Long-term Cost-effectiveness of Two GLP-1 Receptor Agonists for the Treatment of Type 2 Diabetes Mellitus in the Italian Setting: Liraglutide Versus Lixisenatide

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ABSTRACT

Purpose: Maintaining glycemic control is the key treatment target for patients with type 2 diabetes mellitus. In addition, the glucagon-like peptide-1 (GLP-1) receptor agonists may be associated with other favorable treatment characteristics, such as reduction in body weight and reduced risk of hypoglycemia compared with traditional diabetes interventions. The aim of the present analysis was to compare the long-term cost-effectiveness of 2 GLP-1 receptor agonists, liraglutide 1.8 mg and lixisenatide 20 μg (both administered once daily), in the treatment of patients with type 2 diabetes failing to achieve glycemic control with metformin monotherapy in the Italian setting.

Methods: The IMS CORE Diabetes Model was used to project long-term clinical outcomes and subsequent costs (in 2015 Euros [€]) associated with liraglutide 1.8 mg versus lixisenatide 20 μg treatment in a cohort with baseline characteristics derived from the open-label LIRA-LIXI trial (Efficacy and Safety of Liraglutide Versus Lixisenatide as Add-on to Metformin in Subjects With Type 2 Diabetes; NCT01973231) over patient lifetimes from the perspective of a health care payer. Efficacy data were taken from the 26-week end points of the same trial, including changes in glycated hemoglobin, body mass index, serum lipid levels, and hypoglycemic event rates. Outcomes projected included life expectancy, quality-adjusted life expectancy, cumulative incidence and time to onset of diabetes-related complications, and direct medical costs. Outcomes were discounted at 3% annually, and sensitivity analyses were performed.

Findings: Liraglutide 1.8 mg was associated with improved discounted life expectancy (14.07 vs 13.96 years) and quality-adjusted life expectancy (9.18 vs 9.06 quality-adjusted life years [QALYs]) compared with lixisenatide 20 μg. These improvements were mostly attributable to a greater reduction in glycated hemoglobin level with liraglutide 1.8 mg versus lixisenatide 20 μg, leading to reduced incidence and increased time to onset of diabetes-related complications. Compared with lixisenatide 20 μg, liraglutide 1.8 mg was associated with increased total costs over patient lifetimes (€41,623 vs €41,380), but this was offset by lower costs of treating diabetes-related complications (€26,682 vs €27,476). Liraglutide 1.8 mg was associated with an incremental cost-effectiveness ratio of €2001 per QALY gained versus lixisenatide 20 μg. At a willingness-to-pay threshold of €30,000 per QALY gained, liraglutide 1.8 mg had a probability of 77.2% of being cost-effective.

Implications: Based on long-term projections, liraglutide 1.8 mg is likely to be considered cost-effective compared with lixisenatide 20 μg for the treatment of patients with type 2 diabetes in Italy. (*Clin Ther.* 2017;39:1347–1359) © 2017 Elsevier HS Journals, Inc. All rights reserved.

Key words: cost, cost-effectiveness, diabetes mellitus, Italy, liraglutide, lixisenatide.

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INTRODUCTION

In 2015, there were >3.5 million patients with diabetes in Italy, and this number is projected to increase to almost 4 million by 2040.[1] The disease is related to significant mortality, with diabetes directly related to >22,000 deaths per year, and >12% of these deaths occurring before the age of 60 years. As well as a considerable clinical burden, diabetes is associated with a substantial economic burden. It has been estimated that the annual direct cost of diabetes in Italy is €9.6 billion, with cost of hospitalizations after diabetes-related complications comprising the majority of this at €5.1 billion.[2] In addition to the direct costs, diabetes is associated with an annual indirect cost of €10.7 billion, predominantly driven by early retirement. Italian guidelines indicate that the aim of treatment for most patients with type 2 diabetes is to achieve a glycated hemoglobin (HbA_{1c}) target <7.0% (53 mmol/mol), thereby decreasing the risk of diabetes-related complications and resulting in a reduction in the clinical and economic burden of the disease.[3] Currently, only 50% of patients with type 2 diabetes in Italy are reaching the recommended HbA_{1c} target, and there is a need to improve treatment.[4]

The treatment of patients with type 2 diabetes usually requires a change in diet and includes recommendations for regular exercise. Lifestyle changes alone are commonly not successful in achieving treatment targets, and use of the first-line therapeutic metformin is recommended.[5] As type 2 diabetes is a progressive, chronic disease, over time patients require the addition of other treatments for use in combination with metformin to achieve or maintain glycemic control. There are many classes of glucose-lowering drugs available as second-line therapies, including dipeptidyl peptidase 4 inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and sodium glucose cotransporter 2 inhibitors. Traditional therapy options are associated with weight gain and risk of hypoglycemic events, which represent common barriers to achievement of HbA_{1c} targets. In contrast, GLP-1 receptor agonists are associated with reductions in body weight and low rates of hypoglycemic events.[6,7] GLP-1 receptor agonists act by stimulating the GLP-1 receptor, thereby promoting glucose-dependent insulin release, inhibiting the release of glucagon, and delaying gastric emptying.[8] Experimental and observational data have shown that GLP-1 receptor agonists improve key cardiovascular risk factors such as blood pressure and lipid profile.[9] Liraglutide is also associated with improvements in cardiovascular risk markers, including reduction of plasminogen activator inhibitor 1 and B-type natriuretic peptide.[10,11]

Within the Italian setting, GLP-1 receptor agonists currently in use include liraglutide (approved by the European Medicines Agency in June 2009), lixisenatide (approved in February 2013), exenatide (approved in November 2006), and exenatide extended release (approved in June 2011). Recently, results of the LIRA-LIXI (Efficacy and Safety of Liraglutide Versus Lixisenatide as Add-on to Metformin in Subjects With Type 2 Diabetes) trial have been published. The LIRA-LIXI trial was a randomized, open-label, multicenter, 26-week trial that investigated the efficacy and safety of liraglutide 1.8 mg and lixisenatide 20 μg as add-on therapy to metformin in patients with type 2 diabetes who did not achieve glycemic control with metformin alone.[12] In total, 404 patients were randomly allocated 1:1 to receive liraglutide 1.8 mg or lixisenatide 20 μg. The primary end point was the change in HbA_{1c} level from baseline to week 26. For patients receiving liraglutide 1.8 mg, the estimated change was –1.8% (–20.0 mmol/mol) compared with –1.2% (–13.3 mmol/mol) for patients receiving lixisenatide 20 μg. The estimated treatment difference was –0.6% (95% CI, –0.8 to –0.4) (–6.7 mmol/mol [95% CI, –8.7 to –4.8]; $P < 0.0001$), illustrating that liraglutide 1.8 mg was superior to lixisenatide 20 μg.

Following this head-to-head trial focused on clinical outcomes, and with the aim of helping to inform decision-making in clinical practice, data from the LIRA-LIXI trial were used to assess the long-term cost-effectiveness of liraglutide 1.8 mg versus lixisenatide 20 μg in the Italian setting for the treatment of patients with type 2 diabetes who failed to reach HbA_{1c} targets using metformin monotherapy.

PATIENTS AND METHODS

Model Description

Long-term (patient lifetime) projections were made using the IMS CORE Diabetes Model (IMS Health, Basel, Switzerland). The details of the model have been published previously.[13] Briefly, the model is composed of a series of submodels that are designed