NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Overview

Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (including a review of TA140 and TA262)

This overview is a summary of:

- the evidence and views submitted by the manufacturers, the consultees and their nominated clinical specialists and patient experts and
- the assessment report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document is a summary of the information available before comments on the assessment report have been received.

Key issues for consideration

Clinical effectiveness

- Professional groups noted that 'moderately to severely active ulcerative colitis' is not well defined in clinical practice. Does the Committee consider that the inclusion criterion for disease severity (Mayo score of 6–12) used in randomised controlled trials (RCTs) represents patients who would be considered to have moderate to severe disease in clinical practice in the NHS?
- Adalimumab, golimumab and infliximab are licensed in patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine or azathioprine, or who are intolerant to or have medical

contraindications for such therapies. In view of that, is it appropriate to include conventional therapy as a comparator in the decision problem?

RCT evidence

- What is the Committee's view on the extent to which the results generated by the RCTs are generalisable to clinical practice considering that the trials excluded patients who had: ulcerative proctitis, a history of or a risk of having bowel surgery, diseases of the central nervous system, previous serious infection or immunodeficiency, previous malignancy, or signs of dysplasia?
- ULTRA2 for adalimumab was the only RCT that allowed patients to have received a previous anti-TNF-alpha agent. Does this affect the suitability of ULTRA2 for the assessment of adalimumab's clinical effectiveness?
- The primary end point in some RCTs was remission while in others it was clinical response. What is the Committee's view on the appropriateness of the primary end points used in the RCTs?
- All the RCTs identified by the Assessment Group were placebo-controlled, except UC-SUCCESS, which compared infliximab with azathioprine or with infliximab plus azathioprine. Professional groups indicated that adding on azathioprine improves the effectiveness of biological therapy. Does the Committee consider that UC-SUCCESS provides sufficient evidence on the potential benefit of combination therapy?
- No RCT evaluated the efficacy of biological therapy beyond 54 weeks after starting treatment. The Assessment Group stated that this has created the following uncertainties in the evidence base:
  - the optimal duration of treatment in patients whose disease responded
  - whether the treatment effect will be maintained beyond 54 weeks
  - whether the treatment effect will be maintained in patients whose disease responded if they stop anti-TNF-alpha therapy.

  What is the Committee's view on the long-term effects of anti-TNF-alpha therapy?

- What is the Committee's view on the evidence provided by Hyams et al. on the effectiveness of infliximab in children and adolescents?

Network meta-analysis

- For each outcome it assessed in the network meta-analysis, the Assessment Group used between 3 and 5 RCTs. However, a formal assessment of heterogeneity between trials was not done. Does the Committee consider the RCTs comparable enough to be used in a network meta-analysis?
- The Assessment Group presented results for patients who started with a clinical response, and separately for those who started in remission. Is it clinically relevant for the Committee to consider results for these 2 groups separately?
- What is the Committee's conclusion about the relative effectiveness of the biological treatments based on the network meta-analysis?

Cost-effectiveness

- The Assessment Group presented cost-effectiveness results for patients in whom colectomy is an option, and separately for patients in whom it is not. Considering that the scope includes surgery as a comparator, is it appropriate for the Committee to consider cost effectiveness in patients in whom colectomy is not an option separately? If so, how should patient eligibility for colectomy be defined?
- To model drugs received as conventional therapy, the Assessment Group assumed that in any cycle, fixed proportions of patients receive corticosteroids, aminosalicylates and drugs that affect the immune response, rather than a sequential use of these treatments. Does the Committee consider this assumption appropriate?

Utility values

- In the Assessment Group's model, health-related quality of life did not depend on whether the patient received biological or conventional therapy. Would the patient's quality of life be affected by whether or not the patient is receiving biological therapy?
- In the base case, when the Assessment Group used utility values from Woehl et al., colectomy dominated all other alternatives (that is, was cheaper and more effective). When it used utility values from Swinburn et al. in a sensitivity

analysis, colectomy was the least effective option. What is the Committee's view on the most appropriate utility values to use in the model?

- The Assessment Group assumed in the model that a fixed proportion of patients (27%) receive adalimumab 40 mg as maintenance therapy every week instead of every 2 weeks (the licensed regimen). Does the Committee consider this to be in line with the dosage of adalimumab followed in clinical practice?
- The Assessment Group stated that there was considerable uncertainty associated with the extrapolation of short-term trial data (maximum 54 weeks) to a lifetime horizon. Does the Committee consider the Assessment Group's model robust enough to form a view on the cost effectiveness of biological treatments?
- Consultees suggested that the cost of surgery has been underestimated in the Assessment Group's model. What is the Committee's view on the most appropriate costs for surgery to use in the model?
- Professional groups suggested considering separately subgroups of patients likely to respond better to treatment because this would improve cost effectiveness. Are there any patient subgroups in whom biological therapy is expected to be more cost effectiveness than the overall population?
- What is the Committee's view on the cost effectiveness of infliximab in children and adolescents?

1 Background: clinical need and practice

1.1 Ulcerative colitis is a chronic condition in which inflammation develops in the large intestine. Its exact cause is unknown although hereditary, infectious and immunological factors have been proposed as possible causes. Symptoms vary according to the extent and severity of the disease and may include bloody diarrhoea, abdominal pain, weight loss, fatigue, anaemia and an urgent need to defaecate. Some patients may also have extra-intestinal manifestations involving joints, eyes, skin and liver. Symptoms can flare up then disappear for months or even years, but approximately 50% of patients with ulcerative colitis will relapse at least once a year. Ulcerative colitis can cause complications such as inflamed and damaged bile ducts (primary sclerosing cholangitis), bowel cancer,

osteoporosis and toxic megacolon (trapped gases in the colon, causing it to swell).

1.2 Ulcerative colitis can develop at any age, but peak incidence is between 15 and 25 years of age, with a second, smaller peak between 55 and 65 years. It is estimated that approximately 128,400 people in England have ulcerative colitis. Around 80% of the people affected have mild or moderate disease and 20% have severe disease.

1.3 The modified Truelove and Witts severity index is widely used to classify the severity of ulcerative colitis: it defines mild ulcerative colitis as fewer than 4 bowel movements daily; moderate ulcerative colitis as more than 4 daily bowel movements but when the patient is not systemically ill; and severe ulcerative colitis as more than 6 bowel movements daily and when the patient is also systemically ill as shown by tachycardia, fever, anaemia or a raised erythrocyte sedimentation rate. Severe ulcerative colitis, as defined by the Truelove and Witts severity index, is potentially life threatening and normally requires hospitalisation and emergency care. This is aligned with the UK definition of 'acute severe ulcerative colitis'. Ulcerative colitis: Management in adults, children and young people (NICE clinical guideline 166) 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. This appraisal includes moderately to severely active ulcerative colitis but not acute severe ulcerative colitis (that is, severe ulcerative colitis according to the Truelove and Witts severity index). Recommendations for the treatment of acute severe ulcerative colitis can be found in NICE clinical guideline 166 and Infliximab for acute exacerbations of ulcerative colitis (NICE technology appraisal guidance 163).

1.4 There is no cure for ulcerative colitis. Treatment aims to relieve symptoms during a flare-up and then maintain remission. The management of mildly

to moderately active ulcerative colitis involves treatment with oral or topical aminosalicylates (sulfasalazine, mesalazine, balsalazide or olsalazine), or corticosteroids when aminosalicylates are contraindicated or not tolerated. Oral corticosteroids or drugs that affect the immune response can also be added on if the disease does not respond to aminosalicylates. NICE does not recommend infliximab for treating 'subacute' manifestations of moderately to severely active ulcerative colitis in Infliximab for subacute manifestations of ulcerative colitis (NICE technology appraisal guidance 140). NICE was unable to appraise adalimumab for treating moderately to severely active ulcerative colitis in Adalimumab for the treatment of moderate to severe ulcerative colitis (NICE technology appraisal guidance 262) because the company did not make an evidence submission. Colectomy is a treatment option if symptoms are inadequately controlled or the patient has a poor quality of life on conventional therapy.

2 The technologies

2.1 Adalimumab (Humira, AbbVie), golimumab (Simponi, Merck Sharp & Dohme) and infliximab (Remicade, Merck Sharp & Dohme) are monoclonal antibodies that inhibit the pro-inflammatory cytokine, TNF-alpha. All 3 have the same marketing authorisation in the UK for the 'treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine or azathioprine, or who are intolerant to or have medical contraindications for such therapies'. Infliximab is also indicated for the 'treatment of severely active ulcerative colitis, in children and adolescents aged 6 to 17 years, who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine or azathioprine, or who are intolerant to or have medical contraindications for such therapies'.

Adalimumab

2.2 Adalimumab is administered by subcutaneous injection. The recommended induction dose regimen is 160 mg at week 0 and 80 mg at week 2. After induction treatment, the recommended dose is 40 mg every other week. The summary of product characteristics recommends that therapy should be stopped in patients whose disease failed to respond to adalimumab within 2 to 8 weeks after starting treatment.

2.3 The summary of product characteristics lists the following adverse reactions for adalimumab: infections (such as nasopharyngitis, upper respiratory tract infection and sinusitis), injection site reactions (erythema, itching, haemorrhage, pain or swelling), headache, musculoskeletal pain, sepsis, opportunistic infections, tuberculosis, hepatitis B reactivation, various malignancies and serious haematological, neurological and autoimmune reactions. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.4 The price of adalimumab is £352.14 for a 40 mg pre-filled pen or pre-filled syringe, or a 40 mg/0.8-mL vial (excluding VAT; 'British National Formulary' [BNF] edition 67). The average cost of a course of treatment with adalimumab is estimated at £4622, assuming the recommended dosage for adalimumab is followed (see section 2.2) and the patient receives 8 weeks of induction therapy followed by 26 weeks of maintenance therapy. Costs may vary in different settings because of negotiated procurement discounts.

Golimumab

2.5 Golimumab is administered by subcutaneous injection. The dose regimen of golimumab depends on the patient's body weight. For patients with a body weight less than 80 kg, golimumab is licensed at an initial dose of 200 mg, followed by 100 mg at week 2, then 50 mg every 4 weeks thereafter. For patients with a body weight of 80 kg or more, it is licensed at an initial dose of 200 mg, followed by 100 mg at week 2, then 100 mg

every 4 weeks thereafter. The summary of product characteristics recommends that golimumab therapy should be reconsidered in patients who do not benefit within 12 to 14 weeks after starting treatment (that is, after 4 doses).

