Cost-Effectiveness Analysis of Insulin Detemir versus Insulin Glargine in the treatment of Diabetes Mellitus Type 1 in Egyptian patients from the Ministry of health perspective

Health Technology Appraisal

Issued: December 2016

- **بيانات المستحضر محل الدراسة:**

Intervention	Insulin Detemir
Trade name	Levemir
Company name	Novo Nordisk
Comparator	Insulin Glargine

- **الهدف:**

- تقييم الفعالية لقاء التكلفة لمستحضر Insulin Detemir مقارنة بمستحضر Insulin Glargine في علاج مرضى السكري النوع الأول وذلك لضمان أفضل النتائج العلاجية بالنسبة للمريض وبأقل تكلفة ممكنة من خلال الإلتزام بالخطوط العلاجية الاسترشادية العالمية وفي ضوء الممارسة الإكلينيكية المحلية. وذلك في ضوء التوصية بإجراء دراسة جدوي اقتصادية COST EFFECTIVENESS بناء علي اجتماع لجنة وحدة إقتصاديات الدواء بالسادة مديري قطاعات الصيدلة بالتأمين الصحي والمؤسسات العلاجية والأمانة العامة للمستشفيات والهيئة التعليمية.

- علما ان الدراسة التي قامت باجرائها وحدة اقتصاديات الدواء شملت بيانات التكلفة الخاصة بالمستحضرات والتي تم تجميعها من مناقصات مستشفيات وزاره الصحة، بالاضافة إلى باقي التكلفة المرتبطة بالإقامة بالمستشفى والأدوية والمضاعفات المحتملة أثناء علاج المرضى بأنواعها وطبقا لتسعيرة نفقة الدولة.

- تم تجميع البيانات الخاصة بالقيمة العلاجية الناتجة عن جودة الحياة المعيشية للمريض "QUALITY OF LIFE" ونسبة الحالات المستجيبة للعلاج من الدراسات المنشورة عالميًا.

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- **النقاط الهامة:**

بعد دراسة الأدلة العلمية والتجارب الإكلينيكية المتاحة تبين الاتي:

١- تفيد الدراسات المجمعة (Systematic Reviews) والدراسات الاكلينيكية (Clinical Trials) المُقارنة بين المستحضرين بعدم أفضلية مستحضر على الأخر من حيث الفاعلية (HbA1c reduction) في ال indication المذكور أو في الجرعات اليومية المعطاة، فالفروق غير واضحة احصائياً (statistically non-significant) في حالة استعمال ال(Insulin Detemir) مرة واحدة يومياً.

٢- توجد أفضلية طفيفة لصالح ال(Insulin Detemir) من حيث الفاعلية (HbA1c reduction)، وذلك حين إعطاؤه مرتين يومياً.

٣- وبناءاً على الدراسات المتاحة تم بناء الدراسة، والتي خلصت إلى أن مستحضر Insulin Detemir هو الأكفأ من حيث الفعالية لقاء التكلفة (cost effective) مقارنة بمستحضر Insulin Glargine في علاج مرضى Diabetes Type 1. وذلك في ضوء السعر المقترح من الشركة وهو٧٩.٤١ جنيه مصري لقلم Insulin Detemir ٣ ملل مقارنة بسعر ٩٠ جنيه مصري لقلم Insulin Glargine ٣ ملل.

٤- إلا أنه بعد إجراء التحليل الإحصائي (sensitivity analysis)، اتضح أن النتيجة مُعرضة للتغير لصالح مستحضر الInsulin Glargine إذا ما تغيرت بيانات الجرعات والفاعلية، وهذا يعكس بوضوح ما ورد بالنقطة الأولى من عدم وضوح (non-significance) نتائج الدراسات الاكلينيكية وتفضيلها لأحد المستحضرين على الأخر.

