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Second Generation Basal Insulin, Degludec, in the Management of Diabetes; Consensus Report

Saud Alsifri[1], Abdullah Alshahrani[2], Mohammed Aldawish[3], Khalid Alyahia[3], Bandar Alharbi[3], Horeya Moloy[3], Ali Alrumiah[4], Marc Evans[5], Samia Bokhari[6] and Emad R Issak[7*]

[1]*Alhada Military Hospital, Taif, KSA.*

[2]*Khamis Mushait Military Hospotal, Khamis Mushait, KSA.*

[3]*Prince Sultan Military Hospital, Riyadh, KSA.*

[4]*Medical Services Ministry of Defense, Riyadh, KSA.*

[5]*University Hospital Llandough, Cardiff, UK.*

[6]*King Fahad Armed Forces Hospital, Jeddah, KSA.*

[7]*Asalam Center, Cairo, Egypt.*

[*]Correspondence:
Emad R Issak, Asalam Center, Cairo, Egypt.

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ABSTRACT

The best anti-diabetic medication does, in fact, have a low propensity to increase body weight and rate of hypoglycemia as well as glycemic control. The second-generation basal insulins analogues insulin degludec and insulin glargine 300 units/mL have significantly longer half-life and substantially smoother profiles than first-generation. The duration of action of glargine 300 is shorter than that of degludec, and significant residual glycemic variability is still present. Degludec has lower risks of hypoglycemia. Evaluating the therapeutic application in various geographical contexts is necessary, given the inter-country variations in the prescription patterns of glucose-lowering medications for persons with diabetes. A Saudi task force gathered to develop an explicit, evidence-based consensus for insulin degludec utilization in the local setting. This work contains the expert panel's recommendations as a contribution to complement the knowledge gap in this area from the national perspective. Results of the local UPDATES study investigating the treatment effect of degludec in adults with T2DM in Saudi Arabia showed that patients treated with degludec experienced clinically significant improvements in glycaemic control and a lower rate of hypoglycemia compared to baseline, with no new safety concerns. Results confirm that previously published data with degludec are generalizable to a broad population of patients with T2DM in routine clinical practice in Saudi Arabia. Moreover, local cost-utility analyses of degludec versus glargine 300 in T1DM and T2DM showed that it is cost-saving. Degludec was associated with less cost with better quality of life. Thus, the reimbursement of degludec will have a positive impact on the budget.

Keywords

Insulin degludec, T1DM, T2DM, Glycemic control, Hypoglycemia, Value.

Introduction

According to the data of the International Diabetes Federation (IDF) Diabetes Atlas, the prevalence of diabetes mellitus (DM) worldwide is expected to be above 9.5% by the year 2040, with a total number of more than six hundred Million [1]. In addition, the prevalence of DM is escalating rapidly in the Kingdom of Saudi Arabia (KSA), accompanied by the consequent over-exhaustion of the resources related to the healthcare system [2]. Diabetes is linked to several debilitating long-term consequences that considerably impact patient quality of life (QOL) and lead to significant morbidity, mortality, and healthcare resource use [3–5]. As a result, DM was ranked as the 15th leading cause of life years lost in 2015 [6].

The best anti-diabetic medication does, in fact, have a low propensity to increase body weight and cause hypoglycemia, as well as better glycemic control. The innovative ultra-long-acting basal insulin analogue insulin degludec (I-Deg) has a half-life of about 25 hours and acts for up to 42 hours [7].

In this work, a Saudi task force gathered to develop an explicit, evidence-based consensus on I-Deg use in patients with diabetes based on the available literature and cost-utility analysis. This article has the results of the cost-utility analysis and the recommendations of this expert panel.

Novel Second-Generation Basal Insulins

Basal insulin (BI) has been dramatically enhanced, starting from NPH to glargine 100u/mL (the year 2000) & detemir (2005) (first-generation BI insulin analogues), and now to the second-generation BI analogues (glargine 300 u/mL, degludec). With each generation, the profiles of BI turn out to be flatter, and with longer duration of action with less hypoglycemia as a clinical consequence for that. Although the first-generation basal insulin analogues marked a substantial advancement over NPH insulin in terms of BI technology, there was still a residual danger of hypoglycemia, necessitating refinements in the time-action profile. The year 2015 saw the launch of the second-generation BI analogues, insulin degludec (I-Deg) and insulin glargine 300 units/mL (I-G300) [8,9].

Pharmacological Features of Insulin Degludec

Second-generation BI, I-Deg versus first-generation BI:

I-Deg exhibited a significantly longer half-life than insulin glargine 100 (I-G100) and substantially smoother profiles over 24 hours. With estimated half-lives of 25.4 h and 12.1 h, respectively (twice as long half-life of I-Deg compared with I-G100), I-Deg glucose infusion rate (GIR) profiles were flatter and more consistent over the measured 6-h intervals than those for I-G100 across all dosages tested in a 24-h euglycemic clamp trial [10].

In treat-to-target investigations, the **BEGIN** program showed that I-Deg also lowers the risk of hypoglycemia, with comparable glycemic control to I-G100. I-Deg was associated with a 21% lower rate of confirmed hypoglycemia (risk ratio 0.79) and a 52% lower probability of confirmed nocturnal hypoglycemia (risk ratio 0.48) [11].

