Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

CEDAC FINAL RECOMMENDATION and REASONS for RECOMMENDATION

ADALIMUMAB RESUBMISSION #3 (Humira® – Abbott Laboratories Ltd.)

Description:

Adalimumab is a human monoclonal antibody to tumour necrosis factor (TNF). The Canadian Expert Drug Advisory Committee (CEDAC) previously reviewed adalimumab for rheumatoid arthritis (see CEDAC Final Recommendation on Adalimumab, February 11, 2005), psoriatic arthritis (see CEDAC Final Recommendation, November 29, 2006) and ankylosing spondylitis (see CEDAC Final Recommendation, June 27, 2007). A new indication for use in Crohn's disease was the basis for this resubmission. Adalimumab is approved for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderate to severely active Crohn's disease who have had an inadequate response to conventional therapy, including corticosteroids and/or immunosuppressants. It is also indicated for reducing signs and symptoms and inducing clinical remission in patients who have lost response to or are intolerant of infliximab.

Dosage Forms:

40 mg in 0.8 mL solution for subcutaneous injection. The recommended induction dose is 160 mg followed by 80 mg two weeks later. The recommended maintenance dose regimen for adult patients with Crohn's disease is 40 mg every other week, beginning at week four.

Recommendation:

The Committee recommends that adalimumab be listed for moderate to severely active Crohn's disease in patients refractory or with contraindications to an adequate course of 5-aminosalicylic acid and corticosteroids and other immunosuppressive therapy. Eligible patients should receive an induction dose of 160 mg followed by 80 mg two weeks later. Clinical response to adalimumab should be assessed four weeks after the first induction dose, using criteria such as a 100 point reduction in the Crohn's Disease Activity Index (CDAI). Ongoing coverage for adalimumab maintenance therapy should only be provided for responders, as noted above, and for a dose not exceeding 40 mg every two weeks.

Reasons for the Recommendation:

1. Adalimumab has been demonstrated to be superior at inducing and maintaining remission, compared with standard therapy, and it has been shown to improve measures of quality of life when used during the induction and maintenance phases of therapy.

2. Patients who do not respond to the induction phase of treatment with adalimumab appear to derive little benefit from further therapy with adalimumab.

3. The annual cost of adalimumab is $20,700 in the first year and $18,000 for subsequent years of treatment, which is significantly greater than that for standard therapy (corticosteroids, sulfasalazine and immunosuppressants), but less than the cost of infliximab ($29,000 in the first year and $22,000 thereafter), another anti-TNF agent used for this indication. The manufacturer submitted an economic evaluation which reported that adalimumab was cost saving when compared to infliximab and was associated with an incremental cost per quality-adjusted life year (QALY) gained of $113,000 when compared to standard therapy over a 56-week time horizon. Although the incremental cost per QALY gained is in excess of traditional standards, infliximab is currently funded by most public drugs plans for use in Crohn's disease.

4. Given that there are no randomized controlled trials (RCTs) that evaluate the impact of increasing the maintenance dose of adalimumab beyond 40 mg every two weeks, and there are significant safety concerns associated with the use of all anti-TNF agents, the Committee was not supportive of escalating doses beyond 40 mg every two weeks.

Summary of Committee Considerations:

The Committee considered a systematic review of double-blind RCTs in patients with moderate to severely active Crohn's disease. Four placebo controlled trials met the inclusion criteria for the systematic review; two induction trials of four weeks duration and two one-year maintenance trials. While patients enrolled in all four studies were inadequately controlled by conventional therapy, one each of the induction and maintenance trials also enrolled patients who had lost response or were intolerant to infliximab.

In the induction therapy trials, which included a total of 624 patients, adalimumab was associated with a statistically significant improvements in quality of life and rate of remission, defined as a CDAI of less than 150 (number needed to treat [NNT] = 4 to 7).

One of the RCTs evaluating maintenance therapy administered open-label adalimumab for four weeks, after which 499 patients who responded to induction therapy and 279 patients who did not respond to induction therapy were randomized to maintenance therapy with adalimumab or placebo. In the non-responder population, there was no difference in the rate of remission between adalimumab and placebo recipients after one year. In the responder population (defined as a $\geq$ 70 point reduction in CDAI), adalimumab resulted in statistically significant improvements in quality of life, and the rate of remission (NNT = 4) at one year. A second trial randomized 55 patients to adalimumab or placebo. After 56 weeks, there were no statistically significant differences in remission rates, quality of life or discontinuation of corticosteroid therapy.

Because all patients were exposed to adalimumab before randomization in the maintenance therapy RCTs, it is difficult to draw conclusions regarding the potential harms of adalimumab versus placebo. The product monograph for adalimumab highlights the potential for serious adverse events, such as infections and malignancies, which are concerns with the long-term use of all anti-TNF agents.

Of Note:

1. Both published and unpublished data were reviewed and taken into consideration in making this recommendation.

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.