Clinical use of the co-formulation of insulin degludec and insulin aspart


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Abstract

Currently available premixed insulins provide basal and prandial glucose control; however, they have an intermediate-acting prandial insulin component and do not provide as effective basal coverage as true long-acting insulins. The limitations of premixed insulins additionally relate to the physicochemical incompatibility of their individual components, coupled with the inflexibility of adjustment. By contrast, the molecular structure of the two components of the co-formulation of insulin degludec with insulin aspart (IDegAsp), a novel insulin preparation, allows these two molecules to co-exist without affecting their individual pharmacodynamic profiles. The IDegAsp clinical trial programme finds that in people with type 2 diabetes mellitus (T2DM), once- and twice-daily dosing provides similar overall glycaemic control (HbA1c) to current modern insulins, but with lower risk of nocturnal hypoglycaemia. In prior insulin users, such glycaemic control was achieved with lower or equal insulin doses than with other basal + meal-time or premix insulin regimens. Clinically, in insulin-naive patients with T2DM, IDegAsp can be started once or twice daily, based on individual need. People switching from more than once-daily basal or premix insulin therapy can be converted unit-to-unit to once-daily IDegAsp, although this strategy should be assessed by the physician on an individual basis. IDegAsp offers physicians and people with T2DM a simpler insulin regimen than other available basal-bolus or premix-based insulin regimens, with a stable basal coverage throughout the day, a lower rate of hypoglycaemia, and some flexibility in injection timing compared with premix insulins.

(239/250 words)

Review criteria

How did you gather, select and analyse the info you considered in your review?’ (2 or 3 short sentences; 70 words)

Findings from key studies of the IDegAsp clinical trial programme were chosen as a basis for the clinical guidance provided here. The authors had access to all presented and published studies, and the restricted availability of IDegAsp until recently has prevented significant studies outside the development programme. All phase 2 and 3 studies are included.

Message for the clinic

What is the take-home message for the clinician?’ (2 or 3 short sentences; 70 words).
IDegAsp is a novel co-formulation of insulin degludec (IDeg) and insulin aspart (IAsp). It can be used once or twice daily, providing reliable coverage of both basal and prandial insulin requirements with a lower risk of hypoglycaemia than current insulin options. It permits greater flexibility in timing of doses and the possibility of equivalent glycaemic control as basal-bolus, but with the advantage of reduced injection burden, thus simplifying treatment regimens.

(70/70 words)
Introduction

Type 2 diabetes mellitus (T2DM) is characterised by a progressive decline in β-cell function, necessitating the introduction of sequential glucose-lowering therapies, including insulin, to achieve or maintain glycaemic targets [1–3].

Stepwise optimisation involving insulin therapy is often delayed (‘clinical inertia’), sometimes for many years [3]. Many reasons have been identified for this delay, including the perception by both physicians and people with diabetes mellitus of the increased burden of multiple injections and blood glucose monitoring, the complexity of multi-medication regimens, and concerns about the risks of hypoglycaemia and body weight gain [2, 3]. Physicians also express concerns over consequent decreased adherence to therapy [4].

The introduction of longer-acting basal insulins and, more recently, the combination of a long-acting flat basal insulin with a fast-acting prandial insulin, provides some advantages over the combination of intermediate- and fast-acting insulin in current premixed products [5,6]. Potentially this combination addresses some of these concerns through dose reduction and lower injection burden without loss of efficacy and perhaps with less hypoglycaemia. These issues are considered below in the context of the insulin degludec/insulin aspart co-formulation (IDegAsp).

Unmet clinical need

Current premixed insulins, which contain both fast- and intermediate-acting insulin components, aim to provide both basal and meal-time glucose control. Existing premixes are a mixture of unbound fast-acting insulin, and fast-acting insulin, which is protaminated to delay absorption. They have an intermediate duration of action and thus do not provide the basal coverage seen with true long-acting basal insulins. It has not been possible to produce co-formulations of the first-generation long-acting insulin analogues (insulins glargine and detemir) with fast-acting insulins, either due to physicochemical incompatibility or without affecting their individual pharmacokinetic (PK) and pharmacodynamic (PD) profiles [7,8].

