Natalizumab

Product:
NATALIZUMAB (Tysabri®)
300mg vial for injection

Class of drugs:
Recombinant monoclonal antibody

Indication:
Treatment of multiple sclerosis

Manufacturer:
Biogen Idec Canada Inc.

CED Recommendation

The CED recommended that natalizumab (Tysabri®) not be listed on the ODB Formulary but rather be funded through the Exceptional Access Program as monotherapy for adults with relapsing remitting multiple sclerosis, on the basis that natalizumab may be an option for patients with severe debilitating MS who have failed other safer alternative therapies.

Executive Officer Decision

Based on the CED's recommendation and a listing agreement with the manufacturer that addresses cost, the Executive Officer decided to fund natalizumab (Tysabri®) via the Exceptional Access Program according to specific criteria.

Status

Funding available through the Ontario Public Drug Programs under the Exceptional Access Program (EAP).

Highlights of Recommendation:

- Natalizumab is a laboratory-produced antibody used in the treatment of the relapsing-remitting form of multiple sclerosis (RRMS).
- In the AFFIRM study, natalizumab was associated with a reduced risk of disability progression and fewer exacerbations (relapses) compared to placebo.
- A subgroup analysis of patients with rapidly evolving severe (RES)-RRMS showed that the treatment effect for this subgroup of patients appeared to be larger for natalizumab over placebo on outcomes such as disability, quality of life, MS-related hospitalizations and new or enlarging lesions, as seen on magnetic resonance imaging (MRI).
- Natalizumab has been associated with the development of progressive multifocal leukoencephalopathy (PML), a rare viral infection affecting the brain and nervous system. PML can cause severe disability or death.
- Natalizumab costs substantially more than other treatments for multiple sclerosis ($33,700 per year versus $16,000 - $22,000 per year).
- There are currently no good quality studies comparing natalizumab against other multiple sclerosis treatments. Hence, it is unknown whether natalizumab has better efficacy, safety and cost-effectiveness data than other available treatments.
- **Overall, the Committee acknowledged the modest efficacy of natalizumab in the treatment of RES-RRMS, a very debilitating form of MS which has few treatment options and recommended that natalizumab be funded for this subgroup of patients with MS through the EAP.**

Background:

Multiple sclerosis (MS) is a disabling disease that affects the brain and spinal cord. The disease attacks myelin, an insulating material that protects critical portions of nerve cells. MS often destroys myelin in patches, causing swelling and interference with the usual flow of signals along nerve fibres.

The effects of MS vary greatly from one person to another, depending on the way in which the disease strikes the nervous system. Symptoms include blurry vision, difficulties speaking, faulty short-term memory, bowel or bladder problems, extreme fatigue, loss of balance or coordination, muscle stiffness, and even partial or complete paralysis. Not all people with MS experience the same symptoms. In the most common form of MS, attacks are followed by complete or partial recovery.

Canada is a high risk region for MS, which occurs more often in countries further away from the equator. While there is no cure, some approved drugs can alter the course of the disease. Several treatments are based on interferon, a protein that is part of the immune response to foreign agents. Another treatment, glatiramer acetate, consists of some of the same biochemical building blocks found in myelin.

Natalizumab is a laboratory-produced antibody. It is designed to block the movement of potentially damaging immune cells from the bloodstream into the brain and spinal cord. It is indicated in the treatment of the relapsing-remitting form of multiple sclerosis (RRMS).

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Detailed Discussion:

- The CED reviewed natalizumab in 2007 and again in 2009. In their initial review, the CED recommended no funding due to lack of evidence demonstrating efficacy, safety and economic advantage over existing therapies.
- The AFFIRM study (*Polman et al. New England Journal of Medicine, 2006*) found that natalizumab, versus placebo, is associated with statistically significant reductions in the mean rate of relapse at one year (0.27 versus 0.78) and at two years (0.23 versus 0.73). Natalizumab therapy is also associated with statistically significant reductions in the cumulative probability of sustained progression of disability at two years (17% for natalizumab versus 29% for placebo). Quality of life scores increased in the natalizumab treatment group and decreased in the placebo group.
- Results from a second study, the SENTINEL trial (*Rudick et al. N Eng J Med, 2006*), were not included in the CED's consideration because this trial examined the combination use of natalizumab with interferon, while natalizumab is approved only as monotherapy (i.e. single agent use) in Canada.
- There are no randomized controlled trials comparing natalizumab monotherapy with other systemic therapies for the treatment of MS (i.e. interferon beta products or glatiramer); therefore, the comparative efficacy of natalizumab versus these alternate treatments is unknown.
- In the second CED review, an open-label extension of the AFFIRM study, a subgroup analysis of patient with the rapidly evolving severe (RES)-RRMS, was considered by the CED. This analysis showed that the treatment effect for this subgroup of patients appeared to be larger for natalizumab over placebo on outcomes such as disability, quality of life, MS-related hospitalizations and new or enlarging lesions.
- The most frequent adverse events reported with natalizumab were infection and hypersensitivity reactions, including anaphylaxis. Hepatotoxicity (liver toxicity) is also a concern.
- Natalizumab therapy is also associated with an increased risk of progressive multifocal leukoencephalopathy (PML), a rare infection that can cause severe disability or death. In the post-marketing setting, the risk of PML is stated to be 1.59 per 1000 in patients treated with natalizumab for more than 24 months compared to 1 per 1000 in clinical trials. Healthcare professionals should monitor patients for any new sign or symptom that may be suggestive of PML and patients must be enrolled in the Tysabri Care Program™. (http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2009/tysabri_2_hpc-cps-eng.php and http://hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2010/tysabri_3_hpc-cps-eng.php).
- The annual cost of natalizumab therapy is approximately $33,000 per year. This is more costly than other available treatments for MS. Beta interferon products range from $18,000 - $22,000 per year, and glatiramer costs approximately $16,000 per year. For the subgroup of patients with RES-RRMS, 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. The CED noted increases in the rate of PML, which are likely to occur with more patients being exposed, could significantly impact the cost-effectiveness of this therapy.
- The CED had concerns with the potential off-label use of natalizumab (e.g. use in other types of multiple sclerosis where its efficacy has not been examined).
- **Overall, the CED noted that natalizumab appears to have an effect on RES-RRMS and that there are limited treatments for patients with this severe form of MS. The CED recommended that natalizumab be funded through the Exceptional Access Program according to clinical criteria.**

EAP Funding:

Natalizumab is funded through the Exceptional Access Program (EAP) according to specific criteria.

The EAP reimbursement criteria can be found at: http://www.health.gov.on.ca/english/providers/program/drugs/pdf/frequently_requested_drugs.pdf

CEDAC Recommendation:

(http://www.cadth.ca/index.php/en/cdr/recommendations)

The Canadian Expert Drug Advisory Committee (CEDAC) recommended that natalizumab (Tysabri®) be listed according to clinical criteria in their second review.

Ontario

Ministry of
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