2.6 The summary of product characteristics lists the following adverse reactions for golimumab: upper respiratory tract infection and other serious infections (including sepsis, pneumonia, tuberculosis, invasive fungal and opportunistic infections), demyelinating disorders, lymphoma, hepatitis B reactivation, congestive heart failure, autoimmune processes (lupus-like syndrome) and haematologic reactions. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.7 The price of golimumab is £762.97 for a 50 mg pre-filled pen or pre-filled syringe and £1525.94 for a 100 mg pre-filled pen (excluding VAT; BNF edition 67). Based on the list price, the average cost of a course of treatment with golimumab is estimated at £9554 for patients with a body weight less than 80 kg and £14,530 for patients with a body weight of 80 kg or more. This assumes the recommended dosage for golimumab is followed (see section 2.5) and the patient receives 8 weeks of induction therapy followed by 26 weeks of maintenance therapy. Merck Sharp & Dohme has agreed a patient access scheme with the Department of Health. This will make the 100 mg dose of golimumab available to the NHS at the same cost as the 50 mg dose. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

Infliximab

2.8 Infliximab is administered by intravenous infusion. For both the adult and paediatric populations, the recommended dosage of infliximab is 5 mg/kg followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. The summary of product

characteristics recommends that continued infliximab therapy should be carefully reconsidered in adults who do not benefit within 14 weeks after starting treatment, and in children and adolescents aged 6 to 17 years who do not benefit within 8 weeks.

2.9 The summary of product characteristics lists the following adverse reactions for infliximab: upper respiratory tract infection, hepatitis B reactivation, congestive heart failure, serious infections (including sepsis, opportunistic infections and tuberculosis), serum sickness (delayed hypersensitivity reactions), haematologic reactions, systemic lupus erthematosus/lupus-like syndrome, demyelinating disorders, hepatobiliary events, lymphoma, hepatosplenic T-cell lymphoma, and serious infusion reactions. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.10 The price of infliximab is £419.62 for a 100 mg vial containing powder for reconstitution (excluding VAT; BNF edition 67). The average cost of a course of treatment with infliximab is estimated at £10,509 (excluding administration costs), assuming the patient weights 77 kg, the recommended dosage for infliximab is followed (see section 2.8), and the patient receives 8 weeks of induction therapy followed by 26 weeks of maintenance therapy. Costs may vary in different settings because of negotiated procurement discounts.

2.11 Biosimilar versions of infliximab (Inflectra, Hospira; Remsima, Celltrion) have a marketing authorisation in the UK for the same indications. The therapeutic indications, dosage and method of administration for Remisima and Inflectra are identical to those for infliximab. Adverse reactions are similar too. Both Inflectra and Remsima did not have an approved list price in the UK at the time of the appraisal.

Table 1 Summary description of technologies

Non-proprietary name	Adalimumab	Golimumab	Infliximab (biosimilars)

Proprietary name	Humira	Simponi	Remicade (Inflectra and Remisima)
Company	AbbVie	Merck Sharp & Dohme	Merck Sharp & Dohme (Hospira and Celltrion Healthcare)
Dose	160 mg at week 0, 80 mg at week 2 (induction), then 40 mg every other week thereafter (maintenance)	For body weight less than 80 kg: initial dose of 200 mg, followed by 100 mg at week 2, then 50 mg every 4 weeks thereafter For body weight of 80 kg or more: initial dose of 200 mg, followed by 100 mg at week 2, then 100 mg every 4 weeks thereafter	5 mg/kg followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter (for both the adult and paediatric populations)
Acquisition cost (BNF edition 67)	£352.14 for a 40 mg pre-filled pen or pre-filled syringe, or a 40 mg/0.8-mL vial	£762.97 for a 50 mg pre-filled pen or pre-filled syringe; £1525.94 for a 100 mg pre-filled pen	Remicade: £419.62 for a 100 mg vial Biosimilars of infliximab did not have an acquisition cost in the UK at the time of the appraisal

3 Remit and decision problem(s)

3.1 The remit from the Department of Health for this appraisal was: To appraise the clinical and cost effectiveness of infliximab, adalimumab and golimumab within their licensed indications for treating moderately to severely active ulcerative colitis.

	Final scope issued by NICE	**Additional comments or specifications in the Assessment Group's protocol**

Population	People with moderately to severely active ulcerative colitis whose disease has responded inadequately to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who are intolerant of or have medical contraindications to such therapies.	The Assessment Group addressed 2 subpopulations of people with ulcerative colitis whose disease has responded inadequately to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who are intolerant of or have medical contraindications to such therapies: • Adults aged 18 years and over with **moderately to severely active** ulcerative colitis • Children and adolescents aged 6 to 17 years (inclusive) with **severely active** ulcerative colitis
Intervention	For adults: • adalimumab • infliximab • golimumab For children and adolescents: • infliximab	Biosimilar versions of infliximab (Remsima, Celltrion Healthcare; Inflectra, Hospira) are licensed for the same indications and form part of the clinical evidence base for infliximab. Because biosimilars did not have a list price in the UK at the time of the appraisal, their cost effectiveness could not be established.
Comparators	Adalimumab, infliximab and golimumab should be compared with each other and with standard clinical management which may include a combination of aminosalicylates (sulfasalazine, mesalazine, balsalazide or olsalazine), corticosteroids (beclomethasone, budesonide, hydrocortisone or prednisolone), and thiopurines (mercaptopurine or azathioprine), calcineurin inhibitors and surgical intervention.	Surgical intervention refers to elective not emergency surgery because emergency surgery is an option only for acute severe ulcerative colitis, which is not included in this appraisal.

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 • adverse effects of treatment (including leakage and infections following surgery) • health-related quality of life	All these outcomes were addressed by the included clinical trial evidence, except rates of relapse.

4 Clinical-effectiveness evidence

Adult population

4.1 The Assessment Group conducted a systematic review and identified 9 relevant randomised controlled trials (RCTs) in adults: ULTRA1, ULTRA2 and Suzuki et al. for adalimumab; PURSUIT-SC and PURSUIT-Maintenance for golimumab; and ACT1, ACT2, Probert et al. and UC-SUCCESS for infliximab (Table 1). All the RCTs were multicentre, double-blind trials that were conducted worldwide (except Suzuki et al. which was conducted in Japan only). Apart from UC-SUCCESS which compared infliximab with azathioprine or infliximab plus azathioprine, all the trials compared adalimumab, golimumab or infliximab with placebo. Of the 9 trials identified by the Assessment Group, 4 followed up patients in open-label extension studies. Because no head-to-head evidence was available from RCTs for adalimumab, golimumab or infliximab, the Assessment Group performed a network meta-analysis using the placebo-controlled RCTs for each treatment (that is, an analysis combining direct and indirect evidence for particular pairwise comparisons).

Table 1 Overview of the clinical evidence for the adult population

Technology	Trial	Treatment groups
Adalimumab	**ULTRA1** (n=390) Extension study: ULTRA3	• Adalimumab 160 mg at week 0; 80 mg at week 2; 40 mg at weeks 4 and 6 (n=130) • Adalimumab 80 mg at week 0; 40 mg at weeks 2, 4 and 6[1] (n=130) • Placebo (n=130)
	ULTRA2 (n=494) Extension study: ULTRA3	• Adalimumab 160 mg at week 0; 80 mg at week 2; 40 mg at week 4 then every other week (n=248) • Placebo (n=246)
	Suzuki et al. (n=274) Conducted in Japan only	• Adalimumab 160 mg at week 0; 80 mg at week 2; 40 mg every other week (n=90) • Adalimumab 80 mg at week 0; 40 mg every other week[1] (n=87) • Placebo (n=96)
Golimumab	**PURSUIT-SC** (n=1065) Integrated double-blind phase 2 dose-finding and phase 3 dose confirmation trials	• Golimumab 100 mg then 50mg (phase 2 only) 2 weeks later[1] (n=72) • Golimumab 200 mg then 100 mg 2 weeks later (n= 331) • Golimumab 400 mg then 200 mg 2 weeks later[1] (n=331) • Placebo (n=331)
	PURSUIT-Maintenance (n=464) Re-randomised patients whose disease responded to golimumab induction therapy in 2 earlier trials	• Golimumab 50 mg every 4 weeks (n=154) • Golimumab 100 mg every 4 weeks (n=154) • Placebo (n=156)
Infliximab	**ACT1** (n=243) Extension study: ACT1 extension study	• Infliximab 5 mg/kg at weeks 0, 2, and 6, then every 8 weeks through week 46 (n=121) • Infliximab 10 mg/kg at weeks 0, 2, and 6, then every 8 weeks through week 46[1] (n=122) • Placebo (n=121)
	ACT2 (n=241) Extension study: ACT2 extension study	• Infliximab 5 mg/kg at weeks 0, 2, and 6, then every 8 weeks through week 22 (n=121) • Infliximab 10 mg/kg at weeks 0, 2, and 6, then every 8 weeks through week 22[1] (n=120) • Placebo (n=123)
	Probert et al. (n=43)	• Infliximab 5 mg/kg at weeks 0 and 2

	Conducted in 4 centres in the UK and Germany	(n=23) • Placebo (n=20)
	UC-SUCCESS (n=239)	• Infliximab 5 mg/kg at weeks 0, 2, 6 and 14 plus placebo orally (n=79) • Azathioprine 2.5 mg/kg daily plus placebo intravenously (n=80) • Infliximab 5 mg/kg at weeks 0, 2, 6 and 14 plus azathioprine 2.5 mg/kg daily (n=80)
[1] Unlicensed dose		

4.2 All the trials except Probert et al. used the Mayo score to assess the eligibility of patients. The Mayo score assesses 4 outcomes – stool frequency, rectal bleeding, endoscopic findings and physician's global assessment – on a scale of 0 to 12, with the score increasing with disease severity (for further details, see pages 11–12 of the assessment report). In all the trials, patients were eligible if they had a Mayo score of 6–12 (with evidence of endoscopic disease), which represents moderate to severe disease. Probert et al. used instead the ulcerative colitis symptom score, but the Assessment Group considered this to be equivalent to the Mayo score. Conventional therapies patients had to have received varied across the trials but generally included corticosteroids, aminosalicylates and/or a drug that affects the immune response. Only in ULTRA2 were patients allowed to have received a previous anti-TNF-alpha agent (40% of patients had received one). Patients were excluded from the trials if they had any of the following: ulcerative colitis that is limited to the rectum (ulcerative proctitis), a history of or a risk of having bowel surgery, diseases of the central nervous system, previous serious infection or deficient immune system, previous cancer, or signs of abnormal growth of cells (dysplasia).

4.3 Among patients in the included RCTs, the average age ranged from 37 to 42.5 years, 41% to 73% were male and the average duration of disease was 4.9 to 8.5 years. Mayo scores at baseline were consistent across trials and ranged from 8.1 to 8.9. Adalimumab, golimumab and infliximab

are licensed for patients whose disease has had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine or azathioprine, or who are intolerant to or have medical contraindications for such therapies. The Assessment Group noted, however, that none of trials included patients who had received corticosteroids, and 6-mercaptopurine or azathioprine. Specifically, UC-SUCCESS included patients if they had not received azathioprine either at all or within the 3 months that preceded randomisation, which led some patients (90%) who had never received azathioprine to participate. In addition, Suzuki et al. included Japanese patients aged 15 years or older, but the Assessment Group considered it appropriate to use this trial for the adult population because the average age of patients in each treatment group was 41.3 and 42.5 years.

