CEDAC FINAL RECOMMENDATION ON RECONSIDERATION and REASONS for RECOMMENDATION

NATALIZUMAB RESUBMISSION
(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 by Health Canada 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. The Canadian Expert Drug Advisory Committee had previously recommended that natalizumab not be listed (see Notice of CEDAC Final Recommendation on Reconsideration for Tysabri issued on April 26, 2007).

The basis of the resubmission was a new price and new pharmacoeconomic evaluation.

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 recommends that natalizumab be listed as monotherapy for patients with a diagnosis of MS established according to current clinical criteria and MRI evidence. Patients must also meet all of the following criteria:

1. Failure to respond to full and adequate courses of treatment with at least two disease-modifying therapies or have contraindications to, or be intolerant of these therapies;
2. Significant increase in T2 lesion load compared to a previous MRI or at least one gadolinium-enhancing lesion;
3. Two or more disabling relapses in the previous year.

Reasons for the Recommendation:
1. The Committee considered a subgroup analysis of patients with relapsing-remitting MS who had two or more disabling relapses in one year. These patients also had a significant increase in T2 lesion load compared to a previous MRI or at least one gadolinium-enhancing lesion on cranial MRI. Treatment with natalizumab resulted in lower relapse rates compared to placebo after two years. The Committee acknowledged the limitations of this subgroup analysis. There is inadequate evidence of benefit in treatment-experienced patients as most patients in the trial had not previously failed other treatments. The Committee acknowledges the harms associated with natalizumab use (e.g., progressive multifocal leukoencephalopathy), however, the Committee also

recognizes the need for other therapeutic options in people with severe relapsing-remitting MS who have failed treatment with other drugs and are accumulating significant disability.

2. In the cost-utility analysis submitted by the manufacturer for this subgroup of patients, the manufacturer reported an incremental cost per quality adjusted life-year (QALY) gained for natalizumab of $68,600 compared with no therapy.

Summary of Committee Considerations:

The basis of this resubmission was a new pharmacoeconomic evaluation, and a 15% price reduction compared to the initial submission. The lower price of $2,387 per vial results in an annual natalizumab cost of $28,564. The annual cost of natalizumab reported in the original CDR review was $33,710. Other treatments for MS include beta interferon, which costs $18,000 to $22,000 per year and glatiramer acetate which costs $16,000 per year.

The incremental cost per quality adjusted life-year (QALY) gained for natalizumab was $68,600 compared with no therapy and $39,400 compared with beta interferon for the subgroup of patients in the AFFIRM trial. These estimates were significantly lower than the incremental cost per QALY estimates reported for the overall study population in the manufacturer's original submission ($189,000/QALY and $185,000/QALY, compared with no therapy and beta interferon, respectively). The pharmacoeconomic analysis was based on an indirect comparison of natalizumab and beta interferon and the methods used were identified as limitations by the Committee.

There have been no new RCTs since the original natalizumab submission. For this resubmission, the manufacturer provided the results of a post-hoc subgroup analysis of patients with relapsing-remitting MS who had two or more disabling relapses in one year and one or more gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load compared to a previous MRI. Acknowledging the limitations of post-hoc subgroup analyses, natalizumab resulted in lower relapse rates than placebo after two years. In addition, the manufacturer provided post-marketing safety data from the TOUCH and TYGRIS studies. Serious hypersensitivity reactions and hepatotoxicity have been reported.

The Committee reviewed elements of the manufacturer's risk management strategy for patient screening and early identification of progressive multifocal leukoencephalopathy (PML). PML is an opportunistic infection of the central nervous system and there is a lack of early specific signs of PML. PML can result in severe neurological disability and is often fatal. Four new cases of PML have been reported in MS patients receiving natalizumab monotherapy since the time of the original natalizumab submission. There have been seven cases in MS patients reported in total and five of these were in patients using natalizumab as monotherapy. Natalizumab is used for long term treatment of MS and the risk of PML may be related to duration of exposure. Given the severity of this condition and the uncertainties regarding its true incidence, this is of significant concern to the Committee.

In the original submission, 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 taking other current 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 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 $\geq$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 MRI.

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.

The CEDAC Final Recommendation and Reasons for Recommendation neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice. CADTH is not legally responsible for any damages arising from the use or misuse of any information contained in or implied by the contents of this document.

The statements, conclusions, and views expressed herein do not necessarily represent the view of Health Canada or any provincial, territorial or federal government or the manufacturer.