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CPG UPDATE

Practical guide in using insulin degludec/insulin aspart: A multidisciplinary approach in Malaysia

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Abstract

Insulin degludec/insulin aspart (IDegAsp) co-formulation provides both basal and mealtime glycaemic control in a single injection. The glucose level-lowering efficacy of IDegAsp is reported to be superior or non-inferior to that of the currently available insulin therapies with a lower rate of overall hypoglycaemia and nocturnal hypoglycaemia. An expert panel from Malaysia aims to provide insights into the utilisation of IDegAsp across a broad range of patients with type 2 diabetes mellitus (i.e. treatment-naïve or insulin-naïve patients or patients receiving treatment intensification from basal-only regimens, premixed insulin and basal–bolus insulin therapy). IDegAsp can be initiated as once-daily dosing for the main meal with the largest carbohydrate content with weekly dose adjustments based on patient response. A lower starting dose is recommended for patients with cardiac or renal comorbidities. Dose intensification with IDegAsp may warrant splitting into twice-daily dosing. IDegAsp twice-daily dosing does not need to be split at a 50:50 ratio but should be adjusted to match the carbohydrate content of meals. The treatment of patients choosing to fast during Ramadan should be switched to IDegAsp early before Ramadan, as a longer duration of titration leads to better glycated haemoglobin level reductions. The pre-Ramadan breakfast/lunch insulin dose can be reduced by 30%–50% and taken during sahur, while the pre-Ramadan dinner dose can be taken without any change during iftar. Education on the main meal concept is important, as carbohydrates are present in almost all meals. Patients should not have a misconception of consuming more carbohydrates while taking IDegAsp.

Introduction

Diabetes mellitus is one of the three major non-communicable diseases in Malaysia. Approximately 3.9 million adults (18.3%) in the country had raised blood glucose levels in 2019.[1] Furthermore, insulin prescription has increased gradually over the years, with a prescription rate of 30.3% recorded in 2019 compared with 23.1% in 2013.[2]

Although insulin is one of the primary therapeutic options in the management of diabetes mellitus, patient-related challenges, such as the complexity of insulin regimens, multiple daily injections and fear of hypoglycaemia, add to patients' hesitancy towards insulin therapy.[3,4] An insulin formulation that provides a simple dosing regimen with a low risk for hypoglycaemia can overcome these barriers and increase patients' receptiveness towards insulin therapy.

Insulin degludec/insulin aspart (IDegAsp) is a soluble co-formulation of 70% basal insulin degludec (IDeg) and 30% short-acting insulin aspart (IAsp). The combination provides both basal and mealtime glycaemic control in a single injection. The glucose level-lowering effect of single-dose IDegAsp shows a separate action with both components: a rapid onset and peak effect of IAsp followed by a flat, long-lasting glucose level-lowering effect of IDeg (**Figure 1**).

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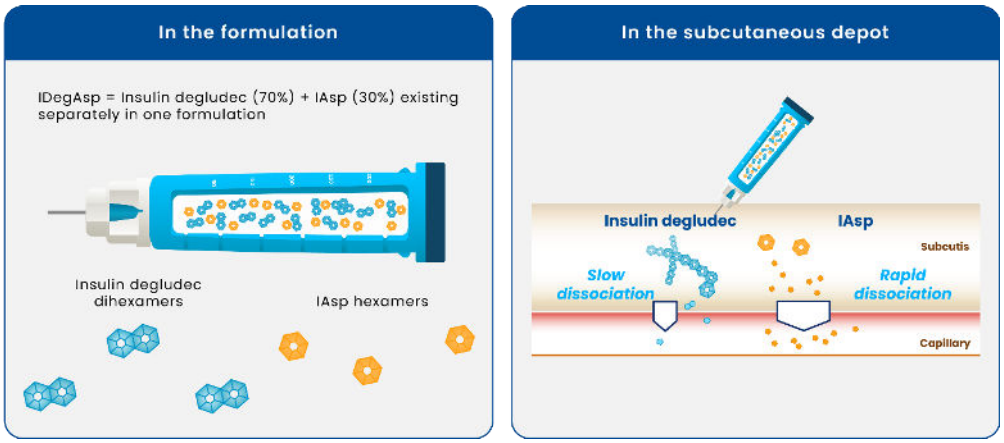

Figure 1. Co-formulation of insulin degludec with rapid-acting insulin is possible because of stable dihexamers in the solution (adapted with modifications).[5]
IDegAsp, insulin degludec/insulin aspart; IAsp, insulin aspart

The effect profile is retained in twice-daily injections with no 'shoulder effect' as seen in premixed insulin preparations. The pharmacological properties of IDegAsp are preserved in different cohorts, including elderly individuals and patients with renal or hepatic impairments.[6] Phase III clinical trials of IDegAsp have shown that the efficacy of this co-formulation is either superior or non-inferior to that of the currently available insulin therapies such as premixed, basal–bolus and basal-only insulin therapies in the reduction of the glycated haemoglobin (HbA1c) level (**Table 1**).

