronic ITP and the pathway of care for people with the condition. It noted the lack of good quality evidence in this clinical area. It heard from clinical specialists that the pathway of care for ITP would vary depending on an individual person’s circumstances, and that no single treatment pathway could be defined as routine practice. It understood that treatment would not normally be determined solely on the basis of the platelet count, but that there was a greater tendency to offer active treatment when the platelet count was low. However, the Committee heard from the clinical specialists that active treatment is more likely to be considered when a person is thought to be at greater risk of bleeding, for example when having surgical procedures or taking part in sport. It is also more likely to be considered when current standard treatments fail to produce satisfactory platelet counts or symptom relief.

4.6 The Committee then discussed the potential place of eltrombopag in the pathway of care for people with chronic ITP. The Committee heard from the clinical specialists that eltrombopag is an innovative treatment that mimics the action of the hormone thrombopoietin and stimulates platelet release from the bone marrow. It heard that,
along with romiplostim (which is also a thrombopoietin receptor agonist), eltrombopag represents a new approach to therapy of ITP. It noted that the marketing authorisation for eltrombopag restricts treatment for people who have undergone splenectomy to those whose condition is refractory to other treatments such as corticosteroids and immunoglobulin. In people in whom splenectomy is contraindicated, eltrombopag may be considered as a second-line treatment. The clinical specialists confirmed that eltrombopag might be an appropriate treatment option for people with chronic ITP for whom other treatments have failed, and whose bleeding is not persistent. However, the clinical specialists informed the Committee that in such a scenario, treatment would not necessarily be restricted to short-term use for 6 months as in the RAISE trial. Regarding the population for long-term continuous use of eltrombopag in the manufacturer’s submission, the Committee noted that these people have a low platelet count with a persistent risk of uncontrolled bleeding. The Committee heard that these people have the greatest unmet need for treatment and that a sequence of treatments, in which eltrombopag might have an appropriate place, would be used to control the persistent risk of bleeding.

**Clinical effectiveness**

4.7 The Committee considered the evidence presented by the manufacturer on the clinical effects of eltrombopag compared with placebo and standard care. The Committee noted that there were a small number of people from the UK in the RAISE trial, but accepted advice from clinical specialists that the data were relevant to clinical practice in England and Wales. The Committee noted that the RAISE trial was generally of acceptable quality; however, it was aware of the ERG’s concerns that non-splenectomised people did not necessarily have contraindications to splenectomy, and therefore may not adequately represent the population for whom eltrombopag is licensed. The Committee also noted that a minority
of the trial population had previously received intravenous immunoglobulin, and was mindful that this conflicts with eltrombopag’s marketing authorisation, which stipulates that it is indicated in people whose ITP is refractory to other treatments, including immunoglobulins. It concluded that a significant proportion of the people entered in the RAISE trial did not correspond to the population for whom eltrombopag is licensed.

4.8 The Committee considered the evidence from the RAISE trial. It noted that eltrombopag plus standard care, when compared with placebo plus standard care, resulted in significantly better odds of achieving the target platelet count, and was also associated with a significant reduction in the requirement for rescue medication. The Committee understood that people who received eltrombopag had also experienced significantly fewer bleeding events of all grades, and significantly fewer bleeding events of WHO grades 2–4. However, it also noted that there were no significant differences between treatment groups in the low incidence of the most serious bleeding events (those assessed at WHO grades 3 and 4).

4.9 The Committee discussed the relevance of the RAISE trial to the proposed place of eltrombopag in the ITP treatment pathway. It discussed whether RAISE data provided an appropriate basis on which to appraise the clinical effectiveness and cost effectiveness of eltrombopag as an alternative to conventional watch and rescue management. The Committee was aware of clinical specialist opinion suggesting that in practice treatment would not stop at 26 weeks. It was also aware of the licensed indication for people for whom treatment has previously failed or who have intolerance or a contraindication to standard treatments, and who therefore require an alternative regular treatment and not a short-term course of treatment. The Committee concluded that short-term use of eltrombopag, as administered in the RAISE trial, was not
representative of the likely clinical management of chronic ITP for people without severe bleeding.

