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National Institute for Clinical Excellence

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Technology Appraisal Guidance - No. 40

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National Institute for Clinical Excellence

Guidance on the use of infliximab for Crohn's disease

April 2002

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This guidance represents the view of the Institute, which was arrived at after careful consideration of the available evidence. Health professionals are expected to take it fully into account when exercising their clinical judgement. This guidance does not, however, override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

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NHS

National Institute for Clinical Excellence

Guidance on the use of infliximab for Crohn's disease

1. Guidance

1.1 Infliximab is recommended for the treatment of patients with severe Crohn's disease who fulfil all three of the following criteria:

- Patients who have severe active Crohn's disease. These patients will already be in very poor general health with weight loss and sometimes fever, severe abdominal pain and usually frequent (3–4 or more) diarrhoeal stools daily. They may or may not be developing new fistulae or have extra-intestinal manifestations of the disease. This clinical definition normally corresponds to a Crohn's Disease Activity Index (CDAI) score of 300 or more and a Harvey-Bradshaw Index of 8/9 or above (see Appendix D)

- Patients whose condition has proved to be refractory to treatment with immunomodulating drugs (e.g. azathioprine or 6-mercaptopurine, methotrexate) and corticosteroids, or who have been intolerant of, or experienced toxicity from, these treatments.

- Patients for whom surgery is inappropriate (e.g. because of diffuse disease and/or a risk of short bowel syndrome).

1.2 Treatment can be repeated for those patients who match the above criteria and have responded to the initial treatment course, but then relapsed. A decision about whether or not to re-administer infliximab after the first course or subsequently should be made only after discussion with the patient who has been fully informed of the potential risks and benefits of repeated therapy (episodic treatment).

1.3 Infliximab should be prescribed by a gastroenterologist experienced in the management of Crohn's disease.

1.4 Infliximab is not recommended for patients with fistulising Crohn's disease who do not have the other criteria for severe active Crohn's disease as detailed in section 1.1.

This section (Section 1) constitutes the Institute's guidance on the use of infliximab for Crohn's disease. The remainder of the document is structured in the following way:

2 Clinical need and practice
3 The technology
4 Evidence
5 Implications for the NHS
6 Further research
7 Implementation
8 Review of guidance

Appendix A: Appraisal Committee members
Appendix B: Sources of evidence
Appendix C: Patient information
Appendix D: Technical detail on the criteria for audit of the use of infliximab for Crohn's disease

A bi-lingual summary is available from our website at www.nice.org.uk or by telephoning 0870 1555 455 and quoting the reference number N0088.

Mae crynodeb ar gael yn Gymraeg ac yn Saesneg ar ein gwefan yn www.nice.org.uk neu drwy ffonio 0870 1555 455 gan ddyfynnu cyfeirnod N0088.

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Clinical need and practice

2.1 Crohn's disease is a chronic inflammatory disease mainly affecting the gastrointestinal tract. It is estimated that about 31,000 people in England and 1,800 in Wales have the disease and that about 2,650 new cases are diagnosed each year in England and Wales. Crohn's disease can occur at any age but most commonly begins in people aged 15 to 25 years. The cause of the disease is unknown.

2.2 People with Crohn's disease have recurrent attacks, with acute 'flares' of the disease interspersed with periods of remission or less active disease.

2.3 Crohn's disease can be complicated by the development of intestinal obstruction, fistulae and perianal disease. Fistulae develop in about one third of patients. Perianal disease is a frequent complication of colonic and ileocolonic disease and is characterised by fissures, fistulae and abscesses. Spontaneous healing is rare, and surgical management is often required, although it is not always possible or wholly successful.

2.4 Other complications of Crohn's disease include acute dilatation and perforation of the gastrointestinal tract, and massive haemorrhage, particularly when the disease affects the colon. Extraintestinal manifestations include articular, ocular, hepatic and skin disorders. These have been reported to develop in more than 15% of patients, occurring predominantly in patients with colonic Crohn's disease. There is also a documented increase in the incidence of cancer of the small and large intestine.

2.5 Crohn's disease is neither medically nor surgically curable. Drug treatment is aimed at reducing symptoms and maintaining or improving quality of life, while minimising toxicity over the short and long term. Corticosteroids and immunomodulators (mainly azathioprine or 6-mercaptopurine) form the mainstay of treatment for active Crohn's disease.

2.6 Surgery will be required eventually by 50–80% of patients with Crohn's disease. The main indications for surgery are strictures causing obstructive symptoms, failure to respond to medical therapy and complications such as fistulae.

