Infliximab for treatment of immunomodulator-naïve patients for treatment of acute and severe colitis refractory to intravenous corticosteroid therapy
Summary of SAMEP review

Receipt of High Cost Medicine (HCM) formulary application: 4th October 2012
Date of SAMEP meetings: 14th Nov 2012 & 16 Jan 2013

<table>
<thead>
<tr>
<th>Name of medicine</th>
<th>Infliximab (Tradename: Remicade®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage form</td>
<td>Powder for infusion</td>
</tr>
</tbody>
</table>

Requested Statewide HCM Formulary Listing

Treatment of immunomodulator-naïve patients as a bridge to thiopurine immunomodulator therapy for treatment of acute and severe:
- Crohn’s disease refractory to intravenous corticosteroid therapy
- Indeterminate colitis refractory to intravenous corticosteroid therapy
- Ulcerative colitis refractory to intravenous corticosteroid therapy in patients who have contra-indications to cyclosporine treatment as per cyclosporine product information (uncontrolled hypertension and renal impairment of any degree of severity).

Cost

The cost of a 100mg vial is $751.66
The proposed treatment course is 5mg/kg at week 0, week 2 and week 6.
The cost per patient per treatment course is therefore:

<table>
<thead>
<tr>
<th>Weight of patient</th>
<th>Dose</th>
<th>No. of vials required</th>
<th>Cost of single dose</th>
<th>Cost of treatment course (3 doses)</th>
</tr>
</thead>
<tbody>
<tr>
<td>60kg</td>
<td>300mg</td>
<td>3</td>
<td>$2,253</td>
<td>$6,759</td>
</tr>
<tr>
<td>70kg</td>
<td>350mg</td>
<td>4</td>
<td>$3,004</td>
<td>$9,012</td>
</tr>
<tr>
<td>80kg</td>
<td>400mg</td>
<td>4</td>
<td>$3,004</td>
<td>$9,012</td>
</tr>
</tbody>
</table>

SAMEP recommendations

Following the review of the current available evidence (appendix 1) and consideration of formal feedback from gastroenterology department heads / gastroenterologists with an interest in this area, SAMEP recommend the following:

- Infliximab is listed on the Statewide High Cost Medicines formulary for the treatment of acute severe colitis in immunomodulator-naïve patients as a bridge to thiopurine immunomodulator therapy for patients 16 years and older with:
  - Crohn’s disease refractory to intravenous corticosteroid therapy
  - Indeterminate colitis refractory to intravenous corticosteroid therapy
  - Ulcerative colitis refractory to intravenous corticosteroid therapy in patients who are contra-indicated to cyclosporine treatment
• The Clinical Pathway developed by SAMEP, in consultation with gastroenterologists specialising in inflammatory bowel disease (IBD), be adopted statewide (Appendix 2)

• The initial dose of infliximab for patients qualifying under this formulary listing is prescribed and administered by a gastroenterologist or trainee gastroenterologist at a recognised IBD service.
  ➢ As highlighted in the proposed clinical pathway, patients must be transferred to a recognised IBD service within 24 hours of admission.
  ➢ Subsequent infliximab doses (after the initial dose) can be administered at sites other than recognised IBD services, if required.

• Written information on the estimated effectiveness and possible risks of treatment with infliximab is provided to patients prior to the administration of the initial dose of the drug.

• For all use of infliximab outside of PBS-approved indications, prescribers must provide on-going prospective outcome data to their local hospital drug committee on a 12-monthly basis. A collated report of infliximab treatment for SAMEP-approved non-PBS indications should be forwarded to SAMEP from the hospital drug committees annually.
  ➢ Outcome data required for all patients who receive infliximab for the listed indications:
    ▪ Response after initial dose of infliximab
    ▪ Response after all 3 doses of infliximab
    ▪ If the patient proceeded to surgery
    ▪ If the patient proceeded to PBS-funded therapy with infliximab

SAMEP agreed that the number of surgeries averted or delayed by the administration of infliximab is the main indicator of effectiveness and therefore cost-effectiveness.

