Cost-Effectiveness Analysis of Insulin Detemir versus Insulin Glargine in the treatment of Diabetes Mellitus Type 2 in Egyptian patients from the Ministry of health perspective

Health Technology Appraisal

Issued: November 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 الثاني 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- توافر العديد من الدراسات المجمعة (Systematic Reviews) والدراسات الاكلينيكية (Clinical Trials) والتي لا تفيد بأفضلية مستحضر على الأخر من حيث الفاعلية (HbA1c reduction) في ال indication المذكور، فالفروق غير واضحة احصائياً (statistically non-significant).

٢- توجد فروق لصالح ال(Insulin Glargine) في عدد الوحدات اليومية المستهلكة من الأنسولين، حيث أن عدد الوحدات أقل ويمكن إعطاؤه مرة واحدة يومياً، بينما نجد أحد الأثار العكسية (severe hypoglycemia) يحدث بنسب أقل مع ال(Insulin Detemir).

٣- وبناءاً على ما سبق فقد تم بناء الدراسة، والتي خلصت إلى أن مستحضر Insulin Detemir ليس الأكفأ من حيث الفعالية لقاء التكلفة (not cost effective) مقارنة بمستحضر Insulin Glargine في علاج مرضى Diabetes Type 2. وذلك في ضوء السعر المقترح من الشركة وهو ٧٩.٤١ 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 Detemir 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- In people with type 2 diabetes, if glycemic targets are not achieved using lifestyle management within 2 to 3 months, antihyperglycemic agent therapy should be initiated. Metformin may be used at the time of diagnosis, in conjunction with lifestyle management.

i. If A1C ≥8.5%, antihyperglycemic agents should be initiated concomitantly with lifestyle management, and consideration should be given to initiating combination therapy with 2 agents, one of which may be insulin.

ii. Individuals with symptomatic hyperglycemia and metabolic decompensation should receive an initial antihyperglycemic regimen containing insulin.

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2. Metformin should be the initial drug used specially for overweight patients.
3. Other classes of antihyperglycemic agents, including insulin, should be added to metformin, or used in combination with each other, if glycemic targets are not met, and these adjustments to and/or additions of antihyperglycemic agents should be made in order to attain target A1C within 3 to 6 months.
4. Choice of pharmacological treatment agents should be individualized, taking into consideration patient characteristics and treatment properties.
5. When basal insulin is added to antihyperglycemic agents, long-acting analogues (detemir or glargine) may be used instead of intermediate-acting NPH to reduce the risk of nocturnal and symptomatic hypoglycemia.

أي ان الغالبية من المرضي يتم علاجهم بشكل أساسي بمستحضر Mixtard حيث يعتبر هو الـ "standard therapy" بينما يحتاج نسبة أقل من مرضي السكري بنوعيه في حالة عدم إتيانه بالنتائج العلاجية المرجوة منه الي العلاج بـ Insulin Analogs مثل مستحضري Detemir و Glargine.

Reference: Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Pharmacologic Management of Type 2 Diabetes. Available at http://guidelines.diabetes.ca/browse/Chapter13. Accessed on November 24, 2016.

English Summary

Economic evaluation of Insulin Detemir versus Insulin Glargine for the treatment of Diabetes Mellitus Type 2 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.

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Type 2 diabetes mellitus is caused by two factors: the reduction in insulin production and the presence of insulin resistance in skeletal muscle and liver. Type 2 diabetes is a progressive disease in which insulin production declines as the disease progresses, resulting in increasing failure of glucose absorption. In early stages of type 2 diabetes, the most significant pathology is insulin resistance. Insulin resistance develops from unknown genetic defects combined with environmental factors, predominantly obesity and physical inactivity (2). As the disease progresses, insulin resistance remains relatively stable and insulin production declines progressively.

Eventually, relative insulin deficiency, and thus hyperglycaemia, will develop. Chronic hyperglycaemia is associated with microvascular complications like retinopathy, nephropathy and neuropathy, and an increased risk of cardiovascular disease. Lowering blood glucose levels by means of intensive therapy has been shown to reduce these vascular complications in type 2 diabetes patients (3).

