CEDAC FINAL RECOMMENDATION

GOLIMUMAB
(Simponi – Schering Plough Inc.)
Indication: Rheumatoid Arthritis

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that golimumab in combination with methotrexate be listed in a similar manner to other tumor necrosis factor alpha inhibitors for moderately to severely active rheumatoid arthritis.

Golimumab dosing should be restricted to a maximum of 50 mg once a month. Response to golimumab should be assessed after 14 to 16 weeks of treatment and therapy be continued only if there is a clinical response.

Reasons for the Recommendation:
1. Four double-blind randomized controlled trials were included in the CDR systematic review evaluating golimumab in patients with moderately to severely active rheumatoid arthritis; one was conducted in methotrexate-naive patients, two were conducted in methotrexate-experienced patients, and one was conducted in patients previously exposed to tumor necrosis factor alpha inhibitors. In three trials, golimumab was evaluated in combination with methotrexate; in the fourth trial, patients remained on prior disease-modifying antirheumatic drug therapy, which could include methotrexate. In all trials, golimumab 50 mg was statistically significantly better than placebo with respect to the proportion of patients achieving ACR 20, ACR 50 and ACR 70 response, as well as other outcomes measuring improvement in the symptoms of moderate to severe rheumatoid arthritis.
2. The annual cost of golimumab is less than the cost of other tumor necrosis factor alpha inhibitors used to treat rheumatoid arthritis when it is administered 12 times per year.

Of Note:
The Committee noted that while there are four other tumor necrosis factor (TNF) alpha inhibitors available for the treatment of rheumatoid arthritis, there are no head-to-head trials of golimumab compared with these other TNF alpha inhibitors.

Background:
Golimumab is a human monoclonal antibody to TNF alpha with a Health Canada indication for use in combination with methotrexate, for reducing signs and symptoms in adult patients with moderately to severely active rheumatoid arthritis. This indication is the focus of this recommendation. Golimumab also has the following Health Canada indications:

- for reducing signs and symptoms of adult patients with active ankylosing spondylitis who have had an inadequate response to conventional therapies;
- for reducing the signs and symptoms in adult patients with moderately to severely active psoriatic arthritis, alone or in combination with methotrexate. In patients with psoriatic arthritis, it can be used in combination with methotrexate in those who have not responded adequately to methotrexate alone.

The Health Canada recommended dose of golimumab for rheumatoid arthritis is 50 mg given as a subcutaneous injection once a month on the same date each month. It is available as an autoinjector and a prefilled syringe containing golimumab 50 mg in 0.5 mL of solution.

Summary of CEDAC Considerations:
The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of double-blind randomized controlled trials (RCTs) of golimumab and a critique of the manufacturer's pharmacoeconomic evaluation.

Clinical Trials
The CDR systematic review included four manufacturer-sponsored, double-blind, placebo-controlled RCTs evaluating golimumab 50 mg and golimumab 100 mg every four weeks in patients with active rheumatoid arthritis (GO-BEFORE, GO-FORWARD, GO-AFTER, and the Kay 2008 study). The Kay 2008 study (N = 172) was a phase two study evaluating two and four-week dosing regimens of golimumab in methotrexate-experienced patients, but was not discussed by the Committee.

Three different patient populations were evaluated in the other three trials:

- GO-BEFORE (N = 637) evaluated golimumab over 52 weeks in methotrexate-naive patients. In all groups randomized to receive methotrexate as part of the intervention, methotrexate doses started at 10 mg per week and were escalated by 2.5 mg every two weeks to 20 mg per week by week eight.
- GO-FORWARD (N = 444) evaluated golimumab over 24 weeks in methotrexate-experienced patients. For patients who received methotrexate as part of the intervention, doses were based on stable pre-study doses.
- GO-AFTER (N = 461) evaluated golimumab over 24 weeks in patients exposed to a TNF alpha inhibitor. Inclusion criteria for GO-AFTER were not limited by previous disease-modifying antirheumatic drug (DMARD) or methotrexate experience and methotrexate was not specifically part of the intervention. Background DMARDs were permitted based on stable pre-study therapies, and approximately two-thirds of patients received concomitant methotrexate during the trial.

For GO-BEFORE, GO-FORWARD, and GO-AFTER, patients with less than 20% improvement in tender and swollen joints at a certain point in the trial met early escape criteria. Early escape

criteria were applied at week 28 in GO-BEFORE, and at week 16 in both GO-FORWARD and GO-AFTER. Early escape time points were always after the primary outcome or first co-primary outcome had been measured. Patients meeting the early escape criteria in the placebo group began receiving golimumab 50 mg, those in the 50 mg group had their dose escalated to golimumab 100 mg and those in the 100 mg group continued receiving 100 mg golimumab. Entry into early escape was double-blinded. Patients who met early escape criteria had observations from that point, carried forward for analyses at future time points. The proportion of patients meeting the early escape criteria ranged from 11.3% to 46.4% across trials and treatment groups. There were an additional 2.2% to 20.0% of patients across trials and treatment groups who discontinued treatment by the end of the study.

Outcomes

The primary and co-primary outcomes in the trials were the proportion of patients with at least a 50% improvement in American College of Rheumatology response criteria (ACR 50) at week 24 and the change from baseline in van der Heijde modified Sharp score (vdH-S) at week 52 in GO-BEFORE; ACR 20 at week 14 and the change from baseline in physical function as assessed by the Health Assessment Questionnaire (HAQ) at week 24 in GO-FORWARD; and ACR20 at week 14 in GO-AFTER.

The ACR response criteria include the following components: swollen joint counts; tender joint counts; patient global assessment of disease activity; physician assessment of disease activity; patient assessment of pain; physical function as assessed by the HAQ; and either C-reactive protein levels or erythrocyte sedimentation rates. Patients are considered ACR 20 responders if they have a 20% improvement from baseline in swollen and tender joint count plus a 20% improvement in three of the five other components.

