Conitec

Recomendation report

DRUGS

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Rifapentine plus isoniazid for treatment of Latent Mycobacterium Tuberculosis Infection (LTBI)

Brasília – DF
2020

Technology: Rifapentine plus isoniazid (3HP regimen).

Indication: Latent *Mycobacterium Tuberculosis* Infection (LTBI).

Applicant: Secretariat of Health Surveillance of the Ministry of Health of Brazil (SVS/MS).

Background: Tuberculosis (TB) is an infectious and contagious disease that primarily affects the lungs, and its determinants include demographic, social and economic factors. Persons with LTBI can remain free of active TB for decades, but they may develop active disease during their lifetime when their immune system gets weakened. Treatment of LTBI with isoniazid available in the Brazilian Public Health System (SUS) consists of patients taking a daily and self-administered therapy of isoniazid pills for long periods of time, and it makes the adherence and the completion of treatment difficult. The combination regimen of once-weekly rifapentine and isoniazid for three months by directly observed therapy (known as the 3HP regimen) has been used as a therapeutic alternative to long-term treatment with isoniazid because it provides dose advantages. This Technical Report provides an evaluation of the 3HP regimen in comparison with treatment with isoniazid available in SUS for treatment of LTBI, in order to address the demand of the Secretariat of Health Surveillance of the Ministry of Health of Brazil (SVS/MS), by the Technical Note No. 14/2019-CGPNCT/DEVIT/SVS/MS (General Coordination of the National Tuberculosis Control Programme/Department of Communicable Disease Surveillance/Secretariat of Health Surveillance/Ministry of Health of Brazil).

Question: The 3-month regimen of rifapentine plus isoniazid (3HP) is effective, safe and cost-effective, when compared to the 9-month regimen of isoniazid (9H), for the treatment of patients with Latent *Mycobacterium Tuberculosis* Infection (LTBI)?

Scientific evidence: Seven studies were retrieved: two randomized controlled trials (RCTs) and five observational studies. These studies showed statistically significant results favouring the 3HP regimen compared to the 9H regimen for the outcome of treatment completion (odds ratio [OR]=2.92; 95% confidence interval [CI]=2.07-4.12; I2=57%; p=0.03). For the outcome of reactivation of tuberculosis, the results were in favour of 3HP, but without statistical significance (risk ratio [RR]=0.47; 95% CI=0.2-1.12; p=0.09). As for the outcome of discontinuation due to Adverse Events (AE), flu-like symptoms were the most common AE in patients receiving 3HP, while hepatotoxicity was the most common AE for the 9H regimen. The results of the studies indicated rates of clinically relevant hepatotoxicity (Grade 3 and 4) in patients receiving 3HP regimen ranging from 0% to 1.5%, and higher rates in patients receiving 9H regimen ranging from 1.2% to 5.3% (Appendix 1).

Economic evaluation: The 3HP regimen was slightly less expensive and more effective than the 9H regimen, that is, it was more cost-effective. In comparison with 3HP regimen, 9H presented an Incremental Cost-Effectiveness Ratio (ICER) of BRL 1,661.93 per QALY (Quality Adjusted Life Years). Therefore, the introduction of 3HP regimen into SUS can result in cost savings by QALY (Appendix 2).

Budget impact analysis: A budget impact model was developed to estimate the costs associated with the incorporation of 3HP into SUS over a five-year time horizon (2020 to 2024). In the first scenario, the incremental budget impact of incorporating 3HP was estimated to be

approximately BRL 1 million in 2020 and BRL 7.6 million after five years, in comparison with the baseline scenario. In the scenario with an overall discount for rifapentine, the incremental budget impact of incorporating 3HP was estimated to be approximately BRL 40,000 in 2020 and BRL 292,000 after five years (Appendix 3).

International recommendations: Seven Health Technology Assessment (HTA) agencies have not made recommendations for the evaluation of 3HP for the treatment of LTBI.

Technology horizon scanning: No other drugs were found in clinical development (phase 3 or 4 clinical trials) for the treatment of latent tuberculosis.

Considerations: The use of 3HP is associated with a higher rate of LTBI treatment completion, and it has been shown to be a safe alternative to the treatment available in SUS. Moreover, the incorporation of 3HP appears to be feasible, cost-effective, with a low incremental budget impact, and without important limitations regarding implementation and acceptability.

Initial Recommendation: Conitec, at its 86th Ordinary Meeting, on March 5th, 2020, decided that the subject matter should be made available in a public consultation with a favourable preliminary recommendation to the incorporation of rifapentine, to be used in combination with isoniazid in the 3HP regimen, for the treatment of patients with Latent *Mycobacterium Tuberculosis* Infection (LTBI), in the scope of SUS.

Public Consultation: The Public Consultation No. 14/2020 was held from March 26th to April 4th, 2020. A total of 655 contributions were received, 20 of which were technical-scientific, and 635 were experience or opinion contributions. All technical-scientific contributions agreed with the preliminary recommendation. As for the experience or opinion contributions, 99.7% (n = 633) agreed, and 0.3% (n = 2) neither agreed nor disagreed. No contributions disagreed with the preliminary recommendation. The most mentioned topics in the contributions were related to 3HP better adherence, shorter duration, weekly doses, and fewer adverse events. After analysing the contributions received in the public consultation, Conitec's plenary session, at its 87th Ordinary Meeting, considered that there was great agreement and no reason to change the preliminary recommendation.

Final Recommendation: The Conitec's members present at the 87th Ordinary Meeting, on June 3rd, 2020, unanimously decided to recommend the incorporation of rifapentine, to be used in combination with isoniazid in the 3HP regimen, for the treatment of patients with Latent *Mycobacterium Tuberculosis* Infection (LTBI), in the scope of SUS. The Deliberation Record No. 518/2020 was signed.

Decision: To incorporate rifapentine plus isoniazid for treatment of Latent *Mycobacterium Tuberculosis* Infection (LTBI), in the scope of SUS, according to Ordinance No. 19, published in the Official Gazette of the Federal Executive No. 112, Section 1, page 143, on June 15th, 2020.