# COST-EFFECTIVENESS ANALYSIS OF IDEG VS IGLAR U100 IN PATIENTS WITH TYPE 1 AND TYPE 2 DIABETES IN PORTUGAL: EVIDENCE FROM THE SWITCH 1&2 TRIALS

**Autores/Authors:  J. Darbà (1),   M. Ascanio (2),   D. Carvalho  (3),   V. Conde  (4),  K.S. Pedersen (5)**

Institution:

*1 – Department of Economics. Universitat de Barcelona, Barcelona, Spain;*

*2 – BCN Health Economics & Outcomes Research S.L., Barcelona, Spain;*

*3– Department of Endocrinology, Diabetes and Metabolism, Centro Hospitalar Universitário São João & Faculty of Medicine & i3S, Porto University, Porto;*

*4 – Novo Nordisk Portugal, Lisbon;*

*5 – Novo Nordisk Region Europe, Copenhagen, Denmark.*

**CONFLICTS OF INTEREST**

**SPONSORSHIP**

Correspondence to:  Josep Darbà
Department of Economics. Universitat de Barcelona, Diagonal 696, 08034 Barcelona, Spain Tel. +34 934020110 / + 34 934021937  -  Fax +34 934039082
E-mail darba@ub.edu

**Abstract**

**Objectives:** To assess the cost-effectiveness of IDeg versus IGlar from a Portuguese healthcare perspective using data from SWITCH1&2 trials.

**Methods:** A short-term cost-effectiveness model was developed to estimate cost and effectiveness data for IDeg versus IGlar. Data to populate the model have been obtained from SWITCH1&2. Number and types of hypoglycaemic events, disutilities related with hypoglycaemic events, insulin dose and cost and the costs of needles and blood glucose tests were used. Benefits were measured in QALYs. One-way and probabilistic sensitivity analyses assessed the robustness of the results.

**Results:** End-of-trial basal insulin dose was significantly lower with IDeg versus IGlar while bolus doses in T1DM B/B were similar. Non-severe nocturnal and all severe hypoglycemic events were significantly lower for IDeg. Non-severe daytime hypoglycemic events did not show any difference in SWITCH 1 while in SWITCH 2 there were a significantly lower number of events for IDeg. IDeg proved to be a cost-effective therapy when compared to IGlar for T1DM B/B and T2DM BOT patients being dominant due to its reduced costs and increased QALY. Sensitivity analyses demonstrated the robustness of results.

**Conclusions:** This cost-effectiveness analysis proves that IDeg is dominant over IGlar for both T1DM B/B and T2DM BOT patients.

**INTRODUCTION**

Diabetes mellitus is a chronic disease that happens when the pancreas does not produce enough insulin (type 1 diabetes) or when the insulin produced is not effectively used by the body (type 2 diabetes)[1]. This chronic disease represents a major economic burden for healthcare systems owing to the costs of treating diabetes and its related complications. According to Relatório Anual do Observatório Nacional da Diabetes (2016)[2] and taking into account the values presented by the International Diabetes Federation in the 7th Edition of the Diabetes Atlas[3], diabetes costs in Portugal in 2015 represented €1,936 million for the population with diabetes aged 20 to 79 years. These costs represented the 1% of the gross domestic product (GDP) and the 12% of the total healthcare expenditure in Portugal in 2015. Furthermore, these costs are expected to increase because of the annual growth of the diabetic population.

The number of people with diabetes has risen from 108 million in 1980 to 422 million in 2014[4]. The global prevalence of diabetes among adults over 18 years of age has risen from 4.7% in 1980 to 8.5% in 2014[4]. It is also noteworthy that in 2012 an estimated 1.5 million deaths were directly caused by diabetes and another 2.2 million deaths were attributable to high blood glucose[4].

In Portugal, diabetes prevalence in 2014 was 13.1% for the population aged 20 to 79 years2, ranging from 522 to 663 new cases per 100,000 people. Besides, it is expected that over the period from 2013 to 2035 the number of people with diabetes would increase a 19.5%[5]. The incidence rate of type 1 diabetes mellitus (T1DM) in Portugal is 17.5 new cases per 100,000 children younger than 15 years old. For type 2 diabetes mellitus (T2DM), the prevalence has been estimated to be 7.5%2 in 2015 and is expected to rise to 15.8% by 20355. T2DM is a progressive disease that can be controlled by healthy habits (e.g. diet, exercise, etc.) when being mild[6], but its progression depends on blood glucose levels and on keeping these levels in the desired target of the patient6. Eventually, patients with higher blood glucose levels will require medication to control them and lower their resistance to insulin[7]. In the end, all T1DM patients

will need insulin therapy to control their diabetes, as well as most T2DM patients who show progression of disease7.

The main objective of the diabetes treatment is to control blood glucose levels and avoid or lower the risk of hypoglycemic events, since these may worse the patients' quality of life and the management of their condition[8]. Further, hypoglycemic events have demonstrated a substantial impact on health costs[9].

