Estimating the budget impact of innovative pharmacological treatments for patients with type 2 diabetes mellitus in Italy: the case of liraglutide (GLP-1)

Stefano Capri[1], Marco Barbieri[2]

ABSTRACT

BACKGROUND: Diabetes is among the most common chronic illnesses worldwide, with escalating rates around the world. Four years after the launch of liraglutide (a human GLP-1 analogue for type 2 diabetes) we aimed to evaluate the impact of its use in terms of resources consumption and also in terms of some clinical outcomes.

METHODS: A budget impact model (BIM) has been developed. The model was used to assess the financial impact for the Italian NHS caused by an increased use of liraglutide in patients with type 2 diabetes (T2DM). The analysis was conducted in a 3-year time horizon considering year 2013 as baseline. We used real data of market consumption, reflecting the budget holder's perspective, and not just a hypothetical cohort of patients.

RESULTS: Increasing the percentage of patients receiving liraglutide over the next 3 years, would lead to an increase of costs, ranging from €2.1 million in the first year to €6.7 million in the third year for a total of €13.7 million. However, for these additional costs, the Italian NHS would get more patients with glycaemic control.

CONCLUSION: This study has shown that an increase in the use of liraglutide would determine an extra cost per patient with T2DM in the Italian NHS. The results could be considered conservative since we did not include savings associated to a reduction of hypoglycaemic events. More comprehensive assessments, considering total costs of treatment and expected health benefits, can help decision-makers analyse whether higher acquisition costs may be offset by higher therapeutic results, leading to future projected savings for the healthcare system.

Key words: Budget impact, liraglutide, diabetes, healthcare system

(1) School of Economics and Management, Cattaneo-LIUC University, Castellanza, Italy
(2) Centre for Health Economics, University of York, York, UK

CORRESPONDING AUTHOR: *Stefano Capri - School of Economics and Management - Cattaneo-LIUC University - Corso Matteotti 22 - 21053 Castellanza (VA) Italy*
e-mail: scapri@liuc.it - Tel. 0331572472- 3358155593
Fax 0331572.382

DOI: ***10.2427/11082***
Accepted on March 3, 2015

SOURCE OF SUPPORT: *This work was supported by a grant from Novo Nordisk Europe AG– EU-HEOR, Branch Office, Zurich, Switzerland*

INTRODUCTION

Diabetes is among the most common chronic illnesses worldwide, with escalating rates around the world, accounting for 347 million people worldwide [1]. In 2012, an estimated 1.5 million people with diabetes died [2] and more than 80% of diabetes deaths occur in low- and middle-income countries [3]. Type 2 diabetes mellitus (T2DM) accounts for approximately 90% of all cases [4].

In general, T2DM appears after the age of 30-40 years; several risk factors are associated with its onset, such as family history for diabetes, poor physical exercise, overweight and belonging to certain ethnic groups. The treatment of hyperglycaemia in T2DM begins with diet, nutrition education, physical activity and the attempt to reduce body weight in obese and overweight subjects. When these measures fail to adequately control diabetes, it may be necessary to start a therapy with oral hypoglycaemic agents, initially as monotherapy with metformin and if diabetes is still uncontrolled after ~3 months (HbA1c > 7%), a further medication in association is required. If HbA1c continues to be above target the combination with more oral or injectable hypoglycaemic agents should be considered. The next step consists in insulin therapy [5]. In any case, a careful and tailored choice of therapy may be taken into consideration for every patient as well as continuous monitoring of the effectiveness of the same fundamental elements for glycaemic control achievement. In situations in which body weight reduction and the risk of hypoglycaemia are the key elements for the choice of treatment, ADA and EASD recommend, in their position statements, the use of GLP-1 receptor agonists (Glucagon-Like Peptide-1) as a primary and effective pharmacological option [5]. The risk of micro and macrovascular complications is strongly associated with hyperglycaemia, in fact every 1% drop in HbA1c reduces the risk of microvascular complications by 40% and death by 21% [6]. Liraglutide is a human GLP-1 analogue reimbursed in Italy since 2010. Four years after the launch it is interesting to evaluate the impact of using this drug in terms of resource consumption and also in terms of some clinical outcomes. Actually, since the number of patients with T2DM is increasing, due to the combined effects of population ageing, obesity and sedentary lifestyle [7], it is necessary to have a better understanding of the impact on healthcare expenditure of innovative treatments. For this purpose, a budget impact model (BIM) was built to simulate the economic impact of liraglutide use in the context of the Italian National Healthcare Service (INHS). The BI (budget impact) analysis combines epidemiological data, estimates of market share and treatment costs to predict the eligible population and the total investment needed for the use of liraglutide in patients. From the public health perspective, a BI analysis addresses the need for decision makers, such as administrators of national or regional healthcare programs, to have a clearly presented information on the cost impact of innovative healthcare intervention, like the drug in this study.

