Conitec

Recomendation report

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Bedaquiline for patients with rifampicin-resistant, multidrug-resistant and extensively drug-resistant tuberculosis

Brasília – DF
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Technology: Bedaquiline (Sirturo®).

Indication: Rifampicin-resistant tuberculosis (RR-TB), multidrug-resistant tuberculosis (MDR-TB), and extensively drug-resistant (XDR-TB).

Applicant: Ministry of Health of Brazil/Secretariat of Health Surveillance/Department of Communicable Disease Surveillance/General Coordination of the National Tuberculosis Control Programme.

Background: Tuberculosis (TB), formerly known as phthisis, is a disease that can be caused by seven species of the Mycobacterium tuberculosis complex, and the most important of which from the public health point of view is M. tuberculosis. In 2018, an estimated 10 million people had TB worldwide, and in Brazil 72,788 new TB cases were diagnosed, which represents an incidence of 34.8 cases per 100,000 population. TB can be classified as pulmonary or extrapulmonary, and the former is more prevalent. It can also be classified according to drug resistance, such as: RR-TB, MDR-TB and XDR-TB.

Research question: Is bedaquiline (BDQ) in combination with standard treatment for adult patients with RR-TB, MDR-TB or XDR-TB, more effective, safe and cost-effective compared with the standard treatment regimens available in the scope of the Brazilian Public Health System (SUS) (levofloxacin, moxifloxacin, amikacin, capreomycin, ethionamide, terizidone, linezolid, clofazimine, pyrazinamide, ethambutol, isoniazid, rifampicin, and para-aminosalicylic acid) or placebo?

Scientific evidence: The systematized review retrieved nine studies: one systematic review (SR) with network meta- analysis (NMA); one randomized controlled trial (RCT) with two reports; and six retrospective cohort studies and one prospective cohort study. The SR with NMA compared BDQ with delamanid, metronidazole, moxifloxacin and levofloxacin, and the evaluation of the outcomes (sputum culture conversion and acceptability) found no statistically significant results. The cohort studies compared BDQ with several treatments available for RR-TB, MDR-TB and XDR-TB, and evaluated the following outcomes: survival, treatment success, complete treatment, cure, sputum culture conversion, and mortality. The results were not statistically significant in the random effects meta-analysis model for all outcomes evaluated; however, the results of the fixed effects model were statistically significant in favour of the treatment with BDQ compared with treatment without BDQ. It is worth noting that in the RCT (TMC207), subgroup analyses were performed to evaluate the efficacy and safety of BDQ in combination with standard treatment compared with placebo in combination with standard treatment, up to 120 weeks, for the outcomes: sputum culture conversion, cure and safety (mortality), but they did not change the direction of the results in both models of the meta-analysis.

Economic evaluation: In the cost-effectiveness analysis, all treatments with BDQ were found to be dominated (less effective and more costly) by treatments available in SUS for RR-TB, MDR-TB and XDR-TB, regarding the patient cured outcome.

Budget impact analysis: For patients with RR-TB, the budget impact analysis ranged from an incremental cost of BRL 936 thousand in the base case to savings of -BRL 1 million after five years in the alternative scenario; for MDR-TB, it ranged from savings of -BRL 44 thousand in the base case to an incremental cost of BRL 110 thousand after five years in the alternative scenario; and for XDR-TB, it ranged from an incremental cost of BRL 188 thousand in the base case to BRL 4 thousand after five years in the alternative scenario.

International recommendations: The National Institute for Health and Care Excellence, the Scottish Medicines Consortium, ant the Pharmaceutical Benefits Advisory Committee have not evaluated BDQ yet. The Canadian Agency for Drugs and Technologies in Health has not evaluated BDQ, but it published a rapid review that included nine systematic reviews and four guidelines addressing this medication. The All Wales Medicines Strategy Group and the Portuguese National Authority of Medicines and Health Products, I.P. recommended BDQ for patients with MDR-TB. The Pharmaceutical Management Agency recommends the use of BDQ in the treatment of patients with MDR-TB/XDR-TB.