There are several insulin treatments in the Portuguese market, where insulin glargine (IGlar) is one of the most used basal insulins to treat T1DM and T2DM. Its pharmacological action starts between 1 and 3 hours after its administration and lasts for 24 hours approximately[10]. IGlar should be administrated with a short-acting insulin treatment in case of T1DM patients or with oral medication in case of T2DM patients. Insulin degludec (IDeg) is a new basal insulin therapy with ultra-long duration of action[11] (more than 42 hours) and a flat and stable action profile[12,13]. In phase 3a trials IDeg has shown equivalent HbA1c reductions with less risk of hypoglycemic event, and at significantly low dose compared to IGlar in T1DM B/B (12% lower) and T2DM BOT patients (10% lower)[14,15,16]. Besides, in phase 3b trials (SWITCH 1 and SWITCH 2) IDeg has demonstrated non-inferiority in terms of reduction in HbA1c and achieved superiority for both the primary and the secondary hypoglycemia endpoints when compared with IGlar[17,18].

The main objective of this analysis is to assess the cost-effectiveness of IDeg when compared with IGlar in patients treated with long-acting basal insulin from the perspective of the Portuguese National Healthcare System. The subgroups of patients considered in this analysis were: T1DM patients treated with basal-bolus (B/B) regimen and T2DM patients treated with basal oral therapy (BOT) regimen. A short-term five-year approach that focuses on the impact of hypoglycemia and dosing has been used. This approach allowed an economic assessment of a new insulin analogue based on data derived from two 2 x 32-week randomized, double-blind, crossover, multicentre, treat-to-target phase 3b clinical trials**¡Error! Marcador no definido.**[,¡Error!

4

**Marcador no definido.** in which patient populations resemble real world patients to a larger degree than in previous trials.

## METHODS

### Model specifications

This cost-effectiveness analysis compared IDeg with IGlar for two different groups of patients: T1DM patients treated with B/B insulin therapy and T2DM patients treated with BOT.

The cost-utility model used in this analysis was previously published[19,20,21]. It was developed in Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA) to evaluate clinical and economic outcomes associated with the use of IDeg and IGlar in T1DM B/B and T2DM BOT over a five-year time horizon. The basal and bolus and insulin doses, incidence of non-severe and severe hypoglycemic events, frequency of SMBG, and timing of dose administration were specified for each insulin therapy in the different diabetes patient subgroups.

Based on these characteristics, the model estimated the total costs associated with insulin use, SMBG, needles, hypoglycemia, as well as change in quality-of-life (in terms of quality-adjusted life years [QALYs]) in both scenarios. A discount of a 3.5% was applied on both costs and clinical parameters. Costs were estimated from a healthcare payer perspective in Portugal. All costs were expressed in 2018 Euros (EUR). The Portuguese Health Authority (INFARMED[22]) does not use an official willingness-to-pay (WTP) threshold when assessing ICERs. We have assumed a WTP threshold of 30,000 Euros per QALY gained, the value for money commonly used for health economic studies in Portugal. Clinical outcomes captured all direct health effects on the patient. Only statistically significant parameters were used to minimize modelling uncertainty. A schematic of the model structure is shown in figure 1.

The clinical data for this analysis were derived from different clinical trials: data for T1DM B/B patients from the SWITCH 1 trial[iError! Marcador no definido.], data for T2DM BOT patients from the SWITCH 2 trial[iError! Marcador no definido.]. The main objective of both trials was to demonstrate superiority of IDeg over IGlar and the as related to the combination of severe hypoglycemia and

5

blood sugar confirmed symptomatic hypoglycemia. Both trials also evaluated the number of severe and nocturnal hypoglycemia and rates of severe hypoglycemia between the two treatments evaluated.

**Clinical data**

Clinical data used in this study were obtained from SWITCH 1 and SWITCH 2 trials. These clinical trials were designed as treat-to-target, with insulin doses adjusted in order to achieve similar HbA$_{1c}$ levels between treatments and therefore no HbA$_{1c}$ level differences were observed.

Insulin doses

The IDeg/IGlar dose ratios for both subgroups of patients were obtained from SWITCH 1 and SWITCH 2 trials to estimate IDeg and IGlar doses. Units of basal IDeg insulin used daily for T1DM B/B and T2DM BOT patients were extracted from the SWITCH 1 and SWITCH 2 trials data**¡Error! Marcador no definido.**[,¡Error! Marcador no definido.], respectively. The IGlar doses were 40.58 units/day for T1DM B/B patients and 82.66 units/day for T2DM BOT patients (Table 1).

The procedure followed to estimate the IDeg dose for T1DM B/B was the following: 1) the IGlar dose for T1DM B/B was 40.58 units/day; 2) the relative dose ratio (IDeg/IGlar) was 0.97; 3) the IDeg dose for T1DM B/B patients was 40.58 x 0.97 = 39.36 units/day (Table 1). To estimate the IDeg dose for T2DM BOT, the calculation was as follows: 1) the IGlar dose for T2DM BOT was 82.66 units/day; 2) the relative dose ratio was 0.96; 3) the IDeg dose for T2DM BOT patients was 82.66 x 0.96 = 79.35 units/day (Table 1).

Hypoglycemic event rates

The frequencies of severe and non-severe hypoglycemic events (SHE and NSHE) were obtained from the full treatment phase of SWITCH 1 and SWITCH 2 trials. In both trials nocturnal NSHE and all (nocturnal and daytime) SHE were significantly lower for patients treated with IDeg. Moreover, daytime NSHE did not show statistically significant difference in SWITCH 1 while in

SWITCH 2 there were a significantly lower number of events in the IDeg group. The event rates used to obtain the number of events for IDeg were derived from an observational study[23]. The event rates for IDeg were determined based on the relative event ratios (IDeg/IGlar) derived from the SWITCH 1 and SWITCH 2 trials multiplied by the events rate for IGlar obtained from the observational study.

