NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

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

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD) 2

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
Amgen	1. Executive Summary We welcome the preliminary recommendation from the Appraisal Committee (AC) that romiplostim is both clinically and cost effective for the treatment of chronic idiopathic (immune) thrombocytopenia purpura (ITP) patients whose condition is refractory to standard active treatments and rescue therapies or who have severe disease and a high risk of bleeding that requires frequent courses of rescue therapies. We have carefully reviewed and assessed the Appraisal Committee's consideration of the evidence on romiplostim. We welcome the opportunity to respond to the appraisal consultation document (ACD), and in our response, we have addressed points of clarification and identified factual inaccuracies.	Comment noted.
Amgen	We would first like to address the four questions posed by the Appraisal Committee. i) Has all of the relevant evidence been taken into account? We believe that all of the relevant evidence has been taken into account. The Committee noted that romiplostim significantly improved platelet count and reduced the frequency of bleeding – particularly the occurrence of moderate to severe bleeding episodes. The Committee also considered that the available data demonstrated that romiplostim was clinically effective in people with severe ITP at high risk of bleeding. These considerations are in line with the existing evidence for romiplostim and are also in line with the considerations in the EMA assessment report. For example, the EMA considered the strength of evidence for romiplostim uncommon in an orphan condition and commented that the effect of romiplostim should be placed in the context of a life-threatening disease where limited therapeutic alternatives are possible.	Comment noted.
Amgen	ii) Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? The summaries of clinical and cost effectiveness of romiplostim in the ACD issued on 29 November 2010 are reasonable interpretations of the evidence. The Committee concluded that the ICERs would be under £20,000 per QALY gained for the treatment of splenectomised patients, and around £30,000 per QALY gained for treatment of non-splenectomised patients. These ICERs are an accurate and clinically appropriate reflection of the cost effectiveness of romiplostim relative to active treatments in the UK.	Comment noted.
Amgen	iii) Are the provisional recommendations sound and a suitable basis for guidance to the NHS? Yes, we believe that the provisional recommendations are sound and a suitable basis for guidance to the NHS.	Comment noted.
Amgen	iv) Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief? None.	Comment noted.

Consultee	Comment	Response
Amgen	v) Are there any equality-related issues that need special consideration and are not covered in the appraisal consultation document? None. We welcome the preliminary recommendations from the Appraisal Committee and believe that all the available evidence for romiplostim in evaluating the clinical and cost-effectiveness and the patient access scheme have been duly taken into account to produce recommendations that form a sound and suitable basis for guidance to the NHS.	Comment noted.
Amgen	**2. The technology** In this section, we would like to clarify a statement contained in paragraph 2.2 as stated below. **ACD Section 2.2** ***"Romiplostim should also be discontinued if a peripheral blood smear indicates increased bone marrow reticulin."*** We would like to point out that this statement is not fully aligned with the SPC. An abnormal blood smear may indicate presence of bone marrow reticulin (and a bone marrow biopsy with appropriate staining for reticulin should be considered). Romiplostim should be discontinued if an abnormal peripheral blood smear as well as a loss of efficacy is observed. We have provided the statement contained in the SPC for clarification (section 4.4, page 4): "*If a loss of efficacy and abnormal peripheral blood smear is observed in patients, administration of romiplostim should be discontinued, a physical examination should be performed, and a bone marrow biopsy with appropriate staining for reticulin should be considered. If available, comparison to a prior bone marrow biopsy should be made. If efficacy is maintained and abnormal peripheral blood smear is observed in patients, the physician should follow appropriate clinical judgment, including consideration of a bone marrow biopsy, and the risk-benefit of romiplostim and alternative ITP treatment options should be re-assessed*."	Comment noted. Section 2.2 of the FAD has been amended.
Amgen	**3. Clinical effectiveness** We would like to clarify a few points in this section as outlined below. **ACD Section 3.1** ***"Outcomes included platelet count, response rate, durable response, need for rescue therapies, use of concurrent treatments, reduction in symptoms, adverse events, mortality and health-related quality of life."*** The outcomes stated here reflect those included in the phase III clinical trials for romiplostim. We would like to seek more clarity on the outcome 'reduction in symptoms', specifically if this refers to a reduction in bleeding symptoms. The data on bleeding events was collected prospectively as part of safety data in the phase III trials. The grading of the severity of bleeds (i.e. mild, moderate, severe, life-threatening and fatal)	Comment noted. The text related to this point has been deleted from section 3.1 and is now incorporated in section 3.4 of the FAD.

