NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Health Technology Appraisal

Cx601 for treating complex perianal fistula in non-active or mildly-active luminal Crohn's disease

Draft scope (pre-referral)

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of Cx601 within its marketing authorisation for treating complex perianal fistula in non-active or mildly active luminal Crohn's disease.

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 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). Luminal Crohn's disease affects the lining of the intestine.

Inflammation of the gut can lead to tissue damage and ulceration. A complication of such tissue damage is the development of fistula. A perianal fistula is an abnormal connection that develops between the bowel and the skin near the anus. The symptoms of perianal fistula include skin irritation around the anus, pain, passing of blood or pus when having a bowel movement and leakage of faecal matter. Fistulas are described as simple or complex depending on the location and whether there is a singular fistula tract or interlinking connections.

There are currently at least 115,000 people in the UK with Crohn's disease.[i] The incidence of Crohn's disease is greatest in people aged between 16 and 30 years. However, it may affect people of any age. Approximately 20% of people with Crohn's disease will develop a perianal fistula, and 30% of these people have recurrent fistulas.[1]

Treatments for perianal fistula aim to treat and drain the underlying infection and heal the fistula. Medications for treating fistulas can include antibiotics, immunosuppressants (such as azathioprine or mercaptopurine) or biological treatments (such as infliximab and adalimumab). For some people surgery is needed. Following drainage of the infection, types of surgery may include use of a seton (in which a piece of thread is passed through the fistula and tied in a loop); fistulotomy (involving surgically opening the tract to allow the tissues to heal from the inside out); advancement flap procedures (attachment of a piece of rectal or anal tissue over the internal opening of the fistula following fistulotomy) or use of biosynthetic plugs to block the internal opening of the

fistula. Fibrin glue is a non-surgical option for treating an anal fistula. The fibrin glue is injected into the fistula to seal the tract.

NICE guidance is available for some, but not all, current treatments for perianal fistula. NICE technology appraisal 187 recommends the anti-tumour necrosis factor (TNF) inhibitors 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. Technology appraisal guidance 187 further recommends infliximab as a treatment option for people with active fistulising Crohn's disease whose disease has not responded to conventional therapy (including antibiotics, drainage and immunosuppressive treatments), or who are intolerant of or have contraindications to conventional therapy. Interventional procedures guidance 410 recommends that there are no major safety concerns with using a suturable biosynthetic plug to block the internal opening of the fistula. However, data on the efficacy of this procedure is limited and the guidance states that the procedure should only be used with special arrangements for clinical governance, consent and audit or research.

The technology

Cx601 (Alofisel, TiGenix) is a suspension of expanded human adipose-derived stem cells of allogeneic origin (adipose-derived stem mesenchymal stem cells). These stem cells have the potential to regulate the function of immune-cells including B lymphocytes, T-lymphocytes, NK cells, monocyte – derived dendritic cells, and neutrophils. Cx601 is administered by a single injection into the fistula

Cx601 does not currently have a marketing authorisation in the UK for treating complex perianal fistula in Crohn's disease. It is being studied in an ongoing placebo controlled trial in people with perianal fistulising Crohn's disease that is refractory to at least one of the following treatments: antibiotics, immunosuppressants or a tumour necrosis factor-alpha inhibitor.

Intervention(s)	Cx601
Population(s)	Adults with non-active or mildly active luminal Crohn's disease who have a complex perianal fistula that is refractory to conventional therapy or biologic therapy.

Comparators	• Infliximab • adalimumab (does not currently have a marketing authorisation for this indication) • Surgical treatment (such as use of a seton, fistulotomy, advancement flap procedures or insertion of biosynthetic plugs) • Fibrin glue • Best supportive care
Outcomes	The outcome measures to be considered include: • closure of fistula • disease activity • continence • mortality • 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. 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
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	Related Technology Appraisals: 'Infliximab and adalimumab for the treatment of Crohn's disease' (2010). NICE Technology Appraisal 187. On static list. 'Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy' (2015) NICE

	Technology Appraisal 352. Review date August 2018 Appraisals in development 'Ustekinumab for treating moderately to severely active Crohn's disease after prior therapy' Proposed NICE technology appraisal [ID 843]. Publication date to be confirmed. Related Guidelines: 'Crohn's disease: management' (2012). NICE guideline 152 Review date Month December 2016. Related Interventional Procedures: 'Closure of anal fistula using a suturable bioprosthetic plug' (2011). NICE interventional procedures guidance 410. Related NICE Pathways: Crohn's disease overview (2012). NICE pathway http://pathways.nice.org.uk/pathways/crohns-disease
Related National Policy	Department of Health, Manual for Prescribed Specialised Services 2013/14, Jan 2014. Chapter 101 Severe intestinal failure service (adults) http://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf Department of Health, NHS Outcomes Framework 2015-2016, Dec 2014. Domain 2. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/385749/NHS_Outcomes_Framework.pdf NHS England (2013) 2013/14 NHS standard contract for colorectal: complex inflammatory bowel disease (adult). Service Specification Number: A08/S/c https://www.england.nhs.uk/wp-content/uploads/2013/06/a08-colore-inflam-bowel-disease-adult.pdf

Questions for consultation

Have all relevant comparators for Cx601 been included in the scope? Which treatments are considered to be established clinical practice in the NHS for treating complex perianal fistula in non-active or mildly active luminal Crohn's disease?

Is adalimumab used for treating complex perianal fistula in non-active or mildly active luminal Crohn's disease in England?

What types of surgery are used for treating complex perianal fistula in non-active or mildly active luminal Crohn's disease?

Is best supportive care an appropriate comparator? If so, how should it be defined?'

Are the outcomes listed appropriate?

Are there any subgroups of people in whom Cx601 is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider Cx601 will fit into the existing NICE pathway 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 Cx601 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 Cx601 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 Cx601 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. Gecse K, Bemelman W, Kamm M et al (2014) A global consensus on the classification, diagnosis and multidisciplinary treatment of perianal fistulising Crohn's disease. Gut 63:1381-1392