4.4 The primary end point in the RCTs was clinical response or remission at pre-specified time points (Table 2). Of the 9 trials in adults, 8 assessed how well the treatment induced clinical response or remission, and 6 assessed how well it maintained it (5 trials assessed both). To assess clinical response or remission, all trials except Probert et al. used the Mayo score, which the Assessment Group considered to be applied consistently in the individual trials (Probert et al. used the ulcerative colitis symptom score). Apart from UC-SUCCESS, all the trials that used the Mayo score defined clinical response as:

- a decrease in Mayo score at baseline of at least 3 points and at least 30%, and
- a decrease in the rectal bleeding sub-score of at least 1 point, or having an absolute rectal bleeding sub-score of 0 or 1.

The definition of remission was also the same across all RCTs except UC-SUCCESS: Mayo score of 2 or less, with no individual sub-score greater than 1. UC-SUCCESS differed in that it neither required a decrease in the

rectal bleeding sub-score to record clinical response nor individual sub-scores of 1 or less to record remission.

Table 2 Assessment of end points in the RCTs for the adult population

Technology	Trial	Primary end point	Week at which induction was assessed	Weeks at which maintenance was assessed
Adalimumab	ULTRA1	Remission	8	Not assessed
	ULTRA2	Remission	8	32 and 52
	Suzuki et al.	Not reported	8	32 and 52
Golimumab	PURSUIT-SC	Clinical response (phase III trial)	6	Not assessed
	PURSUIT-Maintenance	Clinical response	Not assessed	30 and 54
Infliximab	ACT1	Clinical response	8	30 and 54
	ACT2	Clinical response	8	30
	Probert et al.	Remission	6	Not assessed
	UC-SUCCESS	Corticosteroid-free remission	8	16

Adalimumab

4.5 In ULTRA1, 18.5% of patients who received adalimumab 160 mg at week 0 and 80 mg at week 2 (the licensed dose) were in remission at week 8 compared with 9.2% of those who received placebo, a result that was statistically significant (p=0.031). A higher proportion of patients in the adalimumab group had a clinical response (54.6% versus 44.6%), but the difference was not statistically significant. In ULTRA2, the rate of remission was higher in patients treated with adalimumab than in those treated with placebo both at week 8 (16.5% versus 9.3%; p=0.019) and week 52 (17.3% versus 8.5%; p=0.004). The difference at both time points was statistically significant. Of patients who were in remission at week 8, 8.5% and 4.1% receiving adalimumab or placebo, respectively, remained in remission at week 52 (p=0.047). The open-label extension study ULTRA3 showed that patients generally continued to benefit from adalimumab therapy up to week 60, although 23% of the patients did not benefit and stopped treatment.

4.6 The incidence of adverse events with adalimumab and placebo was similar in ULTRA1 (50.2% versus 48.4%) and ULTRA2 (82.9% versus 83.8%). The most frequently reported adverse event in both RCTs was colitis ulcerative (ULTRA1: adalimumab 5.8%, placebo 9.4%; ULTRA2: adalimumab 22.6%, placebo 29.2%). The difference in the incidence of adverse events between the adalimumab and placebo groups was statistically significant only for iron deficiency anaemia, gastroenteritis, and nasopharyngitis, although the incidence was higher with adalimumab for all adverse events. Infections (mostly nasopharyngitis and upper respiratory tract infections) occurred in 14.3% and 45.1% of patients who received adalimumab in ULTRA1 and ULTRA2 respectively. Most of the adverse events were mild or moderate in severity. In ULTRA2, more patients randomised to placebo stopped treatment because of an adverse event (13.1%) than did patients randomised to adalimumab (8.9%).

4.7 ULTRA1, ULTRA2 and ULTRA3 reported health-related quality of life data measured using Inflammatory Bowel Disease Questionnaire (IBDQ) or Short Form-36 (SF-36) for adalimumab (IBDQ scores range from 32 [poor health] to 224 [perfect health]). In ULTRA1, changes from baseline scores on IBDQ and SF-36 at week 8 were similar in the adalimumab (160 mg at week 0 and 80 mg at week 2) and placebo groups. In ULTRA2, however, IBDQ scores at week 52 were higher in the adalimumab group (27 versus 19; $p<0.05$).

4.8 In Suzuki et al., patients were randomised to 3 treatment groups including placebo. Results were reported at 8 weeks and 52 weeks, but the 2 adalimumab groups (one licensed dose and the other unlicensed) were combined for the analysis at 52 weeks. At week 8, remission rates were similar among treatment groups, but more patients treated with adalimumab 160 mg at week 0 and 80 mg at week 2 (the licensed dose) had a clinical response than patients treated with placebo (50% versus 35%; $p=0.044$). At week 52, more patients receiving adalimumab as maintenance therapy had a clinical response (18% versus 31%; $p=0.021$)

and remission (7% versus 23%; p=0.001) than did patients receiving placebo.

Golimumab

4.9 PURSUIT-SC integrated a double-blind phase 2 dose-finding trial and a phase 3 dose confirmation trial in a study of 1064 patients with ulcerative colitis. In the phase III study, rates of clinical response at week 6 were 51.0% among patients given golimumab 200 mg then golimumab 100 mg (the licensed dose), and 30.3% among those given placebo, with a difference that was statistically significant (p<0.0001). That golimumab group was also associated with a statistically significant higher rate of remission than the placebo group (17.8% versus 6.4%; p<0.0001). Health-related quality of life data were available from the phase III trial of PURSUIT-SC; patients receiving golimumab (200 mg then 100 mg) reported a greater change in IBDQ scores from baseline to week 6 than did patients receiving placebo (27.0 versus 14.8, p<0.0001).

4.10 PURSUIT-Maintenance included patients whose disease responded to golimumab induction therapy in 2 previous golimumab trials (including PURSUIT-SC). Patients were randomised to golimumab 50 mg, golimumab 100 mg or placebo. Clinical response was maintained through week 54 in 47.0% of patients who received 50 mg golimumab, 49.7% of patients who received 100 mg golimumab and 31.2% of patients who received placebo (p=0.010 and p<0.001 respectively). The proportion of patients who were in remission at both weeks 30 and 54 was higher in the golimumab 100 mg group (27.8%) and the golimumab 50 mg group (23.2%) than in the placebo group (15.6%; p=0.004 and p=0.122 respectively), although the difference between golimumab 50 mg and placebo was not statistically significant. Because PURSUIT-Maintenance re-randomised patients whose disease had responded to golimumab induction therapy in 2 earlier trials, the Assessment Group indicated that the results of PURSUIT-Maintenance may be biased.

4.11 In PURSUIT-Maintenance, the number of adverse events was similar in the golimumab 50 mg and 100 mg groups. However, the rate at which patients had serious adverse events or stopped treatment because of an adverse event was higher in the 100 mg group. Among patients receiving golimumab 50 mg, 8.4% had a serious adverse event and 5.2% stopped treatment because of an adverse event, compared with 14.3% and 9.1% respectively for patients receiving golimumab 100 mg (most patients who stopped treatment did so because their disease got worse). Infections in PURSUIT-Maintenance were more common in the golimumab 50 mg and 100 mg groups (39.0% in both) than in the placebo group (28.2%).

Infliximab

4.12 Of the patients who received infliximab 5 mg (the licensed dose) in ACT1, 69% had a clinical response at week 8 compared with 37% of those who received placebo ($p<0.001$). In ACT2, 64% of patients who received infliximab 5 mg had a clinical response at week 8 compared with 29 % of patients who received placebo ($p<0.001$). In both ACT1 and ACT2, patients who received infliximab were more likely to have a clinical response at week 30 than patients who received placebo ($p\leq0.002$ in both studies). In ACT1, more patients who received infliximab 5 mg had a clinical response at week 54 (45%) than did patients who received placebo (20%; $p<0.001$). A statistically significant improvement in quality of life was reported in the infliximab group compared with the placebo group.

4.13 In ACT1 and ACT2, similar proportions of patients in the infliximab and placebo groups had an adverse event. However, more adverse events occurred among patients receiving infliximab in ACT1 than among those receiving it in ACT 2 (87.6% versus 81.8%). The most common adverse event in ACT1 was worsening of ulcerative colitis (infliximab 19.0%, placebo 33.1%), whereas in ACT2 it was headache (infliximab 15.7%, placebo 14.6%). There were more serious adverse events reported by patients receiving placebo in both RCTs (ACT1: infliximab 21.5%, placebo

26.4%; ACT2: infliximab 10.7%, placebo 19.5%). More patients randomised to placebo stopped treatment because of an adverse event than those randomised to infliximab in both ACT1 and ACT2. The incidence of infections was higher with infliximab than with placebo in ACT1 (43.8%% versus 38.8%) and ACT2 (27.3% versus 23.6%).

4.14 Probert et al. reported remission rates (ulcerative colitis symptom score less than 2) of 39% in the infliximab group and 30% in the placebo group at week 6, a difference of 9% (95% confidence interval [CI] −19% to 34%; p=0.76). At that time, health-related quality of life measured using IBDQ and EQ-5D improved more with infliximab than with placebo (p-value not reported). In UC-SUCCESS, a greater proportion of patients who received infliximab plus azathioprine were in steroid-free remission at week 16 (39.7%) than patients who received infliximab alone (22.1%; p=0.017) or azathioprine alone (23.7%; p=0.813). The greatest changes in IBDQ and SF-36 scores from baseline were for infliximab plus azathioprine (for both IBDQ and SF-36 score changes, p<0.05 versus azathioprine alone or versus infliximab alone).

4.15 Inflectra and Remsima are biosimilar products to infliximab that were developed as single product, CT-P13, which was evaluated against Remicade (the reference proprietary product) in 2 RCTs:

- PLANET AS: a phase I trial comparing the pharmacokinetics, efficacy and safety of CT-P13 and Remicade in patients with ankylosing spondylitis (n=250).
- PLANET RA: a phase III trial comparing the efficacy and safety of CT-P13 and Remicade in patients with rheumatoid arthritis whose disease had an inadequate response to methotrexate (n=606).

The objective of these trials was to demonstrate that CT-P13 was similar to the reference product. In PLANET AS, the pharmacokinetic profiles of CT-P13 and Remicade were considered to be comparable after 5 doses. PLANET RA reached its primary end point because the 95% CI for the

difference in the American College of Rheumatology 20% response rate at week 30 was contained within the pre-defined equivalence margin (±15%) in both the intention-to-treat (2%, 95% CI −6% to 10%0) and per-protocol (4%, 95% CI −4% to 12%) populations. The European Public Assessment Reports (EPARs) for Inflectra and Remsima acknowledged that the pharmacokinetics, efficacy, safety, and immunogenicity profiles of CT-P13 were similar to those of Remicade in PLANET AS and PLANET RA. Although neither of the trials was for ulcerative colitis, the EPAR states that the totality of the data comparing CT-P13 with Remicade allows for the extrapolation of the evidence generated by PLANET AS and PLANET RA to all other indications of Remicade.

