Executive Summary

Background

- Crohn's disease (CD) is a chronic inflammatory disease of the gastrointestinal tract of unknown aetiology. Crohn's disease occurs in all age groups but most commonly presents in those aged 15 to 25 years and is equally distributed amongst the sexes[i]. Guidelines issued by the British Society of Gastroenterology estimate the prevalence of CD to be 50-100 per 100,000 of the UK population[ii].

- In CD the lining of the affected areas of the gut is swollen and maybe ulcerated with thickening of the wall of the intestine. Crohn's disease can be complicated by the development of strictures, obstructions, fistulae and perianal disease. Most patients are at risk of recurrent attacks, with acute flares of the disease interspersed between periods of quiescent disease, although a subset of severe patients have chronically active disease. In any one year, 50% of patients will experience symptoms and these will be severe in about one quarter of all patients[ii,iii].

- In Crohn's disease surgery is not curative and management of disease is directed to minimising the impact of disease. At least 50% of all patients with CD require surgical treatment during the first 10 years of their disease; one in twelve will require two or more operations during this period. Following resection for ileal or ileocaecal disease, at least 50% of patients relapse within 10 years and about one half require further surgery. Five years after the onset of the disease 15-20% of patients are disabled by their disease and are unable to work[ii]. There are a number of state benefits to which patients with severe Crohn's disease may be eligible. It can be observed that a treatment that is able to maintain Crohn's disease patients in clinical remission could have a significant impact in terms of reducing reliance on state-funded benefits.

- The current treatment options and non-pharmacological interventions within the UK for the treatment of Crohn's disease are as follows:

  i. Aminosalicylates – mesalamine and sulphasalazine
  ii. Corticosteroids – prednisone and budesonide
  iii. Immunosuppressants – thiopurines and methotrexate
  iv. Anti-TNF agents – adalimumab and infliximab
  v. Other – antibiotics and supportive agents (antidiarrhoeals, antidepressants)
  vi. Surgery
  vii. Dietary measures

- In December 2002 and September 2003, adalimumab, a tumour necrosis factor (TNF) antagonist, was approved for reducing signs and symptoms and inhibiting progression of structural damage in adult patients with moderate to severely active rheumatoid arthritis (RA) in the USA and EU respectively. Since adalimumab has been shown to be effective and well-tolerated in RA, psoriatic arthritis and ankylosing spondylitis, and there is increasing evidence that TNF activity has a major role in Crohn's disease (raised levels are seen in all types of cells, tissues and secretory fluids in patients with the disease), a clinical programme was developed to study the safety and efficacy of adalimumab in patients with moderate to severely active Crohn's disease.

- At present, there are very few treatment options for patients with severe Crohn's disease. Corticosteroids are currently used by gastroenterologists to induce clinical remission but they have no role in the maintenance of remission due to their side effect profile[ii]. Furthermore, there is currently only one other licensed therapeutic option for patients with severe disease and that is the anti-TNF agent infliximab (Remicade). Clinical trials have

demonstrated the efficacy of infliximab for induction and maintenance therapy of patients with severe Crohn's disease. However infusions of infliximab, especially when given episodically, may result in the development of antibodies to infliximab, which in turn may lead to infusion reactions, loss of efficacy, and delayed hypersensitivity reactions[iv,v,vi,vii,viii]. As such, there is a large unmet need amongst patients with severe Crohn's disease in the UK.

▪ Adalimumab (HUMIRA®), a fully human monoclonal antibody, is licensed for the treatment of severely active Crohn's disease in patients who have not responded despite a full and adequate treatment with an immunosuppressant and/or corticosteroid. Therefore, adalimumab's suggested place in therapy is for the treatment of patients with severely active Crohn's disease who have failed treatment with one or more of these agents.

Clinical Effectiveness

Efficacy

▪ Due to the unpredictable nature of Crohn's disease (*i.e.* acute flare of symptoms at any given time and spontaneous periods of remission/quiescent disease), the adalimumab clinical development programme focused on both induction of remission (M02-403 - CLASSIC I; M04-691 – GAIN [Section 2.2]) and maintenance of remission (M02-404 – CHARM; M02-433 - CLASSIC II [Section 2.3]).

▪ Induction of clinical remission was clearly shown in the pivotal four week, double-blind, placebo controlled, phase III trial - M02-403 (Clinical Assessment of Adalimumab Safety and Efficacy Studied as Induction Therapy in Crohn's Disease - CLASSIC I), which evaluated adalimumab in anti-TNF naïve patients with moderate to severely active Crohn's disease[ix].

▪ Induction of clinical remission was also clearly demonstrated in the pivotal four-week, double-blind, placebo-controlled, phase III trial - M04-691 (Gauging Adalimumab efficacy in Infliximab Non-responders -GAIN), which evaluated adalimumab in patients with moderate to severely active Crohn's' disease who had experienced loss of efficacy or were intolerant to infliximab[x].

