National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy
Response to consultee and commentator comments on the draft remit and draft scope (post-referral)

Comment 1: the draft scope

Section	Consultees	Comments	Action
Background information	British Society of Paediatric Gastroenterology and Nutrition	Complete	Comment noted.
	British Society of Gastroenterology	In general very accurate. I would also comment on the burden of morbidity associated with ongoing active disease. This can be assessed in terms of a reduced health care utility score, a reduced work productivity score and an impact on quality of life. An emerging treatment goal (in addition to clinical disease remission) is to induce mucosal healing, as this will reduce disease progression. All current guidelines also stress the importance of remission WITHOUT corticosteroids, as these have a negative impact upon morbidity. Anti TNF therapy is used both for induction and maintenance of remission. The text suggests that maintenance therapy is a 'choice' for patients. However, in those with poor prognosis disease, it is a recommendation rather than a choice	Comments noted. The background section of the scope is designed to give a brief overview of the condition and its treatment and describe any existing NICE recommendations. It is acknowledged that current clinical practice may not be fully aligned with NICE's recommendations but it should be noted that NICE clinical guideline 152 does not anti-TNF therapy for maintaining remission in, and that it does state maintenance therapy is a choice. No change to the scope required.
	Napp Pharmaceuticals	The background information appears to be accurate	Comment noted.

Section	Consultees	Comments	Action
	Takeda UK	No comment	Comment noted.
	UK Clinical Pharmacy Association (UKCPA) – Gastroenterology & Hepatology Group UK Clinical Pharmacy Association (UKCPA) – Gastroenterology & Hepatology Group	Medical management is based on current NICE guidance where as actual practice may slightly differ according to BSG/ECCO guidelines.	Comment noted.
The technology/ intervention	British Society of Paediatric Gastroenterology and Nutrition	Yes but they fail to mention the related medication Natalizumab and the significant safety concerns that resulted from its use	Comment noted. This section is restricted to providing a brief outline of the mechanism of action of the technology being appraised. No change to the scope required.
	British Society of Gastroenterology	Correct	Comment noted.
	Napp Pharmaceuticals	Yes	Comment noted.
	Takeda UK	Yes	Comment noted.

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	UK Clinical Pharmacy Association (UKCPA) – Gastroenterology & Hepatology Group UK Clinical Pharmacy Association (UKCPA) – Gastroenterology & Hepatology Group	In view of the importance of ADRs of current medical treatment we think that the ADR profile should be highlighted in the technology such as low infection risk and perceived low cancer risk.	Comment noted. This section is restricted to providing a brief outline of the mechanism of action of the technology being appraised. No change to the scope required.
Population	British Society of Paediatric Gastroenterology and Nutrition	Yes. Children should be considered separately but as part of the scope the company should be encouraged to take part in paediatric trials of the drug.	Comment noted. NICE can only appraise treatments within their European marketing authorisations. In this instance, the population is restricted to adults. No change to the scope required.
	British Society of Gastroenterology	Correct: although I would consider anti TNF naïve as a separate group from anti TNF failures	Comment noted. The other considerations section has been updated so that if evidence allows three subgroups will be considered.
	Napp Pharmaceuticals	1. Yes 2. None identified	Comment noted.
	Takeda UK	The updated 'population' section is now in line with the EMA licenced indication.	Comment noted.

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	UK Clinical Pharmacy Association (UKCPA) – Gastroenterology & Hepatology Group	A group of patient who may not be eligible for anti TNFs and/or immunosuppression due to the ADR profile (with high infection risk and cancer risk) may need to be mentioned separately as it is not clear if they are covered under intolerant in the conventional sense. (It then would not be second line)	Comment noted. The other considerations section has been updated so that if evidence allows three subgroups will be considered.
Comparators	British Society of Paediatric Gastroenterology and Nutrition	Yes – whether it is valid to consider the treatment before anti-tnf or only after is worthy of further consideration both in terms of efficacy and cost data.	Comment noted. The other considerations section has been updated so that if evidence allows three subgroups will be considered.
	British Society of Gastroenterology	Correct. Best alternative care in those naïve to anti TNF therapy would be an anti TNF agent. There is no current best alternative care for those who fail to respond / lose response to anti TNF agents. Surgery may be the only alternative In patients who have already had surgery or who have disease that makes surgery highly undesirable (eg pan-enteric disease) comparators may include HPN / small bowel transplant / stem cell transplant. Other patients may have disease in which surgery is not possible at all – eg oesophageal / gastric disease. These patients are not rare enough to be 'exceptional'	Comments noted. The comparator section has been updated. The other considerations section has been updated so that if evidence allows three subgroups will be considered. It was considered that surgery should be an outcome measure and not a comparator.