٥- ونخلص مما سبق إلى أننا في حاجة لدراسات محلية لتحديد فاعلية كلا المستحضرين والجرعات المستخدمة للوصول للغرض العلاجي، وذلك نظراً للاختلاف في العادات الغذائية والتي بالضرورة تنعكس على الخريطة العلاجية للمريض المصري.

*ملحوظة: نتائج الدراسة صالحة فقط في حالة الاستخدام العلمي الصحيح للدواء (basal insulin analogues) وذلك وفقاً لما ورد بالخطوط الاسترشادية العالمية كالتالي:

1- To achieve glycemic targets in adults with type 1 diabetes, basal-bolus insulin regimens or CSII (continuous subcutaneous insulin infusion) as part of an intensive diabetes management regimen should be used [Grade A, Level 1A].

2- Rapid-acting bolus insulin analogues, in combination with adequate basal insulin, should be used instead of regular insulin to minimize the occurrence of hypoglycemia, improve A1C [Grade B, Level 2] and achieve postprandial glucose targets [Grade B, Level 2].

3- Rapid-acting insulin analogues (aspart or lispro) should be used with CSII in adults with type 1 diabetes [Grade B, Level 2].

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4- A long-acting insulin analogue (detemir, glargine) may be used as the basal insulin [Grade B, Level 2] to reduce the risk of hypoglycemia [Grade B, Level 2 for detemir; Grade C, Level 3 for glargine].

Reference: Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2013 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Can J Diabetes 2013;37(suppl 1):S1-S212.

English Summary

Economic evaluation of Insulin Detemir versus Insulin Glargine for the treatment of Diabetes Mellitus Type 1 in Egypt from payer's perspective

- **Introduction**

According to World Health Organization, diabetes defines as "a metabolic disorder of multiple etiology characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both" (1). There are two main etiological types of diabetes: Type I and II.

Diabetes mellitus is associated with serious long-term complications and premature death (2). The Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS) confirmed the benefits of improved glycemic control (3, 4). To implement intensive insulin therapy, a physiologic model of insulin replacement is applied to most patients with type 1 diabetes mellitus (5). There are many good insulin formulations; however, metabolic control in many patients remains unsatisfactory (6).

For many years, the most commonly used type of insulin that provided a basal insulin supply was NPH (Neutral Protamine de Hagedorn); however, it has been shown to frequently result in nocturnal hypoglycemia due to unintended plasma insulin peaks (7). Injection of regular human insulin does not replicate the postprandial endogenous secretion of insulin. Insulin analogues are modified forms of human insulin that have been developed to address this limitation (2). Since 2000, long-acting insulin analogues have been available. They are progressively replacing NPH insulin as the preferred form of basal insulin for type 1 diabetes because of their favorable pharmacokinetics and pharmacodynamics, namely a less pronounced peak concentration and longer duration of action, which results in lower HbA1c levels and fewer episodes of hypoglycemia (8).

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Two long-acting insulin analogues are currently available: insulin detemir and insulin glargine. Both these long-acting insulin analogues have been shown to be effective treatment options for patients with diabetes, by being able to achieve lower HbA1c levels while reducing hypoglycemia compared to intermediate-acting insulin preparations, such as NPH.

The prevalence of diabetes is increasing rapidly worldwide. Egypt, with a prevalence of 15.6%, is one of the highest across the region, with 86,478 deaths related to diabetes (9). Chronically elevated blood glucose levels are associated with significant morbidity and mortality and many patients will eventually require insulin treatment to maintain good glycaemic control. There are still many uncertainties about the optimal insulin treatment regimens for **type 1 diabetes**, but the long-acting insulin analogues seem promising.

