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Cost-Effectiveness of Canagliflozin versus Sitagliptin as Add-on to Metformin in Patients with Type 2 Diabetes Mellitus in Mexico

Cheryl Neslusan, PhD[1,], Anna Teschemaker, PhD[1], Pierre Johansen, MSc[2], Michael Willis, PhD[2], Atanacio Valencia-Mendoza, MS[3], Andrea Puig, PhD[4]*

[1]*Janssen Global Services, LLC, Raritan, NJ, USA;* [2]*The Swedish Institute for Health Economics, Lund, Sweden;* [3]*Janssen Cilag Mexico, Mexico;* [4]*Johnson and Johnson International, New Brunswick, NJ, USA*

ABSTRACT

Objective: To assess the cost-effectiveness of canagliflozin versus sitagliptin for the treatment of type 2 diabetes mellitus (T2DM) as an add-on to metformin in Mexico. **Methods:** A validated model (Economic and Health Outcomes [ECHO]-T2DM) was used to estimate the cost-effectiveness of canagliflozin 300 or 100 mg versus sitagliptin 100 mg in patients with T2DM inadequately controlled on metformin monotherapy. Data from a head-to-head, phase III clinical trial, including patients' baseline demographic characteristics, biomarker values, and treatment effects, were used to simulate outcomes and resource use over 20 years from the perspective of the Mexican health care system. Costs of complications and adverse events were tailored to the Mexican setting and discounted at 5%. Cost-effectiveness was assessed using willingness-to-pay thresholds equivalent to 1 times the gross domestic product per capita (locally perceived to be "very cost-effective") and 3 times the gross domestic product per capita (locally perceived to be "cost-effective") on the basis of recommendations of the Mexican government and the World Health Organization. **Results:** Owing primarily to better glycated hemoglobin (HbA_{1c}), body weight, and systolic blood pressure values, canagliflozin 300 and 100 mg were associated with an incremental benefit of 0.16 and 0.06 quality-adjusted life-years (QALYs) versus sitagliptin 100 mg, respectively, over 20 years. The mean differences in cost for canagliflozin 300 and 100 mg versus sitagliptin 100 mg were Mexican pesos (MXP) 1797 (US $134) and MXP 7262 (US $540), respectively, resulting in a cost per QALY gained of MXP 11,210 (US $834) and MXP 128,883 (US $9590), respectively. Both of these cost-effectiveness ratios are below the very cost-effective willingness-to-pay threshold in Mexico. The general finding that canagliflozin is cost-effective versus sitagliptin in Mexico was supported by sensitivity analyses. **Conclusion:** In Mexico, both doses of canagliflozin are likely to be cost-effective versus sitagliptin in patients with T2DM who have inadequate glucose control on metformin, primarily because of better biomarker control and higher QALYs.

Keywords: cost-effectiveness, dipeptidyl peptidase-4 inhibitor, SGLT2 inhibitor, type 2 diabetes.

Introduction

The number of people with diabetes in Latin American countries is growing, likely because of widespread increases in obesity in the region, and it is expected to increase by approximately 60%, from 24.1 million today to 38.5 million by 2035 [1]. About 90% of patients have type 2 diabetes mellitus (T2DM) [2]. In Mexico, the prevalence of diagnosed patients increased from 7.3% of the population in 2006 to 9.2% in 2012 [3], and it is believed that many cases remain undiagnosed [2]. Diabetes has been the leading cause of death since 2000, and was estimated to account for nearly 14% of deaths in 2009 [4].