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	Merck Sharp and Dohme	Comparators have been described separately for a) people responding inadequately to conventional treatment and b) for people who are anti-TNFα naïve however, group b are also people responding inadequately to conventional treatment. We would suggest that one consolidated group be considered (people responding inadequately to conventional treatment) and that the comparators for vedolizumab should be infliximab, adalimumab, and conventional treatment. Also, we note that no comparators have been described for an anti-TNFα experienced population. In UK clinical practice clinicians will move patients to another anti-TNFα (following dose optimization for individual patients on their current anti-TNFα). Therefore both adalimumab and infliximab are appropriate comparators for this population.	Comment noted. The comparator section has been updated. The other considerations section has been updated so that if evidence allows three subgroups will be considered.
	Napp Pharmaceuticals	Adalimumab and infliximab have been identified as the TNF-α antagonist comparators. We would suggest that the inclusion of infliximab as a comparator should also extend to all infliximab products including biosimilars e.g. Remsima™. The suggestion in the economic section that biosimilars will not be in use by the time that this guidance is produced is possibly inaccurate. Remsima (infliximab) was approved for use in the EU in September 2013 and will be available after the originator patent expiry date on 24th February 2015. N.B. Remsima, infliximab, has the same INN and molecule name as the originator molecule.	Comment noted. Biosimilars are not in routine clinical use at the time of the appraisal starting and cannot be included as comparators. No change to the scope required.
	Takeda UK	We are pleased to see that NICE has updated this section to group together moderate-severe disease stages; reflecting the patient population in the vedolizumab pivotal studies as well as more representative of patients seen in UK clinical practice. We also note that comparison to anti-TNFα therapies are not required in the anti-TNFα failure population which we would assume is in recognition of the issues regarding lack of comparable clinical evidence to vedolizumab and lack of regulatory approval for anti-TNFα agents in this patient population.	Comment noted. The other considerations section has been updated so that if evidence allows three subgroups will be considered.

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	UK Clinical Pharmacy Association (UKCPA) – Gastroenterology & Hepatology Group	a)Some units are using thioguanin. B) the comparators do not take into account that treatment failures may not be behave in the same way as the population as a whole. The comparators do not distinguish between patients that respond to conventional therapy (including anti-TNF and patients that do not respond) However the treatment population is proposed as non responders or failures. Ttreatment failures comparators should be looked at as this is the group that we would like to treat initially. This group is possibly not behaving the same way as the population as a whole. If it is used as second line to conventional and anti TNF should it not be compared with the patient population that have failed anti TNF therapy as well. Considering that after SONIC many patients will be on as thiopurine and anti TNFs it would be interesting to see it compared with these failures versus the subgroup of vedolizumab patients exposed to thioguanin and anti TNFs prior to the antiintegrin. These are the patients we would be initially trying on vedolizumab, so do they do better on the drug than conventional care which very likely would include surgery? But surgery as such should not be used as comparator but as outcome. In short the additional question is: do anti-TNF and/or thiopurine failure patients better on conventional care or with vedolizumab. It is possible that this questions cannot be answered with the current data available. **We are concerned about the potential difference of the target marketing authorisation population and the comparator population**	Comments noted. The comparator section has been updated. The other considerations section has been updated so that if evidence allows three subgroups will be considered.
Outcomes	British Society of Paediatric Gastroenterology and Nutrition	yes	Comment noted.