The SHE was defined in accordance with ADA guidelines[24] as "an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions". The NSHE was an event with symptoms, with or without blood glucose measurement (BGM), or low BGM without symptoms, which the patient could manage without assistance.

The event rates for IDeg were estimated based on the relative event ratios (IDeg/IGlar) derived from the SWITCH 1 and SWITCH 2 trials (Table 2). Three mutually exclusive groups of hypoglycemia to prevent the possible double counting of events were considered when obtaining event rates: severe events, non-severe events occurring during the day (daytime) and non-severe events occurring during the night (nocturnal).

The following calculations were done to estimate the number of non-severe nocturnal hypoglycemic events for T1DM B/B patients: 1) the number of non-severe nocturnal hypoglycemic events related to IGlar for T1DM B/B patients was 22.56 per patient per year; 2) the relative event ratio (IDeg/IGlar) was 0.76 (only significant differences were used for the modelling); 3) the number of non-severe nocturnal hypoglycemic events related to IDeg was 22.56 x 0.76 = 17.15 per patient per year. The calculation to estimate the number of non-severe nocturnal hypoglycemic events for T2DM BOT was as follows: 1) the number of non-severe nocturnal hypoglycemic events related to IGlar for T2DM BOT patients was 5.53 per patient per year; 2) the relative event ratio was 0.76; 3) the number of non-severe nocturnal hypoglycemic events related to IDeg was 5.53 x 0.76 = 4.20 per patient per year.

Self-Monitoring Blood Glucose tests and Needles

The number of SMBG tests per week associated with IGlar was based on the recommended titration schedule for IGlar in T1DM B/B and T2DM BOT insulin treated patients[25]. The patients treated with IDeg are able to monitor their blood glucose more efficiently and use fewer SMBG tests per week because the IDeg medication has a long half-life and a flat, stable profile in steady state with low variability over the day. Therefore, IDeg has the potential to be monitored and titrated with less number of SMBG tests associated with basal injections per week for T1DM B/B and T2DM. Lastly, the number of needles is equal for each BOT or B/B regimens (Table 3).

**Cost data**

Costs were estimated from the Portuguese National Healthcare System perspective. For all patient groups, direct costs included the drug cost and costs related to severe and non-severe hypoglycemic events. The drug costs included the number of insulin units used, needles and SMBG tests. The rest of the unit costs were assumed to be the same for all treatment groups. All costs were expressed in 2018 Euros.

Cost of Insulin, Needles and SMBG tests

All insulin costs (Table 4) were based on the public sales price (PSP) + VAT for each type of insulin. Further, the costs of needles, SMBG test strips, and lancets were based on a tender resolution[26].

Cost of Hypoglycemic Events

The direct cost of managing a single hypoglycemic event and the cost of extra SMBG tests used in the week after the event were included in the direct cost associated with a hypoglycemic event.

The cost of managing a SHE in Portugal was estimated at €57727 and €1,49328 for T1DM and T2DM patients, respectively. These costs for SHE included the SMBG tests used the week following the severe event. In case of NSHE the costs for the additional SMBG tests used were obtained from Brod et al., 2011[Error! Marcador no definido.], a study based on patient-reported experiences (Table 3).

Patients reported that the number of SMBG strips used the week after a hypoglycemic event or the proportion of patients contacting a healthcare professional or a hospital was the same for both IDeg and IGlar treatment.

Regardless of treatment, the behaviour of patients after a hypoglycemic event was assumed to be similar. Therefore, the difference in treatment costs was not due to the cost per event but only due to the difference in the number of hypoglycemic events.

**Utility data**

A marginal decreasing disutility approach was used in the base case analysis to estimate QALYs by reducing the HRQoL per hypoglycemic event or disutility.

The initial quality of life was reduced according to the number of hypoglycemic events occurred during the year in each treatment group. The relation between the reduction of a patient's average HRQoL and the number of hypoglycemic events followed a diminishing marginal impact pattern. The disutility per hypoglycemic event was multiplied by the number of events observed in each treatment regimen (Table 2). This was carried out for severe and non-severe hypoglycemic events separately.

The disutilities per hypoglycemic event were obtained from a large-scale time trade-off (TTO) study[¡Error! Marcador no definido.]. This TTO study reported a disutility of 0.0565 for a severe event (without significant differences between daytime and nocturnal SHE) and disutilities of 0.0041 and 0.0067 for non-severe daytime and non-severe nocturnal hypoglycemic events, respectively (significant difference in utility was demonstrated for daytime compared to nocturnal non-severe events)**¡Error! Marcador no definido.**.

**Sensitivity analysis**

To assess the impact of varying key assumptions and outcomes used in the base case analysis one-way and probabilistic sensitivity analyses were conducted.

One-way sensitivity analysis

The parameters assessed in the one-way sensitivity analysis for both treatment groups were:

1. Insulin dose from EU-TREAT;

2. No difference in daytime non-severe hypoglycemia;

3. No difference in nocturnal non-severe hypoglycemia;

4. No difference in severe hypoglycemia;

5. No difference in SMBG tests;

6. Costs of severe hypoglycemia -50%;

Probabilistic sensitivity analysis (PSA)

The PSA varied simultaneously all model parameters within a probable range and evaluated the probability that the IDeg treatment would be cost-effective compared to the IGlar treatment under different cost-effectiveness thresholds.

