

REVIEW

# Multinational Consensus: Insulin Initiation with Insulin Degludec/Aspart (IDegAsp)

Sanjay Kalra · Stephen Atkin · Antonio Cervera · Ashok Kumar Das · Ozgur Demir · Tevfik Demir · Md. Fariduddin · Khoa Tuan Vo · Bon Jeong Ku · Ajay Kumar · Zafar A. Latif · Rachid Malek · Bien J. Matawaran · Roopa Mehta · Nam Quang Tran · Araceli Panelo · Sundeep Ruder · Joel Rodriguez Saldana · Khalid A. Shaikh · Amit Shakya · Dina Shrestha · A. G. Unnikrishnan

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## ABSTRACT

Insulin degludec/aspart (IDegAsp) is the first soluble insulin co-formulation, combining a long-acting insulin degludec (IDeg) and rapid-acting insulin aspart (IAsp). In type 2 diabetes patients with oral antidiabetes agent (OAD) inadequacy, insulin initiation with IDegAsp once daily provides superior long-term glycemic

control compared to insulin glargine, with similar fasting plasma glucose (FPG) and insulin doses, and numerically lower rates of overall and nocturnal hypoglycemia. Furthermore, in patients with uncontrolled type 2 diabetes previously treated with insulins, IDegAsp twice daily effectively improves glycated hemoglobin and FPG, with fewer hypoglycemic episodes versus premix insulins and basal bolus therapy. In patients with type 1 diabetes mellitus, IDegAsp once daily with two doses of IAsp is a convenient, yet effective, regimen as compared to the conventional 4–5 injection-based basal bolus therapy. IDegAsp is an appropriate and reasonable option for initiation of insulin therapy in both type 1 and type 2 diabetes.

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S. Kalra (✉)  
Department of Endocrinology, Bharti Hospital  
Karnal, Karnal, India  
e-mail: brideknl@gmail.com

S. Atkin  
Department of Medicine, Weill Cornell Medical  
College, Doha, Qatar

A. Cervera  
Department of Endocrinology, Clínica de Mérida,  
Mérida, Yucatán, Mexico

A. K. Das  
Department of Endocrinology, PIMS, Puducherry,  
India

O. Demir  
Department of Endocrinology and Metabolic  
Diseases, İbni Sina Hospital, Ankara, Turkey

T. Demir  
Department of Endocrinology and Metabolic  
Disease, Dokuz Eylul University, Balcova, İzmir,  
Turkey

Md. Fariduddin  
Department of Endocrinology, Bangabandhu  
Sheikh Mujib Medical University, Dhaka,  
Bangladesh

K. T. Vo  
Department of Endocrinology, 115 Hospital, Ho Chi  
Minh City, Vietnam

B. J. Ku  
Division of Endocrinology and Metabolism,  
Department of Internal Medicine, Chungnam  
National University Hospital, Daejeon, Korea

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## INTRODUCTION

Type 2 diabetes is a progressive disease. The addition of insulin to provide mealtime coverage is needed when oral antidiabetes agents (OADs) and a basal regime of insulin are no longer enough to establish or maintain glycemic control [1]. Existing basal bolus regimens offer both basal and precise postprandial glucose control, but as separate injections [2]. Many patients are reluctant to start with a basal and bolus insulin regimen because of its complexity, the added need to calculate a prandial dose, the need for two injections, and a fear of hypoglycemia [3]. IDegAsp, is a modern insulin co-formulation approved in more than 70 countries across the world [4]. It is a preformulated fixed-ratio combination of rapid-acting insulin aspart (IAsp) (30%) and ultra-long acting insulin degludec (IDeg) (70%). IDegAsp is marketed as a prefilled

disposable pen, as well as in pen fills that can be used with durable pens [5].

## VERSATILITY AND FLEXIBILITY

IDegAsp is a unique formulation that shows great versatility and flexibility. IDegAsp works as both premix and basal plus regimens, and can substitute for basal bolus regimens as well. It can be used once daily, twice daily, or as part of a thrice daily regimen (one IDegAsp and two IAsp doses). Thus, IDegAsp allows freedom and flexibility in diabetes care [6].

