Conitec

Recomendation report

DRUGS

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Riociguat for inoperable or persistent/recurrent after surgical treatment Chronic Thromboembolic Pulmonary Hypertension

Brasília – DF
2020

Technology: Riociguat (Adempas®)

Indication: Inoperable or persistent/recurrent Chronic Thromboembolic Pulmonary Hypertension (CTEPH), World Health Organization (WHO) Group 4

Applicant: Bayer S.A

Background: CTEPH is a rare disease, and to date there is no effective drug treatment. No specific CTEPH treatment is indicated in the current Clinical Protocol and Therapeutic Guidelines for Pulmonary Arterial Hypertension. The current gold standard treatment intervention in CTEPH is surgery, specifically, pulmonary endarterectomy, for mechanical removal of the thrombus located in the pulmonary artery and its branches. Riociguat has label indications for the treatment of a restricted group of patients with CTEPH who are deemed inoperable or have residual or recurrent pulmonary hypertension after pulmonary endarterectomy.

Question: Is riociguat safe, effective and cost-effective when compared with placebo for patients with inoperable/residual/recurrent CTEPH?

Scientific evidence: The literature is limited to one randomized controlled trial (RCT) - the CHEST-1 study. This multicenter, double-blind study included 261 patients with inoperable or persistent/recurrent CTEPH, who were randomly assigned in a 1:2 ratio to receive placebo or riociguat. The primary endpoint was a change from baseline in 6-minute walking distance (6MWD) after 16 weeks of treatment. The 6MWD showed a mean increase of 39 meters from baseline in the riociguat group at week 16 compared with a mean decrease of 6 meters in the placebo group (least-squares mean difference, 46 meters; 95% confidence interval [CI]: 25 to 67; P<0.001). Pulmonary vascular resistance decreased by 226 dyn·sec·cm (-5) in the riociguat group and increased by 23 dyn·sec·cm(-5) in the placebo group (least-squares mean difference, -246 dyn·sec·cm[-5]; 95% CI, -303 to -190; P<0.001). Riociguat was also associated with significant improvements in the N-terminal pro-brain natriuretic peptide (NT-proBNP) level (P<0.001) and World Health Organization functional class (WHO-FC) (P=0.003). The most common serious adverse events were right ventricular failure (in 3% of patients in each group), and syncope (in 2% of the riociguat group and in 3% of the placebo group). In addition to the CHEST-1, its open-label extension study (CHEST-2) was included. Overall, 237 patients from CHEST-1 entered CHEST-2, and were followed for a median of 116 weeks, using riociguat, which was shown effective for functional outcomes (WHO-FC and 6MWT), Borg scale, and quality of life (Living with pulmonary hypertension questionnaire and EQ-5D-3L). The adverse events were mostly mild: 28% nasopharyngitis, 23% peripheral oedema, 22% dizziness, 18% diarrhoea, 16% cough, 10% syncope, 8% hypotension, and 5% haemoptysis.

Economic evaluation: The applicant presented a cost-effectiveness analysis based on a Markov model, with a mean Incremental Cost -Effectiveness Ratio (ICER) of BRL 402,569.52/QALY. The new model presented by the external reviewer indicated a higher ICER – BRL 816,089.17/QALY, even considering the discount on the price per tablet (BRL 90.32).

Budget impact analysis: The applicant estimated a budget impact of BRL 438,398,520.36, over five years. The budget impact was considered to be underestimated, mainly because of the number of cases of pulmonary embolism, which was initially estimated as 50 per 100,000, and then revised to 112 per 100,000, resulting in a new estimate of BRL 889,546,200.08, over five years.

International recommendations: Riociguat is recommended by the Canadian Agency for Drugs and Technologies in Health (Canada), Scottish Medicines Consortium (Scotland), Pharmaceutical Benefits Advisory Committee (Australia), Agence Nationale d'Accréditation et d'Évaluation en Santé (France), Comisíon Interinstitucional del Cuadro Básico de Insumos del Sector Salud (Mexico), and the National Institute for Health and Care Excellence – NICE (United Kingdom).

Technology horizon scanning: Two potential drugs were identified for the treatment of patients with inoperable or persistent/recurrent CTEPH – macitentan and selexipag, both of which have not been registered with the Brazilian National Health Surveillance Agency.

Considerations: The decision of recommending the incorporation based on a single RCT may be subject to errors. Moreover, there is no evidence of increased survival with use of riociguat, and the benefit is mainly related to surrogate outcomes. The economic model of cost-effectiveness had limitations, such as overestimating the benefit of riociguat, and underestimating the current treatment. The budget impact was considered to be underestimated.

Initial Recommendation: Conitec, at its 83rd Ordinary Meeting, on November 6th, 2019, decided not to recommend the incorporation of riociguat in the scope of the Brazilian Public Health System (SUS), for the treatment of inoperable or persistent/recurrent chronic thromboembolic pulmonary hypertension. There were uncertainties in the evidence on effectiveness, especially in the long-term, and the economic studies were not completely consistent.

Public consultation: A total of 3,384 contributions were received, of which the majority (61%) came from people interested in the subject, health professionals (13%), and the remaining contributions from patients or caregivers. The majority (88%) disagreed with the preliminary recommendation. Conitec decided that there was no sufficient reason to change the preliminary recommendation.

Final Recommendation: The Conitec's members present at the 86th Ordinary Meeting, on March 5th, 2020, unanimously decided not to recommend the incorporation of riociguat in the scope of SUS, for the treatment of patients with inoperable or persistent/recurrent CTEPH. The Deliberation Record No. 510/2020 was signed.

Decision: Not to incorporate riociguat for inoperable or persistent/recurrent after surgical treatment Chronic Thromboembolic Pulmonary Hypertension, in the scope of SUS, according to Ordinance No. 11, published in the Official Gazette of the Federal Executive No. 62, Section 1, page 77, on March 31st, 2020.