Appendix G - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy [ID690]

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your names: [redacted]

Names of your organisations: Daisy Hill Hospital, Newry, Southern Health & Social Care Trust, and Guy's and St Thomas' Hospitals NHS Foundation Trust, London, respectively

Are you (tick all that apply):

- **X** specialists in the treatment of people with the condition for which NICE is considering this technology?
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?
- other? (please specify)

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant clinical guidelines and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Patients with Crohn's Disease (CD) are generally treated with a combination of corticosteroids, enteral nutrition, antibiotics and immunosuppressants (azathioprine, mercaptopurine and methotrexate) to induce and maintain remission. Around 30% of patients do not achieve or maintain remission with these treatments because of a lack of therapeutic effect or intolerance to the drugs. Other treatment options for these patients include biologic drugs (anti-TNF therapy: infliximab or adalimumab) or surgery (usually for disease which is limited anatomically or for specific complications; only rarely for pure failure of medical therapy). The anti-TNF agents have proved very successful for the 30% of patients with CD failing on medical therapy with proven reduction in surgery, admission and improvement in quality of life. However, 20% of patients experience primary non-response and a further 30% will have lost their response to anti-TNF after one year of treatment. These individuals form the main patient group in whom Vedolizumab should be available as an important alternative treatment (see below).

There is considerable geographical variation in current practice because of local differences in delivery of care to CD patients. In most institutions, medical care of patients with CD patients is delivered by Gastroenterologists specifically interested in inflammatory bowel disease (IBD). However, this is by no means uniform and in many areas, resource constraints mean than complex medical therapy may be delivered by colorectal surgeons or by general physicians. A lack of up-to-date clinician experience with currently available drugs may therefore lead to disparities in

care. Aminosalicylates (5-ASA) continue to be widely used as a treatment for CD despite limited evidence of efficacy. Thresholds for introducing immunosuppressants and/or biologic drugs vary across hospitals depending on clinician experience with various drugs. Healthcare professionals generally agree on current best practice, often delivered in accordance with National (British Society of Gastroenterology) and European (European Crohn's and Colitis Organisation) guidelines but implementation of this practice across the UK may not be uniform for the reasons stated above.

The current alternatives to the technology include experimental drugs being assessed in a clinical trial setting. However, access to clinical trials is very limited: only 0.5% of patients with CD are entered into a clinical trial in the UK (National UK IBD Audit figures). The other alternative is surgery. Currently, at least half of patients with CD undergo surgery within 10 years of diagnosis and almost 70% of patients will have at least one operation in their lifetime. However, whilst in some patients, surgery is a logical and preferred option (localised disease, complications such a stricture, abscess, fistula, haemorrhage, or malignancy), in those failing on medical therapy it is considered a last resort, as it often involves major abdominal surgery and is more likely to result in stoma (ileostomy, colostomy) formation.

There is a consensus amongst specialists treating CD that certain patients run a more aggressive course and should therefore be targeted for earlier use of biologics. These drugs are associated with a higher likelihood of healing rather than just clinical improvement (similar to the focus on disease modification in Rheumatoid Arthritis) and hence have a greater chance of avoiding complications such as fistula/abscess (penetrating disease) compared to oral immunosuppression. Hence, patients with markers of an aggressive course (younger age at onset, use of corticosteroids at presentation, penetrating disease, rectal disease) should be considered for earlier use of biologics.

Vedolizumab is a novel drug with a unique mechanism of action that represents an alternative in these situations, offering the potential for long-term therapy with the possibility of lower toxicity due to its gut-selective action. It is administered by iv infusion in secondary care, in a similar manner to current administration of infliximab. As such, it is likely to be best administered in secondary care as a day care episode within an infusion unit setting (dedicated to Crohn's disease or shared across other specialties administering infusional drugs e.g. Dermatology, Rheumatology). Community administration is not envisaged at this stage and has only rarely been established in the UK for infliximab). Engagement of specialist pharmacists in secondary care is also important in optimal delivery of complex therapies of this type.

Because it is a new drug, it is not yet included in guidelines as a recommended treatment option.

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The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Vedolizumab has a different mechanism of action to that of current alternative drugs, and therefore has the potential for treating patients who have primary non-response or secondary loss of response to anti-TNF therapy.