Cost–effectiveness and cost–utility analyses evaluate the balance of a treatment's health benefits, often in terms of quality-adjusted life-years (QALYs) gained, and the anticipated costs of achieving those benefits. Such analyses are increasingly important in the current era of soaring medical costs and healthcare budgets under pressure. In a healthcare system with scarce resources, the pressure to control healthcare spending drives the need for treatments that do more than demonstrate efficacy; they must also demonstrate value. To demonstrate such value, a new treatment that has superior efficacy to an existing one must also demonstrate either cost savings, resulting in dominance (greater efficacy at lower cost) or cost–effectiveness, in which case the additional costs are justified by the gain in effectiveness or utility. In order for a treatment to be deemed cost effective, it must have an incremental cost–effectiveness ratio (ICER) below certain, often nationally determined, threshold. The threshold recommended by the WHO is three-times the gross domestic product per capita (10).

Objective

To evaluate the cost-effectiveness of Insulin Detemir (IDet) compared to Insulin Glargine (IGlar) in treating diabetic patients suffering from diabetes mellitus (DM) type 1 from the governmental payer perspective (Pay on the expense of State system).

Economic evaluation Key Features (11):

Key Features:	
year of the document	December 2016
Affiliation of authors	Pharmacoeconomics Unit, Central Administration For Pharmaceutical Affairs
Purpose of the document	Evaluate the Cost-Effectiveness of using IDet versus IGlar for the treatment of DM type 1
Standard reporting format included	Yes
Disclosure	Yes

Target audience of funding/ author's interests	Public, decision makers
Perspective	Pay on The Expense of State (PTES)
Indication	Treatment of DM type 1
Target population	covered patients by the Egyptian health care system and who have eligible criteria to be treated under PTES system
Subgroup analysis	No Subgroup analysis
Choice of comparator	Insulin Glargine
Time horizon	Over 35-year period
Assumptions required	Yes
Analytical technique	Cost-effectiveness analysis
Costs to be included	Direct medical costs include costs of treatment and severe hypoglycemia management strategies, beside the costs of treating complications arising from DM type 1 according to the Egyptian current practice.
Source of costs	The PTES
Modeling	Markov model
Systematic review of evidences	Yes
Preference for effectiveness over efficacy	Yes
Outcome measure	The outcomes of the two treatments were measured in terms of QALY
Method to derive utility	The published literature
Equity issues stated	All lives and life years are valued equally, regardless of age, gender, or socioeconomic status of individuals in the population
Discounting costs	A discount rate of 3.5 % per year
Discounting outcomes	A discount rate of 3.5 % per year
Sensitivity analysis-parameters and range	Critical component(s) in the calculation is varied through a relevant range or from worst case to best case.
Sensitivity analysis-methods	One-way sensitivity analysis is performed.
Presenting results	Insulin Detemir is cost-effective intervention compared to Insulin Glargine in patients with DM type 1
Incremental analysis	Yes
Total costs vs. effectiveness (cost/effectiveness ratio)	Yes
Portability of results (Generalizability)	The generalizability and extent to which the clinical efficacy data and the economic data are representative is identified and discussed.

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- **Discussion:**

It is crucial to identify the most cost-effective insulin for the treatment of patients with DM type 1 from a range of insulin preparations, which differs in their pharmacokinetic and pharmacodynamic properties. To support reimbursement decision-making in Egypt, decision analysis is a quantitative method for synthesizing data from numerous sources for the evaluation of treatment alternatives and was developed to determine the cost-effectiveness of the insulin detemir strategy, as compared to insulin glargine.

The literature search was conducted in Medline, PubMed and Cochrane Library to identify relevant published English articles from January 1990 to September 2016. The decision analytical model was constructed to assess the costs and consequences associated with IDet compared with IGlar.

The structure of the model used here was previously reported in a cost-of-illness study that was done in Colombia (12). The model was constructed as a Markov model with six health states (Diabetes without complications, with mutually exclusive complications (Cardiac and Coronary diseases, amputation, nephropathy, retinopathy), or death). A time horizon of 35 years was used in order to capture long-term complications and their associated costs, with each cycle being 1 year.