Table 1. Results of phase III clinical trials reporting the efficacy of IDegAsp and currently available insulin therapies in the reduction of the HbA1c level.

		Confirmed non-inferiority regarding the HbA1c level	Insulin dose	Confirmed hypoglycaemia	Confirmed nocturnal hypoglycaemia
T1DM OD	BOOST T[17,8]	✓	↓	↓	↓
T2DM OD	BOOST JAPAN[9]	Superiority confirmed	–	↓	↓
T2DM OD/ BID	STEP-BY-STEP INTENSIFICATION TRIAL[10]	✓	↓	↓	↓
T2DM BID	BOOST START TWICE DAILY[11]	✓	–	↓	↓
	BOOST INTENSIFY PREMIX12	✓	↓	↓	↓
	BOOST INTENSIFY ALL[13]	✓	↓	–	↓
	BOOST CHINA[14]	✓	↓	↓	↓
	BOOST TWICE DAILY VS BASAL BOLUS[15]	Not confirmed	↓	↓	↓
	RAMADAN TRIAL[16]	–	–	↓	↓

– No difference between the groups
✓ Non-inferiority confirmed
↓ Lower than the comparator
OD, once daily; BID, twice-daily; HbA1c, glycated haemoglobin; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus

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IDegAsp has also been shown to reduce the fasting plasma glucose (FPG) level with an overall lower insulin dose and a lower incidence of confirmed hypoglycaemia and nocturnal hypoglycaemia. The findings from clinical trials are supported by evidence from several real-world observational studies conducted in different parts of the world.[17,18] In a recent multinational, prospective, real-world study (A Ryzodeg Initiation and Switch Effectiveness study), switching the treatment of patients with uncontrolled glucose levels on other treatment regimens, including oral glucose-lowering drugs (OGLDs), basal insulin, premixed insulin, basal–bolus insulin and glucagon-like peptide-1 receptor agonist, to IDegAsp led to an overall significantly better glycaemic control as well as weight reduction and fewer hypoglycaemic episodes.[19] IDegAsp has the ability to provide both basal and prandial glycaemic control and can therefore be a good option as an insulin treatment for patients with diabetes mellitus in Malaysia.

This paper aims to provide practical guidance to clinicians on the appropriate use of IDegAsp in the local setting to optimise treatment outcomes, individualising treatment in patients with different profiles (e.g. patients with cardiac and renal comorbidities), and on the role of diet in complementing OGLDs to achieve desired glycaemic targets.

Development process of the clinical practice guideline (CPG)

Insights for the CPG were collected following collaboration among 13 experts from key subspecialties. The CPG was endorsed by the Malaysian Endocrine and Metabolic Society, National Heart Association of Malaysia, Malaysian Society of Nephrology, Malaysian Dietitians' Association and Family Medicine Specialists' Association. The expert committee comprising eight consultant endocrinologists, two consultant cardiologists, two consultant nephrologists and one consultant dietician met and discussed the key challenges faced while managing patients with type 2 diabetes mellitus (T2DM) and the benefits rendered by IDegAsp at different phases of the disease. The patient journey was mapped into four key phases – a) treatment-naïve patients, b) patients uncontrolled on OGLDs, c) patients uncontrolled on basal insulin and d) patients uncontrolled on premixed insulin or basal–bolus insulin (Figure 2).

