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Recomendation report

DRUGS

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Bortezomib for the treatment of adult patients with previously untreated multiple myeloma who are ineligible for autologous haematopoietic stem cell transplantation

Brasília – DF
2020

Technology: Bortezomib (VELCADE®).

Indication: Patients with multiple myeloma (MM) who have not received prior therapy and who are not eligible for induction therapy with high-dose chemotherapy and autologous haematopoietic stem cell transplantation (AHSCT).

Applicant: Brazilian Association of Hematology, Hemotherapy, and Cellular Therapy (ABHH in Portuguese).

Background: Multiple myeloma (MM) is a hematologic malignancy characterized by the proliferation of malignant plasma cells in the bone marrow. It accounts for 1% of all malignancies and 10 to 15% of hematologic malignancies. MM is an incurable disease, its course is highly variable with a median survival of about 5 years, and significant morbidity associated with bone pain, kidney damage and anaemia. For eligible symptomatic MM patients, standard treatment is induction chemotherapy followed by high-dose chemotherapy with autologous haematopoietic stem cell transplantation (AHSCT). However, a significant number of patients are not eligible for AHSCT, so that it is only necessary pharmacological treatment, typically with chemotherapy.

Question: Is the use of bortezomib as a component of induction therapy effective, safe and cost-effective in patients with MM ineligible for AHSCT, when compared with other chemotherapy regimens recommended by the diagnostic and therapeutic guidelines of the Ministry of Health of Brazil?

Scientific evidence: In a systematic review of the literature, the applicant selected three meta-analyses that compared bortezomib-containing chemotherapy regimens with non-bortezomib regimens in newly diagnosed multiple myeloma in transplant-ineligible patients. In the methodological quality evaluation, two studies were rated as moderate and one as high quality. The selected studies included relatively few patients, and the results of the meta-analyses varied with regard to the overall survival outcome. The findings of improvement of progression-free survival, complete remission, and overall response with the use of bortezomib were considered consistent. The hazard ratio/odds ratio for progression-free survival ranged from 0.22 (95%CI 0.10-0.51) to 0.57 (95%CI 0.49-0.67); and for complete remission, hazard ratio ranged from 1.24 (95%CI 1.3-1.17) to 3.69 (95%CI 2.71-5.02). Regarding safety, there was an increased risk of general adverse events, especially neurological side effects. Considering a moderate confidence in the body of evidence, there is superiority of bortezomib compared with standard treatment.

Economic evaluation: A cost-effectiveness analysis was conducted using a partitioned survival model, over a 10-year time horizon. The main result was an incremental cost-effectiveness ratio (ICER) estimated at BRL 218,348.27/life-year gained. In the sensitivity analysis, the model was sensitive to the cost of bortezomib and the magnitude of survival/progression-free survival gain. The model had potentially serious methodological limitations, with a tendency to underestimate the cost of the intervention and to produce more favourable ICER, such as not using utility or adverse effects data, and not considering cost of High Complexity Procedures Authorization (APAC in Portuguese) during therapy with bortezomib, or wastage in the administration of doses. Moreover, there should be more extensive sensitivity analyses, as well as alternative scenario analyses.

Budget impact analysis: In the applicant's budget impact analysis, the population eligible for treatment was estimated to be 1,386 patients in the first year, and 64 patients in the subsequent 4 years, resulting in a budget impact of around BRL 14 million in 5 years. There were significant limitations in the analysis, in particular, unclear criteria used to define the target population, and only incident cases were considered for treatment from the second year, resulting in a population estimate that was much lower than expected, taking into account the epidemiological data. Finally, analysis of alternative scenarios was not reported.

International recommendations: The National Institute for Health and Care Excellence - NICE (United Kingdom) and the Scottish Medicines Consortium - SMC (Scotland) recommend bortezomib as part of the chemotherapy regimen as first-line treatment for patients with MM ineligible for AHSCT. The Canadian Agency for Drugs and Technologies in Health - CADTH (Canada) has not carried out a specific review for this indication, but bortezomib regimens are currently reimbursed in some Canadian jurisdictions.

Considerations: The literature review provided consistent data regarding the efficacy of bortezomib in the proposed indication. The cost-effectiveness and budget impact analyses submitted by the applicant had methodological limitations that limited the conclusions about the economic impact of the technology.

Initial Recommendation: It was taken into consideration the benefits of using bortezomib as therapeutic regimens in the outcomes of progression-free survival, complete remission, and response rate, and also other aspects such as the fact that bortezomib is available as a generic drug, it is cost-effective, and does not have a high budget impact. Therefore, the members of CONITEC's plenary session present at the 88th Ordinary Meeting, on July 9th, 2020, unanimously decided to make a preliminary recommendation in favour of the incorporation of bortezomib in the scope of the Brazilian Public Health System - SUS, for the treatment of patients with multiple myeloma who have not received prior therapy and who are not eligible for induction therapy with high-dose chemotherapy and autologous haematopoietic stem cell transplantation, according to the oncological assistance in SUS.

Public consultation: The CONITEC's preliminary recommendation report was made available through the Public Consultation No. 30/2020 between July 27th and August 17th, 2020. A total of 204 contributions were received, 47 of which were technical-scientific contributions, and 157 were experience or opinion contributions; 96% agreed with the CONITEC's preliminary recommendation.

Final Recommendation: The CONITEC's members present at the 90th Ordinary Meeting, on September 3rd, 2020, unanimously decided to recommend the incorporation of bortezomib for the treatment of adult patients with previously untreated multiple myeloma who are ineligible for autologous haematopoietic stem cell transplantation, according to the protocol established by the Ministry of Health of Brazil and the oncological assistance in SUS.

Decision: To incorporate bortezomib for the treatment of adult patients with previously untreated multiple myeloma who are ineligible for autologous haematopoietic stem cell transplantation, in the scope of SUS, according to Ordinance No. 45, published in the Official Gazette of the Federal Executive No. 186, Section 1, page 453, on September 28th, 2020.