From: [redacted]]
Sent: 24 November 2009 15:33
To: [redacted]; David Barnett
Cc: Jeremy Powell
Subject: Consideration of Nplate (Romiplostim)by NICE
Attachments: Provan_ITPConsensus_Blood_2009.pdf

Professor David Barnett
Chairman of the Appraisal Committee
NICE

Dear David,

I hope you will not mind my writing directly regarding your committee's preliminary recommendation on Romiplostim (Nplate). However, I am concerned that the conclusion you have reached, if maintained in the final advice, would deny some of the ITP patients that I, and others, treat – especially those at most risk of bleeding – access to an important new treatment option.

It is disappointing that there seems to have been an emphasis on this as a disease with little clinical risk and that part of the drive for treatment is essentially a life-style one. While this is certainly important for some patients, for a small number there is a significant risk of morbidity and mortality. These risks are particularly apparent in the elderly with long term refractory disease where mortality rates reach 10-15%. It is not however confined to the elderly as within the last year I have had a 20 year old man with refractory disease die of an intra-cerebral bleed.

It is also important to bear in mind that at least 50% of the mortality relates to infection, which reflects the immune suppression seen in patients post-splenectomy who continue to require long term cytotoxic chemotherapy. As the clinical lead of the only tertiary referral centre in the UK for ITP I do see a particularly difficult end of the disease spectrum but my experience does mirror that seen by many who are involved with the long term care of adults with chronic refractory disease.

As Romiplostim has now been accepted by Scotland, Ireland and many countries in Europe, in addition to North America and Australia, it would be demonstrably unfair that it was not available in England where a significant part of the randomized clinical studies were performed, and where there is a clear clinical in a treatment area where there are no comparable alternatives.

In particular I would like to bring to your attention several important changes to the clinical environment that have emerged since your committee last met in February and which, I believe, should have a direct bearing on your conclusions. The three developments of note are:

(i) The publication of a new **'International consensus report on the investigation and management of primary immune thrombocytopenia'-** pre-published online in *Blood*, the weekly medical journal of the American Society of Hematology (see attached for reference) in which TPO-receptor agonists are listed as the only Grade A recommendation for second and third line treatment of ITP;

(ii) The emergence of new data regarding the safety of Rituximab. In particular the recognition of its association with Progressive Multifocal Leucoencephalopathy, especially when associated with other immune suppressive treatment, which has led many of us to question its use as an agent for treatment of ITP. You will be aware of course that similar agents are now being linked to the development of PML in other conditions as well. The reference for Rituximab is Blood, 113, 20, 4834-4840.

(iii) The withdrawal from the UK Market of WinRho SDF, Cangene's Anti-D Treatment – further limiting the treatment options for ITP sufferers.

I would hope that these crucial developments will be taken into account in your current consultation.

I would also like to suggest that it may be valuable to broaden the scope of clinical advice to the committee. Your current advisers, though respected colleagues, have limited experience of treating adult chronic ITP patients, and I believe it is important that you hear from some of the clinicians most active and experienced in this field. To that end, I would respectfully request that I be allowed to address the committee at its next meeting – as the clinical representative of the Royal College of Pathologists, of which I am immediate past President and was put forward by them as one of the possible experts.

