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Recomendation report

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Ocrelizumab for the treatment of adult patients with relapsing-remitting multiple sclerosis (RRMS) as an alternative or when there is a contraindication to natalizumab

Brasília – DF
2020

Technology: Ocrelizumab (Ocrevus®).

Indication: Relapsing-remitting multiple sclerosis (RRMS).

Applicant: Roche Chemical and Pharmaceutical Products (Brazil).

Background: Multiple sclerosis (MS) is an immune-mediated, inflammatory demyelinating and neurodegenerative disease affecting the white and grey matter of the central nervous system. It usually affects young adults between the ages of 20 and 50 years, with the peak incidence occurring at age of 30 years, but onset is less common outside this age group. The estimated number of people with MS worldwide is between 2.0 and 2.5 million. In Brazil, the average prevalence is estimated to be 8.69/100,000 population, and, as in the world, prevalence varies depending on the region where people live: it is lower in the North-East and higher in the South. Disease progression, severity and symptoms are not the same for every person, and progressive forms of MS may be less active to extremely aggressive.

Question: Is ocrelizumab effective, safe and cost-effective in patients with RRMS compared with natalizumab?

Scientific evidence: Based on the research question structured by the applicant, five systematic reviews with network meta-analysis comparing disease-modifying drugs in patients with RRMS were selected. No direct comparison between natalizumab and ocrelizumab was found, so indirect evidence was used to compare the two treatments. Regarding the primary outcomes of annualised relapse rate and incidence of serious adverse events, there was no statistically significant difference between ocrelizumab and natalizumab, and regarding proportion of patients without relapses, ocrelizumab was not shown to have advantage over other treatments. In the assessment of safety, there was no statistically significant difference between treatments for discontinuation due to adverse events. In the risk of bias assessment using the AMSTAR 2 tool, Xu et al. (2018), Li et al. (2019), and Lucchetta et al. (2019) showed critically low, McCool et al. (2019) showed low, and Lucchetta et al. (2018) showed high methodological quality.

Economic evaluation: The applicant submitted a cost-minimization analysis, considering the equivalence of efficacy between natalizumab and ocrelizumab in the first and following years. Taking into consideration medication costs and direct costs (premedication, administration, monitoring, management of adverse events and relapses in MS), the difference between ocrelizumab and natalizumab was estimated to be -BRL 683.69 in the first year and -BRL 841.64 in the following years. When not including administration cost, and recalculating the cost of treating relapses, the difference would be -BRL 412.18 and -BRL 536.13, respectively. In the sensitivity analysis, in a scenario with taxes on ocrelizumab, the incremental cost comparing with natalizumab was estimated to be BRL 7,982.84 in the first year and BRL 7,824.89 in the following years. When not including administration cost, and recalculating the cost of managing relapses, the difference would be BRL 8,254.35 and BRL 8,130.40, respectively.

Budget impact analysis: A budget impact analysis over a five-year time horizon from the perspective of the Brazilian Public Health System – SUS was conducted to estimate the costs associated with the incorporation of ocrelizumab for the treatment of RRMS, as an alternative to natalizumab. Among the proposed scenarios, the scenario presenting a gradual adoption of ocrelizumab was considered to be the one that provided a more realistic estimate of the budget impact of its incorporation in the scope of SUS. In this scenario, considering all direct medical costs, the budget impact was estimated to range from BRL 374,260,086.22 (without taxes) to BRL 449,633,934.38 (with taxes) in five years, and, after a recalculation to reduce uncertainties of the model, it was estimated to range from BRL 364,423,070.70 (without taxes) to BRL 443,708,712.23 (with taxes) in five years. Finally, considering only the acquisition cost of the

medicines, the budget impact of incorporating ocrelizumab in five years was estimated to be BRL 435,679,744.80 (with taxes), that is, an incremental cost of BRL 77.5 million for SUS.

International recommendations: Among the agencies evaluated, all of them recommended ocrelizumab only as a treatment option for RRMS with active disease defined by clinical and imaging features, and based on some conditions such as reduction in price, available through a product access program, and when there is a contraindication to other treatments.

Technology horizon scanning: Six potential drugs were identified for the treatment of adult patients with RRMS as an alternative or when there is a contraindication to natalizumab. Of these six drugs, two are registered with the United States Food and Drug Administration (FDA) since 2019.

Considerations: Currently in Brazil there are several disease-modifying drugs (DMDs) incorporated in SUS for the treatment of MS. Fingolimod and natalizumab are available for patients with high disease activity, who have contraindications and related serious adverse events. In the evidence analysis, five systematic reviews with network meta-analysis evaluating the efficacy and safety of ocrelizumab in the treatment of RRMS were identified, but no direct comparison between natalizumab and ocrelizumab was found. There were no statistically significant differences in most outcomes between ocrelizumab and natalizumab, demonstrating that there was no superiority, but equivalence of efficacy between them. Based on the applicant's proposal of equivalence of their cost of treatment, and tax exemption on ocrelizumab, its incorporation could be an alternative to natalizumab for patients with intolerance, no response or contraindication to therapies currently available in SUS. However, it is noteworthy to mention that the safety of ocrelizumab, one of the supposed advantages over natalizumab, has yet to be demonstrated in the long term.

Initial Recommendation: CONITEC, at its 88th Ordinary Meeting, on July 9th, 2020, decided not to recommend the incorporation of ocrelizumab for the treatment of adult patients with relapsing-remitting multiple sclerosis (RRMS) as an alternative or when there is a contraindication to natalizumab, in the scope of SUS. These drugs have therapeutic equivalence and different treatment costs. Although the applicant proposed to make a donation of doses of ocrelizumab, corresponding to their acquisition cost, such a process would not be possible in view of the SUS legal framework and logistics. Therefore, considering the similar efficacy and the proposed prices, ocrelizumab did not demonstrate a favourable cost-effectiveness ratio that would justify its incorporation to the list of medicines available in SUS for the treatment of RRMS.

Public consultation: The Public Consultation No. 36 was held from August 4th to 24th, 2020. A total of 5,601 contributions were received, of which 190 were technical-scientific contributions, and 5,411 were experience or opinion contributions. Regarding the technical-scientific contributions, 93% disagreed with the preliminary recommendation, mainly pointing out the safety of ocrelizumab compared with natalizumab; when there is a need to switch from natalizumab; the impact on patient's life; its effectiveness; and as an alternative for patients with high disease activity based on scientific evidence; it was also mentioned about indirect and direct costs, cost of technologies, and unmet demand. As for the experience or opinion contributions, 88% disagreed with the preliminary recommendation.

Final Recommendation: The CONITEC's members present at the 90th Ordinary Meeting, on September 3rd, 2020, unanimously decided not to recommend the incorporation of ocrelizumab for the treatment of adult patients with relapsing-remitting multiple sclerosis (RRMS) as an alternative or when there is a contraindication to natalizumab. It was considered that the parity of cost between ocrelizumab and natalizumab would depend on tax exemption and donation of doses of ocrelizumab. However, as the price list of medicines has not been updated since 2014, estimates showed not be made relying on tax

exemption, and the donation proposed does not provide long-term commitments. Therefore, considering that there are alternatives for RRMS available, the incorporation of a more costly technology without evidence of therapeutic superiority would not be justified. The Deliberation Record No. 555/2020 was signed.

Decision: Not to incorporate ocrelizumab for the treatment of adult patients with relapsing-remitting multiple sclerosis (RRMS) as an alternative or when there is a contraindication to natalizumab, in the scope of SUS, according to Ordinance No. 41, published in the Official Gazette of the Federal Executive No. 182, Section 1, page 159, on September 22nd, 2020.