Subgroups

4.16 The scope states that if evidence allows subgroup analysis of patients based on duration of disease will be considered. Only ULTRA2 and PURSUIT-Maintenance reported outcomes by duration of disease. In ULTRA2, disease duration did not predict remission at week 8. However, at week 52, patients who received adalimumab were more likely to be in remission relative to those who received placebo if they had had their disease for longer than 2 years (odds ratio [OR] 3.59, 95% CI 1.9 to 6.9) than if they had had it for 2 years or less (OR 0.22, 95% CI 0.04 to 1.1). In PURSUIT-Maintenance, golimumab 50 mg was more likely to maintain clinical response relative to placebo among patients with disease durations of 5 to 15 years (OR 2.3, 95% CI 1.0 to 5.4) than among those with disease durations of 5 years or less (OR 1.4, 95% CI 0.9 to 2.7). Patients who received golimumab 100 mg were also more likely to have a clinical response if they had a longer duration of disease (>5 to ≤15 years: OR 2.2, 95% CI 1.0 to 4.9; ≤5 years: OR 1.6 95% CI 0.8 to 3.1).

Network meta-analysis

4.17 Because no RCTs compared adalimumab, golimumab or infliximab directly with each other, the Assessment Group performed a network meta-analysis using the placebo-controlled RCTs for each intervention.

RCTs were eligible for inclusion if they reported data on both clinical response and remission at either an induction (6–8 weeks) or maintenance (30 or 52 weeks) time point. Although Probert et al. and UC-SUCCESS provided this, the Assessment Group did not use them because the definitions of clinical response and remission in Probert et al. differed from the other trials and most patients in UC-SUCCESS had not received azathioprine. ULTRA2 was the only trial to include both patients who had previously received and who had not received an anti-TNF-alpha agent. For its base case, the Assessment Group used the data relating only to patients who had not received anti-TNF-alpha. It also excluded Suzuki et al. from the base case because Suzuki et al. was conducted in Japanese patients only. However, the Assessment Group did 3 sensitivity analyses: firstly using data for the overall population in ULTRA2 (patients who had received and those who had not received an anti-TNF-alpha agent), secondly including Suzuki et al., and thirdly combining these 2 together.

4.18 For the base case and each of the sensitivity analyses, the Assessment Group compared the effects of adalimumab, golimumab, and infliximab with respect to each of the following:

- induction of clinical response or remission at week 8
- maintenance of clinical response or remission at **week 32** for patients starting with a **clinical response** at **week 8**
- maintenance of clinical response or remission at **week 32** for patients starting in **remission** at **week 8**
- maintenance of clinical response or remission at **week 52** for patients starting with a **clinical response** at **week 32**
- maintenance of clinical response or remission at **week 52** for patients starting in **remission** at **week 32**.

The Assessment Group used between 3 and 5 RCTs to perform the network meta-analysis for each of the above-listed outcomes, noting mild

to moderate heterogeneity between individual study results in all the analyses. For each outcome, the Assessment Group reported:

- the effect of each treatment compared with placebo and with the other treatments on the probit scale (where negative values indicate that the intervention is more effective than the comparator) together with credible intervals (CrI)
- the probability of each treatment being ranked the best, second-best, third-best and so on
- the probability of the disease being active, responding and remitting at the end of therapy (week 8 for induction and week 32 or 52 for maintenance) with each treatment.

4.19 In the Assessment Group's base case, all treatments had a statistically significant favourable effect relative to placebo when assessed for induction therapy (Table 3). The greatest effect on inducing clinical response or remission was associated with infliximab (effect versus placebo −0.92, 95% CrI −1.27 to −0.56), which had a 93% probability of being the best treatment for that outcome. The probability of the disease remaining active, responding or remitting after 8 weeks of infliximab therapy was 29%, 35% and 36% respectively.

Table 3 Base-case results of the network meta-analysis: induction phase

	Effect on the probit scale (CrI)		
	Versus placebo	*Versus adalimumab*	*Versus Golimumab*
Adalimumab	−0.40 (−0.76 to −0.04)	-	-
Golimumab	−0.49 (−0.97 to −0.01)	−0.10 (−0.69 to 0.50)	-
Infliximab	−0.92 (−1.27 to −0.56)	−0.52 (−1.03 to 0.00)	−0.42 (−1.00 to 0.17)

Adapted from figure 14 on page 95 of the assessment report

4.20 For the maintenance of clinical response or remission (Table 4), golimumab 100 mg had the greatest effect at week 32 in patients who started with a clinical response at week 8 (effect versus placebo −0.42, 95% CrI −1.06 to 0.21), while golimumab 50 mg had the greatest effect in those who started in remission (effect versus placebo −0.63, 95% CrI

−1.36 to 0.11). However, neither of these effects was statistically significant. At week 52, infliximab had the greatest effect in patients who started with a clinical response at week 32 (effect versus placebo −0.36, 95% CrI −1.33 to 0.62), while adalimumab had the greatest effect in those who started in remission (effect versus placebo −1.04, 95% CrI −1.93 to −0.12). Only the effect of adalimumab was statistically significant.

Table 4 Base-case results of the network meta-analysis: maintenance phase

Effect on the probit scale (CrI)	Maintenance at **week 32** for patients starting with a **response** at **week 8**	Maintenance at **week 32** for patients starting in **remission** at **week 8**	Maintenance at **week 52** for patients starting with a **response** at **week 32**	Maintenance at **week 52** for patients starting in **remission** at **week 32**
Versus placebo				
Adalimumab	−0.03 (−0.76 to 0.68)	0.19 (−0.75 to 1.09)	0.31 (−0.58 to 1.27)	**−1.04** (−1.93 to −0.12)
Golimumab 50 mg	−0.31 (−0.97 to 0.30)	**−0.63** (−1.36 to 0.11)	−0.17 (−1.01 to 0.69)	0.05 (−0.80 to 0.89)
Golimumab 100 mg	**−0.42** (−1.06 to 0.21)	−0.61 (−1.32 to 0.11)	0.20 (−0.63 to 1.03)	−0.16 (−1.00 to 0.69)
Infliximab	−0.24 (−0.78 to 0.29)	−0.11 (−0.78 to 0.56)	**−0.36** (−1.33 to 0.62)	−0.24 (−1.21 to 0.75)
Versus adalimumab				
Golimumab 50 mg	−0.29 (−1.24 to 0.67)	−0.82 (−1.96 to 0.39)	−0.49 (−1.77 to 0.77)	1.08 (−0.18 to 2.31)
Golimumab 100 mg	−0.38 (−1.36 to 0.59)	−0.79 (−1.96 to 0.42)	−0.12 (−1.36 to 1.11)	0.87 (−0.38 to 2.11)
Infliximab	−0.20 (−1.09 to 0.69)	−0.29 (−1.41 to 0.85)	−0.67 (−2.04 to 0.66)	0.78 (−0.53 to 2.14)
Versus golimumab 50 mg				
Golimumab 100 mg	−0.10 (−0.72 to 0.55)	0.02 (−0.69 to 0.75)	0.38 (−0.47 to 1.20)	−0.20 (−1.01 to 0.61)
Infliximab	0.07 (−0.75 to 0.91)	0.52 (−0.46 to 1.49)	−0.18 (−1.51 to 1.10)	−0.29 (−1.57 to 1.02)
Versus golimumab 100 mg				
Infliximab	0.18 (−0.68 to 1.01)	0.51 (−0.48 to 1.45)	−0.56 (1.85 to 0.73)	−0.08 (−1.37 to 1.24)

Adapted from the assessment report

4.21 In the maintenance phase, the probability of the treatment associated with the greatest effect being the best treatment to maintain clinical response or remission ranged from 47% to 84% (Table 5). The probability of the disease responding or remitting after maintenance therapy with the best treatment ranged from 63% to 92%.

Table 5 Probability of being best treatment and of ending in each health state at the end of therapy: maintenance phase

Outcome	**Best treatment**	**Probability being best treatment**	**Probability ending**		
			Having no response	Having a response	Being in remission
Maintenance at **week 32** for patients starting with a **response** at **week 8**	Golimumab 100 mg	47%	37%	29%	35%
Maintenance at **week 32** for patients starting in **remission** at **week 8**	Golimumab 50 mg	47%	18%	14%	69%
Maintenance at **week 52** for patients starting with a **response** at **week 32**	Infliximab	56%	25%	34%	41%
Maintenance at **week 52** for patients starting in **remission** at **week 32**	Adalimumab	84%	8%	8%	83%

Adapted from the assessment report

4.22 In all 3 sensitivity analyses, infliximab had the greatest effect on inducing clinical response or remission (effect versus placebo ranged from −0.91 to −0.92), with a 94%–97% probability of being the best treatment for that outcome. The probability of the disease responding or remitting after 8 weeks of infliximab therapy was between 70% and 71%. For maintenance therapy, the best treatment for each outcome remained the same as in the base case in all sensitivity analyses (Table 6).

Table 6 Results of the sensitivity analyses: maintenance phase

	Maintenance at **week 32** for patients starting with a **response** at **week 8**	Maintenance at **week 32** for patients starting in **remission** at **week 8**	Maintenance at **week 52** for patients starting with a **response** at **week 32**	Maintenance at **week 52** for patients starting in **remission** at **week 32**
Base case				
Best treatment (probability)	Golimumab 100 mg (47%)	Golimumab 50 mg (47%)	Infliximab (56%)	Adalimumab (84%)
Effect vs. placebo (CrI)	−0.42 (−1.06 to 0.21)	−0.63 (−1.36 to 0.11)	−0.36 (−1.33 to 0.62)	−1.04 (−1.93 to −0.12)
Probability ending with active, responding or remitting disease	37%, 29%, 35%	18%, 14%, 69%	25%, 34%, 41%	8%, 8%, 83%
Sensitivity analysis 1 (using data for the overall population in ULTRA2)				
Best treatment (probability)	Golimumab 100 mg (43%)	Golimumab 50 mg (44%)	Infliximab (52%)	Adalimumab (78%)
Effect vs. placebo (CrI)	−0.41 (−1.06 to 0.22)	−0.62 (−1.36 to 0.11)	−0.37 (−1.30 to 0.59)	−0.86 (−1.71 to 0.00)
Probability having active, responding or remitting disease	39%, 29%, 32%	20%, 14%, 65%	25%, 34%, 41%	10%, 10%, 80%
Sensitivity analysis 2 (including Suzuki et al.)				
Best treatment (probability)	Golimumab 100 mg (44%)	Golimumab 50 mg (46%)	Infliximab (57%)	Adalimumab (84%)
Effect vs. placebo (CrI)	−0.43 (−1.03 to 0.19)	−0.61 (−1.30 to 0.09)	−0.36 (−1.29 to 0.58)	−0.93 (−1.59 to −0.25)
Probability having active, responding or remitting disease	36%, 29%, 35%	18%, 14%, 68%	23%, 35%, 42%	9%, 11%, 80%
Sensitivity analysis 3 (sensitivity analyses '1' and '2' together)				
Best treatment (probability)	Golimumab 100 mg (40%)	Golimumab 50 mg (46%)	Infliximab (55%)	Adalimumab (80%)
Effect vs. placebo (CrI)	−0.41 (−1.00 to 0.17)	−0.62 (−1.33 to 0.06)	−0.38 (−1.27 to 0.55)	−0.85 (−1.49 to −0.16)
Probability having active, responding or remitting disease	39%, 29%, 32%	20%, 15%, 65%	24%, 36%, 40%	10%, 12%, 78%