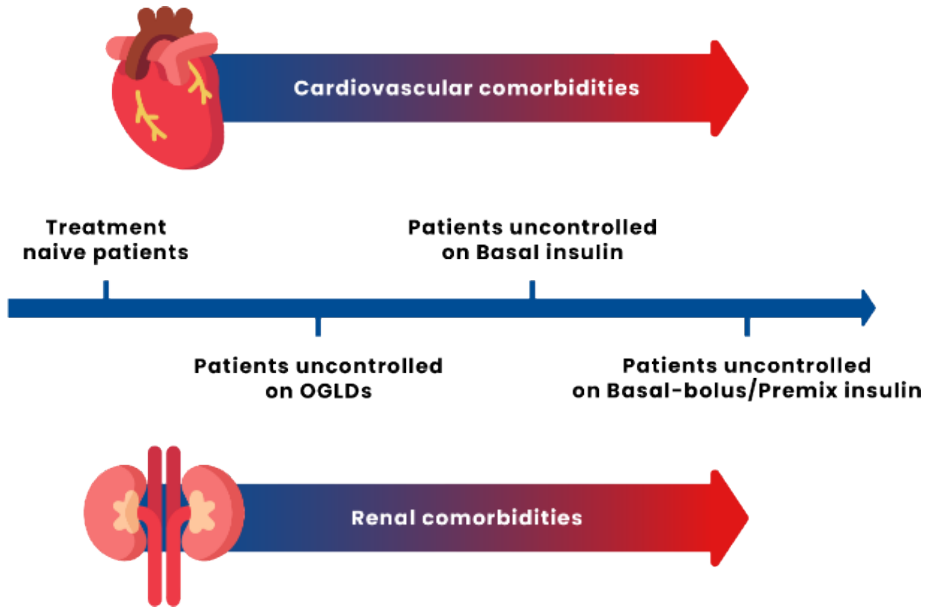

Figure 2. Diabetes mellitus complications.
OGLD, oral glucose-lowering drug

The management of patients during IDegAsp therapy was also discussed in the context of cardiac and renal comorbidities, which are commonly seen in routine clinical practice. Expert recommendations also focused on managing patients with T2DM who undergo fasting during Ramadan, as Malaysia has a predominantly Muslim population. The role of diet in T2DM management was also deliberated considering that carbohydrate-rich foods are a part of the staple diet in Southeast Asian countries.

IDegAsp for treatment-naïve patients

The 6th Malaysian CPG 2020 on the management of T2DM advocates for insulin therapy for the following scenarios: a) HbA1c level of >10%, b) FPG level of >13 mmol/L or c) symptomatic hyperglycaemic state.[20] Several studies have shown that short-term intensive insulin (STII) therapy has an additional benefit in improving β-cell functionality and restoring first-phase insulin secretion beyond achieving glycaemic control.[21] Exogenous insulin helps reduce the β-cell insulin secretion burden and the exposure of gluco- and lipotoxicity on β-cells.[22,23] Improved β-cell function results in extended remissions in patients in whom euglycaemia is subsequently maintained on diet therapy alone.

In a study comparing STII therapy with continuous insulin infusion, multiple daily injections or OGLDs, all three treatments improved the first-phase insulin secretion after 2 weeks of euglycaemia.[24] At 1 year, the first-phase insulin response was maintained in the two insulin-treated groups, while a declined β-cell response was observed in the OGLD-treated group.

However, not all patients may be suitable to start STII therapy. A meta-analysis of studies on STII therapy found that patients with a higher body mass index and lower FPG level at baseline were more likely to achieve remission following cessation of STII therapy.[21]

Panel recommendations

The recommended initiating dose of IDegAsp is 10 units once daily (OD), given with the largest carbohydrate-containing meal of the day. However, the initiating dose may be insufficient to achieve adequate glycaemic control in patients with a high HbA1c level. A high FPG level is also a sign of insulin resistance. IDegAsp can be initiated at a dose of 0.3 units/kg/day with dose titration at 7-day intervals based on the patient glycaemic profile. Dose adjustments can be made on the basis of the lowest value of the three preceding FPG levels measured (**Table 2**).

Table 2. Plasma glucose levels.

Pre-breakfast/pre-main evening meal plasma glucose levela (mmol/L)	Adjustment of dose according to units of insulin (U)
<3.1[b]	−4 (If dose is >45 U, reduce by 10%)
3.1–3.8[b]	−2 (If dose is >45 U, reduce by 5%)
3.9–4.9	0
5.0–6.9	+2
7.0–7.9	+4
8.0–8.9	+6
≥9.0	+8

a Mean of three consecutive measurements for up titration; the pre-breakfast plasma glucose level is used for once-daily dosing and the pre-breakfast and pre-evening meal plasma glucose levels for twice-daily dosing.

b Dose reduction is based on one measurement unless there is an apparent explanation for the low value, such as a missed meal.