2.7 Crohn's disease encompasses a wide spectrum of disease activity with a subset of around 2% of patients who have very severe disease. This group presents with severe symptoms, evidence of systemic toxicity, weight loss and often other complications. Investigation reveals severe and usually extensive intestinal inflammation with associated biochemical and haematological evidence of significant systemic disturbance (e.g. anaemia, very high C-reactive protein and low albumin levels). These patients are often unresponsive to standard drug therapy including immunosuppressants.

2.8 Because of improved surgical and medical management, overall mortality from Crohn's disease has been reduced. Most people with Crohn's disease lead active lives. Nevertheless, 5 years after onset, 15–20% of patients are disabled by their disease to some degree.

2.9 The Crohn's Disease Activity Index (CDAI) is one of the most frequently used indices in assessing the severity of the disease in research studies although it is not commonly used in everyday clinical practice. It is a composite index of overall activity of Crohn's disease as assessed by physicians. This index gives a score, which ranges from 0 to over 600, based on a diary of symptoms kept by the patient for 1–7 days, and other measurements such as the patient's weight and hematocrit. A score of 150 or below is considered to represent inactive disease, whereas scores above 450 represents very severe disease. However, the CDAI may be impractical to use in clinical settings, is based on some subjective evaluations and is inappropriate for some patients (such as patients with stoma). The Harvey-Bradshaw index is another commonly used index, which correlates well with CDAI and is based on assessments of general well-being, abdominal pain, number of liquid stools per day, and the presence of abdominal mass and associated complications (see Appendix D).

3 The technology

3.1 Tumour necrosis factor alpha (TNF-α) is a pro-inflammatory mediator, which is thought to play a central role in the pathogenesis of Crohn's disease. Its over-expression is believed to be partly responsible for the chronic inflammatory processes in the intestinal tissue in many of these patients. Infliximab is a chimeric human-murine monoclonal antibody that binds with high affinity to TNF-a, inhibiting its activity.

3.2 Infliximab (Remicade) is licensed for use in adults (aged 18 years and older) for:

- the treatment of severe active Crohn's disease, in patients who have not responded despite a full and adequate course of therapy with a corticosteroid and an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies.

- the treatment of fistulising Crohn's disease in patients who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy).

Infliximab is not licensed for maintenance treatment, which is defined as infliximab administered at regular intervals (usually every 8 weeks) to maintain the remission/response without waiting for flares.

3.3 Infliximab is given as an intravenous infusion over at least 2 hours. In severe active Crohn's disease the recommended dose is 5 mg/kg body weight as a single infusion. In fistulising Crohn's disease, infliximab is given as an initial 5 mg/kg infusion over at least 2 hours followed by additional 5 mg/kg infusions 2 and 6 weeks later.

3.4 Infliximab costs £451.20 for a single 100 mg vial. For an average adult patient with Crohn's disease (60 kg) the cost for a single infusion at 5 mg/kg is approximately £1,350 (three vials). Vials of infliximab do not contain a preservative and so any unused portion of reconstituted solution must be discarded.

3.5 Infliximab is contraindicated in patients with severe infection and has also been reported to lead to reactivation of tuberculosis. It is also contraindicated in patients with moderate to severe heart failure (NYHA class III/IV) and in patients with a history of sensitivity to infliximab or other murine proteins or to any of the excipients. In addition the manufacturer has issued a health warning regarding potential cardiovascular adverse events associated with infliximab. Use during pregnancy or lactation is not recommended.

3.6 A delayed hypersensitivity reaction has been observed in a significant proportion of patients (25%) with Crohn's disease who were re-treated with infliximab after a 2 to 4 year period without infliximab treatment. The risk of hypersensitivity reaction following re-administration after a drug-free period of 15 weeks to 2 years is unknown. Concurrent administration of immunosuppressant drugs appears to reduce the risk of hypersensitivity.

4 Evidence

4.1 Clinical effectiveness

4.1.1 Five completed and one ongoing clinical trials were identified. Of those, four trials evaluated the effectiveness of single or repeated treatment with various doses of infliximab in patients with moderate to severe active Crohn's disease that had proved to be refractory to conventional treatment. Two trials (one completed and one ongoing) evaluated infliximab treatment in fistulising Crohn's disease.

Moderate to severe active Crohn's disease

4.1.2 In a pivotal Phase II trial, reported by Targan et al (1997), 108 patients with moderate to severe treatment-resistant Crohn's disease were randomised to receive a single infusion of placebo or infliximab (5 mg/kg, 10 mg/kg or 20 mg/kg) and followed up for 12 weeks.