Adapted from the assessment report

Children and adolescents population

4.23 The Assessment Group identified 1 open-label RCT in children and adolescents, Hyams et al., which evaluated infliximab as maintenance therapy. Patients initially received 5 mg/kg infliximab induction therapy at weeks 0, 2 and 6; patients whose disease responded were then randomised to one of 2 infliximab maintenance groups: infliximab 5 mg/kg every 8 weeks (n=22) or infliximab 5 mg/kg every 12 weeks (n=23). Eligible patients were 6 to 17 years old, had moderately to severely active ulcerative colitis defined as a Mayo score of 6–12 (with evidence of endoscopic disease), and had received at least 1 conventional therapy (aminosalicylates, drugs that affect the immune response [6-mercaptopurine or azathioprine] or corticosteroids). The primary end point was clinical response assessed at week 8 for induction therapy (before randomisation) and week 54 for maintenance therapy. Remission was a secondary end point that was defined as a Paediatric Ulcerative Colitis Activity Index (PUCAI) score less than 10 (a PUCAI score of 65 or more reflects severe disease; for a description of the PUCAI, see pages 12–13 of the assessment report). Although infliximab is licensed in children and adolescents for treating severely active ulcerative colitis only, the Assessment Group included Hyams et al. despite it being for moderately to severely active disease. This was because the Assessment Group did not identify placebo-controlled or head-to-head RCTs against other active treatments for infliximab in children and adolescents.

4.24 At week 8, 73.3% (44/60) of patients had a clinical response and 40.0% (24/60) were in remission. Of those who had a response, a greater proportion of patients who then received infliximab 5mg/kg every 8 weeks were in PUCAI remission at week 54 than patients who received infliximab 5mg/kg every 12 weeks (38.1% versus 18.2%; p-values not reported). In addition, 38.5% and 0.0% of patients who received infliximab every 8 weeks or every 12 weeks, respectively, were in PUCAI remission without

the use of corticosteroids at week 54. No health-related quality of life data were available from Hyams et al.

4.25 All patients in Hyams et al. reported having at least 1 adverse event. However, by week 54, more patient receiving infliximab every 12 weeks had stopped treatment because of an adverse event than patients receiving infliximab every 8 weeks (6/23 [26.1%] versus 3/22 [13.6%]). The number of patients who had 1 or more serious adverse event, infections, or reactions at the site of administration was similar in both infliximab groups.

5 Comments from other consultees

5.1 Patient experts indicated that ulcerative colitis affects education, employment, personal relationships, and social and family life because of the unpredictable pattern of disease flare-ups. In addition, the frequent and urgent need to go to the toilet, irregular sleeping patterns, pain and fatigue are symptoms of ulcerative colitis that affect self-esteem and social functioning, which if left untreated can cause anxiety about loss of bowel control. Patient experts also noted that ulcerative colitis presents at an early age when people are beginning their career and long-term relationships. They indicated that 30% of patients continue to experience flares or chronic symptoms despite conventional therapy, so biological treatments offer hope to these patients and can help them resume their normal lives. However, it was noted that access to biological treatments is currently limited to patients who are able to secure exceptional funding through their clinical commissioning group, which sometimes leaves the patient without adequate treatment until their disease becomes so severe that they may require emergency surgery.

5.2 Comments from professional groups indicated that ulcerative colitis is a challenging condition to treat, particularly in patients with treatment-refractory disease who, as a result, have a reduced quality of life, and often no treatment options but colectomy and the formation of an

ileostomy (that is, the diversion of the small intestine through an opening in the abdomen). Comments explained that often this surgery is needed in young people in whom a stoma (the artificial opening made into the abdomen) may be socially disadvantaging. In addition, young patients, who may not have started a family, often delay or dismiss ileo-anal pouch anastomosis (by which an internal reservoir for stool is surgically created) because this is a surgery in the pelvis that can affect fertility. Therefore, for these patients anti-TNF-alpha therapy is a valuable option because it can avoid surgery when the patient is in education, has not formed permanent relationships or a family, or risks losing employment because of their illness. Comments noted, however, that it is difficult to extrapolate from seemingly uniform clinical trials, with rigid inclusion criteria, to assess the impact of anti-TNF-alpha therapy on patients' quality of life compared with surgery.

5.3 Professional groups highlighted that ACT1 and ACT2 showed a statistically significant reduction in the rate of colectomy at week 54 in 10% of patients who received infliximab compared with 17% of those who received placebo. It was also noted that long-term follow-up data from ACT1 and ACT2 demonstrated a persistent response to infliximab and low rates of colectomy at up to 4 years after starting treatment. In addition, patient experts indicated that the risk of colon cancer increases after 8 to 10 years of active disease and that biological therapy could decrease it. Submissions to NICE made by patients with ulcerative colitis suggested that infliximab is an effective treatment that prevented symptoms from recurring and helped patients maintain a good health state for long periods, although it caused reactions in some patients when first taken. Comments from professional groups stated that, while the clinical evidence base is smaller for adalimumab and golimumab than for infliximab, there are high-quality data with broadly similar results to infliximab for both treatments. They suggested considering separately subgroups of patients likely to respond better to treatment because this would improve cost effectiveness. Patient experts stated that while

biological therapy is relatively expensive, it reduces the costs of other services, which may offset the high drug costs in the long term.

5.4 Comments from professional groups noted that NICE guidance on anti-TNF-alpha therapy differs for Crohn's disease and ulcerative colitis, resulting in anti-TNF-alpha treatments being widely available for Crohn's disease but not ulcerative colitis. The comments indicated that there is growing evidence that Crohn's disease and ulcerative colitis share common genetic factors, making it difficult to differentiate between them clinically. In addition, both diseases can be associated with chronic active symptoms that are refractory to conventional therapy. The comments summarised that the benefit of anti-TNF-alpha drugs for ulcerative colitis will be similar to that for Crohn's disease, and so guidance for these 2 conditions should be similar to.

5.5 Clinical specialists stated that outcomes should explicitly include rates of steroid-free remission. They also advised that treatment goals beyond symptom control and improved quality of life, such as complete mucosal healing and reduced complication rates, are important. Patients who received infliximab also stated that the side effects of corticosteroids, notably rounded face and severe acne, lower the patient's self-esteem and that biological treatments can help overcome these problems as the patient tapers off corticosteroids.

6 Cost-effectiveness evidence

6.1 The Assessment Group's systematic review of cost-effectiveness evidence identified 3 published economic evaluations of TNF-alpha inhibitors (Park et al. 2012, Tsai et al. 2008 and Xie et al. 2009). In addition, the companies' submissions to NICE for adalimumab, golimumab and infliximab included economic models, which the Assessment Group critiqued (the models for golimumab and infliximab were critiqued together because they were submitted by the same company and the Assessment Group indicated that they were identical).

The Assessment Group also developed its own economic model to assess the cost-effectiveness of adalimumab, golimumab and infliximab for moderate to severe ulcerative colitis.

6.2 All 3 published economic evaluations used a Markov model to compare 2 or 3 treatment strategies (Table 7). Park et al. modelled patients with severe ulcerative colitis, whereas Tsai et al. and Xie et al. modelled patients with moderate to severe ulcerative colitis.

Table 7 Summary of published economic evaluations

Study	Intervention	Comparator	ICER (intervention vs. comparator)	Most sensitive parameters
Park et al. US perspective Lifetime horizon	Standard medical therapy (a sequence of mesalamine, azathioprine, infliximab and tacrolimus with the possibility of then having colectomy with ileal pouch-anal anastamosis)	Early colectomy with ileal pouch-anal anastamosis	$1,476,783 per QALY gained	Patients' quality of life after colectomy with ileal pouch-anal anastomosis
Tsai et al. UK perspective 10-year time horizon	Infliximab (5 mg/kg) maintenance therapy	Standard care (immuno-modulators and/or cortico-steroids)	In patients starting with a clinical response: £27,424 per QALY gained In patients starting in remission: £19,696 per QALY gained	Time horizon and patient body weight
Xie et al. Canadian perspective 5-year time horizon	A: infliximab 5 mg/kg then adalimumab if no response or if response is lost during maintenance therapy B: infliximab 5 mg/kg then infliximab 10 mg/kg if no response, then adalimumab if response is lost during maintenance therapy	'Usual care' (amino-salicylates plus immuno-suppressants)	For 'A' vs. comparator: CAN$358,088 per QALY gained For 'B' vs. comparator: CAN$575,540 per QALY gained	Remission rates, early surgery rate, and utility values
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year				

6.3 The Assessment Group considered that none of the published studies provided sufficient evidence on the cost-effectiveness of biological treatments from a UK perspective. It indicated that only Park et al. reflected the increased risk of colorectal cancer associated with ulcerative colitis, while Xie et al. did not include mortality at all in the model. In addition, Xie et al. assumed that adalimumab and infliximab 5 mg/kg were clinically equivalent because there was no RCT evidence comparing adalimumab with infliximab at the time of the analysis. The Assessment Group considered this uncertain given the existing evidence from the RCTs for adalimumab and infliximab. The Assessment Group also noted that the time horizons in the models ranged from 5 years to lifetime, making the results difficult to compare. Furthermore, Tsai et al. and Xie et al. used different assumptions around utility values, which the Assessment Group indicated may partly explain why Tsai et al. reported favourable results for infliximab (incremental cost-effectiveness ratios [ICERs] of less than £30,000 per quality-adjusted life year [QALY] gained), while Xie et al. did not (ICERs of more than CAN$350,000 per QALY gained).

Company's model: adalimumab

6.4 The company's analysis compared the cost-effectiveness of adalimumab plus conventional therapy with conventional therapy alone for moderately to severely active ulcerative colitis that responded inadequately to conventional therapy. The population in the base case comprised both patients who had previously received an anti-TNF-alpha other than adalimumab and those who had not received any anti-TNF-alpha. The company also presented a sensitivity analysis in which it modelled only patients who had not previously received an anti-TNF-alpha agent. The analysis estimated the direct healthcare costs to the NHS and QALYs over a 10-year time horizon using a cycle length of 2 weeks.

6.5 The company used a Markov model simulating 8 states: 3 states before surgery (‘remission’, ‘mild’, and ‘moderate-to-severe’), 1 ‘surgery’ state, and 4 states after surgery (‘post-surgery without complication’, ‘transient complication’, ‘chronic complication’, and ‘surgery-related death’). For a diagram of the model, see figure 17 on page 71 of the company’s submission. The company derived the probabilities of patients moving between states before surgery primarily from ULTRA2 and the extension study ULTRA3. It derived the transition probabilities for the surgery and post-surgery states based on published literature.