A lognormal distribution around the hypoglycemic event rates and normal distributions around continuous variables were assumed and the standard errors around the parameters were used. Further, 5,000 iterations were used to run the PSA.

**RESULTS**

IDeg proves to be a cost-effective option when compared to IGlar for both T1DM B/B and T2DM BOT being dominant due to its reduced costs and increased QALY (Table 5). For T1DM B/B patients IDeg shows a cost difference of -483.16€ and a QALY gain of 0.0757 while for T2DM BOT IDeg shows a cost difference of -436.90 and a QALY gain of 0.0701. In both cases the cost difference is mainly driven by basal insulin costs, but is partially offset by the reduction of severe hypoglycemic events and non-severe nocturnal hypoglycemic events costs related to IDeg. The number of SMBG tests also contributes to the cost difference.

Sensitivity analysis

The one-way sensitivity analysis showed that IDeg remains dominant over IGlar and the ICERs were stable to feasible variations in non-severe daytime and nocturnal hypoglycemic event rates, number of SMBG tests, but also when the insulin dose from EU TREAT study is considered (Table 6). Besides, it is noteworthy that the most sensitive parameter was the severe hypoglycemic event rates which affected both patient groups, obtaining an ICER of 8,320.13 €/QALY for T1DM B/B and 27,322.58 €/QALY for T2DM BOT. In addition, the cost of sever hypoglycemia resulted a sensitive variable for T2DM BOT group, with an ICER of 2,189.70 €/QALY, but a stable parameter for T1DM B/B group.

The cost-effectiveness acceptability curves display the increasing probability that IDeg is a more cost-effective treatment than IGlar given a threshold that reflects the willingness-to-pay (WTP) for this treatment, in this case, 30,000 Euros per QALY gained. For T1DM B/B patients, there is a 91.68% probability of IDeg being more cost-effective than IGlar while for T2DM BOT there is an 82.16% probability (see Figure 2 and Figure 3).

**DISCUSSION**

The economic evaluation is a common practice apart from clinical analysis. Given that diabetes has shown to be an expensive condition, costing the European Union €50 billion per year[29], economic modelling should be a tool to allocate resources in a more transparent and consistent way. Concretely, this study assessed the cost-effectiveness of IDeg compared with IGlar in patients with T1DM and T2DM. The analysis was conducted from the perspective of the Portuguese National Healthcare System for two particular groups of patients: T1DM patients treated with B/B therapy and T2DM patients treated with BOT.

The results of this short-term cost-effectiveness analysis suggest that the use of IDeg is highly likely to be cost-effective compared with IGlar in Portugal. IDeg is a dominant therapy versus IGlar in both T1DM B/B and T2DM BOT patients. In both T1DM B/B and T2DM BOT patients,

lower costs are primarily driven by lower costs of SHE, due to the significant reduction in the number of SHE in both patient groups.

One-way and probabilistic sensitivity analyses demonstrate the consistency of the model showing stable ICERs results to reasonable variations on the parameters analysed. In patients with T1DM B/B and T2DM BOT, the ICER remains dominant in most of the analyses conducted. The PSA shows that it is a highly likely that IDeg will be cost-effective when compared to IGlar for both T1DM B/B and T2DM BOT patients.

In phase 3a trials**¡Error! Marcador no definido.**,**¡Error! Marcador no definido.** IDeg proved equivalent reductions in HbA$_{1c}$ levels with a lower risk of hypoglycemia compared to IGlar. These hypoglycemia benefits of IDeg have been also observed in real clinical practice, with reductions of up to 90% in patients switching to IDeg due to problems of hypoglycemia on IGlar[30]. The two phase 3b trials, SWITCH 1**¡Error! Marcador no definido.** with T1DM patients and SWITCH 2**¡Error! Marcador no definido.** with T2DM patients, were designed to confirm the hypoglycemia benefit observed with IDeg compared with IGlar in the phase 3a clinical trials. SWITCH 1 trial has also confirmed the hypoglycemia benefit with IDeg compared to IGlar. Regarding SWITCH 2 trial, it has confirmed the hypoglycemia benefit with IDeg versus IGlar and has provided some clinically relevant results in T2DM patients. It is known that hypoglycemia is the main problem to achieve a good glycemic control. In this trial results confirmed less hypoglycemic events with IDeg compared with IGlar. Therefore, doctors could have more confidence to treat patients with IDeg to lower target fasting glucose levels in order to achieve better HbA$_{1c}$ control.

In general, the cost-effectiveness study has some limitations and it is not easy to introduce social costs[31], such as future costs[32] associated with diabetes' progression. This information gap might distort the results, minimizing the benefits of an efficient treatment. For example, the higher likelihood that patients adhere to the treatment or the inclusion of reduction of absenteeism

caused by hypoglycemic events are values that may increase the cost-effectiveness ratio in favour of IDeg[6,9,¡Error! Marcador no definido.]. Health economic guidance for Portugal[33] states that a societal perspective should be used for health economic analyses. This approach was investigated, but the required Portugal-specific days off work estimates for each diabetes-related complication could not be identified. Therefore indirect costs were not included in the present base case analysis. This is likely to be a conservative approach, as IDeg was associated with a reduced incidence of complications, and therefore less lost productivity.

