Conitec

Recomendation report

DRUGS

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Empagliflozin and Dapagliflozin for the treatment of Type 2 Diabetes Mellitus

Brasília – DF
2020

Technology: Sodium-glucose cotransporter 2 (SGLT2) inhibitors: Empagliflozin (JARDIANCE®) and Dapagliflozin (FORXIGA®)

Indication: Type 2 diabetes mellitus without adequate glycemic control

Applicant: Secretariat of Science, Technology and Strategic Inputs (SCTIE/Ministry of Health of Brazil)

Background: Diabetes is a chronic disease that has a social and economic impact. Its treatment includes non-pharmacological interventions, such as diet and exercise, as well as drugs for patients who do not achieve adequate glycemic control through behavioral interventions. Currently, there are several classes of hypoglycemic agents available on the market, with different mechanisms of action and dosages. The drugs in the SGLT2 inhibitor class that are addressed in this report have been associated with a reduction of cardiovascular events and mortality, and also reduction of blood pressure and weight, without an increased risk of hypoglycemia. The expansion of therapeutic options available in the Brazilian Public Health System (SUS) for patients with diabetes helps to promote equity and can reduce the impact of this disease.

Scientific evidence: A network meta-analysis showed that SGLT2 inhibitors were superior to sulfonylureas, reducing the risk of major adverse cardiac events (MACE) (risk ratio [RR] 0.49, 95% confidence interval [CI] 0.28-0.83), and severe hypoglycemia (RR 0.23, 95% CI 0.14-0.37). No significant differences indicating the superiority of SGLT2 inhibitors over sulfonylureas and insulin were identified for the outcomes of glycated hemoglobin, mortality and stroke. In pivotal randomized controlled trials, empagliflozin was superior to standard treatment for the following outcomes: Mortality (hazard ratio [HR] 0.68, 95% CI 0.57-0.82, with an absolute reduction of 26 deaths per 1,000); MACE (HR 0,86, 95% CI 0.74-0.99, with an absolute reduction of 16 events per 1,000); cardiovascular death (HR 0.62, 95% CI 0.49-0.77, with absolute reduction of 22 deaths per 1,000); hospitalization due to heart failure (HR 0.65, 95% CI 0.50-0.85, with an absolute reduction of 14 events per 1,000); and kidney disease (HR 0.54, 95% CI 0.40-0.75). Dapagliflozin was superior to standard treatment for hospitalization due to heart failure (HR 0.73, 95% CI 0.61-0.88), and kidney disease (HR 0.53, 95% CI 0.43-0.66) . In these studies, patients aged 65 years or older and/or with high cardiovascular risk had the greatest benefit, and regarding safety, there was a higher risk of amputation, fracture and genital infections in 13 patients treated with canagliflozin, but an increased risk was not associated with empagliflozin and dapagliflozin. Cases of Fournier's gangrene (necrotizing fasciitis) were reported in patients taking a SGLT2 inhibitor between 2013 and 2018 in the United States. However, only 12 cases were detected in hundreds of thousands to millions of patients, which suggests that the incidence is very low and less than the potential clinical benefit. The analysis of systematic reviews showed that there was no significant difference between SGLT2 inhibitors, which were superior to the comparators. Regarding the limitations of the evidence presented, the following should be noted:: (a) studies used heterogeneous treatments as co-interventions and comparators (different standard treatments, including drugs not available in SUS), and different levels of intensification; (b) a part of the patients used insulin as standard therapy, but the benefit in these patients was similar or even higher than in those who did not use it; (c) studies included patients with and without cardiovascular disease in their samples; (d) network analysis has statistical limitations inherent to the analysis method, such as intransitivity due to the number of comparisons involved. However, there were consistent results in different studies and analyzes, including greater benefit in subgroups that are of greater interest for the incorporation in the scope of SUS, such as patients over 65 years of age, with increased

