REPORT 147

Erythropoietin for the treatment of Sickle-Cell Disease

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EXECUTIVE SUMMARY

**Technology:** Erythropoietin.

**Indication:** Sickle-cell disease with renal impairment.

**Applicant:** Coordenação Geral de Sangue e Hemoderivados [General Coordinating Office for Blood and Blood Products] (CGSH/DAHU [Departamento de Atenção Hospitalar e Urgência – Hospital Assistance and Urgency Department]/SAS).

**Context:** Sickle-cell disease (SCD) and thalassemia are hemoglobinopathies affecting the production of hemoglobins. Generally, the production of variant hemoglobins in sickle-cell disease makes cells to undergo the process of becoming sickle-shaped and, with this format, they tend to block blood flow, causing anemia, pain and damage to several organs. One of the main complications of sickle-cell disease is renal impairment, a condition that worsens anemia. The treatment of serious anemia in patients with sickle-cell disease currently has two approaches as options in SUS: hydroxyurea, which is not always effective for anemia, and regular transfusion, which may lead to alloimmunization, iron overload, and hyper-hemolysis in pregnant women. Erythropoietin, a hormone released by kidneys for the purpose of regulating red blood cell production and, consequently, keeping hemoglobin (Hb) concentration constant, could be an option for the treatment of anemia, mainly in patients not tolerating high hydroxyurea doses.

**Question:** Is the use of erythropoietin effective and safe for the treatment of anemia in patients with sickle-cell disease and renal impairment?

**Scientific evidence:** From the systematized search, 16 studies in patients with sickle-cell disease were found and assessed, out of which 7 assessed erythropoietin in patients with sickle-cell disease with no other complications, 7 in patients with renal impairment, 2 in pregnant women and 1 in children. The studies were generally very heterogeneous regarding erythropoietin dose (400 to 3,000 U/Kg/week), the combination of hydroxyurea and ferrous sulfate and the results found, and also included few patients. In the largest study found in patients with sickle-cell disease/kidney disease (13 patients), doses of 107 to 2,700 U/Kg/week for 16 weeks were used, and hydroxyurea was administered before, during or after the treatment with EPO. The response found was an increase in hemoglobin, hemoglobin F and F-cells. The investigators concluded that, despite the treated groups are small, with heterogeneous treatments and retrospectively defined, EPO could be helpful in this group of patients not tolerating HU doses of 15 mg/kg, where the addition of EPO could allow higher HU dosages.
Budget Impact Assessment: According to the estimation informed by CGSH, there are 27,325 patients with SCD in Brazil, with an estimation of 683 patients (2.5%) that would meet the proposed inclusion criteria. At a monthly cost of BRL 350.00 per patient, the annual expense value for EPO for this indication would be BRL 2,863,222.80 (Annex I, budget impact table).

Recommendation made by CONITEC: During the CONITEC meeting, it has been discussed that the scenario is of much uncertainty regarding the benefits, damages, dose, combination with hydroxyurea and subgroups of patients with sickle-cell disease that could benefit from using erythropoietin and, then, adopting the use of erythropoietin in SUS, as per the application made by CGSH, would be very questionable. Thus, CONITEC members unanimously deliberated in favor of recommending not to incorporate into SUS Erythropoietin for the treatment of anemia in patients with sickle-cell disease and associated renal impairment, as per the application made by General Coordinating Office for Blood and Blood Products.

Public Consultation: In the public consultation, a total of 11 contributions have been received, originating from Biomanguinhos/Fiocruz, Municipal Secretariat of Health, health and educational institutions and doctors. Overall, results achieved with the use of EPO in patients with sickle-cell disease were reported, such as reduction in the number of transfusions and pain crises, in addition to causing the return to baseline hematocrit and patient quality of life improvement. Some contributions brought suggestions for the preparation of a national protocol, and the need for using only one type of EPO was reinforced. Bio-Manguinhos/Fiocruz informed that, in December, 2014, the 10000-IU presentation was approved by ANVISA.

Final Deliberation: At the 34th CONITEC Meeting held on April 2, 2015, the plenary session members unanimously deliberated in favor of recommending not to incorporate erythropoietin for the treatment of sickle-cell disease. At the end of discussion, there was the recommendation of conducting a study - with resources provided by Departamento de Ciência e Tecnologia [Science and Technology Department] of SCTIE [Secretaria de Ciência, Tecnologia e Insumos Estratégicos – Secretariat of Science, Technology and Strategic Inputs] - to assess the efficacy and safety of EPO in patients with SCD and, depending on the results, to standardize its use in SUS.