Yours Sincerely

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Delivered via MessageLabs

Comments on the ACD Received from the Public Through the NICE Website

Name	[redacted]
Role	Patient
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	It is disappointing that those who are most severely affected by ITP will not have the opportunity of using this new treatment in order to maintain a safe platelet count. Â I do not think that the degree of clinical need of patients with refractory ITP has been fully considered. Â Those who have tried many different treatments with no lasting effect are forced to treat on a cyclical basis with whatever will raise the platelet count. Â For some that is IVIG which is time consuming to administer and expensive (the less time consuming anti-D is no longer available in the UK) and for others it is to take high dose steroids on an almost permanent on and off basis with all the side effects that brings including steroid induced diabetes, facial bloating, water retention, redistribution of body fat, insomnia and depression, with the possible long term effects of cataracts and osteoporosis. Â Others are forced to simply live with platelet counts in the single digits. Â The cost to the NHS of treating the result of drug side effects and any bleeding episodes that need to be attended to needs to be taken into account when considering permitting the use or otherwise of romiplostim.
Section 2 (the technology)	This is a new technology which has potential for benefit to patients with other diseases and in time will no doubt become cheaper to use. Â Medical innovation should be encouraged.
Section 3 (manufacturer's submission)	
Section 4 (consideration of the evidence)	For those patients who have tried many different treatments, none of which work long term, the only way left is to live with a watch and rescue regime although the rescue periods come very close together. Â IVIG and steroids appear to be most often used in these circumstances neither of which is satisfactory long term. Â I would therefore suggest that the manufacturer is correct in comparing the use of romiplostim with watch and rescue as that is the result for the most severe ITP patients.
Section 5 (implementation)	For those currently taking part in drug studies with romiplostim, if they are to continue on the drug under paragraph 1.2 of this report, three months from the issuance of the report to receiving the drug is too long. Â They need to have immediate access.
Section 6 (proposed recommendations for further research)	
Section 7 (related NICE guidance)	

Section 8 (proposed date of review of guidance)	
Date	11/25/2009 8:52:00 PM

Name	[redacted]
Role	NHS Professional
Other role	Consultant haematologist Hammersmith Hospital
Location	England
Conflict	no
Notes	I have been involved in advisory boards during the development of this therapy.
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	It would be a shame for this treatment not to be made available to patients with difficult to manage ITP. While many patients may not have problems related to their ITP, a proportion of patients are severely limited by their disease. Current treatments include steroids, which have very serious adverse effects and to which some patients are not responsive and immunoglobulins, which are blood products and which require inpatient admissionand loss of days work for use - and again, are not always useful. Romiplostin is the first therapy to be shown in randomised controlled studies to have benefit in patients with ITP and in some patients, this has dramatically improved their quality of life. It is well tolerated and so far appears to have few short term or intermediate term (up to 2 years) side effects. It has been better tolerated than other therapies and is likely to be safer than steroids rituximab and possibly splenectomy. ITP should be assessed as an orphan disease with a variable phenotype. A small number of patients have gone through all available treatments and have either not responded to them or have had severe side effects and are at risk of life threatening bleeds.
Section 2 (the technology)	The aim in treating patients with ITP is not necessarily to achieve a normal platelet count. The aim is to achieve a count which will stop serious bleeding and prevent serious bleeding and to improve quality of life, which is severely affected in patients with chronic ITP. Treatment with romiplostin may not need to be long term. In fact, some patients with ITP may go in to remission with whatever treatment they are given. In addition, it is not anticipated that there will be many patients who require romiplostin long term. The costs therefore, although high for one individual are unlikely to have a high overall burden. Given the increase in quality of life, which has not been shown with other therapies, the added benefit of improving ability and quality of life is likely to have economic costs with patients being able to continue to work and being able to avoid hospital. This isnt much different from patients with haemophilia being given high cost treatments to avoid bleeding and to avoid serious side effects.
Section 3 (manufacturer's submission)	

