Review Article

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Review of new ultra-long-acting basal insulin: Insulin degludec

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Abstract

Long-acting basal insulin analogs were introduced in clinical practice for more than 10 years ago and designed to provide basal insulin requirement for both Type 1 (T1DM) and Type 2 (T2DM) diabetes mellitus. However, there has been a concern with the existing basal insulin such as insulin glargine 100U (IGla 100U) and insulin determir (IDet) because of the risk of hypoglycemia, weight gain, management complexity and rigid dosing schedule associated with their pharmacokinetic and pharmacodynamic properties. Recently, US Food and Drug Administration (FDA) approved new long-acting basal insulin analog, insulin degludec (IDeg) in 2015. IDeg was derived from human insulin by removal of B30 threonine amino acid residue and acylating the DesB30 at the LysB29 with hexadecandioic acid via a gamma-L-glutamic acid spacer. IDeg has long half-life, providing flat, peakless and stable blood glucose lowering effect when injected once daily. Clinical studies have shown that IDeg is not superior to IGla 100U in antihyperglycemic efficacy but it has significant lower hypoglycemic episode. Moreover, IDeg has less blood glucose variability and broad dosing window with flexible dosing interval. Coformulation of IDeg with Insulin Aspart (IAsp) and Glucagon-like-peptide receptor agonist (GLP-1 agonist) have been designed for basal-bolus administration. They have a benefit of improvement in glycated haemoglobin and reduce the number of daily doses. Overall, IDeg, with its unique pharmacokinetic properties, will provide effective glycemic control while minimizing the risk of hypoglycemia.

Keyword: Long-acting-basal insulin, Insulin Degludec, Type 1 diabetes mellitus, Type 2 diabetes mellitus, Coformulation, Hypoglycemia.

1. INTRODUCTION

Patients with diabetes often require insulin supplementation to maintain optimal blood glucose level in order to prevent the undesirable complications of diabetes. Over a past decade, long acting basal insulin analogs have a contribution to improvement in diabetes management. The main role of basal insulin is to limit hepatic glucose production and lipolysis in the fasting state, particularly overnight, without impairing glucose availability for brain function.[1] Basal insulin is essential for all patients with both T1DM and T2DM. Unlike endogenous insulin which is secreted from pancreas in glucose dependent manner, the dose of currently available basal insulin analogs should be titrated to maintain the appropriate level to avoid hypoglycemia or hyperglycemia. Available basal insulin analogs had been IDet and IGla 100U. Unfortunately, IDet and IGla 100U have significant residual within-patient variability, short half-life, glycemic control less than 24 hours and less predictable glucose lowering effect with once-daily dosing. This can result in inadequate dose titration due to fear of hypoglycemia, restriction of patient's lifestyle and inflexible dosing regimen[2]. Currently, US FDA has given marketing authorization to IDeg in September, 2015. It is an ultra-long-acting basal insulin which has been formulated with a depot, slow-release from the site of injection in order to address the unmet needs of basal insulins. It comparatively reduces within-subject variability and has fewer hypoglycemic

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episodes, more predictable glucose lowering effect and long duration of action (>42 hours) due to its unique, flat and stable pharmacokinetic properties. IDeg is also available in combination with insulin aspart (IAsp) and liraglutide[3]. IDeg is not routinely used in clinical practice. The purpose of this review is to discuss about the previous findings of IDeg with its pharmacokinetic and pharmacodynamic properties for application in clinical practice.

2. FORMULATION, STRUCTURE AND MECHANISM OF ACTION

IDeg is available in two strengths of 3 ml (U100) [1-80 units per injection, in steps of 1 unit] and 3 ml (U200) [2-160 units per injection, in steps of 2 units]. U200 is bioequivalent with U100 and gives the same amount of insulin but with the half of its volume, resulting in a single injection with low volume which is beneficial for patients requiring high daily insulin. IDeg is available in market as Tresiba 100U/ml, 3ml and 200U/ml, 3ml. Unlike other long acting insulin, IDeg can be given anytime of the day with wide dosing interval of 8-40 hours and once daily dosing regimen without compromising the safety and efficacy.[4,5]

IDeg is modified from human insulin by removal of B30 threonine amino acid residue and acylating the DesB30 human insulin at the amino group of LysB29 with hexadecandioic acid via a gamma-L-glutamic acid spacer. IDeg (pH 7.4) is a clear, colorless solution with a pH-dependent solubility. It is formulated as a dihexamer in the presence of zinc and phenol at T_3R_3 state. After subcutaneous injection, with the removal of phenol, dihexamer self-dissociate into multihexamer and forms a depot formation at the site of injection at T_6 state. Subsequent diffusion of zinc from multihexamer results in a gradual disassembling to release monomers and then are absorbed in circulation and bind to insulin receptor.[6,7]