6.6 The company assigned a utility value to each state in the model. Although UTRA2 collected health-related quality of life data using the Short Form-36 (SF-36) survey, the company did not transform these data to SF-6D, arguing that this may overestimate the utility value for patients who had severe disease in ULTRA2. Instead, it obtained the utility values for the states before surgery from a study by Swinburn et al. and those for the states after surgery mainly from a study by Tsai et al. For the utility values used in the model, see table 5 on page 18 of appendix 1 of the company’s submission. Costs in the model included drug costs, disease state costs, hospitalisation costs, surgery costs, costs of complications after surgery, and costs associated with surgery-related death. All costs were derived from published literature.

6.7 The base-case ICER for adalimumab plus conventional therapy compared with conventional therapy alone was £34,417 per QALY gained. When the company varied key parameters in the model 1 at a time, ICERs ranged from £29,437 to £38,073 per QALY gained. The probability of adalimumab plus conventional therapy being cost-effective compared with conventional therapy alone at a maximum acceptable ICER of £30,000 per QALY gained was 30%. In the sensitivity analysis relating to patients who had not previously received an anti-TNF-alpha agent, the ICER for adalimumab plus conventional therapy was close to the base-case ICER at £35,970 per QALY gained.

6.8 Critiquing the company's decision problem, the Assessment Group stated that the company – having excluded other anti-TNF-alpha agents (golimumab and infliximab) and surgery as comparators – deviated from the final scope. In addition, it stated that the company unnecessarily used a shorter cycle length than the time point for assessing induction in ULTRA2 (6 weeks); did not transform the data collected in ULTRA2 using SF-36 to SF-6D utility values; assumed that surgery improves the utility score by only 0.06 compared with active disease; and modelled the rate at which patients had surgery inaccurately.

Company's model: golimumab and infliximab

6.9 The company's model compared adalimumab, golimumab and infliximab with each other and with colectomy for moderate to severe ulcerative colitis that failed previous treatment. Conventional therapy was not a comparator in the analysis. The company chose a cycle length of 2 months and a 10-year time horizon. The perspective on costs was that of the NHS. Costs and health effects were discounted at an annual rate of 3.5%.

6.10 The company's model was hybrid in that it used a 'decision tree' to model the probabilities of biological treatments inducing a response or remission, and the probabilities of surviving and of having surgery-related complications after colectomy; then a Markov model (simulating 11 states) to estimate the long-term outcomes of maintenance therapy and colectomy. For a diagram of the model, see figures 78 and 79 on page 175 of the assessment report. Patients receiving biological treatments in the model started with active, responding or remitting disease. If patients had responding or remitting disease at the end of induction therapy, they received maintenance therapy. Patients whose disease did not respond to induction therapy, and those in whom previous response was lost during maintenance therapy, received steroids intravenously. They could then continue on steroids or have colectomy. The probabilities of patients

moving between states in the induction and maintenance phases were based on network meta-analyses conducted by the manufacturer.

6.11 Costs and utility values were attached to each state. The model incorporated the patient access scheme for golimumab. Utility values were based on PURSUIT-SC in the golimumab model and on ACT1 in the infliximab model. For the utility values used in each model, see table 43 on page 181 of the assessment report. Golimumab and infliximab were assumed to be administered at the licensed dose. For adalimumab, the company used the licensed induction dose regimen of 160 mg at week 0 and 80 mg at week 2, but after induction it assumed that only 50% of patients receive the licensed maintenance dose of 40 mg every other week while the other 50% receive 40 mg every week. It stated that this was because 22.9% of patients in the ULTRA2 trial received 40 mg every week instead of every other week, but it also stated that based on clinical advice, up to 80% of patients would receive weekly doses in clinical practice. The company assumed that in each treatment group some patients also receive background conventional therapy.

6.12 The company presented the cost-effectiveness results as pairwise ICERs (that is, ICERs comparing technologies head-to-head rather than incrementally from the least costly to the most costly). For golimumab, it reported ICERs of £27,994 per QALY gained compared with colectomy, and £80,318 saved per QALY lost compared with infliximab. Adalimumab was more expensive and less effective than golimumab in this analysis (dominated). The ICERs for infliximab were £38,307 per QALY gained compared with colectomy, £54,564 per QALY gained compared with adalimumab, and £75,998 per QALY gained compared with golimumab.

6.13 The Assessment Group stated that generally the company's analysis was in line with the NICE reference case, but deviated from the final scope in that conventional therapy was not included as a comparator. Furthermore, it stated that the company – having assumed that patients can only have

steroids or colectomy after biological therapy fails – modelled a treatment pathway associated with severe disease, not moderate to severe disease for which further medical treatment would still be considered. The Assessment Group also indicated that the company did not describe its network meta-analyses in sufficient detail, did not explain how it estimated the probabilities of moving between states, and did not justify the selection of the data sources for certain parameters. The 2 company models used different sources for the utility values and made different assumptions about resource use, which the Assessment Group did not consider appropriate given that the 2 models addressed identical decision problems. The Assessment Group indicated that in an incremental analysis, infliximab should be compared with golimumab, which results in ICERs of approximately £75,000 to £80,000 per QALY gained.

Assessment Group's model

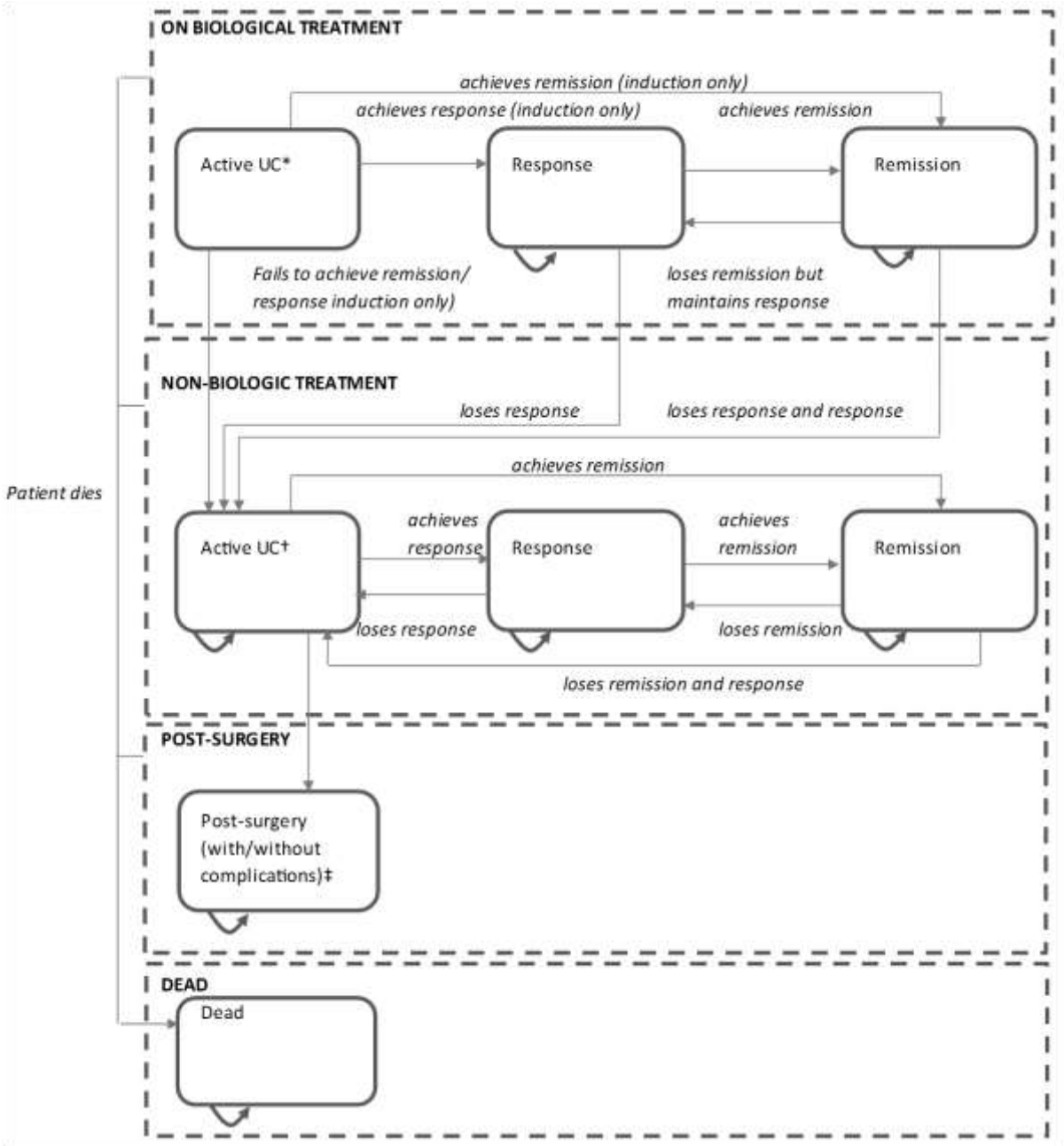
6.14 The Assessment Group developed a de novo economic model to assess the cost-effectiveness of adalimumab, golimumab and infliximab (at their licensed doses) compared with each other and with conventional therapy or surgery for moderate to severe ulcerative colitis that had failed at least 1 previous therapy. Conventional therapy comprised corticosteroids, aminosalicylates and drugs that affect the immune response. The Assessment Group used a lifetime time horizon, which it divided into 2 phases, induction and maintenance. The cycle length for the induction phase was 8 weeks and for the maintenance phase, it was 26 weeks. The perspective of the analysis was that of the NHS and personal social services, and costs and health effects were discounted at an annual rate of 3.5%. The model was fully probabilistic (that is, produced results by varying the input parameters simultaneously with values from a probability distribution).

6.15 The Assessment Group's model was a state-transition Markov cohort model simulating 8 states (Figure 1):

- 1. on biological therapy (adalimumab, golimumab or infliximab) – active disease (that is, no response or remission)
- 2. on biological therapy – response
- 3. on biological therapy – remission
- 4. on conventional therapy – active disease
- 5. on conventional therapy – response
- 6. on conventional therapy – remission
- 7. post-surgery (with or without complications)
- 8. dead.

Surgery was incorporated as an event rather than a state (that is, patients had colectomy then moved to the post-surgery state if they survived or to the death state if not). The probability of patients moving between states was based on the Assessment Group's network meta-analysis. The model used the same definitions of clinical response and remission as the RCTs identified from the systematic review (see section 4.4).

Figure 1 Assessment Group's model structure



Source: Figure 88 on page 217 of the assessment report

6.16 The Assessment Group assumed that patients enter the model at the age of 40 years and have an average body weight of 77 kg, in line with the patient characteristics in RCTs. In the model, all patients started in the induction phase and received biological or conventional therapy, or had surgery (early colectomy). Patients who received biological therapy were assumed to also receive conventional background therapy. If the

biological treatment led to a clinical response or remission, the patient continued on the same treatment in the maintenance phase; if not, they stopped that treatment and received conventional therapy. Patients who continued biological therapy in the maintenance phase received it for as long as response or remission was maintained; if response was lost, they moved to conventional therapy. Patients who started on conventional therapy and those who received a biological treatment then moved to conventional therapy continued conventional therapy in the maintenance phase whether or not their disease responded or remitted, but they could have colectomy if their disease remained active. Therefore, colectomy was included in the analysis both as a comparator (early colectomy) and as an intervention received further down the treatment pathway after biological or conventional therapy. All patients who had colectomy remained in the post-surgery state until they died.