Patients with type 1 diabetes (T1DM) or type 2 diabetes (T2DM) treated with I-Deg in the **SWITCH 1** and **SWITCH 2** clinical trials saw a lower incidence of overall symptomatic hypoglycemia than those treated with Gla-100 (SWITCH 1, risk ratio 0.89; SWITCH 2, risk ratio 0.70) [12, 13]. Also, participants with T2DM who received I-Deg in the **DEVOTE** study experienced significantly fewer cases of severe hypoglycemia than those who received Gla-100 (4.9% vs. 6.6%, respectively; rate ratio 0.60) [14].

In T2DM, I-Deg has been shown in real-world investigations to cause less hypoglycemia than I-G100 [15,16]. In the **DELIVER D+** research, patients switching from other basal insulins experienced significantly lower rates of hypoglycemia when treated with I-Deg (adjusted odds ratio: 0.97) [16].

Second-generation BIs compared to each other: I-Deg versus I-G300

It is well known that second-generation BI analogues have advantages over first-generation. Comparing within the same class is therapeutically beneficial, and such comparisons are expanding. In a study comparing the steady-state pharmacokinetics (PK) and pharmacodynamics (PD) profiles of I-Deg 100 and I-G300 in patients with T1DM, I-G300 offered a steadier PK profile and a more evenly distributed PD profile (20% less within-day fluctuation in GIR) at a dose of 0.4 units/kg/day. However, no significant differences were observed at the higher dose of 0.6 units/kg/day. [17] However, the study was not without limitation as it is company sponsored, based only on morning dosing, and the clamp needed to be rigorously euglycaemic. On the other hand, Individualized, clinically titrated dosages of Deg-100 and I-G300 in T1DM produce PD equivalency during euglycemic clamps and comparable glycemic control. Clinical doses of Gla-300 compared to Deg-100 are higher and linked with effects on PD and antilipolytic activity that are relatively similar, even throughout 24 hours [18]. A third study showed that I-Deg's PK/PD profiles result in significantly less intra-patient glycemic variability and lower risks of hypoglycemia than I-G100 [19]. With these contradicting outcomes of all mentioned studies, we can conclude that there is a need for further well-designed studies on this topic.

People with T2DM who switched from existing BI to second-generation BI analogues had comparable glycemic control, incidence, and rates of hypoglycemia, according to a direct comparison of real-world clinical outcomes with I-G300 and I-Deg in the **DELIVER D+** trial [16].

Similar levels of glycemic control were found among BIs in the **LIGHTNING** study's real-world analysis of electronic health records. However, patients moving to I-G300 or I-Deg had considerably lower rates of severe hypoglycemia than those on I-G100 or I-Det [20]. According to the **CONFIRM** real-world study, among insulin-naive T2DM patients, the group receiving I-Deg had better insulin retention, glycemic control, and less hypoglycemia than the group receiving I-G300 [21].

Real-world observational analyses have limitations, and randomized controlled clinical trials are necessary to grasp the distinctions between various treatments fully. In insulin-naive patients with T2DM, the **BRIGHT** study is the initial randomized controlled trial to compare I-G300 and I-Deg in a head-to-head fashion. The trial showed comparable rates and levels of hypoglycemia and similar overall incidence and glycemic control rates [22].

In a **systematic review and meta-analysis**, the novel ultra-long-acting BI I-Deg was compared with I-G300 to manage T2DM in terms of efficacy and safety. The authors found fifteen studies (9619 patients in the I-Deg) and (7075 patients in the I-G300). The analysis showed that I-Deg yielded an improved mean reduction in fasting plasma glucose (FPG) (mean difference= − 5.20 mg/dL; 95%CI: − 7.34 to − 3.07, P-value < 0.00001) compared with I-G300. Also, the results showed a lower ratio of patients having ≥ 1 severe hypoglycemic (relative risk [RR] 0.68, 95%CI: 0.50 to 0.93, P-value = 0.01). Nocturnal hypoglycemia was less frequent in the I-Deg than in I-G300 (RR 0.81, 95% CI 0.75, 0.88, P < 0.0001). However, in the I-Deg group, there was a lower ratio of

participants with HbA1c ≤ 7.0% (RR 0.92; 95%CI: 0.86 to 0.98, P-value = 0.01). There was no statistically significant difference between the two treatment groups for HbA1c reduction, body weight gain, and the proportion of participants with serious adverse events (SAEs). The systematic review and meta-analysis concluded that I-Deg and I-G300 provide similar glycemic control, but I-Deg also lowers the risk of hypoglycemia. Consequently, I-Deg may be an alternative treatment for managing patients with T2DM who are prone to hypoglycemia with I-G300 [7].

The outcomes of a further direct comparison study (**CONCLUDE**) of I-G300 and I-Deg in patients with suboptimal glycemic control in BI were presented at the European Society for the Study of Diabetes' 55th Annual Meeting in 2019. It is challenging to draw a conclusion from the between-treatment differences reported for secondary and exploratory endpoints because the study's primary endpoint was not met, showing no significant difference between treatments for the number of severe or blood glucose-confirmed symptomatic hypoglycaemic episodes during the 36-week maintenance period [RR: 0.88 (95% CI: 0.73-1.06)] [23].

Insulin Degludec at the Local Setting: Saudi Arabia Data

Evaluating the therapeutic application in various geographical contexts is necessary, given the inter-country variations in the prescription patterns of glucose-lowering medications for persons with T2DM [24].

The **UPDATES** study was a prospective non-interventional study investigating the treatment effect of I-Deg in adults with T2DM in Saudi Arabia (NCT number: **NCT03785522**). The study aimed to investigate glycaemic control and other clinical outcomes in patients with T2DM in routine clinical practice [25].

