CEDAC FINAL RECOMMENDATION
and
REASONS for RECOMMENDATION

ADALIMUMAB RESUBMISSION
(Humira® - Abbott Laboratories Ltd.)

Description:
Adalimumab is a human monoclonal antibody to tumour necrosis factor (TNF). The Canadian Expert Drug Advisory Committee had previously recommended that adalimumab be listed for patients with moderate to severe active rheumatoid arthritis who meet current drug plan criteria for funding of infliximab or etanercept (see Notice of CEDAC Final Recommendation on adalimumab issued on February 11, 2005). A new indication for use in psoriatic arthritis was the basis for the resubmission. Adalimumab is approved for reducing the signs and symptoms of active arthritis in adult psoriatic arthritis patients.

Dosage Forms:
40 mg in 0.8 mL solution for subcutaneous injection. The recommended dose is 40 mg every two weeks by subcutaneous injection.

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that adalimumab be listed for patients with active psoriatic arthritis who meet all of the following criteria:

1. Have at least three active and tender joints.
2. Failure to respond to non-steroidal anti-inflammatory therapy and, failure to respond to at least three adequate courses of disease modifying anti-rheumatic drugs (DMARDs) (eg. sulfasalazine, methotrexate, leflunomide, cyclosporine) or contraindications to, or intolerance of these agents.

Response to adalimumab should be assessed after 12 weeks of therapy and the criteria for continued coverage of adalimumab by drug plans beyond 12 weeks be assessed using an outcome such as a 20% improvement in the American College of Rheumatology response criteria (ACR 20) or response using the Psoriatic Arthritis Response Criteria. Adalimumab dosage should be restricted to a maximum of 40 mg every two weeks.

Reasons for the Recommendation:
1. The Committee considered a systematic review of randomized controlled trials (RCTs) of adalimumab in adult patients with a diagnosis of psoriatic arthritis and having signs and symptoms of active arthritis. Two placebo controlled RCTs of 12 and 24 weeks duration met the inclusion criteria for the systematic review. Significantly more patients achieved ACR 20, ACR 50 and ACR 70 responses, with numbers need to treat (NNT) to achieve these responses of 2-4, 3-4 and 5-7 respectively, in the two RCTs.

2. Data from RCTs support the effectiveness of DMARDs in patients with psoriatic arthritis, including sulfasalazine, methotrexate, leflunomide, and cyclosporine, and these agents are considerably less expensive than adalimumab.

3. Although the RCTs did not demonstrate significant differences between adalimumab and placebo in the incidence of serious adverse events or withdrawals due to adverse events, these trials were relatively small and of short duration. The product monograph for adalimumab highlights the potential for serious adverse events such as infections and malignancies which are concerns with long-term use of all anti-TNF agents.

4. Adalimumab costs $680 per 40 mg dose, which is similar in price to other anti-TNF agents such as etanercept and infliximab, which are used in the treatment of psoriatic arthritis. An economic evaluation submitted by the manufacturer indicated that the incremental cost per quality adjusted life year (QALY) gained for adalimumab in comparison to traditional DMARDs was at least $70,000. Although this incremental cost-effectiveness ratio is in excess of traditional standards, other anti-TNF agents are currently funded by public drugs plans for use in psoriatic and rheumatoid arthritis.

Summary of Committee Considerations:

Patients in the RCTs had mild to moderate psoriasis and the use of adalimumab was associated with statistically significant improvements in the number of patients who achieved 75% (NNT 2) and 90% (NNT 3) improvements in the Psoriasis Area and Severity Index and, ratings of “clear” or “almost clear” (NNT 2-3) on the Physicians Global Assessment for Psoriasis.

The RCTs measured quality of life using the SF-36 scale. In the trial which enrolled patients who were “NSAID non-responders”, adalimumab patients experienced clinically significant improvements in the physical composite score of the SF-36 compared to placebo. In the other RCT which enrolled patients who had failed at least one DMARD, there was no statistically significant difference between the groups in changes in quality of life as assessed by the SF-36.

Of Note:

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

2. Adalimumab should not be used concomitantly with other anti-TNF agents.

3. To reduce patient exposure to anti-TNF agents which, though effective, have the potential for serious adverse effects that are not well quantified with long term use and are significantly more costly than other DMARDs, the Committee has recommended that patients have failed to respond or cannot tolerate three rather than two previous DMARDs.

4. CEDAC recommends that patients treated with adalimumab should be reassessed after 12 weeks of therapy since in the 24 week RCT, response rates were similar at 12 and 24 weeks.

5. A number of anti-TNF agents are now approved for use in psoriatic arthritis and drug plans may have already made formulary listing decisions for some of these agents. Drug plans should consider a drug class review of anti-TNF agents to assess their relative effectiveness, harms, cost and place in therapy in order to develop harmonized formulary listing decisions for these drugs.

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.