

# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## GUIDANCE EXECUTIVE (GE)

### Review of TA187 Infliximab (review) and adalimumab for the treatment of Crohn's disease

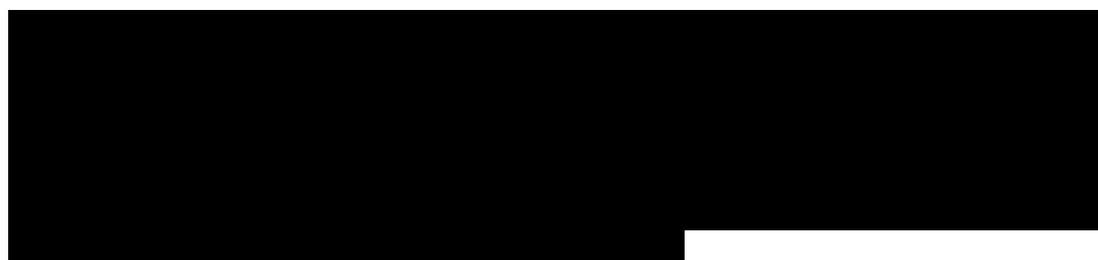
This guidance was issued in May 2010  
The review date for this guidance is September 2011

#### Recommendation

- The guidance should be incorporated, verbatim, into the ongoing Clinical Guideline: 'Crohn's disease: the management of Crohn's disease'.
- TA187 will remain in existence alongside the clinical guideline and will be moved to the static guidance list.
- We highlight that this proposal will have the consequence of preserving the funding direction.
- That we consult on the proposal.

#### Consideration of options for recommendation

This review proposal has been prepared taking into account the principles outlined in the Department of Health policy document PWG IB (10)05.



Below is a table summarising the consideration of review options:

Options	Comment
A review of the guidance should be planned into the appraisal work programme.	There are currently no new or ongoing trials whose outcome would significantly affect TA187.
The decision to review the guidance should be deferred [to a specified date].	There are currently no new or ongoing trials whose outcome would significantly affect TA187.
A review of the guidance should be combined with a review of a related technology and conducted at the scheduled time for the review of the related technology.	No suitable new technology appraisals have recently been referred.

Options	Comment
A review of the guidance should be combined with a new appraisal that has recently been referred to the Institute.	No suitable new appraisals have recently been referred.
<b>The guidance should be incorporated into an on-going clinical guideline.</b>	<b>The guidance will be incorporated, verbatim, into the clinical guideline currently under development ‘Crohn’s disease: the management of Crohn’s disease’. This has been stated in the final scope for this clinical guideline. TA187 will remain in existence alongside the clinical guideline and will be moved to the static guidance list. This proposal will have the consequence of preserving the funding direction.</b>
The guidance should be updated into an on-going clinical guideline.	There is no new evidence to suggest that the recommendations of TA187 will change. The guidance will be incorporated, but not updated, within the clinical guideline currently under development ‘Crohn’s disease: the management of Crohn’s disease’.
The guidance should be transferred to the ‘static guidance list’.	TA187 will remain in existence alongside the clinical guideline and will be moved to the static guidance list.

### Original remit(s)

To appraise the clinical and cost effectiveness of the tumour necrosis factor alpha (TNF  $\alpha$ ) inhibitors and natalizumab within their licensed indications for the treatment of Crohn's disease.

### Current guidance

- 1.1 Infliximab and adalimumab, within their licensed indications, are recommended as treatment options for adults with severe active Crohn’s disease (see 1.6) 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. Infliximab or adalimumab should be given as a planned course of treatment until treatment failure (including the need for surgery), or until 12 months after the start of treatment, whichever is shorter. People should then have their disease reassessed (see 1.4) to determine whether ongoing treatment is still clinically appropriate.
- 1.2 Treatment as described in 1.1 should normally be started with the less expensive drug (taking into account drug administration costs, required

dose and product price per dose). This may need to be varied for individual patients because of differences in the method of administration and treatment schedules.