3. PHARMACOKINETIC AND PHARMACODYNAMIC PROPERTIES

IDeg has a terminal half-life of approximately 25 hours and a state of equilibrium is reached in approximately 2-3 days of dose administration. The duration of action is above 42 hours and remained detectable in the circulation during the entire study period for up to 120 hours. It has high protein binding of > 99%. A pharmacokinetic study of IDeg dose (0.4, 0.6 and/or 0.8 U/kg subcutaneous, once daily injection for two 6-day treatment periods) in T2DM patients showed evenly distributed glucose lowering effect at all dose interval with the area under the curve (AUC) for each of 6 hours intervals being approximately 25% of total AUC ($AUC_{GIR,\tau,SS}$). The glucose-lowering effect of IDeg for the first 12 hours after dosing was similar to that for the following 12 hours. $AUC_{GIR,0–12h,SS}/AUC_{GIR,\tau\ ,SS}$ was close to 50% for all three dose levels.[8] The pharmacokinetic and pharmacodynamic data for T1DM and T2DM are summarized in **Table 1**.[8,9] IDeg has four times lower day-to-day pharmacodynamic variability than IGla 100U under steady state in T1DM patients. The supporting data was $AUC_{GIR,0\text{-}24hrs,SS}$ coefficient variation (CV) 20% vs 82% ($P < 0.0001$) for IDeg and IGla 100U respectively.[10] It also has two folds longer half-life than IGla 100U (mean terminal half-life 25.4 vs 12.5 hours) in a more evenly distributed and stable pharmacokinetic picture at the steady state in T1DM.[11]

4. SPECIAL POPULATION

4.1. Children, Adolescents and Elderly patients

For IDeg, a two-period crossover trial was conducted in children (6-11 years), adolescents (12-17 years) and adults (18-65 years) with T1DM by administration of IDeg 0.4U/kg single dose and compared with IGla 0.4U/kg. No statistically significant difference in maximum concentration (C_{max}) of IDeg was observed. Estimated treatment ratio of $C_{max,IDeg,SD}$ were 1.2, 95% confidence interval (CI) 0.9-1.60 for children/adults and 1.23, 95% CI 1.00-1.51 for adolescents/adults.[12] A multiple-dose two-period crossover study was conducted in younger adults (18-35 years) and elderly group (≥ 65 years) with T1DM by giving IDeg 0.4U/kg once daily for six days. Similar pharmacokinetic profile was observed in both populations with estimated

Table 1. Pharmacokinetic and Pharmacodynamic parameters of IDeg in T1DM and T2DM[9,8]

	T1DM study[9]		T2DM study[8]		
Unit	100 U	200 U	100 U		
Dose	0.4 U/kg	0.4 U/kg	0.4U/kg	0.6 U/kg	0.8 U/kg
Number of subjects	33		22	37	21
Pharmacokinetic parameters					
$AUC_{\tau,SS,IDeg}$ (pmol_h/L) Geometric mean (CV)	112,358 (27)	110,805 (33)	89643.2 (35.0)	130164 (22.6)	177408 (26.5)
$C_{max,SS,IDeg}$ (pmol/L) Geometric mean (CV)	6568 (26)	6065 (37)	-	-	-
$AUC_{IDeg,0–12h,SS}$/ $AUC_{IDeg,\tau,SS}$ Geometric mean (CV)	55	53	53.3 (4.1)	52.5 (5)	52.7 (5.3)
$t_{1/2,IDeg,SS}$, h Harmonic mean	-	-	24.6	24.4	26.8
Pharmacodynamic parameters					
$AUC_{GIR,\tau,SS,}$ mg/kg Geometric mean (CV)	2,255 (48)	2,123 (48)	827.5 (67.9)	1694.0 (55.9)	2482.3 (45.5)