• For patients < 16 years of age, applicable drug committees can assess individual applications to use infliximab in patients with acute severe colitis who are immune-modulator naïve.

  ➢ SAMEP recommend applicable drug committees refer to the following practice guidelines when considering IPU requests in patients under 16 years of age:


• A pharmacy checklist form must be signed by the prescriber to ensure patient eligibility prior to dispensing of the high cost medicine.
Appendix 1  Review of the evidence

Comparator:

Ulcerative colitis: Cyclosporin or surgery  
Crohn’s disease: Surgery

Evaluations by other Jurisdictions

| Pharmaceutical Benefits Advisory Committee (PBAC) | · Ulcerative colitis → Infliximab has not been evaluated by PBAC for the treatment of ulcerative colitis.  
| · Crohn’s Disease:  
| | The PBAC have evaluated infliximab in Crohn’s Disease and it is listed on the PBS for patients who have failed treatment with prior systemic therapy (see summary document of PBS listings)  
| | March 2010: for complex fistulising Crohn disease with a draining enterocutaneous or rectovaginal fistula → recommended  
| | July 2007: the treatment of refractory moderate to severe Crohn’s disease in paediatric patients (aged 6-17 years inclusive) → recommended |

| Canadian Agency for Drugs and Technologies in Health (CADTH) / Canadian Expert Drug Advisory Committee (CEDAC) | · April 2009: Treatment of Ulcerative Colitis. CEDAC advice → listing not recommended  
| · July 2009: Overview of anti-TNFα drugs for refractory inflammatory bowel disease |

| Scottish Medicines Consortium (SMC) | · May 2007: Treatment of moderately to severely active ulcerative colitis. SMC Advice → not recommended  
| · March 2008: Treatment of severe, active Crohn’s disease in paediatric patients. SMC Advice → accepted  
| · July 2009: Treatment of ulcerative colitis. SMC Advice → not recommended  
| · October 2011: Treatment of moderately active Crohn’s disease. SMC advice → not recommended |

Clinical Guidelines

- **European Crohn’s and Colitis Organisation (ECCO)**

- **American College of Gastroenterology**

- **Canadian Association of Gastroenterology**

- **National Institute for Health and Clinical Excellence (NICE)**

Search strategy for additional evidence

**Population**  
Acute, severe Crohns Diease, Ulcerative Colitis, or indeterminate colitis as defined by Truelove & Witts criteria (Truelove and Witts 1955):

- More than 6 bloody stools per day
- Temperature >37.8°C
- Heart rate >90 beats per minute
- Haemoglobin < 135g/L (males) or <115g/L (females)
- Erythrocyte sedimentation rate (ESR) >30mm/hr;

Only ‘immunomodulator-naive’ patients (patients who have not been treated and failed treatment with azathioprine;

Infectious causes excluded

**Intervention**  
Infliximab (Tradename: Remicade®)

**Comparator(s)**  
Cyclosporin

OR

Surgery

**Outcome(s)**  
Timely induction of remission from colitis, avoidance of colectomy

**Databases searched (refer to appendix 4 for search terms)**

- Cochrane Database of Systematic Reviews
- Cochrane Central Register of Controlled Trials
- Medline

Selection criteria: Randomised controlled trials, Systematic reviews. No language restrictions.
Citations identified

The following applicable systematic reviews were identified in the Cochrane Database of systematic reviews (see Appendix 1 for search strategy):


The following applicable randomised controlled trials have been published since the publication of the Cochrane reviews listed above:


Summary of evidence

It is important to note that the formulary listing being proposed is for patients who are immunomodulator naïve. That is, they have not been previously treated with azathioprine or 6-mercaptopurine and are likely to be new patients presenting with severe disease.

Systematic reviews & meta-analyses

The majority of published systematic reviews of infliximab in Crohn’s disease focus on the efficacy and safety of maintenance therapy, rather than the induction of remission in severe acute disease. In many published trials, the initial dose of infliximab is often open-label with randomisation occurring in ‘responders’ following the first dose. This may be one reason why the evidence to support infliximab in maintenance therapy is stronger than for acute induction of remission.