Initiation of insulin therapy in treatment-naïve patients can be challenging owing to the fear of injections and possible side effects of therapy. A thorough discussion between clinicians and patients is vital for clinicians to share information to alleviate patient concerns. Insulin therapy should ideally be initiated in a hospital setting for patients with a high HbA1c level (>10%) and/or a) a catabolic state precipitated by acute illnesses or b) diabetes mellitus-associated infections or wounds. The primary objective of initiating insulin in this group of patients is rapid stabilisation of the blood glucose levels. Reduction of both FPG and postprandial glucose (PPG) levels is achieved using rapid-acting insulin infusion or a basal–bolus insulin regimen. Once the blood glucose level is stable, IDegAsp can be a good treatment option for maintaining glycaemic control (**Table 3**). Although STII therapy has shown favourable results in retaining the first-phase insulin response in patients treated with insulin, the data are of limited duration, and further studies are required to investigate whether the benefits are maintained beyond the initial phase.

Table 3. Panel recommendations for the use of IDegAsp in different patient categories.

Category of patients with diabetes mellitus	Panel recommendations
Treatment-naïve patients	• Acutely symptomatic patients with hyperglycaemia should be admitted with efforts to normalise the FPG and PPG levels via insulin infusion or a basal–bolus insulin regimen. • The target HbA1c level can be achieved with OGLDs or intensive insulin therapy in stable patients. • IDegAsp can be initiated in clinically stable patients at a dose of 0.3 units/kg/day with proper counselling.
Patients uncontrolled on OGLDs	• IDegAsp is initiated with 10-unit OD dosing, which is then titrated to 0.3–0.5 units/kg/day at a weekly interval. • IDegAsp may be initiated in combination with OGLDs with no dose adjustment, except for sulphonylureas. • The dose of sulphonylureas should be reduced in patients who are prone to developing hypoglycaemia or when the HbA1c level is closer to the target level.
Patients uncontrolled on basal insulin	• Patients on a high basal insulin dose (0.5 units/kg/day) with uncontrolled HbA1c levels are suitable candidates for switching to IDegAsp. • Switching is on a unit-to-unit conversion at the same total insulin dose and injection schedule. • Further dose intensification (0.6–0.7 units/kg/day) may warrant splitting of IDegAsp into BD dosing. • IDegAsp BD dosing does not need to be split at a 50:50 ratio but should be adjusted to match the carbohydrate content of meals.
Patients uncontrolled on premixed/basal–bolus insulin	**Switching from premixed insulin*** • Switching to IDegAsp can be considered for patients who are on high doses of premixed insulin, and a further increase in the dose can lead to hypoglycaemic episodes. • A unit-to-unit conversion of the total daily dose is used for switching to IDegAsp. • Rapid-acting insulin can be added to the insulin regimen in patients requiring additional prandial insulin for meals not covered by IDegAsp. **Switching from basal–bolus insulin.** • Switching to IDegAsp can be considered if there are issues of non-compliance with the basal–bolus insulin regimen. • Switching to IDegAsp can be considered for patients who are on high doses of basal insulin and have a higher risk for hypoglycaemia. • Dose conversion to IDegAsp is based on individual needs. In general, patients are initiated on the same number of basal units.
Patients with cardiac comorbidities	• Patients with T2DM with a CV risk experiencing severe or nocturnal hypoglycaemia are a good target group for switching to IDegAsp. • A lower IDegAsp starting dose of 8–10 units can be considered for patients at risk for hypoglycaemia. • Metformin, dipeptidyl peptidase-4 inhibitor, sodium–glucose cotransporter-2 inhibitor and glucagon-like receptor agonist can be continued when initiating IDegAsp, while sulphonylureas can be continued with close monitoring if the baseline HbA1c level is high. • Nocturnal hypoglycaemia should be checked with early SMBG (from 2 a.m. to 4 a.m.) when the basal insulin requirement reaches 0.5 units/kg/day.

Table 3. Continued

Category of patients with diabetes mellitus	Panel recommendations
Patients with renal comorbidities	• Patients on low-dose basal–bolus/premixed insulin who are struggling with multiple doses on their insulin regimen are good candidates for switching to IDegAsp. • Patients with CKD at risk for hypoglycaemia can be initiated with 8–10 units of IDegAsp. • IDegAsp is a good option when flexibility is a challenge, especially during the dialysis phase. Patients can opt to take the insulin dose before or after the dialysis owing to the consistent pharmacokinetic properties.
Patients on Ramadan fasting	• Switching to IDegAsp is recommended early before Ramadan, as a longer duration of titration leads to better HbA1c level reductions. • The pre-Ramadan breakfast/lunch insulin dose can be reduced by 30%–50% and taken during sahur, while the pre- Ramadan dinner dose can be taken without any change during iftar. • Patients should be advised to monitor their glucose level more frequently during the month of Ramadan and consider not fasting if it is detrimental to their health. • Patients with cardiac and renal comorbidities are advised to reduce their insulin dose by half during sahur and to omit or reduce sulphonylureas during Ramadan.
Patients on insulin (dietary considerations)	• Education on the main meal concept is important, as carbohydrates are present in almost all meals. • Patients must not be mistaken that they can consume more carbohydrates when they are taking the IDegAsp dose. • Healthy eating patterns, including the consumption of foods high in fibre, such as vegetables, fruits, legumes, whole grains, dairy products and vegetable-derived protein, which can also act as cardio- and reno-protective nutrition to improve the overall health, should be promoted.