Section 4 (consideration of the evidence)	1. ITP is an uncommon disease with a variable phenotype. Until recently, there have been no randomised controlled trials of any therapy and practice varies both between countries and within countries. It is therefore difficult to provide a standard of care and any design of comparative study is therefore difficult. It appears inappropriate to disregard a therapy because of the difficulty of studying the disease. 2. Current therapies for ITP in those who require therapy are suboptimal: i) Steroids are poorly tolerated and have high short and long term effects and should be restricted to only weeks and maximal months of treatment. ii) rituximab induces remissions in only 50% of patients and in some, relapses will occur, requiring further therapy. In addition, for the 50% who do not respond, remaining therapies are limited. iii) IVIG may not be more cost effective iv)Ciclosporin and other T cell therapies are poorly tolerated with many short and long term side effects v)some patients do not respond to any of the above and have no alternatives vi)the aim of treatment is to avoid serious bleeds such as intracranial haemorrages.
Section 5 (implementation)	
Section 6 (proposed recommendations for further research)	
Section 7 (related NICE guidance)	This review has assessed the use of romiplostin for all patients with ITP. Â However, it has failed to assess the real need of a small number of patients who have no other therapy and therefore remain at risk of life threatening bleeds. I feel it is inappropriate not to review the use of romiplostin in at least patients who do not respond to any other therapy. Further studies on the efficacy and safety of romiplostin and post marketing surveilence should also be reviewed before 2012.
Section 8 (proposed date of review of guidance)	
Date	11/25/2009 8:30:00 PM

Name	[redacted]
Role	NHS Professional
Other role	[redacted]
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	The first recommendation is acceptable for those patients who can live and work with their bruising and bleeding but it does not take into account the burden of the patient and the NHS when these are severe and the benefits and risks of other

	treatment modalities Â are respectively inadequate and unacceptable (e.g. risk of infection from prolonged immunosuppression). It should be possible to define a higher risk group for whom this modality could be recommended.
Section 2 (the technology)	
Section 3 (manufacturer's submission)	These analyses are valid if one accepts that the patients and physicians qualitative experience or even the health care systems resource and financial burden can be analysed numerically by these methods. These methods and the conclusions drawn from them are not always valid when the conclusions are applied to the individual case. The absence of haematological expertise from the ERG is relevant.
Section 4 (consideration of the evidence)	It is difficult to see how one could construct the RCT which this conclusion implies is missing. The ERG has not considered the extreme variability in bleeding risk in these patients or the impact of the disease and treatment on their ability to contribute to society. The SMC has sensitively and intelligently recommended this new therapy for those patients at high risk.
Section 5 (implementation)	Try to make consultation and recommendations more sensitive to the needs of individual patients.
Section 6 (proposed recommendations for further research)	
Section 7 (related NICE guidance)	
Section 8 (proposed date of review of guidance)	
Date	11/25/2009 1:15:00 PM

Name	[redacted]
Role	Carer
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	I urge NICE to reconsider their recommendation and to support the licensing of Romiplostim for people with chronic ITP. The Scottish Medicines Consortium (SMC) decision to license the medicine should give NICE pause for thought, particularly as it was based on the same set of RCTs. It shows that the economic case against licensing put forward by NICE cannot be clear cut and should be carefully reconsidered. The two most significant economic objections raised by NICE, pertaining to vial wastage and comparator treatments appear illogical and should not be used to justify the refusal of a licence. Moreover, the evaluation methodology used by NICE is biased against treatments of rare conditions such as ITP where per capita costs are inevitably high, but this is offset by the relatively small number of potential patients, producing a more manageable