METHODS

A budget impact model (BIM) has been developed using Microsoft Excel (Microsoft Corp., Redmond, WA). The model was used to assess the financial impact for the Italian NHS caused by an increased use of liraglutide in patients with T2DM. The model has been built according to the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines [8].

The following categories of drugs marketed in Italy are considered:

- Glucagon-like peptide-1 (GLP- 1): liraglutide, exenatide and exenatide LAR, lixisenatide
- Inhibitors of dipeptidyl peptidase 4 (DPP- 4i): sitagliptin, vidagliptin, saxagliptin, linagliptin
- DPP -4i combined with metformin (MET)
- Sodium-glucose contrasporter 2 inhibitors (SLGT -2i): dapagliflozin*

**not yet marketed at the time of the study*

Other categories of drugs for T2DM available in the Italian market are excluded from this model since only the direct comparators of liraglutide are taken into account as they are the most recently marketed drugs in Italy and as they are universally recognized as the more reliable both in terms of safety and efficacy.

The analysis was conducted with a 3-year time horizon considering year 2013 as baseline. We used real data of market consumption (IMS Health Datafile) for the year 2013 to estimate the number of patients receiving the included drugs at baseline. Therefore the BIM reflects the budget holder's perspective, and not just a hypothetical cohort of patients.

In the following 3 years (2014-2016) two scenarios were compared:

1. A scenario based on a forecast of market consumption using current trends;
2. An alternative scenario where the use of liraglutide was increased.

In the latter scenario, the more patients you treat with liraglutide, the fewer patients you treat with the other drugs considered in the model. The reduction of the latter is proportional to their market share in 2013. For example, a 1% increase of liraglutide would mean a higher loss of patients for a drug having a 50% of market share, than for a drug having a 5% of market share. Liraglutide budget impact is, therefore, simply the difference between costs relating to its increased use and costs relating to substituted drugs.

Population data

Starting from the total Italian population in the year 2013 and the prevalence of diabetes and T2DM in Italy (obtained from the Italian Institute of Statistics [9]), the number of patients with T2DM in the year 2013 was calculated. On the basis of IMS data on market share for that year, we obtained the total number of patients receiving liraglutide, DPP-4i, other GLP1s or DPP4i+MET (table 1).

This represents the baseline cohort of patients and the number of patients receiving each drug was based on the real data of market consumption in year 2013. This is presented together with the forecast of market consumption in the following 3 years in table 2.

Therefore in the year 2013, a proportion of 14.34% of patients among the drug classes considered in our analysis has received liraglutide (n= 38,690), that is assumed to increase to 14.52% in year 2014 and then decrease to 13.62% and 13.20% in the following 2 years. This scenario, which reflects the current trends in the drugs consumption, is compared to a scenario in which the proportion of patients receiving liraglutide is assumed to be 16% in year 2014, 17% in year 2015 and 18% in year 2016 (expected market share from the producer).

Costs

The analysis was conducted from the Italian NHS perspective and only costs of drugs and needles (for GLP-1) were considered. The drug costs on the basis of cost per pack of each drug and the number of days of therapy, the annual cost associated to each drug regimen was calculated. Ex-factory prices were used including discounted prices for public centres negotiated with the Italian Agency of Medicines (AIFA). For GLP-1 the cost of needles was added, where necessary.