* Premixed insulin refers to either 25/75 or 30/70 formulation, as these two formulations are commonly used in Malaysia. The 25/75 insulin formulation is a mixture of insulin with 25% insulin lispro solution and 75% insulin lispro protamine suspension. The 30/70 premixed insulin formulation is a co-formulation of 30% short-acting IAsp and 70% basal IDeg.

BD, twice-daily; CKD, chronic kidney disease; CV, cardiovascular; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; IAsp, short-acting insulin aspart; IDeg, insulin degludec; IDegAsp, insulin degludec/insulin aspart; OD, once daily; OGLD, oral glucose-lowering drug; PPG, postprandial glucose; SMBG, self-monitoring of blood glucose; T2DM, type 2 diabetes mellitus.

IDegAsp for patients uncontrolled on OGLDs

Insulin therapy is recommended for patients not achieving the target HbA1c, FPG and PPG levels despite maximum OGLD treatment. The progressive decline of β-cell function in patients with T2DM eventually results in the need for insulin therapy to maintain glycaemic control. IDegAsp can be considered as one of the options for insulin therapy alongside basal insulin and premixed insulin.

The BOOST Japan trial showed that IDegAsp OD combined with OGLDs was superior to insulin glargine (IGlar) in reducing the HbA1c level in patients with T2DM.[24] The reduction in the FPG level and mean daily insulin dose was similar in both insulin-treated groups. IDegAsp also yielded a lower nocturnal and overall hypoglycaemia rate than did IGlar.

Panel recommendations

The starting dose of IDegAsp is 10 units OD with a weekly dosage adjustment of 0.3–0.5 units/kg/day. Alternatively, dose titration can be made on the basis of the pre-breakfast or pre-dinner blood glucose level.

The aspart component in IDegAsp can be beneficial when postprandial hyperglycaemia is a concern. IDegAsp is also a suitable option for patients who are at risk for hypoglycaemia. The role of insulin therapy is to supplement OGLDs in patients with T2DM to achieve glycaemic control. IDegAsp may be initiated in combination with OGLDs with no dose adjustment, except for sulphonylureas. The dose of sulphonylureas should be reduced in patients who are prone to experiencing hypoglycaemic episodes, those closer to achieving the target HbA1c level or those requiring further intensification of insulin therapy (**Table 3**).

IDegAsp for patients uncontrolled on basal insulin

Treatment intensification with IDegAsp may be considered in patients who do not achieve adequate glycaemic control with basal insulin. The Step-by-Step trial showed that IDegAsp was non-inferior to the combination of IGlar and IAsp in lowering the HbA1c level.[25] The mean FPG and PPG levels were also similar in both insulin-treated groups. IDegAsp showed a similar efficacy but with a lower rate of hypoglycaemia and significantly fewer nocturnal hypoglycaemic episodes compared with IGlar and IAsp.

Panel recommendations

Postprandial hyperglycaemia may be the cause of the high HbA1c level in patients with controlled FPG levels. The co-formulation of IDegAsp can address both fasting and postprandial hyperglycaemia with a lower risk for hypoglycaemia.

Patients on a high basal insulin dose (0.5 units/kg/day) with an uncontrolled HbA1c level are suitable candidates for switching to IDegAsp. Further dose intensification with basal insulin may lead to an increased risk for hypoglycaemia and/or weight gain.

The treatment of patients switching from basal insulin therapy can be converted on a unit-to-unit basis with the same total insulin dose and injection schedule. Splitting of IDegAsp into BD dosing can be considered when further dose intensification (0.6–0.7 units/kg/day) is needed to achieve the target HbA1c level.

Splitting of IDegAsp into BD dosing can be conducted at a 50:50 ratio. However, this ratio can be adjusted to match the carbohydrate content of meals with a higher dose of IDegAsp for the largest carbohydrate-containing meal of the day. In the context of the dietary pattern in Malaysia, breakfast and dinner are the two meals ideal for IDegAsp administration should BD dosing be required (**Table 3**).