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	British Society of Gastroenterology	May want to consider mucosal healing. Hospitalisation	Comment noted. The outcomes were discussed at the scoping workshop and disease activity and surgery were agreed to be the key outcome measures.
	Napp Pharmaceuticals	Yes	Comment noted.
	Takeda UK	Relapse is not a typical outcome relevant in CD; usually only response and remission outcomes are considered in CD as these are in line with treatment goals.	Comment noted.
	UK Clinical Pharmacy Association (UKCPA) – Gastroenterology & Hepatology Group	Should endoscopic remission be mentioned separately particularly as it is not defined in the NICE guidance 152	Comment noted. The manufacturer will be able to put forward evidence supporting the induction of remission according to the criteria of its choice. No change to the scope required.
Economic analysis	British Society of Paediatric Gastroenterology and Nutrition	I am unclear when biosimilars will be available in the UK market – this will need to be borne in mind especially in any cost analysis	Comment noted. Biosimilars are not included as comparators in this appraisal. No change to the scope required.
	British Society of Gastroenterology	Correct: the time horizon should be at least one year (there will be little data to go further than this at present).	Comment noted.
	Merck Sharp and Dohme	Given that "biosimilars are not expected to be in established NHS clinical practice at the time of appraisal and are not included as comparators", we would suggest that originator infliximab (Remicade) should be clearly described in order to distinguish it from biosimilar infliximab, in line with BNF and MHRA recommendations around biosimilar prescribing.	Comment noted. It is stated in the scope that biosimilars are not included as comparators in this appraisal.

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	Napp Pharmaceuticals	The reference to biosimilars is possibly inaccurate, Remsima will be available as discussed above. It would therefore be appropriate to conduct sensitivity analysis around a lower acquisition cost for infliximab.	Comment noted. Biosimilars are not in routine clinical use at the time of the appraisal starting and cannot be included as comparators. No change to the scope required.
	Takeda UK	No comment We acknowledge and agree with comment that biosimilars are not relevant comparators.	Comment noted.
	UK Clinical Pharmacy Association (UKCPA) – Gastroenterology & Hepatology Group	Is there scope to incorporate the productivity of the patients as this is a young economically productive patient group and loss to the overall economy ?value based assessment not yet being used?	Comment noted. Value-based assessment methodology has not yet been finalised and will not be used in this technology appraisal. The economic analysis should be conducted from an NHS/PSS perspective, in line with the NICE reference case. No change to the scope required.
Equality and Diversity	British Society of Paediatric Gastroenterology and Nutrition	None identified	Comment noted.
	British Society of Gastroenterology	None	Comment noted.
	Napp Pharmaceuticals	No perceived equality issues.	Comment noted.
	Takeda UK	No comment.	Comment noted.

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	UK Clinical Pharmacy Association (UKCPA) – Gastroenterology & Hepatology Group	We are concerned about the small population of indeterminate colitis as they are not included in either the CD or the imminent UC guidance.	Comment noted. NICE appraises treatments within their European marketing authorisations. The eligible population is restricted to 'the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor alpha (TNFα) antagonist'.
Innovation	British Society of Paediatric Gastroenterology and Nutrition	Yes	Comment noted.
	British Society of Gastroenterology	This is the first agent that has a novel mechanism of action to be assessed since the anti TNF agents. Therefore it may represent a 'step change' in treatment It will always be important to consider the cumulative negative impact of surgery on disease The Gemini I and III trials are the pivotal trials for this drug in CD	Comments noted. The manufacturer will be able to make a case for vedolizumab being an innovative treatment in its submission. No change to the scope required.
	Napp Pharmaceuticals	The technology may provide further treatment strategies for clinicians to manage patients who have failed existing treatments or who have become intolerant to them in line with the evidence from the Gemini trial; and the marketing authorisation.	Comment noted.

