CEDAC FINAL RECOMMENDATION
and
REASONS for RECOMMENDATION

INFLIXIMAB
(Remicade® – Centocor Inc.)
Indication: Ulcerative Colitis

Description:
Infliximab is a chimeric monoclonal antibody which binds to tumour necrosis factor alpha (TNFα). It is approved for use by Health Canada for reducing signs and symptoms, inducing and maintaining clinical remission, inducing and maintaining mucosal healing, and reducing or eliminating corticosteroid use in patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy. The review of infliximab by the Common Drug Review was initiated in response to a submission from the Advisory Committee on Pharmaceuticals.

Dosage Forms:
Supplied as infliximab 100 mg sterile powder for reconstitution. Infliximab is administered as an intravenous infusion. The recommended induction regimen is 5 mg/kg at 0, 2 and 6 weeks, followed by 5 mg/kg every 8 weeks thereafter. Doses up to 10 mg/kg may be used.

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that infliximab not be listed.

Reasons for the Recommendation:
1. The manufacturer reported an incremental cost per quality adjusted life year (QALY) estimate for infliximab of $125,000 compared to standard care, when continuing treatment in patients who achieve and maintain a mild ulcerative colitis state (Mayo score ≤5), based on utility values from the ACT 1 trial. The analysis was based on assumptions regarding a 5 mg/kg dose of infliximab and a 10-year time horizon. Upon reanalysis, where the time horizon is reduced and doses of infliximab are increased, the incremental cost per QALY estimate will significantly increase. The Committee felt that treatment with infliximab was not cost effective.

2. The ACT 1 and 2 trials were designed to test a primary outcome of clinical response at week 8. Follow up data to week 54 were available, however, patients who achieved response during the induction period were not re-randomized to infliximab or placebo. Without this trial design feature, uncertainty remains regarding the durability of effect and cost effectiveness of long term infliximab therapy.

Summary of Committee Considerations:

The Committee considered a systematic review that included five double-blind, placebo controlled, randomized controlled trials (RCTs) in patients with moderate to severe ulcerative colitis (n=827). The focus of the review was on the two largest trials, ACT 1 (n=364) and ACT 2 (n=364), where patients received 46 and 22 weeks of treatment, respectively, with infliximab 5 mg/kg, 10 mg/kg or placebo. The duration of follow up was 54 weeks for ACT 1 and 30 weeks for ACT 2. ACT 2 also had a 24 week extension period in which patients continued in their double blind randomized groups. No RCTs were identified which compared infliximab to other therapies for ulcerative colitis.

The primary outcome in the ACT 1 and 2 trials was clinical response at week 8. Other outcomes measured in the ACT 1 and 2 trials included clinical remission, quality of life (measured by the inflammatory bowel disease questionnaire and SF-36), rectal bleeding, mucosal healing, and reduction in corticosteroid use.

Colectomy data were retrospectively collected in the patients who participated in ACT 1 and 2. There were no statistically significant differences in colectomy rates at week 54 when intention to treat data were pooled for ACT 1 and 2 trials for the 5 mg/kg dose, versus placebo. However, there was a statistically significant improvement observed using these pooled data for the 10 mg/kg dose, versus placebo.

In ACT 1 and 2 at week 8 and week 30, both doses of infliximab demonstrated statistically significant improvements in quality of life, clinical response and clinical remission, relative to placebo. In ACT 1 and 2, sustained clinical remission at 30 weeks was defined as those who were in remission at 8 weeks and also at week 30. The percent of patients with sustained remission at week 30 was statistically significantly greater in the infliximab 10 mg/kg group compared to placebo, but no statistically significant difference was observed between infliximab 5 mg/kg and placebo. Assessments conducted at week 30 also showed statistically significant improvement in total serious adverse events, rectal bleeding, mucosal healing, and reduction in corticosteroid use, in patients continuing on infliximab relative to placebo. No clear advantage was seen for infliximab 10 mg/kg compared to infliximab 5 mg/kg, but the studies were not powered to detect differences between infliximab doses.