Technology horizon scanning: Five drugs were identified for patients with MDR-TB and XDR-TB (kanamycin, cycloserine, sutezolid, pretomanid, and prothionamide).

Considerations: There are conflicting results in the evidence analysed in this report. The RCT, assessed as high risk of bias (Risk of Bias 2.0), showed that BDQ in combination with standard treatment is effective compared with placebo in combination with standard treatment, but with a higher number of deaths and episodes of nausea compared with the treatment group without BDQ. The results of the SR with NMA, rated as moderate quality, did not show statistically significant differences among the technologies evaluated. The results of the meta-analyses of the cohort studies, considered of low methodological quality (Newcastle-Ottawa Scale), in combination with the RCT evaluating BDQ, were demonstrated in fixed and random effects. The outcomes of treatment success, complete treatment, cure, sputum culture conversion, and mortality, were not statistically significant in the random effects meta-analysis model. However, the results of the fixed effects model were statistically significant in favour of the treatment with BDQ compared with treatment without BDQ. The economic evaluation demonstrated that treatments with BDQ were dominated (less effective and more costly) by the treatments available in SUS without BDQ for the patient cured outcome. For patients with RR-TB, the budget impact analysis ranged from BRL 936 thousand in the base case to -BRL 1 million after five years in the alternative scenario; for MDR-TB, it ranged from -BRL 44 thousand in the base case to BRL 110 thousand after five years in the alternative scenario; and for XDR-TB, it ranged from BRL 188 thousand in the base case to BRL 4 thousand after five years in the alternative scenario.

Initial Recommendation: CONITEC, at its 87th Ordinary Meeting, on June 3rd and 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 bedaquiline for patients with rifampicin-resistant tuberculosis (RR-TB), multidrug-resistant tuberculosis (MDR-TB), and extensively drug-resistant (XDR-TB), in the scope of SUS, subject to monitoring and presentation of real-life data, effectiveness and safety, of the use of bedaquiline by the Brazilian population, according to criteria established by the Ministry of Health.

Public consultation: The Public Consultation No. 24/2020 was held from June 22nd to July 13th, 2020. A total of 66 contributions were received, of which 19 (29%) were technical-scientific contributions, and 47 (71%) were experience or opinion contributions of patients, relatives, friends or caregivers of patients, health professionals or people interested in the subject. Regarding the 19 technical-scientific contributions, 95% agreed with the preliminary recommendation. Only one disagreed, but it was mistakenly submitted, since it was a contribution to another public consultation, so it was not taken into consideration. Regarding the 47 experience or opinion contributions, 32 forms were not filled out properly or completely, or were addressing another issue, and the remaining 15 agreed 100% with the preliminary recommendation. After analysing the contributions received, the CONITEC's plenary session considered the following: I) tThe new price for bedaquiline of USD 340 proposed by Johnson & Johnson, corresponding to a discount of 15% compared with the price considered in the preliminary recommendation (USD 400); II) nNew estimates of incidence of patients with multidrug-resistant tuberculosis (MDR-TB), as well as evidence about limitations in the budget impact analysis; III) uUpdated budget impact analysis, based on the new parameters presented in the public consultation, showing cost savings for patients with MDR-TB, and an incremental cost for RR-TB and XDR-TB in the scenario without a gradual market share of bedaquiline (100% in the first year of incorporation). However, considering the scenario with a gradual market share of bedaquiline, 30% in the first year of incorporation and 70% after five years, there would be cost savings for patients with RR-TB, and an incremental cost for patients with MDR-TB and XDR-TB.

Final Recommendation: The CONITEC's members present at the 89th Ordinary Meeting, on August 5th, 2020, unanimously decided to recommend the incorporation of bedaquiline for patients with rifampicin-resistant, multidrug-resistant and extensively drug-resistant tuberculosis, subject to the presentation of real-life data, and as recommended by the Ministry of Health of Brazil. The Deliberation Record No. 538/2020 was signed.

Decision: To incorporate bedaquiline for patients with rifampicin-resistant, multidrug-resistant 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. 36, published in the Official Gazette of the Federal Executive No. 168, Section 1, page 77, on September 1st, 2020.