RESULTS

From the Italian NHS perspective, increasing the percentage of patients receiving

TABLE 1

ESTIMATION OF PATIENTS RECEIVING THE DRUGS INCLUDED IN THE ANALYSIS (YEAR 2013)	
Italian population (year 2013)	61,178,355
Prevalence of diabetes in Italy	5.50%
Prevalence of Type 2 diabetes	90.00%
Total number of patients with Type 2 diabetes in year 2013	3,028,329
Proportion of patients receiving liraglutide DPP-4i, other GLP1, DPP4i+MET (with respect to the total Italian market)	8.91%
Number of patients receiving liraglutide DPP-4i, other GLP1, DPP4i+MET	**269,813**

TABLE 2

MARKET CONSUMPTION YEAR 2013 (IMS DATA) AND FORECAST FOR THE 3 FOLLOWING YEARS

	DRUG	2013	2014	2015	2016
GLP-1	Liraglutide	14.34%	14.52%	13.62%	13.20%
	Exenatide	2.68%	0.27%	0.11%	0.00%
	Exenatide LAR	0.00%	0.23%	0.22%	1.40%
	Lixisenatide	0.00%	0.94%	2.08%	3.00%
DPP-4	Sitagliptin	27.95%	27.01%	26.54%	25.00%
	Vildagliptin	4.79%	3.80%	3.67%	3.67%
	Saxagliptin	6.60%	4.34%	3.00%	3.00%
	Linagliptin	0.02%	3.57%	4.85%	5.10%
DPP-4 + MET	Sitagliptin + MET	30.17%	29.49%	28.73%	27.80%
	Vildagliptin + MET	12.38%	10.98%	10.15%	9.70%
	Linagliptin + MET	1.08%	2.30%	2.42%	2.50%
SGLT-2 *	Dapagliflozin	0.00%	2.55%	4.59%	5.60%

* not yet marketed

TABLE 3

EXAMPLE OF A FINANCIAL IMPACT AMONG DIFFERENT TREATMENTS

	2014			2015			2016		
DRUG	CURRENT SCENARIO	ALTERNATIVE SCENARIO	COST DIFFERENCE	CURRENT SCENARIO	ALTERNATIVE SCENARIO	COST DIFFERENCE	CURRENT SCENARIO	ALTERNATIVE SCENARIO	COST DIFFERENCE
LIRAGLUTIDE	€ 40,897,596	€ 45,064,196	€ 4,166,600	€ 38,363,864	€ 47,880,708	€ 9,516,844	€ 37,177,501	€ 50,697,221	€ 13,519,720
DPP-4I	€ 51,138,119	€ 50,253,098	-€ 885,021	€ 50,164,678	€ 48,202,350	-€ 1,962,327	€ 48,585,548	€ 45,898,703	-€ 2,686,845
DPP-4I + MET	€ 56,632,990	€ 55,652,871	-€ 980,118	€ 54,698,162	€ 52,558,495	-€ 2,139,667	€ 52,854,527	€ 49,931,602	-€ 2,922,925
EXENATIDE	€ 826,777	€ 812,468	-€ 14,309	€ 352,957	€ 339,150	-€ 13,807	€ 0	€ 0	€ 0
EXENATIDE LAR	€ 820,274	€ 806,078	-€ 14,196	€ 764,284	€ 734,387	-€ 29,897	€ 4,847,054	€ 4,579,005	-€ 268,048
LIXISENATIDE	€ 2,600,631	€ 2,555,623	-€ 45,008	€ 5,792,493	€ 5,565,904	-€ 226,589	€ 8,376,158	€ 7,912,946	-€ 463,213
DAPAGLIFLOZIN*	€ 3,391,352	€ 3,332,660	-€ 58,692	€ 6,101,167	€ 5,862,503	-€ 238,664	€ 7,423,606	€ 7,013,070	-€ 410,535
TOTAL (ITALIAN POPULATION)	€ 156,307,739	€ 158,476,995	€ 2,169,255	€ 156,237,604	€ 161,143,498	€ 4,905,893	€ 159,264,394	€ 166,032,547	€ 6,768,153
TOTAL (PER PATIENT)	€ 579.32	€ 587.36	€ 8.04	€ 579.06	€ 597.24	€ 18.18	€ 590	€ 615	€ 25

*dapagliflozn not yet marketed in Italy

liraglutide over the next 3 years, would lead to an increase of costs, ranging from €2.1 million in the first year to €6.7 million in the third year for a total of €13.7 million. The increase of drug cost with liraglutide is offset by a reduction of drug consumption and costs of other classes.