Patients with T2DM enrolled were treated with degludec for 26–34 weeks, at physicians' discretion and following the local label, at 19 sites in Saudi Arabia between Dec-2018 and Nov-2020. The primary endpoint was the change in HbA1c from baseline to end of study (EOS). Secondary endpoints included change in fasting plasma glucose (FPG), total daily insulin dose, and the number of patient-reported severe and nonsevere hypoglycaemic episodes. Data were also stratified in an exploratory analysis according to previous treatment with IGlar U100 or IGlar U300 [25].

Results of the study showed significant changes from baseline to EOS in mean [SE] HbA1c (−1.1 [0.08%] [95% confidence interval, CI: −1.29 to −0.98; p<0.0001]). Patients previously treated with I-G100 or I-G300 also significantly improved after being treated with I-Deg. The estimated incidence rate ratio of overall severe hypoglycaemic episodes was 0.14 (95% CI: 0.04;0.54; p=0.0042). The estimated incidence rate ratio of overall nonsevere or nocturnal nonsevere hypoglycaemic episodes was 0.19 (95% CI: 0.13;0.28; p<0.0001) and 0.10 (95% CI: 0.05;0.18; p<0.0001), respectively. The authors concluded that patients treated with I-Deg experienced clinically significant improvements in glycaemic control and a lower rate of hypoglycemia compared to baseline, with no new safety concerns. Results confirm that previously published data with I-Deg are generalizable to a broad population of T2DM patients in the routine clinical practice in Saudi Arabia [25].

Clinical Insights: More Discussion of the Available Evidence

The best anti-diabetic medication does have a low propensity to increase body weight and rate of hypoglycemia as well as glycemic control. The duration of action of I-G300 is shorter (18–26 h) than I-Deg's, and significant residual glycemic variability is still present [7,9]. Solid physiological and clinical justifications add credence to the possible advantages of I-Deg in this situation. First, because I-Deg has a longer duration of effect, it may be possible to reduce the insulin dosage and the number of insulin treatments, encouraging patients to optimize their insulin therapy. Second, I-Deg's PK/PD profiles result in significantly less intra-patient glycemic variability and lower risks of hypoglycemia [19]. The risk of SAEs and mortality may be reduced due to the lower risk of severe hypoglycemia [26].

In light of this convincing evidence, other clinical studies have compared I-G300 with I-Deg. The objective analysis of the possible relevance of I-Deg therapy in the management of T2DM could be carried out by assembling information from several research studies, realizing that individual studies might need to be able to give sufficient data on their own to guide actual medical practice [7].

I-Deg has a much-extended action, which could delay insulin adjustments and stacking, especially when more dosages are needed and hypoglycemia risk increases. As a result, various studies have examined whether I-Deg is more clinically effective and safe than I-G300. Therefore, Zhou et al. (2019), in their meta-analysis, combined their findings and found that I-G300 reduced HbA1c more effectively than I-Deg; however, there was statistically significant between-study heterogeneity. After the exclusion of two trials using I-Deg three times per week, a sensitivity analysis was conducted, and it was discovered that there was no statistically significant between-study heterogeneity for the HbA1c reduction, which suggests that the effectiveness of the two treatment groups is dependent on the dosing schedules (once-daily vs. three times a week) [7,27].

There was no statistically significant difference in the reduction of HbA1c, according to subgroup analysis based on the background treatment (insulin-naïve or insulin). In addition, compared to I-Deg, I-G300 was linked to a more significant proportion of patients with HbA1c < 7.0% after the research. Additionally, the findings of Zhou et al. (2019) demonstrate that there was no discernible between-study heterogeneity and that I-G300 OD resulted in a lower drop in FPG than I-Deg OD. These findings imply that I-G300 might offer a comparable glycemic control to I-Deg [7].

Because of its reduced fluctuation of daily fasting glycemia, I-Deg is associated with a lower ratio of patients experiencing severe hypoglycemia than I-G300 [28]. Comparing I-Deg to I-G300, there was a decrease in the frequency of nocturnal hypoglycemia

occurrences, which is consistent with its PK/PD profiles. Since it is widely established that nocturnal hypoglycemia - particularly severe hypoglycemia- raises the risk of mortality, cardiovascular events, and SAEs, patients are sometimes reluctant to optimize their insulin therapy. I-Deg is an improvement in the management of hypoglycemic episodes in T2DM patients since it can significantly lower the incidence of nocturnal and severe hypoglycemia [19,26,29].

The ratio of patients with SAEs was lower in the I-Deg group than in the I-G300 group in the studies that made up the meta-analysis of Zhou et al., but the difference was not statistically significant. This outcome may be explained by the possibility that the definitions of SAEs utilized in the various trials were only partially consistent. According to the results of this meta-analysis, I-Deg has a more positive overall impact on the management of T2DM than I-G300, primarily shown in the lower risks of severe and nocturnal hypoglycemia [7].

Which Patient Groups Will Benefit From Insulin Degludec?

Both adults and children one year of age and older can use I-Deg. In adults with T1DM or T2DM, it should be begun at the same dose as that of the long-acting or intermediate-acting insulin. In children with T1DM or T2DM, I-Deg should be begun at 80% of the entire daily dose of the long- or intermediate-acting insulin to reduce the risk of hypoglycemia [30,31].