IDeg = Insulin Degludec, T1DM = Type 1 Diabetes Mellitus, T2DM = Type 2 Diabetes Mellitus, $AUC_{\tau,SS,IDeg}$ = Area under the steady-state serum IDeg concentration time curve during a dosing interval (τ = 0-24 hours), $C_{max,SS,IDeg}$ = Maximum steady state IDeg concentration during a dosing interval τ, $AUC_{IDeg,0–12h,SS}/AUC_{IDeg,\tau,SS}$ = Area under the steady-state serum IDeg concentration time curve from 0 to 12 h divided by the same parameter from 0 to 24 h, CV= coefficient of variation (%), $t_{1/2}$ = half life

mean age group ratios (elderly/younger adult) for $AUC_{IDeg, \chi,SS}$ and $C_{max,IDeg,SS}$ were 1.04, 95% CI 0.73-1.47 and 1.02, 95% CI 0.74-1.39 respectively.[13] These data suggest that the ultra-long pharmacokinetic properties of IDeg was preserved in children and adults with T1DM. In summary, IDeg can be used in elderly patients (age ≥ 65 years), adolescents and children from the age of one year.[14] However, dosage should be titrated according to individual basis to reduce the risk of hypoglycemia. Great caution should be taken in geriatric patients since greater sensitivity of some older patients to the effect of IDeg cannot be ruled out.

4.2. Renal and Hepatic impairment

Insulin clearance is specifically mediated by the trafficking and internalization of the insulin receptor. It might be more predominant in high albumin-bound insulin that cannot be filtered via renal route as easily as unbound 'free' insulin. So, renal and hepatic impairment may not have large effect on pharmacologic profiles of IDeg. A single dose (IDeg 0.4 U/kg), open-label, parallel group trial was conducted in 30 subjects, dividing into five groups (6 person/group) according to their renal function: normal renal function [creatinine clearance (CrCl > 80 ml/min)], mild (CrCl 50-80 ml/min), moderate (CrCl 30-49 ml/min) or severe (CrCl < 30ml/min) renal impairment or subjects with end stage renal disease (ESRD) requiring haemodialysis. There was no statistically significant difference between the groups. The data were shown in **Table 2**[15]. Another single dose (IDeg 0.4 U/kg), open–labelled parallel group study was conducted in 24 patients, allocated into 4 groups (n = 6 person/group) based on the level of hepatic function [normal hepatic function or stable hepatic impairment classified as mild, moderate, or severe (Child–Pugh grades A, B and C, respectively)]. No difference was observed in pharmacokinetic parameters in terms of AUC_{120hrs}, C_{max} and apparent clearance (Cl/F) The data were presented in **Table 2**.[16] In summary, no specific dosage adjustment is required in renal and hepatic impairment but glucose monitoring should be intensified and dosage should be adjusted on individual basis.

Table 2. Relationship between degree of renal or hepatic impairment and insulin degludec pharmacokinetic parameters[15,16].

Comparison of grades of renal/hepatic impairment	Renal impairment study[15]		Hepatic impairment study[16]		
	$AUC_{0-\infty}$	C_{max}	$AUC_{0-120hr}$	C_{max}	CL/F
Mild vs normal	1.11 (0.80-1.54)	1.14 (0.81-1.61)	0.95 (0.77-1.16)	0.90 (0.67-1.20)	1.05 (0.86-1.29)
Moderate vs normal	1.11 (0.80-1.53)	1.06 (0.76-1.49)	1.00 (0.82-1.22)	0.77 (0.58-1.03)	0.98 (0.80-1.19)
Severe vs normal	1.19 (0.86-1.65)	1.23 (0.87-1.73)	0.92 (0.74-1.14)	0.75 (0.55-1.02)	1.06 (0.85-1.31)
ESRD vs normal	1.02 (0.74-1.40)	1.05 (0.75-1.46)	N/A	N/A	NA

Data are expressed as ratio (90 % confidence interval). Pair-wise comparisons are shown for subjects with impaired renal function and those with normal renal function after a single dose of IDeg. Data in ESRD groups are based on pharmacokinetic profiles (excluding a haemodialysis session).[14] For the data from the hepatic impairment study, the endpoints were log-transformed and analysed using an analysis of variance model with hepatic function group, sex and age at baseline as fixed effects.[15] Abbreviation: $AUC_{0-\infty}$: area under the insulin degludec serum concentration–time curve from zero to infinity, $AUC_{0-120\ hr}$: area under the 120-hr serum insulin degludec concentration–time curve, C_{max}: maximum serum insulin degludec concentration, ESRD: end-stage renal disease, IDeg: insulin degludec, CL/F: apparent insulin degludec clearance, N/A: not available

5. EFFICACY

5.1. Insulin Degludec (IDeg)

The efficacy of IDeg was investigated in a large clinical trial programme (namely BEGIN studies) which involve >11,000 patients with T1DM and T2DM. IGla 100U was generally used as a comparator and overall randomization of patients ratio was between 2:1 and 3:1 in phase 3 studies. The efficacy was assessed by mean HbA1C reduction and mean change in fasting plasma glucose (FPG) at the end of trial. With the exception of IDeg compared with Sitagliptin, all the trials were non-inferiority trials and efficacy was confirmed if the upper bound of the two sided 95% CI for the estimated treatment difference (ETD) (IDeg minus comparator) was below or equal to the non-inferiority limit of 0.4%.[17] The duration of studies is 26 to 52 weeks.

