

CEDAC FINAL RECOMMENDATION

GOLIMUMAB

(Simponi – Schering Plough Inc.)

Indication: Ankylosing Spondylitis

Recommendation:

The Canadian Expert Drug Advisory Committee (CEDAC) recommends that golimumab be listed in a similar manner to other tumor necrosis factor alpha inhibitors for active ankylosing spondylitis.

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. In the one double-blind randomized controlled trial included in the CDR systematic review, golimumab 50 mg was statistically significantly better than placebo with respect to the proportion of patients with active ankylosing spondylitis achieving ASAS 20, ASAS 40, ASAS 5/6 and ASAS partial remission as well as other outcomes measuring improvement in ankylosing spondylitis symptoms. A statistically and clinically significant improvement in SF-36 components favouring golimumab 50 mg over placebo was also observed.
2. The annual cost of golimumab is less than the cost of other tumor necrosis factor alpha inhibitors used to treat ankylosing spondylitis when it is administered 12 times per year.

Of Note:

The Committee noted that while there are three other tumor necrosis factor (TNF) alpha inhibitors available for the treatment of ankylosing spondylitis, 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 reducing the signs and symptoms of ankylosing spondylitis in adults who have had an inadequate response to conventional therapies. This indication is the focus of this recommendation. Golimumab also has the following Health Canada indications:

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- in combination with methotrexate, for reducing signs and symptoms of adult patients with moderately to severely active rheumatoid arthritis;
- 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 ankylosing spondylitis is 50 mg given as a subcutaneous injection once a month on the same date each month. It is available as an autoinjector and as 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 one manufacturer-sponsored, double-blind, 24-week RCT, GO-RAISE (N = 356). GO-RAISE evaluated the efficacy of golimumab 50 mg and golimumab 100 mg compared with placebo when given every four weeks. Patients included in GO-RAISE had active ankylosing spondylitis despite having received maximal doses of nonsteroidal anti-inflammatory drugs (NSAIDs) for three months, or they were intolerant to NSAIDs due to toxicity or contraindications. TNF alpha inhibitor-experienced patients and those with complete ankylosis of the spine were excluded. Concomitant background therapies including NSAIDs, disease-modifying antirheumatic drugs (DMARDs) and corticosteroids were permitted. During the trial, approximately 20% of patients received methotrexate, and 13% to 19%, across treatment groups, received corticosteroids. Patients randomized to placebo were noted to have a longer duration of disease with greater extraspinal involvement compared with the golimumab patients.

At 16 weeks patients with less than 20% improvement from baseline in both total back pain and morning stiffness, as measured by visual analog scales, met the early escape criteria (53%, 18% and 23% of placebo, golimumab 50 mg, and golimumab 100 mg patients, respectively). 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 golimumab 100 mg. Entry into early escape was double-blinded. There were an additional 2.6% to 6.6% of patients across treatment groups who discontinued treatment by week 24. Patients who met early escape criteria at week 16 had their week 14 values carried forward for the week 24 analyses.

Outcomes

The primary outcome of GO-RAISE was the proportion of patients with at least 20% improvement in the Ankylosing Spondylitis Assessment Study (ASAS 20) criteria at week 14. Other outcomes were defined a priori in the CDR systematic review protocol. Of these outcomes, the Committee discussed the following: ASAS 40; ASAS partial remission; ASAS 5/6; disease activity, measured using the Bath Ankylosing Spondylitis Disease Activity

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Index (BASDAI); physical function, measured using the Bath Ankylosing Spondylitis Functional Index (BASFI); spinal mobility measured using the Bath Ankylosing Spondylitis Metrology Index (BASMI); enthesitis, measured using the Maastricht Ankylosing Spondylitis Enthesitis Score (MASSES), Berlin Enthesitis Index or the University of California San Francisco (UCSF) Enthesitis Index; and quality of life measured using the SF-36.

The ASAS20 criteria are comprised of four domains: patient global assessment of disease; spinal pain; physical function as measured by the BASFI; and inflammation as measured by components of the BASDAI. ASAS 20 requires at least a 20% improvement or 10 unit absolute change, on a 100 unit visual analog scale, in at least three of four domains, and no worsening in the fourth domain.