- 1.3 Infliximab, within its licensed indication, is recommended 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. Infliximab should be given as a planned course of treatment until treatment failure (including the need for surgery) or until 12 months after the start of treatment, whichever is shorter. People should then have their disease reassessed (see 1.4) to determine whether ongoing treatment is still clinically appropriate.
- 1.4 Treatment with infliximab or adalimumab (see 1.1 and 1.3) should only be continued if there is clear evidence of ongoing active disease as determined by clinical symptoms, biological markers and investigation, including endoscopy if necessary. Specialists should discuss the risks and benefits of continued treatment with patients and consider a trial withdrawal from treatment for all patients who are in stable clinical remission. People who continue treatment with infliximab or adalimumab should have their disease reassessed at least every 12 months to determine whether ongoing treatment is still clinically appropriate. People whose disease relapses after treatment is stopped should have the option to start treatment again.
- 1.5 Infliximab, within its licensed indication, is recommended for the treatment of people aged 6–17 years with severe active Crohn's disease whose disease has not responded to conventional therapy (including corticosteroids, immunomodulators and primary nutrition therapy), or who are intolerant of or have contraindications to conventional therapy. The need to continue treatment should be reviewed at least every 12 months.
- 1.6 For the purposes of this guidance, severe active Crohn's disease is defined as very poor general health and one or more symptoms such as weight loss, fever, severe abdominal pain and usually frequent (3–4 or more) diarrhoeal stools daily. People with severe active Crohn's disease may or may not develop new fistulae or have extra-intestinal manifestations of the disease. This clinical definition normally, but not exclusively, corresponds to a Crohn's Disease Activity Index (CDAI) score of 300 or more, or a Harvey-Bradshaw score of 8 to 9 or above.
- 1.7 When using the CDAI and Harvey-Bradshaw Index, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the scores and make any adjustments they consider appropriate.

- 1.8 Treatment with infliximab or adalimumab should only be started and reviewed by clinicians with experience of TNF inhibitors and of managing Crohn's disease.

### **Relevant Institute work**

#### *Published*

IPG126 [Leukapheresis for inflammatory bowel disease](#) Issued Jun 2005

IPG288 [Extracorporeal photopheresis for Crohn's disease](#). Issued Feb 2009.

IPG101 [Wireless capsule endoscopy for investigation of the small bowel](#).  
Issued Dec 2004.

#### *In progress*

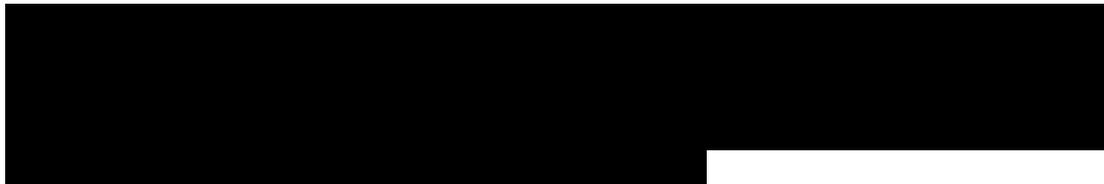
[Colonoscopic surveillance for colorectal cancer in high-risk groups: inflammatory bowel disease and polyps](#). Clinical Guideline. Anticipated publication date Nov 2010.

[Crohn's disease](#). Clinical Guideline. Anticipated publication date TBC

#### *Suspended/terminated*

None

#### *In topic selection*



### **Safety information**

NeLM August 2009. [FDA issues safety warnings of increased risk of malignancy with TNF blockers in children and adolescents](#)

Details of changes to the indications of the technology



### Details of new products

Drug (manufacturer)	Details
Abatacept (Bristol Myers Squibb)	Phase III trials completed in UK Dec 2009. No details of launch date
Briakinumab (Abbott Laboratories)	Currently in phase II trials. Anticipated launch date Q1 2014.
CCX282-B (GSK)	Currently in phase III trials. No details of launch date
Teduglutide (NPS Pharmaceuticals)	Currently in phase II trials. No details of launch date
Vedolizumab (Millennium Pharmaceuticals)	Currently in phase III trials. Anticipated launch date Q1 2013.