4.10 The Committee then discussed the relevance of the RAISE trial to the long-term continuous treatment setting in the manufacturer’s economic model. The Committee repeated its concern that the trial population did not accurately reflect the licensed indication for eltrombopag (see section 4.7). It further noted that the RAISE trial had included all people with chronic ITP with a low platelet count, and not only those with a persistent risk of bleeding (as envisaged in the long-term continuous treatment setting). The Committee was also concerned about the lack of follow-up data and therefore the uncertainty about the long-term effects of eltrombopag in people with chronic ITP and a persistent risk of bleeding. Additionally, the Committee noted a 17% response rate for people in the RAISE trial receiving placebo plus standard care, while the model assumed that previous ITP treatment had failed. The Committee concluded that the trial data were not applicable to the population in the long-term continuous treatment model.

4.11 The Committee noted that adverse events were similar between the eltrombopag and placebo groups in RAISE. However, the Committee noted that there was no direct evidence comparing the adverse effects of eltrombopag with active comparator treatments. It was aware that comparator treatments such as immunosuppressants and cytotoxic drugs can be associated with undesirable effects. The Committee concluded, on the basis of the RAISE trial, that there was little difference in the adverse event rate of eltrombopag compared with placebo, but there was no evidence to assess the adverse event rate of eltrombopag compared with other active treatments.

4.12 The Committee understood that there is no evidence directly comparing romiplostim with eltrombopag. It noted that indirect comparisons provided by the manufacturer and the ERG suggested
that eltrombopag is associated with a lower overall response rate than romiplostim. The Committee noted that these indirect comparisons were subject to uncertainty because of differences between the populations enrolled in the romiplostim and eltrombopag trials and because overall response had not been a prespecified outcome in the eltrombopag trial.

**Cost effectiveness**

Watch and rescue model

4.13 The Committee considered the manufacturer's economic model for the watch and rescue population. It broadly accepted the model structure, but had concerns about the appropriateness of several assumptions used in the model. In particular, it noted the key assumption that differences between treatments arise solely because of bleeding events. It was also mindful of its concerns about the applicability of data from the RAISE trial to this model, as discussed in section 4.8.

4.14 The Committee was aware of the ERG’s concerns about a number of aspects of the economic model, such as the choice of a 26-week time horizon, with the assumption that costs and benefits could be presumed to be similar in all future 26-week periods. Based on clinical specialist opinion that a 26-week treatment period is not necessarily a basis for determining the likely duration of treatment, the Committee concluded that the model’s time frame was not long enough to capture the full costs and benefits of eltrombopag added to standard care in watch and rescue management, which therefore increases the uncertainty in the ICER.

4.15 The Committee considered the sensitivity analyses provided by the manufacturer. It noted the increased variation in ICERs from analyses conducted around the price of eltrombopag and accepted that the model was largely driven by cost, with a very small observed difference in health benefit. The Committee also
considered the ERG’s exploratory multivariate analyses and concluded that there was a high degree of uncertainty in the model results. The Committee therefore concluded that the model was unable to provide a precise ICER for eltrombopag in this setting.

4.16 The Committee considered the revised ICERs presented by the manufacturer following consultation (see section 3.38), with subsequent correction by the ERG (see section 3.41). It understood that the revised and corrected model addressed concerns it had previously raised that the model, as initially submitted, overestimated both the life expectancy of people with ITP and their quality of life. The Committee noted the conclusion that, as an alternative to watch and rescue management in a broad population with chronic ITP, eltrombopag provides health gains at a cost of £104,100 per QALY for splenectomised people and £116,800 per QALY for non-splenectomised people. The Committee concluded that these ICERs substantially exceed the range usually considered as a cost-effective use of NHS resources.

4.17 The Committee understood that during consultation consultees suggested that the Committee had failed to consider the low impact on the health budget of treating individuals with severe chronic ITP, since relatively few people would require treatment. The Committee noted that the NICE ‘Guide to methods of technology appraisal’ specifically states that the potential budget impact of the adoption of a new technology does not determine its decision. The Committee had also been asked to take into account technical challenges in modelling the disease pathway. It noted that the NICE ‘Guide to methods of technology appraisal’ states that, where there is substantial uncertainty about cost-effectiveness analyses, the Committee should be cautious about recommending a technology. The Committee had also been asked to consider the innovative nature of eltrombopag. It noted that, although eltrombopag represents a new class of medication for ITP, it had
not received any evidence demonstrating distinctive benefits of a substantial nature that were not adequately captured in the QALY measure. The Committee concluded that there were no exceptional circumstances in which eltrombopag as an alternative to watch and rescue management could be considered to represent an effective use of NHS resources.