T2DM imposes a significant economic burden on health care in Latin America due to the increasing prevalence and chronic nature of T2DM and associated comorbidities. There are direct costs incurred in managing the hyperglycemia associated with T2DM. It is notable, however, that most of the costs are attributable to T2DM-related complications (e.g., myocardial infarction, stroke, nephropathy, neuropathy, and retinopathy), the rates of which are inversely related to disease control [5]. In Mexico, the direct costs of diabetes were estimated at approximately US $1.16 billion (~15 billion Mexican pesos [MXP]) in 2006, and these figures have steadily increased [4]. Estimates suggest that diabetes-related complications can substantially increase patient costs in Mexico [4]. As noted in a recent consensus statement from the Latin American Diabetes Association, the Latin American health care system has historically focused on the treatment of acute health conditions, primarily

Conflicts of interest: C.N. and A.T. are full-time employees of Janssen Global Services, LLC. M.W. and P.J. are employees of the Swedish Institute for Health Economics, which has provided consulting services for Janssen Global Services, LLC. A.V.-M. is a full-time employee of Janssen Cilag Mexico. A.P. is a full-time employee of Johnson & Johnson International.

* *Address correspondence to:* Cheryl Neslusan, Janssen Global Services, LLC, 920 Route 202 South, Raritan, NJ 08869.

E-mail: cneslusa@its.jnj.com.

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due to limited resources [5]. As chronic diseases such as T2DM become more common in Latin America, payers and clinicians will face challenges unique to this region in helping patients achieve health-related goals.

Maintaining near-normal blood glucose levels has been shown to improve key T2DM-related outcomes [6]. The Latin American Diabetes Association and the Institute of Mexican Social Security (IMSS) recommend maintaining a glycated hemoglobin (HbA_{1c}) level of less than 7.0%, blood pressure of less than or equal to 130/80 mmHg, and low-density lipoprotein cholesterol (LDL-C) level of less than 100 mg/dL in most patients [5,7], consistent with the recommendations of the American Diabetes Association [8]. In addition, guidelines emphasize the importance of weight loss/control in T2DM management, reflecting acknowledgement of the detrimental effects of excess weight on health outcomes [5,7,8].

Many patients do not meet or maintain glycemic goals with available treatments [9,10]. According to data from the 2006 Mexican National Nutrition Survey, only 5.3% of the patients with T2DM were found to have an HbA_{1c} level of 7.0% or less despite treatment [11]. Notably, more than half had an HbA_{1c} ≥11.0%. Similarly, data indicate widespread failure to meet blood pressure and lipid goals in Mexico. In 2006, for example, approximately one-third of the Mexican population had a systolic blood pressure (SBP) of ≥140 mmHg and approximately 75% had LDL-C ≥100 mg/dL [12,13]. Moreover, two-thirds were classified as being overweight or obese [14].

Canagliflozin is an agent that inhibits sodium glucose cotransporter 2 (SGLT2), which is approved in numerous countries [15], including Mexico, for the treatment of adults with T2DM [16,17]; the efficacy and safety of canagliflozin have been demonstrated in phase III clinical trials of up to 2 years in a broad range of patients with T2DM [18–27]. Canagliflozin leads to inhibition of glucose reabsorption and increased urinary glucose excretion, thereby reducing blood glucose, body weight (predominantly due to fat loss), and SBP (from weight loss and mild osmotic diuresis), with a low risk of hypoglycemia, which can be a limiting factor for achieving treatment goals [28]. This insulin-independent mechanism differentiates canagliflozin from other classes of antihyperglycemic agents (AHAs), such as dipeptidyl peptidase-4 inhibitors, including sitagliptin, which act directly on β cells to lower blood glucose.

The present analysis is based on results from a clinical study that directly compared canagliflozin 300 and 100 mg versus sitagliptin 100 mg in dual therapy with metformin in patients with T2DM [20]. This was a randomized, double-blind, four-arm, parallel-group, placebo- and active-controlled, phase III study. Change in HbA_{1c} from baseline to week 52 was a key end point, with a hypothesis that canagliflozin 300 mg or both doses would demonstrate noninferiority in lowering HbA_{1c} versus sitagliptin 100 mg. In the clinical study, canagliflozin 300 mg demonstrated superiority and canagliflozin 100 mg demonstrated noninferiority compared with sitagliptin 100 mg in lowering HbA_{1c} at 52 weeks (–0.88%, –0.73%, and –0.73%, respectively). Canagliflozin 300 and 100 mg also provided reductions compared with sitagliptin 100 mg in body weight (–4.2%, –3.8%, and –1.3%, respectively) and SBP (–4.7, –3.5, and –0.7 mmHg, respectively). Both doses of canagliflozin were generally well tolerated. Although the incidences of adverse events (AEs) potentially related to the mechanism of SGLT2 inhibition, such as male and female genital mycotic infections (e.g., yeast infections), osmotic diuresis–related AEs (e.g., pollakiuria, polyuria, and nocturia), and volume depletion–related AEs (e.g., orthostatic hypotension and postural dizziness), were higher with both canagliflozin doses than with sitagliptin in the study, AE-related discontinuation rates were similar across treatment groups.