Existing premixed insulins, most commonly in a 30/70 fast/basal ratio (thus ‘biphasic’), utilise either human insulin (BHI30) or analogue insulins, such as biphasic insulin aspart (BIAsp 30) or insulin lispro (75/25) [9]. The advantage of fewer daily injections with premixed insulins compared with basal + meal-time regimens [9] is, to some extent, offset by lack of flexibility of individual dose adjustment of the meal-time and basal components. There is some evidence to suggest that when administered once or twice daily, premixed insulins demonstrate a greater reduction in glycated haemoglobin (HbA1c) when compared with basal...
insulin analogues, but at the cost of increased risk of hypoglycaemia and weight gain [2,10,11], which may affect treatment adherence [4]. The outstanding need was then for a co-formulated insulin retaining the fast-acting analogue advantage at meal-times with a truly flat 24-h basal coverage.

**Physicochemical properties of IDegAsp**

The co-formulation of IDeg and IAsp in IDegAsp is a clear, colourless, neutral pH solution [12]. The two components do not interact and remain molecularly separate, as shown in Figure 1A [13]. Being fully dissolved, resuspension to homogeneity before injection is not necessary, which to date is not possible with other current insulin analogues.

Insulin glargine (IGlar) is presented as a solution at pH 4, and consequently co-formulation with meal-time insulins (usually formulated to neutral pH) is not possible [14]. Following subcutaneous injection, IGlar forms microprecipitates and must be re-dissolved prior to absorption, rendering its absorption inherently variable [15]. The early pharmacodynamic action of IAsp is markedly blunted and its time–action profile prolonged when mixed with insulin detemir (IDet), compared with a separate injection of these analogues [7]. This is as a result of the different formulation needed to maintain the physicochemical stability of these analogues.

The molecular structure of the two components of IDegAsp allows them to co-exist without affecting their individual PK and PD profiles [13]. The basal component, IDeg, exists in the form of stable di-hexamers in the pharmaceutical preparation, forming long multi-hexamer chains after subcutaneous administration (Figure 1B). Subsequently, continual release of IDeg monomers from the ends of the chains ensures a flat PK/PD profile, lasting long enough to meet basal insulin requirements over 24 h once at steady state [16]. In contrast, IAsp in IDegAsp exists as hexamers in the vial, which rapidly dissociate into monomers after subcutaneous administration, providing a near-physiological meal-time concentration profile [14]. This has been confirmed by size exclusion chromatography, in conditions simulating pharmaceutical preparations as well as after subcutaneous administration, clearly showing the existence of two separate components that do not affect each other’s PK/PD profile, either in solution or once injected [13]. Furthermore, a clamp study carried out in people with type 1 diabetes mellitus (T1DM) at steady state demonstrated the basal and meal-time effects of the two components in a dose-dependent manner [14].
Pharmacokinetic/pharmacodynamic properties of IDegAsp

The PK and PD properties of IDegAsp are summarised in Table 1. The basal component, IDeg, is characterised by a PK half-life of > 25 h, and thus an ultra-long duration of action (> 42 h) [17]. The flat profile means that the within-person, within-day variability in glucose-lowering effect is four times lower compared with IGlar [18]. The consistent insulin absorption rate in combination with a flat profile would be predicted to be associated with a decreased risk of hypoglycaemia.

A randomised, single-centre, double-blind, glucose clamp study in a cohort of 33 people with T1DM found that IDegAsp has a clear glucose-requirement-to-dose relationship [19] that is observed for both the basal and meal-time components.

Modelling of glucose infusion rate during 24-h dosing in a glycaemic clamp setting, based on a study of once-daily dosing at steady state, suggests that total glucose-lowering effect was independent of daily dosing frequency. Therefore, the glucose-lowering effect of IDegAsp is dependent on total dose given, whether one or more injections per day are used (Figure 2) [14]. As a result, the Summary of Product Characteristics suggests that if a dose is missed, it can be taken with the next main meal of that day [12]. After any dose change, including commencing the insulin, steady-state plasma levels of the degludec component are reached in 2–3 days, and plasma insulin does not accumulate further (‘stacking’) [20], with the results from the 24-h elimination rate equalling the 24-h absorption rate [21].