Size exclusion chromatography studies of IDegAsp indicate that IDeg and IAsp exist as stable dihexamers and hexamers, respectively, in the formulation [7]. Moreover, at steady state, the prandial and basal glucose-lowering effects of IDeg and IAsp were distinct and clearly separated. A clear dose–response relationship was observed in patients with type 1 and type 2 diabetes treated with IDegAsp [8]. The glucose-lowering effects of basal and prandial components of IDegAsp are maintained in elderly ( $\geq 65$  years of age) patients

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A. Kumar

Department of Diabetology, Diabetes Care and Research Center, Patna, Bihar, India

Z. A. Latif

Department of Endocrinology, General, BIRDEM Hospital, BIRDEM Academy, Dhaka, Bangladesh

R. Malek

Department of Medicine, Ferhat Abbas University of Setif, Setif, Algeria

B. J. Matawaran

Department of Medicine, Section of Endocrinology, Diabetes and Metabolism, University of Santo Tomas, Manila, Philippines

R. Mehta

Department of Endocrinology and Nutriti3n, Instituto nacional de ciencias m3dicas y nutriti3n, Salvador Zubir3n, Mexico City, Mexico

N. Q. Tran

Head of Endocrinology Department, Ho Chi Minh City University of Medicine and Pharmacy, Ho Chi Minh City, Vietnam

A. Panelo

Department of Medicine, UERMMMM College of Medicine, Manila, Philippines

S. Ruder

Department of Endocrinology and Metabolism, Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa

J. R. Saldana

Centro Multidisciplinario de Diabetes, Mexico City, Mexico

K. A. Shaikh

Department of Diabetes, Faculty of Internal Medicine, Royal Oman Police Hospital, Muscat, Oman

A. Shakya

Department of Endocrinology, Diabetes Thyroid Endocrine Center, Kathmandu, Nepal

D. Shrestha

Department of Endocrinology, Norvic International Hospital, Kathmandu, Nepal

A. G. Unnikrishnan

Chellaram Diabetes Institute, Pune, India

with type 1 diabetes [9]. In addition, the PK and clearance of IDeg and IAsp are not affected by mild, moderate, or severe renal or hepatic impairment [8]. The presence of two distinct insulin analogues as a soluble co-formulation of a basal component with an ultra-long duration of action makes IDegAsp an advance over earlier premix insulins. To overcome the burden of multiple daily injections, co-formulating basal and bolus insulins in a single injection could allow a simple regimen with fewer injections [6].

## EVIDENCE FROM RANDOMIZED CONTROLLED TRIALS

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

The efficacy and safety of IDegAsp were evaluated in the BOOST clinical trial program. BOOST was a phase 3 trial designed to represent a large population of diabetes from various geographic areas. IDegAsp has been studied in both type 1 and type 2 diabetes and it has been used in once daily or twice daily regimen [10–15].

In a Japanese study, comparing IDegAsp once daily with insulin glargine (IGlar) once daily for 26 weeks in insulin-naïve type 2 diabetes patients, IDegAsp demonstrated superiority in terms of HbA1c reduction, which was achieved as a result of the reduction in fasting plasma glucose (FPG) and evening meal postprandial glucose (PPG). The superiority was realized with less risk of nocturnal and overall hypoglycemia with IDegAsp [10].

IDegAsp has also been studied in a twice daily regimen in comparison to basal bolus therapy in type 2 diabetes mellitus (T2DM) patients. IDegAsp achieved similar efficacy with less risk of hypoglycemia, with a reduction in the overall dose and fewer self-monitoring blood glucose values required compared to the basal (IDeg) bolus (IAsp) regimen [11].

When compared to premix, IDegAsp has consistently demonstrated effective glycemic control with superior FPG reduction and less risk of both nocturnal and overall hypoglycemia [12, 13].

In a study performed in type 1 diabetes, comparing IDegAsp once daily with insulin

detemir (IDet) + mealtime IAsp, both the arms revealed that IDegAsp achieved similar HbA1c with better FPG reduction and less risk of nocturnal and overall hypoglycemia [14].