Our approach to investigate the true ICER of IDeg compared with IGlar does not reflect the plausible reduction of the hypoglycemia rate[34,35] because is quite static. This possible hypoglycemia rate reduction may lead to a more efficient dosage, influencing the number of SMBG tests that could diminish the burden of the disease, and consequently the cost-effectiveness ratio could be even more positive.

## CONCLUSIONS

Based on this analysis, IDeg is a cost-effective alternative to IGlar for both T1DM B/B and T2DM BOT patients from the perspective of the Portuguese National Healthcare System. Further, the IDeg resulted the dominant strategy (fewer costs and higher effectiveness) compared to IGlar for both groups of patients.

Further, potential improvements in quality of life related to IDeg have been confirmed for both alternative treatment regimens. These improvements in quality of life have been reflected in the incremental QALYs.

Finally, sensitivity analyses found that the conclusions were robust for most of the changes in the input parameters and modelling assumptions.

**Figure 1. Schematic model: utilities from hypoglycemic events**
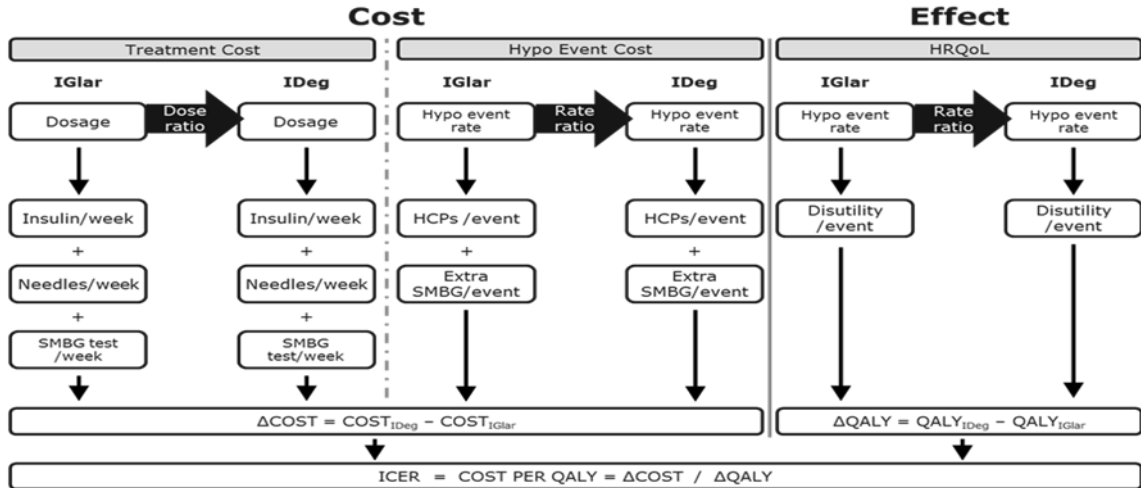


Abbreviations: Δ: change in; IDeg: insulin degludec; IGlar: insulin glargine; SMBG: self-monitoring blood glucose; HCP: healthcare professional; HRQoL: health-related quality of life; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

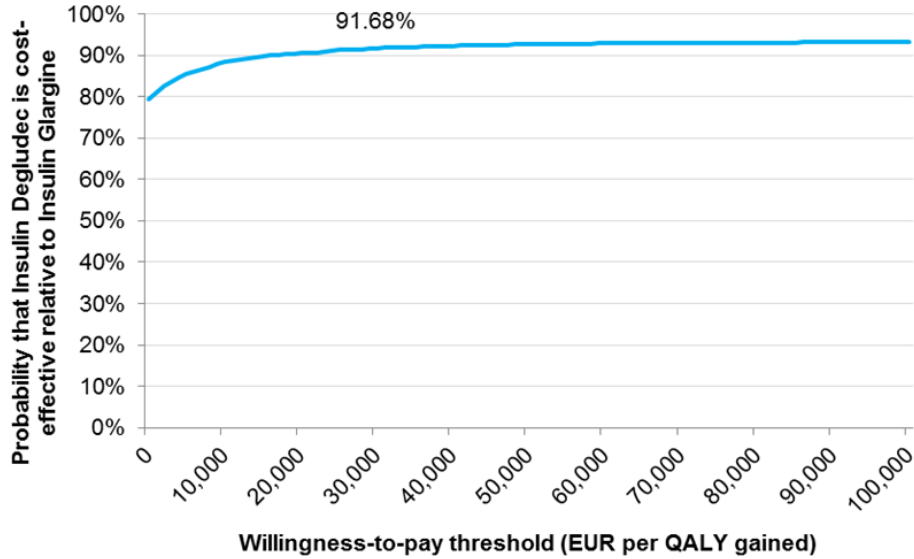**Figure 2. Cost-effectiveness acceptability curve for T1DM B/B**



