Comments on behalf of the Royal College of Pathologists and the BSH on the Appraisal Consultation Document (ACD) produced for the NICE single technology appraisal of *Thrombocytopenic purpura – romiplostim*

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 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.

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.

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.

Paula-I understood both will be available

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.

4.18 I agree with the committee that there are no issues of potential discrimination on racial, gender or religious grounds.

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.

Documentation of Fatigue in patients with immune thrombocytopenic purpura (ITP) and its association with autonomic dysfunction

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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 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.

Variable	Stratified OR (95% CI), Bleeding (n=105)	Stratified OR(95% CI), No bleeding (n=490)
Active ITP (Yes vs. No)	**4.64 (1.58, 13.63)**	1.27 (0.79, 2.02)
Other medical conditions (Yes vs. No)	1.14 (0.45, 2.91)	**1.76 (1.09, 2.84)**
OGS (≥4 vs. <4)	**3.09 (1.21, 7.93)**	**4.76 (2.98, 7.60)**
ESS (≥10 vs. <10)	1.93 (0.78, 4.77)	**5.51 (3.50, 8.66)**
Country (UK vs. US)	0.37 (0.05, 2.62)	0.59 (0.27, 1.28)

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.

- **Conclusion**: 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.

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