IDegAsp for patients uncontrolled on premixed/basal–bolus insulin

The treatment of patients who do not achieve adequate glycaemic control on premixed insulin may be switched to IDegAsp. In the Intensify Premix trial, IDegAsp was as effective as biphasic insulin aspart 30 (BIAsp 30) in improving the HbA1c level with a better FPG level-lowering effect and a lower final mean daily insulin dose.[25] The overall rates of confirmed, confirmed nocturnal and severe hypoglycaemic episodes were lower in the IDegAsp group.

Similar efficacy results were also observed in the Intensify All trial on the Asian population, with IDegAsp effectively improving glycaemic control and reducing the FPG level with a lower daily insulin dose and fewer nocturnal hypoglycaemic episodes.[13]

Switching from basal–bolus insulin to IDegAsp is advantageous for patients with difficulties complying with daily multiple injections or those who prefer a simpler insulin regimen. The efficacy of IDegAsp was proven in the Step-by-Step trial wherein IDegAsp demonstrated non-inferiority to IGlar and IAsp. The effectiveness of IDegAsp was retained in treatment intensification (BD dosing) with significantly fewer nocturnal hypoglycaemic episodes.

Panel recommendations

Switching from premixed insulin

Patients with uncontrolled hyperglycaemia on high-dose premixed insulin may consider switching to IDegAsp, as further intensification may predispose patients to hypoglycaemia. IDegAsp is a suitable treatment option for patients experiencing postprandial hypoglycaemia due to the absence of the 'shoulder effect' observed with premixed insulins.

A unit-to-unit conversion of the total daily dose is used for switching to IDegAsp. Rapid-acting insulin can be added to the insulin regimen in patients requiring additional prandial insulin for meals not covered by IDegAsp (**Table 3**).

Switching from basal–bolus insulin

The benefit of a customised glycaemic management in basal–bolus insulin therapy may not be achieved in patients with poor treatment compliance. A simpler insulin regimen and reduced number of injections with IDegAsp can address this patient-related challenge. IDegAsp shows a similar efficacy to basal–bolus insulin for glycaemic control with lower dose requirements. Patients with a high risk for hypoglycaemia are suitable candidates for switching to IDegAsp, as these patients may adopt defensive eating habits for fear of hypoglycaemia, which could lead to an increased need for insulin.

Switching can be an option for patients who are looking to reduce the complexity of multiple insulin injections with basal insulin and mealtime bolus insulin injections. The flexibility of IDegAsp administration is an advantage, as the timing of the daily dose can be changed as long as it is dosed with the main carbohydrate meal, and the missed dose can be taken with the next main meal.

Patients treated with human insulin (basal + bolus) who are unable to achieve their glycaemic target can benefit more after switching to IDegAsp, as the targets are achieved even with a lower total daily dose with a reduced number of hypoglycaemic episodes (**Table 3**).

IDegAsp for patients with cardiac comorbidities

Clinical data have shown a significant relationship between glycaemic variability (GV) and cardiovascular events, especially in patients with diabetes mellitus receiving intensive treatment for glycaemic control.[26] A high GV has been associated with an increased risk for microvascular and macrovascular complications and mortality in individuals with diabetes mellitus with a cardiovascular risk. In addition, a high GV has been proven to be associated with an increased risk for hypoglycaemia, which is correlated with an increased risk for cardiac arrhythmia, stroke and death.[27]

The DEVOTE trial showed that IDeg was non-inferior to IGlar in terms of cardiovascular safety.[28] At 24 months, the mean HbA1c level was similar in both IDeg and IGlar groups, with the IDeg group having a significantly lower FPG level than the IGlar group. The rate of both severe hypoglycaemia and severe nocturnal hypoglycaemia was significantly lower in the IDeg group.

A secondary analysis of the DEVOTE trial showed that a higher day-to-day fasting GV is associated with increased risks for severe hypoglycaemia and all-cause mortality.[26] Furthermore, severe hypoglycaemia is associated with an increased risk for cardiovascular events and mortality.[27]

Panel recommendations

Patients with a cardiovascular risk who have frequent episodes of hypoglycaemia or are at risk for nocturnal hypoglycaemia are a good target group that can benefit from IDegAsp.

A lower IDegAsp starting dose of 8–10 units can be considered for patients at risk for hypoglycaemia. Metformin, dipeptidyl peptidase-4 inhibitor (DPP-4i), sodium–glucose cotransporter-2 inhibitor (SGLT-2i) and glucagon-like peptide-1 receptor agonist can be continued when initiating IDegAsp. Meanwhile, sulphonylureas can be continued with close monitoring if the baseline HbA1c level is high; however, their dose may need to be reduced.