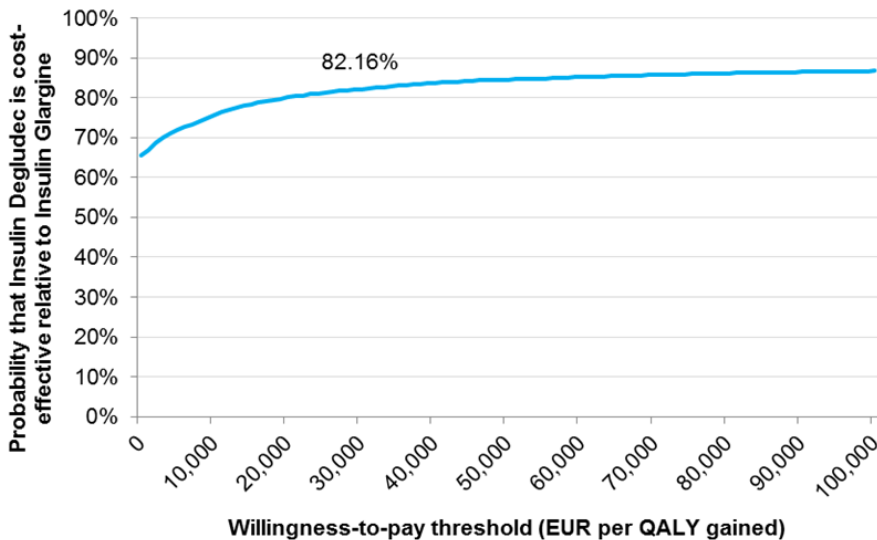**Figure 3. Cost-effectiveness acceptability curve for T2DM BOT**



14

**Table 1. Insulin doses in units per day and dose ratios**

|  |  | T1DM B/B | T2DM BOT |
| --- | --- | --- | --- |
|  | Insulin | Insulin units/day | Insulin units/day |
| **Basal** | IDeg | 39.36 | 79.35 |
|  | IGlar | 40.58 | 82.66 |
|  |  |  |  |
| **Bolus** | IAsp (IDeg) | 31.93 | - |
|  | IAsp (IGlar) | 31.93 | - |
|  |  |  |  |
|  | Insulin | Ratio | Ratio |
| **Basal/Bolus** | IDeg/IGlar | 0.97 | 0.96 |
|  | IAsp (IDeg)/IAsp (IGlar) | 1* | - |

Abbreviations: IDeg: insulin degludec; IGlar: insulin glargine; IAsp: insulin aspart; B/B: basal bolus; BOT: basal oral therapy; T1DM: type 1 diabetes; T2DM; type 2 diabetes.
*This is not significant and therefor set to 1.


**Table 2. Relative hypoglycemic event rate-ratios (RR) per patient/year per treatment regimen**

|  | T1DM B/B | | | T2DM BOT | | |
| --- | --- | --- | --- | --- | --- | --- |
|  | Frequency | IDeg RR | IGlar RR | Frequency | IDeg RR | IGlar RR |
| **Daytime NSHE** | 65.40 | 1* | 1 | 12.74 | 0.80 | 1 |
| **Nocturnal NSHE** | 22.56 | 0.76 | 1 | 5.53 | 0.76 | 1 |
| **SHE** | 0.90 | 0.74 | 1 | 0.30 | 0.49 | 1 |

Abbreviations: B/B: basal bolus; BOT: basal oral therapy; T1DM: type 1 diabetes; T2DM: type 2 diabetes; IDeg: insulin degludec; IGlar: insulin glargine; NSHE: non-severe hypoglycemic event; SHE: severe hypoglycemic event; RR: rate-ratio.
*In case of non-significant results, a relative rate of 1 was used in the calculation.


**Table 3. Number of needles and SMBG tests associated with IDeg and IGlar**

|  |  | T1DM B/B | | T2DM BOT | |
| --- | --- | --- | --- | --- | --- |
|  |  | IDeg | IGlar | IDeg | IGlar |
| **Number of SMBG** | Total | 25 | 28 | 4 | 7 |
| **test/week** | Basal injections | 4 | 7 | 4 | 7 |
|  | Bolus injections | 21 | 21 | - | - |
| **Number of needles** | Basal injections/day | 1 | 1 | 1 | 1 |
|  | Bolus injections/day | 3 | 3 | - | - |
| **Number of additional** | Daytime NSHE | 5 | 5 | 5.90 | 5.90 |
| **SMBG test per** | Nocturnal NSHE | 5 | 5 | 5.90 | 5.90 |
| **hypoglycemia** | SHE | - | - | - | - |

Abbreviations: B/B: basal bolus; BOT: basal oral therapy; IDeg: insulin degludec; IGlar: insulin glargine; SMBG: self-monitoring blood glucose; T1DM: type 1 diabetes; T2DM: type 2 diabetes; NSHE: non-severe hypoglycemic event; SHE: severe hypoglycemic event.

**Table 4. Unit costs for insulin, needles and SMBG tests**

| Product | Type | | Price per pack size | Units per pack size | Price per unit |
|---|---|---|---|---|---|
| **Insulin** | **Basal** | **IDeg** | €70.29 | 1,500 | €0.0469 |
| | | **IGlar** | €36.90 | 1,500 | €0.0246 |
| | **Bolus** | **IAsp** | €27.90 | 1,500 | €0.0186 |
| | | **Resource** | **Pack cost** | **Units per pack size** | **Price per unit** |
| **Needles** | | | €6.26 | 100 | €0.06 |
| **SMBG tests** | | **Test strip** | €20 | 100 | €0.20 |
| | | **Lancet** | €10 | 200 | €0.05 |
| | | **SMBG test** | - | - | €0.25 |

Abbreviations: IDeg: insulin degludec; IGlar: insulin glargine; IAsp: insulin aspart; SMBG: self-monitoring blood glucose.

