NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Consideration of consultation responses on review proposal

Review of TA221; Romiplostim for the treatment of chronic immune or idiopathic thrombocytopenic purpura, and TA293; Eltrombopag for the treatment of chronic immune or idiopathic thrombocytopenic purpura

TA221 was issued in April 2011 and TA293 in July 2013.

The review date for both appraisals is March 2014.

Background

At the GE meeting of 4 March 2014 it was agreed we would consult on the review plans for this guidance. A four week consultation has been conducted with consultees and commentators and the responses are presented below.

Proposal put to consultees:	The guidance should be transferred to the 'static guidance list'.
Rationale for selecting this proposal	No new evidence has been identified that could be expected to lead to a change in the recommendations. Particularly, there are no data with which to directly compare the clinical effectiveness of romiplostim and eltrombopag. Therefore, it is proposed to place these appraisals on the static list.

GE is asked to consider the original proposal in the light of the comments received from consultees and commentators, together with any responses from the appraisal team. It is asked to agree on the final course of action for the review.

Recommendation post consultation:	The guidance should be transferred to the 'static guidance list'.

Respondent	Response to proposal	Details[1]	Comment from Technology Appraisals
GlaxoSmithKline	Agree	GlaxoSmithKline is supportive of the proposal to move the guidance for TA221 and TA293 to the static list, and to update the wording of the recommendations in TA221 in line with current NICE wording conventions and TA293.	Comment noted.
Amgen	Agree	We support the recommendation by the Institute not to conduct a review of TA221 (and TA293) and to transfer the existing guidance of romiplostim (and eltrombopag) to the static guidance list. We agree with the rationale in the proposal paper that no new evidence has been identified that could be expected to lead to a change in the recommendations and particularly, there are no data to enable a direct comparison of the clinical effectiveness of romiplostim and eltrombopag.	Comment noted. It will be stated on the NICE website that the update of the wording of TA221 has been made to clarify that romiplostim and eltrombopag are recommended treatment options for the same patient population and to be consistent with current NICE wording conventions, and that the update does not constitute a material change to the existing recommendations for romiplostim.

[1] Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

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		In addition to the recommendation to transfer TA221 and TA293 to the static guidance list, the review paper proposes an update to the wording in section 1 of the romiplostim guidance to be in line with current NICE wording conventions. We agree in principle with the proposed update to the wording but would like to emphasise the importance of making clear, for the avoidance of any doubt to patients and NHS stakeholders alike, that this update does not constitute a material change to the existing recommendation for romiplostim. We have outlined our comments on the proposal below. 1. Proposed recommendation not to review TA221 and TA293 and to transfer the guidance for romiplostim and eltrombopag to the 'static' guidance list. With regards romiplostim, we acknowledge that the evidence base to conduct a review of romiplostim remains unchanged since the publication of TA221 in April 2011 and as such, we agree with the recommendation by the Institute to move the current guidance for romiplostim from the 'active' appraisal list to the 'static' list. 2. Proposed recommendation to update the wording of the recommendations in TA221 in line with current NICE wording conventions and	

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		TA293 We acknowledge that the recommendations for romiplostim and eltrombopag are intended for exactly the same patient population, despite the recommendations for the two treatments being worded differently in their respective technology appraisals. In order to support consistent implementation of the guidance for romiplostim and eltrombopag across England and Wales, we agree in principle with the proposal to update the wording of TA221 to be consistent with the current NICE wording conventions and to be consistent with the wording for eltrombopag in TA293. It would however, be imperative for the Institute to state clearly in the final review decision that the proposed wording update to the guidance for TA221 does not constitute a material change to the existing recommendation for romiplostim and does not restrict nor expand the existing guidance. The current review proposal, as it stands, may be misinterpreted by patients and NHS stakeholders as a material change in the existing recommendation for romiplostim, and it would be therefore necessary for the final review decision document to provide absolute clarity that the proposed wording change does not constitute a material change to the existing	