Consultee	Comment	Response
	was prospectively graded for severity by the clinical investigators. The statistical analysis on the reduction in bleeding symptoms was conducted as a post-hoc data analysis of prospectively reported and graded safety data in the phase III trials.	
Amgen	**ACD Section 3.1** ***"In both RCTs, patients with ITP (defined as the mean of three platelet counts being below or equal to 30 × 10^9 per litre, with none of the three counts being above 35 × 10^9 per litre) whose condition was refractory to at least one previous treatment were randomised to romiplostim plus standard care or to standard care alone (placebo) for 24 weeks."*** We would like to add to the statement above that while the requirement for entering the trials was that the mean of three platelet counts be below or equal to 30×10^9 per litre, the actual mean platelet count at baseline in the trials was even lower at 18×10^9 in the non-splenectomised group and 15×10^9 in the splenectomised group. This demonstrates that the patients enrolled into the phase III trials were a particularly severe group of ITP patients.	Comment noted. Section 3.2 of the FAD includes this information.
Amgen	**ACD Section 3.3** ***"Six non-RCTs investigating safety of romiplostim and one open-label extension study of the phase III RCTs were reported in the manufacturer's submission. In the latter, patients treated with romiplostim or placebo who had completed the phase III studies, and whose platelet counts subsequently fell to below 50 x 10^9 per litre after discontinuation of romiplostim or placebo, were eligible to enrol in the study and to receive open-label romiplostim. Data from patients going into this extension study were used to calculate time to failure for romiplostim, as this could not be calculated from the phase III studies alone because the interventions ended after 24 weeks."*** As stated above, we used data from the extension study to calculate time to failure for romiplostim. This could not be calculated from the phase III studies alone because the studies ended after 24 weeks. We would like to clarify that the open-label extension study allowed enrolment of patients who completed the phase III trials and whose platelet counts subsequently fell to ≤ 50×10^9 per litre, as well as patients completing other studies of romiplostim (phase I, II and IIIb studies) again once their platelet counts were less than or equal to 50×10^9. We would like to propose that the description in Section 3.3 be changed to reflect this as follows: "*In the latter, patients treated with romiplostim or placebo who had completed the phase III and other clinical studies of romiplostim, and whose platelet counts subsequently fell to ≤ 50×10^9 per litre after discontinuation of romiplostim or placebo, were eligible to enrol in the study and to receive open-label romiplostim".* We apologise for the lack of clarity on this point in our original evidence submission. The majority of the data used to estimate time to failure in the model came from the phase III studies as they made up 70% of patients in this data set. We would like to point out that the resulting impact on the ICERs (of including only phase III patients enrolled in the open-label extension study to estimate time to failure for romiplostim) is negligible and within an acceptable margin of error at £25,041 for non-splenectomised patients (versus £24,795 in the base case) and £5,309 for splenectomised	Comment noted. Section 3.3 of the FAD has been amended.

Consultee	Comment	Response
	patients (versus £4,615 in the base case).	
Amgen	**4. Cost effectiveness** We would like to clarify one point in this section as outlined below. **ACD Section 3.33** ***"The ERG conducted one-way sensitivity analyses by varying individual parameters in the revised base-case model to check the impact on the ICERs. These changes included increasing the use of comparator treatments by 25%; increasing the response time for comparators by 50%; increasing response rates for comparators by 25%; reducing the use of rescue therapies to 80% of the base case in both the comparator and romiplostim arms; using alternative utility values; and assuming a 'worst case scenario' where all patients who withdrew from treatment with romiplostim before the end of the follow-up period no longer responded to romiplostim."*** ***"The ERG noted that when it was assumed that patients who withdrew from treatment before the end of the follow-up period no longer responded to romiplostim the ICER rose from £24,795 to £31,601 per QALY gained for non-splenectomised patients and from £4,615 to £18,647 per QALY gained for splenectomised patients."*** The description of the 'worst case scenario' here seems incorrect as it refers to all patients who withdrew from treatment with romiplostim when it should be described as all patients who were censored from treatment with romiplostim in the open-label extension study. In addition, the description above does not seem to be in line with the description contained in the ERG report (commenting on the patient access scheme submission) in which the ERG assumed a 'worst case scenario' where all censored patients no longer responded to romiplostim, in effect assuming that all censored patients would be treated as withdrawals. Therefore, we propose that the description in Section 3.3 reflect that in the ERG report and read as: *"…. assuming a 'worst case scenario' where all patients who were censored in the open-label extension study were assumed to have no longer responded to romiplostim and were treated as withdrawals"* *"The ERG noted that when it was assumed that patients who were censored in the open-label extension study were assumed to have no longer responded to romiplostim and were treated as withdrawals"* We would like to clarify that patients who withdrew from the open-label extension study before the end of the follow-up period were indeed treated as withdrawals (i.e. assumed to have no longer responded to romiplostim and were withdrawn) in the evaluation of time to failure for romiplostim. We would also like to provide further clarity on censored patients. Censored patients were those who had a last observed visit that was not recorded as a withdrawal in the open-label extension study. However, at the time of the cut-off date for this analysis, there was no further information on whether these patients continued up to the final time point for this analysis or withdrew from the study. Hence, censored patients were treated as 'lost	Comment noted. Sections 3.30 and 3.33 of the FAD have been amended.