The budget impact analysis results are shown in table 3.

However, it should be noticed that this increase in costs to the INHS would lead to a better glycaemic control in the population, since a higher proportion of patients is assumed to reach glycaemic target using liraglutide. No data were available to estimate the cost savings associated with this improvement in glycaemic control, but an attempt was made to estimate the incremental number of patients achieving two clinical endpoints:

1. percentage of patients at glycaemic target (HbA1c < 7 %) [10]
2. the proportion of patients achieving the '"COMPOSITE ENDPOINT" (target HbA1c, no weight gain, no hypoglycaemia) [11].

TABLE 4

BUDGET IMPACT WHEN LIRAGLUTIDE SUBSTITUTES ONLY OTHER GLP-1 DRUGS			
	2014	2015	2016
TOTAL COSTS CURRENT SCENARIO	€ 156.307.739	€ 156.237,604	€ 159.264.393
TOTAL COSTS ALTERNATIVE SCENARIO	€ 156.220,949	€ 156.170.979	€ 158.599.824
COST DIFFERENCE (WHOLE POPULATION)	-€ 86.789	-€ 66.625	-€ 664.569
COST DIFFERENCE (PER PATIENT)	-€ 0.32	-€ 0.25	-€ 2.46

In both cases the analysis was based on the results of published clinical trials. A randomised controlled trial (RCT) comparing liraglutide (1.2 or 1.8mg/day) and sitagliptin (100mg/day) have showed that HbA1c < 7% at 52 weeks was achieved in 50.3% of patients with liraglutide 1,2 mg but only in 27.1% of patients with sitagliptin[10]. In the meta-analysis of randomised clinical trials comparing liraglutide 1.2 mg/day, sitagliptin 100mg/day and exenatide 10µg/day calculated that the percentage of patients achieving the "composite endpoint" is 32%, 11% and 25%, respectively.[11]

Considering the number of patients receiving liraglutide or sitagliptin with the current trend scenario for the next 3 years and those that would receive these two drugs in the alternative scenario that implies an increase of liraglutide and a decrease of sitagliptin (as made in the cost analysis), it was found that the incremental number of patients achieving target (HbA1c < 7) is 1,293 in year 2014, 3,005 in year 2015, and 4,370 in year 2016. When also considering exenatide, the incremental number of patients achieving the "composite endpoint" due to an increased use of liraglutide is 981 in year 2014, 2.267 in year 2015 and 3.222 in year 2016. Details of the analysis are presented in the appendix.

Finally, we have considered an alternative scenario, in which a change in the proportion of patients treated with liraglutide has an impact only on the number of patients treated with GLP-1 and not on other drug classes as in the base case. Specifically, in the current scenario the market share of liraglutide with respect to other GLP-1 drugs would be 90,82% in 2014, 84,92% in 2015 and 75% in 2016. We assessed the financial impact of increasing the use of liraglutide to 95% each year in the next 3 years.

Table 4 shows the results of the analysis. In the case that liraglutide substitutes only other GLP-1 drugs, there would be a decrease in the total costs for the INHS ranging from €86,789 in the first year to €664,569 in the third year. This is due to the fact that the price of liraglutide is slightly lower than that of exenatide.

DISCUSSION

This study has aimed to assess the actual financial impact for the INHS for treating patients with T2DM, with an increased use of liraglutide in eligible patients for such treatment.