Studies of IDeg in T2DM showed that with titration of glycemic targets, IDeg has similar efficacy of HbA1C reduction with observed mean change in HbA1C range from approximately 0.93 to 1.52 % with IDeg and 1.09 to 1.35 % with comparators (sitagliptin, IGla, IDet).[18-27] There was a trend towards lower FPG level with IDeg compared with IGla in five trials namely BEGIN Once Long (2012), BEGIN basal bolus Type 2 (2012), BEGIN Low Volume (2013), Philis-TA et al. (2013) and Pan C et al. (2016). The data are shown in **Table 3.**

Likewise, clinical studies in T1DM showed that IDeg is non-inferior to IGla 100U in terms of mean HbA1C reduction concentration. IDeg was compared with IDet and IGla in BEGIN basal bolus type 1 study (2012), BEGIN Flex T1 (2013) and Davies M et al. (2016) with mealtime insulin as part of basal bolus regimen. The observed mean HbA1C reduction was ranged from 0.4 to 0.5 % for IDeg and 0.39 to 0.58 % for comparators. FPG decreased substantially in both IDeg and IGla in a basal bolus regimen. With IDeg, FPG reduction was evident at the first post baseline assessment (12 weeks) and the lower FPG was maintained until the end of the trial. The observed mean FPG reduction range from 22.9 to 46.8 mg/dl with IDeg and from 11.3 to 25.1 mg/dl with comparator.[28-30] The data are summarized in **Table 3**.

In summary, for both T1DM and T2DM, the mean HbA1C reduction of IDeg was not significantly different with comparators. The mean HbA1C reduction was ranged from 0.4 to 1.52 % for IDeg and 0.39 to 1.35 % for comparators. In insulin naïve patients, mean HbA1C reduction was ranged from 0.93 to 1.52 %[18-26] whereas in insulin treated patients, mean HbA1C reduction was ranged from 0.4 to 1.10 %.[27-31] The data are summarized in **Table 3**.

5.2. Insulin Degludec/Insulin Aspart (IDegAsp)

IDeg molecular structure can be coformulated with insulin aspart (IAsp) in the presence of Zinc and phenol without the risk of hybrid hexamer formation. IDegAsp is available in market as Ryzodec® 70/30, 100U/ml, 3ml which contain 70% of basal analog IDeg and 30% short-acting analog IAsp.[32]

The studies which assess the efficacy of IDegAsp compared with Biphasic Aspart (BiAsp), IGla and IDet are 26 weeks, phase 3 studies which were conducted in insulin treated patients. For T2DM, the efficacy of IDegAsp was superior to IGla alone with mean HbA1C reduction of 1.4% vs 1.2% but inferior to BiAsp 30.[33-35] For T1DM, the efficacy of IDegAsp was not significantly different with standard basal-bolus regimen (IDet + Asp) with mean HbA1C reduction of 0.75% vs 0.7%.[45] The efficacy data are expressed in **Table 4**.

5.3. Insulin degludec/Liraglutide (IDegLira)

IDegLira is a fixed–ratio combination of IDeg and GLP-1 receptor agonist (liraglutide). The efficacy of once daily, subcutaneous IDegLira as add-on therapy to oral antidiabetic drugs in adult patients (age ≥18 years) with T2DM was investigated in five 26- weeks, randomized multinational, treat-to-target, phase 3 trials (DUAL-I, II, III, IV and V), as well as a 26-week extension of the DUAL-I trial.