### On-going trials

Trial name and contact	Details
Use of Combined Measurements of Serum Infliximab and Anti-infliximab Antibodies in the Treatment of Patients With Crohns Disease Failing Infliximab Therapy NCT00851565	Phase IV. Estimated completion date Feb 2014.
A Multicenter Trial Comparing REMICADE (Infliximab) and Placebo in the Prevention of Recurrence in Crohn's Disease Patients Undergoing Surgical Resection Who Are at an Increased Risk of Recurrence. NCT01190839	Phase III. Estimated completion date Sep 2015.
The Efficacy of Open Label Infliximab for the Induction and Maintenance of Mucosal Healing in Small Bowel Crohn's Disease Assessed Through Wireless Camera Endoscopy (the ICE Study) (AM1)(P05088) NCT01181765	Phase IV. Estimated completion date Mar 2012.
Adalimumab in Combination With Ciprofloxacin/Placebo Treatment of Perianal Fistulas in Crohn's (Adafi) NCT736983	Phase III. Estimated completion date Mar 2011.
Study Registry to Evaluate the Long-term Safety of Infliximab and Clinical Status of Pediatric Patients With Inflammatory Bowel Disease NCT00606346	Phase IV. Estimated completion date Dec 2035.
Efficacy and Safety of Adalimumab in Pediatric Subjects With Moderate to Severe Crohn's Disease NCT00409682	Phase III. Completed, no results reported yet. Last Updated: November 2010.

Efficacy and Long Term Safety of Adalimumab in Pediatric Subjects Who Have Demonstrated Clinical Response in M06-806 NCT00686374	Phase III. Estimated completion date May 2012.
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### **Proposal for updating the guidance**

If the guidance is to be updated as an appraisal, it would be scheduled into the work programme accordingly.

### **New evidence**

The search strategy from the original assessment report was re-run on the Cochrane Library, Medline, Medline(R) In-Process and Embase. References from 2007 onwards were reviewed. The results of the literature search are discussed in the 'Appraisals comment' section below.

### **Implementation**

A submission from Implementation is attached at the end of this paper.

As noted in the implementation paper, the 'data do not link to diagnosis so needs to be treated cautiously in relation to the specific recommendations of the guidance'.

### **Equality issues**

No equality issues were raised.

### **Appraisals comment**

At the time of this review proposal (December 2010) there are currently two drugs recommended by NICE for the treatment of Crohn's disease: infliximab and adalimumab. There are currently no other drugs being appraised by NICE for the treatment of Crohn's disease.

Originally, the final scope of the appraisal included natalizumab and certolizumab pegol as interventions, but these were excluded because they did not receive regulatory approval. At the time of this review proposal (December 2010) both natalizumab and certolizumab pegol are not licensed for the treatment of Crohn's disease.

There are currently no ongoing clinical trials that directly compare infliximab and adalimumab. There is one study for infliximab (SONIC study, Colombel et al., 2010) that has recently been published. This study compared infliximab monotherapy, azathioprine monotherapy, and infliximab in combination with

azathioprine in people with moderate-to-severe Crohn's disease who had not undergone previous immunosuppressive or biologic therapy (n= 508). The results of this study suggest that people with moderate-to-severe Crohn's disease treated with infliximab in combination with azathioprine or infliximab monotherapy were more likely to have a corticosteroid-free clinical remission than those receiving azathioprine monotherapy.

There is one study for adalimumab (EXTEND study) that has recently been published. This was a randomised, placebo-controlled study of patients with moderate to severe ileocolonic Crohn's disease and baseline mucosal ulceration. All patients (n=135) received open-label adalimumab induction therapy and at week 4, 129 patients were randomised to maintenance therapy with adalimumab or placebo. At 52 weeks adalimumab was statistically significantly better than placebo in achieving clinical remission and mucosal healing.

There is an ongoing clinical guideline on the management of Crohn's disease, and as per 5.1.1 of the final scope of this guideline, technology appraisal guidance 187 will be incorporated into the guideline.

[REDACTED]

[REDACTED]

To produce optimal guidance to the NHS, the guidance should be incorporated into the clinical guideline 'Crohn's disease: the management of Crohn's disease'.

### **Key issues**

The technology appraisal for Crohn's disease was published recently (May 2010) and there are no new or ongoing trials that are considered likely to change the current guidance. Therefore it is appropriate to incorporate the guidance into the ongoing clinical guideline.

[REDACTED]