Consultee	Comment	Response
	to follow-up' in the evaluation of time to failure for romiplostim.	
Amgen	We agree that there could be uncertainty around patients who were censored in the open-label extension study as they may not have had the same outcomes as patients for whom data were available (i.e. those who continued up to the final time point for this analysis or withdrew from the study) and consequently this could affect the calculation of time to failure for romiplostim. We have performed additional analysis to understand the outcomes of patients who were censored during any time period in the open-label extension study compared to the outcomes of those for whom data were available (see Table 6.4.2 in original submission for data used in this analysis). Censored patients had similar outcomes, measured by mean platelet count, as those for whom data were available. This is illustrated in Fig. 1 below where the mean platelet count of all censored patients, before they were censored and excluded from the sample in subsequent periods, is compared to the mean platelet count of all non-censored patients (i.e. those for whom data were available). It is evident from Fig. 1 that the mean platelet counts for censored patients are comparable to and not systematically different from those for non-censored patients. It is also noteworthy that in both groups, the mean platelet count is consistently above 50×10^9 (as shown by the mean counts that consistently lie above the dotted line drawn at 50×10^9 mark) in Fig. 1. [redacted] [redacted] It is reasonable to conclude that censoring, in this instance, can be assumed to be independent of the risk of non-response and that the worst-case scenario explored by the ERG, where all censored patients are treated as non-responders and withdrawn, is unlikely to be plausible.	Comment noted.

Consultee	Comment	Response
Amgen	**5. Consideration of the evidence** We are of the view that all relevant evidence has been taken into account in the consideration of evidence and the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence. We would like to clarify two points in this section as outlined below. **ACD Section 4.2** ***"The Committee considered the nature of the condition and noted evidence submitted and presented by the patient experts and clinical specialists on the clinical signs and symptoms associated with chronic ITP. The Committee heard that the signs and symptoms associated with low platelet counts vary, and that bleeding and bruising can have considerable impact on the daily activities of people with chronic ITP, may attract a social stigma associated with the appearance of bruises, and can limit lifestyle choices. The Committee heard that many people with ITP experience fatigue, but that there is no clear relationship between fatigue and platelet count or haemoglobin concentration. The Committee understood that anxiety about the risk of bleeding can affect a person's quality of life and the ability to work, travel and/or undertake leisure activities. The Committee understood from patient experts that a bleed could result in a person seeking medical care to receive rescue therapies, and if the bleeding was severe the person could require hospitalisation."*** We note and welcome the addition to this paragraph, from the ACD issued in October 2009, that severe bleeding could require hospitalisation in this section describing the nature of ITP condition. We would like to highlight the debilitating nature of chronic ITP in this group of patients with severe symptoms and high risk of bleeding. We heard from the patient expert at the last Appraisal Committee meeting about the devastating nature of this condition and the detrimental impact it has on a patient's quality of life in terms of frequent and potentially life-threatening emergency visits to the hospital as well as the potentially life limiting adverse side effects of existing treatments. Indeed, romiplostim was designated as an orphan medicine by the EMA based on the combination of disease severity and rarity. The EMA report considered that "the effect of romiplostim should be placed in the context of a life threatening disease where limited therapeutic alternatives are possible"1. Published literature provides further evidence that ITP patients who are refractory to currently available treatments and have a persistently low platelet count are the ones who appear to be at the highest risk of severe bleeding and mortality. One study found a 60% increased mortality (with evidence of bleeding or infection as the cause of death) in a substantial number of ITP patients, illustrating that ITP is a serious and potentially life-threatening illness.	Comment noted.
Amgen	**ACD Section 4.15** ***"The Committee noted the ERG's concern that if romiplostim were no longer effective in patients lost to follow-up during the trial period, the ICERs increased substantively. However, the Committee heard from the manufacturer that a response to romiplostim had still been observed in***	Comment noted. Section 4.15 of the FAD has been amended.