4.1.3 A statistically significantly ($p<0.05$) greater proportions of patients had a clinical response (defined as a reduction of at least 70 points in CDAI from baseline) at 4 weeks after treatment with infliximab than after treatment with placebo. The response rates at week 4 were 17% for placebo, 81% for infliximab 5 mg/kg, 50% for infliximab 10 mg/kg and 64% for infliximab 20 mg/kg. Although the difference between the proportion of responders in placebo and treatment groups remained statistically significant throughout the 12-week follow-up, the response to treatment was lost by week 12 in approximately 40% of patients in the infliximab groups (compared with 25% in placebo group). The response rates at week 12 were 12% for placebo, 48% for infliximab 5 mg/kg, 29% for infliximab 10 mg/kg and 46% for infliximab 20 mg/kg.

4.1.4 In line with the clinical response, the proportion of patients in clinical remission (defined as a CDAI score of less than 150) was statistically significantly higher in the infliximab groups compared with the placebo group at week 4 (remission rate: 4% in the placebo group, 48%, 25% and 25% in the infliximab 5 mg/kg, 10 mg/kg and 20 mg/kg groups, respectively; $p=0.005$ for all infliximab treatments versus placebo). However, for clinical remission rates there were no statistically significant differences between the infliximab groups and the placebo group by week 12 (remission rate: 8% in the placebo group, 30%, 18% and 25% in the infliximab 5 mg/kg, 10 mg/kg and 20 mg/kg groups, respectively, $p=0.31$ for all infliximab groups versus placebo). Analysis of a small subset of patients who were responders to treatment at week 4 showed a median duration of response of 16 weeks.

4.1.5 In the Targan trial, patients who did not respond at 4 weeks after the initial blinded infusion were offered an infusion of infliximab 10 mg/kg on an open-label basis and were followed up for a further 12 weeks. Among the patients who received placebo initially, the response rate at 4 weeks after the open-label infusion of infliximab was 58% (11 of 19). However, 34% of patients (10 of 29) who received infliximab as their initial blinded infusion responded to a second dose of infliximab. These results suggest that people with Crohn's disease who do not respond to the initial infusion of infliximab may be less responsive to anti-TNF therapies.

4.1.6 A 36-week extension study of the Targan trial, has evaluated the efficacy of repeated treatment with infliximab in 73 patients who demonstrated a clinical response at week 8. These patients were randomised to double-blind treatment with four infusions of placebo

(n=36) or infliximab 10 mg/kg (n=37) at 8-week intervals and were assessed at 4-week intervals, with follow-up for a further 12 weeks after the last treatment (week 48).

4.1.7 Repeated treatment with infliximab was associated with a statistically significant improvement in clinical response relative to the placebo group only at week 36 (72% vs 44%; p=0.018). A statistically significant difference between the treatment groups in the proportion of patients in clinical remission was apparent only at week 28 (60% vs 31% p=0.045) and week 44 (53% vs 20% p=0.013).

4.1.8 The ACCENT I trial (currently reported in abstract form only) compared the effectiveness of a single infusion of infliximab with repeated infusions of the drug in 573 patients with moderate to severe active Crohn's disease. At present only limited data have been reported. In this trial all enrolled patients received an initial infusion of infliximab 5 mg/kg at week 0. At week 2, patients were classified as 'responders' or 'non-responders', and within each response classification, patients were randomised to receive placebo or infliximab (5 or 10 mg/kg) infusion at weeks 2 and 6 and then every 8 weeks through to week 54. Therefore, the patients in the placebo arms of the study received at least a single infliximab infusion, and were also eligible for episodic treatment if they flared after an initial response. The median time to loss of response was 19 weeks and the mean duration of response was around 24 weeks for the placebo maintenance group during weeks 2 to 54. At week 30, 21% of patients who received only the first infliximab infusion followed by placebo were in remission. In the placebo maintenance group, an average of 1.2 infliximab injections were given for episodes of flare or relapse during weeks 2 to 54.

Fistulising Crohn's disease

4.1.9 One completed trial evaluated the effectiveness of infliximab treatment in fistulising Crohn's disease. This trial compared a three-dose treatment course of infliximab (5 mg/kg or 10 mg/kg) with placebo in 94 patients with single or multiple draining abdominal or perianal fistulae of at least 3 months' duration. The primary endpoint of the study was a reduction of at least 50% in the number of draining fistulae over two or more consecutive study visits. A series of secondary endpoints was defined including complete response (i.e. absence of draining fistulae at two consecutive study visits), the length of time to the beginning of the response and the duration of the response.