As the clinical pharmacology profiles of the IDeg and IAsp components of IDegAsp are distinct, evidence from PK and PD studies of IDeg and IAsp development programmes can be applied to IDegAsp. Moreover, no clinically relevant differences in the pharmacodynamics of IDegAsp in older people were found following a phase 1, double-blind crossover trial of IDegAsp in young adults (18–35 years of age) and older (≥ 65 years of age) people with T1DM [22]. In addition, no clinically relevant differences have been observed in the PK or PD of IDeg or IAsp in patients with renal or hepatic impairment [23–25]. Together, these findings indicate that IDegAsp may be used in people with renal impairment, and in older people (≥ 65 years old), with the usual clinical cautions over differences in insulin sensitivity in these populations. However, glucose monitoring should be optimised and insulin dose adjusted on an individual basis [12].

Clinical evidence in T1DM

In T1DM, IDegAsp has been assessed in a single study (Table 2). Here, IDegAsp was given once daily in a regimen with IAsp at other meals and compared with an IDet + IAsp multiple
injection regimen. IDegAsp was non-inferior to IDet + IAsp for reduction in HbA1c despite a 13% lower insulin dose (Table 2) [26]. Per protocol, the meal at which IDegAsp was dosed could be changed during the study; however, few participants chose to do so. Lower rates of hypoglycaemia were also observed in a 26-week extension of the same study [(IDegAsp once daily + IAsp at meal-times vs IDet once or twice daily + IAsp at meal-times)] [27].

Clinical evidence in T2DM

Efficacy and safety of IDegAsp once daily vs. IGlar once daily: Phase 2 data

In an insulin-naïve population, once-daily, pre-dinner IDegAsp provides similar overall (HbA1c) glycaemic control at 16 weeks compared with IGlar, despite a lower daily insulin dose, but with better control of post-evening meal glucose (Table 2) [28]. In a subpopulation using continuous glucose monitoring for 72 h before the last visit, people using IDegAsp had significantly lower post-evening meal glucose excursions than those using IGlar. These individuals also had less nocturnal hypoglycaemia, which may be partly explained by the smaller fluctuation in nocturnal glucose levels, attributable to the consistent pharmacodynamics effect of IDeg [29].

Once-daily IDegAsp use in T2DM: Phase 3 data

In Japan, IDegAsp administered once daily to insulin-naïve people with T2DM demonstrated superiority to IGlar in lowering HbA1c (difference –0.28 [95% confidence interval (CI) –0.46; –0.10 %]-units) with similar end-of-trial fasting plasma glucose (FPG). The estimated rate of nocturnal confirmed hypoglycaemia was numerically lower by 25%; however, it was not statistically significant (Table 2). Daily insulin dose and adverse events did not differ [30].

Twice-daily IDegAsp use in T2DM

IDegAsp treatment in insulin-naïve people

In a global study in insulin-naïve people comparing twice-daily IDegAsp with twice-daily BIAsp 30, there was no difference in HbA1c, despite FPG being 1.0 mmol/l lower (p < 0.001). However, in this study there was a 75% reduction in nocturnal confirmed hypoglycaemia in favour of IDegAsp, together with a 54% reduction in any-time hypoglycaemia (p < 0.001) (Table 2) [31].

IDegAsp treatment in prior insulin users

In studies comparing twice-daily administration of IDegAsp with BIAsp 30, one in a global population and one in an Asian population, IDegAsp was non-inferior to BIAsp 30 for change
in HbA\textsubscript{1c}, but superior in lowering FPG and at a lower daily insulin dose (Table 2) [29, 30]. IDegAsp demonstrated a 32\% reduction in confirmed hypoglycaemia rate (\( p = 0.005 \)) and a 73\% reduction in rate of nocturnal confirmed hypoglycaemia (\( p < 0.001 \)) [5]. In the Asian population, there was no effect on any-time (confirmed) hypoglycaemia and the rate ratio for nocturnal confirmed hypoglycaemia (reduction of 33\%) did not meet statistical significance [6].