A systematic review of the efficacy of infliximab in inducing remission in patients with acute moderate to severe ulcerative colitis, refractory to corticosteroids and/or immunomodulators, concluded that three IV infusions (at weeks 0, 2 and 6) is effective compared to placebo for inducing clinical remission, promoting mucosal healing and reducing the short-term need for colectomy (RR 3.22; 95% CI 2.18 – 4.76) (Lawson, Thomas et al. 2009).
The health technology assessment of infliximab in Crohn’s disease conducted by the Canadian Agency for Drugs and Technologies in Health (CADTH) noted that due to the limited number of clinical trials available it was difficult to pool the data quantitatively (CADTH 2002). The review identified one clinical trial for fistulising Crohn’s disease (CADTH, 2002). Results of the trial found that three infusions of infliximab (5 or 10mg/kg) at weeks 0, 2 and 6 was superior to placebo in achieving partial (62% vs. 26%, p=0.002) and complete (46% vs. 13%, p=0.001) closure of fistulas over 18 weeks. No significant dose response was observed.

**Randomised controlled trials**

The ACT I and ACT 2 trials are both multi-centre randomised double-blind placebo-controlled trials comparing infliximab to placebo for the treatment of moderate to severe acute ulcerative colitis (Rutgeerts, Sandborn et al. 2005). Compared to placebo, infliximab at a dose of 5mg/kg administered at weeks 0, 2 and 6 showed double the remission rate at week 8. In ACT 2, which included 364 patients, the response and remission rates at week 8 were:

<table>
<thead>
<tr>
<th></th>
<th>Response</th>
<th>Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>29.3%</td>
<td>5.7%</td>
</tr>
<tr>
<td>Infliximab 5mg/kg</td>
<td>64.5%</td>
<td>33.9%</td>
</tr>
<tr>
<td>Infliximab 10mg/kg</td>
<td>69.2%</td>
<td>27.5%</td>
</tr>
</tbody>
</table>

Although infliximab appears to be effective compared to placebo in treating severe active ulcerative colitis as shown in ACT 1 and ACT2, head-to-head clinical trials comparing infliximab to cyclosporin published to date have not had sufficient numbers to be adequately powered.

The recent publication by Laharie et al published online in October 2012 is the largest head-to-head study with 115 adult patients (Laharie, Bourreille et al. 2012). 93% of the patients in both groups (infliximab or cyclosporine) were azathioprine-naïve. There are a number of limitations with the trial, including it is not double-blinded, but open-label which introduces the possibility of measurement bias, especially as the Lichtiger score used includes very subjective measurements. Full blinding of trials involving cyclosporin are virtually impossible due to the therapeutic drug monitoring required in order to achieve the required therapeutic serum levels. Despite this trial not being blinded, it is the best directly comparative evidence published comparing the efficacy and safety of infliximab and cyclosporin for induction of remission in acute ulcerative colitis. Treatment failure was similar between the infliximab and cyclosporine groups, occurring in 35 out of 58 (60%) in the cyclosporin group and in 31 out of 57 (54%) in the infliximab group. Details of the trial are provided below:


<table>
<thead>
<tr>
<th>Funding of study</th>
<th>Association Francois Aupetit (registered charity for French IBD patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>The Societe Nationale Francaise de gastroenterology</td>
</tr>
<tr>
<td></td>
<td>The International Organisation for the Study of Inflammatory Bowel Disease</td>
</tr>
<tr>
<td>Design</td>
<td>Parallel, open-label, randomised controlled trial</td>
</tr>
<tr>
<td>Duration of treatment</td>
<td>Cyclosporin: IV for one week then oral up to day 98</td>
</tr>
<tr>
<td></td>
<td>Infliximab: IV on days 0,14 and 42</td>
</tr>
</tbody>
</table>
Patient population

- Adults ≥ 18 years
- Had acute ulcerative colitis defined by Lichtiger* score of greater than 10 points
- Had failed high dose IV steroid therapy defined as a minimum of 0.8mg/kg per day of methylprednisolone or equivalent for at least 5 days.
- Had not previously received cyclosporin or infliximab

Exclusions:
- Proctitis only
- History of colorectal dysplasia
- Crohn’s Disease
- +ve stool test for Clostridium difficile B toxin
- +ve chest Xray for tuberculosis or tuberculin skin test
- Active Hep B or C infection
- Uncontrolled bacterial or viral infection
- History of myocardial infarction, heart failure or malignant disease in past 5 years
- Renal failure
- Uncontrolled high blood pressure

Intervention

Infliximab 5mg/kg IV on days 0, then if responds, a repeat infusion on days 14 and 42.

