CEDAC FINAL RECOMMENDATION on RECONSIDERATION
and
REASONS for RECOMMENDATION

ADALIMUMAB RESUBMISSION #2
(Humira® for Ankylosing Spondylitis – Abbott Laboratories Ltd.)

Description:
Adalimumab is a human monoclonal antibody to tumour necrosis factor (TNF). The Canadian Expert Drug Advisory Committee (CEDAC) previously recommended that adalimumab be listed for patients with moderate to severe active rheumatoid arthritis (see Notice of CEDAC Final Recommendation on adalimumab issued on February 11, 2005) and psoriatic arthritis (see Notice of CEDAC Final Recommendation on adalimumab issued on November 29, 2006). A new indication for use in ankylosing spondylitis was the basis for the resubmission. Adalimumab is approved for reducing the signs and symptoms in patients with active ankylosing spondylitis who have had an inadequate response to conventional therapy.

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 Committee recommends that adalimumab be listed with restrictions for the treatment of ankylosing spondylitis in a similar manner that drug plans currently list other anti-TNF agents for ankylosing spondylitis. Use of adalimumab should be restricted to patients who have failed to respond to an adequate trial of at least three different nonsteroidal anti-inflammatory drugs (NSAIDs) and, in patients with peripheral joint involvement, have failed to respond to methotrexate or sulfasalazine. Response to adalimumab should be assessed after 12 weeks of therapy and criteria for continued coverage of adalimumab by drug plans beyond 12 weeks should be developed using an outcome such as a 50% improvement in the Assessment in Ankylosing Spondylitis response criteria (ASAS 50) or the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI 50). Adalimumab dosage should be restricted to a maximum of 40 mg every two weeks. Adalimumab should not be used in combination with other anti-TNF agents.

Reasons for the Recommendation:
1. The Committee considered a systematic review of randomized controlled trials (RCTs) of adalimumab in adult patients with active ankylosing spondylitis who had an inadequate response to conventional therapy. Two RCTs compared adalimumab to placebo, while allowing continued background therapy with NSAIDs, methotrexate, sulfasalazine, hydroxychloroquine and corticosteroids. Enrolled patients had active ankylosing spondylitis, an inadequate response to at

least one NSAID and may have had failed one or more disease modifying anti-rheumatic drugs (DMARDs). Both RCTs restricted the number of patients with total spinal and lumbar ankylosis of cervical and lumbar spine to 10% of the study population.

Compared with placebo, adalimumab resulted in significantly more patients achieving ASAS 20, ASAS 50 and ASAS 70 after 12 weeks of treatment, with numbers needed to treat (NNT) ranging from three to six for these outcomes. Adalimumab was also associated with statistically significant improvements in measures of quality of life and disease activity at week 12. One of the two RCTs reported a statistically significant improvement in spinal mobility (as assessed by the Bath Ankylosing Spondylitis Metrology Index) in favour of adalimumab.

2. Adalimumab costs $18,000 per year of treatment. An economic evaluation submitted by the manufacturer reported that the incremental cost per quality adjusted life year (QALY) gained for adalimumab in comparison to NSAIDs was $79,000, when the time horizon for treatment benefit was 48 weeks.

Summary of Committee Considerations:

Both RCTs were 24 weeks in duration but assessed the efficacy of adalimumab versus placebo after 12 weeks of treatment, after which non-responders (as assessed by ASAS 20) in either group were allowed to switch to open label adalimumab. A high proportion of patients in both the placebo (73.5%) and adalimumab (42.3%) groups were switched from the double blind to the open-label phase of the two trials, and this limits the ability to assess the efficacy of adalimumab beyond 12 weeks of treatment. As such, the Committee was concerned that the efficacy of adalimumab has only been assessed in short-term RCTs, though ankylosing spondylitis is a chronic condition with waxing and waning periods of disease activity. The long term benefits and risks of adalimumab in patients with ankylosing spondylitis are therefore unknown.

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. Compared to placebo, adalimumab use is associated with higher incidence of overall adverse events, drug-related adverse events, infectious adverse events and injection site reactions.

Of Note:

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

2. A number of anti-TNF agents are now approved for use in ankylosing spondylitis and drug plans may have already made formulary listing decisions for some of these agents. Given the lack of clear evidence of disease modification, the high cost of these agents and the lack of evidence for effectiveness in patients who have already failed anti-TNF therapy, it is unknown if drug plans should provide coverage for a trial of a second anti-TNF agent in patients who have failed to respond to a trial of an initial anti-TNF agent. 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.

3. Given that the effectiveness of adalimumab in ankylosing spondylitis is based on short-term RCTs, drug plans should re-evaluate its listing status when long-term data on effectiveness and safety are available.

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.