4.1.10 The primary endpoint was reached by 62% of patients on infliximab (5 or 10 mg/kg), compared with 26% of patients treated with placebo ($p=0.002$). Complete healing of fistulae was observed for at least 2 consecutive visits in 46% of patients treated with infliximab compared with 13% of patients who received placebo ($p \leq 0.001$).

4.1.11 The median onset of response was earlier with infliximab than with placebo (14 days vs 42 days), but the duration of response was similar (median about 3 months). By week 22 there was no significant difference between treatment groups in the proportion of patients with ≥50% reduction in the number of draining fistulae.

4.1.12 The ongoing ACCENT II trial will provide data on the efficacy of repeated treatment with infliximab in patients with fistulising Crohn's disease.

4.2 Cost effectiveness

4.2.1 One published economic evaluation was identified, which evaluated the cost effectiveness in US settings of infliximab compared with 6-mercaptopurine and metronidazole in patients with Crohn's disease who had perianal fistulae. The incremental cost per quality-adjusted life year (QALY) ranged between $355,450 and $377,000 depending on the infliximab regimen used.

4.2.2 Two economic evaluations were provided by the manufacturer: one estimated the cost effectiveness of infliximab treatment in patients with chronic active Crohn's disease; the other estimated the cost effectiveness of treatment in patients with fistulising disease.

4.2.3 The manufacturer's evaluation for chronic active Crohn's disease estimated the incremental cost per QALY (compared with standard care) as:

- £6,700 for a single infliximab infusion
- £10,400 for episodic infliximab treatment (defined as repeated infusion for disease flares in individuals who had an initial response)
- £84,400 for maintenance treatment (defined as repeated dosing every 8 weeks in responders).

4.2.4 The manufacturer's evaluation assumed a flare rate of 10% at 2 months. Increasing the model flare rate to 20% and 50% led to an incremental cost per QALY of £20,000 and £55,000, respectively, for episodic infliximab infusion. The manufacturer's evaluation also used a number of optimistic assumptions, most notably that the benefits gained due to infliximab treatment are continued over the patients' lifetime (assumed to be over 40 years).

4.2.5 For fistulising disease, the manufacturer's estimates for incremental cost per QALY ranged between approximately £80,000 and £120,000. These results were insensitive to cost offsets.

4.2.6 An economic model developed by the University of Birmingham, West Midlands Development and Evaluation Service evaluated the cost effectiveness of single and episodic infliximab treatment for patients with chronic active Crohn's disease within a time frame of 1 year and using fewer health states than were used in the manufacturer's model. This evaluation estimated the incremental cost per QALY to be between £105,000 and £165,000 per QALY for single infliximab treatment, and approximately £65,000 per QALY for episodic infliximab treatment, based on an initial treatment and three subsequent treatments.

4.3 Consideration

4.3.1 The Committee reviewed the evidence on both the clinical effectiveness and the cost effectiveness of infliximab, having considered evidence from people with Crohn's disease, those that represent them, and clinical experts, on the nature of the condition and the value placed by users on the effects of infliximab treatment. It was also mindful of the need to ensure that its advice took account of the efficient use of NHS resources. The Committee concluded that there was convincing evidence of the clinical effectiveness of infliximab in the short term, and that the data from the ACCENT I trial indicated that the mean duration of benefit from a single dose may be as long as 24 weeks.

4.3.2 While accepting the general outline of the economic model developed by the University of Birmingham, the Committee sought more data to validate the accuracy of the key variables such as the extent of the quality-of-life gain, duration of response and the number of episodes of relapse in each year for which infliximab might be used. Although the ACCENT I trial which was designed to evaluate maintenance therapy (which currently is not licensed), and was not intended to evaluate the effectiveness of episodic infliximab

treatment, the placebo arms of this trial comprised patients who had either received single or episodic infliximab injections. At the Committee's request, the manufacturer made available additional patient-level data, for up to 54 weeks in the ACCENT I trial, on quality-of-life gains, mean duration of response, and number of treatments with infliximab for episodes of relapse during 1 year. However, the quality-of-life data at week 54 were derived from only 36% of the patients who were initially enrolled into the trial as placebo maintenance patients. After considering the estimates derived by using these data in the Birmingham model, the Committee concluded that on the balance of probabilities the incremental cost per QALY for episodic infliximab treatment approached £27,500 in patients with the severest form of Crohn's disease.

4.3.3 The Committee also considered the potential adverse effects of infliximab treatment such as increased risk of tuberculosis, and was made aware of the recent health warning from the manufacturer on the nature of potential cardiovascular adverse events particularly in patients with heart failure.

