

## Executive Summary

### Crohn's Disease

A chronic inflammatory bowel disorder with unknown aetiology, Crohn's Disease (CD) affects approximately 60,000 individuals in the UK. The estimated prevalence of the condition is 1 in 1,000, with 3,000 – 6,000 newly diagnosed cases each year(1). The condition is most common in individuals between the ages of 15 and 30 and is often characterized by acute episodes interspersed with periods of remission.(2) Common symptoms include diarrhoea (90%), abdominal pain (54%), and weight loss (22%)(3). Patients with an active form of the disease can present with more severe symptoms including anal lesions, fever, and rectal bleeding. Two significant complications of CD include the development of fistulae in 17 to 43% of patients(3) and the need for surgery in up to two-thirds of patients.(2) In the longer term, as much as one-fifth of individuals suffering from CD will be greatly restricted in their daily activities within 5-10 years.(4)

### Current management of Crohn's Disease

The foundation of effective treatment for severe active CD is built upon chronic disease management and inflammation control. Goals of treatment include the induction and maintenance of remission as well as improvement in quality of life. To help patients achieve these goals, several drug therapy options are available including 5-aminosalicylate derivatives, oral or IV corticosteroids and immunomodulators such as 6-mercaptopurine (6-MP), azathioprine (AZA) and cyclosporine. Dietary and surgical interventions are also alternatives. Approximately 70% of patients will undergo at least one surgical procedure within 15 years of diagnosis. For patients with severe active CD (Harvey Bradshaw index >8, CD activity index >300) who are refractory to or intolerant of steroids and immunosuppression, and for whom surgery is inappropriate the TNF- $\alpha$  inhibitor infliximab is recommended (NICE, British Society for Gastroenterology).

### Infliximab (Remicade®) – product characteristics and license indications

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

Infliximab is indicated for the treatment of severe, active Crohn's disease, in patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies. Infliximab is also indicated for the treatment of fistulising, active Crohn's disease, in patients who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy). It is also indicated for the treatment of severe, active Crohn's disease, in paediatric patients aged 6 to 17 years, who have not responded to conventional therapy including a corticosteroid, an immunomodulator and primary nutrition therapy; or who are intolerant to or have contraindications for such therapies.

### The clinical effectiveness of infliximab in Crohn's Disease

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Evidence for infliximab as episodic treatment for severe active Crohn's disease has previously been assessed by NICE(5). Further clinical evidence is now available, as demonstrated through the randomized controlled trial ACCENT I, that supports the use of infliximab as a scheduled maintenance therapy. ACCENT I investigated the efficacy of 5 mg/kg infliximab at week 0, 2, 6, and every 8 weeks thereafter until week 46 (scheduled maintenance) and 5 mg/kg infliximab at week 0 (episodic). Results suggest that at week 30, 51% of CD patients treated with infliximab as scheduled maintenance demonstrated response (vs. 27% of patients randomized to episodic therapy).(6) At the final time point of 54 weeks, 28% (vs. 14%) of patients treated with scheduled maintenance (vs. episodic) infliximab were still in response. Among the patients with Crohn's Disease Activity Index scores of greater than 300, 21% achieved clinical remission.(7) Remission was associated with a reduction in hospitalizations and surgeries, an increase in employment, and quality of life similar to the general population.(8, 9)

Data from ACCENT II are similarly encouraging. This trial examined the efficacy of scheduled maintenance infliximab 5 mg/kg given at weeks 0, 2, 6, and every 8 weeks thereafter in fistulising CD.(10) By week 54, 46% of fistulising CD patients treated with scheduled maintenance infliximab achieved a response.(7) Secondary outcomes again prove the benefit of infliximab: active treatment significantly reduced hospitalizations, surgeries, and procedures compared with placebo.(11) A small retrospective analysis further highlights the benefit of scheduled maintenance versus episodic therapy with infliximab.(12) Williams et al. (2006) showed an improvement in rates of hospitalization, surgery and permanent disability in the long term among patients treated with scheduled maintenance. Indeed, this long-term improvement in outcomes suggests the potential superiority of scheduled maintenance over episodic therapy.

Mucosal healing is another clinical benefit of infliximab. The down-regulation of mucosal inflammation by infliximab is profound and rapid, leading to complete healing of the mucosa within weeks of initial treatment in many cases. Moreover, this healing can be sustained over time with scheduled maintenance treatment every 8 weeks and is associated with clinical remission and a reduction in hospitalizations and surgical procedures. This association of improved clinical outcomes with endoscopic healing is potentially unique to infliximab. It has not been observed in patients receiving other immunomodulating therapies in Crohn's disease.

### The cost-effectiveness of infliximab in Crohn's Disease

The average cost of scheduled maintenance treatment with infliximab per patient is estimated to be £10,839 for the first year of treatment (8 infusions, 5mg/kg at weeks 0, 2 and 6 and every 8 weeks thereafter), decreasing to £8,807 in a normal maintenance year (6.5 infusions) including the costs of administration. The estimated cost of infliximab as episodic treatment is estimated to be £2,981 per year.

An economic evaluation was performed to estimate the cost per Quality Adjusted Life Year (QALY) gained associated with each infliximab treatment strategy compared to usual care without infliximab in each patient population (severe active Crohn's, fistulising Crohn's, paediatric Crohn's). A Markov model was constructed to simulate the progression of hypothetical cohorts of patients receiving each relevant treatment strategy. Clinical outcomes for the purposes of this health economic evaluation were derived from available clinical

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studies and were supplemented with data from the literature for costs and outcomes where appropriate.

For adult patients with severe active CD, infliximab scheduled maintenance and episodic infliximab therapy were compared to standard care without infliximab. Episodic treatment with infliximab dominates a standard care treatment strategy; in other words it derives additional QALYs for a lower cost to the NHS. Maintenance therapy with infliximab is estimated on average to derive an additional 0.19 QALYs compared to standard care at an additional cost of £4,380. The expected cost per QALY gained for a maintenance treatment strategy with infliximab is £25,903.

In fistulising CD, a maintenance treatment strategy with infliximab is estimated to derive an additional 0.20 QALYs at an additional cost of £6,049. The incremental cost per QALY gained is estimated at £30,005. In paediatric Crohn's disease, a maintenance treatment strategy with infliximab is estimated to derive an additional 0.42 QALYs at a cost of £5,833 with an incremental cost per QALY gained of £13,891.

It is estimated that recommending infliximab scheduled maintenance therapy in England and Wales for patients licensed for infliximab (severe active, fistulising and paediatric), would cost £26.6 million at year 1 and £38.9 million at year 5 following introduction, assuming an 8-week dosing interval.

## Conclusion

Infliximab is a highly effective and well-tolerated therapy for the management of moderate-to-severe and fistulising adult and paediatric CD patients and provides significant clinical benefit over standard care. Economic analyses demonstrate that the incremental costs associated with achieving these clinical benefits are reasonable, and that infliximab represents a cost-effective treatment option, particularly if used episodically in patients with severe active CD. While the ICER for infliximab scheduled maintenance therapy in fistulising CD is slightly above the ICER threshold, it is still within the acceptable range while considering the clinical superiority of this dosing regimen has been proven in clinical practice during the past five years. Outcomes as measured in trials as well as routine care are vastly improved with infliximab scheduled maintenance therapy.