6.17 To derive the rate at which patients have colectomy, the Assessment Group used a study by Solberg et al., estimating that every 6 months 0.51% of patients have colectomy. Based on another study by Arai et al., it assumed that 47.3% and 5% of those patients will develop transient or chronic complications respectively. In patients who survived surgery, all transient complications were assumed to occur and resolve during the first cycle after surgery, whereas chronic complications continued until the patient died.

6.18 The model included 2 types of mortality: mortality during colectomy and mortality from causes other than ulcerative colitis and colectomy. The Assessment Group assumed that 3% of patients who had colectomy died during surgery, an estimate it obtained from the UK Inflammatory Bowel Disease audit. All patients in the model had a probability of dying from other causes, which the Assessment Group modelled based on data from the Office for National Statistics.

6.19 In the model, the patient's health-related quality of life depended on the outcome of drug therapy (whether the disease remained active, responded or remitted), whether the patient had colectomy, and if so, whether they developed complications afterwards. It did not depend on whether the patient received biological or conventional therapy. The Assessment Group stated that the studies by Woehl et al. and Swinburn et al. were the most useful to source utility values in the model because they were UK-based, included reasonably large number of patients (n=180 and n=230 respectively) and reported EQ-5D utility values for most states in the model (Table 8).

- Woehl et al.: patients in the study may or may not have had surgery. Among patients who did not have surgery, utility values were reported to be 0.87 (standard deviation [SD] 0.15) for remitting disease, 0.76 (SD 0.18) for mild disease, and 0.41 (SD 0.34) for moderate to severe disease. These categories of disease severity were based on the Simple Colitis Activity Index. The Assessment Group assumed that the utility value for moderate to severe disease that responded to treatment was equal to the value for mildly active disease in Woehl et al. (0.76). In patients who had surgery, the utility value was 0.71, which the Assessment Group adjusted to account for the effect of chronic complications after colectomy on the patient's quality of life, estimating a utility value of 0.70 in the post-surgery state.
- Swinburn et al.: of the 230 patients included in the study, 30 had previously had surgery. EQ-5D utility values were collected through an online survey across different categories of disease severity measured using the IBDQ. The utility value for patients who had surgery was 0.59 (95% CI 0.55 to 0.63). For patients who did not have surgery, utility values were 0.91 (95% CI 0.87 to 0.95) for remitting disease (n=78); 0.80 (95% CI 0.70 to 0.85) for mild disease (n=47); 0.68 (95% CI 0.58 to 0.78) for moderate disease (n=31); and 0.45 (95% CI 0.35 to 0.55) for severe disease (n=44). Because the model included patients who had 'moderate to severe disease' disease (rather than moderate or

severe disease), the Assessment Group averaged the utility values for 'moderate' and 'severe' disease in Swinburn et al. to derive a value for moderately to severely active disease (no response). It also assumed that the utility value for moderate to severe disease that responded to treatment was equal to the value for mildly active disease in Swinburn et al. (0.80). The Assessment Group noted that Swinburn et al. reported that utility values were, on average, lower in patients who had surgery than in those who did not (p=0.016).

The Assessment Group chose Woehl et al. for its base case and used Swinburn et al. in a sensitivity analysis (see section 6.24). This was because the utility value after surgery in Woehl et al. (0.71) was more consistent with those reported in other studies than Swinburn et al (0.59).

Table 8 Utility values applied in the model

	No response		**Response**		**Remission**		**Post-surgery**	
	Woehl et al.[1]	*Swin-burn et al.*	*Woehl et al.*[1]	*Swin-burn et al.*	*Woehl et al.*[1]	*Swin-burn et al.*	*Woehl et al.*[1]	*Swin-burn et al.*
Adalimumab	0.41	0.55	0.76	0.80	0.87	0.91	0.71	0.59
Golimumab	0.41	0.55	0.76	0.80	0.87	0.91	0.71	0.59
Infliximab	0.41	0.55	0.76	0.80	0.87	0.91	0.71	0.59
Conventional therapy	0.41	0.55	0.76	0.80	0.87	0.91	0.71	0.59
Colectomy	-	-	-	-	-	-	0.71	0.59

[1] Study used in the base case

Adapted from tables 70 and 71 on pages 226 and 227 of the assessment report

6.20 The Assessment Group modelled the cost of adalimumab, golimumab and infliximab assuming that each treatment would be received at its licensed dosage. However, it assumed that a fixed proportion of patients (27%) receive adalimumab 40 mg as maintenance therapy every week instead of every 2 weeks (the licensed regimen) based on data reported in the company's submission for adalimumab. The summary of product characteristics for golimumab recommends that therapy should be reconsidered in patients who do not benefit within 12 to 14 weeks after starting treatment (that is, after 4 doses). However, only the first 2 doses

of golimumab were costed in the induction phase. This was because PURSUIT-SC, from which the data for golimumab were obtained, evaluated golimumab after 2 doses (at week 6). Only infliximab incurred administration costs in the model (adalimumab and golimumab are administered subcutaneously and so are not associated with administration costs). The model incorporated the patient access scheme for golimumab. For the costs of biological treatments used in the model, see table 72 on page 228 of the assessment report. For conventional therapy, the Assessment Group assumed that in both the induction and maintenance phases, 100% of patients receive corticosteroids and aminosalicylates, 80% receive 6-mercaptopurine, and 20% receive azathioprine. Costs associated with consultant visits, endoscopy, hospitalisation, blood tests and surgery (including surgery-related complications) were also included in the model, see tables 74, 75 and 76 on pages 231 and 232 of the assessment report.

6.21 The Assessment Group presented results for patients in whom colectomy is a potential option, and separately for those in whom it is not. In addition, it performed one-way sensitivity analyses, varying parameters in the model 1 at a time. Parameters varied included the dataset used to estimate clinical effectiveness, the time horizon, utility values, health state costs, and assumptions around hospitalisations, surgery and chronic complications after surgery. For details of the individual parameters varied, see box 5 on page 234 of the Assessment Report.

For patients in whom colectomy is a potential option

6.22 The Assessment Group's probabilistic base-case results estimated that colectomy provides 14.72 QALYs at a cost of £41,921. Adalimumab, golimumab, infliximab and conventional therapy provided fewer QALYs at a higher cost than colectomy; that is, they were dominated by colectomy (Table 9).

Table 9 Base-case results when colectomy is a comparator

	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Colectomy	41,921	14.72	-	-	-
Conventional therapy	71,592	10.48	-	-	Dominated
Golimumab	82,625	10.65	-	-	Dominated
Adalimumab	89,289	10.83	-	-	Dominated
Infliximab	94,665	10.82	-	-	Dominated
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year					

Adapted from table 1 on page 2 of the addendum to the assessment report

6.23 The probability of colectomy being the most cost-effective treatment at maximum acceptable ICERs of £20,000 and £30,000 per QALY gained was 97% and 96% respectively. Adalimumab, golimumab and infliximab had a 0% probability of being cost-effective compared with colectomy at these maximum acceptable ICERs. For the cost-effectiveness acceptability curve, see figure 1 on page 3 of the addendum to the assessment report.

6.24 In all one-way sensitivity analyses but 1, adalimumab, golimumab and infliximab were dominated by colectomy. This result changed only when the Assessment Group incorporated utility values (except post-surgical complications) from Swinburn et al. In this analysis, colectomy became the least effective option. In the incremental analysis, golimumab and conventional therapy were dominated and excluded from the analysis. Among the remaining alternatives, colectomy was the cheapest, followed by adalimumab then infliximab. The ICER for adalimumab compared with colectomy was £80,315 per QALY gained and that for infliximab compared with adalimumab was £179,374 per QALY gained.

For patients in whom colectomy is not a potential option

6.25 When medical options only were compared with each other, infliximab was dominated by adalimumab (although the difference in QALYs was small), and golimumab was extendedly dominated by adalimumab and conventional therapy (that is, a QALY was attained at a higher cost with

golimumab than with adalimumab because the ICER for golimumab compared with conventional therapy [£97,149 per QALY gained] was higher than that for adalimumab compared with conventional therapy). The incremental ICER for adalimumab compared with conventional therapy was £50,624 per QALY gained (Table 10).

Table 10 Base-case results when colectomy is not a comparator

	Costs (£)	QALYs	Incremental costs (£)	Incremental QALYs	ICER[1] (£/QALY)	Incremental ICER[2] (£/QALY)
Conventional therapy	71,592	10.48	-	-	-	-
Golimumab	82,625	10.65	11,033	0.17	64,900	Extendedly dominated
Adalimumab	89,289	10.83	1181	0.18	6560	**50,624** (vs. conventional therapy)
Infliximab	94,665	10.82	5376	−0.01	Dominated	Dominated

[1] ICER from moving to the next more costly and effective alternative
[2] ICER after excluding dominated and extendedly dominated strategies

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Adapted from table 2 on page 3 of the addendum to the assessment report

6.26 At a maximum acceptable ICER of £20,000 per QALY gained, adalimumab had a 0% probability of being cost-effective compared with conventional therapy. Its probability of being cost-effective compared with conventional therapy at a maximum acceptable ICER of £30,000 per QALY gained was approximately 5%. For the cost-effectiveness acceptability curve, see figure 2 on page 4 of the addendum to the assessment report.

6.27 Because the difference in effectiveness between adalimumab and infliximab was small (0.01 QALY), the results were sensitive to the dataset used to estimate the clinical effectiveness of biological treatments. In all the sensitivity analyses in which alternative datasets were used, golimumab was extendedly dominated and excluded from the analyses. When the Assessment Group used data from ULTRA2 for the overall

population or included Suzuki et al., infliximab provided more QALYs than adalimumab, but the ICER for infliximab compared with adalimumab was greater than £250,000 per QALY gained in both analyses. For adalimumab compared with conventional therapy, the ICER was £54,309 per QALY gained in the first analysis and £56,656 per QALY gained in the second (the base-case ICER was £50,624 per QALY gained). When the Assessment Group included data from ULTRA2 for the overall population and data from Suzuki et al. in the same analysis, infliximab was dominated by adalimumab; the ICER for adalimumab compared with conventional therapy was £56,014 per QALY gained. The Assessment Group also presented pairwise analyses comparing adalimumab, golimumab and infliximab head-to-head with conventional therapy using direct evidence from the respective RCTs. Compared with conventional therapy, the ICER for adalimumab was £70,075 per QALY gained, for golimumab it was £90,720 per QALY gained, and for infliximab it was £96,682 per QALY gained.