4.3.4 The Committee considered the uncertainty around the cost-effectiveness estimates generated by different economic models, and the concerns about adverse events and concluded that on the balance of its clinical and cost effectiveness, infliximab should be made available only for patients with severe Crohn's disease, as defined in section 1.1. This definition should be used to identify people for whom infliximab treatment will have the most benefit. This clinical definition corresponds to a CDAI score of 300 or more and a Harvey-Bradshaw Index of 8/9 or above (see Appendix D)

4.3.5 For fistulising Crohn's disease, although there was some evidence to support the clinical effectiveness of infliximab in the short term, the Committee concluded that the extent of the benefits for these patients was not sufficient to consider infliximab to be cost effective for the treatment of fistulising disease except in the context of severe active Crohn's disease as previously defined.

5 Implications for the NHS

5.1 The manufacturer's cost-effectiveness models assumed that 7–20% of patients had severe Crohn's disease and that approximately 20% of those would not receive treatment for various reasons such as contraindications and personal preferences. It can also be estimated that about 20% of patients who would be eligible for and opt for treatment would have fistulising disease alone, while the rest would have fistulae in the context of severe active Crohn's disease. On the basis of these estimates, of the 32,800 people with Crohn's disease in England and Wales, between 1,500 and 4,200 would be eligible for treatment.

5.2 On the more strict definition of severity given in the guidance section, it is likely that the proportion of patients with severe disease will be near to or below the lowest estimate given by the manufacturer, perhaps being 5% of all patients. On this basis around 1050 patients would be eligible for treatment.

5.3 Assuming that the drug and treatment costs for an average patient (60 kg) is around £1,457, the average number of episodes of treatment in 1 year is 2.2, and the response rate is 48%, the cost of treatment for people who currently have severe chronic active Crohn's disease is estimated to be around £2.5 million for the first year. This figure will also be proportionately less, dependent on the present usage of infliximab. In subsequent years, the annual cost to the NHS will be less as the drug will only be offered to patients who have previously responded to infliximab or to new patients who have not previously received infliximab.

6 Further research

6.1 Further good quality studies are needed to investigate:

- methods to identify the subsets of the patients who may respond better than others to infliximab, for example by using micro-satellite halotypes and perinuclear anti-neutrophil cytoplasmic antibody (pANCA)
- the role of infliximab in long-term prevention of surgery for patients with Crohn's disease
- the value of treatment with infliximab in adolescents with Crohn's disease
- the long-term toxicity of regular or intermittent use of infliximab, including the potential for infliximab to increase the development of lymphoproliferative disorders
- the observation that the risk of delayed hypersensitivity reaction may be reduced in patients using concomitant immunosuppressants.

7 Implementation

7.1 All clinicians treating people with Crohn's disease should review their current practice in line with the guidance set out in Section 1.

7.2 Clinical teams treating people with Crohn's disease should integrate the guidance set out in Section 1 into any existing local practice guidelines, care pathways or protocols that refer to people with Crohn's disease.

7.3 To enable clinicians to audit their own compliance with this guidance, it is recommended that a system for identifying people with Crohn's disease and their treatment is maintained at a local level and that a complete and current assessment and treatment plan is recorded for each patient.

7.4 To measure compliance locally with the guidance set out in Section 1, the following criteria should be used. Further details of suggestions for audit are presented in Appendix D.

- Infliximab is provided for an individual with severe Crohn's disease only if the individual meets all of the following circumstances: The individual has severe active disease, the individual's condition has proved refractory to treatment with immunomodulating drugs and corticosteroids or the individual has become intolerant of or has experienced toxicity from these treatments, and surgery is inappropriate for the individual.

- Infliximab treatment is repeated for those individuals whose condition is consistent with the criteria above and who have responded to the initial treatment course but then relapsed. The decision to proceed with repeated therapy is made by a gastroenterologist experienced in the management of Crohn's disease and only after discussion with the individual who has been fully informed of the potential risks and benefits of repeated therapy.

- Infliximab is not recommended for patients with fistulising Crohn's disease who do not meet the criteria above.

8 Review of guidance

8.1 This advice will be reviewed in the light of new evidence in May 2005.

Andrew Dillon
Chief Executive

April 2002

APPENDIX A

Appraisal Committee members

The Appraisal Committee is a statutory committee whose members sit for 3 years. Two meetings are held per month and the majority of members attend one or the other. Declared interests may also exclude a member from individual technology appraisals. The committee are supplemented by technology specific experts as indicated in Appendix B.

