National Institute for Health and Clinical Excellence

Romiplostim for the treatment of chronic idiopathic (immune) thrombocytopenic purpura

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Amgen	Amgen believes romiplostim is a topic ideally suited for appraisal by NICE. Adult ITP is a chronic disease with potentially serious consequences, including increased risk of clinically significant bleeding and death. It is heterogeneous in disease course, clinical presentation and individual response to treatment. Many current treatments for chronic ITP demonstrate transient effectiveness, serious side effects and poor durability of response. Romiplostim is a novel, first in class treatment that represents a major breakthrough for adult patients with chronic ITP by targeting platelet production rather than platelet destruction caused by the immune system. As a consequence, it avoids many of the problems seen with current therapies and addresses a number of unmet needs in the treatment of chronic adult ITP. The provision of NICE Guidance would help patients with this serious, chronic condition gain access to this innovative therapy.	Comments noted.
	ITP Support Association	Yes	Comment noted.
	BSH, RCP, RCPath	Yes, the current treatment for chronic refractory ITP is limited and any treatment that has a satisfactory safety profile and is effective, is adventageous to this patient group who have poor responses to current treatment regimes	Comment noted
	RCPCH	Standard third line therapies carry significant toxicity and therefore alternative treatments should be assessed for clinical and cost effectiveness	Comment noted
Wording	Amgen	The wording is appropriate but Amgen recommends stating this appraisal is for adult patients only.	The technology will be appraised within its licensed indications. It is anticipated that the marketing authorisation will be limited to adults.
	ITP Support Association	Yes	Comment noted.

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	BSH, RCP, RCPath	Yes, although information re cost	Technology costs are not usually specified in the scope. Issues relating to economic evaluation are included in the relevant section of the scope.
Timing Issues	Amgen	Amgen would welcome more discussion on this issue. No timing has been suggested apart from the wave it would be included in.	Appraisal scheduling was discussed during the scoping workshop.
	ITP Support Association	For patients with severe refractory ITP a new approach to treatment is urgently needed!	Comment noted.
	BSH, RCP, RCPath	or length of time treatment should/can be used	Technology dose is not usually specified in the scope.
Additional comments on the draft remit	Amgen	- AMG531 can now be formally referred to by its INN: romiplostim	Comment noted. The remit and appraisal title have been changed to refer to the technology as 'romiplostim'.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Amgen	Incidence figures will include children and that is not within the proposed licence for romiplostim	Incidence data for adults now specified in scope.
	ITP Support Association	There are some inaccuracies: 1. "characterised by increased platelet destruction and/or inadequate platelet production" incorrectly suggests that ITP could be due solely to inadequate platelet production. That would not be called ITP. Instead of "and/or" it should read "and additionally, in some cases," 2. The British Society for Haematology is incorrectly called the British Haematology Society. 3. You quote the BSH Guidelines and although I was on the working party I had not noticed before that the wording of the UK incidence is confusing. The best estimate of figures quoted in most medical Ipublications are as follows: There are only about 120 new cases of adult ITP and 400 new cases of childhood ITP per year. The figure of 3000 - 3500 patients refers to the average total number of ITP patients in England and Wales at any one time. Additional information 1. Treatment is also required for some symptomatic patient whose count is >30,000. 2. An effective short term treatment is needed to cover women and girls during heavy periods.	1. Text reworded as advised. 2. Relevant text reworded to British Society for Haematology. 3. Text reworded as advised. Incidence data for adults now specified in scope The technology will be appraised within its licensed indications.
	BSH, RCP, RCPath	yes	Comment noted.

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	RCPCH	The guidelines state that treatment should be **considered** at a level of less than 30,000 and that whilst there is an increased mortality in this group, at least half of this was due to treatment, not thrombocytopenia. In children >70% recover spontaneously from ITP and most begin that recovery by 3 weeks. Treatment should not be given for count alone and a count of 30 x 10^9/l is not a threshold in children at all. The recommendation is not to treat, even with platelet counts of 1, unless there are complicating factors or life-threatening bleeding e.g. intracranial or severe GI haemorrhage.	Comments noted. The technology will be appraised within its licensed indications. (The marketing authorisation is anticipated to specify treatment threshold, duration of treatment and to specify adults.)
The technology/ intervention	Amgen	Yes, this is accurate although NICE might want to include other factors relevant to romiplostim, for example: - weekly injectable dose - titratable dosing - no known hepatic metabolism - no known contraindications - no fasting or dietry requirements	Comments noted. Technology dose is not usually specified in the scope. These features of the technology, however, may be presented in submissions to NICE in the support of any resultant appraisal.
	BSH, RCP, RCPath	yes	Comment noted.
Population	Amgen	This is accurate	Comment noted.
	ITP Support Association	I would like to see wider use available as necessary	Comment noted. Any resultant appraisal will consider the appropriate use of the technology, within its market authorisation, considering evidence on its clinical and cost effectiveness.