Therefore, it can be used in varying stages of beta-cell dysfunction, in patients who need to start insulin or switch from another BI, when hypoglycemia, multiple injections, and lack of flexibility are barriers to glycaemic control, in patients with irregular lifestyle, and when FPG and HbA1c are not at target. It is also recommended for T2DM patients using BID BI or I-Glar U300 and will be switched to I-Deg to reduce their basal insulin dose by 20% [12,13,32-34].

What about the Safety of Insulin Degludec in Special Populations?

The pharmacokinetics properties of I-Deg are not affected in special populations by increasing age, renal impairment, or hepatic impairment [35-37].

Efficacy and safety of I-Deg in children and adolescents with T1DM were evidenced. Thus, I-Deg was approved for patients one year & older by the European Medicines Agency (EMA), United States Food and Drug Administration (US FDA), and Saudi Food and Drug Authority (SFDA) [30-32,38].

In patients with T2DM at high risk for cardiovascular events, the **DEVOTE** study confirmed its cardiovascular safety and non-inferiority to I-G100. Also, the incidence ratios for hypoglycemia across kidney impairment subgroups were consistent with the original analyses, according to the **CONCLUDE** post hoc analysis. In addition, I-Deg, compared to I-G300, resulted in a minor but more consistent increase in HbA1c reduction from baseline and a lower total daily insulin dose. Therefore, I-Deg is a well-tolerated and effective therapy for persons with T2DM and kidney impairment [14,26].

In the **EXPECT** trial, pregnant women with T1DM were investigated to compare the effectiveness and safety of I-Deg versus I-Det. I-Deg was comparable to I-Det in terms of HbA1c levels before delivery. I-Deg and I-Det had equivalent pregnancy results and safety profiles for T1DM mothers and their fetuses/infants. Hence, I-Deg is the first and only new-generation basal insulin approved by the SFDA for pregnancy in Saudi Arabia [38,39].

Flexibility in Timing of Insulin Degludec Adminstration; Practical Implications

Patients who find it challenging to administer insulin simultaneously every day can benefit from flexibility in timing. Compared to I-G300, the steady-state profile of I-Deg once daily has a lower peak: trough ratio, which reduces the frequency of nocturnal hypoglycemia and allows for some dose flexibility without sacrificing effectiveness and safety. Compared to I-G100 administered at the same time every day, a study that investigated the extremes of dosage intervals of 8 and 40 hours found no negative effects on glycemic control or hypoglycemia. The flexible administration of I-Deg was evident in both T1DM and T2DM. These results reassure us. Elderly patients, individuals with difficulty with learning, those who travel frequently, and shift workers may benefit the most from this [33,34,40,41].

Family and Societal Aspects of Insulin Degludec

I-Deg provides a superior pharmacological profile from a healthcare standpoint. The benefits from less hypoglycemia, less weight gain, and variable doses are essential for patients. According to the **DAWN2 study**, about 30% of family members said that having diabetes significantly burdened their psychological well-being, financial status, ability to engage in leisure activities, and physical health. According to one HAT (Hypoglycaemia Assessment Tool) study, hypoglycemia caused an average of 1.8 days of absence from work or school. Due to the lower risk of hypoglycemia, insulin analogues have more considerable societal benefits [42].

Pharmaco-Economic Evaluation of Insulin Degludec

Cost-effectiveness analyses are utilized to determine a drug's or intervention's long-term benefit. It strikes a balance between the two. Resource consumption, medical expenses, doctor visits, ER visits, hospital stays, and productivity costs are all expenditures that are measured. Better glycaemic control, decreased hypoglycemia, weight gain, and simplicity of treatment, as evaluated by quality-adjusted life years (QALY), positively influence health [43].

Consideration should be given to the possible cost offset in terms of the overall value of the healthcare system from the viewpoints of the various stakeholders (patients, payers, HCPs, and society). It is crucial to consider value beyond the expenses of purchasing the product and broader system-based costs. Compared to first-generation insulins, newer-generation insulins have better clinical results and cost savings [12,13]. However, direct cost-benefit analyses evaluating I-Deg versus I-G300 are scarce and conflicting.

Two studies have reported contradictory findings that directly compared the cost-benefit profiles of I-G300 and I-Deg. One study found that I-G300 offered a more cost-effective profile than I-Deg in T2DM based on models of clinical outcomes and costs. This was primarily due to lower treatment- and hypoglycemia-related medical costs and higher QALY due to fewer hypoglycemia events compared to I-Deg [44].

Another study found that I-Deg was more cost-effective than I-G300 in T1DM and T2DM based on assumptions made using the data provided (since no head-to-head studies comparing I-G300 and IDeg were available at the time of submission) [43]. Given the negligible clinical differences between these two second-generation basal insulin analogues, even small changes to the assumptions made for factors like dose, dosing flexibility, injection frequency, and country-specific drug prices may have a significant impact on the predicted cost-effectiveness.