Consultee	Comment	Response
	94% of the patients who were subsequently lost to follow-up." In the open-label extension study that was used to calculate time to failure for romiplostim, patients were categorised as censored if they had a last observed visit that was not recorded as a withdrawal, or as withdrawn, if they withdrew from the study. At the last Appraisal Committee meeting, we clarified that of the 31 patients who withdrew during the open-label extension study (see Table 6.4.2 in original submission), only 2 patients, i.e. 6%, withdrew for reasons of lack of response to romiplostim (implying that 94% of patients withdrew for reasons other than lack of response to romiplostim). This statistic does not relate to the patients who were censored. We apologise for any lack of clarity on this point during the Appraisal Committee meeting.	
Amgen	We have since performed additional analysis to understand how the censored patients behaved immediately before they were censored during any time period in the open-label extension study. We analysed their last observed platelet count before they were censored (74% of patients had their last platelet count within one week of being censored) to evaluate the potential number of patients who were responders at time of censoring; defined as achieving a platelet count of $\geq 50\times10^9$. The vast majority of censored patients, 81%, continued to respond immediately before they were censored. The ERG evaluation report notes that the cut-off of 50×10^9 is likely to be higher than would typically be used in practice in the UK. Using a lower cut-off of 30×10^9, an even higher proportion of censored patients, 89%, continued to respond immediately before they were censored. This provides assurance that the vast majority of patients who were censored during the extension study continued to achieve a response to romiplostim immediately before they were censored and it is therefore unlikely that romiplostim would no longer be effective in these patients.	Comment noted.
Amgen	**6. Other issues** We would also like to highlight two typographical errors in the ACD, 4.5 and 4.16, where ITP has been incorrectly written as IPT.	Comment noted. The typographical errors in the FAD have been amended.
Amgen	**References** 1. The European Medicines Agency (EMEA) European Public Assessment Report. Romiplostim (Nplate®). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/000942/WC500039475.pdf 2. Nplate. Summary of Product Characteristics. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000942/WC500039537.pdf 3. Gernsheimer TB, George JN, Aledort LM, Tarantino MD et al. Evaluation of bleeding and thrombotic events during long-term use of romiplostim in patients with chronic immune thrombocytopenia (ITP). J Thromb Haemost 2010; 8:1372–82	Comment noted.

Consultee	Comment	Response
	4. Amgen Clinical Summary of Efficacy, Data on file, Amgen. 2007 5. Kuter DJ, Bussel JB, Lyons RM, Pullarkat V, Gernsheimer TB, Senecal FM et al. Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: a double-blind randomised controlled trial. Lancet 2008; 371(9610):395-403 6. Schoonen MW, Kucera G, Coalson J, Li L, Rutstein M et al. Epidemiology of immune thrombocytopenic purpura in the General Practice Research Database. British Journal of Haematology, 2009:145, 235–244	
Department of Health	Thank you for the opportunity to comment on the appraisal consultation document and evaluation report for the above single technology appraisal. I wish to confirm that the Department of Health has no substantive comments to make regarding this consultation.	Comment noted.
ITP Support Association	**Has all of the relevant evidence been taken into account?** Yes	Comment noted.
ITP Support Association	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Para 4.2 Although para 4.2 does not specifically mention the small group of patients whose lives are devasted by frequent severe bleeding episodes. The ITP Support Association is satisfied that the Committee has understood the severe nature of ITP in these patients, given the Committee's provisional recommendations. Para 4.3 The ITP Support Association is satisfied that the Committee has understood the lack of a standard treatment pathway, and the toxicity of current treatments. Para 4.4 The ITP Support Association is satisfied that the Committee has understood the long-term side effects of current treatments which can lead to serious chronic conditions which themselves become difficult to treat because of the underlying ITP. Para 4.5 The ITP Support Association is satisfied that the Committee has understood that not everyone with ITP requires active treatment, and in UK clinical practice treatment is dictated by the severity of bleeding symptoms.	Comment noted.
ITP Support Association	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** Yes, The ITP Support Association welcomes the provisional recommendations. The committee has understood that licensed treatments for ITP are very limited and that the place for romiplostim in clinical practice will be for people with ITP whose condition is refractory to standard active treatments and rescue therapies or people who have severe disease and a high risk of bleeding that requires frequent courses of rescue therapies, i.e. as per NICE's provisional recommendations.	Comment noted.
ITP Support Association	**Are there any aspects of the recommendations that need particular consideration to avoid unlawful discrimination against any group of people on the grounds of gender, race, disability,**	Comment noted.