cardiovascular risk, and without insulin use. It is important to note that it was taken into consideration a large number of comparator drugs (standard treatment), many of which are not available in SUS, suggesting a conservative bias, as well as other classes of hypoglycemic agents. Among such hypoglycemic agents are: Dipeptidyl peptidase 4 (DPP-4) inhibitors, alpha glucosidase inhibitors, meglitinides, and thiazolidinediones, which did not provide a clinically significant benefit compared with the alternatives available in SUS, and showed results inferior to SGLT2 inhibitor, therefore, they were not considered for incorporation; glucagon-like peptide 1 (GLP1) analogues, which showed benefits compared with the alternatives available in SUS, but less than SGLT2 inhibitors, with a higher cost, therefore, they were not considered for incorporation. Furthermore, analogue insulins were not considered in this Report because they had recently been evaluated by CONITEC. Regarding the SGLT2 inhibitors, in all studies considered, the same representative of the class was used, with no evidence for interchangeability, and parameters for withdrawal, once therapy is started, were not established.

Economic evaluation: The annual cost was estimated at BRL 932.40 for dapagliflozin – Forxiga® 10 mg (Maximum Price for Sales to the Government [PMVG] 0% Brazilian Drug Market Regulation Chamber [CMED]), and BRL 1,070.52 for empagliflozin 10mg or 25mg (price proposed by the manufacturers for incorporation in 2018). For the main cost analysis, PMVG 0% of dapagliflozin was used. The evaluation was carried out against the drugs currently available in SUS, and GLP1 analogues, which are not available in SUS, but showed benefits in the outcomes assessed. GLP1 was found to be dominated by SGLT2 inhibitors (more costly and less effective), so its incorporation was not considered. The following six scenarios were developed for the economic evaluation: 1) diabetic patients over 35 years of age who need first intensification with hypoglycemic agents; 2) diabetic patients with cardiovascular disease who need first intensification with hypoglycemic agents; 3) diabetic patients with cardiovascular disease over 65 years of age who need first intensification with hypoglycemic agents; 4) diabetic patients over 35 years of age who need second intensification with hypoglycemic agents; 5) diabetic patients with cardiovascular disease who need second intensification with hypoglycemic agents; and 6) diabetic patients with cardiovascular disease above 65 years of age who need second intensification with hypoglycemic agents. The incremental cost-effectiveness ratio (ICER) ranged from BRL 21,525.00/QALY to BRL 26,537.94/QALY. This evaluation used an adapted microsimulation model of the University of Oxford, England. Its main limitation is that the risk equations that determine health outcomes are based on The United Kingdom Prospective Diabetes Study (UKPDS), and cannot be edited. In order to mitigate it, a posteriori adaptation was made to the cohort studies with estimates of the effect of the SGLT2 inhibitors on macrovascular events and mortality. Another important limitation is that the same effectiveness parameters of SGLT2 inhibitors were used for the different scenarios, so the effect for the subgroups that showed the greatest benefit (patients with cardiovascular disease over 65 years of age) may be underestimated, and overestimated for the other scenarios.

Budget impact analysis: An incorporation rate of 40% to 90% over a five-year period (2019-2023) was used in the six different scenarios. In scenario 1, based on diabetic patients over 35 years of age who need first intensification with hypoglycemic agents, the incremental cost was BRL 8,850,080,120. In scenario 2, based on diabetic patients with cardiovascular disease who need first intensification with hypoglycemic agents, the incremental cost was BRL 1,539,144,368. In scenario 3, based on diabetic patients with cardiovascular disease over 65 years of age who need first intensification with hypoglycemic agents, the incremental cost was BRL 738,096,682. In scenario 4, based on diabetic patients over 35 years of age who need second intensification with hypoglycemic agents, the incremental cost was BRL 1,110,650,183. In scenario 5, based on diabetic patients with cardiovascular disease who need second intensification with hypoglycemic agents, the incremental cost was BRL

193,156,553. In scenario 6, based on diabetic patients with cardiovascular disease above 65 years of age who need second intensification with hypoglycemic agents, the incremental cost was BRL 92,628,225. A limitation of this analysis is that it is not possible to estimate the appropriate adoption curve for this technology, which was mitigated by carrying out conservative sensitivity analyses. Finally, considering incorporation into specialized care, it is expected that the budget impact would be less.