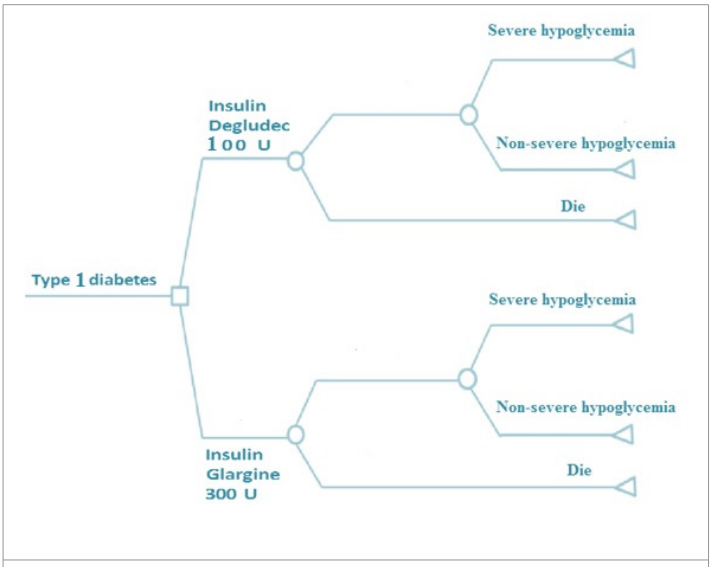
Therefore, ***local-based economic evaluation*** studies are necessary to reimburse any new drugs. Thus, the conduction of economic evaluation in the form of cost-effectiveness analysis (CEA), cost-utility analysis (CUA), or budget impact analysis (BIA) is mandatory for the introduced drugs to help decision-making of the reimbursement process of these drugs. In light of the previous data, based on Saudi Arabia data, we developed our pharmaco-ecnomic models in the form of CUA comparing I-Deg to I-G300 in T1DM and T2DM.

Saudi Arabia Pharmaco-Economic Evaluation of Insulin Degludec

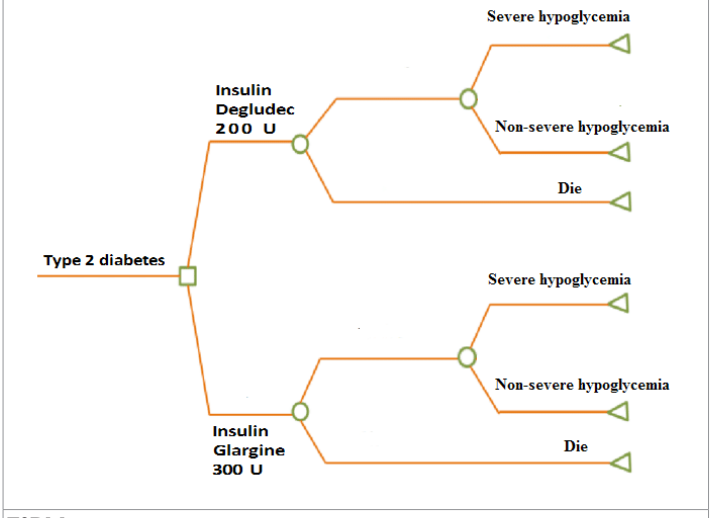
A decision analysis model was used in the local pharmaco-economic evaluation of I-Deg versus I-G300. The decision analysis model (Figure 1) in a spreadsheet-based country-specific population model was developed functioning in full-year time unit depending upon the specific population. The model conformed to the actual practice of management of diabetes in Saudi Arabia and was validated by experts. The costs of treatment units were calculated using Saudi Arabia list prices. Both simulation arms assumed that patients received one basal injection per day with four self-measured blood glucose (SMBG) test strips. Insulin costs were calculated by multiplying the unit cost by the mean yearly dose. The costs and disutilities of hypoglycemia were derived from the literature, and the expenses were adjusted for inflation using a discounting rate of 3.5%.

The total cost of hypoglycemia was determined as the sum of the hospital, informal care, and other costs. Hypoglycemia disutilities [45] were calculated by multiplying an annualized disutility by the annual event rate. This analysis did not include treatment expenses for OADs since they were considered identical between simulation arms due to randomization and the continuation of any pre-trial OADs at the pre-trial dose. The modeled time horizon covers time spent on maintenance treatment—at a generally stable insulin dose and glycaemic control—and hence does not have to represent the initial year of treatment. The time horizon was extended by five years, assuming that patients remain in a steady state.

Figure 1: Dicision Tree Model Schematic in both T1DM and T2DM



T1DM



T2DM

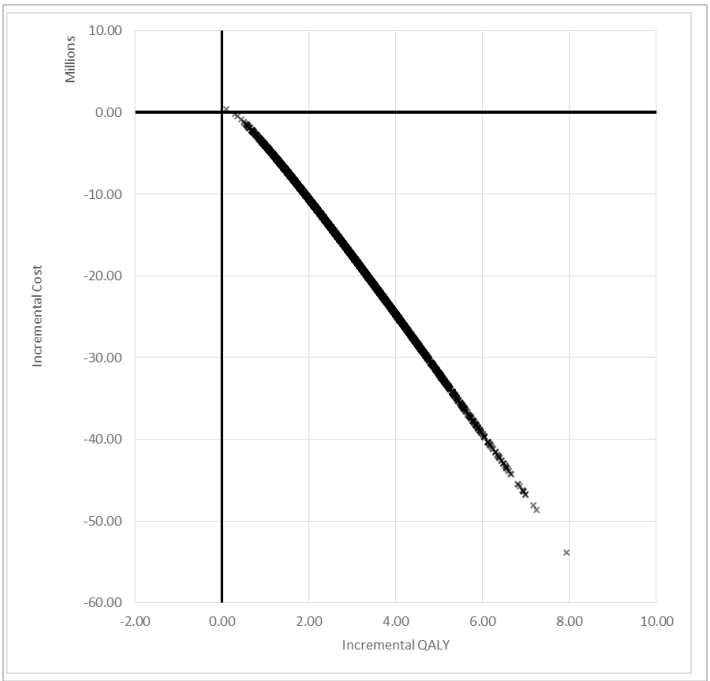
In the base case analysis, one-way deterministic sensitivity analyses were used to identify major drivers of outcomes. Hypoglycemia sensitivity analysis looked at different baseline rates, costs, and disutilities. Additional sensitivity analyses were carried out on treatment effects for insulin dosing and hypoglycemia rates. To quantify the influence of statistical uncertainty around all key stochastic input parameters employed in the model, a probabilistic sensitivity analysis (PSA) was performed. PSA results were based on 5000 model iterations using the Monte Carlo Simulation method, with each iteration sampling from all modified distributions. Incremental costs and QALYs were estimated for each simulated set of values.

