

LMMG New Medicine Recommendation

Golimumab (Simponi[®]) for moderate to severe ulcerative colitis

LMMG Recommendation: BLACK

Golimumab is **not** recommended 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 (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

There is insufficient evidence available to justify the use of golimumab ahead of alternative biologic agents, which themselves are not recommended in moderate-to-severely active ulcerative colitis in NICE technology appraisals or the clinical guideline.

Summary of supporting evidence:

- There are no direct comparative data for golimumab against other biologic agents that are licensed to treat ulcerative colitis. Placebo-controlled trials have been conducted in patients who were largely classed as moderately severe based on Mayo scores and none were candidates for surgery.
- The subcutaneous induction trial demonstrated clinical response to the licensed golimumab induction regimen at 6 weeks. Responding patients were enrolled into a golimumab maintenance treatment trial.
- The maintenance/withdrawal trial enrolled patients responding to the licensed induction regimen, and those responding to a higher dose subcutaneous induction regimen and an intravenous induction regimen, were randomised into the maintenance/withdrawal trial. A high proportion of the maintenance phase trial participants had therefore not received the licensed induction regimen. Furthermore, only responders at 6 weeks were included in the maintenance/withdrawal trial, which may be a more selective patient group than would be seen in practice; the SPC suggests reconsideration of treatment in those not achieving response at 12-14 weeks.¹
- The maintenance/withdrawal trial observed significantly greater maintenance of clinical response with both 50mg and 100mg maintenance doses of golimumab compared with placebo.
- CHMP noted that induction and maintenance of clinical remission, rather than clinical response, is the preferred primary endpoint for ulcerative colitis trials.⁴ A significantly greater proportion of patients treated with golimumab 100mg achieved clinical remission at 30 and 54 weeks compared with placebo; however, there was no statistically significant difference between golimumab 50mg and placebo for this endpoint. Of those in remission following induction, there was no statistically significant difference between golimumab 100mg or 50mg compared with placebo in the proportions maintaining that remission. Similarly, for a key endpoint of steroid-free remission, there was no statistically significant difference for golimumab and placebo recipients. However, these data are based on small patient numbers. There is no evidence that golimumab treatment leads to reduced rates of

surgery.

- CHMP concluded that there was sufficient evidence of additional benefit to support the 100mg maintenance dose for patients weighing ≥ 80 kg, but in patients weighing < 80 kg there were no major differences apparent between the 50mg and 100mg maintenance dose for clinical response/remission rates.⁴ There is also insufficient data to support increasing the maintenance dose to 100mg in patients who lose clinical response on the 50mg dose.
- Data from the ulcerative colitis trials generally suggest the safety profile of golimumab is similar to that when used for other licensed indications; however, this is based on 54 week data and long-term benefits and risks of golimumab treatment in ulcerative colitis are currently unknown.
- Following induction, golimumab as maintenance treatment is administered subcutaneously every 4 weeks, in contrast to infliximab that is administered by IV infusion every 8 weeks and adalimumab that is administered by subcutaneous injection every 2 weeks.
- Based on current list prices, subcutaneous golimumab is more costly than subcutaneous adalimumab and less costly than intravenous infliximab[†]. The administration costs and resource impacts are greater with infliximab.

[†]Assumes that 100mg prefilled pen is available at the same cost as 50mg as in previous patient access schemes. If not, the first year annual drug acquisition cost of golimumab would be more expensive than infliximab in patients with body weight < 80 kg and significantly more expensive for patients with body weight ≥ 80 kg.