Professor R. L. Akehurst
Dean, School of Health Related Research
Sheffield University

Professor David Barnett (Chairman)
Professor of Clinical Pharmacology
University of Leicester

Professor Sir Colin Berry
Professor of Morbid Anatomy
St Bartholomew's and Royal London School of Medicine

Dr Sheila Bird
MRC Biostatistics Unit,
Cambridge

Professor Martin Buxton
Director of Health Economics Research Group
Brunel University

Dr Karl Claxton
Lecturer in Economics
University of York

Professor Sarah Cowley
Professor of Community Practice Development
Kings College, London

Professor Nicky Cullum
Reader in Health Studies
Department of Health Sciences
University of York

Mr Chris Evennett
Chief Executive
Mid-Hampshire Primary Care Group

Professor Terry Feest
Clinical Director and Consultant Nephrologist
Richard Bright Renal Unit and Chairman of the UK Renal Registry

Ms Jean Gaffin
Formerly Executive Director
National Council for Hospice and Specialist Palliative Care Service

Mrs Sue Gallagher
Chief Executive
Merton, Sutton and Wandsworth Health Authority

Dr Trevor Gibbs
Head, Global Clinical Safety & Pharmacovigilance
GlaxoSmithKline

Mr John Goulston
Director of Finance
The Royal Free Hampstead NHS Trust

Professor Philip Home
Professor of Diabetes Medicine
University of Newcastle

Dr Terry John
General Practitioner
The Firs, London

Dr Diane Ketley
Research into Practice Programme Leader
NHS Modernisation Agency

Dr Mayur Lakhani
General Practitioner, Highgate Surgery, Leicester and Lecturer,
University of Leicester

Mr M Mughal
Consultant Surgeon
Chorley and South Ribble NHS Trust

Mr James Partridge
Chief Executive
Changing Faces

Professor Philip Routledge
Professor of Clinical Pharmacology
University of Wales

Professor Andrew Stevens (Vice Chairman)
Professor of Public Health
University of Birmingham

Dr Cathryn Thomas
General Practitioner/Senior Lecturer
Department of Primary Care & General Practice
University of Birmingham

APPENDIX B

Sources of evidence

1. The following documentation and opinion was made available to the Committee:

a. Assessment Report:
- prepared by the Department of Public Health and Epidemiology, University of Birmingham (*Infliximab for the treatment of Crohn's disease,* July 2001)

b. Manufacturer/sponsor submissions :
- Schering-Plough Ltd

c. Professional/specialist group Submissions:
- British Society of Gastroenterology
- Royal College of General Practitioners
- Royal College of Physicians

d. Patient group submissions:
- National Association for Colitis and Crohn's disease

e. External expert and patient advocate perspectives:
- Professor Jonathan M Rhodes, Professor of Medicine, Gastroenterology Research Group, Department of Medicine, University of Liverpool
- Dr D S Rampton, Reader and Consultant in Gastroenterology, Department of Gastroenterology, Royal London Hospital
- Mr Richard Driscoll, Director, National Association for Colitis and Crohn's Disease (NACC)
- Elaine Steven, Trustee, National Association for Colitis and Crohn's Disease (NACC)

APPENDIX C

Patient information

Guidance on the use of infliximab for the treatment of Crohn's disease

The patient information in this appendix has been designed to support the production of your own information leaflets. You can download it from our website at www.nice.org.uk where it is available in English and Welsh. If you would like printed copies of the leaflets please ring the NHS Response Line on 0870 1555 455 and quote reference number N0089 for the English patient leaflet and N0090 for the bi-lingual patient leaflet.

What is NICE guidance?

The National Institute for Clinical Excellence (NICE) is part of the NHS. It produces guidance on the use of medicines, medical equipment and clinical procedures for people working in the NHS in England and Wales, and for patients and their carers.

To produce this guidance, NICE looks at how well the medicine, equipment or procedure works and also how well it works in relation to how much it costs. This process is called an appraisal. The appraisal process involves the manufacturer of the medicine or equipment for which guidance is being produced, and the organisations that represent the healthcare professionals, patients and carers who will be affected by the guidance. Each appraisal takes about 12 months to complete.

What is this guidance about?

NICE has looked at the evidence available on the use of infliximab for treating people who have Crohn's disease.

What is Crohn's disease?

Crohn's disease is a severe inflammatory disease that affects the gastrointestinal tract. About 32,800 people in England and Wales have Crohn's disease and there are about 2,650 new cases each year. Crohn's disease can start in people of any age but it most commonly begins in people aged between 15 and 25.The cause of the disease is not known.