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	BSH, RCP, RCPath	Yes, although having a platelet count below 30x10(9)/L does not necessarily require treating.	Decisions to treat should be taken in consultation between the response clinician and patient. The technology will be appraised within its market authorisation.
	RCPCH	The group is of idiopathic thrombocytopenic purpura. It should state that causes of secondary thrombocytopenia have been excluded. Platelet production is increased in this condition and I would be very wary of trying an agent in children that stimulated megaryocytes. Previous trials of thrombopoietin (albeit used in different clinical circumstances)had significant toxic effects, some of which were long lasting and severe. The College do not currently think that this drug should be trialled in children with ITP until there is toxicity data from the adult population. Efficacy may be difficult to interpret as ITP in children and adults can really be thought of as distinct entities. However, if toxicity is low, then extending the drug for trial in children may be considered.	Comment noted. The technology will be appraised within its licensed indications. It is anticipated that the marketing authorisation will be limited to adults
Comparators	Amgen	- A number of the products listed in the scope are not licensed for ITP and NICE will need to address this issue in their deliberations. - according to UK clinical experts Amgen has consulted, alemtuzumab is not a relevant comparator for this appraisal as it is not commonly used in ITP treatment - immunosuppressive agents would normally be corticosteroids and i.v. immunoglobulins - Amgen would welcome the opportunity to discuss the issue of comparators at the scoping meeting on Feb 19th	Unlicensed comparators may be included in technology appraisals. Following discussion at the scoping workshop the listing of comparators has been altered and alemtuzumab omitted from the scope.

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	ITP Support Association	I have never come across alemtuzumab! My list would be: corticosteroids (prednisolone) intravenous immunoglobulin dexamethasone Anti-D immunoglobulin splenectomy immunosuppressives (azathioprine, cyclophosphamide, cyclosporin A) vinca-alkaloids (vincristine and vinblastine) rituximab tranexamic acid dapsone danazol	Following discussion at the scoping workshop, the listing of comparators has been altered. Alemtuzumab is omitted from the scope.
	BSH, RCP, RCPath	Yes, as listed Yes	Following discussing at the scoping workshop the listing of comparators has been altered
	RCPCH	Comparing this agent with eltrombopag in a multiple technology appraisal should be considered as this would better identify the most cost and clinically effective agent as it would be unlikely that more than one new agent would be put forward by NICE.	Comment noted. The appropriateness of single or multiple technology appraisal process options were discussed at the scoping workshop.
Outcomes	Amgen	Amgen would propose the additional specific outcome measures - reduction in the need for rescue medication relative to placebo - reduction in the need for chronic ITP therapies, particularly corticosteroids -number of bleeding events as determined by a post-hoc analysis of reported adverse events	Comment noted. Specified outcomes now include concomitant therapies.
	ITP Support Association	Yes	Comment noted.

Section	Consultees	Comments	Action
	BSH, RCP, RCPath	yes	Comment noted.
	RCPCH	It is necessary to define level to justify response. Complete response would be normalisation of platelet count. Partial response would be to greater than 30,000.	Comment noted. The technology will be appraised within its licensed indications.
Economic analysis	Amgen	Amgen believes a lifetime modelling time horizon is appropriate in a chronic condition such as ITP	Comment noted.
	BSH, RCP, RCPath	Not answered satisfactorily	Unclear on meaning of comment.
Equality	BSH, RCP, RCPath	n/a	Comment noted. The relevance of the appraisal to equalities issues was discussed at the scoping workshop.
Other considerations	Amgen	See below	Comment noted.
	BSH, RCP, RCPath	long term side effect profile	Scope specifies adverse effects as an outcome.

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Questions for consultation	Amgen	Are the suggested comparators appropriate. - this is discussed above but we would also like to emphasise that ITP treatment is often managed according to individual patient characteristics. This means a number of different treatments are used in this condition and vary widely from patient to patient STA or MTA process - Amgen believes romiplostim should be appraised via the STA process to ensure patients with unmet needs gain access as quickly as possible. There is no justification for undertaking a joint MTA when NICE have already shown a dual STA process is operating successfully in hepatitis B. An MTA would also deny patients early access to romiplostim. Definition of response - please see attached document that discusses the definitions of response used for romiplostim (Romiplostim Endpoints) Sub-groups that should be examined separately - Amgen had trials in 2 separate defined patient groups (splenectomised and non-splenectomised) and these might be considered - other possible sub-groups relevant for the economic analysis might include age and sex (although Amgen have not undertaken these analyses or can advise on if these are possible with the clinical trial data available)	Comment noted Comment noted. The appropriateness of single or multiple technology appraisal process options were discussed at the scoping workshop. The scope now specifies that appraisal of the technology should consider patients who have undergone splenectomy as a subgroup. Comment noted.
Additional comments on the draft scope.		No	Comment noted.

Comment 4: Regulatory issues

Section	Consultees	Comments	Action
Remit	Amgen	Yes	

Section	Consultees	Comments		Action
Current or proposed marketing authorisation	Amgen	*What are the current indications for the technology?*	Product is not approved	
		What are the planned indications for the technology?	Romiplostim is indicated for treatment of thrombocytopenia in adult patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP): [redacted]	
		FOR EACH PLANNED INDICATION:		
		What is the target date (mm/yyyy) for regulatory submission?	The European Marketing Authorisation Application was submitted to the EMEA on [redacted]	
		Which regulatory process are you following?	[redacted]	
		What is the anticipated date (mm/yyyy) of CHMP positive opinion (if applicable) and regulatory approval?	CHMP opinion likely in [redacted] European Commission Approval expected within 67 days of CHMP positive opinion.	
		Please indicate whether the information you provide concerning the proposed marketing authorisation is in the public domain and if not when it can be released. All commercial in confidence information must be highlighted and underlined.	All the information is NOT in the public domain. Information should only be released following European Commission Approval of the product and only with the express agreement of Amgen Limited to do so.	

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

1. Board of Community Health Councils in Wales (not participating)
2. Department of Health
3. National Public Health Service for Wales
4. NHS Quality Improvement Scotland
5. Rosemont Pharmaceutical Ltd
6. Splenectomy Trust