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Reviewer:	Brent Horrell	
Clinical Reference Group (if appropriate)		
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Date of recommendation to member organisations by LMMG:	9th January 2014	

Details of Review

Name of medicine (generic & brand name): Golimumab (Simponi®)
Strength(s) and Form(s): 50mg, 100mg pre-filled syringe/pen for subcutaneous injection.
Licensed indication(s): For 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 (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies. ¹
Reason for Review: Horizon scanning
Proposed use (if different from or in addition to licensed indication above): n/a

Background and context

Ulcerative colitis is a chronic inflammatory disease of the colon and rectum that follows a relapsing-remitting course. Symptoms of active disease or relapse include bloody diarrhoea, an urgent need to defecate and abdominal pain, which may significantly impact on quality of life.⁵ Long-lasting disease may also be a risk for development of colon dysplasia and cancer.⁴

NICE Clinical Guideline 166,⁵ published in June 2013, indicates that current medical approaches focus on treating active disease to address symptoms, improve quality of life, and then maintain remission. The treatment chosen for active disease is likely to depend on clinical severity, extent of disease and the person's preference.

For induction of remission at first presentation of mild to moderate disease, rectal or oral aminosalicylates, oral corticosteroids and oral tacrolimus may be used depending on response and extent of disease.

For induction of remission in acute severe episodes (first presentation or inflammatory exacerbation), intravenous (IV) corticosteroids are recommended, and patients should be assessed for likelihood of need for surgery. If IV corticosteroids are not an option, not tolerated or ineffective, consideration may be given to use of IV ciclosporin as an add-on or as an alternative. IV infliximab, given for 3 doses, is recommended in NICE Technology Appraisal 163 as a treatment option for inducing remission where IV ciclosporin is contraindicated or is otherwise not a clinical option.⁶

Maintenance of remission is recommended with low dose aminosalicylate. If remission is not maintained, oral azathioprine or oral mercaptopurine should be considered.⁵

Golimumab is licensed 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 (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.¹ Infliximab and adalimumab are also licensed for this use. NICE Technology Appraisal 140 recommended against the use of infliximab for the treatment of *subacute* manifestations of moderately to severely active ulcerative colitis,⁷ and in the absence of a submission from the manufacturer, adalimumab was not recommended by NICE for use in the treatment of moderate to severe ulcerative colitis.⁸ NICE is intending to complete a multiple technology appraisal of all three agents in February 2015, excluding use in the treatment of acute severe episodes.⁹

Evidence in Proposed Use

Summary of Efficacy Data in Proposed Use:

There are no direct comparative efficacy data for golimumab against adalimumab or infliximab.

Key efficacy data are available from two randomised, allocation concealed, double-blind, placebo-controlled trials.^{2,3} These were conducted in patients who had an inadequate response to, or not tolerated, one or more conventional therapies including oral mesalazine, oral corticosteroids, 5-aminosalicylate, azathioprine and / or 6-mercaptopurine, or patients who were unable to taper corticosteroids without recurrence of symptoms. Exclusion criteria included severe disease requiring surgery, disease limited to 20cm of the colon, those with history of colonic dysplasia, and prior treatment with anti-TNF agents.

The first trial² was a phase 3 induction trial. Following an initial dose-finding phase, 774 patients were randomised equally to subcutaneous placebo or golimumab induction doses of 200mg at week 0 followed by 100mg at week 2, or 400mg at week 0 followed by 200mg at week 2. The primary endpoint was clinical response assessed at 6 weeks, defined as a decrease of at least 30% and 3 or more points in Mayo score (a composite of stool frequency, rectal bleeding, endoscopic findings and physician's global assessment, score ranges 0 to 12). This was achieved in a significantly greater proportion of patients randomised to golimumab 200 / 100mg (51.8%) and 400 / 200mg (55.0%) compared with placebo 29.7%, $p < 0.0001$). A significantly greater proportion of patients on golimumab also achieved clinical remission (secondary endpoint, defined as Mayo score of 2 or less, with no sub score greater than 1) compared with placebo (18.7% on 200mg / 100mg; 17.8% on 400mg/200mg vs. 6.3% on placebo, $p < 0.0001$). Improvements in mucosal healing and changes in disease-specific health-related quality of life scores also significantly favoured golimumab up to 6 weeks.² It should be noted that only the 200mg / 100mg induction regimen has been licensed.¹

The second trial³ was a 54-week, phase 3 maintenance/withdrawal trial that enrolled patients who responded to golimumab in the above induction trial and in another induction trial of intravenous golimumab that was terminated early.⁴ Pre-induction, enrolled patients had mean baseline Mayo score of 8.3 and 93% had moderate severity disease. Those taking conventional therapies at baseline (94%) had to have stable doses throughout and those taking corticosteroids (54%) were required to taper doses at weekly intervals. Patients were randomised to placebo or to 50mg or 100mg golimumab administered every 4 weeks. In cases of loss of clinical response, placebo-treated patients received golimumab 100mg, golimumab 50mg-treated patients were re-randomised to 50mg or 100mg, and golimumab 100mg-treated patients remained on that dose.