4.18 The Committee considered the cost-effectiveness analysis comparing eltrombopag with romiplostim that the manufacturer submitted during consultation. It discussed the ERG’s view that the model was subject to limitations in the estimation of treatment effect, utility gain and resource use. It also noted that there is an ongoing appraisal of romiplostim by NICE, and that it is not routinely used in UK clinical practice. The Committee therefore concluded that the cost effectiveness of eltrombopag in comparison with romiplostim was both uncertain and not directly relevant to the decision problem being considered.

**Long-term continuous treatment model**

4.19 The Committee next considered the manufacturer’s economic model for the long-term continuous treatment of chronic ITP with eltrombopag. The Committee had concerns about the suitability of RAISE trial data for this population, as discussed in section 4.9, and concluded that the results of the model were not applicable to the treatment of people with chronic ITP and persistent bleeding.

4.20 The Committee considered the base-case ‘lead’ treatment sequences presented by the manufacturer. It was aware of clinical specialist opinion that it would be more likely that a licensed treatment such as eltrombopag would be used before an unlicensed treatment such as rituximab. It therefore considered that the base-case sequences (which placed rituximab before eltrombopag) did not represent the most likely treatment pathway. The Committee noted that no ICERs were presented for sequences led by eltrombopag; however, the base-case analysis had
discarded treatment sequences that were not as cost effective as those presented. The Committee therefore concluded that it was unlikely that a long-term treatment sequence in which eltrombopag was the first treatment would be cost effective.

4.21 The Committee then considered the position of eltrombopag compared with romiplostim in the treatment sequence. It noted evidence from the indirect comparison which suggested that eltrombopag is associated with a lower overall response rate than romiplostim. The Committee noted that in all the sequences identified on the cost-effectiveness frontier in the manufacturer’s base-case analyses, eltrombopag was placed before romiplostim, and it did not consider this to be a clinically plausible sequence of treatment. The Committee noted that changes in the order of treatments led to very large increases in the ICER. The Committee concluded that the base-case results were highly uncertain, and that if the order of eltrombopag and romiplostim in the treatment sequence was changed, the ICER would probably be much higher, though by an unknown amount.

4.22 In addition, the Committee had concerns that the base-case sequences contained treatments that might be unlikely to be used as long-term continuous treatments. It noted clinical specialist opinion about the supply of intravenous immunoglobulin and the withdrawal of the marketing authorisation for anti-D immunoglobulin. It recognised that, while intravenous immunoglobulin is used as an acute rescue therapy, it was modelled as maintenance therapy in the long-term continuous analysis. The Committee was also mindful that the appraisal of romiplostim is ongoing and its use is not routine in clinical practice. The Committee considered that if these treatments were to be removed from the sequence, eltrombopag would be the only remaining treatment. It noted that eltrombopag alone had already
been modelled in the watch and rescue analysis and had not represented a cost-effective use of NHS resources.

4.23 The Committee next discussed the base-case cost–utility results presented by the manufacturer for the long-term continuous model. It noted the large variation in ICERs with changes in the order of treatments following rituximab. It noted the ERG’s comments that the model was driven by large incremental changes in cost with very small differences in health gains (less than a 0.001 increase in QALYs across all four treatment sequences). The Committee also noted that the model demonstrated no survival benefit across the different treatment sequences. The Committee did not agree that it was appropriate to assume equivalence in the number and severity of adverse events between eltrombopag and comparator treatments. However, it recognised the lack of adverse event data for comparator treatments and was unable to judge what effect the exclusion of adverse effects would have on the cost per QALY gained. The Committee concluded that the long-term continuous model did not provide a valid basis on which to appraise the cost effectiveness of eltrombopag. In particular, it was concerned that comparators and sequences of care had been simulated in a way that did not reflect routine NHS care, and that the eltrombopag treatment effect was based on trial evidence from a population that was much broader than the patient group under consideration.