International recommendations: The National Institute for Health and Care Excellence – NICE (United Kingdom), Canadian Agency for Drugs and Technologies in Health – CADH (Canada), Pharmaceutical Benefits Advisory Committee – PBAC (Australia), and Scottish Medicines Consortium – SMC (Scotland) recommend the use of drugs in the SGLT2 inhibitor class as intensification therapy and / or monotherapy.

Technology horizon scanning: There are five drugs in the technological horizon: ertugliflozin and bexagliflozin (SGLT2 inhibitors), sotagliflozin (SGLT1 and SGLT2 inhibitor), efpeglenatide and tirzepatide (GLP1 analogues). Of these, only ertugliflozin is registered with the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA), but none of them is registered with the Brazilian National Health Surveillance Agency (ANVISA).

Initial Recommendation: Conitec's plenary session, at the meeting on December 4th, 2019, recommended the incorporation of a SGLT2 inhibitor (empagliflozin or dapagliflozin) in the scope of SUS, for patients with type 2 diabetes mellitus, aged 65 years or older, and established cardiovascular disease (previous acute myocardial infarction, previous myocardial revascularization surgery, previous coronary angioplasty, stable or unstable angina, previous ischemic stroke, previous transient ischemic attack, heart failure with ejection fraction less than 40%), who do not achieve adequate control with a combination therapy of metformin and sulfonylurea. Based on the evidence presented, it was considered that the effectiveness of dapagliflozin and empagliflozin is similar, and the drug with the lowest price should be incorporated.

Public consultation: The Public Consultation No. 01/2020 was held from January 14th to February 3rd, 2020. A total of 3,618 contributions were received, of which 3,587 were accepted: 1,231 were technical-scientific contributions, and 2,356 were experience or opinion contributions of patients, relatives, friends or caregivers of patients, health professionals or people interested in the subject. The participation was mainly by health professionals and patients. Regarding the technical-scientific contributions, 98.5% agreed with the preliminary recommendation, 1% disagreed, and 0.5% neither agreed nor disagreed. As for the experience or opinion contributions, 97.8% agreed, 0.8% disagreed, and 1.4% neither agreed nor disagreed. All contributions were analyzed, discussed and answered. The main points raised were: 1) Effectiveness (empagliflozin versus dapagliflozin); 2) Expansion of the technology for all age groups with cardiovascular diseases; 3) Other contributions. A new price was proposed by the manufacturers for incorporation (box with 30 tablets of BRL 54.60 for dapagliflozin, and BRL 82.11 for empagliflozin), resulting in a new budget impact for scenario 6 of BRL 51,937,164 for dapagliflozin, and BRL 100,396,518 for empagliflozin, over five years. Additional discussion and references were added to the report. After analyzing the contributions received, Conitec considered that its result was in line with the favorable preliminary recommendation to the incorporation of technology in a scenario previously defined, based on scientific evidence, expert consensus, and efficient allocation of public resources.

Final Recommendation: The Conitec's members present at the 86th Ordinary Meeting, on March 5th, 2020, decided to recommend the incorporation of dapagliflozin in the scope of SUS, for the treatment of type 2 diabetes mellitus, and not to recommend the incorporation of empagliflozin for the treatment of type 2 diabetes mellitus. The Deliberation Records No. 515/2020 and No. 516/2020 were signed.

Decision: To incorporate dapagliflozin for the treatment of type 2 diabetes mellitus, and not to incorporate empagliflozin for the treatment of type 2 diabetes mellitus, in the scope of SUS, according to Ordinance No. 16, published in the Official Gazette of the Federal Executive No. 83, Section 1, page 89, on May 4th, 2020.