**GE paper sign off:** Janet Robertson, 6th December 2010

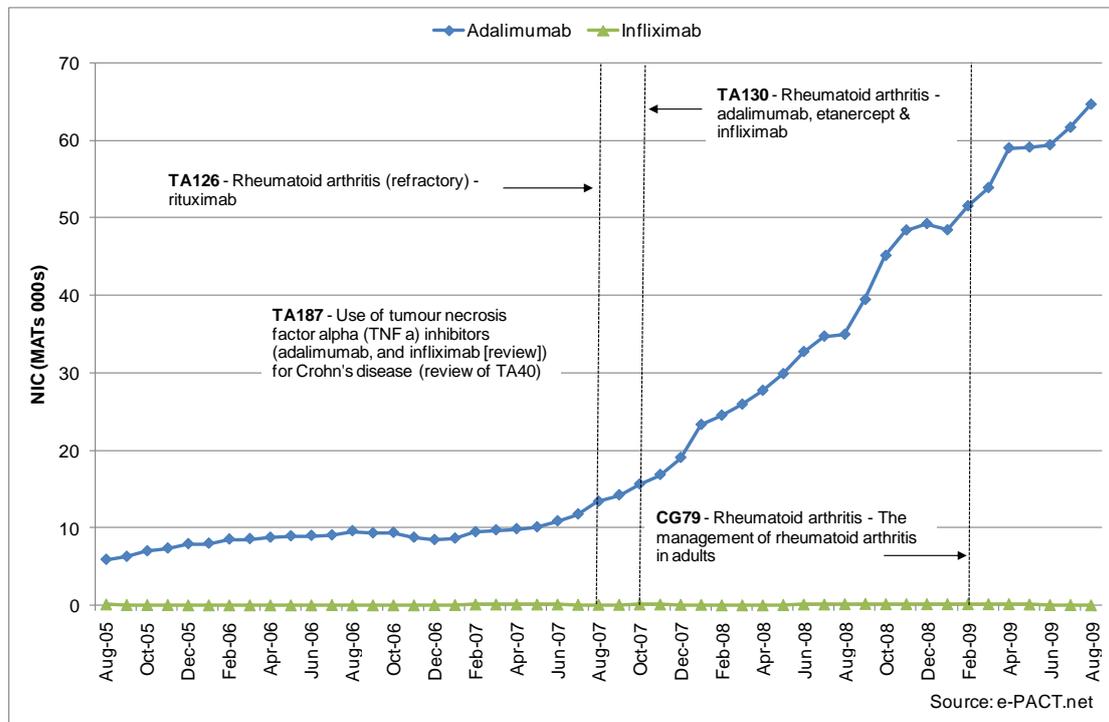
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## Implementation information

### 1. Routine healthcare activity

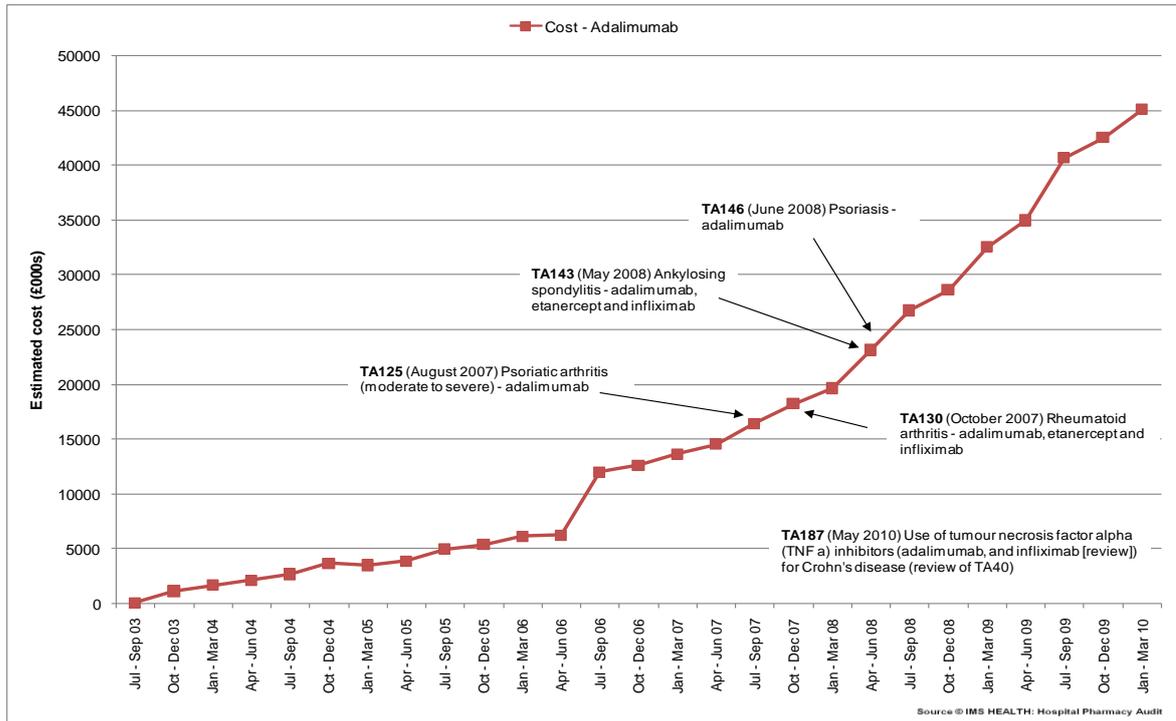
This section provides information on prescribing cost for adalimumab and infliximab in primary care in England. The data are obtained from the electronic Prescribing Analysis Cost Tool (ePACT) system which is maintained by the Prescription Services Division of the NHS Business Services Authority (BSA). All costs stated in this report are based on net ingredient cost (NIC). Unfortunately this data does not link to diagnosis so needs to be treated cautiously in relation to the specific recommendations of the guidance.