In T2DM insulin naïve patients, add on therapy of IDegLira provides better glycemic control than add-on insulin degludec, liraglutide or

Table 3. Efficacy of IDeg on the HbA1C and FPG reduction

Study	Populati-on, Duration	Arm	Baseline HbA1C % ± SD	Mean HbA1C reduction % ± SD	ETD (%) for HbA1C reduction CI 95%	Baseline FPG mmol/L ± SD	Mean FPG reduction mmol/L ±SD	ETD mmol/L for FPG, CI 95%
BEGIN Once Long[18] 2012	T2DM Insulin naïve, 1year	IDeg100U N=773	8.2(0.8)	-1.06 (1.01)	0.09 (-0.04,0.22)	9.6(2.6)	-3.8 (3.04)	-0.43 (-0.74, -0.13) P= 0.005
		IGla 100U N=257	8.2(0.8)	-1.19 (0.97)	P = NA	9.7(2.6)	-3.3(2.87)	
BEGIN Once Long Extension[19] 2013	T2DM Insulin naïve, 2 yrs	IDeg100U N=551	8.1(0.8)	-1.1	0.07 (-0.07,0.22)	9.7(2.4)	-4.17	-0.36 (-0.67, -0.05) P=0.021
		IGla 100U N=174	8.2(0.8)	-1.3	P=0.339	9.5(2.4)	-3.56	
BEGIN Once Asia[20] 2013	T2DM Insulin naïve, 26wk	IDeg100U N=289	8.4(0.8)	-1.24	0.11 (-0.03,0.24)	8.4(2.1)	-2.88	-0.09 (-0.41, 0.23) P=0.59
		IGla 100U N=146	8.5(0.8)	-1.35	P=NA	8.6(1.9)	-2.97	
BEGIN Low Volume[21] 2013	T2DM Insulin Naïve, 26wks	IDeg200U N=228	8.3(1)	Both reduce	0.04 (-0.11,0.19)	9.2(2.9)	-3.7	-0.42 (-0.78, -0.06) P=NA
		IGla100U N=229	8.2(0.9)	-1.3 (1.01)	P=NA	9.7(2.6)	-3.4	
BEGIN FLEX T2 [5] 2012	T2DM Insulin naïve or Insulin treated, 26wks	$IDeg_{flex}$ 100U OD N=203	8.5(1)	-1.28	$IDeg_{flex}$ OD vs IGla OD: 0.04 (-0.12,0.20) P=NA	9(2.6)	NA	$IDeg_{Flex}$ OD vs IDeg OD: -0.05 (-0.45, 0.35) P = NS $IDeg_{Flex}$ OD vs IGla OD: -0.42 (-0.82, -0.02) P=0.04
		IDeg 100U OD N=204	8.4(0.9)	-1.07		8.8(2.8)	NA	
		IGla 100U OD N=203	8.4(0.9)	-1.26		9(2.8)	NA	
BEGIN Once Simple [22] 2013	T2DM Insulin naïve, 26wks	$IDeg_{Simple}$ N=111	8.1(0.9)	-1.09	-0.16 (-0.39,0.07)	9.3(2.6)	-3.27	-0.57 (-1.3,0.17) P=NA
		$IDeg_{Stepwise}$ N=111	8.2(0.9)	-0.93	P=NA	9.7(2.6)	-2.68	
Philis-TA et al.[23] 2013	T2DM Insulin naïve, 26wks	IDeg100U N=225	8.8(1)	-1.52	-0.43 (-0.61, -0.24) P=NA	9.4(2.6)	-3.41	-2.17 (-2.59, -1.74) P=NA
		Sitagliptin N=222	9(1)	-1.09		9.9(3.1)	-1.24	