The budget impact analysis indicated that an increase in the use of liraglutide would lead to higher pharmaceutical costs in the first three years, since the increase in drug costs for liraglutide is only partially offset by a reduction in drug costs of other therapies. One limitation of the study is that the model did not consider costs occurring from adverse events, thus this should be considered a conservative approach: some savings could be obtained as a result of lower costs related to adverse events. However, it should be noticed that this increase in costs to the INHS would lead to a better glycaemic control, since a higher proportion of patients is assumed to use liraglutide. More comprehensive assessments, considering total costs of treatment and expected health benefits, can help decision-makers analyse whether higher acquisition costs may be offset by higher therapeutic results, leading to future projected savings for the health care system [12-13]. The association between glycaemic control and occurrence of diabetes complications is well-established and it is believed that strategies targeting the maintenance of adequate levels of HbA1c reduce costs related to complications [14-16]. It should be noticed that the model is based on real life data on drug consumptions in the Italian market (year 2013) directly related to the number of patients treated each year (and not as a simulation of a hypothetical cohort of patients as done in several BIMs).

CONCLUSIONS

This study has shown that the increased use of liraglutide would determine an extra-cost per patient with T2DM in the INHS ranging from €8.04 in the first year to €25.00 in the third year. However, the results could be considered conservative since we did not include savings associated to a potential reduction of hypoglycaemic events with liraglutide. In addition, liraglutide would increase the proportion of patients achieving the "composite endpoints" (target HbA1c, no weight gain, no hypoglycaemia). Future studies should investigate the potential advantages of liraglutide on a cost-effectiveness basis.

APPENDIX

1. GLYCAEMIC CONTROL			
	LIRAGLUTIDE 1.2MG/DAY	SITAGLIPTIN 100MG/DAY	
Percentage of patients at glycaemic target (HbA1c < = 7 %)	50,3%	27,1%	Pratley et al, 2011

2. PATIENTS ACHIEVING GLYCAEMIC CONTROL OVER THREE YEARS									
	2014			2015			2016		
	CURRENT SCENARIO	ALTERNATIVE SCENARIO	DIFFERENCE	CURRENT SCENARIO	ALTERNATIVE SCENARIO	DIFFERENCE	CURRENT SCENARIO	ALTERNATIVE SCENARIO	DIFFERENCE
PATIENTS TREATED WITH LIRAGLUTIDE	39179	43170	3991	36751	45868	9117	35615	48566	12951
PATIENTS ACHIEVING GLYCAEMIC TARGET WITH LIRAGLUTIDE	19707	21715	2008	18486	23072	4586	17914	24429	6515
PATIENTS TREATED WITH SITAGLIPTIN	152431	149793	-2638	149136	143302	-5834	143100	135187	-7914
PATIENTS ACHIEVING GLYCAEMIC TARGET WITH SITAGLIPTIN	41309	40594	-715	40416	38835	-1581	38780	36636	-2145
TOTAL NUMBER OF PATIENTS ACHIEVING GLYCAEMIC TARGET	**61016**	**62308**	**1293**	**58902**	**61907**	**3005**	**56694**	**61064**	**4370**
PERCENTAGE OF PATIENTS ACHIEVING GLYCAEMIC TARGET	**31,84%**	**32,29%**	**0,45%**	**31,69%**	**32,73%**	**1,04%**	**31,72%**	**33,23%**	**1,51%**

3. COMPOSITE ENDPOINT (TARGET HBA1C, NO INCREASE IN WEIGHT, ABSENCE OF HYPOGLYCAEMIA)				
	LIRAGLUTIDE 1.2MG/DAY	SITAGLIPTIN 100MG/DAY	EXENATIDE 10µG/DAY	
Percentage of patients achieving composite endpoint	32%	11%	25%	Zinman et al, 2012