▪ Maintenance of remission at 26 and 56 weeks was effectively shown in the pivotal, phase III trial M02-404 (Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance - CHARM), which evaluated adalimumab in both anti-TNF naïve and experienced patients with moderate to severely active Crohn's disease[xi]. Improvements in the signs and symptoms of Crohn's disease were seen in both adalimumab treatment arms as indicated by statistically significant improvements in:

  o Percentage of responders in clinical remission (CDAI < 150)
  o Percentage of responders achieving $\geq$ 70 and $\geq$ 100 change from baseline in CDAI score
  o Mean IBDQ scores
  o Closure of draining fistulas

▪ Maintenance of remission has also been demonstrated in M02-433 (CLASSIC II), a phase II/III follow-up trial to M02-403, which evaluated adalimumab in anti-TNF naïve patients with moderate to severe Crohn's disease[xii]. The randomised cohort demonstrated maintenance of remission over 1 year and the open label cohort demonstrated continued improvements in response and remission through to 1 year.

▪ The aforementioned clinical trial programme comprehensively evaluates the safety and efficacy of adalimumab for both induction and maintenance of clinical remission in adult

patients with Crohn's disease. Clinical remission was the primary efficacy end-point in all the adalimumab trials. This is a more rigorous measure of response than the primary endpoints used in either the certolizumab pegol (decrease in CDAI score of 100 points from baseline) or natalizumab (decrease in CDAI score of 70 points from baseline) clinical trials.

- Furthermore, maintenance of remission was evaluated in controlled conditions up to 56 weeks for both adalimumab and natalizumab; this is in comparison to certolizumab pegol, for which maintenance therapy was evaluated for 26 weeks only.

Safety

- As of 14 February 2006, a total of 1,459 subjects with moderate to severe Crohn's disease had at least one dose of adalimumab during the clinical development programme, which equates to 1506 patient years (PY) of adalimumab exposure. Of these, 883 subjects were exposed to adalimumab for greater than six months and 661 were exposed to the anti-TNF agent for greater than one year[xiii].

- Across all the studies in the Crohn's disease clinical trial programme, the mean duration of adalimumab treatment and the mean number of all injections received were 377.0 days and 37.1 injections, respectively.

- In the induction of remission study, M02-403, adverse events occurred at similar frequencies in the adalimumab and placebo groups.

- In the pivotal maintenance of remission study, M02-404, adverse events occurred at similar frequencies in the adalimumab and placebo groups. A greater percentage of patients in the placebo group discontinued treatment because of an adverse event (13.4%) than in the adalimumab groups (6.9% and 4.7% for 40mg every other week and 40mg weekly groups, respectively).

- Serious adverse events that were reported in all the adalimumab-treated subjects were not suggestive of any new risks requiring changes to the current prescribing information.

- Antibodies to adalimumab were measured in M02-403 (CLASSIC I), M04-691 (GAIN) and M02-433 (CLASSIC II). In M02-403, only 2 patients developed antibodies against adalimumab. One patient in the placebo group had a positive assay for antibody to adalimumab at Week 0, and one patient in the adalimumab 160mg/80mg group had a positive assay at Week 2 with a subsequent negative assay at Week 4. In M04-691, none of 159 patients treated with adalimumab were positive for anti-adalimumab antibodies at Week 4. Finally, in M02-433, blood concentrations of adalimumab and antibodies to adalimumab were collected for 269 of the 276 patients. Of these 269, 7 (2.6%) were determined to have developed antibodies to adalimumab.

Cost Effectiveness

- This analysis estimated the cost-effectiveness of the proposed adalimumab Crohn's disease (CD) treatment regimen versus standard of care for patients with severe active disease and separately for moderate to severe active CD. The adalimumab regimen included induction doses of 80mg at initiation and 40mg at week two, followed by adalimumab maintenance therapy of 40mg every other week (eow) for responders at week 12, with potential to escalate the dose to every week (ew) dosing after flares. The time horizon was 56 weeks and lifetime respectively. Adalimumab was also compared to infliximab 5mg/kg maintenance therapy over one year. The analysis measured the utility and costs for the different treatment regimens using the NHS perspective for the base case analysis.

- A model was constructed that combined clinical, utility, and cost data. Four disease states (*i.e.*, remission; moderate; severe; very severe) based on CD activity index (CDAI) ranges were used as measures of patient disease status over time. Each disease state was linked to a standard gamble utility measured using independent, primary CD patient data. Similarly each disease state was also linked to expected number of hospitalisations and non-hospitalisation direct medical costs using data from trials and published literature. For the adalimumab arm, a cohort was constructed for the proposed adalimumab regimen using actual observations from the eow arm in a randomised controlled clinical trial (CHARM). For the standard care arm, the model simulated patient disease states based on randomised controlled trial data (CLASSIC I and CHARM) and calculated the probability of individuals being in each of the four disease states. The model analysed patient clinical status for 56 weeks. The model was also extended to lifetime, although it was recognised that the 56-week results rely on fewer assumptions. For both the adalimumab and standard care arms, time spent in disease states was converted to expectations of utility and direct non-hospitalisation medical costs. Hospitalisation costs were estimated from hospitalisation unit cost and a regression model based on CHARM trial data. Disease state specific non-hospitalisation, non-anti-TNF costs were summarised over time for each patient to include other direct medical costs. For the adalimumab vs. infliximab model, the adalimumab regimen was compared to infliximab 5mg/kg maintenance therapy. Percentage of patients in remission over time was used as the measure of clinical efficacy. Hospitalisation costs were primarily based on the rates reported in the trial.