All patients who “responded” at day 7, were initiated on azathioprine (Clinical response at day 7 – defined by Lichtiger* score response at days 5,6 and 7. That is, scores of <10 points with a decrease of at least 3 points from baseline)

No. of patients on intervention 57 (47% female, mean age: 36 years)

Comparator

Cyclosporin 2mg/kg IV for one week (dose adjusted at 48 hrs according to trough concentrations) then (if respond) followed by 4mg/kg orally (in two divided doses) until day 98.

All patients who “responded” at day 7 were initiated on azathioprine (Clinical response at day 7 – defined by Lichtiger* score response at days 5,6 and 7. That is, scores of <10 points with a decrease of at least 3 points from baseline).

No. of patients on comparator 58 (48% female, mean age: 39 years)

Primary efficacy outcome(s)

- Treatment failure at any time – defined as any of:
  - absence of clinical response at day 7
  - relapse between day 7 and 98
  - absence of steroid-free remission at day 98
  - severe adverse event leading to treatment cessation
  - colectomy
  - death

Secondary outcome(s)

- Clinical response at day 7
- Daily Lichtiger scores from day 0 to day 7
- Time to clinical response
- Mucosal healing at day 98
- Quality of life changes from baseline to day 98
- Colectomy-free survival
- Safety

Blinding of patients No
Blinding of outcome assessors No
Allocation concealment Yes
Withdrawals from intervention arm of study | 2
Withdrawals from placebo arm of study | 2

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Infliximab n=57</th>
<th>Cyclosporin n=58</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment failure (day 7)</td>
<td>9 (16%)</td>
<td>8 (14%)</td>
</tr>
<tr>
<td>Treatment failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(between day 7 and 98)</td>
<td>11 (19%)</td>
<td>13 (22%)</td>
</tr>
<tr>
<td>Treatment failure at day 98</td>
<td>11 (19%)</td>
<td>14 (24%)</td>
</tr>
<tr>
<td>Colectomy</td>
<td>12 (21%)</td>
<td>10 (17%)</td>
</tr>
<tr>
<td>Relapse</td>
<td>17 (30%)</td>
<td>19 (33%)</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Treatment failure (total)</td>
<td>31 (54%)</td>
<td>35 (60%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Infliximab n=57</th>
<th>No treatment n=58</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe infection</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Worsening of UC</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Other**</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Total adverse events</td>
<td>14 (25%)</td>
<td>9 (16%)</td>
</tr>
</tbody>
</table>

*Lichtiger score is a clinical index of 8 factors ranging from 0 to 21 points – See appendix 3. Acute severe colitis is defined as a score greater than 10 (Lichtiger, Present et al. 1994).

** Includes hepatic events that authors thought may have been attributed to azathioprine, MI, suspected pneumonia

**Effectiveness**

Clinical guidelines unanimously agree that intravenous corticosteroids are the most effective first-line treatment for acute severe colitis, and stress the importance of early consideration for surgery or second line therapy (within 72 hours) in those who fail to improve (Travis, Stange et al. 2008; Kornbluth and Sachar 2010; D’Haens, Panaccione et al. 2011; Bitton, Buie et al. 2012; NICE 2012, Oct).

**Ulcerative Colitis:** The largest head-to-head clinical trial comparing cyclosporin and infliximab in acute severe ulcerative colitis, in patients who had failed to respond to IV corticosteroids, found no strong evidence of a difference between the two drugs. Treatment failure occurred in 60% of the cyclosporin group and 54% of the infliximab group (absolute risk difference 6%; 95% CI -7 to 19%, p=0.52) (Laharie, Bourreille et al. 2012).