4. PATIENTS ACHIEVING COMPOSITE END POINT OVER THREE YEARS									
	2014			2015			2016		
	CURRENT SCENARIO	ALTERNATIVE SCENARIO	DIFFERENCE	CURRENT SCENARIO	ALTERNATIVE SCENARIO	DIFFERENCE	CURRENT SCENARIO	ALTERNATIVE SCENARIO	DIFFERENCE
PATIENTS TREATED WITH LIRAGLUTIDE	39179	43170	3991	36751	45868	9117	35615	48566	12951
PATIENTS ACHIEVING COMPOSITE ENDPOINT WITH LIRAGLUTIDE	12537	13814	1277	11760	14678	2917	11397	15541	4144
PATIENTS TREATED WITH SITAGLIPTIN	152431	149793	-2638	149136	143302	-5834	143100	135187	-7914
PATIENTS ACHIEVING COMPOSITE ENDPOINT WITH SITAGLIPTIN	16767	16477	-290	16405	15763	-642	15741	14871	-871
PATIENTS TREATED WITH EXENATIDE	1357	1333	-23	899	863	-35	3737	3531	-207
PATIENTS ACHIEVING COMPOSITE ENDPOINT WITH EXENATIDE	339	333	-6	225	216	-9	934	883	-52
TOTAL NUMBER OF PATIENTS ACHIEVING GLYCAEMIC TARGET	**29644**	**30625**	**981**	**28390**	**30657**	**2267**	**28072**	**31294**	**3222**
PERCENTAGE OF PATIENTS ACHIEVING GLYCAEMIC TARGET	**15,36%**	**15,76%**	**0,40%**	**15,20%**	**16,13%**	**0,93%**	**15,39%**	**16,71%**	**1,32%**

References

[1] Danaei G, Finucane MM, Lu Y, Singh GM, Cowan MJ, Paciorek CJ et al. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. Lancet, 2011, 378(9785):31–40.

[2] World Health Organization. Global Health Estimates: Deaths by Cause, Age, Sex and Country, 2000-2012. Geneva, WHO, 2014.

[3] Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med, 2006, 3(11):e442.

[4] WHO, World Health Organization. Diabetes, Fact sheet N°312 Reviewed October 2013.

[5] Position statement ADA/EASD. Inzucchi et al., Diabetes Care. Apr 19 2012;35(6):1264-79.

[6] Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ. Aug 12 2000; 321:405-12.

[7] van Dieren S, Beulens JW, van der Schouw YT et al., The global burden of diabetes and its complications: an emerging pandemic. European Journal of Cardiovascular Prevention & Rehabilitation May 2010 17: s3-s8.

[8] Sullivan SD, Mauskopf JA, Augustovski F, et al., Budget impact analysis-principles of good practice: report of the ISPOR 2012 Budget Impact Analysis Good Practice II Task Force. Value Health. 2014 Jan-Feb;17(1):5-14.

[9] ISTITUTO NAZIONALE DI STATISTICA (ISTAT), available from: http://demo.istat.it [cited April 12 2014].

[10] Pratley RE, Nauck M, Bailey T et al. One year of liraglutide treatment offers sustained and more effective glycaemic control and weight reduction compared with sitagliptin, both in combination with metformin, in patients with type 2 diaabetes : a randomised, parallel-group, open-label trial. Int J Clin Pract. 2011 Apr;65(4):397-407.

[11] Zinman B, Schmidt WE, Moses A, et al. Achieving a clinically relevant composite outcome of an HbA1c of <7% without weight gain or hypoglycaemia in type 2 diabetes: a meta-analysis of the liraglutide clinical trial programme. Diabetes, Obesity and Metabolism, 2012, Volume 14,1: 77–82.

[12] Davies MJ, Chubb BD, Smith IC et al., Cost–utility analysis of liraglutide compared with sulphonylurea or sitagliptin, all as add-on to metformin monotherapy in Type 2 diabetes mellitus. Diabet.Med. 2012; 29:313–20.

[13] M. J. Davies, R. Kela & K. Khunti. Liraglutide – overview of the preclinical and clinical data and its role in the treatment of type 2 diabetes. Diabetes, Obesity and Metabolism.2011; 13: 207–20.

[14] Stratton IM, Adler AI, Neil HA, et al., Association of glycaemia with macrovascular and microvascular complica¬tions of type 2 diabetes (UKPDS 35): prospective observational study. BMJ. 2000;321(7258):405-12.

[15] Stettler C, Allemann S, Jüni P, et al. Glycemic control and macrovascular disease in types 1 and 2 diabetes mellitus: meta-analysis of randomized trials. Am Heart J. 2006;152(1):27-38.

[16] Adler AI, Erqou S, Lima TA, et al., Association between glycated hae-moglobin and the risk of lower extremity amputation in patients with diabetes mellitus-review and meta-analysis. Diabetologia. 2010;53(5):840-9.

*