Consultee	Comment	Response
	age, sexual orientation, religion or belief? The committee had noted that certain religious groups may not consent to the use of blood products such as IVIG. Within this context, romiplostim can provide an alternative viable treatment intervention.	
ITP Support Association	**Are there any equality-related issues that need special consideration not covered in the ACD?** No.	Comment noted.
Royal College of Nursing	The Royal College of Nursing welcomes the opportunity to review this document. The RCN's response to the four questions on which comments were requested is set out below: i) **Has the relevant evidence has been taken into account?** The evidence considered seems relevant and comprehensive.	Comment noted.
Royal College of Nursing	ii) **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence, and are the preliminary views on the resource impact and implications for the NHS appropriate?** The summaries of the clinical and cost effectiveness of this appraisal seem appropriate.	Comment noted.
Royal College of Nursing	iii) **Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS?** Nurses working in this area of health have reviewed the recommendations of the Appraisal Committee and do not have any other comments to add. The RCN would welcome guidance to the NHS on the use of this health technology.	Comment noted.
Royal College of Nursing	iv) **Are there any equality related issues that need special consideration that are not covered in the ACD?** We are not aware of any specific issue at this stage. We would however, ask that any guidance issued should show that equality issues have been considered and that the guidance demonstrates an understanding of issues concerning patients' age, faith, race, gender, disability, cultural and sexuality where appropriate. Any guidance on the use of this technology should also be mindful of the impact it may have on reducing socio-economic inequalities.	Comment noted. See section 4.19 of the FAD. Equality issues were considered by the Committee and the Committee concluded that its preliminary recommendations do account for the individual needs of people to receive romiplostim, and do not make it more difficult for any particular group to access the treatment with romiplostim compared with any other group.
Royal College of Pathologists and the British	1.1 We welcome the revised assessment of Romiplostim as treatment for people which severe and/or refractory chronic ITP. The ACD has taken more notice of the clinical evidence, the variability of ITP and the need for new therapies which have been demonstrated by randomised controlled clinical trials to be	Comment noted.

Consultee	Comment	Response
Society for Haematology	effective and safe. It is appropriate that splenectomy has been left out as a criterion for the use of this agent, especially in the UK where it is not considered standard practice as documented in other European countries/North America.	
Royal College of Pathologists and the British Society for Haematology	1.2 We agree that this treatment should be initiated and supervised by an expert, but the term 'specialist in haematology' is somewhat vague. Does this mean consultant haematologist, consultant haematologist with a special interest in ITP, a specialist registrar in haematology, a staff grade in haematology? While allowing that this term may be deliberately imprecise I believe some thought should be given to this, and possibly to the need for an independent central register with continued monitoring for adverse events given that the experience with this agent is still short (up to 5 years in some cases, recently published data for 52 weeks – Kuter et al. NEJM 2010; 363: 1889-99, 11th November 2010). There is an important balance between making this agent available and the possibility of less appropriate use as clinicians and patients will want to use it.	Comment noted. Section 1.2 in the FAD has been amended to 'haematologist'.' See section 4.17 of the FAD for the Committees consideration of this point. The Committee was aware of the UK ITP registry and supported the collection of data on treatment with romiplostim and concluded that these data would be useful for any future appraisal of romiplostim. See section 4.17 of the FAD.
Royal College of Pathologists and the British Society for Haematology	2.4 Please confirm that both the 250 and 500 mcg vials will be available, which will provide a more cost effective option (The 250mcg vial would suffice for an 80kg person receiving up to 3mcg/kg per week), but similarly, patients who have used one 500mcg vial are now finding it difficult to use two 250mcg vials instead.	Comment noted. Section 2.4 of the FAD has been amended. The SPC states that romiplostim supplied in both 500 mcg and 250 mcg vials has a marketing authorisation, but only the 250 mcg vial is available in the UK.
Royal College of Pathologists and the British Society for Haematology	4.2 to 4.6 The reconsideration of the clinical evidence from experts and patients is welcomed, particularly the acknowledgement of the variability of the condition and the ways in which it interferes with life. There is now further evidence for the impact of fatigue in ITP presented at the American Society of Hematology meeting December 2010 (abstract attached on the next page) and submitted for publication.	Comment noted.
Royal College of Pathologists and the British Society for	4.18 I agree with the committee that there are no issues of potential discrimination on racial, gender or religious grounds.	Comment noted.