**Table 5. Base case cost-effectiveness analysis results**

| | T1DM B/B | | T2DM BOT | |
|---|---|---|---|---|
| | IDeg | IGlar | IDeg | IGlar |
| *Cost (€)* | | | | |
| Basal injections | 3,224.36 | 2,614.24 | 6,290.86 | 5,153.63 |
| Bolus injections | 1,408.38 | 1,408.38 | 0.00 | 0.00 |
| Needles | 743.50 | 743.50 | 185.88 | 185.88 |
| SMBG test | 2,857.74 | 3,200.67 | 457.24 | 800.17 |
| NSHE daytime | 716.35 | 716.35 | 131.47 | 164.66 |
| NSHE nocturnal | 187.33 | 247.15 | 54.16 | 71.46 |
| SHE | 1,996.96 | 2,687.49 | 1,136.67 | 2,317.38 |
| Total | 11,134.62 | 11,617.78 | 8,256.27 | 8,693.17 |
| Δ Cost | -483.16 | | -436.90 | |
| Δ QALY | 0.0757 | | 0.0701 | |
| *Incremental Cost-Effectiveness* | | | | |
| ICER | **Dominant** | | **Dominant** | |

Abbreviations: T1DM: type 1 diabetes; T2DM: type 2 diabetes; B/B: basal bolus; BOT: basal oral therapy; IDeg: insulin degludec; IGlar: insulin glargine; SMBG: self-monitoring blood glucose; NSHE: non-severe hypoglycemic event; SHE: severe hypoglycemic event; QALY: quality-adjusted life years; ICER: incremental cost-effectiveness ratio.

**Table 6. One-way sensitivity analyses of CEA of IDeg vs. IGlar**

| IDeg vs. IGlar | T1DM B/B | T2DM BOT |
|---|---|---|
| Base case | Dominant | Dominant |
| Insulin dose from EU-TREAT | Dominant | Dominant |
| No difference in daytime non-severe hypoglycemia | Dominant | Dominant |
| No difference in nocturnal non-severe hypoglycemia | Dominant | Dominant |
| No difference in severe hypoglycemia | 8,320.13 €/QALY | 27,322.58 €/QALY |
| No difference in SMBG tests | Dominant | Dominant |
| Costs of severe hypoglycemia -50% | Dominant | 2,189.70 €/QALY |

Abbreviations: CEA: cost-effectiveness analysis; IDeg: insulin degludec; IGlar: insulin glargine; T1DM: type 1 diabetes; T2DM: type 2 diabetes; B/B: basal bolus; BOT: basal oral therapy; SMBG: self-monitoring blood glucose; QALY: quality-adjusted life years.

**REFERENCES**

1 Definition, diagnosis and classification of diabetes mellitus and its complications: report of a WHO consultation. In Definition, diagnosis and classification of diabetes mellitus and its complications: report of a WHO consultation. World Health Organization. 1999; p. 59.

2 Correia et al. Diabetes: factos e números 2015. 2016. Relatório Anual do Observatório Nacional da Diabetes. Portugal. Sociedade Portuguesa de Diabetologia.

3 International Diabetes Federation (IDF). IDF Diabetes Atlas - Seventh Edition. Brussels, Belgium. 2015.

4 Global report on diabetes. World Health Organization. (2016).

5 Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnenkamp U, Shaw JE. Global estimates of diabetes prevalence for 2013 and projections for 2035. Diabetes Res Clin Pract. 2014;103(2):137-149.

6 IMAGE project: Development and Implementation of a European Guideline and Training Standards for Diabetes prevention [Internet]. IMAGE project; 2010 [cited 2017 March 17]. Available from: http://www.image-project.eu/

7 Guías Clínicas-Diabetes Mellitus [Clinical Guidelines-Diabetes Mellitus][Internet].Fisterra; 2014 [cited 2014 Sept 15]. Available from: http://www.fisterra.com/guias-clinicas/diabetes-mellitus-tipo-2/#21311.

8 Brod M, Christensen T, Thomsen TL, Bushnell DM. The impact of non-severe hypoglycemic events on work productivity and diabetes management. Value Health. 2011;14(5):665-671.

9 Orozco-Beltrán D, Mezquita Raya P, Ramirez de Arellano A, Galan M. Incidence and Frequency of Patient-Reported Hypoglycaemic Events in Spain. Poster submitted to ADA Congress; 2013 June 21; Chicago (USA).

10 Principios activos: Insulina Glargina. Vademecum; accessed 2017 March 17. Available from: http://www.vademecum.es/principios-activos-insulina+glargina-a10ae04.

11 Jonassen I, Havelund S, Hoeg-Jensen T, Steensgaard DB, Wahlund PO, Ribel U. Design of the novel protraction mechanism of insulin degludec, an ultra-long-acting basal insulin. Pharm Res. 2012;29(8):2104-2114.

12 Heise T, Nosek L, Bøttcher SG, Hastrup H, Haahr H. Ultra-long-acting insulin degludec has a flat and stable glucose-lowering effect in type 2 diabetes. Diabetes Obes Metab. 2012;14(10):944-950.

13 Heise T, Hermanski L, Nosek L, Feldman A, Rasmussen S, Haahr H. Insulin degludec: four times lower pharmacodynamics variability than insulin glargine under steady-state conditions in type 1 diabetes. Diabetes Obes Metab. 2012;14(9):859-864.