Transition probabilities between the different health states were extracted from a health-economic analysis that compared porcine islet transplantation with standard insulin therapy for type 1 diabetes patients (13). The analysis states that most of the data came from the DCCT (14), with assuming that the annual probability does not change during the 35-year time period of the model. Mortality rates were derived from the Egyptian life expectancy tables of 2013, and converted to probabilities using the normal equation.

Excess mortality rates due to vascular and nonvascular causes were extracted from a publication done by The Emerging Risk Factors Collaboration (15). This was an analyses focusing on individual-participant data from 97 prospective studies that had information about the diagnosis of diabetes or the fasting blood-glucose level at baseline, that did not select participants on the basis of having previous chronic disease (including vascular disease or diabetes), that included recording of cause-specific deaths classified according to clearly defined criteria, and that had accrued more than 1 year of follow-up data. There were 820,900 participants who had no known preexisting vascular disease at baseline and for whom there was complete information about age, sex, smoking status (current smoker vs. any other status), body-mass index (BMI), history of diabetes or fasting glucose level (measured after ≥8 hours of fasting or overnight fasting), and subsequent cause-specific death recorded during follow-up. Hazard ratios were calculated with the use of Cox proportional-hazards regression models stratified according to study, sex, and when appropriate, trial group.

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The clinical parameters for DM type 1 are reported in the form of efficacy data, in which primary endpoints considered is the reduction percentage of glycosylated haemoglobin (HbA1c); and safety data, in which rates of mild to severe hypoglycemia are considered.

Searching medical literature revealed many randomized clinical trials comparing between IDet and IGlar; two of the most informative are Pieber 2007 and Heller 2009 (16 & 17). Pieber 2007 was a 26-week, multicenter, open-label, parallel-group trial, 320 subjects with Type 1 diabetes received either insulin detemir twice daily or insulin glargine once daily, each in combination with premeal insulin aspart (16). All reductions in hazard ratios of complications and mortality due to HbA1c reduction were extracted from (Stratton et al), a prospective observational study that was done on 3642 diabetic patients to compute relative risks of diabetes complications and the reduction in them due to HbA1c reduction (18).

The utility values used in the model were obtained from the published literature. They were cited directly from Beckwith et al 2010 (13). Following references, these utilities were extracted from UKPDS (UK Prospective Diabetes Study) Outcomes model (UKPDS 62) (19). The EuroQol EQ-5D instrument was administered in 1996 to 3667 UKPDS patients with type 2 diabetes. Tobit and censored least absolute deviations (CLAD) regression analysis based on data from the 3192 respondents was used to estimate the impact of major complications on (1) the visual analog scale (VAS) and (2) the EQ-5D utilities derived from population-based time trade-off values (19).

Direct medical costs were obtained from the Pay-on-The-Expense-of-State price list in Egypt, while usual regimens used for treating complications were reported by experts' opinion. Deterministic sensitivity analyses and discounting were conducted. All input data used can be found in table (1).

Total costs for IDet and IGlar were EGP 11,826,965 and EGP 11,726,292 respectively. QALYs for IDet and IGlar were 898.072 and 880.698 respectively. The incremental cost-effectiveness ratio (ICER) for IDet versus IGlar was 5,795 EGP/QALY. This study showed that IDet is a cost effective choice compared to IGlar in treating diabetes type 1 from a payer's perspective in Egypt. However, one way sensitivity analysis showed that the model is very sensitive to the daily doses used in both drugs, and the HbA1c reduction each drug achieves. The non-significance of clinical efficacy points yielded the model's results to be non-significant if the efficacy confidence intervals are to be regarded. Figure 1 depicts the tornado chart of the performed sensitivity analysis.