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		guidance for romiplostim. We agree to the proposal by NICE to update the wording of TA221 as follows and would alongside like to underscore the importance of ensuring absolute clarity on this update (as explained above): *1.1. Romiplostim is recommended as an option for treating adults with chronic immune (idiopathic) thrombocytopenic purpura, within its marketing authorisation (that is, in adults who have had a splenectomy and whose condition is refractory to other treatments, or as a second-line treatment in adults who have not had a splenectomy because surgery is contraindicated),* *only if:* • *their condition is refractory to standard active treatments and rescue therapies,* ***or*** • *they have severe disease and a high risk of bleeding that needs frequent courses of rescue therapies* ***and*** • *if the manufacturer makes romiplostim available with the discount agreed in the patient access scheme.* *1.2. People currently receiving romiplostim whose*	

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		disease does not meet the criteria in 1.1 should be able to continue treatment until they and their clinician consider it appropriate to stop."	
ITP Support Association	Disagree	The ITP Support Association agrees that the wording for these two drugs should be consistent, and strongly believes it is the indication for eltrombopag, not romiplostim, which should be changed. It is unacceptable and barbaric that patients should be pushed into a surgical procedure that has only a 50 - 60% success rate, and which at best, swaps ITP for a lifelong risk of overwhelming sepsis, and at worst leaves a patient with both medical problems. At a time when hospital infection is of serious and increasing concern, and clinicians are being advised to reduce their prescribing of antibiotics to avoid antibiotic resistance, NICE guidance is forcing patients into having a splenectomy that requires a lifelong regime of prophylactic antibiotics. Patients who have had their spleens removed are advised to seek immediate attention at the first sign of fever or infection. In the current climate of NHS cost cutting receipt of immediate attention by a GP or in A & E seems an unlikely scenario. NICE guidance for Eltrombopag includes the statement that it may be used as a secondline treatment for patients who have not had a	Comment noted. Romiplostim and eltrombopag have marketing authorisations that stipulate that these treatments should only be used if a person has had a splenectomy, or has not had a splenectomy because such surgery is contraindicated. This was because the regulatory body could not consider the benefit-harm balance of romiplostim and eltrombopag to be positive for patients for whom a splenectomy remained a therapeutic option that could potentially affect the course of the disease. The stipulation of splenectomy in the recommendations it therefore not NICE's choice. NICE is bound by marketing authorisation of romiplostim and eltrombopag. The wording of the licences for both The wording of the recommendations in section 1 of TA221 and TA293 must therefore reflect the wording of the marketing authorisation for

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		splenectomy because surgery is contraindicated, but it does not clarify what contraindication might mean, and whether this includes patients who do not wish to lose their spleens, or patients whose platelet count remains too low for any surgery to take place. It is not sensible or acceptable to remove a healthy organ that defends the body against infection as a stepping stone to trying another drug which also may not work. This increases the disease burden of the patient and may lead to an early death. In addition, NICE proposes to remove the statement in the romiplostim guidance that a haematologist should start and supervise treatment. To ensure appropriate use of both drugs (and to avoid wasted expenditure on inappropriate use) there is a pressing need for a firm recommendation that all patients on these drugs should be monitored by a specialist haematologist and be enrolled on the (existing) ITP Registry for long term follow up. Such data collection would ensure that the cost effectiveness, efficacy and safety of these two drugs can be assessed. This proposal of NICE to change the indication of romiplostim will make access to TPO drugs harder for patients who are refractory to treatment and have severe symptoms. On behalf of ITP patients I plead with you to heed the comments above and to bring the indication for eltrombopag into line with that of	romiplostim and eltrombopag. Because the summaries of product characteristics for romiplostim and eltrombopag stipulate that treatment with either drug should remain under the supervision of a physician who is experienced in the treatment of haematological diseases, NICE does not need to repeat this in its recommendations. Given the difficulties of conducting randomised controlled trials with romiplostim and eltrombopag and in generalising their results, NICE supports generating and analysing observational data including, but not limited to, the existing UK ITP Registry.