Other considerations

4.24 The Committee discussed whether there might be other groups of people with ITP who would benefit from treatment with eltrombopag for whom results had not been presented. The Committee noted that, despite its potential for maintaining platelet counts in people with ITP having surgery, eltrombopag does not have a marketing authorisation for perioperative use. The Committee also noted that, given the high cost of rescue therapy with intravenous immunoglobulin and the associated impacts on quality of life and
mortality, there was reason to believe that eltrombopag may be cost effective in a small population of people whose ITP has proved refractory to all other maintenance therapies and for whom frequent use of rescue therapy is necessary. The Committee had heard from patient experts and clinical specialists that the most important unmet clinical need was in this population. However, the manufacturer and other consultees had not presented any evidence relating to such use, and the Committee was mindful that all available trial evidence relates to a broader population of individuals with chronic ITP. Therefore the Committee could not make any conclusions about the use of eltrombopag in people with refractory ITP requiring frequent rescue therapy. The Committee noted that research establishing the clinical effectiveness and resource use associated with eltrombopag and its comparators in this clinical scenario would be very helpful.

4.25 In summary, the Committee concluded that the available evidence suggests that eltrombopag is associated with raising platelet levels for the duration of treatment when compared with standard care alone. However, the Committee was aware that this finding is based on a 26-week trial, and in practice eltrombopag would not be discontinued after 26 weeks. The long-term effectiveness of eltrombopag for this chronic condition is uncertain. The Committee noted that the manufacturer’s revised and corrected base-case estimates of the ICER for eltrombopag as an alternative to conventional watch and rescue management were very high: £104,100 per QALY gained for the splenectomised population and £116,800 per QALY gained for the non-splenectomised population. Additionally, the Committee identified a number of areas of uncertainty in this model and concluded that eltrombopag in addition to standard care alone does not represent a cost-effective use of NHS resources. The Committee also considered the use of eltrombopag as a long-term continuous treatment for a subgroup of people with persistent bleeding. It did not consider the trial
evidence to be generalisable to this population; in addition, it did
not consider the economic modelling of the position of eltrombopag
in the treatment sequence to be consistent with clinical practice for
the management of ITP. The Committee therefore considered the
sequential analyses to be highly uncertain and noted that, if
eltrombopag was considered without being part of a sequence, the
results of the watch and rescue analysis would apply. The
Committee therefore concluded that it could not identify any
circumstances under which eltrombopag could be considered a
cost-effective use of NHS resources.
### Summary of the Appraisal Committee’s key conclusions