According to the American Diabetes Association (ADA) / European Association for the Study of Diabetes (EASD) consensus algorithm for the management of type 2 diabetes "anHbA1c level of ≥ 7% should serve as a call to action to initiate or change therapy with the goal of achieving an HbA1c level of < 7%". The authors also advise that initial therapy should consist of lifestyle intervention and the oral glucose-lowering drug metformin. As the disease progresses treatment is usually intensified by the addition of one or more oral agents. However, when lifestyle interventions and oral therapy no longer achieve the currently recommended glycaemic goal of an HbA1c level of less than 7%, the introduction of a basal insulin preparation is advocated (4). Traditionally, the intermediate-acting Neutral Protamine Hagedorn (NPH) insulin has been used, but this agent has pharmacodynamics limitations (5, 6), predisposing to both hypoglycaemia and hyperglycaemia (7). In order to reach glycaemic targets more effectively and safely, insulin analogues with a modified structure compared to the human insulin molecule were developed. Two long-acting insulin analogues are currently available: insulin detemir and insulin glargine.

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 (8). 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 2 diabetes, but the long-acting insulin analogues seem promising.

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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 2 from the governmental payer perspective (Pay on the expense of State system).

Economic evaluation Key Features (9):

Key Features:	
year of the document	November 2016
Affiliation of authors	Pharmacoeconomic 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 2
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 2
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 2 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 *not* cost-effective intervention compared to Insulin Glargine in patients with DM type 2
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.

- **Discussion:**

It is crucial to identify the most cost-effective treatment in patients with DM type 2 from a range of different alternatives that work with different mechanisms. 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 2000 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 (10). The model was also a Markov model with the same health states (Diabetes without complications, with mutually exclusive complications (CVS, amputation, nephropathy, retinopathy, stroke), or death). We used the same starting age (age at diagnosis at 40 years old), and the same model length (35 years), with each cycle being 1 year.

Transition probabilities between the different health states were extracted from the above mentioned study, with mortality rates extracted 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 (11). This was an analyses focusing on individual-participant data from 97 prospective studies that had information about the diagnosis of

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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.

The clinical parameters for DM type 2 are reported in the form of efficacy data; in which primary endpoints considered is the percentage of glycosylated haemoglobin (HbA1c) reduction, and safety data; in which rates of mild to severe hypoglycemia are considered.

Searching medical literature revealed a lot of systematic reviews including comparative clinical trials between IDet and IGlar (12-16). One of the reviews (Swinnen et al 2011) examined four trials lasting 24 to 52 weeks involving 2250 people randomised to either insulin detemir or glargine, from which previously stated efficacy and safety data were extracted (12), while one input parameter (annual probability of severe hypoglycemia on IGlar) was extracted from another review (15). All reductions in hazard ratios of complications and mortality due to HbA1c reduction was 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 (17).

The utility values used in the model were obtained from the published literature. They were reported as decrements based on UKPDS (UK Prospective Diabetes Study) Outcomes model (UKPDS 62 & 68) (18, 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 (18).

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).

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Total costs for IDet and IGlar were EGP 12,447,699 and EGP 8,872,245 respectively. QALYs for IDet and IGlar were 1028.558 and 1019.879 respectively. The incremental cost-effectiveness ratio (ICER) for IDet versus IGlar was 411,968 EGP/QALY. This study showed that IDet is not a cost effective choice compared to IGlar in treating diabetes type 2 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 achieve. 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

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
Basal Insulin Detemir daily dosing (units)	76.5	20
Basal Insulin Glargine daily dosing (units)	43.5	20
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
Stroke cost	EGP 5,060	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	0.785	21
Diabetes + cardiac and coronary disease utility	0.701	18
Diabetes + Stroke utility	0.621	18
Diabetes + blindness utility	0.711	18
Diabetes + amputation utility	0.505	18
Diabetes + Renal failure utility	0.307	21
Hypoglycemia utility decrement	0.047048	21
Transition probabilities		
TP_cardiac and coronary disease	0.0331	10
TP_nephropathy	0.0016	10

