National Institute for Health and Clinical Excellence

Single Technology Appraisal (STA)

Eltrombopag for the treatment of chronic idiopathic (immune) thrombocytopenic purpura (review of technology appraisal 205)

Response to consultee and commentator comments on the draft remit and draft scope

Comment 1: the draft scope

Section	Consultees	Comments	Action
Background information	ITP Support Association	This is accurate although you refer to very old BSH guidelines. The International Consensus Report on the investigation and management of primary immune thrombocytopenia is the current standard because of the introduction of new classes of therapeutic agents, and a greater understanding of the disease pathophysiology. Treatment is also required for some symptomatic patients whose count is >30.	Comments noted. The background section is only intended to be a very brief overview. A more detailed description of the disease and treatment options will be submitted by the manufacturer and made available to the Committee.
	NHS North Yorkshire & York	Agreed	Comment noted.
	Royal College of Pathologists and BSH	Usage of idiopathic for immune thrombocytopenic purpura should be avoided	Comment noted. The scope has been amended. The wording of the original remit cannot be amended.
The technology/ intervention	ITP Support Association	Yes [in response to 'is the description of the technology accurate']	Comment noted.
	NHS North Yorkshire & York	Agreed	Comment noted.

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	Royal College of Pathologists and BSH	Yes [in response to 'is the description of the technology accurate']	Comment noted.
Population	Amgen	Whilst the licensed populations for eltrombopag and romiplostim are identical, the description of the population is not consistent across the current draft scope for eltrombopag and the final scope for romiplostim. In contrast to the final scope for romiplostim, the definition of population in this draft scope is broad and could be defined more precisely, in line with the pivotal phase III trial for eltrombopag and consistent with the final scope of romiplostim, i.e. *"Adults with primary immune thrombocytopenia with baseline platelet counts lower than 30 000 per µL and whom had responded to one or more previous treatments for their disorder"*.[i] [i] Cheng G, Saleh MN, Marcher C, et al. Eltrombopag for management of chronic immune thrombocytopenia (RAISE): a 6-month, randomised, phase 3 study. Lancet 2011;377(9763):393-402.	The description of the population has been amended in line with the marketing authorisation of eltrombopag.
	ITP Support Association	Yes [in response to 'is the population defined appropriately?']	Comment noted.
	NHS North Yorkshire & York	Agreed	Comment noted.

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	Royal College of Pathologists and BSH	Pregnant adults should not be included Also secondary immune thrombocytopenic purpura due to other diseases should be considered separately	It is noted that the Summary of Product Characteristics states that eltrombopag is not recommended during pregnancy and in women of childbearing potential not using contraception. The remit of the scope states that the appraisal should consider eltrombopag within its licensed indication which would exclude the above population. The Committee will make recommendations for specific populations, such as those with secondary ITP should evidence allow and if clinical evidence suggests different effectiveness in this group.
Comparators	ITP Support Association	Yes [in response to 'are these the standard treatments currently used in the NHS with which the technology should be compared?]	Comment noted.
	NHS North Yorkshire & York	As we understand it, there is no standard single treatment pathway, and agree with the majority of comparators proposed. It is important that rituximab and romiplostim are included. Feedback we have received indicates that intravenous anti-D immunoglobulin is not used, there is not a licensed formulation listed in the BNF and a local consultant haematologist indicates that there is not an anti-D preparation available for this indication in this country.	The final scope has been amended accordingly.
	Royal College of Pathologists and BSH	Yes [in response to 'are these the standard treatments currently used in the NHS with which the technology should be compared?]	Comment noted.

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	Amgen	One of the outcomes listed in the draft scope is the reduction in symptoms of which bleeding episodes is key. Given the differences in the methodology, specification, definition and collection of bleeding events (pre-defined secondary endpoint for eltrombopag trial versus post-hoc analysis of reported safety data for romiplostim trial) across eltrombopag and romiplostim trials, it is highly likely that any comparison performed on the relative risk of bleeding events between eltrombopag and romiplostim is likely to be crude, inappropriate and unreliable. For example, it will be inappropriate to compare significant bleeding events defined as Grade 3-4 (severe, life-threatening or fatal) for romiplostim with bleeding events defined as WHO Grades 2-4 for eltrombopag as the latter definition also includes mild/moderate bleeding events. Therefore, any such comparison is likely to be spurious and lead to factually inaccurate claims and conclusions.	Comment noted.
Outcomes	ITP Support Association	Yes [in response to 'will these outcome measures capture the most important health related benefits (and harms) of the technology'	Comment noted.
	NHS North Yorkshire & York	Agreed, we consider tolerability of the drug a relevant consideration and would seek to qualify whether this is captured within adverse effects and/or quality of life	Comment noted. If clinical evidence demonstrates adverse reactions, they will be considered under adverse effects of treatment. If adverse events affect quality of life, the Committee will also consider the impact on quality of life.
	Royal College of Pathologists and BSH	Yes [in response to 'will these outcome measures capture the most important health related benefits (and harms) of the technology'	Comment noted.