The vdH-S scale, also known as the modified Sharp scale, measures radiographic progression and has scores ranging from zero to 440 with higher scores indicating greater disease severity. A consensus panel has estimated that in patients with rheumatoid arthritis the minimum clinically important difference on the vdH-S scale is 4.6 points.

The HAQ, a self-reported instrument, includes a disability index that is used to assess functional status and disability in rheumatic diseases. Scores range from zero to three; higher scores indicate a greater disability. A reduction of 0.22 units is considered clinically relevant in patients with rheumatoid arthritis.

Other outcomes were also defined a priori in the CDR systematic review protocol. Of these outcomes, the Committee discussed the following: work productivity and quality of life.

Results

Efficacy or Effectiveness

- In all trials, the proportion of patients achieving an ACR 20, ACR 50 or ACR 70 response was statistically significantly greater in the golimumab 50 mg groups compared with placebo.
- Golimumab 50 mg significantly inhibited radiographic progression compared with placebo in GO-BEFORE at 52 weeks. In GO-FORWARD, radiographic progression (as measured by

the change from baseline in vdH-S score) was not observed in either the golimumab group or the placebo group at week 24. The lack of progression may be attributed to the short duration of the trial and the low disease activity observed in patients included in GO-FORWARD (e.g. high CRP levels, low tender and swollen joint counts, low baseline vdH-S scores).

- Statistically significant and clinically relevant improvements in HAQ were observed for golimumab 50 mg compared with placebo in all trials.
- Statistically significant improvements in quality of life and work productivity outcomes were not consistently observed across the four trials for golimumab 50 mg compared with placebo.
- Efficacy appeared similar between the 50 mg and 100 mg golimumab dose groups. Among patients entering early escape and who had their golimumab dose escalated from 50 mg to 100 mg, very few achieved an ACR 20 response, indicating limited benefit for a dose escalation strategy in patients who are non-responders.
- In GO-AFTER, a manufacturer pre-specified subgroup analysis based on ACR 20 response found that the efficacy of golimumab was similar in patients regardless of the reason why they had previously discontinued a TNF alpha inhibitor. Reasons for discontinuation included a lack of efficacy; intolerance; and other reasons such as financial burden or lack of access.

Harms (Safety and Tolerability)

- The proportion of patients reporting a serious adverse event was similar between golimumab 50 mg groups and placebo groups in GO-BEFORE (11% versus 14% respectively), GO-FORWARD (6.7% versus 3.8% respectively) and GO-AFTER (7.2% versus 9.7% respectively).
- The proportion of patients reporting a serious infection was similar between golimumab and placebo groups, ranging from 0.8% to 3.8% across trials and treatment groups. There was one (0.6%) case of tuberculosis in a patient receiving golimumab 50 mg in GO-BEFORE.
- In GO-BEFORE, there were four malignancies, one (0.6%) in the golimumab 50 mg group, one (0.3%) in the golimumab 100 mg groups and two (1.2%) in the placebo group. In GO-FORWARD, there were three malignancies, two (0.9%) in the golimumab 100 mg group, and one (0.7%) in the placebo group. In GO-AFTER, there were two malignancies, one (0.6%) in the golimumab 100 mg group and one (0.6%) in the placebo group.
- Across all studies, there were no reports of lupus and only one (0.7%) report of congestive heart failure in a golimumab patient in the Kay study.
- In all studies, withdrawals due to adverse events were low and similar between golimumab 50 mg groups and placebo groups.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-minimization analysis comparing golimumab with etanercept, adalimumab, infliximab, rituximab, anakinra, and abatacept in patients with active rheumatoid arthritis and who had not responded to adequate trials of DMARDs. The Committee accepted the cost minimization analysis and considered the costs of golimumab and other TNF alpha inhibitors. The annual cost of golimumab ($17,364; 50 mg monthly) is less than etanercept ($18,995; 50 mg weekly) and adalimumab ($18,438; 40 mg every other week). Golimumab may cost more or less than infliximab depending on patient weight, dosing of infliximab and potential vial wastage.

Other Discussion Points:

- The Health Canada recommended dosing regimen is golimumab 50 mg once a month (12 doses per year) but the regimen evaluated in clinical trials is golimumab 50 mg every four weeks (13 doses per year). If golimumab was administered 13 times per year, its cost would be more similar to other TNF alpha inhibitors.
- The maximum duration of therapy of golimumab is unknown.
- The Committee discussed the range of trials and populations in which golimumab has been evaluated and that GO-AFTER is the first RCT evaluating the effect of TNF alpha inhibitors in patients previously exposed to TNF alpha inhibitors. The uncertainty surrounding the cost-effectiveness of sequential TNF alpha inhibitor therapy was also discussed.

CEDAC Members Participating:
Dr. Robert Peterson (Chair), Dr. Michael Allan, Dr. Ken Bassett, Dr. Bruce Carleton, Dr. Doug Coyle, Mr. John Deven, Dr. Alan Forster, Dr. Laurie Mallery, Mr. Brad Neubauer, Dr. Lindsay Nicolle and Dr. Kelly Zarnke.

Regrets:
Dr. Anne Holbrook (Vice-Chair) and Dr. Yvonne Shevchuk.

Conflicts of Interest:
CEDAC members reported no conflicts of interest related to this submission.

About this Document:
CEDAC provides formulary listing recommendations to publicly funded drug plans. Both a technical recommendation and plain language version of the recommendation are posted on the CADTH website when available.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CEDAC made its recommendation.

The manufacturer has reviewed this document and has not requested the removal of confidential information in conformity with the CDR Confidentiality Guidelines.

The CEDAC 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.