A patient-level combined analysis of the global and Asian studies found that IDegAsp was associated with a greater reduction in FPG from baseline (\( p < 0.001 \)) and less weight gain (\( p = 0.012 \)). The rates of overall confirmed, nocturnal confirmed, and severe hypoglycaemic events were, respectively, 19\% (\( p = 0.03 \)), 57\% (\( p < 0.001 \)) and 39\% (not significant [NS]) lower with IDegAsp compared with BIAsp 30, but heterogeneity between study results limits the robustness of this approach. Furthermore, the lower risk of hypoglycaemia was more pronounced during the maintenance period (> 16 weeks) in the two studies. The analysis also found that daily insulin doses at end of trial were 16\% lower for IDegAsp than BIAsp 30 (estimated dose ratio [95\% CI]: 0.84 [0.80; 0.89], \( p < 0.0001 \)) [32].

**Twice-daily IDegAsp vs. basal + meal-time insulin therapy in prior insulin users**

Comparing two treatment-optimisation regimens from basal-only therapy, IDegAsp (twice daily) showed final HbA\textsubscript{1c} comparable to the one achieved with a meal-time + basal regimen of IDeg + IAsp (7.0\% and 6.8\%, NS) [33]. Although non-inferiority for IDegAsp was not achieved, insulin dose was 12\% lower using combination insulin, while both confirmed and nocturnal hypoglycaemia rates were 19\% and 20\% lower, respectively (Table 2) [33]. Additionally, although the health-related quality of life questionnaire (SF-36v2) revealed no difference between treatment groups for physical scores, there was a higher overall change from baseline for mental scores with IDegAsp than for IDeg + IAsp, potentially driven by change from baseline in the mental health domain score for social functioning, which was significantly higher for IDegAsp (end-of-treatment difference 2.2 [95\% CI 0.3; 4.1]; \( p < 0.05 \)) [33].

**Clinical use of IDegAsp**

**Use of IDegAsp in clinical practice**

**Administration**

As currently licensed in Europe, IDegAsp can be used once daily or twice daily and allows for flexibility in the timing of administration as long as it is dosed with the main meal(s) [12]. IDegAsp is a clear solution and does not require resuspension. Shelf life is 30 months,
provided it is stored below 30°C; it should not be refrigerated. After first opening, IDegAsp may be used for up to 4 weeks [12]. Subcutaneous use should be into the abdominal wall, upper arm or the thigh (owing to a lack of experience in studies with other injection sites) [12].

Based on the available data from the IDegAsp clinical trial programme, the following section will aim to provide some recommendations for the use of IDegAsp in a clinical setting.

Beginning IDegAsp in T2DM

Based on clinical trial data, the recommended usual starting dose is 10 U with the largest meal(s), followed by individual dose titration [12]. In clinical trials of IDegAsp, doses were titrated up by 2-U increments to achieve an FPG target of < 5.0 mmol/l (< 90 mg/dl), but this strategy was reassessed by investigators if hypoglycaemia occurred. If FPG levels were < 3.1 mmol/l (< 56 mg/dl), reductions of 4 U (or –10% if the dose was > 45 U) were advised [29, 30]. In clinical practice, the FPG target and rate of change of doses should be individualised according to the clinical characteristics and preferences of the person using the insulin [1].

The choice of starting IDegAsp once daily or twice daily can also be individualised. Once-daily administration may be generally preferred, but if two main meals show marked hyperglycaemic excursions on prior non-insulin therapy, then twice-daily administration may be logical. Switching from once- to twice-daily dosing would be indicated if hyperglycaemia persisted at other meal-times throughout the day, or if hypoglycaemia or tight control in the period after the injection at the main meal suggested that a reduction in dose of insulin is needed. In these circumstances, the daily single dose can be divided into two doses, before further dose titration is initiated.