**Crohn’s Disease:** Infliximab has been used for nearly 15 years for the induction of remission in Crohn’s disease. While the quality of evidence to support maintenance therapy to prevent relapse of Crohn’s disease is high, the quality of published evidence to support the use of infliximab for the induction of remission in severe active Crohn’s disease is moderate, and there is much heterogeneity between clinical trials. However a number of systematic reviews have been published which show more patients respond to infliximab than placebo and clinical guidelines worldwide have based their recommendation for infliximab as a second-line option, following systemic corticosteroids, on the basis of these systematic reviews (NICE 2012; Travis, Stange et al. 2008; Kornbluth and Sachar 2010; D’Haens, Panaccione et al. 2011; Bitton, Buie et al. 2012). A recent systematic review identified three trials of infliximab in acute severe Crohn’s disease with a followup period of between 10-12 weeks (Ford, Sandborn et al. 2011). Overall, remission was not achieved in 169 of 309 patients (55%) receiving infliximab, compared with 189 of 253 (75%) patients receiving placebo (RR = 0.68; 95%CI 0.52 – 0.90, p=0.01).
Safety

A Cochrane review and network meta-analysis of the adverse effects of the biologic drugs, including infliximab, was published in 2012 (Singh, Wells et al. 2012). The review included randomised controlled trials (RCTs), controlled clinical trials (CCTs) and open-label extension studies (OLEs) which used one of nine biologics and reported adverse outcomes. Data was extracted independently by 10 reviewers. Although the review was limited by lack of head-to-head comparison studies of biologic drugs and a relatively low event rate for indirect comparisons, infliximab was associated with a statistically significant higher rate of total adverse events (OR = 1.57; 95%CI: 1.06 – 2.32) and withdrawals due to adverse events compared to controls (OR=2.34; 95% CI 1.40 – 4.14).

The most common adverse reactions related to infliximab treatment reported in clinical trials are injection site reactions, headache, upper respiratory tract infections, nausea, fatigue, joint pain, infections and fever. Delayed hypersensitivity reactions due to the development of antibodies to infliximab is common. In the ACCENT I trial, 14% of patients developed antibodies to infliximab (Hanauer, Feagan et al. 2002).

Post-marketing surveillance by the FDA has resulted in the publication of a safety alert in 2011 due to an increased reported number of a rare cancer of white cells, hepatosplenic T-cell lymphoma (HSTCL), in adolescents and young adults. HSTCL is an aggressive cancer and is usually fatal. All cases reported to the FDA to date have been in patients with Crohn’s disease or ulcerative colitis, and the majority were adolescent or young adult males. 18 out of 20 cases reported to the FDA received infliximab with concomitant azathioprine or 6-mercaptopurine (FDA 2011).

An increased risk of serious infection has also been identified by post-marketing surveillance, including reactivation of latent tuberculosis, invasive fungal infections and other opportunistic infections (FDA 2011). Before treatment with infliximab, patients should be screened for active and inactive tuberculosis (NICE 2010, May).

References


Laharie, D., A. Bourreille, et al. (2012). "Ciclosporin versus infliximab in patients with severe ulcerative colitis refractory to intravenous steroids: a parallel, open-label randomised controlled trial." The Lancet([Published online 9 Oct 2012]).


Appendix 2  Approved place in therapy / clinical pathway

TREATMENT ALGORITHM FOR IMMUNOMODULATOR-NAÏVE PATIENTS (≥16YRS OF AGE) WITH ACUTE SEVERE COLITIS

Acute Severe Colitis*

Admit to hospital. IV hydrocortisone 100mg four times daily. Transfer to recognised Inflammatory bowel disease (IBD) service within 24 hours. Consider colorectal surgical referral. Reassess at day 3.

No response

Colorectal surgical referral

Review diagnosis

Ulcerative colitis

Contraindicated to cyclosporin? (refer to appendix)

Yes

No

IV cyclosporin 2mg/kg/day. (Tritrate dose according to trough levels) Assess response at day 5.

