NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Health Technology Appraisal

Ustekinumab for treating moderately to severely active ulcerative colitis

Draft scope (pre-referral)

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of ustekinumab within its marketing authorisation for treating moderately to severely active ulcerative colitis.

Background

Ulcerative colitis is the most common inflammatory bowel disease. The cause of ulcerative colitis is unknown. Hereditary, infectious and immunological factors have been proposed as possible causes. It can develop at any age, but peak incidence is between the ages of 15 and 25 years, with a second, smaller peak between 55 and 65 years. It has been estimated that around 146,000 people in England have ulcerative colitis, of whom about 52% have moderate to severe disease.

Ulcerative colitis usually affects the rectum, and a variable extent of the colon proximal to the rectum. The symptoms of ulcerative colitis are bloody diarrhoea, colicky abdominal pain, urgency and tenesmus. Some patients may have extra-intestinal manifestations involving joints, eyes, skin and liver. Ulcerative colitis is a lifelong disease that is associated with significant morbidity; symptoms can relapse and then go into remission for months or even years. Around 50% of people with ulcerative colitis will have at least one relapse per year. About 80% of these are mild to moderate and about 20% are severe. Complications of ulcerative colitis may include haemorrhage, perforation, stricture formation, abscess formation and anorectal disease. People with long-standing disease have an increased risk of bowel cancer.

NICE clinical guideline 166 on ulcerative colitis equates 'subacute ulcerative colitis' to moderately to severely active ulcerative colitis, which would normally be managed in an outpatient setting and does not require hospitalisation or the consideration of urgent surgical intervention. The scope of this appraisal does not include severe ulcerative colitis that is a medical emergency requiring intensive inpatient treatment.

The aim of treatment in active disease is to address symptoms of urgency, frequency and rectal bleeding, and thereafter to maintain remission. NICE recommendations for managing moderately to severely active ulcerative colitis are found in NICE clinical guideline 166. Initial management depends on clinical severity, extent of disease and the person’s preference, and may include corticosteroids, or topical or oral aminosalicylates (sulfasalazine, mesalazine, balsalazide or olsalazine). If the disease does not adequately respond to oral corticosteroids (beclometasone, budesonide, hydrocortisone

or prednisolone) then an immunosuppressant (such as mercaptopurine or azathioprine) may be considered. NICE technology appraisal 329 recommends infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis in adults whose disease has responded inadequately to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who cannot tolerate, or have medical contraindications for, such therapies. NICE technology appraisal 342 recommends vedolizumab for treating moderately to severely active ulcerative colitis. NICE is also currently appraising tofacitinib for treating moderately to severely active ulcerative colitis (NICE technology appraisal guidance ID1218). Colectomy (with the creation of either an ileostomy or an ileo-anal pouch) is a treatment option for some patients, to improve the quality of life in chronic or treatment-refractory active disease or to treat cancer or precancerous changes.

The technology

Ustekinumab (Stelara, Janssen) is a humanised IgG_1 monoclonal antibody that is targeted against the p40 subunit of interleukin-12 (IL-12) and interleukin-23 (IL-23), which is expressed in certain white blood cells which cause bowel tissue to become inflamed. It is available for administration by intravenous infusion or subcutaneously.

Ustekinumab does not currently have a marketing authorisation in the UK for moderately to severely active ulcerative colitis. It has been studied in clinical trials as intravenous induction therapy in people with moderately to severely active ulcerative colitis who are intolerant of, or whose disease has had an inadequate response or loss of response to conventional therapy (oral corticosteroids and/or immunosuppressants) or a biologic agent (a TNF-alpha inhibitor or vedolizumab), and as subcutaneous maintenance therapy in people whose disease has responded to intravenous induction therapy.

Ustekinumab currently has a marketing authorisation in the UK treating 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 TNF-alpha antagonist, or have medical contraindications to such therapies.

Intervention(s)	Ustekinumab
Population(s)	People with moderately to severely active ulcerative colitis who are intolerant of, or whose disease has had an inadequate response to previous biologic therapy (a TNF-alpha inhibitor or vedolizumab), or conventional therapy (oral corticosteroids and/or immunomodulators).

Comparators	• TNF-alpha inhibitors (infliximab, adalimumab and golimumab) • Vedolizumab • Tofacitinib (subject to ongoing NICE appraisal) • Conventional therapies, without biological treatments
Outcomes	The outcome measures to be considered include: • mortality • measures of disease activity • rates of and duration of response, relapse and remission • rates of hospitalisation • rates of surgical intervention • time to surgical intervention • achieving mucosal healing • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.

Other considerations	If the evidence allows the following subgroups will be considered: • people who have been previously treated with one or more biologics and people who have not received prior biologics therapy. The availability and cost of biosimilar products should be taken into account. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: Vedolizumab for treating moderately to severely active ulcerative colitis (2015).Technology appraisal guidance TA342. Review date: June 2018. Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (2015). Technology appraisal guidance TA329. Review date: TBC. Appraisals in development Tofacitinib for moderately to severely active ulcerative colitis. NICE technology appraisals guidance [ID1218]. Publication expected: January 2019 Related Guidelines: Ulcerative colitis: management. NICE clinical guideline CG166. Published date: June 2013. Review date: TBC. Related Interventional Procedures: Leukapheresis for inflammatory bowel disease (2005). NICE interventional procedures guidance 126. Transanal total mesorectal excision of the rectum (2015) NICE interventional procedures guidance 514. Related NICE Pathways: Ulcerative colitis (2017) NICE pathway
Related National Policy	NHS England (2017) Manual for Prescribed Specialised Services 2017/18. https://www.england.nhs.uk/wp-content/uploads/2017/10/prescribed-specialised-services-manual-2.pdf

	NHS England (2017) Next steps on the five year forward view NHS England (2014) NHS Five year forward view NHS England (2013) 2013/14 NHS standard contract for colorectal: complex (adult) particulars, schedule 2- the services, A - service specifications. Reference: A08/S/c Department of Health and Social Care, NHS Outcomes Framework 2016-2017 (published 2016): Domains 1, 2 https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017

Questions for consultation

Have all relevant comparators for ustekinumab been included in the scope? Which treatments are considered to be established clinical practice in the NHS for moderately to severely active ulcerative colitis?

Are the outcomes listed appropriate?

Are the subgroups suggested in 'other considerations appropriate? Are there any other subgroups of people in whom ustekinumab is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider ustekinumab will fit into the existing NICE pathway, Ulcerative colitis?

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 the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which ustekinumab 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 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.

Do you consider ustekinumab to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of ustekinumab can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).

NICE has published an addendum to its guide to the methods of technology appraisal (available at https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/methods-guide-addendum-cost-comparison.pdf), which states the methods to be used where a cost comparison case is made.

- Would it be appropriate to use the cost comparison methodology for this topic?
- Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?
- Is the primary outcome that was measured in the trial or used to drive the model for the comparators still clinically relevant?
- Is there any substantial new evidence for the comparator technologies that has not been considered? Are there any important ongoing trials reporting in the next year?

References

1 Rutgeerts P, Sandborn W J, Feagan B G et al. (2005) Infliximab for Induction and Maintenance Therapy for Ulcerative Colitis. N Engl J Med 353:2462–2476.