Identification of nocturnal hypoglycaemia is important, and early-morning (from 2 a.m. to 4 a.m.) plasma glucose monitoring should be conducted periodically via self-monitoring of blood glucose (SMBG). SMBG from 2 a.m. to 4 a.m. is also recommended when the basal insulin requirement reaches 0.5 units/kg/day and above, as it is an indication of possible late-night or early-morning glucose level fluctuations (**Table 3**).

IDegAsp for patients with renal comorbidities

Chronic kidney disease (CKD) is a risk factor for the development of hypoglycaemia, with the risk being even higher in patients with CKD with diabetes mellitus.[29] CKD prolongs the half-life of insulin, and most OGLDs lead to a lower insulin requirement, further predisposing patients to hypoglycaemia.[30]

Patients with T2DM and CKD have a higher GV than patients with T2DM without CKD even when there is no significant difference in the HbA1c level between them.[31] The extent of GV depends on the stage of CKD. GV is also a significant factor for patients on dialysis, particularly on the day of dialysis. One of the challenges in managing patients

with diabetes mellitus with CKD is the limited choice of drug therapy, especially when the eGFR is less than 30 mL/min/1.73 m^2.

There are no clinically relevant differences in the pharmacokinetics of IDegAsp between healthy individuals and patients with renal or hepatic impairments.

Panel recommendations

The therapeutic drug options for glycaemic control are reduced with the progression of CKD. IDegAsp can be considered in patients who experience multiple hypoglycaemic episodes or when the disease progresses to CKD stage 4 or 5, wherein most OGLDs are contraindicated. The pharmacokinetic properties of IDegAsp are not affected by haemodialysis, providing patients with the flexibility to use IDegAsp before or after the dialysis depending on their preference.

IDegAsp can be initiated at a dose of 8–10 units OD with any main carbohydrate meal in insulin-naïve patients with CKD. The progression of CKD can affect body weight and appetite significantly, which poses a challenge in dose adjustment for patients using short-acting insulins for PPG level control. IDegAsp may be considered an option for PPG control owing to its aspart component.

DPP-4i can be continued when initiating IDegAsp with similar or reduced dosing, depending on standard DPP-4i recommendations. SGLT-2i should not be initiated for lowering the glucose level if the eGFR is below 30 mL/min/1.73 m^2. However, it can be continued if it is already initiated for reno-protection.

Frequent SMBG should be strongly emphasised especially during the initial titration phase owing to the higher risk for hypoglycaemia in patients with CKD (**Table 3**).

IDegAsp for patients with T2DM during Ramadan fasting

Carbohydrate-rich foods such as rice and bread are regularly consumed in Malaysia and are part of the staple diet. Malaysia is also home to a large Muslim population, and fasting during Ramadan can pose a challenge to patients with T2DM.

Patients' decision to fast should be made after a pre-Ramadan assessment of the possible risks involved. Changes may need to be made on meal choices, SMBG and adjustment to administration time for insulin therapy.[32]

Fasting can increase the risk for dehydration and hypoglycaemia, and the risk is further increased for patients on insulin therapy. Consumption of high-carbohydrate meals during Ramadan also increases the risk for postprandial hyperglycaemia and diabetic ketoacidosis.

In a study comparing the safety and efficacy between BIAsp 30 BD and IDegAsp BD for patients with diabetes mellitus who fasted during Ramadan, it was observed that IDegAsp yielded a lower rate of overall and nocturnal hypoglycaemia during the treatment duration, which included the 4-week Ramadan period, with glycaemic control similar to that with BIAsp 30.[16]

Panel recommendations

Switching the treatment of patients to IDegAsp is recommended early before Ramadan, especially when a patient intends to fast during Ramadan. An early switch is advantageous, as demonstrated by Hassanein et al.[16] The study found that the HbA1c level reduction was better when the titration was performed 17–20 weeks pre-Ramadan than when it was conducted 8–9 weeks pre-Ramadan.

The pre-Ramadan breakfast/lunch insulin dose can be reduced by 30%–50% and taken during sahur (during Ramadan), while the pre-Ramadan dinner dose can be taken without any change during iftar.

Patients should be advised to monitor their blood glucose level more frequently during the month of Ramadan and consider not fasting if it is detrimental to their health. Hypoglycaemia is a concern for patients with diabetes mellitus with cardiovascular comorbidities when fasting during Ramadan. Patients are advised to reduce their insulin dose by half during sahur and omit or reduce sulphonylureas during Ramadan.

