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Recomendation report

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Bortezomib for the treatment of adult patients with previously untreated multiple myeloma who are eligible 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 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). When successful, this approach can significantly improve progression-free survival and quality of life, and, in some cases, keep MM in remission for several years. Bortezomib, in combination with other chemotherapeutics, can be used as a component of the above-mentioned induction therapy, prior to AHSCT.

Question: Is the use of bortezomib as a component of induction therapy effective, safe and cost-effective in patients with MM eligible 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 four meta-analyses that compared bortezomib-containing chemotherapy regimens with non-bortezomib regimens in newly diagnosed multiple myeloma in transplant-eligible patients. In the methodological quality evaluation, three studies were rated as moderate and one as high quality. There were some limitations related to the heterogeneity of the included studies and the quality of the primary data, but the finding of improvement of progression-free survival, complete remission, and overall response with the use of bortezomib was considered consistent. The hazard ratio for progression-free survival ranged from 0.66 (95% CI 0.51-0.84) to 0.76 (95% CI 0.6-0.83); and for complete remission, it was 1.4 (95% CI 1.17-1.69). Regarding safety, the main finding was the increased risk of 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 incremental cost-effectiveness ratio (ICER) was estimated at BRL 20,150.59/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 766 patients in the first year, and 35 patients in the subsequent 4 years, resulting in a budget impact of around BRL 1.44 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 Canadian Agency for Drugs and Technologies in Health - CADTH (Canada) recommend bortezomib as part of the induction chemotherapy regimen as first-line treatment for patients with MM eligible for AHSCT.

Considerations: Based on the analysis of the clinical evidence presented, with good confidence, and in accordance with the current recommendations for its use in international guidelines, bortezomib was considered to be more effective than the alternatives available in the Brazilian Public Health System - SUS. However, the economic evaluations submitted by the applicant had important methodological limitations, reducing the reliability of the conclusions regarding cost-effectiveness and budget impact in the Brazilian scenario.

Initial Recommendation: It was taken into consideration the benefits of using bortezomib as induction therapy for AHSCT, the outcomes of improvement of progression-free survival, complete remission, and global response, 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 SUS, for the treatment of patients with multiple myeloma who have not received prior therapy and who are 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. 32/2020 between July 27th and August 17th, 2020. A total of 420 contributions were received, 91 of which were technical-scientific contributions, and 329 were experience or opinion contributions; 100% and 98%, respectively, 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 multiple myeloma who have not received prior therapy and who are eligible for induction therapy with high-dose chemotherapy and 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 eligible for autologous haematopoietic stem cell transplantation, in the scope of SUS, according to Ordinance No. 43, published in the Official Gazette of the Federal Executive No. 186, Section 1, page 453, on September 28th, 2020.