For children and adolescents

6.28 The Assessment Group presented a scenario analysis comparing infliximab with conventional therapy or colectomy in children and adolescents (golimumab and adalimumab are not licensed for this population). However, it advised that this analysis should be treated as exploratory because there were no RCTs comparing infliximab with placebo or with other active treatments in children and adolescents, so the data on the efficacy of infliximab were those provided by trials conducted in adults. This analysis differed from the base case in adults only in that the starting age of patients in the model was set to 15 years (the median age in Hyams et al.).

6.29 In children and adolescents in whom colectomy is a potential option, colectomy provided 17.55 QALYs at a cost of £47,871. Infliximab provided fewer QALYs (13.01) at a higher cost (£106,759), and so was dominated by colectomy. The probability of infliximab being cost-effective compared

with colectomy or conventional therapy at a maximum acceptable ICER of £20,000 per QALY gained was 0%.

6.30 When colectomy was not a potential option, infliximab provided an additional 0.34 QALYs at an additional cost of £23,268 to conventional therapy, resulting in an ICER of £68,364 per QALY gained for infliximab compared with conventional therapy. The probability of infliximab being cost-effectiveness compared with conventional therapy at a maximum acceptable ICER of £20,000 per QALY gained was 0%.

Key differences between the Assessment Group's and the companies' models and limitations in the Assessment Group's model

6.31 A summary of the key differences between the Assessment Group's and the companies' models is presented in Table 11.

Table 11

	Assessment Group's model (base case)	**Golimumab and infliximab models**	**Adalimumab model**
Treatment options	(i) infliximab (ii) adalimumab (iii) golimumab (iv) conventional therapy (v) colectomy	(i) infliximab (ii) adalimumab (iii) golimumab (iv) colectomy	(i) adalimumab (ii) conventional therapy
Time horizon	Lifetime	10 years	10 years
Source of clinical evidence	Network meta-analysis using unpublished data	Network meta-analysis using published data (includes manipulation of data from PURSUIT-Maintenance)	Unpublished data from ULTRA2 and ULTRA3 (extension study) supplemented with estimates from the literature
Treatment options after failure of biological therapy	Conventional therapy, with the possibility of having colectomy	'Relapse management' and imminent colectomy	Conventional therapy, with the possibility of having colectomy
Possible transitions between states for active, responding and remitting disease	All transitions allowed	Patients losing remission move to 'response'; patients who had response cannot be in remission	All transitions allowed

Source of utility values	Woehl et al. (chronic complications valued based on Arseneau et al.)	ACT1/PURSUIT-Maintenance; Woehl et al. (chronic complications valued based on Arseneau et al.)	Swinburn et al; Tsai et al; complications valued using weighted average of Arseneau et al., Hu et al., and Smith and Roberts

6.32 The Assessment Group listed the following as the main limitations in its model:

- There was considerable uncertainty associated with the extrapolation of short-term trial data (maximum 54 weeks) to a lifetime horizon.
- The model assumed that conventional therapy would not be given sequentially, but that in any cycle, fixed proportions of patients would receive corticosteroids, 5-aminosalicylates and drugs that affect the immune response.
- Evidence on the complications of colectomy was not identified through a systematic review.

7 Comments received during consultation on the Assessment Report

7.1 Summary of the comments received:

- **Treatment pathway**: It was noted by a consultee that in the Assessment Group's model, patients who stopped biological treatment because their disease did not respond or lost response could have surgery after receiving at least 1 cycle of conventional therapy. The consultee indicated that conventional therapy had been shown to be ineffective in these patients and so the model should allow at least some, if not all, patients to proceed directly to surgery after the biological treatment fails.
  Another consultee suggested that the transition in the Assessment Group's model from induction to maintenance appears to be based on the outcome of induction therapy, but the rate of patients actually going

forward is not clear and questioned whether it included both patients whose disease responded and remitted, and that if so this would be considered to be an extreme assumption.

- **Comparators**: A consultee noted that the Assessment Group considered patients for whom surgery is not an option separately. The consultee considered that for these patients, biological treatments are the only option because conventional therapy will have already failed at an earlier stage of the disease.
  Another consultee stated that the accepted conventional treatment in the UK is to avoid surgery if at all possible. Furthermore, they suggested that the complications of surgery, ongoing care when stomas are formed and the overall impact on patients and carers after surgery seemed to have been underestimated in the model. The consultee noted that the outcomes of surgery vary from centre to centre, which is something that the Assessment Group did not take into account when it assessed the rate at which surgery fails, complications and care after surgery, bed days and follow-up care in the community.
- **Clinical effectiveness data**: A consultee highlighted that the adalimumab trials used the 'worst-ranking Mayo score', which was not used in the other trials, to measure clinical response. This classified all patients who withdrew from the study for any reason, those who had missing Mayo Scores and those who received a higher dose of adalimumab as 'non-responders'. The consultee suggested that the Assessment Group, having used such data in the model, underestimated the efficacy of adalimumab.
  Another consultee noted that the Assessment Group used data from weeks 32–52 that it extrapolated over the entire time horizon. The consultee suggested that this inflated the benefit of adalimumab, and considered that it would be more appropriate to use data from the whole maintenance period (8–52 weeks), in line with the design of the RCTs.

- **Modelling conventional treatments**: Some consultees highlighted that most patients take considerably higher doses of 5-aminosalicylates than those modelled by the Assessment Group, although they accepted that low dose 5-aminosalicylates are likely to be used for maintenance but will be stopped after surgery. It was noted that the model uses the cheapest 5-aminosalicylates preparation but takes no account of the range of products available. Comments suggested that the model should be based on market share and the higher doses used. It was also highlighted that patients taking repeated courses of steroids are likely to have DEXA scans and those with bone loss will be prescribed bisphosphonates, both of which are associated with additional costs.
- **Utility values**: A consultee highlighted that the model is very sensitive to assumptions about the utility values for remission, response, active UC and post-surgery. It was noted that Woehl et al., which was used to source utility values in the base case, was in abstract form only, and although it included 180 patients, only 10 had pouches and 19 ileostomies (that is, only 29 patients had surgery). Using such a small dataset is uncertain in the consultee's opinion.
- **Dose escalation of adalimumab**: It was highlighted that the Assessment Group model assumes that a fixed proportion of patients (27.4%) receive adalimumab 40 mg as maintenance therapy every week instead of every 2 weeks (the licensed regimen). It was noted that ULTRA2 used a 'non-responder imputation' method by which anyone who received a higher dose was considered to have disease that did not respond. As such, the model considered the additional costs associated with dose escalation without incorporating the additional benefits.

  It was also suggested that the Assessment Group underestimated the rate at which patients receive higher doses of adalimumab (every other week rather than weekly). Gastroenterologist clinical specialists indicated that in clinical practice up to 80% of patients receiving adalimumab receive a higher dose after some time. A recent

independent study also indicated that adalimumab dose escalation was necessary in 76% of patients (Ferrante et al.).

- **Modelling surgery:** A consultee noted that the Assessment Group's model uses Solberg et al. to source surgery rates. It was suggested that Solberg et al. is likely to underestimate this rate because it focused on newly diagnosed patients and included patients with any degree of disease severity. The Hillson et al. study reported that, although the overall 1-year prevalence of surgery was small (2.7%), the percentage of patients with severe disease requiring colectomy was substantially higher (18.2%).

  Consultees also highlighted that the cost of surgery was likely to be underestimated in the Assessment group's model. It was stated that a proportion of patients will keep their ileostomy in the medium to long term; the cost of this is £3000 per year (although clinical commissioning groups estimate it to be as high as £5000 per year). For younger patients who keep their stoma for life, the cost of 50 years of stoma care was estimated at £150,000. Patients may keep their ileostomy for a range of reasons, notably issues around fertility/impotence in men and fecundity in women. Older patients may refuse further surgery to avoid hospital admissions. Patients with stomas require lifelong stoma care, loperamide and risk hospitalisation because of stoma-related problems. Many patients would undergo second and third operations to create an ileoanal pouch. For these patients, the cost of surgery itself is thus 2 or 3 times that used in the model. They would also require stoma care while awaiting surgery. Consultees also noted that the Assessment Group's model assumed that pouchitis (chronic complications) is infrequent and only occurs soon after surgery. However, in clinical practice, 10% of patients have pouchitis that require recurrent or maintenance medication. Of these patients, 50% will ultimately remove their pouch and revert to an ileostomy, which is associated with costs. It was also highlighted that the model does not

incorporate a terminal care cost, in particular, the terminal care cost which may be incurred after surgery.

- **Cost of hospitalisation**: It was noted that in the clinical trials, adalimumab reduced the risk of hospitalisation by 30% for all-cause hospitalisation compared with placebo, and by 50% for ulcerative colitis-related hospitalisation compared with placebo. The risk reduction in the model was 30%, but it is not clear if this relates to all-cause or ulcerative colitis-related hospitalisations. It was suggested that by using a 30% risk reduction when it should be 50% increases the cost associated with adalimumab.

8 Equality issues

8.1 During the scoping process, it was noted that there is a need to give isoniazid as tuberculosis prophylaxis for 6 months in at risk patients, such as those from South Asia, concurrently with anti TNF-alpha therapy. This issue was not considered an equality issue relevant for the Committee discussions because it is inherent in the use of the agents being appraised and was not expected to lead to unfair restrictions of access to treatment. No additional equality issues were identified in the evidence submitted.

9 Innovation

9.1 A company indicated that there is a high unmet need for effective therapeutic options in patients with moderately to severely active ulcerative colitis that is uncontrolled on conventional therapy. It was noted that no anti-TNF-alpha treatments are currently recommended by NICE for this indication, and that adalimumab, golimumab and infliximab represent important medical options in patients who would otherwise have surgery as their only option.

9.2 Celltrion Healthcare noted that Remsima will provide a treatment option that is clinically equivalent to Remicade, the reference product, but at a

significantly lower acquisition cost to the NHS (this cost was not available at the time of the appraisal). This would improve the cost effectiveness of infliximab, thus allowing more patients to access anti-TNF-alpha treatment.

10 Authors

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Appendix A: Supporting evidence

Related NICE guidance

Published

- Ulcerative colitis. NICE clinical guideline 166 (2013).
- Adalimumab for the treatment of moderate to severe ulcerative colitis. Terminated NICE technology appraisal guidance 262 (2012).
- Infliximab for the treatment of acute exacerbations of ulcerative colitis. NICE technology appraisal guidance 163 (2008).
- Infliximab for subacute manifestations of ulcerative colitis. NICE technology appraisal guidance 140 (2008).

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

- Vedolizumab for treating moderately to severely active ulcerative colitis. NICE technology appraisal. April 2015.

NICE pathways

- There is a NICE pathway on Ulcerative colitis, which is available from http://pathways.nice.org.uk/pathways/ulcerative-colitis.

Appendix B: European public assessment report

Links to European public assessment reports:

- Adalimumab
- Golimumab
- Infliximab: adults
  - Inflectra (biosimilar)
  - Remsima (biosimilar)
- Infliximab: children and adolescents