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		romiplostim.	
UK ITP Forum	Disagree	We believe that the current indication for romiplostim should remain unchanged. Patients with severe disease at high risk of bleeding and refractory to rescue therapies would benefit from romiplostim, which is a treatment that has been shown to be highly effective irrespective of splenectomy status, in high quality clinical studies. Many patients will not agree to the removal of a healthy organ, there are emerging concerns [1,2] about the cardiovascular risk of splenectomy and splenectomy is no longer a routine second line therapy in clinical practice in the United Kingdom. 1) Boyle S, White RH, Brunson A, Wun T. Splenectomy and the incidence of venous thromboembolism and sepsis in patients with immune thrombocytopenia. Blood. 2013 Jun 6;121(23):4782-90. 2) Crary SE, Buchanan GR. Vascular complications after splenectomy for hematologic disorders. Blood 2009;114:2861-2868.	Comment noted. The update of the wording of TA221 does not constitute a material change to the existing recommendations for romiplostim. It has been made to clarify that romiplostim and eltrombopag are recommended treatment options for the same patient population and to be consistent with current NICE wording conventions. The stipulation of splenectomy in the recommendation is based on the marketing authorisation. NICE is bound by the marketing authorisation of romiplostim. The wording of the licences for both romiplostim and eltrombopag stipulates that these treatments should only be used if a person has had a splenectomy or has not had a splenectomy because such surgery is contraindicated. This was because the regulatory body could not consider the benefit-harm balance of romiplostim and eltrombopag to be positive for patients for whom a splenectomy remained a therapeutic option that could potentially

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			affect the course of the disease. The wording of the recommendations in section 1 of TA221 and TA293 must therefore reflect the wording of the licences for romiplostim and eltrombopag.

No response received from:

<u>Patient/carer groups</u> • Afiya Trust • Black Health Agency • Equalities National Council • Muslim Council of Britain • Muslim Health Network • South Asian Health Foundation • Specialised Healthcare Alliance • Splenectomy Trust UK <u>Professional groups</u> • Association of Anaesthetists • Association of Surgeons of Great Britain and Ireland • British Blood Transfusion Society • British Committee for Standards in Haematology • British Geriatrics Society • British Society for Haematology • National Blood Service	<u>General</u> • Allied Health Professionals Federation • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Commissioning Support Appraisals Service • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Hospital Information Services - Jehovah's Witnesses • Medicines and Healthcare Products Regulatory Agency • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium

• Royal College of Anaesthetists • Royal College of General Practitioners • Royal College of Nursing • Royal College of Pathologists • Royal College of Physicians • Royal College of Surgeons • Royal Pharmaceutical Society • Royal Society of Medicine • United Kingdom Clinical Pharmacy Association <u>Others</u> • Department of Health • NHS Aylesbury Vale CCG • NHS England • NHS Southampton City CCG • Welsh Government	<u>Comparator manufacturers</u> • Actavis UK (azathioprine, dapsone) • Amgen (romiplostim) • Arrow Generics (azathioprine) • Baxter Healthcare (intravenous anti-D immunoglobulin) • Bio Products Laboratory (intravenous normal immunoglobulin) • CSL Behring (intravenous normal immunoglobulin) • Genus Pharmaceuticals (vinblastine) • Grifols UK (intravenous normal immunoglobulin) • Hospira UK (vinblastine sulphate, vincristine sulphate) • Mylan UK (azathioprine, danazol) • Novartis (cyclosporin) • Pfizer (cyclophosphamide) • Roche Products (mycophenolate mofetil, rituximab) • Sanofi (danazol) <u>Relevant research groups</u> • Health Research Authority • MRC Clinical Trials Unit • National Institute for Health Research • Research Institute for the Care of Older People <u>Assessment Group</u> • Assessment Group tbc • National Institute for Health Research Health Technology Assessment Programme <u>Associated Guideline Groups</u> • National Clinical Guideline Centre

	Associated Public Health Groups • Public Health England • Public Health Wales NHS Trust

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17 04 2014