

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**Proposed Health Technology Appraisal****Ustekinumab for treating moderately to severely active Crohn's disease after prior therapy****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 Crohn's disease in people who are intolerant of, or whose disease has not responded or is resistant to either conventional therapy or a tumour necrosis factor-alpha inhibitor.

Background

Crohn's disease is a chronic inflammatory condition of the gastrointestinal tract (gut) that may affect any part of the gut from the mouth to the anus. People with Crohn's disease have recurrent attacks, with acute exacerbations ('flares') in between periods of remission or less active disease. These flares may affect any part of the gut and are defined by location (terminal ileal, colonic, ileocolic, upper gastrointestinal), or by the pattern of the disease (inflammatory, fistulising, or stricturing).

The clinical features of Crohn's disease are variable and are determined partly by the site of the disease. Common symptoms include diarrhoea, abdominal pain, extreme tiredness, unintended weight loss and blood and mucus in stools. Less common symptoms include fever, nausea, vomiting, arthritis, inflammation and irritation of the eyes, mouth ulcers and areas of painful, red and swollen skin.

Crohn's disease can be complicated by the development of strictures (a narrowing of the intestine), obstructions, fistulae and perianal disease. Other complications include acute dilation, perforation and massive haemorrhage, and carcinoma of the small bowel or colon.

There are currently at least 115,000 people in the UK with Crohn's disease.¹ The incidence of Crohn's disease is greatest in people aged between 16 and 30 years. However, it may affect people of any age.²

Crohn's disease is not medically or surgically curable. Treatment aims to control manifestations of Crohn's disease to reduce symptoms, and to maintain or improve quality of life while minimising short- and long-term adverse effects. Clinical management depends on disease activity, site, behaviour of disease, response to previous treatments, side-effect profiles of treatments and extra-intestinal manifestations, such as uveitis and arthritis.

NICE clinical guideline 152 recommends monotherapy with a corticosteroid (prednisolone, methylprednisolone or intravenous hydrocortisone) to induce remission in people with a first presentation or a single inflammatory exacerbation of Crohn's disease in a 12-month period. Budesonide or 5-aminosalicylates are considered for some people who decline, cannot tolerate or in whom a conventional corticosteroid is contraindicated. When 2 or more inflammatory exacerbations are experienced in a 12-month period, azathioprine, mercaptopurine and methotrexate may be considered as add-on treatments to conventional corticosteroids or budesonide to induce remission of Crohn's disease.

NICE technology appraisal 187 recommends infliximab and adalimumab as treatment options for adults with severe active Crohn's disease whose disease has not responded to conventional therapy (including immunosuppressive and/or corticosteroid treatments), or who are intolerant of or have contraindications to conventional therapy. At the time of NICE technology appraisal 187, marketing authorisations for infliximab and adalimumab did not include treating adults with moderately active Crohn's disease and so moderately active disease is not covered by that guidance. The marketing authorisations for infliximab and adalimumab have subsequently been expanded to include treating people with both moderately and severely active disease that has not responded to conventional therapy (including immunosuppressive and/or corticosteroid treatments).

NICE technology appraisal 352 recommends vedolizumab as an option for treating moderately to severely active Crohn's disease if a tumour necrosis factor-alpha inhibitor has failed, cannot be tolerated or is contraindicated.

In addition to pharmacological treatment, between 50 and 80% of people with Crohn's disease will require surgery during the course of their disease. The main reasons for surgery are strictures causing obstructive symptoms, lack of response to medical therapy, and complications such as fistulae and perianal disease.

The technology

Ustekinumab (Stelara, Janssen) is a humanised IgG₁ monoclonal antibody derived from a newly engineered cell line. It 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 administered by intravenous infusion.

Ustekinumab does not currently have a marketing authorisation in the UK for treating Crohn's disease. It has been studied in clinical trials compared with placebo in people with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to conventional therapy and/or a tumour necrosis factor-alpha inhibitor (such as adalimumab and infliximab).

Intervention(s)	Ustekinumab
Population(s)	People with moderately to severely active Crohn's disease in whom the disease has responded inadequately to, or is no longer responding to, either conventional therapy or a tumour necrosis factor-alpha inhibitor, or who are intolerant to either of them.
Comparators	<ul style="list-style-type: none"> Conventional therapy (which can include drug treatment with conventional corticosteroids alone or in combination with azathioprine, mercaptopurine or methotrexate; aminosalicylates; budesonide alone or in combination with azathioprine, mercaptopurine or methotrexate) Tumour necrosis factor-alpha inhibitors (infliximab and adalimumab) Vedolizumab
Outcomes	<p>The outcome measures to be considered include:</p> <ul style="list-style-type: none"> disease activity (remission, response, relapse) surgery adverse effects of treatment health-related quality of life.
Economic analysis	<p>The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.</p> <p>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.</p> <p>Costs will be considered from an NHS and Personal Social Services perspective.</p> <p>The availability of any patient access schemes for the intervention or comparator technologies will be taken into account.</p>
Other considerations	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	<p>Related Technology Appraisals:</p> <p>‘Vedolizumab for treating moderately to severely active Crohn’s disease after prior therapy (2015). NICE Technology Appraisal 352. Review date August 2018.</p> <p>‘Adalimumab and infliximab for the treatment of Crohn’s disease (2010). NICE Technology Appraisal 187. Guidance on static list</p> <p>Related Guidelines:</p> <p>‘Crohn’s disease: management’ (2012). NICE guideline 152. Review date December 2016.</p> <p>Related Interventional Procedures:</p> <p>‘Extracorporeal photopheresis for Crohn’s disease’ (2009). NICE interventional procedure 288.</p> <p>Related NICE Pathways:</p> <p>Crohn’s disease overview (2012) NICE Pathway http://pathways.nice.org.uk/pathways/crohns-disease</p>
Related National Policy	<p>Department of Health, Manual for Prescribed Specialised Services 2013/14, Jan 2014. Chapter 101 Severe intestinal failure service (adults).</p> <p>https://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf</p>

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 Crohn’s disease?

Are the outcomes listed appropriate?

Are there any 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 for Crohn’s disease?

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.

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>)

References

- 1 Crohn's and Colitis UK (2015) [What is Crohn's disease?](#) Accessed October 2015.
2. NHS Choices. (2015) [Crohn's disease: Overview.](#) Accessed October 2015.