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Table (1): Model input parameters

Item Labels	Input Value	Reference
Treatment data		
Insulin Detemir pen cost (3 ml pen) (100U/ml)	٧٩.٤١ ج.م.	Educational hospitals
Insulin Glargine pen cost (3 ml pen) (100U/ml)	٩٠.٠٠ ج.م.	Pricing
Insulin Aspart pen cost (3 ml pen) (100U/ml)	٤١.١١٨ ج.م.	Educational hospitals
Basal Insulin Detemir daily dosing (units)	36.19	16
Basal Insulin Glargine daily dosing (units)	26.95	16
Bolus Insulin Aspart daily dosing (units) with Detemir	27.72	16
Bolus Insulin Aspart daily dosing (units) with Glargine	30.03	16
Complications annual cost		
cardiac and coronary disease cost - 1st year	EGP 10,362	PTES
cardiac and coronary disease cost - subsequent years	EGP 5,029	PTES
Amputation cost (new cases only)	EGP 27,500	PTES
Renal complications cost - 1st year	EGP 10,210	PTES
Renal complications cost - subsequent years	EGP 5,280	PTES
Blindness cost	EGP 27,772	PTES
Severe hypoglycemia cost	EGP 1,950	PTES
Utilities & QALY decrements		
Diabetes without complications utility	0.81	13
Diabetes + cardiac and coronary disease utility	0.7	13
Diabetes + blindness utility	0.67	13
Diabetes + amputation utility	0.64	13
Diabetes + Renal failure utility	0.43	13
Hypoglycemia utility decrement	0.06	13
Transition probabilities		
TP_cardiac and coronary disease	0.0043	13
TP_nephropathy	0.05	13
TP_amputation	0.01	13
TP_retinopathy	0.02	13
TP_mortality (40-44)	0.011735	20
TP_mortality (45-49)	0.0242125	20
TP_mortality (50-54)	0.0438215	20

TP_mortality (55-59)	0.059814	20
TP_mortality (60-64)	0.0929465	20
TP_mortality (65-69)	0.1427705	20
TP_mortality (70-74)	0.223972	20
HR_mortality from vascular causes	2.32	15
HR_mortality from nonvascular causes	1.73	15
Efficacy indicators		
HRR of macrovascular complications for 1% HbA1c reduction	14%	18
HRR of microvascular complications for 1% HbA1c reduction	37%	18
HRR of amputation for 1% HbA1c reduction	43%	18
HRR of death for 1% HbA1c reduction	21%	18
%HbA1C reduction_Insulin Detemir	0.74	16
%HbA1C reduction_Insulin Glargine	0.61	16
TP_severe hypoglycemia_Insulin Glargine	0.218	16
RR_severe hypoglycemia_Insulin Detemir to Insulin Glargine	0.28	16
Discount rates		
Costs Discount rate	3.5%	11
Utilities Discount rate	3.5%	11