The primary endpoint of maintenance of clinical response throughout 54 weeks was achieved in statistically significantly greater proportions of patients treated with golimumab 50mg and 100mg (47.1% and 50.6%, respectively) compared with placebo (31.4%, $p = 0.01$ and $p < 0.001$, NNTs 6 and 5, respectively). In pre-specified secondary analyses, the proportion of patients in clinical remission

at both 30 weeks and 54 weeks was statistically significantly greater in golimumab 100mg-treated patients compared with placebo (28.6% vs. 15.4%, $p=0.003$, NNT 8) but not for golimumab 50mg-treated patients (23.5%). There was no significant difference between placebo and golimumab 50mg- and 100mg-treated patients in the proportions maintaining remission from baseline (24.1%, 36.5% and 40.4%, respectively) or those achieving corticosteroid-free clinical remission (18.4%, 27.8% and 22.9%, respectively), but numbers of patients providing these data are limited. Dose adjustment due to loss of clinical response was required in 44% of placebo-, 30.8% of golimumab 50mg- and 25% of golimumab 100mg-treated patients. A post hoc analysis suggested median time to loss of clinical response was longer with golimumab compared with placebo. In 53 golimumab 50mg-treated patients who lost response, there was no statistically significant difference in clinical response at 54 weeks between those re-randomised to 50mg or those increasing the dose to 100mg (28% vs. 37%).³

Summary of Safety Data:

Data from the ulcerative colitis trials generally suggest the safety profile of golimumab is similar to that when used for other licensed indications.

In the 6-week induction study, similar proportions of patients receiving the licensed induction regimen of golimumab and placebo experienced adverse events (37.5% vs. 38.2%). The most common observed adverse events were headache and nasopharyngitis, which occurred at similar frequencies. Injection site reactions occurred in 3.3% and 1.5% of golimumab and placebo recipients, respectively, and there were no cases of hypersensitivity or anaphylaxis. Serious adverse events occurred in 2.7% and 6.1% of the licensed dose of golimumab and placebo recipients, respectively. Discontinuations due to adverse events were low at 0.3% and 0.9%, respectively.²

In the 54-week maintenance/withdrawal study, 72.7%, 73.4% and 66.0% of golimumab 50mg, 100mg and placebo-treated patients, respectively, experienced any adverse event. The most common was ulcerative colitis flare, which occurred at similar rates in all arms (15-19%). Patients receiving golimumab 100mg experienced numerically higher rates of serious adverse events and discontinuations due to adverse events. Serious adverse events occurred in 8.4%, 14.3% and 7.7%, and discontinuations due to adverse events occurred in 5.2%, 9.1% and 6.4% of golimumab 50mg, 100mg and placebo-treated patients, respectively. Discontinuations were mainly due to ulcerative colitis flares.

Anti-TNF agents have a number of known adverse events of special interest, including infections (tuberculosis, pneumonia, opportunistic infections), congestive heart failure, hypersensitivity, anaphylactic reactions, and malignancy. Pooled rates of these adverse events with golimumab were similar in the ulcerative colitis trials and in all trials of golimumab use.⁴ In the 54 week trial, infections were reported numerically more often in golimumab 50mg and 100mg recipients than in placebo (39.0%, 39.0% and 28.2%), as were infections requiring antimicrobial treatment (25.3%, 28.6% and 15.4%). Serious infection rates were 3.2%, 3.2% and 1.9%, respectively. Three patients on golimumab 100mg and one patient on placebo developed tuberculosis, in centres located where tuberculosis is endemic.³ No serious injection site reactions occurred and no cases of anaphylaxis. Colon cancer is a potential risk for patients with longstanding ulcerative colitis. Across all ulcerative colitis trials, the rate of any malignancy per 100 patient years of follow up was 0.46 (95% confidence interval 0.15 to 1.08).⁴ However, it should be noted that only short-term data are available for use in this patient population.

