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Recomendation report

DRUGS

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Delamanid for the treatment of multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis

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Technology: Delamanid (Deltyba®).

Indication: Multidrug-resistant tuberculosis (MDR-TB), after previous treatment failure, or extensively drug-resistant tuberculosis (XDR-TB).

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. TB can be classified according to drug resistance as RR-TB (rifampicin-resistant TB), when resistance to rifampicin is detected by a rapid molecular test for tuberculosis, and drug resistance profiles are not available; MDR-TB, with resistance to at least rifampicin and isoniazid; and XDR-TB, with resistance to rifampicin, isoniazid, any fluoroquinolone, and injectable second-line drugs (amikacin, capreomycin or kanamycin). According to the World Health Organization (WHO), the estimated incidence of RR/MDR-TB in Brazil is 1.2 cases per 100,000 population, a rate of 1.5% of new cases. In 2017, 713 new cases of RR/MDR-TB and 2 cases of XDR-TB were estimated. Currently, the treatment regimens available in the scope of the Brazilian Public Health System (SUS) for MDR-TB should include at least four new drugs (not previously used): fluoroquinolone; one injectable drug; two companion drugs; pyrazinamide; and ethambutol. When four new drugs are not available, drugs with limited clinical experience, such as delamanid, should be used. However, delamanid has not been incorporated in SUS. This Technical Report provides an evaluation of delamanid as part of the optimised background regimen for MDR-TB, after previous treatment failure, or XDR-TB, compared to the regimen without delamanid currently available in SUS, in order to address the demand of SVS/MS, by the Technical Note No. 4/2019-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: Is delamanid efficacious, safe and cost-effective, as part of the optimised background regimen, in the treatment of adult patients with MDR-TB and XDR-TB, when compared to the optimised background regimen without delamanid?

Scientific evidence: Four studies were included: one randomized controlled trial (RCT), one extension study, and two observational cohort studies. However, only the RCT had a comparator group so that it was considered the main evidence. The following outcomes did not show a statistically significant difference between the optimised background regimen with and without delamanid: treatment success (RR = 0.991; 95% CI = 0.872-1.127; p = 0.90); QT interval prolongation (with delamanid: 5.3%, n = 18; without it: 2.9%, n = 5); mortality (RR = 1.496; 95% CI = 0.410-5.453; p = 0.54); serious adverse events (RR = 0.944; 95% CI = 0.698-1.276); and resistance to delamanid (0.9%, n = 3). Therefore, regarding efficacy and safety, there was no superiority or inferiority in the use of delamanid for the treatment of MDR-TB. The quality of evidence for all outcomes was rated as moderate, except for the development of resistance to delamanid, which was rated as low quality (Appendix 1).

Economic evaluation: The optimised background regimen with delamanid was more costly than the regimen without it, with similar efficacy and safety. Compared to the optimised background regimen without delamanid, the regimen with it had an incremental cost of BRL 7,151.63 for the complete treatment (18 months) of patients with MDR-TB, after previous failure, or XDR-TB, in the scope of SUS (Appendix 2).

Budget impact analysis: In order to estimate the budget impact of incorporating delamanid, a market share of 100% from the first to the fifth year of incorporation (2021 - 2025) was considered. In the main scenario, considering the average number of patients who failed treatment for MDR-TB or those who had been treated for XDR-TB in recent years (n = 43), the incremental budget impact was estimated to be BRL 1,529,849.49 in five years. This amount could range from BRL 640,402.11 to BRL 1,823,251.35, depending on the exchange rate variation and the population eligible to receive treatment with delamanid (Appendix 3).

International recommendations: Seven health technology assessment (HTA) agencies have not made recommendations for the evaluation of delamanid in the treatment of MDR-TB, with the comparator considered in this report. However, the Portuguese National Authority of Medicines and Health Products, I.P. (INFARMED), when comparing to the optimised background regimen with bedaquiline, concluded that the use of delamanid, as part of the optimised background regimen, showed no clinical benefit in the treatment of MDR-TB.

Technology horizon scanning: Six drugs were identified as part of the therapeutic regimen for the treatment of MDR-TB: clofazimine, kanamycin, cycloserine, sutezolid, pretomanid, and prothionamide, which are in phase 3 or 4 clinical trials for the treatment of MDR-TB and XDR-TB.

Considerations: It was concluded that the use of delamanid as part of an optimised background regimen has similar efficacy and safety to the optimised background regimen without delamanid. Moreover, the regimen with delamanid was shown to be more costly in both economic evaluation and budget impact analysis. Despite a lack of evidence, and its higher cost, WHO recommends the use of delamanid in patients with MDR-TB or XDR-TB, when adequate treatment regimens cannot be constructed with previously available drugs, as in Brazil. This indicates that there will be good acceptance of the technology by stakeholders and no major barriers to its implementation.

Initial Recommendation: The members of CONITEC's plenary session present at the 87th Ordinary Meeting, on June 4th, 2020, decided that the subject matter should be made available in a public consultation with a preliminary recommendation in favour of the incorporation of delamanid as part of the optimised background regimen for the treatment of patients with XDR-TB, in the scope of SUS. The recommendation is subject to monitoring and presentation of real-life data, effectiveness and safety, of the use of delamanid by the Brazilian population, according to criteria established by the Ministry of Health of Brazil.

Public consultation: A total of 21 contributions were received, four of which were technical-scientific contributions, and 17 were experience or opinion contributions. Nineteen contributions agreed with CONITEC's preliminary recommendation, and only two neither agreed nor disagreed. The most mentioned topics were related to the importance of incorporating another therapeutic option for resistant tuberculosis; delamanid efficacy in association with other drugs; as an oral medication, it may result in greater adherence to treatment; shorter duration of treatment; and incorporation of delamanid also for MDR-TB patients. In general, the contributions agreed with the recommendation in favour of the incorporation of delamanid for XDR-TB, and there was no additional evidence. The members of CONITEC's plenary session decided that there was sufficient reason to change the preliminary recommendation, and agreed to include the MDR-TB patients in its recommendation on delamanid as part of the optimised background regimen.

Final Recommendation: The CONITEC's members present at the 89th Ordinary Meeting, on August 5th, 2020, unanimously decided to recommend the incorporation of delamanid for the treatment of multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis, subject to the presentation of real-life data, and as recommended by the Ministry of Health of Brazil. The CONITEC's members considered that, despite the limitations of the available evidence on the use of delamanid, its incorporation represents a new therapeutic option for patients with drug resistance, contraindication or toxicity to the drugs currently available in SUS for the treatment of MDR-TB and XDR-TB. The Deliberation Record No. 539/2020 was signed.

Decision: To incorporate delamanid for the treatment of multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis, subject to the presentation of real-life data, and as recommended by the Ministry of Health, in the scope of SUS, according to Ordinance No. 33, published in the Official Gazette of the Federal Executive No. 164, Section 1, page 133, on August 26th, 2020.