In people with Crohn's disease, parts of the gastrointestinal tract become inflamed. The inflammation can occur in any part of the gastrointestinal tract, from the mouth to the anus, but the parts most often affected are the small intestine and the colon (the large intestine). Crohn's disease can cause diarrhoea, pain in the abdomen, weight loss and tiredness. Ulcers can form in the wall of the gastrointestinal tract and when they heal the scar tissue makes the tract narrower. Sometimes the disease causes the formation of abnormal passageways ('fistulas') between parts of the intestine or between the intestine and the skin. Sometimes Crohn's disease can have effects on other parts of the body, such as the eyes or the joints.

People with Crohn's disease have recurrent attacks – that is, they have times when their disease flares up and in between they have periods of 'remission', when they have mild symptoms or no symptoms at all. The majority of people with Crohn's disease lead active lives though 15-20% of people assessed after 5 years with Crohn's are likely to be disabled to some degree.

Crohn's disease cannot be cured by medicines or surgery. There are medicines that can reduce the symptoms of the disease and improve people's quality of life. The main medicines used are corticosteroids and drugs known as immunomodulators, which change the way in which the body's immune system works. People with Crohn's disease often need surgery to remove narrowed or damaged parts of the intestine.

The effects of Crohn's disease can range from mild to severe. Treatment with corticosteroids or immunomodulators often does not work for people with severe Crohn's disease.

What is infliximab and how does it work?

TNF-α is a protein in the body that is believed to be partly responsible for causing the inflammation of the intestine in people with Crohn's disease. Infliximab is a drug that targets TNF-α and helps to prevent it causing the inflammation.

Infliximab is used to treat adults aged 18 years and older who have severe Crohn's disease.

What has NICE recommended?

NICE has recommended that infliximab should be used to treat people with severe Crohn's disease provided that **all three** of the following conditions are fulfilled.

1. The person has severe active Crohn's disease. People with severe active Crohn's disease will be in very poor general health. They will have severe symptoms of the disease such as weight loss, severe pain and frequent diarrhoea. In addition to symptoms such as these, new fistulas may be developing and the disease may be affecting parts of the body away from the intestines. The doctor can measure the severity of the disease by comparing a patient's symptoms with a standard checklist that can be used to calculate a severity 'score'. Two 'scoring measures' that are often used are the Crohn's Disease Activity Index (or CDAI) and the Harvey-Bradshaw Index. Severe active Crohn's disease would usually have a score of 300 or more on the Crohn's Disease Activity Index or at least 8 to 9 on the Harvey-Bradshaw Index.

and

2. Treatment with immunomodulators and corticosteroids has not worked, or has caused side effects that make it impossible or unsafe for the person to take them.

and

3. Because of the person's condition, surgery would not be the right form of treatment.

Infliximab treatment can be repeated for someone who matched criteria 1–3 (above) for treatment with infliximab and who responded to the initial treatment but whose condition then got worse. The doctor should explain the likely risks and benefits of repeating the treatment with infliximab before a decision is made about whether to give another round of treatment.

NICE recommends that infliximab should be prescribed by a gastroenterologist (a doctor who specialises in treating diseases of the gastrointestinal tract) who is experienced in treating people who have Crohn's disease.

NICE recommends that infliximab should not be used to treat people who have Crohn's disease with fistulas unless they fulfil the other criteria for severe active Crohn's disease described in all three points above.

What should I do?

If you or someone you care for has severe Crohn's disease, you may want to talk to your doctor about this guidance at your next appointment.

Will this guidance be reviewed?

Yes. This guidance will be reviewed in May 2005.

Further information:

Further information on NICE and the full guidance on the use of infliximab for the treatment of severe Crohn's disease that has been issued to the NHS are available on the NICE website at www.nice.org.uk. The full guidance can also be requested by calling 0870 1555 455 and quoting reference number N0087.

APPENDIX D

Technical detail on criteria for auditing the use of infliximab for Crohn's disease

Objectives for an audit

An audit could be carried out to ensure that infliximab is provided appropriately for people with severe Crohn's disease.

Individuals to be included in the audit

All adults with severe Crohn's disease seen on an inpatient or outpatient basis in a reasonable time period for audit, eg, a year.

Patients to be included in the audit might be identified through discharge diagnosis coding or clinic registers.