Optimising insulin treatment with IDegAsp in T2DM

In clinical practice, a switch of insulin therapy may be indicated, particularly where basal insulin is failing to achieve adequate glycaemic control despite active dose titration to FPG target. Use of IDegAsp to replace basal insulin alone, either once or twice daily is an option, but does require some postprandial monitoring before switching if the timing and number of injections is to be optimal. For example, if a change is made from neutral protamine Hagedorn basal insulin, then better control before breakfast with IDegAsp may minimise the postprandial glucose excursions.

The switch from other human or analogue premix insulins will usually be indicated by failure to obtain adequate control due to hypoglycaemia, lack of insulin action predictability from day
to day, or self-measured glucose ranges that indicate an increased risk of hypoglycaemia. Most people will be on twice-daily therapy; those switching from a single morning injection of premix to twice-daily IDegAsp should be carefully monitored for nocturnal hypoglycaemia. In general, a switch from twice-daily premix therapy to IDegAsp will have the same timing of injections. However, the properties of IDegAsp are such that people can change the time of administration as long as it is dosed with the main meal(s).

Evidence from clinical trials confirms that people with T2DM can switch from other once-daily or twice-daily insulins (basal or premix) to IDegAsp, on a unit-to-unit basis, without risk of increase in hypoglycaemia [5,12]. This was demonstrated in the sub-analysis of people on a high total dose of basal insulin at baseline (> 40 U/day and up to 60 U at end of trial) who were switched to 1:1 IDegAsp once daily; after the first 4 weeks of switching, IDegAsp was not associated with an increased rate of hypoglycaemia [34].

Glucose control responses, including hypoglycaemia, to changing insulins vary markedly between individuals, so the usual clinical advice regarding switching regimens is recommended when switching to IDegAsp. This advice includes close glucose self-monitoring and special care when risk of hypoglycaemia may be particularly important (e.g. when driving). Adjustment of concurrent glucose-lowering therapies may also be needed [12]. If the reason for switching is recurrent hypoglycaemia or large day-to-day variation in FPG, it may be prudent to reduce the dose of IDegAsp by 10–20%, as trial data indicate that IDegAsp gives similar glycaemic control at lower doses than BIAsp 30 or basal + meal-time injection regimen (Table 2) [5,6,32,33]. However, if the reason for switching is uncontrolled hyperglycaemia, then no dose reduction is needed.

People who have previously been receiving once-daily basal or premixed/self-mixed insulin may be started on twice-daily doses of IDegAsp by splitting the prior total dose into two equal doses of IDegAsp, although meal pattern may suggest a different balance of doses [6,33,35].

Several factors may influence the need for switching treatment regimens, including lack of adherence to therapy, complexity of multidrug regimens and the higher risk of hypoglycaemia [2,3]. When switching from basal + meal-time bolus insulin regimen to IDegAsp, careful assessment of the conversion of insulin doses will need to be based on individual need, with consideration of meal pattern, physical activity and self-measurement profiles. In general, conversion with the total basal dose may be administered twice daily.

General insulin management issues
Steady-state serum IDeg concentrations are reached after 2–3 days [12]. With IDegAsp, meal-time insulin stacking can be of concern and the duration of action of IAsp (3–5 h) [36] should be taken into consideration if IDegAsp is being used as a multiple injection regimen, particularly when used with BIASp 30, where a 'shoulder effect' has been observed between 6 and 12 h due to the overlapping effects of the IAsp in IDegAsp and protaminated Asp in BIASp 30 [19].

Studies of IDeg alone have demonstrated flexibility of time of daily injection [37]. Accordingly, the European label for IDegAsp recognises that some meal-time flexibility is acceptable [12], with the proviso that it is given with the largest meal. It is expected that injection flexibility may help with adherence to an IDegAsp insulin regimen.