## REAL-WORLD EVIDENCE

The efficacy and tolerability data of IDegAsp are supported by real-world evidence across the globe. Kaneko et al. illustrated that IDegAsp provided a simple, helpful intensification for poorly controlled T2DM patients on OADs, special populations in whom it is difficult to escalate/intensify insulin therapy, and T2DM patients dosed with conventional premix [15]. Kalra and Baruah presented 1-year data from India highlighting the efficacy, safety, and tolerability of IDegAsp in patients with poor glycemic control [6]. Results from the major clinical studies on IDegAsp are summarized in Table 1.

All the evidence suggests that a co-formulation of basal and bolus insulin allows for basal and prandial coverage with fewer injections compared to basal and bolus therapy whilst offering simplicity and convenience. The comprehensive fasting and prandial control achieved with this preparation is especially useful for people who consume high carbohydrate meals, as in Africa, Asia, and Latin America.

## EMINENT EXPERIENCE

An earlier multinational consensus identified and defined seven patient profiles in which IDegAsp can be a preferred choice of insulin preparation. Of these profiles, five relate to type 2 diabetes, and two to type 1 diabetes [16]. IDegAsp is described as an insulin for initiation in two, intensification in three, and interchange in two clinical profiles. A South Asian consensus statement provides pragmatic guidance regarding the safe and effective use of IDegAsp during Ramadan [17].

## CONCORDANCE

Current guidelines released by the American Diabetes Association (ADA) acknowledge the

**Table 1** Summary of clinical trials and real-world evidence on insulin degludec/insulin aspart

Study	Study details	Study endpoints summary
IDegAsp OD with largest meal of the day (BOOST: JAPAN) Comparator: IGlax OD [10]	26-week, open-label, randomized, treat-to-target trial Patients: T2DM, Insulin-naïve previously treated with OADs ( $n = 296$ )	Superior long-term glycemic control with IDegAsp vs. IGlax (ETD IDegAsp–IGlax, $-0.28\%$ (95% CI $-0.46; -0.10$ ), $p < 0.001$ ) IDegAsp was superior to IGlax with respect to lowering postprandial glucose at the main evening meal ( $p < 0.001$ ) Lower rates of overall confirmed (27%) and nocturnal confirmed hypoglycemia (25%) with IDegAsp vs. IGlax
(TWICE DAILY IDegAsp vs. BB) Comparator: IDeg OD + IAsp (2–4 injections/day) [11]	26-week, randomized, open-label, crossover trial. Patients: T2DM, currently treated with basal insulin (IDet, IGlax, NPH) $\pm$ OADs ( $n = 274$ )	Reduction in HbA1c was comparable between treatment groups but non-inferiority was not confirmed [ETD, 0.10% points (95% CI $-0.04; 0.41$ )] Change in body weight and insulin dose were both lower with IDegAsp BID compared with IDeg OD + IAsp Total insulin was significantly lower for IDegAsp BID vs. IDeg + IAsp [1.11 vs. 1.34 U/kg; estimated ratio, 0.88 (95% CI 0.78; 1.00), $p < 0.05$ ] Rates of confirmed (19%) and nocturnal confirmed hypoglycemia (20%) were numerically lower with IDegAsp BID compared with IDeg OD + IAsp
IDegAsp OD with main meal and IAsp with other meals (BOOST:T1) Comparator: IDet OD or BID + IAsp as mealtime insulin [14]	26-week, multinational, open-label, parallel-group, treat-to-target trial Patients: T1DM, treated with basal bolus, premixed insulin, or self-mix regimens ( $n = 548$ )	Non-inferiority for IDegAsp vs. IDet in HbA1c reduction [0.75% vs. 0.70%; ETD, $-0.05\%$ (95% CI $-0.18; 0.08$ )] 37% lower rates of nocturnal confirmed hypoglycemia with IDegAsp vs. IDet (3.71 vs. 5.72 episodes/patient-year, $p < 0.05$ ) Total insulin dose was 13% lower in the IDegAsp group ( $p < 0.0001$ )