Table 3. Efficacy of IDeg on the HbA1C and FPG reduction

Study	Populati-on, Duration	Arm	Baseline HbA1C % ± SD	Mean HbA1C reduction % ± SD	ETD (%) for HbA1C reduction CI 95%	Baseline FPG mmol/L ± SD	Mean FPG reduction mmol/L ±SD	ETD mmol/L for FPG, CI 95%
Kadowaki et al.[24] 2016	T2DM Japanese Insulin treated, 26wks	$IDeg_{flex}$ 100U N=229	7.8(0.6)	-0.54 (0.76)	0.08 (-0.05, 0.22)	7.4(2)	-1.6	-0.18 (-0.48, 0.12)
		$IDeg_{fix}$ 100U N=229	7.8(0.6)	-0.62 (0.75)	P=NA	7.4(2)	-1.4	P=NA
Pan C et al.[25] 2016	T2DM Insulin naïve, 26wks	IDeg OD 100U N=555	8.3(0.9)	-1.3 (1.1)	-0.05 (-0.18, 0.08)	9.4(2.4)	-3.35 (2.91)	-0.26 (-0.53, 0.02)
		IGla OD 100U N=278	8.3(0.8)	-1.2 (1)	P=NA	9.4(2.5)	-3.14 (2.71)	P=NA
Zinman B et al. [26] 2013 BEGIN Easy (AM) BEGIN Easy (PM)	T2DM Insulin naïve, 26wks				$IDeg_{3TWAM}$ Vs IGla			$IDeg_{3TWAM}$ vs IGla
		$IDeg_{3TWAM}$ N=229	8.2(0.8)	-0.93	OD: 0.34 (0.18,0.51)	9.3(2.4)	NA	OD: 0.72 (0.29,1.14)
		IGla OD N=230	8.3(0.9)	-1.28	P=NA	9.6(2.4)	NA	P=0.001
		$IDeg_{3TWPM}$ N=233	8.3(0.8)	-1.09	$IDeg_{3TWPM}$ vs IGla	9.9(2.2)	NA	$IDeg_{3TWPM}$ vs IGla
		IGla OD N=234	8.3(0.8)	-1.35	OD: 0.26 (0.11,0.41) P=NA	9.9(2.4)	NA	OD: 0.5 (0.1,0.9) P=0.0144
BEGIN Compare[27] 2014	T2DM Insulin treated 22wks	IDeg 200U N=186	8.1(0.9)	-0.8	-0.11 (-0.28, 0.05) P=NA	8.3(3)	-2.3	0.11 (-0.34, 0.55) P=NA
		IDeg 100U N=187	8.2(0.9)	-0.7		8.3(3.4)	-2.4	
BEGIN BB T1[28] 2012	T1DM Insulin treated 52 wks	IDeg100U N=472	7.7(0.9)	-0.4 (SE0.03)	-0.01 (-0.14, 0.11) P< 0.0001	9.1(4)	-1.3 (SE 0.2)	-0.33 (-1.03, 0.36) P=0.35
		IGla 100U N=157	7.7(1)	-0.39 (SE0.07)		9.7(4.4)	-1.4 (SE 0.4)	
Davies M et al.[29] 2016	T1DM Insulin treated 1year	IDeg OD N=302	8(1)	-0.5	-0.01 (-0.17,0.14) P=NA	9.9(4)	-2.2	-1.11 (-1.83, -0.4) P<0.05
		IDet N=153	8(0.9)	-0.5		9.5(4)	-0.8	

Table 3. Efficacy of IDeg on the HbA1C and FPG reduction

Study	Populati-on, Duration	Arm	Baseline HbA1C % ± SD	Mean HbA1C reduction % ± SD	ETD (%) for HbA1C reduction CI 95%	Baseline FPG mmol/L ± SD	Mean FPG reduction mmol/L ±SD	ETD mmol/L for FPG, CI 95%
BEGIN FLEX T1[30] 2013	T1DM Insulin treated 26 wks	$IDeg_{forced/flex}$ + IAsp N=164	7.7(1)	-0.4 (0.59)	$IDeg_{forced/flex}$ vs IDeg: 0.01 (-0.13, 0.14) P=NA	9.6(4.1)	-1.28 (5.03)	$IDeg_{forced/flex}$ vs IDeg: 0.95 (0.15,1.75) P=0.021
		IDeg+Asp N=165	7.7(0.9)	-0.41 (0.71)		10.0(4)	-2.54 (5.11)	
		IGla+Asp N=164	7.7(0.9)	-0.58 (0.72)	$IDeg_{forced/flex}$ vs IGla: 0.17 (0.04,0.3)	9.7(4.2)	-1.33 (5.2)	$IDeg_{forced/flex}$ vs IGla: -0.05 (-0.85,0.76)
BEGIN BBT2[31] 2012	T2DM Insulin treated, 52wks	IDeg100U N=744	8.3(0.8)	-1.10	0.08 (-0.05,0.21) P=NA	9.2(3)	-2.3	-0.29 (-0.65, 0.06) P=0.1075
		IGla 100U N=248	8.4(0.9)	-1.18		9.2(3.2)	-2	

