Comments on from The Royal College of Pathologists and the BSH on the NICE Appraisal consultation document (ACD)
Romiplostim for the treatment of chronic idiopathic (immune) thrombocytopenic purpura

i) Do you consider that all of the relevant evidence has been taken into account?

No.

a) There is a small group of patients who are unresponsive to any other therapy, who are symptomatic and who are at increased risk of dying from their disease. Discussion with haematologists who work in local district general hospitals (rather than tertiary referral centres) indicates that there might be 2-3 patients per year in this category. Intracranial haemorrhage, although rare, is unpredictable and when it occurs is usually associated with a count of less than $20x10^9$/l. Many of these patients are also heavily treated with immune suppression and have an increased risk of death from infection.

1. Examination of a cohort of 152 patients *(Portielje et al. Blood 2001: 97; 2549)* demonstrated an increase mortality ratio of 4.2 in those patients whose count remained below $30x10^9$/l and who were refractory to treatment. The mortality in refractory ITP is as high from infection related to treatment with immunosuppressive agents as from bleeding. Use of a TPO mimetic is not associated with this risk of infection and is likely safer as well as more effective. In addition this report demonstrates an increased frequency of hospital admissions due to complications of therapy compared to controls

2. The bleeding risk in ITP patients was examined (*Cohen et al. Arch Int Med 2000: 160;1630-8)* in a review of 17 studies including 1817 patients with persistent low counts. There were 47 cases of fatal haemorrhage from which they calculated the fatal bleeding risk at 1.6-3.9% per patient year, and the risk was greater in patients over 60 years of age. They conclude that people with ITP and persistent low counts have a 'grave prognosis' and warrant active treatment.

3. A review of 114 patients with ITP who failed splenectomy and who required additional therapy found that 17 died as a result of their disease, 11 of bleeding and 6 from treatment related complications.*(McMillan and Durette, Blood 2004: 104; 956-60)*. TPO mimetic treatment is needed for the subgroup of patients with severe symptomatic ITP who are unresponsive to other therapies.

b) The position has changed somewhat since the committee examined this agent. Firstly, anti-D has been withdrawn from the European market, the use of IvIg has been restricted due to short supplies and serious lethal side effects of rituximab in ITP have been published

(progressive multifocal leukoencephalopathy – *Carson et al. Blood 2009; 113; 4834-40*). This infectious complication is associated with immune suppression. Further unusual infections may occur as has recently been reported in a lymphoma patient treated with rituximab (neuronal invasion by an enterovirus – *Kiani-Alikhan et al. Br J Haematol 2009:146; 333-5*. Better agents are badly needed.

In the consultation document (4.5) the committee notes that 'these two RCTs (of romiplostim) did not provide clear evidence about the relative effectiveness of romiplostim compared with the effective comparator treatments...' and '..there is no clinical trial evidence to demonstrate its relative effectiveness compared with other active treatments'. This reasoning seems to be a convenient excuse to refuse approval. However, further updated information, although not RCT, has recently been carefully examined by an international group of experts in ITP and published in 'International consensus report on the investigation and management of primary immune thrombocytopenia' – *(Provan et al. Blood 2009, online from October 21*). This reports that for rituximab about 60% of patients respond with 40% achieving a complete response and for all other agents response rates are lower – azathioprine about 45%, cyclosporine 42% complete response, and cyclophosphamide varied from 24-85%. However the side effects are a serious concern (see below).

c) Further evidence on 'the burden of illness' in ITP has been examined and published in abstract. 35 European clinicians participated in two structured interviews for opinions on a variety of management options in ITP. In addition researchers undertook a retrospective review of the case notes of patients treated between January 2005 and March 2007, recording 12-months of data in 610 patients. The views of the 35 clinicians indicated a trigger platelet count for treatment of 10-30x10^9/l in the non-bleeding patients, but all would treat for bleeding. The clinicians identified an unmet treatment need for patients with chronic ITP; 94% indicated a need for agents with improved efficacy and 89% a need for reduction in side effects of treatment. The case notes review demonstrated that 61% of patients had needed treatment during the observation period, and 60% were treated with agents other than steroids. 14% required admission to hospital with duration of about 10 days but some needed admission to ICU (data submitted for publication).

ii) Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence, and that the preliminary views on the resource impact and implications for the NHS are appropriate?

I am unable to comment on the calculations of cost-effectiveness as I do not understand them. However, I believe that the consequences of failure to offer this agent to people with refractory symptomatic ITP has not been adequately explored.

iii) Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?

No, for the reasons given above. Moreover, this agent has been reviewed by the Scottish Medicines Consortium examining the same evidence and have come to different and opposing conclusions to NICE. Romiplostim is accepted for restricted use within Scotland according to its licensed indications. This inequity will result in 'postcode prescribing'. Romiplostim is approved by the FDA and in many European countries.

The appraisal consultation document notes that the trials on which the evidence is based are 'small'. It is very difficult to do a RCT in this condition. It should be noted that there is no trial data available for any of the agents used as second line long term therapy (anti-D and IVIG are indicated in the acute and not long term setting). The other drugs used as second line therapy are not licensed for use in ITP and all have significant side effects – see table

Current ITP Medical Therapies Have Risk for Serious Consequences

Corticosteroids	Depression/psychosis, diabetes, hypertension, adrenocortical suppression, osteoporosis, cataracts, life-threatening infection
Anti-D Ig	Anaphylaxis, intravascular haemolysis, infection transmission
IV Ig	Anaphylaxis, infusion reactions, infection transmission
Rituximab	Fatal infusion reaction, severe mucocutaneous reaction, progressive multifocal leukoencephalopathy, hepatitis B reactivation with fulminant hepatitis
Danazol	Lipoprotein alterations, androgenic effects
Azathioprine	Immunosuppression, increased risk of neoplasia, serious infection, pancytopenia, hematologic toxicity
Cyclophosphamide	Renal failure, heart failure, impaired fertility and mutagenesis, carcinogenesis

Individual product prescribing information

Long term steroid therapy is associated with serious side effects. Patients started on TPO mimetics have been shown in the trials to reduce their use of concomitant medications, to have a lower risk of bleeding and a better quality of life *(George et al. Br J Haematol 2008: 144: 409-415)*. Clinical experience with these agents in the UK confirms that patients who have been on steroids for several years are able to withdraw them with the substitution by romiplostim.

iv) Are there any equality related issues that need special consideration that are not covered in the ACD? Yes, patients in Scotland will be able to receive this agent while south of the border it is refused.

[redacted] November 25, 2009
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