CDEC FINAL RECOMMENDATION

GOLIMUMAB
(Simponi — Janssen Inc.)
New Indication: Ulcerative Colitis

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that golimumab not be listed at the submitted price for the treatment of ulcerative colitis (UC).

Reasons for the Recommendation:

1. Given the limitations identified with the manufacturer's pharmacoeconomic submission, CDEC noted that the cost-effectiveness of golimumab could not be properly assessed.
2. Two randomized controlled trials (RCTs) demonstrated that golimumab was superior to placebo for achieving clinical response and clinical remission in patients with UC.

Background:
Golimumab is a human monoclonal antibody to tumour necrosis factor (TNF)-alpha indicated for the management of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and UC. The current Common Drug Review (CDR) submission is for the treatment of adult patients with moderately to severely active UC who have had an inadequate response to, or have medical contraindications for, conventional therapy including corticosteroids, aminosalicylates, azathioprine, or 6-mercaptopurine, for inducing and maintaining clinical response (reduction in signs and symptoms), inducing clinical remission, achieving sustained clinical remission in induction responders, and improving endoscopic appearance of the mucosa during induction.

The product monograph recommends the following dosage regimen for adults with UC: 200 mg administered by subcutaneous injection at week 0, followed by 100 mg at week 2 and then 50 mg every four weeks thereafter. The treating physician may utilize 100 mg every four weeks as a maintenance dose if necessary.

Submission History:
Golimumab has been previously reviewed by the Canadian Expert Drug Advisory Committee (CEDAC) for the treatment of patients with moderately to severely active rheumatoid arthritis, moderate to severe psoriatic arthritis, and ankylosing spondylitis. All three indications received a recommendation to "list in a similar manner" to TNF inhibitors (see Notice of CEDAC Final Recommendations, March 17, 2010).

Summary of CDEC Considerations

CDEC considered the following information prepared by CDR: a systematic review of RCTs of golimumab for UC, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients.

Patient Input Information

The following is a summary of information provided by two patient groups that responded to the CDR call for patient input:

- Individuals with UC can experience a range of gastrointestinal symptoms including rectal bleeding, diarrhea, abdominal pain, and constipation. If the diarrhea and blood loss are severe, anemia can result. In addition, some patients have extra-intestinal manifestations of UC, including fever, inflammation of the eyes or joints, ulcers of the mouth or skin, tender inflamed nodules on the shins, and reduced fertility in women. Respondents indicated that sustained remission/treatment response is more important than relieving any one symptom.
- UC often has a profound effect on the lives of those living with the condition, affecting their physical, emotional, and social well-being. Challenges for caregivers include absences from work, which may jeopardize job security; high costs of care; and dealing with negative emotional and mental health such as fatigue, stress, and depression.
- Patient groups indicated that individuals with UC have seen remarkable results from biologics when other treatments have failed; however, not everyone responds to the currently available treatments, so more options are essential. It was noted that subcutaneous administration can be more convenient than the intravenous infusions required for some of the drugs that are currently in use.

Clinical Trials

The CDR systematic review included two placebo-controlled, double-blind, RCTs. PURSUIT-SC was a two-part induction study that included a dose-finding phase (N = 169) where patients were randomized to one of four doses of golimumab in order to establish the doses that would be used in the next part of the study. In Part 2, 896 new patients were randomized to golimumab 200 mg to 100 mg (GO200-100; start 200 mg at week 0, then 100 mg at week 2), golimumab 400 mg to 200 mg (GO400-200; start 400 mg at week 0, then 200 mg at week 2), or placebo for six weeks. PURSUIT-MAINTENANCE included patients who were responders in PURSUIT-SC and in PURSUIT-IV (not included in this review due to the route of administration). PURSUIT-MAINTENANCE enrolled 464 patients, and treatment with golimumab 50 mg (GO50), golimumab 100 mg (GO100), or placebo continued for 52 weeks.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- Clinical response — defined as a decrease from baseline in the Mayo score by ≥ 30% and ≥ 3 points, with either a decrease from baseline in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1. The Mayo score is calculated as the sum of the four subscores of stool frequency, rectal bleeding, physician's global assessment, and the findings of endoscopy. A score of 3 to 5 points indicates mildly active disease, a score of 6 to 10 points indicates moderately active disease, and a score of 11 to 12 points indicates severely active disease.
- Clinical remission — defined as a Mayo score ≤ 2 points, with no individual subscore > 1.

- Health-related quality of life (HRQoL) — assessed using the Inflammatory Bowel Disease Questionnaire (IBDQ), the EuroQol 5-Dimension Health-Related Quality of Life Questionnaire (EQ-5D) instrument, the SF-36 physical component summary (PCS), and the SF-36 mental component summary (MCS).
- Serious adverse events, total adverse events, and withdrawals due to adverse events.

The primary outcome of both PURSUIT-SC and PURSUIT-MAINTENANCE was clinical response through the end of treatment.

Efficacy

- A greater proportion of golimumab-treated patients demonstrated a clinical response compared with placebo-treated patients in both studies:
  - GO200-100 (52%) versus placebo (30%); *P* < 0.0001 in PURSUIT-SC.
  - GO400-200 (55%) versus placebo (30%); *P* < 0.0001 in PURSUIT-SC.
  - GO50 (47%) versus placebo (31%); *P* = 0.010 in PURSUIT-MAINTENANCE.
  - GO100 (51%) versus placebo (31%); *P* < 0.001 in PURSUIT-MAINTENANCE.
- A greater proportion of golimumab-treated patients versus placebo demonstrated clinical remission in each of the studies.
  - GO200-100 (19%) versus placebo (6%), *P* < 0.0001, in PURSUIT-SC.
  - GO400-200 (18%) versus placebo (6%), *P* < 0.0001, in PURSUIT-SC.
  - GO50 (24%) versus placebo (15%), *P* = 0.091, in PURSUIT-MAINTENANCE.
  - GO100 (29%) versus placebo (15%), *P* = 0.003, in PURSUIT-MAINTENANCE.