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	Takeda UK	We re-state our case previously presented that Takeda UK considers vedolizumab to be an innovative technology defined by its unique mechanism of action and published data outcomes for efficacy and safety[1] in its potential to make a significant and substantial impact on health-related benefits and address current unmet need. There is a significant unmet need for new treatments for Crohn's disease patients who fail conventional therapies and for those who fail to respond, lose response, or cannot tolerate current systemically acting tumour necrosis factor-alpha (TNFα) antagonists. Specifically, there are unmet needs for Crohn's disease therapies demonstrating a favourable safety profile, as well as improved efficacy on key endpoints such as mucosal healing, durable remission, and corticosteroid-free remission, when compared to conventional therapy or tumour necrosis factor-alpha (TNFα) antagonists currently in use. Current medical therapies have important limitations; Aminosalicylates are only modestly effective; glucocorticoids can cause unacceptable adverse events and do not provide a benefit as maintenance therapy. Tumour necrosis factor (TNFα) antagonists, although efficacious, predispose patients to serious infection. **1** Sandborn et al. Vedolizumab as Induction and Maintenance Therapy for Crohn's Disease N Engl J Med 2013;369:711-721.	Comments noted. The manufacturer will be able to make a case for vedolizumab being an innovative treatment in its submission. No change to the scope required.

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	UK Clinical Pharmacy Association (UKCPA) – Gastroenterology & Hepatology Group	Yes Currently there is nowhere to go medically for patients that have failed conventional treatment and this technology offers additional choice for this patient group. The economical productivity potential for patients responding to this technology can currently not be measured in a meaningful way but must be of great importance to the overall economic Sub-analysis and stratification of problem patient groups would be of high importance in the decision making of the place in therapy of vedolizumab.	Comments noted. The manufacturer will be able to make a case for vedolizumab being an innovative treatment in its submission. No change to the scope required.
Other considerations	British Society of Paediatric Gastroenterology and Nutrition	Should its use in UC where the data is stronger be considered at the same time?	Comment noted. Vedolizumab for ulcerative colitis is being appraised separately by NICE (further details available on the NICE website)
	Takeda UK	No comment.	Comment noted.
	UK Clinical Pharmacy Association (UKCPA) – Gastroenterology & Hepatology Group	Subgroup analysis such as elderly patients at risk of cancer and infections with conventional therapies.	The other considerations section has been updated so that if evidence allows three subgroups will be considered.
Questions for consultation	British Society of Paediatric Gastroenterology and Nutrition	What is the proposed time lines for paediatric trials as these drugs clearly could benefit children too and as soon as they come to market for adults paediatric off label use will begin.	Comment noted. NICE is not aware of this information because this appraisal will be in line with vedolizumab's European marketing authorisation, which is restricted to adults. No change to the scope required.

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	British Society of Gastroenterology	None	Comment noted.
	Takeda UK	Patient Population We believe the group for whom TNFα antagonists would be used has been appropriately defined as it reflects the licence for infliximab and adalimumab. Equality Vedolizumab will be the only α4β7 integrin inhibitor treatment with a licence for use in patients who have failed anti-TNFα therapy. Societal Impact and Burden of Illness In line with NICE's current thinking on value based assessment, vedolizumab can have a positive impact on the productivity and consumption equation for wider societal impact. This is condition which typically affects working age patients therefore has an impact on productivity impact. Crohn's disease also has significant burden on patient's quality of life. These will be explored further in our submission.	Comments noted.
Additional comments on the draft scope.	Takeda UK	No comment.	Comment noted.

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

Department of Health

NATIONAL INSTITUTE FOR HEALTH CARE EXCELLENCE

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Response to consultee and commentator comments on the provisional matrix of consultees and commentators (pre-referral)

Version of matrix of consultees and commentators reviewed: Provisional matrix of consultees and commentators sent for consultation					
Summary of comments, action taken, and justification of action:					
	Proposal:	Proposal made by:		Action taken: Removed/Added/Not included/Noted	Justification:
1.	British Association for Services to the Elderly	NICE Secretariat		Removed	This organisation has ceased to exist and have been removed from the matrix of consultee and commentators under 'patient groups'
2.	British Society of Gastroenterology	British Society of Gastroenterology		Noted	Thank you for your comment, to include paediatric IBD representation groups. They are listed on the matrix under 'professional groups'.

3.	Napp Pharmaceuticals	Napp Pharmaceuticals		Not included	Thank you for informing us that Napp Pharmaceuticals is also the UK distributor for Remsima (infliximab) manufactured by Celltrion Healthcare'. We will not be listing infliximab next to Napp because comparators should represent established practice in the NHS in England. Remsima is not on the market in the UK yet and therefore cannot be considered to be established practice.