In ***T2DM***, after one year, for the entire cohort of 10,000 cases, treatment with I-Deg was associated with mean annual total cost savings (SAR -1,281,855) relative to I-G300. In addition, treatment with I-Deg was also associated with improved effectiveness (0.45

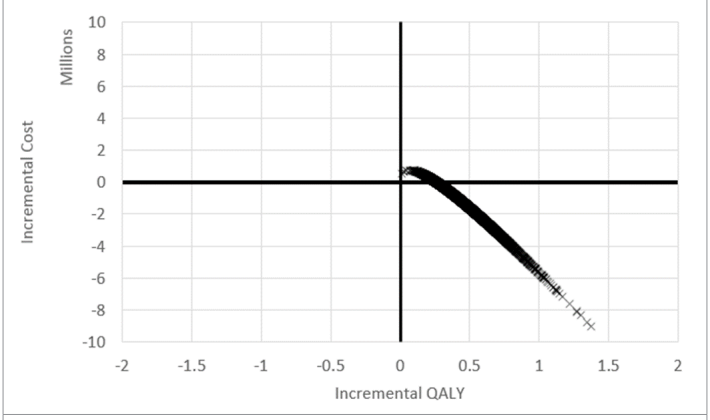
QALYs) compared with I-G300. Quality-of-life benefits with degludec were associated with lower rates of non-severe nocturnal and severe hypoglycemia compared with I-G300. Overall, I-Deg was a dominant treatment option relative to I-G300 over one year in this patient population with incremental cost-utility ratio (ICUR) -2,824,714 SAR/QALY. That was evident in each year of the five years included in the model.

In the PSA, all estimates fell in the eastern quadrants, demonstrating an improvement in QALYs with I-Deg compared with I-G300 (Figure 2). Furthermore, most estimates were located in the southeast quadrant, indicating that, in addition to improved effectiveness, there were lower costs with I-Deg compared to I-G300 treatment. Overall, the PSA showed that I-Deg is likely to be cost-effective.

Figure 2: Probabilistic sensitivity analysis.



T1DM



T2DM

In ***T1DM***, after one year, for the entire cohort of 10,000 cases, treatment with I-Deg was associated with mean annual total cost savings (SAR -16,272,785.00) relative to I-G300. In addition, treatment with I-Deg was also associated with improved effectiveness (2.82 QALYs) compared with I-G300. Quality-of-life benefits with I-Deg were associated with lower rates of non-severe nocturnal and severe hypoglycemia compared with I-G300. Overall, I-Deg was a dominant treatment option relative to I-G300 over one year in this patient population with incremental cost-utility ratio (ICUR) -5,774,074.34 SAR/QALY.

In the PSA, all estimates fell in the eastern quadrants, demonstrating an improvement in QALYs with I-Deg compared with I-G300 (Figure 2). Furthermore, all estimates were located in the southeast quadrant, indicating that, in addition to improved effectiveness, there were lower costs with I-Deg compared to I-G300 treatment. Overall, the PSA showed that I-Deg is cost-effective.

In conclusion, in both T1DM and T2DM, the results of the previous models conclude that I-Deg is a dominant treatment option relative to I-G300. It is cost-saving: less cost with better quality of life. Thus, the reimbursement of Degludec will positively impact the budget.

Conclusions and Recommendations

In conclusion, I-Deg is non-inferior to I-G300, with lower rates of nocturnal hypoglycemia. It has significantly less intra-patient glycemic variability. In addition, it can be used safely in special populations by increasing age, renal impairment, hepatic impairment, and pediatrics one year of age and older with T1DM or T2DM and pregnant women. The flexible administration of I-Deg makes it suitable for elderly patients, individuals who have difficulty learning, those who travel frequently, and shift workers.

The local CUA of I-Deg versus I-G300 in T1DM and T2DM showed that I-Deg is cost-saving. It has associated with less cost, a better quality of life, and a positive impact on the budget.

Recommendation 1
The expert panel recommends the utilization of I-Deg in both T1DM and T2DM adults and pediatrics one year of age and older, as well as in pregnant women.
Recommendation 2
Because of the flexible administration of I-Deg, we recommend it for elderly patients, individuals who have difficulty with learning, those who travel frequently, and shift workers.
Recommendation 3
Due to the wide range of its safety profile, the panel recommends I-Deg in special populations by increasing age, renal impairment, or hepatic impairment.

Data sharing statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

References

1. International Diabetes Federation, IDF Diabetes Atlas, International Diabetes Federation, Brussels, Belgium, 8th edition, 2017. http://www.diabetesatlas.org.