Summary of Evidence on Cost Effectiveness and Patient Outcomes:

No published evidence of cost effectiveness has been identified for golimumab in this indication. Relevant comparators would be adalimumab, infliximab and possibly other non-biologic conventional therapies, against which there are no direct comparative efficacy data. Key patient

and economic outcomes of interest would be attainment of remission (including steroid-free remission), prevention of surgery and improvements in health-related quality of life.

In the 6-week induction study, health-related quality of life was measured with the inflammatory bowel disease questionnaire. The mean change from baseline in total score with the licensed golimumab induction regimen exceeded the 20 points considered reflective of response and was significantly greater than that with placebo (27.0 vs. 14.8, $p < 0.0001$).⁴ No health-related quality of life data are reported for the 54 week trial.

Key Points to Note from the Available Evidence:

- There are no direct comparative data for golimumab against other biologic agents that are licensed to treat ulcerative colitis. Placebo-controlled trials have been conducted in patients who were largely classed as moderately severe based on Mayo scores and none were candidates for surgery.
- The subcutaneous induction trial demonstrated clinical response to the licensed golimumab induction regimen at 6 weeks. Responding patients were enrolled into a golimumab maintenance treatment trial.
- The maintenance/withdrawal trial enrolled patients responding to the licensed induction regimen, and those responding to a higher dose subcutaneous induction regimen and an intravenous induction regimen. These, were randomised into the maintenance/withdrawal trial. A high proportion of the maintenance phase trial participants had therefore not received the licensed induction regimen. Furthermore, only responders at 6 weeks were included in the maintenance/withdrawal trial, which may be a more selective patient group than would be seen in practice; the SPC suggests reconsideration of treatment in those not achieving response at 12-14 weeks.¹
- The maintenance/withdrawal trial observed significantly greater maintenance of clinical response with both 50mg and 100mg maintenance doses of golimumab compared with placebo.
- CHMP noted that induction and maintenance of clinical remission, rather than clinical response, is the preferred primary endpoint for ulcerative colitis trials.⁴ A significantly greater proportion of patients treated with golimumab 100mg achieved clinical remission at 30 and 54 weeks compared with placebo; however, there was no statistically significant difference between golimumab 50mg and placebo for this endpoint. Of those in remission following induction, there was no statistically significant difference between golimumab 100mg or 50mg compared with placebo in the proportions maintaining that remission. Similarly, for a key endpoint of steroid-free remission, there was no statistically significant difference for golimumab and placebo recipients. However, these data are based on small patient numbers. There is no evidence that golimumab treatment leads to reduced rates of surgery.
- CHMP concluded that there was sufficient evidence of additional benefit to support the 100mg maintenance dose for patients weighing ≥ 80 kg, but in patients weighing < 80 kg there were no major differences apparent between the 50mg and 100mg maintenance dose for clinical response/remission rates.⁴ There is also insufficient data to support increasing the maintenance dose to 100mg in patients who lose clinical response on the 50mg dose.
- Data from the ulcerative colitis trials generally suggest the safety profile of golimumab is similar to that when used for other licensed indications; however, this is based on 54 week data and long-term benefits and risks of golimumab treatment in ulcerative colitis are currently unknown.
- Following induction, golimumab as maintenance treatment is administered subcutaneously every 4 weeks, in contrast to infliximab that is administered by IV infusion every 8 weeks and adalimumab that is administered by subcutaneous injection every 2 weeks.