Note: ETD (mmol/L) for FPG in favor of IGla, mean ±SD; Abbreviations: CI: confidence interval; ETD: estimated treatment difference; FPG: fasting plasma glucose; IGla: Insulin Glargine , IDeg: Insulin degludec, IDegfix: Insulin degludec with fixed dose scheme; IDegflex: Insulin degludec with flexible dose scheme; IDegForced-Flex: Insulin degludec with forced-flexible scheme; IDet: detemir insulin; NA, not available; SD: standard deviation; NS: not significant; BBT1: Basal Bolus Type 1; BB T2: Basal Bolus Type 2, IDegSimple: IDeg simple algorithm with dose adjustment based on one pre-breakfast self-monitoring blood glucose measurement(SMBG), IDegStepwise: IDeg stepwise algorithm with dose adjustment based on three consecutive pre-breakfast SMBG values, IDeg 3TWAM=insulin degludec administered three times a week between waking up and first meal of day, IDeg 3TWPM=insulin degludec administered three times a week with the main evening meal, Sitagliptin: Sitagliptin 100mg OD, SD: Standard Deviation, SE: Standard Error

placebo or unchanged GLP-1 receptor agonists (ie liraglutide or exenatide). The HbA1C reduction range from 1.04 to 1.9 % in IDegLira and 0.16 to 1.4 % in comparators. For T2DM insulin experienced patients, IDegLira is superior to add-on insulin degludec or ongoing insulin glargine with HbA1C reduction range from 0.74 to 1.9 % in IDegLira and 0.39 to 1.13 % in comparators.[36-43] The data are summarized in **Table 4.**

6. SAFETY

6.1. Hypoglycemia

6.1.1. Insulin Degludec (IDeg)

The results of BEGIN program related to hypoglycemia are expressed in **Table 5**. On criterion of overall confirmed hypoglycemia rate in T2DM, BEGIN Once Long (2012), BEGIN Once Asia (2013) and BEGIN basal bolus type 2 (2012) showed similar (but not statistically significant) reduction of overall hypoglycemia (episode/patients/year) with IDeg compared with IGla 100U.

Pooled patient level data meta-analysis showed that in T2DM population, a significantly lower rate of overall confirmed and nocturnal confirmed hypoglycemic episodes were reported with IDeg compared with IGla 100U. The supporting data were rate ratio (RR) 0.83 (95% CI 0.74-0.94) for overall confirmed hypoglycemia and RR 0.68 (95% CI 0.57-0.82) for nocturnal confirmed hypoglycemia. For Type 1 DM, although there is no significant difference between IDeg

and IGla 100U in overall hypoglycemic episode [RR 1.10 (95% CI 0.96-1.26)], a lower rate of nocturnal hypoglycemia was seen in IDeg group compared with IGla 100U group [RR 0.83 (95% CI 0.69-1)] for entire treatment period.[44]

In summary, for both T2DM and T1DM, a lower rate of nocturnal hypoglycemia was found in IDeg compared with IGla 100U.[44]

6.1.2. Insulin Degludec/Insulin Aspart (IDegAsp)

When compared IDegAsp with IDet, both in combination with mealtime insulin aspart (IAsp), IDegAsp has a benefit of 37% reduction in nocturnal hypoglycemia compared with IDet. The administration of IDegAsp with a single meal with additional bolus rapid-acting insulin at remaining meal time can simplify the treatment regimen in T1DM by reducing the number of daily injections (3 for IDegAsp and 4-5 for IDet) and a lower insulin dose.[45]

Overall, for both T1DM and T2DM, the estimated rate of overall hypoglycemia and overall nocturnal hypoglycemia was lower in IDegAsp compared with comparators (IGla, BiAsp and IDet).[33,34,35,45] The safety data of IDegAsp are summarized in **Table 6**.

Table 4. Efficacy of IDegAsp and IDegLira on HbA1C and FPG reduction

Study	Population Duration	Arm	Baseline HbA1C % ± SD	Mean HbA1C reduction % ± SD	ETD (%) for HbA1C reduction CI 95%	Baseline FPG mmol/L ± SD	Mean FPG reduction mmol/L ±SD	ETD mmol/L for FPG, CI 95%
Fulcher GR et al.[33] 2014	T2DM Insulin treated, ±OADs, 26wk	IDegAsp N=224	8.3(0.8)	-1.2	-0.03 (-0.18, 0.13) P=NA	8.9(2.9)	-3.1	-1.14 (-1.53, -0.76) P<0.001
		BiAsp 30 N=222	8.4(0.9)	-1.3		8.6(2.6)	-1.8	
Onishi Y et al.[34] 2013	T2DM Japanese Insulin naïve, discontinue SU, DPP4i, glinides, 26wks	IDegAsp N=147	8.3(0.8)	-1.4 (0.9)	-0.28 (-0.46, -0.1) P < 0.01	9(1.6)	-3.3 (2.4)	0.15 (-0.29, 0.6) P=NS
		IGla N=149	8.5(0.8)	-1.2(1)		9.1(1.9)	-3.5 (2.4)	
Kaneko S et al. BOOST Asia [35] 2015	T2DM Insulin treated, +MET, 26wks	IDegAsp N=280	8.4(0.8)	-1.38	0.05 (-0.1, 0.20) P=NA	7.9(2.5)	-2.5	-1.06 (-1.43, -0.7) P<0.001
		BiAsp 30 N=142	8.4(0.9)	-1.42		7.9(2.5)	-1.4	
Hirsch IB et al.[45] 2012	T1DM Insulin treated, 26wks	IDegAsp+ IAsp N=366	8.3(0.8)	-0.75	-0.05 (-0.18, 0.08) P=NA	10.3(4.7)	-1.6	0.23 (-0.46, 0.91) P=NS
		IDet+IAsp N=182	8.3(0.7)	-0.70		11.0(4.8)	-2.4	