<table>
<thead>
<tr>
<th>TA205 (STA)</th>
<th>Appraisal title: Eltrombopag for the treatment of chronic immune (idiopathic) thrombocytopenic purpura</th>
<th>ACD section</th>
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<tr>
<td><strong>Key conclusion</strong></td>
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| Eltrombopag is not recommended for the treatment of chronic immune (idiopathic) thrombocytopenic purpura (ITP):  
• in splenectomised adults whose condition is refractory to other treatments (for example, corticosteroids, immunoglobulins) or  
• as second-line treatment in non-splenectomised adults where surgery is contraindicated. | 1.1 |
| **Reasons for recommendations** | | 4.16 and 4.17 |
| The Committee's decisions were based on two clinical scenarios detailed in the manufacturer's submission. For eltrombopag as an alternative to standard watch and rescue management, the ICERs presented substantially exceeded the range usually considered as a cost-effective use of NHS resources, and the Committee concluded that there were no exceptional circumstances in which eltrombopag could be considered to represent an effective use of NHS resources. The Committee also considered the use of eltrombopag as a long-term continuous treatment for a subgroup of people with persistent bleeding, concluding that the economic modelling presented was inconsistent with clinical practice for the management of ITP and that, if eltrombopag was considered without being part of a sequence, the results of the watch and rescue analysis would apply. | 4.21 and 4.22 |
| **Current practice** | | 4.4 |
| Clinical need, including the availability of alternative treatments | The Committee understood that options for treatment of chronic ITP are limited when conventional treatments fail to reduce the risk of bleeding. It noted the following about potential comparators, having heard from clinical specialists that:  
• Rituximab is unlicensed for the treatment of ITP and may be associated with adverse effects. There are little safety data on its long-term use in people with ITP. The optimal dosage is not known.  
• Intravenous immunoglobulin is routinely used in severe chronic ITP only as a rescue medication because of its limited supply and the inconvenience of hospital administration.  
• Anti-D immunoglobulin is no longer available because its UK marketing authorisation has been withdrawn.  
• Romiplostim (currently undergoing NICE appraisal) has a UK marketing authorisation for the treatment of ITP.  
• The clinical specialists generally prefer to use licensed treatments before unlicensed options. |
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<tr>
<td><strong>The technology</strong></td>
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<tr>
<td>Proposed benefits of the technology</td>
<td>Eltrombopag mimics the action of the hormone thrombopoietin and stimulates platelet release from the bone marrow. In raising platelet counts, it could reduce incidence of spontaneous bleeding events, which are associated with quality of life impact and can be life-threatening. The Committee heard that, along with romiplostim (which is also a thrombopoietin receptor agonist), eltrombopag represents a new approach to therapy of ITP.</td>
<td>4.2 and 4.6</td>
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<td>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</td>
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<td>4.6</td>
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<td>What is the position of the treatment in the pathway of care for the condition?</td>
<td>Eltrombopag might be an appropriate treatment option for people with chronic ITP for whom other treatments have failed, and whose bleeding is not persistent. It might also be appropriate for people with a low platelet count and persistent uncontrolled bleeding.</td>
<td>4.6</td>
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<td><strong>Adverse events</strong></td>
<td>The Committee concluded, on the basis of the RAISE trial, that there was little difference in the adverse event rate of eltrombopag compared with placebo, but there was no evidence to assess the adverse event rate of eltrombopag compared with other active treatments.</td>
<td>4.11</td>
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<td><strong>Evidence for clinical effectiveness</strong></td>
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<td>Availability, nature and quality of evidence</td>
<td>The Committee discussed the clinical management of chronic ITP and the pathway of care for people with the condition. It noted the lack of good quality evidence in this clinical area. The evidence for this appraisal is based on one randomised controlled trial (RAISE) that compared the addition of eltrombopag to standard care (treatment with steroids, non-selective immunosuppressants and rescue medication as required) with standard care alone. The Committee noted that the RAISE trial was generally of acceptable quality; however, it was aware of the Evidence Review Group's concerns that non-splenectomised participants did not necessarily have contraindications to splenectomy and that only a minority of participants had prior exposure to intravenous immunoglobulin, so the trial may not adequately represent the population for whom eltrombopag is licensed. There is no evidence directly comparing eltrombopag with romiplostim. Evidence from indirect comparisons conducted by the manufacturer and the ERG suggests that eltrombopag is associated with a lower overall response rate than romiplostim.</td>
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<td>Relevance to general clinical practice in the NHS</td>
<td>The Committee noted that there were a small number of people from the UK in the RAISE trial, but accepted advice from clinical specialists that the data were relevant to clinical practice in England and Wales.</td>
<td>4.7</td>
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| Uncertainties generated by the evidence | The Committee was concerned about the lack of follow-up data and therefore the uncertainty about the long-term effects of eltrombopag.  
The Committee was aware of the ERG's concerns that non-splenectomised people in the RAISE trial did not necessarily have contraindications to splenectomy and that only a minority of participants had prior exposure to intravenous immunoglobulin, so the trial may not adequately represent the population for whom eltrombopag is licensed.  