Measures to be used as a basis for the audit

The measures that can be used in an audit of the appropriateness of prescribing infliximab for people with Crohn's disease are as overleaf:

Measures to be used as a basis for the audit

The measures that can be used in an audit of the appropriateness of prescribing for infliximab for pe

Criterion	Standard
1. A. patient with all of the following is prescribed infliximab: a. The patient has severe active Crohn's disease **and** b. The patient's condition is refractory to treatment with immunomodulating drugs and corticosteroids or the patient is intolerant of or has experienced toxicity from these treatments **and** c. Surgery is inappropriate for the patient	100% of patients whose condition is consistent with the criterion
2. Infliximab treatment is repeated for patients who meet 1a-c above in the following circumstances: a. The patient has responded to the initial or subsequent treatment course and then relapsed **and** b. The decision is made by a gastroenterologist experienced in the management of Crohn's disease	100% of eligible patients
3. Infliximab is not provided to patients with fistulising Crohn's disease except when provided because the patients meet the other criteria for severe disease (above).	100% of patients with fistulising disease

Calculation of compliance with the measure

Compliance with each measure described in the table is calculated as follows:

$$\frac{\text{Number of patients whose care is consistent with the } \textbf{Criterion}}{\text{Number of of patients in the audit to which the } \textbf{Criterion} \text{ and } \textbf{Exception(s)}, \text{ where applicable, apply}} \times \mathbf{100}$$

ople with Crohn's disease are as follows:

Exception	Definition of Terms
A. The patient declines treatment with infliximab	Severe active Crohn's disease = patient in very poor general health with weight loss and sometimes fever, severe abdominal pain and usually frequent (3-4 or more) diarrhoeal stools daily; patients may or may not be developing new fistulae or have extra-intestinal manifestations of the disease. This corresponds to a CDAI score of 300 or more and a Harvey-Bradshaw Index of 8/9 or above. Refractory to treatment with immunomodulating drugs and corticosteroids = patient has received a full and adequately dosed course of azathioprine or 6-mercaptopurine, methotrexate and corticosteroids and has not responded to the therapy; clinicians should agree locally what constitutes intolerance or toxicity from these treatments Surgery is inappropriate = presence of diffuse disease and/or a risk of short bowel syndrome
A. The patient declines repeated treatment after being fully informed of the potential risks and benefits of repeated therapy	Clinicians should agree locally on what constitutes fully informing the patient of the potential risks and benefits of repeated infliximab therapy. Clinicians should agree locally on what constitutes an adequate level of response to previous treatment with infliximab.
The patient meets all the criteria in 1a-c	The patient meets the (other) criteria for severe Crohn's disease (above).

Clinicians should review the findings of measurement, identify if practice can be improved, agree on a plan to achieve any desired improvement and repeat the measurement of actual practice to confirm that desired improvement is being achieved.

APPENDIX E

Crohn's Disease Activity Index[1]

The CDAI score is derived from summation of information collected from a diary card completed by the patient for the preceding 7 days, together with current clinical data, as follows.

9 Days 1 to 7	Sum	X factor	Score
Number of liquid/very soft stools	.....	**2**	.....
Abdominal pain rating 0=none; 1=mild; 2=moderate; 3=severe	.....	**5**	.....
General well-being 0=generally well; 1=slightly under par; 2=poor; 3=very poor; 4=terrible	.....	**7**	.....
Number of six listed categories patient now has: arthritis/arthralgia iritis/uveitis erythema nodosum/pyoderma gangrenosum/ aphthous stomatitis anal fissure, fistula or abscess other fistula fever of >37°c in past week	.....	**20**	.....
Taking opioids for diarrhoea No=0; Yes= 30 points			.....
Abdominal mass none=0; questionable=20; definite=50 points			.....
Haematocrit(%) males: 47 – 'crit Females: 42- 'crit		**6**	.....
Body weight (kg) %age below standard weight for height add if below standard weight; subtract if overweight			.....
Total CDAI			.....

[1] Best WR, Becktel JM, Singleton JW, Kern F Jr. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. Gastroenterology 1976; 70:439-444

Harvey-Bradshaw Index[2]

A five point score is based on:

A	General well-being	0=very well; 1=slightly below par; 2=poor; 3=very poor; 4=terrible
B	Abdominal pain	0=none; 1=mild; 2=moderate; 3=severe
C	Number of liquid stools per day	
D	Abdominal mass	0=none; 1=dubious; 2=definite; 3=definite and tender
E	Complications	Score 1 for each of arthralgia, uveitis, erythema nodosum, pyoderma gangrenosum, aphthous ulcers, anal fissure, new fistula, abscess.

[2] Harvey RF, Bradshaw JM. A simple index of Crohn's disease activity. Lancet 1980; i:514