TP_amputation	0.0022	10
TP_retinopathy	0.0029	10
TP_stroke	0.0112	10
TP_mortality (40-44)	0.011735	22
TP_mortality (45-49)	0.0242125	22
TP_mortality (50-54)	0.0438215	22
TP_mortality (55-59)	0.059814	22
TP_mortality (60-64)	0.0929465	22
TP_mortality (65-69)	0.1427705	22
TP_mortality (70-74)	0.223972	22
HR_mortality from vascular causes	2.32	11
HR_mortality from nonvascular causes	1.73	11
Efficacy indicators		
HRR of macrovascular complications for 1% HbA1c reduction	14%	17
HRR of microvascular complications for 1% HbA1c reduction	37%	17
HRR of amputation for 1% HbA1c reduction	43%	17
HRR of death for 1% HbA1c reduction	21%	17
%HbA1C reduction_Insulin Detemir	1.54	20
%HbA1C reduction_Insulin Glargine	1.46	20
TP_severe hypoglycemia_Insulin Glargine	0.084	15
RR_severe hypoglycemia_Insulin Detemir to Insulin Glargine	0.82	12
Discount rates		
Costs Discount rate	3.5%	9
Utilities Discount rate	3.5%	9

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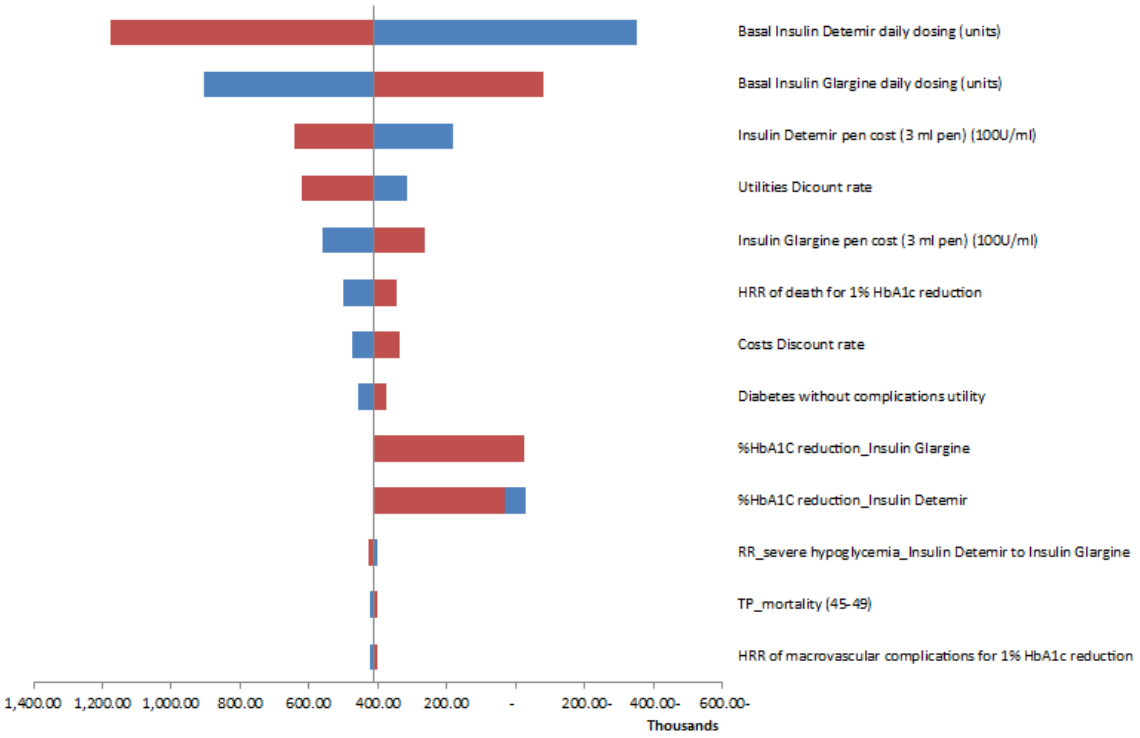
Figure (1): Deterministic sensitivity analysis result



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 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 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 2 DM is an appropriate investment of healthcare resources. However, published studies gave contradicting conclusions to which analog is the more cost effective. A Chinese health economic model found that conversion to IDet from an IGlar regimen improved life expectancy and was a cost-saving treatment approach (23), another review assessed 15 modeling studies, most of which found IDet to be cost effective compared with neutral protamine Hagedorn and as cost effective as IGlar (24). On the other hand, a Canadian cost-minimization analysis found that similar HbA1c change from baseline can be achieved with a lower IGlar than IDet dose and that treatment of Type 1 DM and Type 2 DM patients with IGlar instead of IDet can generate long-term cost savings from the perspective of a Canadian provincial government (25).

- **Conclusion**

Results from this study suggest that insulin detemir is not cost effective intervention compared to insulin glargine in treating type 2 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 analogs. 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.

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