Consultee	Comment	Response
Haematology		
Royal College of Pathologists and the British Society for Haematology	5. Implementation: I consider it to be very important to monitor (audit) the implementation of this guidance across the UK to ensure appropriateness and balance in the use of Romiplostim. I would recommend the establishment of an audit group to take this forward. Amgen have set up such a programme in the USA (the NEXUS Program www.nplatenexus.com) but I would prefer to see an independent monitoring group set up for example through the British Society for Haematology or the Royal College of Pathologists. This would form a basis for the guidance review in 2014.	Comment noted. The Committee heard from the manufacturer of their registry in the USA. The Committee was aware of the UK ITP registry and supported the collection of data on treatment with romiplostim and concluded that these data would be useful for any future appraisal of romiplostim. See section 4.17 of the FAD.
Royal College of Pathologists and the British Society for Haematology	**Documentation of Fatigue in patients with immune thrombocytopenic purpura (ITP) and its association with autonomic dysfunction** Jessica A. Reese, Julia L. Newton, Shirley Watson, Sara K.Vesely, Paula H.B. Bolton-Maggs, James N. George, Deirdra R. Terrell Bleeding is the characteristic symptom of ITP but recent data from development of quality-of-life questionnaires have suggested that fatigue may be a common problem. Previous studies of another autoimmune disease, primary biliary cirrhosis, have documented that fatigue is common and is associated with autonomic nervous system dysfunction and daytime sleepiness (Hepatology 2007;45:1496). The goals of this study were to survey adult patients with ITP to [1] estimate the prevalence of fatigue among ITP patients, [2] describe characteristics of ITP that are related to the occurrence of fatigue, and [3] determine if fatigue in ITP, as in primary biliary cirrhosis, may be associated with autonomic dysfunction manifested by orthostatic symptoms and excessive daytime sleepiness. The survey contained questions about ITP, bleeding symptoms, and symptoms of fatigue that were developed specifically for this study together with established, validated questionnaires that quantitatively score symptoms of fatigue (Fatigue Impact Scale [FIS]), symptoms of autonomic dysfunction (Orthostatic Grading Scale [OGS]), and symptoms of daytime sleepiness (Epworth Sleepiness Scale [ESS]). 585 (31%) of 1871 members of the UK ITP Support Association and 69 (74%) of 93 patients in the Oklahoma ITP Registry completed and returned their surveys. Both groups of patients were combined for our analysis. 68% of patients had had ITP for ≥5 years; 31% had had a splenectomy; 63% had active ITP defined by a platelet count <100,000/μL and/or current treatment for ITP; 17% reported that they had bleeding problems daily/weekly/monthly (described as “bleeding”) vs. rarely/never (described as no bleeding). 63% had other diagnosed medical conditions. 78% of patients reported that their energy levels had changed since	Comment noted.