	overall cost for the NHS. This point seems to have been accepted by the SMC. I urge NICE to show a similar flexibility in their approach, and to consider licensing for a limited subset of patients, such as those with severe symptomatic ITP or a high risk of bleeding, as agreed in Scotland.
Section 2 (the technology)	
Section 3 (manufacturer's submission)	There are a number of alleged ambiguities in the manufacturer?s evidence, e.g. whether patients in one of the RCTs were restricted to those with contraindication to splenectomy (para 3.1), the maximum dose (para 3.2), and vial usage (para 3.17). It seems very strange that such issues could not be clarified by NICE before it issued its recommendations, and gives the impression that NICEs evaluation process is hampered by an unnecessarily adversarial approach. Given how important this decision is for patients with ITP - a condition that can be life threatening ? Â surely NICE and the manufacturer should work together to establish the facts on such basic matters. It is not clear whether para 3.20 is criticising the quality of the manufacturer?s own submission or reflecting more widely on the lack of information available on a rare condition such as ITP. The detailed evaluation report suggests that both these arguments are being made. As such, whatever one?s view about quality of the manufacturer?s own submission, it seems unfair to penalise them (and, in effect, patients) for the lack of detailed research on other comparator treatments generally available in medical literature.
Section 4 (consideration of the evidence)	Para 4.2 overlooks some serious complications with ITP, e.g. problems such as rapid or irregular heartbeat. It is exasperating that assumptions about vial size/wastage are by far the largest factor increasing the potential ?cost per QALY gained? under the ERG?s sensitivity modelling, especially for splenectomised patients. The ERG assumes the smallest vial is 250 mcg, but the manufacturer?s clarification response of 21/11/08 (section C10) states that in addition to 250mcg and 500mcg a third vial size will be commercially available from Q4 of 2009. Details have been redacted from the text but the implication is that this refers to a smaller vial size ? if this is available it may radically alter the ERG?s analysis of increased costs. I urge NICE to reconsider this issue. NICE?s view that the manufacturer should have used ?active treatments? as a comparison to Romiplostim rather than ?watch and rescue? is illogical for patients with permanently low platelet levels who have already tried most if not all the other ?active treatments? and found that they do not work. Para 4.3 accepts there are no routine care pathways, so more flexibility is needed on the ?comparator? issue.
Section 5 (implementation)	The public consultation process is unreasonably restricted by the 1200 character limit on comments for each section of this guidance, which has been imposed regardless of the length of each section. I would have liked to comment at greater length

	on the issues raised in section 4 but am prevented from doing so by an entirely arbitrary character limit.
Section 6 (proposed recommendations for further research)	
Section 7 (related NICE guidance)	If NICE does not change its preliminary guidance I urge it to reconsider its proposal to wait almost three years before reviewing the decision. The most significant factor in increasing the ?cost per QALY gained? calculations was the issue of vial size and wastage. Can it really be justifiable to leave ITP patients waiting for three years while an issue with such an obvious solution blocks their access to this treatment? Can NICE not undertake to monitor the experience of the NHS in Scotland over the coming months, to see how they deal with the practical issue of vial wastage and their success in limiting costs by restricting Romiplostim to those patients most in need of it? Moreover, NICE notes in the conclusions of Â its main evaluation report that further research on the economic effectiveness of Romiplostim against ?comparator treatments? would be welcome. For those patients where these ?comparator treatments? do not work, such a wait will be futile since such research will not help NICE make the decision whether it is prepared to license Romiplostim for those patients with limited remaining treatment options.
Section 8 (proposed date of review of guidance)	
Date	11/23/2009 3:33:00 PM

Name	[redacted]
Role	Public
Other role	
Location	England
Conflict	no
Notes	
Comments on individual sections of the ACD:	
Section 1 (Appraisal Committee's preliminary recommendations)	The recommendation seems too sweeping particularly at this stage in the knowledge of trials, the recognition that Romiplostin offers real benefits for some sufferers, and given the sensitivity of the cost benefit to wastage which could be significantly reduced by alternative packaging.
Section 2 (the technology)	
Section 3 (manufacturer's submission)	The basic conclusion is that the drug appears effective for a significant proportion of patients.
Section 4 (consideration of the evidence)	The committee recognises that the drug works for many, and also that for some patients current standard treatments do not. Â A more flexible and targeted approach should be considered whereby patients who do not respond well to current treatments should be allowed to try Romiplostim at least for long enough to establish whether it would be effective for them. Efforts should

	also be made to negotiate a lower price and vials of smaller size to reduce wastage costs.
Section 5 (implementation)	
Section 6 (proposed recommendations for further research)	
Section 7 (related NICE guidance)	Further review is welcome. Â It would be likely to be better based if an approach along the lines set above were adopted, which would allow a larger evidence base to be considered.
Section 8 (proposed date of review of guidance)	
Date	11/22/2009 4:36:00 PM