[redacted]

Harms (Safety and Tolerability)

- The proportion of patients with at least one adverse event was reported as follows:
  - GO200-100 (38%), GO400-200 (39%), placebo (38%) in PURSUIT-SC.
  - GO50 (73%), GO100 (73%), placebo (66%) in PURSUIT-MAINTENANCE.
- The proportion of patients with at least one serious adverse event was reported as follows:
  - GO200-100 (3%), GO400-200 (3%), placebo (6%) in PURSUIT-SC.
  - GO50 (8%), GO100 (14%), placebo (8%) in PURSUIT-MAINTENANCE.
- Withdrawals due to adverse events were reported as follows:
  - GO200-100 (0.3%), GO400-200 (0.3%), placebo (0.9%) in PURSUIT-SC.
  - GO50 ([redacted]), GO100 ([redacted]), placebo ([redacted]) in PURSUIT-MAINTENANCE.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis (CUA) and a cost-minimization analysis. The CUA was considered the primary analysis as biologic therapies are not listed by the majority of public drug plans for the treatment of UC, and the results of the manufacturer's indirect treatment comparison (ITC) suggested that there may be differences in clinical outcomes across

biologic therapies for UC. Therefore, CDEC focused primarily on the CUA for the purpose of making a recommendation.

In the CUA, golimumab was compared with conventional therapy (defined by the medication regimen of the placebo cohort from the PURSUIT-SC and PURSUIT-MAINTENANCE trials — oral corticosteroids, immune-modulators [6-mercaptopurine, azathioprine, and methotrexate], and/or oral 5-aminosalicylate compounds), infliximab, and adalimumab. The target population were patients with moderately to severely active UC (defined by a Mayo score of 6 to 12 and an endoscopic subscore of ≥ 2), following an inadequate response to conventional treatments during a 10-year time horizon. Treatment efficacy in terms of inducing clinical response or clinical remission was reportedly taken from an ITC conducted by the manufacturer. Quality of life was estimated using utilities based on the EQ-5D visual analogue scale from published literature for post-colectomy health states. The manufacturer reported that when compared with conventional therapy, golimumab 50 mg and 100 mg were associated with an incremental cost per quality-adjusted life-year (incremental cost-utility ratio [ICUR]) of $41,591 and $42,271 respectively. Infliximab and adalimumab were associated with ICURs of $65,982 and $68,722 respectively, compared with conventional therapy.

A key limitation with the manufacturer's economic evaluation was the lack of transparency regarding its methods and how data were included in the model. The lack of clarity about the methods applied in the model, with respect to estimating transition probabilities for response and remission for each treatment and the transformations of the ITC data before they were incorporated into the model, limited the ability of CDR to independently review and verify the results. In addition, the model was based on a manufacturer-sponsored ITC that was limited by the small number of trials and patients, differences in trial design, and heterogeneity in placebo comparator groups. Due to the identified limitations of the submitted economic evaluation, CDR was unable to conduct re-analyses to investigate the impact of alternate values for input variables and varying the association among outcomes. To attempt to address this uncertainty, CDR conducted additional re-analyses reducing the time horizon of the analysis from 10 years to shorter durations to align with clinical data. The results of these analyses indicate that the ICUR for golimumab compared with conventional therapy could be as high as $104,000 per QALY when the time horizon is reduced to 1.25 years (15 months) from $52,000 for a time horizon of 2.5 years. The issues identified by CDR in the review of the manufacturer's economic evaluation suggested that the results may be biased in favour of golimumab; however, given the issues identified with the manufacturer's economic model, a full assessment of the uncertainty was not possible and likely cost-effectiveness of the golimumab could not be determined.

Golimumab is available in 50 mg/0.5 mL and 100 mg/1.0 mL pre-filled syringes at a price of $1,490.41 per syringe regardless of strength. The annual cost of golimumab is $22,356 in the first year and $19,375 in subsequent years (200 mg week 0, 100 mg week 2, and 50 or 100 mg every 4 weeks thereafter) and the annual cost of infliximab is $29,046 in the first year and $23,600 in subsequent years (5 mg/kg at weeks 0, 2, and 6, and every 8 weeks thereafter) - assuming a patient weight of 75 kg.

Other Discussion Points:
CDEC noted the following:

- The clinical data reported in the PURSUIT-SC and PURSUIT-MAINTENANCE trials supported the clinical benefit of golimumab for the treatment of UC; however, because of the limitations noted with the manufacturer's pharmacoeconomic submission, CDR was unable to fully evaluate the cost-effectiveness of golimumab, and CDEC could not be confident that golimumab is cost-effective at the submitted price.

Research Gaps:
CDEC noted that there is an absence of evidence regarding the following:

- There are no direct comparisons of golimumab against other biologic drugs approved for use in the treatment of UC.

CDEC Members:
Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

Regrets:
January 15, 2014: One CDEC member could not attend the meeting.
February 19, 2014: One CDEC member could not attend the meeting.

Conflicts of Interest:
None

About this Document:
CDEC provides formulary listing recommendations or advice to CDR participating drug plans.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The CDEC recommendation or record of advice neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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