**Table 1** continued

Study	Study details	Study endpoints summary
IDegAsp BID (BOOST: INTENSIFY PREMIX I) Comparator: BIAsp 30 BID [13]	26-week, phase 3a, open-label, randomized, treat-to-target trial Patients: T2DM, previously treated with premixed insulin (OD or BID) $\pm$ OADs $\geq$ 3 months ( $n = 447$ )	Non-inferiority for IDegAsp vs. BIAsp 30 in HbA1c reduction from baseline [ETD, – 0.03% (95% CI – 0.18; 0.13)] Superior FPG reduction with IDegAsp vs. BIAsp 30 [ETD, – 20.54 mg/dL (95% CI – 27.57; – 13.70), $p < 0.001$ ] Estimated mean of the 9-point SMPG profile was significantly different between treatments [ETD IDegAsp–BIAsp 30, – 7.21 mg/dL (95% CI – 13.52; – 0.90), $p < 0.05$ ] Total insulin dose at the end of trial was 11% lower for IDegAsp vs. BIAsp 30 [rate ratio IDegAsp/BIAsp 30, 0.89 (95% CI 0.83; 0.96), $p = 0.0021$ ] 32% lower rates of confirmed hypoglycemia ( $p = 0.0049$ ) and 73% lower rates of nocturnal confirmed hypoglycemia with IDegAsp vs. BIAsp 30 ( $p < 0.0001$ )
IDegAsp BID (BOOST: INTENSIFY ALL) Comparator: BIAsp 30 BID [15]	26-week, phase 3, open-label, randomized, treat-to-target trial. Patients: T2DM, Asian/previously treated with basal, premixed or self-mixed insulin $\pm$ metformin $\geq$ 3 months ( $n = 424$ )	Non-inferiority for IDegAsp vs. BIAsp 30 in HbA1c reduction (ETD, 0.05% (95% CI – 0.10; 0.20), $p = 0.20$ ) Superior FPG reduction with IDegAsp vs. BIAsp 30 (ETD IDegAsp–BIAsp 30, – 19.10 mg/dL, $p < 0.001$ ) Total insulin dose at the end of trial was 21% lower for IDegAsp vs. BIAsp 30 [rate ratio IDegAsp/BIAsp 30, 0.79 (95% CI 0.73; 0.85), $p < 0.0001$ ] Lower rates of overall confirmed and severe hypoglycemia and numerically lower rate for nocturnal confirmed hypoglycemia (33%) were observed for IDegAsp vs. BIAsp 30

**Table 1** continued

Study	Study details	Study endpoints summary
IDegAsp BID Comparator: BIAsp 30 BID [12]	26-week, multinational, open-label, parallel-group, treat-to-target trial  Patients: T2DM, insulin-naïve uncontrolled on their current therapy of metformin ( $\geq 1000$ mg daily) $\pm$ one additional OHA for at least 12 weeks before randomization ( $n = 394$ )	Insulin degludec/insulin aspart was non-inferiority to BIAsp 30 (ETD, 0.02%; 95% CI 0.12, 0.17)  Insulin degludec/insulin aspart was superior in lowering fasting plasma glucose (ETD 1.00 mmol/l; 95% CI 1.4, 0.6; $p < 0.001$ )  Superiority of IDegAsp was demonstrated, with a 54% reduction in overall confirmed hypoglycemia at similar overall insulin dose compared to biphasic insulin aspart 30  Superiority of IDegAsp was also demonstrated for nocturnal hypoglycemia, with a 75% reduction (estimated rate ratio, 0.25; 95% CI 0.16, 0.38; $p < 0.001$ )
IDegAsp use in Indian population for initiation and intensification [6]	52 weeks, retrospective study  Patients: all subjects who had received IDegAsp for 52 weeks at two endocrine centers ( $n = 48$ )	HbA1c was $7.51 \pm 0.46\%$ at 26 weeks and $7.48 \pm 0.40\%$ at 52 weeks  FPG was $108.58 \pm 22.26$ mg % at 26 weeks and $102.17 \pm 12.79$ mg % at 52 weeks  39 (81.25%) achieved a target of HbA1c $< 7.0\%$ at both 26 and 52 weeks  No episode of hypoglycemia was reported in 4 weeks preceding the analysis  Dose of IDegAsp fell from $43.17 \pm 21.18$ to $37.75 \pm 17.13$ U/day at 24 weeks and $41.41 \pm 15.33$ U/day at 52 weeks