IDegAsp treatments may be titrated weekly; IDeg serum concentrations take 2–3 days to reach steady state [12], after which the average of the 3 days' plasma glucose measurements can be taken. Appropriate dosing of the basal component is best indicated by self-measured FPG for either regimen, as pre-evening meal levels may reflect uncontrolled glucose excursions after the midday meal. The success of the prandial component is best judged by postprandial glucose levels (0–120 minutes after the beginning of the meal), and by those before the next meal. Again, as with all insulin regimens, the occurrence of hypoglycaemia, or risk of it, will modulate insulin dose adjustment, depending in part on the time of day it occurs.

IDegAsp has the potential to benefit a wide range of people with T2DM, but some may have particular treatment needs. Thus, if FPG is within the individualised target range, but meal-time control is an issue, perhaps as indicated by high HbA1c on basal insulin or premix insulin after optimisation, then IDegAsp can be useful. Those for whom the basal insulin dose is adequate, as indicated by FPG levels – but who are unable to achieve HbA1c target levels, due to large day-to-day pre-breakfast glucose variability and fear of nocturnal hypoglycaemia – may also benefit from the flatter night-time profile of IDegAsp. Anyone on premix insulin having hypoglycaemia due to overlap of the meal insulin component and variability of the protaminated components would also be a logical candidate.

Finally, people on any insulin regimen who previously would require optimisation with a full basal + meal-time bolus insulin regimen may also be offered twice-daily IDegAsp [12], although care needs to be taken with glucose excursions at the third main meal. At present, the European licence extends only to twice-daily injection, even while the data of the PK/PD studies could be extrapolated to suggest that a higher injection number would not be detrimental, and may even facilitate the achievement of glycaemic targets, provided the relevant meal intervals were maintained.
Summary

Most patients with T2DM will eventually need insulin. Intensification of the dose and the change of regimen is important to maintain individualised glycaemic targets. Concerns over complicated injection regimens, hypoglycaemia and weight gain, among other factors, can unnecessarily delay treatment intensification. There is an unmet need for a better, simpler insulin regimen that provides both basal and prandial insulin control that may lead to improved treatment adherence.

IDegAsp is a novel combination of IDeg and IAsp in a single injection that is able to provide a flat and stable 24-h basal insulin coverage and bolus meal-time insulin control with reduced injection burden compared with standard basal and bolus therapy. This feature makes IDegAsp particularly applicable for use in patients with T2DM.

Clinical trials with a treat-to-target design have demonstrated that IDegAsp is associated with effective glycaemic control and reduced rates of hypoglycaemia in comparison with other insulin analogues, which may allow for easier initiation and optimisation of insulin therapy. IDegAsp may be added to oral glucose-lowering therapy. The decision to move from once-daily to twice-daily dosing is guided by preferences and meal-time glucose excursions, but may also require some postprandial monitoring in order to optimise the timing and number of injections on an individual basis.

IDegAsp twice daily has been shown to provide effective HbA1c control and superior reductions in FPG compared with BIAsp 30 twice daily, while achieving lower rates of hypoglycaemia. Clinical data further indicate that IDegAsp twice daily offers a simpler alternative to basal-bolus treatment in patients who require intensification of basal insulin regimens. In conclusion, IDegAsp is a novel co-formulation that may offer patients with progressive T2DM a simpler, injectable insulin regimen with fewer injections than with basal-plus or basal-bolus insulin therapy. IDegAsp offers flexibility in administration to suit individual lifestyle needs compared with existing premixed insulins in terms of differences in timing of meals and dietary patterns. Finally, IDegAsp twice daily may help to improve adherence in patients who may find the use of more complex regimens challenging.

Author contributions

All authors participated in conceiving, drafting and finalising the manuscript, and provided critical revision and approval of the manuscript.
Acknowledgements

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### Figures and Tables

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<td>Mechanism of action</td>
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IAsp, insulin aspart; IDeg, insulin degludec; IDegAsp, insulin degludec/insulin aspart.
Table 2 Summary of the phase 2/3 clinical trials in the insulin degludec/insulin aspart (IDegAsp) clinical programme