Frail patients or patients with end-stage renal failure are not encouraged to fast during Ramadan. Fluid intake management for patients with CKD who fast can be challenging. However, a study on kidney transplant patients has found that fasting during Ramadan did not have any significant adverse effect on kidney function.[16]

The dietary considerations for patients on

IDegAsp during Ramadan are similar to those during the non-Ramadan period. Patients should have a complete, balanced meal during sahur and should not consume excessive carbohydrates. Patient education and preparation for fasting during Ramadan are essential (**Table 3**).

Dietary considerations for patients on insulin

Medical nutrition therapy (MNT) for managing diabetes mellitus is structured to achieve glycaemic control through regular consumption of healthy food choices. Clinical trials and Cochrane reviews have reported reductions of the HbA1c level and other beneficial outcomes from MNT interventions depending on the type and duration of diabetes mellitus.[33]

MNT for patients with diabetes mellitus incorporates many aspects of the nutritional status, including the eating pattern, body weight, body composition, biochemical data, weight, lifestyle and personal preference (cultural, religious or economical), during assessment of their diet to help reduce the PPG level and manage GV.

A meal plan with consistent carbohydrate intake with a lower glycaemic index/glycaemic load is important to reduce GV. There are no optimal proportions of calories from carbohydrates, protein and fat for patients with T2DM. A balanced diet consisting of 45%–60% of calories from carbohydrates, 15%–20% from protein and 25%–35% from fat is encouraged and must be individualised.[20] Both very low (<40%) and high (>70%) carbohydrate intakes confer a higher mortality risk than does a moderate carbohydrate intake.[34] Mortality is increased when animal-derived fat or protein is substituted with carbohydrate but is reduced when substituted with plant-based protein. Hence, it is recommended to emphasise the intake of nutrient-dense carbohydrate sources that are high in fibre, including vegetables, fruits, legumes, whole grains and dairy products.

MNT also plays a role in weight management for patients with T2DM. Weight loss through a low-calorie diet can help improve the prognosis of diabetes mellitus and other related outcomes.

Panel recommendations

Nutritional assessment is important to determine patients' eating habits, carbohydrate intake and mealtime in addition to identification of the ideal meal for intake of IDegAsp accordingly.

Patient education on the main meal concept is important, as carbohydrates are present in almost all meals, and the carbohydrate content for the main meal can vary from 4 to 10 carbohydrate exchanges. Hence, monitoring the amount of carbohydrate intake remains a fundamental strategy in achieving glycaemic control. A practical guide is to recommend three to six carbohydrate exchanges for men and three to four exchanges for women for main meals depending on their physical activity levels.[20]

Emphasis must be placed on patient understanding of the largest carbohydrate-containing meal, focusing on a consistent carbohydrate intake, which should not be misunderstood as being able to eat more carbohydrates while taking the IDegAsp dose.

MNT also encourages healthy eating patterns in appropriate portion sizes, focusing on cardio- and/or reno-protective nutrition where relevant in improving the overall nutritional status with beneficial health outcomes (**Table 3**).

Conclusion

The glucose level-lowering efficacy of IDegAsp was found to be superior or non-inferior to that of the currently available insulin therapies with a lower rate of overall hypoglycaemia and nocturnal hypoglycaemia. In this practical guide, the experts provided their insights into the use of IDegAsp across a broad range of patients with T2DM, including treatment-naïve patients, patients uncontrolled on OGLDs, patients uncontrolled on basal insulin and patients uncontrolled on premixed insulin. The constitution of the IDegAsp practical guide from a multidisciplinary approach in a Southeast Asian country provides a unique perspective, which, to our knowledge, is the first of its kind at the time of publication.

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Author contributions

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Conflicts of interest

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How does this paper make a difference in general practice?

- This practical guide is the first of its kind to summarise key recommendations from multidisciplinary experts from Malaysia on insulin degludec/insulin aspart (IDegAsp)use for a broad range of patients with type 2 diabetes mellitus (T2DM).
- The expert panel provided recommendations for IDegAsp administration in patients with diabetes mellitus uncontrolled on basal insulin/premixed/basal–bolus insulin, patients with cardiac/renal comorbidities and patients on Ramadan fasting as well as dietary considerations for patients on insulin.
- This study serves as a practical guide for educating physicians in Malaysia about the use of IDegAsp for patients with T2DM in clinical practice.

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