<table>
<tr><th>Consultee</th><th>Comment</th><th>Response</th></tr>
<tr><td></td><td>having ITP and 67% reported that they had less energy when their platelet count is low. Fatigue (FIS≥40) was present for 37% of patients. Odds ratios (OR) with 95% confidence intervals were calculated using logistic regression to estimate the association between fatigue (FIS≥40) and other variables while controlling for confounders. A multivariate model was created and active ITP, bleeding, other medical conditions, OGS≥4, and ESS≥10 were all independently associated with fatigue (P<0.05). Country was included in the model, even though it was not independently associated with fatigue. The data were then stratified by bleeding status, because interactions between bleeding and active ITP (P=0.034) and bleeding and ESS (P=0.026) were significant.
<table>
<tr><th>Variable</th><th>Stratified OR (95% CI), Bleeding (n=105)</th><th>Stratified OR(95% CI), No bleeding (n=490)</th></tr>
<tr><td>Active ITP (Yes vs. No)</td><td>4.64 (1.58, 13.63)</td><td>1.27 (0.79, 2.02)</td></tr>
<tr><td>Other medical conditions (Yes vs. No)</td><td>1.14 (0.45, 2.91)</td><td>1.76 (1.09, 2.84)</td></tr>
<tr><td>OGS (≥4 vs. <4)</td><td>3.09 (1.21, 7.93)</td><td>4.76 (2.98, 7.60)</td></tr>
<tr><td>ESS (≥10 vs. <10)</td><td>1.93 (0.78, 4.77)</td><td>5.51 (3.50, 8.66)</td></tr>
<tr><td>Country (UK vs. US)</td><td>0.37 (0.05, 2.62)</td><td>0.59 (0.27, 1.28)</td></tr>
</table>
Among patients who report bleeding problems, having active ITP and having a high OGS (≥4) remain independently associated with fatigue. Among patients with no bleeding, having other medical conditions, a high OGS (≥4), and a high ESS (≥10) are independently associated with fatigue.

<u>Conclusion</u>: Patients with ITP frequently report energy changes that appear to be greater when their platelet count is lower. In this analysis, we document that fatigue is associated with bleeding problems and that predictors of fatigue are different among patients with and without bleeding problems. Fatigue is associated with orthostatic symptoms in patients with and without bleeding problems. Fatigue is associated with active ITP only in patients with bleeding problems; fatigue is associated with other medical conditions and sleepiness symptoms only in patients without bleeding problems. The association of orthostatic and sleepiness symptoms with fatigue in patients with ITP suggests that the fatigue symptoms may be related to autoimmune autonomic abnormalities.</td><td></td></tr>
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Comments received from commentators

Commentator	Comment	Response
GlaxoSmithKline	Thank you for the opportunity to comment on the Appraisal Consultation Document for romiplostim. We would like to point out that there is an inconsistency in the numbers for the trial population presented in the extended dosing study on pages 5 and 6 of the ACD, which suggests that 83 and 42 patients were in the romiplostim and placebo arms respectively (consistent with Kuter et al, 2008). However, figure 1 of the Gernsheimer 2010 paper suggests that the corresponding numbers were 84 and 41 patients. This may require clarification, depending on which is correct. Kuter DJ, Bussel JB, Lyons RM, Pullarkat V, et al. Effi cacy of romiplostim in patients with chronic immune thrombocytopenic purpura: a double-blind randomized controlled trial. Lancet 2008; 371: 395–403 Gernsheimer TB, George JN, Aledort LM, Tarantino MD et al. Evaluation of bleeding and thrombotic events during long-term use of romiplostim in patients with chronic immune thrombocytopenia (ITP). J Thromb Haemost 2010; 8:1372–82 Otherwise we have no further comments.	Comment noted. For clarity, the following wording was added to section 3.6 of the FAD: 'All patients included in both RCTs received at least one dose of either romiplostim or placebo. One non-splenectomised patient randomly assigned to placebo received three doses of romiplostim in error and was included in the safety analysis as a patient given romiplostim and in the efficacy analysis as a patient randomised to placebo.'

Comments received from members of the public

Role*	Section	Comment	Response
NHS Professional	**Section 1** (Appraisal Committee's preliminary recommendations)	I welcome the recommendations from the appraisal committee, which would bring treatment into line with Europe and North America. Treatment using thrombopoietin receptor agonists in Immune Thrombocytopenia (ITP) is one of the few treatments in this condition that has good quality, randomised, placebo controlled studies confirming its utility. This is in accord with the published concensus document on the management of ITP published earlier this year in BLOOD. There has been some misconceptions over the status of this document. This was produced independently by a writing group and assessment group of over 20 international experts in the condition. Unrestricted grants were obtained from Amgen, Baxter and GSK to support the meetings and logistics of producing the consensus guidelines, however, none of the companies were involved in any way with the production of the document and had no access to it prior to publication. Â This has been acknowledged recently by means of a letter published in the New England Journal of Medicine.	Comments noted.
	Section 2 (The technology)	1 year is now accepted as the cut-off point for diagnosing chronic ITP (2.1) as even in adults spontaneous remissions may occur up to this point.	Comment noted. Section 2.1 of the FAD has been amended.