<table>
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<td>T2DM (insulin-naïve) (n = 178)</td>
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<td>IDegAsp vs IGlar (all + metformin)</td>
<td>–0.11 (–0.41; 0.19)</td>
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<td>Hirsch et al. [26]</td>
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<td>T1DM (n = 548)</td>
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<td>Nocturnal confirmed: 37% lower IDegAsp vs IDet (p &lt; 0.05)</td>
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<td>Onishi et al. [30]</td>
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<td>T2DM Japanese population (n = 296)</td>
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<td>IDegAsp vs IGlar</td>
<td>–0.28 (–0.46; –0.10), p &lt; 0.01</td>
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<td>Confirmed: RR 0.47 (95% CI 0.35; 0.61), p &lt; 0.001 Nocturnal: RR 0.20 (95% CI 0.16; 0.23), p &lt; 0.001</td>
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<td>IDegAsp twice daily vs IDeg + IAsp 2–4 times daily 0.18 (–0.04; 0.41), p = NS  0.81 (95% CI 0.61; 1.06), p = NS  0.80 (95% CI 0.50; 1.29), p = NS</td>
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</table>

BIAsp 30, biphasic insulin aspart 30; CI, confidence interval; HbA1c, glycosylated haemoglobin; IAsp, insulin aspart; IDeg, insulin degludec; IDegAsp, insulin degludec/insulin aspart; IDet, insulin detemir; IGlar, insulin glargine; NS, not significant; PYE, patient-years of exposure; RR, rate ratio; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.
Table 3 Clinical guidance for the use of IDegAsp

**Clinical use of IDegAsp**

| Dosing | Licensed once or twice daily with main meal(s)  
|        | Timing of meals not important if interval >4 hours  
|        | Timing of meals can vary between days  
| Insulin-naive starting dose | Should be individualised  
|        | Recommended starting dose is 10 U with a main meal, based on clinical trial protocols  
|        | Dose adjustment should be weekly  
|        | If appropriate, additional IAsp dose(s) can be given at other meals  
|        | Combination with oral agents is often optimal  
| Prior insulin user switching doses | From full multiple injection regimen: choose dose(s) to keep the total basal dose unchanged  
|        | From premix insulin: keep total dose unchanged  
|        | From basal insulin only: keep total dose unchanged, unless in very poor control when some increment may be appropriate  
|        | For all switches, doses should be determined by individual requirements  
| Titration | Dose adjustments should be based on FPG measurements and hypoglycemia  
|        | A dose-titration algorithm is provided in the IDegAsp European SmPC [12]  
| Practical advantages compared with premixed or multiple injection regimens | Stable consistent glucose-lowering effect due to ultra-long flat pharmacodynamics of IDeg basal component  
|        | Fewer injections leading to a less-complex regimen  
|        | Straightforward dose titration  
|        | Less hypoglycemia in some circumstances, especially nocturnal hypoglycemia  
| Dose timing | Before any main meal, or combination of main meals (but not within 4 hours), and can be varied from day to day  

FPG, fasting plasma glucose; IAsp, insulin aspart; IDegAsp, insulin degludec/insulin aspart; SmPC, Summary of Product Characteristics, U, unit

**Figure 1** The mechanism of action of IDegAsp insulin co-formulation. In the pharmaceutical preparation (A), the IDeg component forms soluble di-hexamers at neutral pH, whereas IAsp
remains as distinct hexamers. Upon injection (B), IDeg di-hexamers immediately form stable multi-hexamers in the subcutaneous tissue from which IDeg monomers dissociate slowly and continuously. IAsp hexamers promptly dissociate to monomers and the depot is thus rapidly absorbed into the circulation. IAsp, insulin aspart; IDeg, insulin degludec; IDegAsp, insulin degludec/insulin aspart.
Figure 2 Differences in mean glucose infusion rate (GIR) profiles of IDegAsp and BIAsp 30. GIR profile at steady state following once-daily administration of IDegAsp 0.6 U/kg [14] and GIR profile of single-dose BIAsp 30 0.6 U/kg [19]. Both GIR profiles are from studies conducted in people with type 1 diabetes mellitus. BIAsp 30, biphasic insulin aspart 30; IDegAsp, insulin degludec/insulin aspart.