- Compared to standard care (*i.e.*, conventional therapy), adalimumab is cost-effective for the treatment of patients with severe CD. It also appears to be cost-effective even for treating patients with moderate to severely active CD. Compared to standard care, adalimumab had a 56-week incremental cost-effectiveness ratio (ICER) of £10,959/quality adjusted life year (QALY) for treating severe patients and £29,268/QALY for treating patients with moderate to severe disease. Sensitivity analyses showed that the findings are robust. When treating patients over lifetime, the ICER was £868/QALY for severe patients and £12,035/QALY for moderate to severe patients.

- Compared to infliximab, using data from the indirect treatment comparison, adalimumab dominates infliximab maintenance therapy in costs and clinical outcomes, because of the lower costs and higher efficacy of adalimumab in terms of clinical remission.

- The balance between costs and effectiveness in comparison to standard care implies that adalimumab maintenance therapy is reasonably cost-effective. Furthermore, the proposed adalimumab regimen appears to be a cost-saving strategy over infliximab 5mg/kg maintenance therapy. Given its higher clinical remission rate and substantially lower total costs, adalimumab dominates infliximab maintenance therapy.

Conclusion

This submission demonstrates that adalimumab represents a clinical and cost-effective option for the treatment of adults with severe Crohn's disease for the NHS in England and Wales.

[i] Stange EF, Travis SPL, Vermeire S, Beglinger C, Kupcinkas L, Geboes K, Barakauskiene A *et al.* European evidence based consensus on the diagnosis and management of Crohn's disease: definitions and diagnosis. *Gut* 2006;**55**;1-15.

[ii] Carter MJ, Lobo AJ, Travis SPL; Guidelines for the management of inflammatory bowel disease in adults. *Gut* 2004;**53**;1-16.

[iii] Jewell D. Crohn's Disease. *Medicine* 1998; **26**(9):87-92.

[iv] Baert F, Noman M, Vermeire S, Van Assche G, D'Haens G, Carbonez A, Rutgeerts P. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. *N Engl J Med* 2003; **348**:601–608.

[v] Cheifetz A, Smedley M, Martin S, Reiter M, Leone G, Mayer L, Plevy S. The incidence and management of infusion reactions to infliximab: a large center experience. *Am J Gastroenterol* 2003; **98**:1315–1324.

[vi] Farrell RJ, Alsahli M, Jeen YT, Falchuk KR, Peppercorn MA, Michetti P. Intravenous hydrocortisone premedication reduces antibodies to infliximab in Crohn's disease: a randomized controlled trial. *Gastroenterology* 2003;**124**:917–924.

[vii] Hanauer S, Rutgeerts P, Targan S, Kam L, Present D, Mayer L, Wagner C, LaSorda J, Sands B, Livingston R. Delayed hypersensitity to infliximab (Remicade) re-infusion after a 2-4 year interval without treatment (abstr). *Gastroenterology* 1999;**116**:A731.

[viii] Hanauer SB, Wagner CL, Bala M, Mayer L, Travers S, Diamond RH, Olson A, Bao W, Rutgeerts P. Incidence and importance of antibody responses to infliximab after maintenance or episodic treatment in Crohn's disease. *Clin Gastroenterol Hepatol* 2004; **2**:542–553.

[ix] Hanauer S, Sandborn W, Rutgeerts P, Fedorak R, Lukas M, MacIntosh D, Panaccione R, Wolf D, Pollack P. Human Anti–Tumor Necrosis Factor Monoclonal Antibody (Adalimumab) in Crohn's Disease: the CLASSIC-I Trial. *Gastroenterology* 2006;130:323–333.

[x] *Sandborn W, Rutgeerts P, Enns R, Hanauer S, Colombel J, Pannacione R* et al. *Adalimumab Induction Therapy for Crohn Disease Previously Treated with Infliximab.* Annals of Internal Medicine *2007:***146***(12). Avaliable online at:*

http://www.annals.org/cgi/content/full/0000605-200706190-00159v1 - published on 19 June 2007.

[xi] Colombel J, Sandborn W, Rutgeerts P, Enns R, Hanauer S, Panaccione R, Schreiber S, Byczkowski, Li J, Jent J, Pollack P. Adalimumab for Maintenance of Clinical Response and Remission in Patients With Crohn's Disease: The CHARM Trial. *Gastroenterology 2007;132:52-65*

[xii] Sandborn W, Rutgeerts P, Hanauer S, Fedorak R, Luka M, MacIntosh D *et al.* Adalimumab for Maintenance Treatment of Crohn's Disease: Results of the CLASSIC II Trial. *Gut* 2007. First published online 13 February 2007 at: http://gut.bmj.com/cgi/content/abstract/gut.2006.106781v1

[xiii] Colombel JF, Sandborn WJ, Reinish W, Hanauer SB, Rutgeerts P, Sands B *et al.* Adalimumab Safety in Crohn's disease clinical trials. American Society of Gastroenterology