Because T2DM is chronic and progressive, the costs and health benefits of interventions are fully realized only over long time horizons. Ideally, therefore, cost-effectiveness analyses of T2DM interventions would be informed by long-term, naturalistic, randomized clinical trials [29,30]. Clinical trials of sufficient duration, however, are rarely (if ever) available at the time that initial coverage decisions are made. As such, economic computer modeling that extrapolates the available clinical trial data to long-term health economic outcomes has been widely accepted as a way to assess the cost-effectiveness of alternative T2DM treatment strategies [29,30].

Given the growing economic burden of T2DM in Latin America and specifically in Mexico, cost-effectiveness evaluations can inform decisions about the efficient allocation of limited health care resources. Mexico's independent health technology assessment body, Centro Nacional de Excelencia Tecnológica en Salud, encourages the use of cost-effectiveness analysis and states a willingness-to-pay (WTP) threshold of 1 times the gross domestic product (GDP) per capita as "very cost-effective" (MXP 141,120 or US $10,500; exchange rate as of September 26, 2014 of US $1 = MXP 13.44) [31]. Centro Nacional de Excelencia Tecnológica en Salud further states that for treatments with costs per QALY gained of ≥1 and ≤3 times the GDP per capita, a detailed analysis should be performed; those with costs per QALY gained of >3 times the GDP per capita should not be considered "cost-effective" [32,33]. These WTP thresholds are in line with those recommended by the World Health Organization [34].

Comparing diabetes treatment alternatives over the long term from the perspective of the Mexican health care system is necessary to direct resources in the most efficient manner, enabling better patient outcomes from available resources. In this study, the cost-effectiveness of adding canagliflozin 300 or 100 mg versus sitagliptin 100 mg in patients with T2DM inadequately controlled on metformin monotherapy was determined using the 1 and 3 times the GDP per-capita thresholds. The incremental cost-effectiveness ratios (ICERs) were estimated using a validated microsimulation model, Economic and Health Outcomes (ECHO)-T2DM, with local cost data [35].

Methods

Model Overview and Simulation Description

ECHO-T2DM is a stochastic microsimulation (patient-level) cost-effectiveness model of the treatment of T2DM (see Fig. 1 for a diagrammatic overview) [35]. The physiology of T2DM is captured using Markov health states for microvascular and macrovascular complications and death. The cycle length is 1 year, and the time horizon is defined by the user. ECHO-T2DM accounts explicitly for both first-order uncertainty (associated with interpatient variability) and second-order uncertainty (uncertainty regarding the true value of the underlying parameters) and is programmed in R using user-friendly front- and back-end Excel interfaces. Because of space limitations, technical details including a conceptual walk through, parameterization of macrovascular and microvascular complications (i.e., chronic kidney disease, neuropathy, retinopathy), and parameters related to uncertainty and heterogeneity can be found in the Appendix in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2014.12.017.

Cohorts of hypothetical patients are generated at the start of the simulation. Each patient is defined by age, sex, disease duration, HbA_{1c}, biomarker values, smoking status, and preexisting health conditions (micro- and macrovascular disease). Biomarker values at the individual level tend to be correlated; for example, the clustering of poor glycemic control, hypertension, dyslipidemia, and overweight affected 41.6% of the Mexican