*BB* basal bolus, *BID* twice daily, *ETD* estimated treatment difference, *FPG* fasting plasma glucose, *OAD* oral antidiabetes agent, *OD* once daily, *OHA* oral hypoglycemic agent, *SMPG* self-measured plasma glucose, *T1DM* type 1 diabetes mellitus, *T2DM* type 2 diabetes mellitus

role of premix insulin in the management of type 2 diabetes. Both premix and basal plus insulin regimens are suggested as an option for intensification of insulin. Intensive insulin regimes are also listed as a therapeutic choice in persons presenting with hyperglycemic symptoms or cachexia [18].

As discussed earlier, the versatile IDegAsp preparation can be used as a premix, basal plus, or basal bolus regimen. It can also be used for

once daily initiation of insulin in place of basal insulin. Therefore, there is a need to revisit the use of IDegAsp and highlight its concordance with current ADA guidelines.

While the earlier consensus has described the clinical utility of IDegAsp in detail, a focus is required on earlier use of appropriate insulins. This implies initiation of the right insulin at the right time. This multinational consensus, therefore, seeks to define the situations where

IDegAsp can be used for initiation of insulin therapy. It also suggests simple clinical tips that will help promote efficient implementation of IDegAsp.

## CONSENSUS: INITIATION WITH INSULIN DEGLUDEC/ASPART (IDEGASP)

### Indications

- The consensus group recommends the use of IDegAsp for initiation of insulin in
  - Drug-naïve persons with
  - Symptoms of hyperglycemia.
  - High carbohydrate diet.
  - High HbA1c.
  - High postprandial excursion.
  - Insulin-naïve persons with inadequate response to metformin, dual or triple oral therapy.
  - Long-acting sulfonylureas and IDegAsp, if used together, should be administered at antipodal meals.

### Administration and Titration

- The consensus group recommends the use of IDegAsp for insulin initiation in once daily or twice daily subcutaneous dosage, depending upon
  - Meal pattern and quantity
  - Gluco-phenotype (glucose profile)
- The starting dose of IDegAsp is usually 10 U or 0.1–0.2 U/day, but will vary according to
  - Severity of hyperglycemia
  - Risk of hypoglycemia
  - Meal pattern and quantity
  - Weight of the patient

The consensus group recommends titration of IDegAsp to be performed using a simple 2-0-2 algorithm (add 2 U if target fasting or premeal glucose is not achieved; zero change if target is achieved; reduce by 2 U if hypoglycemia occurs).

- IDegAsp use should be monitored by regular self-monitoring of blood glucose

- Twice weekly when glycemic control is unstable, hypoglycemia is anticipated, or urgent resolution of hyperglycemia is needed.
- Once weekly when glycemic control is stable and no fluctuations are anticipated.
- More frequently if glycemic control is brittle.
- Once prebreakfast and predinner control is achieved, postprandial glucose monitoring can be done to titrate doses further.

### Advantages

As compared to other insulin regimens and preparations, IDegAsp provides

- Glycemic control better or equivalent to
  - Basal regimen, if used once daily
  - Basal plus regimen, if used once daily
  - Basal bolus regimen, if used twice daily
  - Premix therapy
- Flexibility in timing of administration
- Lower risk of
  - Hypoglycemia
  - Nocturnal hypoglycemia

### Special Situations

The consensus group recommends IDegAsp should not be used

- In pregnancy and lactation
- As the only insulin in diabetic ketoacidosis
- Intravenously

The consensus group recommends IDegAsp to be used safely in special situations such as

- Shift workers/those with erratic meal patterns
- Ramadan fasting
- Renal impairment
- Hepatic impairment
- Elderly population

The consensus group recommends IDegAsp to be initiated as part of a three-dose regimen (IAsp–IAsp–IDegAsp) in

- Type 1 diabetes
- Persons in whom early correction of hyperglycemia is required

## CONCLUSION

This consensus provides information on the efficacy, safety, and ease of administration of IDegAsp in comparison with other insulin regimens and highlights the benefits of IDegAsp. It also provides a simple consensus for the use of IDegAsp in various populations with an algorithm for dose titration.

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