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment	Response
	Section 3 (The manufacturer's submission)	There have been disappointingly few comparative studies using conventional treatments in ITP. Most are open labelled studies in small numbers. Most use platelet count to recruit, which is also a surrogate for response. Randomised comparative studies using bleeding episodes, as well, have only been seen in TPO studies. Thus there are few analysis of cost and clinical effectiveness (3.3, 3.10). In the TPO studies most patients had relapsed or refractory disease and fell into the category where treatment would be expected. In this sub-group of ITP although there may be a policy of watch and rescue many, because of previous bleeding history will go straight onto a new treatment. There is a reluctance to withdraw previous treatments and as such many patients end up on multiple treatments without a clear therapeutic rationale. Following initial therapy there is no general agreement on treament policy, this being individual to each clinician, and is reflected in the consensus document where treatments are described alphabetically. No conventional treatments are effective in more than 25-30% explaining the lack of clear consensus (3.22, 3.28)	Comments noted.
	Section 4 (Consideration of the evidence)	There is an assumption that ITP mainly impacts on life-style. In the group we are considering for treatment it is much more a health issue. 40% of patients require no treatment with minor or no problems but 20% fall into the relapsed or refractory category and half of these will require treatment for bleeding. First line treatments are generally agreed but the main side-effects that patients complain about in our Adult ITP Registry relate to the long (and short) term effects of steroids, which need to be stopped at the earliest opportunity. IVIG is now severely restricted and anti-D immunoglobulin is not available in Europe for ITP. It is worth noting that 50% of deaths in ITP are due to infection relating to immune-suppressive treatment (often in association with splenectomy) not bleeding. Safer treatments are desperately required. The non-licensed treatment Rituximab while effective immediately in much greater numbers than other treatments (50-60%) has long term responses of 20%, no more than conventional treament. Its association with Progressive Multifocal Leucoencephalopathy has led to a swing against its use in non-malignant conditions in Europe and N America.	Comments noted.
	Section 5 (Implementation)	As stated in the preliminary recommendatiosn treatment should be restricted to specialists in haematology and good practice will be disseminated through the specialist society, the British Society for Haematology.	Comment noted.

Role*	Section	Comment	Response
	Section 6 (Related NICE guidance)	Although NICE did not recommend use of eltrombopag in ITP in pratical terms there is no significant clinical difference between the two agents at the level of clinical response required. Each agent shows a response that is haemaostatically worthwhile (increments of up to 50) in over 80% but the drugs are not interchangeable. As an oral agent it has some benefits and if the final recommendations for romiplostim are positive NICE should have further discussions with GSK on a patient access scheme that will make eltrombopag available as an alternative.	Comment noted.
NHS Professional	**Section 1** (Appraisal Committee's preliminary recommendations)	Given this is a therapy for a long term condition, consideration should be given to the use of shared care arrangements between the specialist in haematology and the patients GP to aid access to therapy Also need to define "standard active treatments" i.e. is it splenectomy/steroids/immunoglobulins What about rituximab, esp. as mentioned in DH policy for immunoglobulins?	Comments noted. See section 4.17 of the FAD.
	Section 2 (The technology)	Costs are inaccurate as they presume no waste As dosing is weekly and reconstituted vials have a 24 hour shelf life, it is inevitable that each weekly dose will require its own vial Therefore at a dose of 1 microgram/kg there will be significant waste from a 250 microgram vial unless the vial is manipulated in a licenced aseptic unit and patients are seen as cohorts to enable vial sharing as each vial should provide doses for 2-3 patients depending upon their weight (more if the 500 microgram vial is used) Given the proportion of non-repsonders in the RCT would it not be prudent to propose stopping criteria?	Comments noted. See section 4.8 of the FAD.
	Section 3 (The manufacturer's submission)	I would suggest that in clinical practice immunoglobulins are a standard therapy (not rescue therapy as per RCT) Reference is given to comparison with rituximab, what dose was used in the comparison as ritux is not licenced here and is often used at a dose of 100mg (rather than 375mg/m2) which has a marked impact on cost comparison	Comments noted. See section 4.17 of the FAD.