Conitec

Recomendation report

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Expansion of the use of sirolimus for the treatment of adult patients with lymphangioleiomyomatosis

Brasília – DF
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Technology: Sirolimus.

Indication: Treatment of adult patients with lymphangioleiomyomatosis (LAM).

Applicant: Pfizer Laboratories Ltd. (Brazil).

Background: LAM is a rare systemic disease, characterized by the proliferation of abnormal smooth muscle cells, which can lead to obstruction of airways and blood vessels in the lungs and, over time, to inadequate oxygenation. There are two types of LAM: sporadic LAM (S-LAM, not inherited) and LAM associated with tuberous sclerosis complex (TSC-LAM, inherited). It primarily affects women of childbearing age, with prevalence of about 3 to 5 per 1 million women. The cause of LAM is associated with inadequate activation of the Mammalian Target of Rapamycin (mTOR), which regulates cell growth and lymphangiogenesis. Treatment is based on monitoring and treating complications and pulmonary involvement. Sirolimus, a drug indicated for the treatment of patients with LAM, is an immunosuppressant that inhibits cell proliferation and antibody production. It acts by binding to the mTOR protein, inhibiting its activity, thereby suppressing cell proliferation.

Question: Is sirolimus more effective, safe or cost-effective for the treatment of patients with LAM when compared with the options available in the Brazilian Public Health System (SUS)?

Scientific evidence: The evidence supporting the use of sirolimus for the treatment of patients with LAM was based on three cohort studies, four clinical trials, and one sub-analysis of data. These studies were of low methodological quality and high risk of bias. The results of the outcomes were reported with different forms and units of measurement, making interpretation, summarization and analysis difficult. Six studies reported that changes in Forced Expiratory Volume in 1 second (FEV_1) were lower in patients using sirolimus, compared with placebo or before using it. After 12 months of treatment with sirolimus, there was an improvement in FEV_1, and a significant reduction in patients not using it. Regarding Forced Vital Capacity (FVC), four studies reported an improvement in FVC values in patients using sirolimus ($p \leq 0.001$). A quality of life outcome was reported by three studies, and in two of them there was an improvement in the quality of life of patients using sirolimus ($p<0.05$). In relation to Functional Residual Capacity (FRC), Vital Capacity (VC), Residual Volume (RV), and Total Lung Capacity (TLC), there were no clinically significant differences between sirolimus and placebo ($p>0.05$). The most common adverse events were gastrointestinal, infectious, pulmonary or upper respiratory tract, dermatological, and neurological events.

Economic evaluation: The applicant submitted a Cost-Utility Analysis (CUA) of sirolimus compared with conservative treatment of patients with LAM, which showed an incremental cost of BRL 5,643.12 and a gain of 0.0985 Quality Adjusted Life Years (QALY), and an Incremental Cost-Effectiveness Ratio (ICER) of BRL 57,290.55 per QALY gained. The CUA presented uncertainties, especially with regard to the model design and use of utility values from a study that had evaluated a specific subgroup of patients with LAM.

Budget impact analysis: The incremental value of incorporating sirolimus was estimated to range from BRL 896.2 thousand in the first year to BRL 1.22 million after five years. The incremental budget impact was estimated to be approximately BRL 5.3 million after five years. The analysis was considered to be underestimated due to the assumptions used to estimate the population.

International recommendations: The following agencies have not made recommendations for the evaluation of sirolimus for the treatment of LAM: The National Institute for Health and Care Excellence – NICE (United Kingdom), Scottish Medicines Consortium – SMC (Scotland), and Pharmaceutical Benefits Scheme – PBS (Australia).

Technology horizon scanning: Potential drugs for the treatment of lymphangioleiomyomatosis (LAM) were not identified.

Initial Recommendation: Conitec, at its 86th Ordinary Meeting, on March 4th and 5th, 2020, decided that the subject matter should be made available in a public consultation with a favourable preliminary recommendation for the expansion of the use of sirolimus for the treatment of adult patients with LAM, in the scope of the SUS.

Public consultation: A total of 1,923 contributions were received, of which 18 were technical-scientific, and 1,905 were experience or opinion contributions. Almost all of them (1,902 [99%]) agreed with the favourable preliminary recommendation. The most mentioned topic in the contributions was the absence of a therapeutic alternative for the treatment of LAM. Many contributions addressed the improvement in patients' quality of life, possibility of stabilization of LAM, improvement in lung function, and the difficulty in accessing the medication due to its high cost.

Final Recommendation: Conitec's plenary session discussed and considered the need to incorporate in the scope of SUS a drug treatment that acts directly on the disease. They also took into account the clinical benefits of sirolimus in LAM, such as reduction in the progression of the disease, and the difficulty in accessing the medication due to its high cost. Therefore, the Conitec's members present at the 88th Ordinary Meeting, on July 8th, 2020, unanimously decided to recommend the expansion of the use of sirolimus for the treatment of adult patients with LAM, in the scope of SUS.

Decision: To expand the use of sirolimus for the treatment of adult patients with lymphangioleiomyomatosis (LAM), in the scope of SUS, according to Ordinance No. 24, published in the Official Gazette of the Federal Executive No. 149, Section 1, page 91, on August 5th, 2020.