The validity of the ACT 1 and 2 trial results is limited by several issues. A high proportion of patients were lost to follow up in the ACT 1 and 2 trials. Response and remission data were reported at week 30 and some assessments were made at later timepoints, but high attrition reduces confidence in the estimates. At week 30, data were missing for 39% of placebo and 20% of infliximab patients. Although a large proportion of patients were using azathioprine or 6-mercaptopurine, it is unknown how many patients previously failed immunosuppressants because failure was not clearly defined. Additionally, instead of one treatment arm stopping infliximab after 3 infusions, all patients received ongoing infliximab or placebo. Therefore, the ACT 1 and 2 study design does not allow a definitive assessment of whether additional doses of infliximab provide an advantage over the initial three infusions provided at the induction stage.

The other three smaller trials evaluated were studies by Jarnerot et al (n=45, 90 day follow up) in hospitalized patients with acute fulminant colitis, Probert et al (n=43, 8 weeks) in patients who failed to respond to glucocorticoids and Sands et al, which was terminated early due to low enrolment (n=11, 10 weeks follow up). The Jarnerot trial reported a statistically significant difference in colectomy rates between one dose of infliximab 5 mg/kg versus placebo [odds ratio: 4.9 (95% CI 1.4 to 17, P=0.017)], in favour of infliximab. This small trial was conducted in a highly selected, hospitalized population which falls outside of the listing consideration for this recommendation.

In the cost-utility analysis submitted by the manufacturer, infliximab plus standard care was compared to standard care alone over a 10-year analysis time frame. Two treatment strategies were considered: continued treatment with infliximab for patients achieving and maintaining at least mild ulcerative colitis (Mayo score ≤ 5), and continued treatment with infliximab for patients achieving and maintaining remission (Mayo score ≤ 2). The manufacturer reported that infliximab is associated with an incremental cost per QALY of $70,000 when continuing treatment in patients maintaining a Mayo score ≤ 5, or $54,000 when continuing treatment in patients maintaining a Mayo score ≤ 2. When using the utility values from the ACT 1 trial, the manufacturer reported that the incremental cost per QALY increased to $125,000 for patients maintaining a Mayo score ≤ 5 and $115,000 for patients maintaining a Mayo score ≤ 2. The manufacturer noted that the results are sensitive to changes in the analysis time frame. When considering a 2-year analysis, the manufacturer reported that the incremental cost per QALY estimates increased to $126,000 for patients maintaining a Mayo score ≤ 5 and $78,000 for patients maintaining a Mayo score ≤ 2. CDR identified a number of limitations that would further increase the cost per QALY estimate for infliximab: exclusion of the cost of infusion; potential wastage of partially used vials of infliximab; treatment strategies considered by the manufacturer in their economic model may not be reflective of actual practice since clinicians may not base assessment of response on Mayo criteria; and, the analyses have not considered the possible use of infliximab at doses higher than 5 mg/kg.

At recommended maintenance doses for a 70 kg patient, the annual cost of infliximab 5 mg/kg is $30,080 in the first year and $22,440 thereafter.

Of Note:
1. Both published and unpublished data were reviewed and taken into consideration in making this recommendation.
2. The ACT 1 and 2 trials provide some evidence suggesting that infliximab is effective for induction of remission (3 doses) versus placebo, however, the cost effectiveness of infliximab relative to other currently available induction therapies for ulcerative colitis has not been demonstrated.
3. The Committee considered the fact that there may be patients with ulcerative colitis who are not candidates for surgery and therefore have fewer treatment alternatives. However, clinical data was not available for this patient subgroup and the economic evaluation submitted by the manufacturer was not reflective of these patients, therefore, the cost effectiveness of infliximab use in such groups is unknown.
4. The manufacturer has reviewed this document and has not requested the removal of any confidential information, in conformity with the CDR Confidentiality Guidelines.

Background:
CEDAC provides formulary listing recommendations to publicly funded drug plans. Recommendations are based on an evidence-based review of the medication's effectiveness and safety and an assessment of its cost-effectiveness in comparison to other available treatment options. For example, if a new medication is more expensive than other treatments, the Committee considers whether any advantages of the new medication justify the higher price. If the recommendation is not to list a drug, the Committee has concerns regarding the balance between benefit and harm for the medication, and/or concerns about whether the medication provides good value for public drug plans.

The CEDAC Final Recommendation and Reasons for Recommendation neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice. CADTH is not legally responsible for any damages arising from the use or misuse of any information contained in or implied by the contents of this document.

The statements, conclusions, and views expressed herein do not necessarily represent the view of Health Canada or any provincial, territorial or federal government or the manufacturer.