CEDAC FINAL RECOMMENDATION and REASONS for RECOMMENDATION

ADALIMUMAB

(**Humira™--Abbott Laboratories, Limited**)

Description:
Adalimumab is indicated for reducing the signs and symptoms, and inhibiting the progression of structural damage, in adult patients with moderate to severe active rheumatoid arthritis (RA) who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). Adalimumab can be used alone or in combination with methotrexate or other DMARDs.

Recommendation:
CEDAC recommends that adalimumab be listed for patients with moderate to severe active RA who meet current drug plan criteria for funding of infliximab or etanercept (i.e. patients must be refractory to or intolerant of at least two potent DMARDs, including methotrexate and leflunomide). The number of doses should be limited to twenty-six 40 mg doses per year with no dose escalation permitted. Adalimumab should not be used in combination with other tumor necrosis factor (TNF) antagonists.

Reasons for recommendation:

1. Listing with criteria is recommended because scientific evidence is not sufficient to adequately assess long-term benefit or harm. Relatively short-term studies support symptomatic improvement in patients with moderate to severe rheumatoid arthritis, but longer term evidence on safety (i.e. occurrence of cancer and infections) is required.

2. Three 6 month and one 12 month double-blind randomized controlled trials (RCTs) have been performed in adult patients with active RA who have had an inadequate response to ≥ 1 DMARDs. Two RCTs used adalimumab in combination with methotrexate , one RCT used adalimumab with standard antirheumatic therapy and one RCT used adalimumab as monotherapy. In each case, adalimumab was compared to placebo.

3. In all trials considered, there was a statistically and clinically significant difference noted in symptomatic improvement versus placebo in the tender joint count, the swollen joint count, patient and physician global assessment of disease activity, and patient assessment of functional ability. Composite scores of these measures (ACR20, and ACR 50) were also improved significantly compared with placebo.

4. Health-related quality of life was measured in 2 studies using the SF-36. Clinically and statistically significant improvements were noted in the majority of the SF-36 subscale domains when comparing patients treated with adalimumab 40 mg biweekly, and placebo.

5. In the one RCT (12months) evaluating structural change, adalimumab plus methotrexate was found to have a statistically significant difference versus methotrexate alone in the Total Sharp Score (2.6 points in a total score 398; composite of erosion scores and joint space narrowing). The clinical significance of this difference has not been shown.

6. Lymphomas have been observed in patients with TNF antagonists, including adalimumab. According to the product monograph, "In clinical trials, patients treated with adalimumab had a higher incidence of lymphoma than the expected rate in the general population". In the 4 randomized clinical trials, more patients developed cancer in the adalimumab group (1.23%) than in the control group (0.29%), and the difference almost reached conventional statistical significance (p=0.08). As with other TNF antagonists, patients should be warned of this risk. The rate of any infection was higher in the adalimumab-treated groups than in the placebo groups (RR 1.2 (95% CI 1.07,1.34; p<0.01).

7. Adalimumab is administered by subcutaneous injection, once every 2 weeks, which may be more convenient for patients in comparison to etanercept, which is administered by subcutaneous injection twice per week, or infliximab, which is administered by intravenous infusion at weeks 0, 2, 6 and every 8 weeks thereafter.

8. The cost of adalimumab ($17,160 per year) is similar to or less than the annual cost of etanercept or infliximab, although the cost of infliximab varies substantially depending on a variety of factors including patient weight.

Of Note:

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

2. The long-term (i.e. > 1 year) effectiveness and risks of adalimumab and other TNF antagonists in patients with RA is not known. CEDAC recommends that all patients treated with these agents should be entered into a prospective registry, in particular to record the occurrence of adverse events (i.e. serious infections, autoimmune disorders and cancers).

3. ACR 20 and ACR50 response rates appeared higher in the adalimumab arms of the 3 RCTs in which patients received adalimumab in combination with other DMARDs, compared to patients in the one study where adalimumab was used as monotherapy. Moreover, development of human anti-human antibodies (HAHAs) occurred in 12% of patients receiving adalimumab monotherapy compared to 1% of patients receiving adalimumab in combination with other DMARDS. In the one RCT where adalimumab was used as monotherapy, among patients receiving adalimumab, the ACR20 response was significantly lower among patients who developed a HAHA (26%) compared with patients who did not (46%) (p=0.0048).