The Committee had concerns about the applicability of the RAISE trial data for the two treatment settings set out in the manufacturer's submission.  
The Committee noted that the indirect comparison of eltrombopag and romiplostim was subject to uncertainty because of differences between the populations enrolled in the romiplostim and eltrombopag trials and because overall response had not been a prespecified outcome in the eltrombopag trial.  
The Committee noted that adverse events were similar between the eltrombopag and placebo groups in RAISE and that there was no direct evidence comparing the adverse effects of eltrombopag with active comparator treatments. | 4.7 and 4.10 |
<p>| Are there any clinically relevant subgroups for which there is evidence of differential effectiveness? | The Committee felt there was reason to believe that eltrombopag may be particularly valuable in a small population whose ITP has proved refractory to all other maintenance therapies and for whom frequent use of rescue therapy is necessary. However, the manufacturer had not examined any clinical scenarios or evidence relating to such use. Therefore the Committee could not come to any conclusions about the use of eltrombopag in this population. | 4.24 |
| Estimate of the clinical effectiveness including strength of supporting evidence | The Committee concluded that the available evidence suggests that eltrombopag is associated with raising platelet levels for the duration of treatment when compared with standard care alone. | 4.25 |
| <strong>Evidence for cost effectiveness</strong> | <strong>Availability and nature of evidence</strong> | <strong>ACD section</strong> |
| | Watch and rescue model: The Committee broadly accepted the model structure, but had concerns | 4.13 |</p>
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<td>about the appropriateness of several assumptions used in the model. Long-term continuous model: The Committee did not believe that the results of the model were applicable to the treatment of people with chronic ITP and persistent bleeding. It did not consider the trial evidence to be generalisable to this population and also did not consider the economic modelling of the position of eltrombopag in the treatment sequence to be consistent with clinical practice for the management of ITP.</td>
<td>4.19 and 4.25</td>
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| Uncertainties and plausibility of assumptions and inputs in the economic model | Watch and rescue model: The Committee had concerns about a number of assumptions in the model, including:  
• The RAISE trial was not applicable to the population in this model.  
• The model assumed that differences in treatment arise solely because of bleeding events.  
• The choice of a 26-week time horizon with the assumption that costs and benefits could be presumed to be similar in all future 26-week periods.  
• Using the watch and rescue model to estimate the cost-effectiveness of eltrombopag compared with romiplostim, on the basis of data that had been measured in a different way to the same model inputs for eltrombopag. Long-term continuous model: The Committee had concerns about a number of assumptions in the model, including:  
• The RAISE trial was not applicable to the population in this model.  
• The assumed treatment sequences were not likely to be consistent with clinical practice for the management of ITP.  
• The most appropriate place of eltrombopag in the treatment pathway was uncertain  
• The assumed equivalence in the number and severity of adverse events between eltrombopag and comparator treatments.  
• Uncertainties in the relative clinical effectiveness of eltrombopag compared with comparator treatments. | 4.13–4.18 and 4.25 4.19–4.23 and 4.25 |
<p>| Incorporation of health-related quality | Watch and rescue model: Reservations that were initially expressed about the adoption of constant | 4.16 |</p>
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<td>of life benefits and utility values</td>
<td>utility values in the projection of life expectancy were addressed in a revised model submitted during consultation.</td>
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<td>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?</td>
<td>The Committee concluded that, although eltrombopag represents a new class of medication for ITP, it had not received any evidence demonstrating distinctive benefits of a substantial nature that were not adequately captured in the QALY measure.</td>
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<tr>
<td>Most likely cost-effectiveness estimate (given as an ICER)</td>
<td>Watch and rescue model: The Committee noted that the manufacturer’s revised and corrected base-case estimates of the ICER for eltrombopag as an alternative to conventional watch and rescue management were very high: £104,100 per QALY gained for the splenectomised population and £116,800 per QALY gained for the non-splenectomised population. Additionally, the Committee identified a number of areas of uncertainty in this model and concluded that eltrombopag in addition to standard care alone does not represent a cost-effective use of NHS resources. Long-term continuous model: The Committee also considered the use of eltrombopag as a long-term continuous treatment for a subgroup of people with persistent bleeding. It did not consider the trial evidence to be generalisable to this population; in addition, it did not consider the economic modelling of the position of eltrombopag in the treatment sequence to be consistent with clinical practice for the management of ITP. The Committee therefore considered the sequential analyses to be highly uncertain and noted that, if eltrombopag was considered without being part of a sequence, the results of the watch and rescue analysis would apply.</td>
<td></td>
</tr>
<tr>
<td>Additional factors taken into account</td>
<td>Patient access scheme</td>
<td>No patient access scheme has been submitted.</td>
</tr>
<tr>
<td></td>
<td>End-of-life considerations</td>
<td>The end-of-life criteria were not applicable for this population.</td>
</tr>
<tr>
<td></td>
<td>Equalities considerations, social</td>
<td>No equality issues were raised.</td>
</tr>
</tbody>
</table>
5 Implementation

