Conitec

Recomendation report

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Natalizumab for the treatment of relapsing-remitting multiple sclerosis after the first treatment failure

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Technology: Natalizumab (Tysabri®).

Indication: Treatment of Relapsing-Remitting Multiple Sclerosis (RRMS) after the first treatment failure, as an alternative to fingolimod.

Applicant: *Biogen Brasil Produtos Farmacêuticos Ltda.*

Background: Multiple Sclerosis (MS) is an immune-mediated, inflammatory demyelinating and neurodegenerative disease that usually affects young adults and it is, on average, twice as frequent in women. In Brazil, the average prevalence of MS is estimated to be 8.69/100,000 population. Disease progression, severity and symptoms are not the same for every person, and progressive forms of MS may be less active to extremely aggressive. MS can be classified into three forms according to the progression of disability and incidence of relapses. In Brazil, pharmacological treatment is only available for patients with RRMS, consisting of six drugs in four lines of treatment, including natalizumab recommended as a fourth-line treatment.

Question: Is natalizumab effective and safe for the treatment of RRMS, after the first treatment failure, when compared with fingolimod?

Scientific evidence: Three Systematic Reviews (SRs) with network meta-analysis evaluating the efficacy and safety of several Disease-Modifying Antirheumatic Drugs (DMARDs) in the treatment of RRMS were identified, in addition to 21 observational studies comparing the effectiveness of natalizumab versus fingolimod. Regarding the primary efficacy outcomes, there was a statistically significant difference in the annualized relapse rate, with a result in favour of natalizumab in one of the SRs included (Lucchetta et al., 2018). Regarding the outcome of incidence of relapses, evaluated at 12 and 24 months, there was no difference between treatments at 12 months (Tramacere et al., 2015); and at 24 months, results were conflicting with Tramacere et al. (2015) in favour of natalizumab, while Li et al. (2019) found no difference between the interventions. In terms of effectiveness, a total of 17 meta-analyses of the 21 observational studies were performed. Among the primary outcomes assessed, superiority of natalizumab was demonstrated, with statistical significance, for absence of relapse in 12 months, including in the analysis of subgroups (patients with or without high activity). However, this benefit does not seem to be long-lasting for all patients, as at 24 months the meta-analysis showed a protective effect of natalizumab only for RRMS patients with high disease activity. The secondary outcomes of effectiveness that demonstrated superiority of natalizumab were expressed only in patients with high disease activity. Therefore, it is not possible to infer that treatment with natalizumab would work in the same way for all RRMS patients. In regard to safety, most studies only assessed the outcome of treatment discontinuation in less than 24 months. However, safety is an important concern when treating patients with natalizumab, especially in relation to the risk of developing Progressive Multifocal Leukoencephalopathy (PML) after two years of natalizumab treatment. In this respect, it is worth mentioning that Oshima et al. (2019) demonstrated that natalizumab (OR 115.72; 95% CI 83.83-159.74; p <0.001) was associated with statistically significant higher odds compared to fingolimod (OR 4.98; 95% CI 3.64-6.81) for the incidence of PML.

Economic evaluation: The applicant presented a cost-effectiveness analysis based on a Markov model over a 50-year time horizon. The outcome of effectiveness used in the model was the Quality-Adjusted Life Years (QALY) and the economic outcomes were direct medical costs. The inputs used were extracted from published or unpublished studies, with the same transition probabilities over the entire time horizon. The evaluation resulted in a scenario of both higher cost and higher effectiveness for natalizumab compared with fingolimod, with an incremental cost-effectiveness ratio of approximately BRL 29 thousand per QALY gained.