14 Rodbard HW, Gough S, Lane W, Korsholm L, Bretler DM, Handelsman Y. Reduced risk of hypoglycemia with insulin degludec versus insulin glargine in patients with type 2 diabetes requiring high doses of basal insulin: a meta-analysis of 5 randomized begin trials. Endocr Pract. 2014;20(4):285-292.

15 Ratner RE, Gough SC, Mathieu C, Del Prato S, Bode B, Mersebach H, Endahl L, Zinman B. Hypoglycaemia risk with insulin degludec compared with insulin glargine in type 2 and type 1 diabetes: a pre-planned meta-analysis of phase 3 trials. Diabetes Obes Metab. 2013;15(2):175-184.

16 Onishi Y, Iwamoto Y, Yoo SJ, Clauson P, Tamer SC, Park S. Insulin degludec compared with insulin glargine in insulin-naïve patients with type 2 diabetes: A 26-week, randomized, controlled, Pan-Asian, treat-to-target trial. J Diabetes Investig. 2013;4(6):605-612.

17 Lane W, Bailey TS, Gerety G, Gumprecht J, Philis-Tsimikas A, Thim-Hansen C, et al. SWITCH 1: reduced hypoglycemia with insulin degludec (IDeg) versus insulin glargine (IGlar), both U100, in patients with T1D at high risk of hypoglycemia: a randomized, double-blind, cross-over trial. 87-

LB. Presented at the ADA 76th Annual Scientific Sessions, New Orleans, LA, USA; June 10-14, 2016, p.10-14.

18 Wysham C, Bhargava A, Chaykin L, de la Rosa R, Handelsman Y, Troelsen LN, et al. SWITCH 2: reduced hypoglycemia with insulin degludec (IDeg) versus insulin glargine (IGlar), both U100, in patients with T2D at high risk of hypoglycemia: a randomized, double-blind, crossover trial. 90-LB. Presented at the ADA 76th Annual Scientific Sessions, New Orleans, LA, USA; June 10-14, 2016, p.10-14.

19 Ericsson Å, Pollock RF, Hunt B, Valentine WJ. Evaluation of the cost-utility of insulin degludec vs insulin glargine in Sweden. J Med Econ. 2013;16(12):1442-1452.

20 Evans M, Wolden M, Gundgaard J, Chubb B, Christensen T. Cost-effectiveness of insulin degludec compared with insulin glargine for patients with type 2 diabetes treated with basal insulin- form the UK health care cost perspective. Diabetes Obes Metab. 2014;16(4):366-375.

21 Evans M, Wolden M, Gundgaard J, Chubb B, Christensen T. Cost-effectiveness of insulin degludec compared with insulin glargine in a basal-bolus regimen in patients with type 1 diabetes in the UK. J Med Econ. 2015;18(1):56-68.

22 INFARMED [Webpage on the internet]. Accessed 18 June 2019. Accessible from: http://www.infarmed.pt/web/infarmed-en/

23 Orozco-Beltrán D, Mezquita-Raya P, De Arellano AR, Galán M. Self-reported frequency and impact of hypoglycemic events in Spain. Diabetes Ther. 2014;5(1):155-168.

24 Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. Diabetes Care. 2013;36(5):1384-1395.

25 Sanofi-Aventis. Lantus (insulin glargine): Structure titration to target fasting glucose. [Internet]. Lantus; c2002-2016 [cited 2017 April 6]. Available from: https://www.lantus.com/hcp/dosing-titration/%20titration-guide.

26 Data not published. Novo Nordisk Tender HUC-CA-022/10. Resolution Date 06/20/2011.

27 Hammer M, Lammert M, Mejías SM, Kern W, Frier BM. Costs of managing severe hypoglycaemia in three European countries. J Med Econ. 2009;12(4):281-290.

28 Laires PA, Conceição J, Araújo F, Dores J, Silva C, Radican L, et al. The costs of managing severe hypoglycemic episodes in Type 2 diabetic patients. Expert Rev Pharmacoecon Outcomes Res. 2016;16(2):315-25.

29 The role of B.I.R.O in implementing the diabetes EU Policy Recommendations. A policy document by the B.I.R.O EU Project Consortium [Internet]. BIRO; accessed 2014 Jul 20. Accessible from: http://www.biro-project.eu.

30 Evans M, McEwan P, Foos V. Insulin degludec early clinical experience: does the promise from the clinical trials translate into clinical practise- a case-based evaluation. J Med Econ. 2015;18(2):96-105.

31 Poley MJ, Stolk EA, Tibboel D, Molenaar JC, Busschbach JJ. The cost-effectiveness of treatment for congenital diaphragmatic hernia. J Pediatr Surg. 2002;37(9):1245-1252.

32 Garber AM, Phelps CE. Future costs and the future of cost-effectiveness analysis. J Health Econ. 2008;27(4):819-821.

33 INFARMED. Guidelines for economic drug evaluation studies. 1998. Accessed 2017 April 18. Available from: www.infarmed.pt/documents/281/1432055/PCAEC04_vering.pdf.

34 Ahrén B. Avoiding hypoglycemia: a key to success for glucose-lowering therapy in type 2 diabetes. Vasc Health Risk Manag. 2013;9:155-163.

35 Henderson JN, Allen KV, Deary IJ, Frier BM. Hypoglycaemia in insulin-treated Type 2 diabetes: frequency, symptoms and impaired awareness. Diabet Med. 2003;20(12):1016-1021.