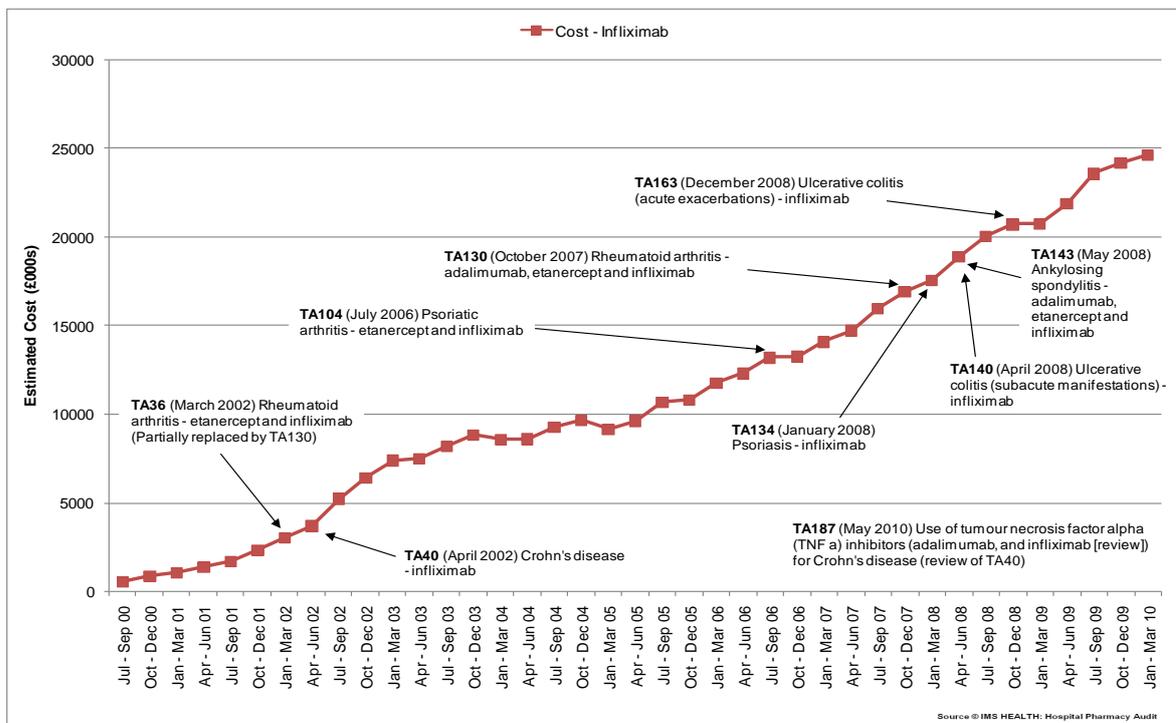
Data showing trends in prescribing costs are presented below. Unfortunately this data does not link to diagnosis or stage of cancer so needs to be treated cautiously in relation to the specific recommendations of the guidance.

Adalimumab and infliximab have multiple indications which are not reflected in the data presented below. The data is taken from the IMS Hospital Pharmacy Audit Index Database.

## Adalimumab – Estimated Cost



## Infliximab – Estimated Cost



## **2. Implementation studies from published literature**

Information if taken from the ERNIE website

The Healthcare Commission (2007) [The best medicine: the management of medicines in acute and specialist trusts](#) London: Healthcare Commission

A national review of medicines management in 173 acute and specialist NHS trusts in England. Data from a trust questionnaire as part of this review found that 95% of organisations treat some patients according to guidance and 70% treat all patients according to the guidance. 86% of trusts have an agreement about funding in place with commissioners and 45% of organisations reported having an audit completed or in progress.