5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. The NHS is not required to fund treatments that are not recommended by NICE.

5.2 NICE has developed tools to help organisations put this guidance into practice (listed below). These are available on our website (www.nice.org.uk/guidance/TA205).

- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Recommendations for future research

6.1 Research should be performed to enable both prospective identification of individuals whose ITP, having proved refractory to all maintenance therapy, requires frequent rescue treatment, and estimation of the resource use associated with ITP treatment over a suitable time frame to support robust estimates of the cost effectiveness of eltrombopag and its comparators.
7 Related NICE guidance

Published

- There is no related guidance for this technology.

Under development
NICE is developing the following guidance (details available from www.nice.org.uk):

- Romiplostim for the treatment of chronic immune or idiopathic thrombocytopenic purpura. NICE technology appraisal guidance (publication date to be confirmed).

8 Review of guidance

8.1 The guidance on this technology will be considered for review by the Guidance Executive in June 2013. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators. The Committee agreed that, at that time, consideration should be given to undertaking a combined review of guidance on this technology and guidance produced on romiplostim (see section 7).

Andrew Dillon
Chief Executive
October 2010
Appendix A: Appraisal Committee members and NICE project team

A Appraisal Committee members

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

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

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

Dr Darren Ashcroft
Senior Clinical Lecturer, School of Pharmacy and Pharmaceutical Sciences, University of Manchester

Dr Matthew Bradley
Value Demonstration Director, AstraZeneca

Mr Mark Campbell
Director of Standards, Bury Primary Care Trust

Professor Usha Chakravarthy
Professor of Ophthalmology and Vision Sciences, The Queen’s University of Belfast

Professor Peter Clark (Chair)
Consultant Medical Oncologist, Clatterbridge Centre for Oncology
Dr Ian Davidson
Lecturer in Rehabilitation, University of Manchester

Professor Simon Dixon
Professor of Health Economics, University of Sheffield

Dr Martin Duerden
Medical Director, Conwy Local Health Board

Dr Alexander Dyker
Consultant Physician, Wolfson Unit of Clinical Pharmacology, Newcastle upon Tyne

Dr Jon Fear
Consultant in Public Health Medicine, Head of Healthcare Effectiveness NHS Leeds

Miss Paula Ghaneh
Senior Lecturer and Honorary Consultant, University of Liverpool

Professor Carol Haigh
Professor in Nursing, Manchester Metropolitan University

Dr Kevin Hardy
Consultant Physician, St Helens & Knowsley Teaching Hospitals NHS Trust

Mrs Alison Hawdale
Lay Member

Professor John Hutton
Professor of Health Economics, University of York

Professor Peter Jones
Pro Vice Chancellor for Research & Enterprise, Keele University
Professor of Statistics, Keele University

Dr Steven Julious
Senior Lecturer in Medical Statistics, University of Sheffield
Rachel Lewis
Practice Development Manager, Manchester Primary Care Trust

Professor Jonathan Michaels (Vice Chair)
Professor of Vascular Surgery, University of Sheffield

Dr Neil Milner
General Medical Practitioner, Tramways Medical Centre

Professor Oluwafemi Oyebode
Professor of Psychiatry and Consultant Psychiatrist, The National Centre for Mental Health, Birmingham

Mr Mike Pinkerton
Chief of Business Development, Rotherham NHS Foundation Trust

Dr John Radford
Director of Public Health, Rotherham Primary Care Trust

Dr Phillip Rutledge
GP and Consultant in Medicines Management, NHS Lothian

Dr Stephen Saltissi
Consultant Cardiologist, Royal Liverpool University Hospital

Dr Brian Shine
Consultant Chemical Pathologist, John Radcliffe Hospital

Mr Paddy Storrie
Lay Member

Dr Cathryn Patricia Thomas
GP and Associate Professor, University of Birmingham

Dr Lok Yap
Consultant in Acute Medicine and Clinical Pharmacology, Whittington Hospitals NHS Trust
B NICE project team

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

Joanne Holden
Technical Lead

Gabriel Rogers
Technical Lead

Eleanor Donegan
Technical Adviser

Nicola Hay
Technical Adviser

Kate Moore
Project Manager
Appendix B: 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:

- Bowers D, Jia X, Crowther M et al. Eltrombopag for the treatment of chronic idiopathic (immune) thrombocytopenic purpura (ITP): a single technology appraisal (December 2009)

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 Society for Haematology
- ITP Support Association
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians

III Other consultees:

- Department of Health
- Welsh Assembly Government

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

- NHS Quality Improvement Scotland
- Roche Products
• Sanofi – Aventis
• Aberdeen HTA Group
• National Institute for Health Research Health Technology Assessment Programme

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 Jennie Wimperis, nominated by ITP Support Association – clinical specialist
• Dr Paula Bolton-Maggs, nominated by Royal College of Pathologists and British Society for Haematology – clinical specialist
• Derek Elston, nominated by ITP Support Association – patient expert
• Shirley Watson MBE, nominated by ITP Support Association – patient expert

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

• GlaxoSmithKline