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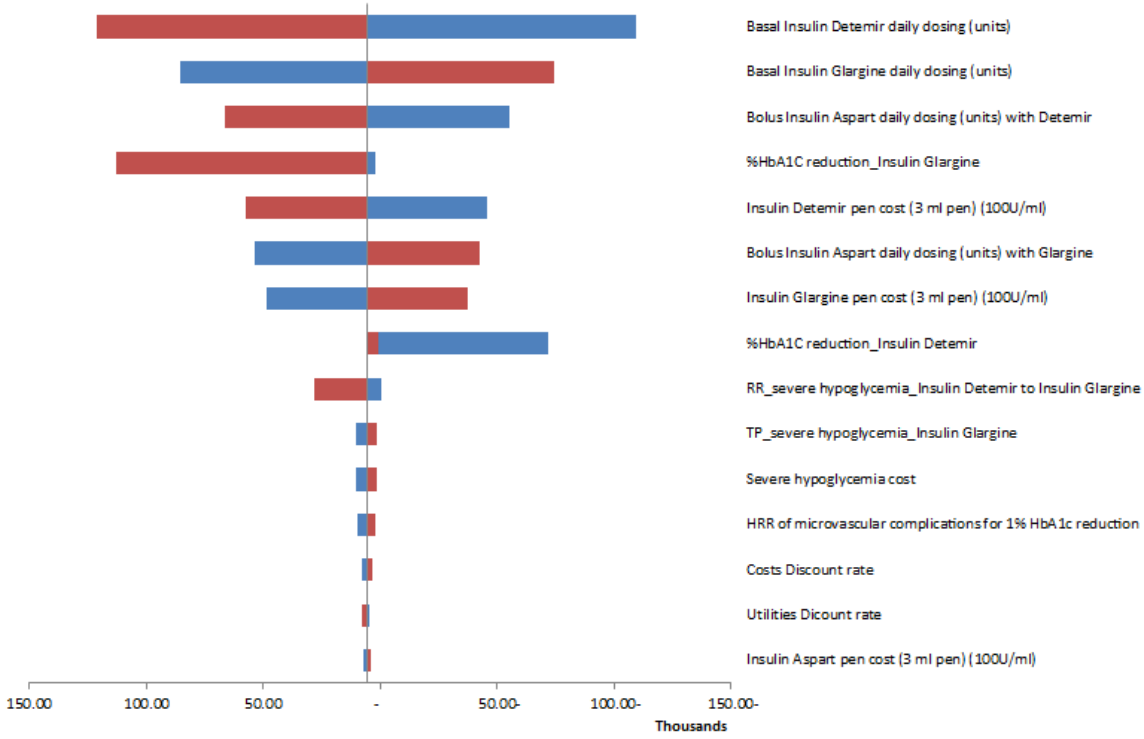
Figure (1): Deterministic sensitivity analyses results



As the case with other diabetes Markov models, one of the main limitations of this study is that although it is possible (and may often occur) that patient may has more than one complication simultaneously, those compound health states were not included for the sake of simplicity. Consequently, there could be some minor underestimation of costs. Also, we combined both cardiac (i.e., congestive heart failure and stroke) and coronary (i.e., myocardial infarction) disease into one health state, which may not be accurate for patients suffering from only one of them.

As in all modeling exercises, several assumptions were made in this study leading to uncertainties in the results. In this analysis, we explicitly accounted for these uncertainties by assigning confidence intervals and plausible ranges of the relative risks, utilities, transition probabilities and costs based on published sources. To assess the influences of other model structures and assumptions on the cost-effectiveness estimates, one-way sensitivity analyses of various parameters were performed.

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Pharmacoeconomic models and retrospective analyses of healthcare databases have consistently shown that treatment with insulin analogs is cost-effective versus other options on the long run. Therefore, the use of insulin analogs in type 1 DM is an appropriate investment of healthcare resources. However, published studies gave contradicting conclusions to which analog is the more cost effective. The only cost–effectiveness studies to date that compare IDet with IGlar were both conducted in North America. Valentine et al. compared the cost–effectiveness of IDet versus IGlar and found IDet to be dominant from a US payer setting (21). The analysis was based on a 26-week head-to-head RCT in patients with Type 1 diabetes that compared twice-daily IDet with once-daily IGlar, both in a basal-bolus regimen with insulin aspart (22). By contrast, Guillermin et al. reported twice-daily IDet to be not cost effective compared with once-daily IGlar in Canada (23). The model projected lifetime direct medical costs for insulin therapy and management of complications based on patients' daily insulin dose using data Guillermin et al. derived from their own meta-analysis of randomized head-to-head trials in people with Type 1 (16,17).

- **Conclusion**

Results from this study suggest that insulin detemir is cost effective intervention compared to insulin glargine in treating type 1 diabetic patients, based on the willingness to pay threshold stated by world health organization (3xGDP/capita) for low and middle income countries. The conclusion should be regarded with caution regarding the used doses and local effectiveness data of both analogues. These findings will help inform health care decisions regarding the allocation of health care system resources and improving outcomes.

- **Declaration of interest**

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

- **PEU project team**

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