Productivity, Service Delivery and Implementation Considerations:

Infliximab (3 IV doses) is recommended in NICE TA 163 as a treatment option for inducing remission in acute severe episodes of ulcerative colitis when IV cyclosporine is not a treatment option.⁶ Adalimumab (subcutaneously administered every 2 weeks) is not currently recommended by NICE for use in moderate to severe ulcerative colitis, as no submission was provided by the manufacturer.⁸ Golimumab may provide a subcutaneous alternative (administered every 4 weeks following induction) to the use of IV infliximab, which could potentially reduce impact on outpatient clinic time and resources. However, golimumab trial data relate to its use in induction followed by golimumab maintenance therapy, rather than induction followed by a switch to conventional (non-biologic) maintenance therapy. There is currently no evidence to demonstrate reduced need for surgery with golimumab treatment.

Innovation, Need and Equity Considerations:

Given the availability of alternative licensed biologics with the same indication in ulcerative colitis, there is no evidence to suggest golimumab provides a significant innovation or addresses significant unmet needs. No equity considerations are anticipated.

Recommended Place in Therapy

Golimumab is **not** recommended 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 (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

There is insufficient evidence available to justify the use of golimumab ahead of alternative biologic agents, which themselves are not recommended in moderate-to-severely active ulcerative colitis in NICE technology appraisals or the clinical guideline.

Financial and Service Implications

Comparative unit costs:

Table 1. Example annual acquisition costs of Golimumab and potential comparators when used for induction and maintenance in moderate to severe ulcerative colitis

Drug name and presentation	Example regimen	First-year cost per patient (ex VAT)
Golimumab 50mg , 100mg pre-filled pen for sc injection	Patient weight <80kg: 200mg at week 0, then 100mg at week 2, then 50mg every 4 weeks Patient weight ≥80kg 200mg at week 0, then 100mg at week 2, then 100mg every 4 weeks	£11,445†
Adalimumab 40mg prefilled pen/syringe for sc injection	160mg week 0, then 80mg week 2, then 40m every other week	£10,564

Infliximab 100mg vial for IV infusion	5mg/kg at week 0, then 5mg/kg at week 2 and week 6, then 5mg/kg every 8 weeks	£13,428*
<p>Costs based on BNF 66, September 2013.</p> <p>†Assumes that 100mg prefilled pen is available at the same cost as 50mg as in previous patient access schemes. If not, the first year annual cost would be £13,733 in patients with body weight <80kg and £22,889 for patients with body weight ≥80kg.</p> <p>*Assumes 70kg adult body weight for infliximab dosing. Excludes costs of IV administration</p> <p>This table does not imply therapeutic equivalence of drugs or doses.</p>		

Anticipated patient numbers and net budget impact:

Golimumab is licensed for the treatment for moderate to severe ulcerative colitis having 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 costing report for NICE CG 166 estimates a prevalence of ulcerative colitis of 240 per 100,000 population. Of these patients, the NICE report estimates that 36 per 100,000 population would experience 2 or more exacerbations per year and would require maintenance treatment with oral azathioprine (5%) or oral mercaptopurine (95%). Of these, 79% are assumed to be adults.¹⁰ This would equate to around 2,850 adults with ulcerative colitis in Lancashire, of which around 430 would require maintenance treatment with mercaptopurine or azathioprine.

The proportion of patients who would have an inadequate response to these treatments, or in whom these would not be clinical options, is currently uncertain. A Cochrane review of mercaptopurine and azathioprine for maintenance of remission¹¹ reported that available evidence was of poor quality for these agents. Based on evidence from 4 trials, 44% of azathioprine -treated patients failed to maintain remission compared with 65% on placebo. One small trial observed 58% of azathioprine treated patients failed to maintain remission compared with 83% of sulfasalazine. A further small trial observed 50% of mercaptopurine recipients failed to maintain remission compared with 100% on mesalazine.¹¹ Therefore, using a crude assumption that 50% of patients on azathioprine or mercaptopurine may fail to maintain remission, a crude estimate of 215 patients could potentially be eligible for golimumab treatment. Current prescribing of anti-TNFs in this patient group is unknown, but given the current NICE recommendations for infliximab and adalimumab, is likely to be negligible. Prescribing of golimumab in all potentially eligible patients would cost around £2.5million (assuming 100mg pre-filled pen available at 50mg list price, as in previous patient access schemes).

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