Budget impact analysis: The applicant submitted a budget impact analysis to estimate the impact of anticipating the use of natalizumab after the first treatment failure, over a five-year time horizon. The eligible population was based on the database of the Outpatient Information System of the Brazilian Public Health System (SIA-SUS in Portuguese), and the annual growth rate of patients observed between January 2017 and December 2018

(4.6%) to estimate the population over the five-year time horizon. Additionally, based on the evidence found, it was estimated the RRMS population with high disease activity who could benefit from the use of natalizumab after the first treatment failure, and treatment discontinuation for 57% of patients after two years of use of natalizumab in regard to the proportion of patients who are anti-John Cunningham Virus (JCV) antibody-positive. Therefore, considering the anticipation of natalizumab for patients with high disease activity, the budget impact was estimated to be BRL 4.86 million in the first year, reaching up to BRL 7.14 million in the fifth year, resulting in an incremental cost of BRL 32.4 million in five years.

International recommendations: The National Institute for Health and Care Excellence (NICE) recommends natalizumab as a treatment option for RRMS patients with high disease activity. The Canadian Agency for Drugs and Technologies in Health (CADTH) recommends the use of natalizumab in RRMS patients with an established diagnosis of MS, and who meet specific criteria such as treatment failure with at least two disease-modifying antirheumatic drugs. The Pharmaceutical Benefits Advisory Committee (PBAC) recommends natalizumab for initial and continuing treatment of clinically definite RRMS in ambulatory patient eighteen years of age or older. The Scottish Medicines Consortium (SMC) does not recommend natalizumab as a treatment option for patients with RRMS.

Technology horizon scanning: Six potential drugs were identified for patients with relapsing-remitting multiple sclerosis after the first treatment failure; so far, none of them is registered with the Brazilian National Health Surveillance Agency (Anvisa), in the United States or in Europe.

Considerations: The evidence presented showed the benefits of treatment with natalizumab, especially in RRMS patients with high disease activity. However, the results found for patients without high disease activity were similar to those obtained with the comparator (fingolimod). Considering the safety profile of natalizumab and the evidence of efficacy and effectiveness, it is possible that its use outweighs the risks only for RRMS patients with high disease activity, as they have a worse prognosis for disease progression.

Initial Recommendation: Conitec, at its 88th Ordinary Meeting, on July 9, 2020, decided not to recommend the expansion of the use of natalizumab in the scope of SUS, for the treatment of RRMS after the first treatment failure, as an alternative to fingolimod. It was taken into consideration that evidence demonstrated superiority of natalizumab only for patients with high disease activity (in the outcome of absence of relapse after 24 months of treatment). However, currently the Clinical Protocol and Therapeutic Guidelines for Multiple Sclerosis does not include this classification. Moreover, it was also taken into consideration the estimated incremental budget impact of BRL 32 million in five years and safety issues related to the risk of PML with natalizumab.

Public consultation: A total of 706 contributions were received, of which 87 were technical-scientific contributions, and 619 were experience or opinion contributions of patients, relatives, friends or caregivers of patients, health professionals or people interested in the subject. After analysing the contributions received – which outlined the clinical benefits of the early use of natalizumab for the treatment of patients with high disease activity –, and considering the new proposal to update the Clinical Protocol and Therapeutic Guidelines for Multiple Sclerosis – which should include this classification of RRMS –, Conitec's plenary session decided that there was sufficient reason to change the preliminary recommendation on the subject.

Final Recommendation: Conitec, at its 91st Ordinary Meeting, on October 8, 2020, recommended the expansion of the use of natalizumab for the treatment of patients with relapsing-remitting multiple sclerosis with high disease activity, as established by the Ministry of Health of Brazil. It was taken into consideration that evidence demonstrated superiority of natalizumab for patients with high disease activity, and that the current proposal to update the Clinical Protocol and Therapeutic Guidelines for multiple sclerosis includes this classification of RRMS.

Decision: To expand the use of natalizumab for the treatment of patients with relapsing-remitting multiple sclerosis with high disease activity, in the scope of the Brazilian Public Health System - SUS, as established by the

Ministry of Health of Brazil, according to Ordinance No. 49, published in the Official Gazette of the Federal Executive No. 217, Section 1, page 144, on November 13, 2020.