Conitec

Recomendation report

DRUGS

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Ruxolitinib for the treatment of patients with primary myelofibrosis, postpolycythaemia vera myelofibrosis or postessential thrombocythaemia myelofibrosis, in people with intermediate-2 or high-risk disease

Brasília – DF
2020

Technology: Ruxolitinib (Jakavi®).

Indication: Treatment of patients with primary myelofibrosis, postpolycythaemia vera myelofibrosis or postessential thrombocythaemia myelofibrosis, in people with intermediate-2 or high-risk disease and with a platelet count of more than 50,000/mm3.

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

Background: Myelofibrosis is a clonal myeloproliferative disorder, characterized by inefficient hematopoiesis and bone marrow fibrosis. The disease can present itself again (primary myelofibrosis - PMF) or following a previously known polycythemia vera or essential thrombocythemia. Clinical manifestations include anaemia, splenomegaly, and cachexia. The disorder occurs when blood stem cells develop somatic mutations in the JAK2, MPL, CALR, and TET2 genes. Other genes may also be involved. Although myelofibrosis can occur at any age, it typically develops after the age of 50 years. Treatment is aimed at relieving signs and symptoms and may include medications, blood transfusions, chemotherapy, radiation therapy, and surgery. Bone marrow or stem cell transplant may improve symptoms and may cure the disease.

Question: Is ruxolitinib effective, safe and cost-effective for the treatment of intermediate-2 or high-risk myelofibrosis, classified according to the International Prognostic Scoring System (IPSS), when compared with placebo or the best available therapy?

Scientific evidence: The evidence demonstrated that ruxolitinib provided benefits in relieving symptoms of the disease (odds ratio [OR] 15.3; 95% Confidence Interval [CI] 6.9-33.7). The long-term data from COMFORT-I and II trials showed a statistically significant difference in overall survival for ruxolitinib (about five years). Reduction in spleen size ≥35% was observed in all subtypes of myelofibrosis and in patients with intermediate-2 or high-risk disease. Anaemia was the most common grade 3 or 4 Adverse Event (AE) in both COMFORT-I and II trials, followed by thrombocytopenia. These AEs rarely led to discontinuation and were generally managed by dose modifications or blood transfusions.

Economic evaluation: In the scenario where the comparator cost was the average of the APACs 03.04.03.003-1 and 03.04.03.004-0 (APAC stands for High-Complexity Procedure Authorisation), the Incremental Cost-Utility Ratio (ICUR) of the treatment with ruxolitinib was estimated at BRL 298,767 per QALY (Quality Adjusted Life Years) saved. Considering only the 5-year overall survival data from COMFORT-II trial adjusted for crossover, ICUR would be of the order of BRL 308,394 per QALY saved. The applicant did not include the costs related to the treatment of leukaemia, since primary myelofibrosis progression to leukaemia can be frequent. Variation in the cost of treatment was not included in the sensitivity analysis, which was the second factor with most impact.

Budget impact analysis: The incremental value of incorporating ruxolitinib was estimated to be approximately BRL 44 million in the first year, and BRL 300 million after five years. The main limitation of the data was the eligible population. There were no epidemiological data published for Brazil, therefore, the applicant made some assumptions, such as considering the prevalence data for the Federal District representative for the entire Brazilian territory. In the international literature, the prevalence of any myelofibrosis ranged from 0.51 to 2.7/100,000 patients. The impact of incorporating ruxolitinib into the Brazilian Public Health System (SUS) was unclear.

International recommendations: The National Institute for Health and Care Excellence - NICE (England), Canadian Agency for Drugs and Technologies in Health - CADTH (Canada), Health Technology Assessment (HTA) agency of Australia, and National Authority of Medicines and Health Products - INFARMED (Portugal) recommended ruxolitinib as an option for treating disease-related splenomegaly or symptoms in adults with PMF, post polycythaemia vera myelofibrosis (post-PV MF) or post essential thrombocythaemia myelofibrosis

(post-ET MF), in people with intermediate-2 or high-risk disease. Nevertheless, this recommendation is conditional on an improvement in the cost-effectiveness ratio of ruxolitinib compared with placebo.

Technology horizon scanning: It was identified momelotinib, an oral JAK1 and JAK2 inhibitor. It was also identified fedratinib, a JAK 2 inhibitor that targets JAK2 V617F and FLT3ITD mutations, approved by the FDA in 2019, for the treatment of patients with PMF and post-PV/ET MF, previously treated with ruxolitinib.

Considerations: Low-quality evidence showed that ruxolitinib demonstrated superiority compared to placebo or the best available therapy in the treatment of PMF and post-PV/ET MF, with higher rates of splenomegaly control, improvement of symptoms and quality of life. There is uncertainty on overall survival, but in general, patients treated with ruxolitinib had longer survival than control patients. The responses were sustained for a median period lower than five years, and the benefit occurred regardless of the myelofibrosis subtype, age group, presence or absence of the JAK2 V617F mutation, haemoglobin levels, and platelet counts.

Initial Recommendation: After analysing the evidence, Conitec's plenary session considered that ruxolitinib is palliative and not a substitute. It was also pointed out that the adverse events may require interventions such as blood transfusions. Despite improving constitutional symptoms and quality of life, and reducing spleen size, ruxolitinib cannot be considered cost-effective in comparison with the best available therapy. Therefore, Conitec, at its 85th Ordinary Meeting, on February 4th, 2020, decided not to recommend the incorporation of ruxolitinib for the treatment of myelofibrosis in patients with intermediate-2 or high-risk disease and with a platelet count of more than 50,000/mm3, in the scope of SUS. The subject matter was made available in a public consultation.

Public consultation: The Conitec's Recommendation Report was made available through the Public Consultation No. 04/2020 between February 21st and March 17th, 2020. A total of 1.347 contributions were received, 284 of which were technical-scientific, and 1,063 were experience or opinion contributions. There were no additional references that could change the analysis of the evidence presented in this report. Additional information on international guidelines recommending ruxolitinib as a first-line treatment in patients with myelofibrosis was added. In both experience/opinion and technical-scientific contributions, improvements in the constitutional symptoms and quality of life were mentioned.

Final Recommendation: The Conitec's members present at the 87th Ordinary Meeting, on June 4th, 2020, unanimously decided not to recommend the incorporation of ruxolitinib for the treatment of patients with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis, in people with intermediate-2 or high-risk disease and with a platelet count of more than 50,000/mm3. The Deliberation Record No. 523/2020 was signed.

Decision: Not to incorporate ruxolitinib for the treatment of patients with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis, in people with intermediate-2 or high-risk disease, in the scope of SUS, according to Ordinance No. 20, published in the Official Gazette of the Federal Executive No. 113, Section 1, page 35, on June 16th, 2020.