Oral cyclosporin (5-6mg/kg/day)

Response

IV infliximab 5mg/kg (at weeks 2 & 6) Report outcome to drug committee

Start azathioprine 2-2.5mg/kg before discharge. Check thiopurine metabolites at 4 weeks.

No response

Surgery

Partial response

Continue steroids. Reassess days 5-7.

Response

No response

Continue steroids. Initiate oral prednisolone 40mg daily

Surgery

No response

Crohn’s Disease Or Undefined

IV infliximab 5mg/kg (Stat dose at week 0) Assess after first dose → report outcome to drug committee

Start azathioprine 2-2.5mg/kg before discharge.

*Acute severe colitis – defined as:
6 bloody bowel motions/day + one of the following:
- HR > 90 beats/min
- Temp > 37.8°C
- Hb < 135g/L (males) or Hb < 115g/L (females)
- ESR > 30mm/hr

* Refer to Appendix for detailed description

Day 1 examinations:
- Stool x 3 for C difficile toxin + microscopy, culture & sensitivity x 1
- Flexible sigmoidoscopy and biopsies to determine histopathological diagnosis
- Blood for HBsAg/Ab, HBcIgG, quantiferon gold
- Chest X-ray (and history for TB exposure)
- Abdominal X-ray

NB: Consider surgery at any time point if clinical deterioration or toxic megacolon
APPENDIX TO TREATMENT ALGORITHM

- Truelove & Witts criteria used to define acute severe colitis (Truelove & Witts, 1955).
  - Severe diarrhoea (≥6 motions a day) with macroscopic blood in stools and one or more of the following signs of systemic toxicity:
    - Fever (mean evening temperature greater than 37.5°C, or a temperature of 37.8°C or more on at least two days out of four).
    - Tachycardia (mean pulse rate > 90 beats per minute)
    - Haemoglobin < 10.5g/L
    - ESR >30mm/hr
    - CRP > 30mg/L

Severe colitis as defined according to Truelove and Witts' criteria is easy to apply in outpatients, mandates hospital admission for intensive treatment and defines an outcome (only 70% respond to intensive therapy). These criteria are recommended for identifying acute severe colitis by The American College of Gastroenterology (ACG) and the Association of Coloproctology of Great Britain and Ireland (ACPGBI), as well as ECCO (Dignass, Eliakim et al, 2012).

- Definitions of response to IV hydrocortisone (based on criteria described by Travis, 1996):
  - ‘Response’ = Decreased stool frequency and urgency, systemic signs of toxicity resolved (i.e. no tachycardia, fever), reduction in C-reactive protein (CRP) - if raised on day 1. Albumin and haemoglobin levels stable.
  - ‘Partial response’ = Stool frequency reduced (but still greater than 3/day), some clinical improvement but unclear if actual ‘responder’. If albumin (Alb) and haemoglobin (Hb) falling, define as ‘no response’.
  - ‘No response’ = Clinical condition unchanged (or worse) from day 1. Stool frequency same or increased from day 1, no improvement in systemic signs of toxicity, no reduction in CRP.

- Contra-indications to cyclosporin:
  - Renal impairment: Cyclosporin is not recommended for patients with an eGFR less than 60ml/min/1.73m² unless considered appropriate following renal specialist advice. Careful monitoring of renal function is required → cyclosporin may cause an increase in serum creatinine and urea levels due to a dose-dependent reduction in GFR.
  - Known hypersensitivity to cyclosporin or polyoxyethylated castor oil
  - Malignancy (excluding superficial squamous-cell carcinomas(SCC) or basal-cell carcinomas (BCC) in the last 10 years.
  - Uncontrolled hypertension
  - Severe infection

- Reporting of outcomes:

For all immunomodulator-naïve patients who are administered infliximab for acute severe colitis, the following outcomes must be reported to the local hospital drug committee, who in turn will supply de-identified data to SAMEP:
  - Response after initial dose of infliximab
  - Response after all three doses of infliximab
  - If the patient proceeded to surgery
  - If the patient proceeded to PBS-funded infliximab

REFERENCES


should obtain any appropriate professional advice relevant to their particular circumstances. The Department cannot guarantee and assumes no legal liability or responsibility for the accuracy, currency or completeness of the information.