Vedolizumab is given by IV infusion and will likely have dosing intervals identical to infliximab (i.e. induction at weeks 0, 2 and 6 and then maintenance every 8 weeks) so would require the use of infusion facilities and nursing support as are currently used for anti-TNF infusions for CD. This will likely mean that overall more patients with CD will be treated by infusion so will have resource implications for Day Case Clinical Centres /Infusion Units. First infusions with these types of drug are often preferred as an in-patient so there will also be a small in-patient resource implication. Clinical experience in use of this drug will rapidly increase as clinicians become familiar with it. Treatment and monitoring protocols for the drug will be similar to those already in use and it should be relatively easy to use. The monitoring of neurological status for symptoms potentially consistent with PML that occurred in clinical trials will need to continue in clinical practice.

The GEMINI 2 trial was both an induction and a maintenance trial to assess vedolizumab in CD. The trial enrolled a relevant group of CD patients who had failed either corticosteroids or immunosuppressive therapy. The proportion of patients with

previous exposure to anti-TNF therapy was 50%. This would be in keeping with current UK practice as the point at which further therapy would be considered. The two primary end-points in the induction trial (clinical remission at week 6 as assessed by CDAI score of less than 150 and a greater than 100 point drop from baseline) are standard end-points for such trials – there is continued debate about whether measuring these end-points at week 12 is more meaningful as clinical experience suggests that it may take more than 6 weeks for patients to fully respond to these types of drug in CD. The primary end-point in the maintenance trial (clinical remission at week 52) is relevant and stringent.

A recent trial published in *Gastroenterology* further assessed the effects of vedolizumab in patients in whom anti-TNF treatment failed. In the trial, 76% of patients had prior exposure to anti-TNF therapy. The trial failed to reach its primary endpoint of clinical remission at week 6 but by week 10 a higher proportion of patients were in clinical remission. A similar finding was observed in earlier trials of a related drug, natalizumab, currently used to treat patients with multiple sclerosis. The mode of action of vedolizumab may mean that response to treatment is slower than with anti-TNF agents, but this remains unproven. In practice, we think that a trial of vedolizumab treatment of at least 12 weeks duration (hence 4 infusions) should be given before efficacy is determined.

As mentioned, the measure used to assess response in the GEMINI 2 trial was CDAI: whilst this is a standard measure used in clinical trials, it is a laborious measure and not practical in clinical practice (patients need to complete a 7-day diary of symptoms a part of the score). In clinical practice, it is anticipated that response to vedolizumab will be assessed in the usual manner using a combination of clinical symptoms (the Harvey-Bradshaw Index or HBI can be used to quantify these), C-reactive protein level (CRP). Faecal calprotectin, where available, is often helpful particularly where blood markers are not reliable. Endoscopy (usually colonoscopy, is important to evaluate response or healing at a mucosal (gut lining) level, but it not necessary in all cases.

Antibody formation to anti-TNF therapy is one of the main disadvantages of this group of drugs. The incidence of antibodies to vedolizumab was low (4%) in published trials and the drug appears to be particularly good at maintenance of remission: if borne out in clinical practice, this would be a real advantage for patients as CD is not curable and long term remission is one of the key goals of therapy.

Monitoring for side-effects of therapy would be largely the same to that needed for other currently used biologic therapies. Upper respiratory tract infections appear to be more common among patients receiving vedolizumab in trials but are generally mild or moderate and don't require intervention. To date, no cases of PML, a devastating and fatal neurological disease caused by reactivation of JC virus, have been observed with vedolizumab; however, stringent post-marketing surveillance for this condition will be required. There are no data available on further toxicity not already identified in trials of vedolizumab.

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Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

As yet there are no additional sources of evidence giving further information about Vedolizumab beyond the published papers:

Sandborn WJ, Feagan BG, Rutgeerts P, et al. Vedolizumab as Induction and Maintenance Therapy for Crohn's Disease N Engl J Med 2013;369:711-21. (The GEMINI 2 trial)

Sands BE, Feagan BG, Rutgeerts P, et al. Effects of vedolizumab induction therapy for patients with Crohn's disease in whom tumor necrosis factor antagonist treatment failed. Gastroenterology 2014;147:618-27.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within
3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

The resources required to adopt Vedolizumab include attendance at Day Clinical Centres/ infusion Centres as for anti-TNF therapy for CD patients. Given that the

population of patients with CD receiving iv infusions overall will likely increase, resourcing of these facilities will need to be assessed.

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

We do not think that any particular group of patients will be disadvantaged by this technology.