2. Al Dawish MA, Robert AA, Braham R, et al. Diabetes Mellitus in Saudi Arabia: A Review of the Recent Literature. Curr Diabetes Rev. 2016; 12: 359-368.
3. Hayes A, Arima H, Woodward M, et al. Changes in quality of life associated with complications of diabetes: results from the ADVANCE study. Value Health. 2016; 19: 36-41.
4. Chapman D, Foxcroft R, Dale-Harris L, et al. Insights for care: the healthcare utilisation and cost impact of managing type 2 diabetes-associated microvascular complications. Diabetes Ther. 2019; 10: 575-585.
5. American Diabetes Association. Economic costs of diabetes in the US in 2017. Diabetes Care. 2018; 41: 917-928.
6. GBD 2015 Mortality and Causes of Death Collabo- rators. Global, regional, and national life expec- tancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016; 388: 1459-1544.
7. Zhou W, Tao J, Zhou X, et al. Insulin Degludec, a Novel Ultra-Long-Acting Basal Insulin versus Insulin Glargine for the Management of Type 2 Diabetes: A Systematic Review and Meta-Analysis. Diabetes Ther. 2019; 10: 835-852.
8. Cheng AYY, Patel DK, Reid TS, et al. Differentiating Basal Insulin Preparations: Understanding How They Work Explains Why They Are Different. Adv Ther. 2019; 36: 1018-1030.
9. Pettus J, Santos Cavaiola T, et al. The past, present, and future of basal insulins. Diabetes Metab Res Rev. 2016; 32: 478-496.
10. Heise T, Hövelmann U, Nosek L, et al. Comparison of the pharmacokinetic and harmacodynamic profiles of insulin degludec and insulin glargine. Expert Opin Drug Metab Toxicol. 2015; 11: 1193-1201.
11. Rodbard HW, Gough S, Lane W, et al. 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: 285-292.
12. Wysham C, Bhargava A, Chaykin L, et al. Effect of insulin degludec vs insulin glargine U100 on hypoglycemia in patients with type 2 diabetes: the SWITCH 2 randomized clinical trial. JAMA. 2017; 318: 45-56.
13. Lane W, Bailey TS, Gerety G, et al. Effect of insulin degludec vs insulin glargine U100 on hypoglycemia in patients with type 1 diabetes: the SWITCH 1 randomized clinical trial. JAMA. 2017; 318: 33-44.
14. Marso SP, McGuire DK, Zinman B, et al. Efficacy and safety of degludec versus glargine in type 2 diabetes. N Engl J Med. 2017; 377: 723-732.
15. Landstedt-Hallin L. Changes in HbA1c, insulin dose and incidence of hypoglycemia in patients with type 1 diabetes after switching to insulin degludec in an outpatient setting: an observational study. Curr Med Res Opin. 2015; 31: 1487-1493.
16. Sullivan SD, Bailey TS, Roussel R, et al. Clinical outcomes in real-world patients with type 2 diabetes switching from first- to second-generation basal insulin analogues: comparative effectiveness of insulin glargine 300 units/mL and insulin degludec in the DELIVER D+ cohort study. Diabetes Obes Metab. 2018; 20: 2148-2158.
17. Bailey TS, Pettus J, Roussel R, et al. Morning administration of 0.4U/kg/day insulin glargine 300U/mL provides less fluctuating 24-hour pharmacodynamics and more even pharmacokinetic profiles compared with insulin degludec 100U/mL in type 1 diabetes. Diabetes Metab. 2018; 44: 15-21.
18. Lucidi P, Candeloro P, Cioli P, et al. Pharmacokinetic and Pharmacodynamic Head- to-Head Comparison of Clinical, Equivalent Doses of Insulin Glargine 300 units and Insulin Degludec 100 units in Type 1 Diabetes. Diabetes Care. 2021; 44: 125-132.
19. Heise T, Hermanski L, Nosek L, et al. Insulin degludec: four times lower pharmacodynamic variability than insulin glargine under steady-state conditions in type 1 diabetes. Diabetes Obes Metab. 2012; 14: 859-864.
20. Meneghini L, Zhou FL, Bosnyak Z, et al. Hypoglycemia risk associated with basal insulin use in type 2 diabetes (T2DM): the LIGHTNING study. Poster presented at Page | 18 the 11th Annual Conference on Advanced Technologies and Treatments for Diabetes (ATTD), Vienna, Austria; February 1, 2018; poster ATTD8-0420.
21. Tibaldi JM, Haldrup S, Sandberg V, et al. Clinical outcome assessment of the effectiveness of insulin degludec (degludec) in real-life medical practice (CONFIRM) – a comparative effectiveness study of degludec and insulin glargine 300U/mL (Glargine U300) in insuline-naïve patients with type 2 diabetes (T2D). Diabetes. 2018; 67: LB27.
22. Rosenstock J, Cheng A, Ritzel R, et al. More similarities than differences testing insulin glargine 300 units/mL versus insulin degludec 100 units/mL in insuline-naïve type 2 diabetes: the randomized head-to-head BRIGHT trial. Diabetes Care. 2018; 41: 2147-2154.
23. Philis-Tsimikas A, Klonoff DC, Bajaj HS, et al. Reduced risk of hypoglycaemia and lower HbA1c with degludec compared to glargine U300 in insulin-treated patients with type 2 diabetes [Abstract 90]. In: 55th EASD Annual Meeting of the European Association for the Study of Diabetes, Barcelona, Spain, 16 - 20 September 2019. Diabetologia. 2019; 62: 1-600.
24. Fulcher GR, Jarlov H, Piltoft JS, et al. ARISE—a prospective, non-interventional, single-arm study assessing clinical parameters associated with the use of insulin degludec/insulin aspart in patients with type 2 diabetes in real-world settings: rationale and design. Endocrine. 2021; 74: 530-537.
25. AlMalki M, Aldesokey H, Alkhafaji D, et al. A prospective non-interventional study of glycaemic control with insulin degludec in people with type 2 diabetes treated in routine clinical practice in Saudi Arabia. SHAPED 2022 – UPDATES study abstract. Presented as poster at the SHAPED 2022 congress, February 27-28, 2022 at the Voco Hotel in Riyadh Saudi Arabia.

