CEDAC FINAL RECOMMENDATION on RECONSIDERATION and REASONS for RECOMMENDATION

NATALIZUMAB
(Tysabri™ – Biogen Idec Canada Inc.)

Description:
Natalizumab is a recombinant monoclonal antibody that binds to the α4-subunit of human integrin. It is approved for use as monotherapy for the treatment of patients with the relapsing-remitting form of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations, to delay the progression of physical disability and to decrease the number and volume of active brain lesions identified on magnetic resonance imaging (MRI) scans. Natalizumab is generally recommended in MS patients who have had an inadequate response to, or are unable to tolerate, other MS therapies.

Dosage Forms:
300 mg vial for intravenous infusion. The recommended dose is 300 mg administered every four weeks.

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that natalizumab not be listed.

Reasons for the Recommendation:
1. There are no randomized controlled trials (RCTs) comparing natalizumab monotherapy with other drug therapy for MS (beta interferon products or glatiramer acetate).

2. The annual cost of natalizumab is $33,700, which is more costly than other treatments for MS (beta interferon products cost $18,000 - $ 22,000 per year and glatiramer acetate costs $16,000 per year). An economic model submitted by the manufacturer reported an incremental cost per quality adjusted life-year (QALY) gained for natalizumab in relapsing-remitting MS patients who progress while receiving beta interferon of $189,000 compared with no therapy, or $185,000 per QALY compared with continued beta interferon therapy, values greater than those conventionally accepted to be cost-effective. There were no sensitivity analyses provided for this estimate and given the uncertainty regarding the clinical efficacy of natalizumab in this patient population, the true cost-effectiveness could be significantly less attractive.

Summary of Committee Considerations:
The Committee considered a systematic review of double-blind RCTs of natalizumab monotherapy in adult patients with relapsing-remitting MS. One RCT of 942 patients with MS not being treated with other drug therapy for MS and who had not previously received more than six months of beta interferon or glatiramer therapy, met the inclusion criteria for the systematic review. Compared to placebo,

natalizumab use resulted in statistically significant reductions in the mean rate of relapse at one year (0.27 vs 0.78) and at two years (0.23 vs 0. 73), and the cumulative probability of sustained progression of disability at two years (17% vs 29% for natalizumab and placebo, respectively). Sustained progression of disability was defined as an increase of 1.0 or more on the Expanded Disability Status Scale from a baseline score of 1.0 or an increase of ≥1.5 from a baseline score of 0, sustained for 12 weeks. Compared to placebo, natalizumab resulted in statistically significant but numerically small changes in the physical component summary (mean difference of 2.01 on a 100 point scale) and mental component summary (mean difference of 2.53 on a 100 point scale) of the SF-36 measure of quality of life. Natalizumab was also associated with a statistically significant reduction in the accumulation of new or enlarging lesions detected by magnetic resonance imaging.

One other RCT that compared natalizumab plus interferon beta-1a with continued interferon beta-1a therapy was also considered by the Committee. However, since natalizumab is only approved for use as monotherapy, this trial was not felt to be relevant to this recommendation.

Natalizumab therapy is associated with rare cases of progressive multifocal leukoencephalopathy (PML), a condition which can cause severe disability or death. In clinical trials in MS, two cases of PML were observed (both cases occurred in combination with beta interferon) in 1869 patients treated for a median of 120 weeks. The most frequent adverse events reported during natalizumab therapy include infection and hypersensitivity reactions, including anaphylaxis.

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.