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	Amgen	Section 3.35 of the existing published guidance for eltrombopag (TA205) states that *"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 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."* It is noteworthy that the recently published paper by Boyers et al[ii] concludes the same, i.e. indirect comparison showed a statistically significantly greater overall response for romiplostim compared to eltrombopag. In any economic modelling comparison versus romiplostim for this review, it is necessary that the economic analysis appropriately incorporates the effect of the indirect evidence comparing the overall response rates of eltrombopag with romiplostim. [ii] Boyers D, Jia X, Jenkinson D et al. Eltrombopag for the treatment of chronic immune or idiopathic thrombocytopenic purpura (ITP): A NICE Single Technology Appraisal.	Comment noted.
Economic analysis	ITP Support Association	Over complex. It seems ridiculous to compare cost effectiveness of a modern drug that has had to go through so many rigours with an older drug like steroids which did not.	Comment noted.
	NHS North Yorkshire & York	Agreed	Comment noted.
	Royal College of Pathologists and BSH	Yes [in response to 'comments on aspects such as the appropriate time horizon']	Comment noted.

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	NHS North Yorkshire & York	Agreed	Comment noted.
Equality and Diversity	Royal College of Pathologists and BSH	Preferably prescribed by haematologists with an interest in managing patients with immune thrombocytopenic purpura	Comment noted. The equality and diversity consideration refers to people with characteristics that are protected by the current equality legislation.
	NHS North Yorkshire & York	Patients unfit for surgery, who have received rituximab and intravenous immunoglobulin are a group of patients where understanding the clinical and cost effectiveness of this treatment is considered to be a priority.	Comment noted. The final scope states that people who have undergone splenectomy should be considered separately from those who have not had splenectomy due to contraindication to surgery.
Other considerations	Royal College of Pathologists and BSH	Secondary Immune thrombocytopenia should be considered separately for evaluation and response to Eltrombopag	Comment noted. Please see the response to your comment in the 'population' section above.

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	ITP Support Association	There is no one treatment that is effective for all patients. The most common treatment of corticosteroids is hated by patients and well recognised as being high in side effects. Long term immunosuppressants also have nasty side effects and can increase risk of death from infection above risk of bleeding. TPO drugs offer an excellent alternative and as Eltrombopag is in pill form this will be the preferred TPO for patients who hate injections and/or do not wish to attend hospital appointments on a weekly basis. Feedback from those in our membership who have been able to take Eltrombopag in a clinical trial and subsequently has been very good, with minimal side effects reported. The ITP Support Association would like to see all ITP patients (especially those on either of the TPO drugs) included on the UK ITP Registry (Royal London Hospital) to enable long term data to be accrued.	Comments noted.
Questions for consultation	NHS North Yorkshire & York	Eltrombopag and romiplostim both activate the primary growth factor for regulation of platelet function, therefore, given romiplostim is already recommended for the treatment of chronic ITP with the patient access scheme, eltrombopag does not appear to be innovative. However, it is recognised that eltrombopag is an oral therapy, therefore avoids weekly subcutaneous injection which may generate subsequent resource savings and may be considered as a step change in the management of the condition.	Comment noted.

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	Royal College of Pathologists and BSH	The technology is likely to make substantial impact and would allow for an oral alternative to the currently available treatment. This may also benefit QALY due to better compliance.	Comment noted.

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	Amgen	NICE explains that the rationale for bringing forward this review significantly earlier than planned, i.e. starting now instead of consideration for review in June 2013 (as stated in TA205), is that there is significant new evidence available now that is likely to change the recommendations. The significant new evidence prompting this review is twofold: one that the manufacturer of eltrombopag has agreed a patient access scheme (PAS) with the Department of Health and the other that positive guidance for romiplostim was published after negative guidance for eltrombopag was published. We would like to seek clarity on the rationale for early review as we understand that the PAS has already been considered under a rapid review appraisal process conducted last year (the meeting schedule and the topic of discussion with respect to the PAS was published on the NICE website) and therefore is not new evidence. Further, we understand that reviews of existing guidance conducted by NICE are driven by the assessment of the existing evidence base to ascertain the need for a review of a current guidance, i.e. the availability of new evidence in relation to the recommendations for future research etc. It is not clear in this instance whether there is new evidence that adds to the existing evidence base for eltrombopag that warrants this early review. When considering review of existing guidance, the recommendations made in the existing guidance for future research are usually considered. As far as we are aware, there is no new evidence to inform the recommendations for future research made by the NICE Appraisal Committee in the existing guidance for eltrombopag (TA205): *"6.1 Recommendations for future research* *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."* In view of this, we would therefore appreciate clarification around the rationale for this early review of TA 205.	A PAS represents new information, irrespective of whether it went through a Rapid Review. A comparison with romiplostim represents a new decision problem, as it was not considered part of the decision problem in TA205 (see TA 205 section 4.18).

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Additional comments on the draft scope.	ITP Support Association	Please ensure that the person (GP or other) who summarises ITP at the Eltrombopag technology appraisal meeting has done their homework this time and has some understanding of the disease.	Comment noted.
	Royal College of Physicians	Please take this email as confirmation that the RCP would like to endorse the comments submitted by RCPath/BSH.	Comment noted.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

CSL Behring
GlaxoSmithKline
Healthcare Improvement Scotland
Royal College of Nursing