26. Pieber TR, Marso SP, McGuire DK, et al. DEVOTE 3: temporal relationships between severe hypoglycaemia, cardiovascular outcomes and mortality. Diabetologia. 2018; 61: 58-65.

27. Zinman B, DeVries JH, Bode B, et al. Efficacy and safety of insulin degludec three times a week versus insulin glargine once a day in insulin-naive patients with type 2 diabetes: results of two phase 3, 26 week, randomised, open-label, treat-to-target, non- inferiority trials. Lancet Diabetes Endocrinol. 2013; 1: 123-131.

28. Zinman B, Marso SP, Poulter NR, et al. Day-to-day fasting glycaemic variability in DEVOTE: associations with severe hypoglycaemia and cardiovascular outcomes (DEVOTE 2). Diabetologia. 2018; 61: 48-57.

29. Heise T, Nosek L, Bøttcher SG, et al. Ultra-long-acting insulin degludec has a flat and stable glucose-lowering effect in type 2 diabetes. Diabetes Obes Metab. 2012; 14: 944-950.

30. Tresiba® PI, November 2018 (https://www.accessdata.fda.gov/ drugsatfda_docs/label/2018/203314s010lbl.pdf. Accessed August 2022)

31. Tresiba® SmPC, November 2018 (https://www.ema.europa.eu/documents/product-information/tresiba-epar-product-information_en.pdf.Accessed August 2022

32. Thalange N, Deeb L, Iotova V, et al. Insulin degludec in combination with bolus insulin aspart is safe and effective in children and adolescents with type 1 diabetes. Pediatr Diabetes. 2015; 16: 164-176.

33. Meneghini L, Atkin SL, Gough SC, et al. NN1250-3668 (BEGIN FLEX) Trial Investigators. The efficacy and safety of insulin degludec given in variable once-daily dosing intervals compared with insulin glargine and insulin degludec dosed at the same time daily: a 26-week, randomized, open-label, parallel-group, treat-to-target trial in individuals with type 2 diabetes. Diabetes Care. 2013; 36: 858-864.

34. Mathieu C, Hollander P, Miranda-Palma B, et al. NN1250-3770 (BEGIN: Flex T1) Trial Investigators. Efficacy and safety of insulin degludec in a flexible dosing regimen vs insulin glargine in patients with type 1 diabetes (BEGIN: Flex T1): a 26-week randomized, treat-to-target trial with a 26-week extension. J Clin Endocrinol Metab. 2013; 98: 1154-1162.

35. Kupčová V, Arold G, Roepstorff C, et al. Insulin degludec: pharmacokinetic properties in subjects with hepatic impairment. Clin Drug Investig. 2014; 34: 127-133.

36. Kiss I, Arold G, Roepstorff C, et al. Insulin degludec: pharmacokinetics in patients with renal impairment. Clin Pharmacokinet. 2014; 53: 175-183.

37. Korsatko S, Deller S, Mader JK, et al. Ultra-long pharmacokinetic properties of insulin degludec are comparable in elderly subjects and younger adults with type 1 diabetes mellitus. Drugs Aging. 2014; 31: 47-53.

38. https://beta.sfda.gov.sa/sites/default/files/2020-11/Tresiba%20DHCPL%202015.pdf

39. Presented at the European Association for the Study of Diabetes (Virtual) Congress, 27 Sept – 1 Oct 2021. https://easd-elearning.org/type-1-diabetes-and-pregnancy-two-insulins-compared/

40. Aye MM, Atkin SL. Patient safety and minimizing risk with insulin administration - role of insulin degludec. Drug Healthc Patient Saf. 2014; 6: 55-67.

41. Meneghini LF, Miranda-Palma B. Insulin degludec: a novel ultra-long-acting basal insulin for use in Type 1 and 2 diabetes. Expert Rev Endocrinol Metab. 2012; 7: 9-14.

42. Evans M, Morgan AR, Bain SC. One Hundred Years of Insulin: Value Beyond Price in Type 2 Diabetes Mellitus. Diabetes Ther. 2021; 12: 1593-1604.

43. Evans M, Chubb B, Gundgaard J. Cost-effectiveness of Insulin Degludec Versus Insulin Glargine in Adults with Type 1 and Type 2 Diabetes Mellitus. Diabetes Ther. 2017; 8: 275-291.

44. Murphy D, Yu X, Fournier M, et al. Cost-effectiveness of insulin glargine 300 units/ml (GLA-300) vs insulin degludec 100 units/ml (IDEG) IN T2D.Diabetes.2017; 66: A354.

45. Evans M, Khunti K, Mamdani M, et al. Health-re- lated quality of life associated with daytime and nocturnal hypoglycaemic events: a time trade-off survey in five countries. Health Qual Life Out- comes. 2013; 11: 90