Minimally clinically important changes for most of the scales used in GO-RAISE are uncertain, with the exception of the SF-36, for which the minimal clinically important difference ranges from 2.5 to 5 units.

Results

Efficacy or Effectiveness

- At week 14 there was a statistically significantly greater proportion of ASAS20 responders in the golimumab 50 mg group compared with placebo (59% versus 22%, $P < 0.001$). There were also statistically significant improvements favouring golimumab 50 mg over placebo in all other measures of ASAS response (including ASAS 40, ASAS 5/6, and ASAS partial remission), BASDAI 50 and night and back pain measured by visual analog scale.
- Statistically and clinically significant differences in SF-36 mental and physical components favouring golimumab 50 mg over placebo were also observed.
- Golimumab 50 mg was only statistically significantly better than placebo in improving enthesitis when measured using the UCSF Enthesitis Index, but not the other two enthesitis scales.
- Spinal mobility was similar between golimumab 50 mg and placebo groups at both 14 weeks and 24 weeks based on the mean change from baseline in BASMI scores.
- The amount of time lost from work was similar between golimumab 50 mg and placebo groups at 24 weeks but self-reported productivity, a more subjective outcome, was statistically significantly greater in the golimumab 50 mg group compared with placebo.
- Efficacy appeared similar between the 50 mg and 100 mg golimumab doses for most outcomes.

Harms (Safety and Tolerability)

- There were no statistically significant differences in serious adverse events, adverse events or withdrawals due to adverse events at 24 weeks. Twenty-four weeks was considered a short duration for controlled assessment of harms given that ankylosing spondylitis is a chronic disease.
- Infections and malignancies appeared similar between the golimumab and placebo groups. There were three serious infections, one in the placebo group (1.3%) and two in the golimumab 100 mg group (1.4%), none of which were active tuberculosis. There were two malignancies, one in the golimumab 100 mg group (0.7%) and one in the placebo group (1.4%). There were no reports of lupus or congestive heart failure.

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Cost and Cost-Effectiveness

The manufacturer submitted a cost minimization analysis comparing golimumab with etanercept, adalimumab, and infliximab in patients with active ankylosing spondylitis and failure to respond to conventional therapies. The cost minimization analysis was based on the results of an indirect comparison conducted by the manufacturer, which included a meta-analysis of placebo-controlled trials evaluating golimumab, etanercept, adalimumab, and infliximab, and which suggested that there were no statistically significant differences between golimumab and comparators.

The annual cost of golimumab (\$17,364; 50 mg monthly) is less than adalimumab (\$18,438; 40 mg every other week), etanercept (\$18,995; 50 mg weekly or \$20,542; 25 mg twice weekly) and infliximab (\$20,538 to \$27,387; 5 mg/kg every six to eight weeks based on 70 kg patient).

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.
- Based on up to two-year uncontrolled long-term extension data from RCTs, there is no evidence to suggest that any TNF alpha inhibitor slows radiographic progression or disease progression. It is also uncertain whether or not NSAIDs inhibit radiographic progression.
- It was noted that liver enzyme abnormalities were more frequently observed in golimumab patients than placebo patients in the GO-RAISE study.
- The Committee noted that DMARDs, such as methotrexate and sulfasalazine, are effective in treating peripheral disease but may not be effective for treating axial disease.
- In patients with ankylosing spondylitis, spinal and hip involvement can lead to significant disability over the years. Impact on work potential and productivity are important outcomes in a disease such as ankylosing spondylitis, which affects a relatively young population.
- While there appears to be good evidence of symptomatic benefit with golimumab, there are no head-to-head trials comparing golimumab with other TNF inhibitors. The long-term disease-modifying benefits and harms also remain unclear.

CEDAC Members Participating:

Dr. Robert Peterson (Chair), Dr. Anne Holbrook (Vice-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. Yvonne Shevchuk

Conflicts of Interest:

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

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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.

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