Table 4. Efficacy of IDegAsp and IDegLira on HbA1C and FPG reduction

Study	Population Duration	Arm	Baseline HbA1C % ± SD	Mean HbA1C reduction % ± SD	ETD (%) for HbA1C reduction CI 95%	Baseline FPG mmol/L ± SD	Mean FPG reduction mmol/L ±SD	ETD mmol/L for FPG, CI 95%
B E G I N ADD TO GLP-1[36] 2016	T2DM Insulin naïve +MET± SU, DPP4i, exenatide, 26wks	IDeg +Lira N=174	7.6(0.6)	-1.04 (0.89)	-0.92 (-1.1, -0.75)	8.7(2.1)	NA	-2.55 (-3.07, -2.02)
		Lira+Pbo N=172	7.6(0.6)	-0.16 (0.86)	P <0.0001	9.1(2.2)	NA	P <0.0001
BEGIN VICTOZA ADD-ON[37] 2014	T2DM IDeg+MET treated 26wks	IDeg+Lira N=88	7.7(0.6)	-0.74	-0.32 (-0.53,-0.12) P=0.0024	6.4(2.4)	-0.14	0.06 (-0.65, 0.77) P=NA
		IDeg+Asp N=89	7.7(0.8)	-0.39		6.1(1.7)	-0.04	
DUAL I[38] 2014	T2DM, Insulin naïve + MET, PIO, 26wks	IDegLira N=833	8.3(0.9)	-1.9 (1.1)	IDegLira vs IDeg: - 0.47 (-0.58,-0.36) P<0.0001 IDegLira vs Lira: -0.64 (-0.75,0.53) P<0.0001	9.2(2.4)	-3.6	IDegLira vs IDeg: -0.17 (-0.41, 0.07) P=0.16 IDegLira vs Lira:-1.76 (-2, -1.53) P < 0.0001
		IDeg N=413	8.3(1)	-1.4 (1.0)		9.4(2.7)	-3.6	
		Lira N=414	8.3(0.9)	-1.3 (1.1)		9(2.6)	-1.8	
DUAL I extensio-n[39] 2015	T2DM Insulin naïve + MET, PIO, 52wks	IDegLira N=833	8.3(0.9)	-1.84	IDegLira vs IDeg: -0.46 (-0.57,-0.34) P<0.0001 IDeLira vs Lira: -0.65 (-0.76,-0.53) P < 0.0001	9.2(2.4)	-3.45	IDegLira vs IDeg: -0.20 (-0.45, 0.05) P=0.11 IDegLira vs Lira: -1.67 (-1.92, -0.42) P<0.0001
		IDeg N=413	8.3(1)	-1.4		9.4(2.7)	-3.4	
		Lira N=414	8.3(0.9)	-1.21		9.0(2.6)	-1.67	
DUAL II[40] 2014	T2DM Insulin treated +MET± SU, 26wks	IDegLira N=199	8.7(0.7)	-1.9	-1.1 (-1.3,-0.8) P < 0.0001	9.7(2.9)	-3.5 (2.9)	-0.73 (-1.19, -0.27) P= .0019
		IDeg N=199	8.8(0.7)	-0.9		9.6(3.1)	-2.6 (3.3)	

Table 4. Efficacy of IDegAsp and IDegLira on HbA1C and FPG reduction

Study	Population Duration	Arm	Baseline HbA1C % ± SD	Mean HbA1C reduction % ± SD	ETD (%) for HbA1C reduction CI 95%	Baseline FPG mmol/L ± SD	Mean FPG reduction mmol/L ±SD	ETD mmol/L for FPG, CI 95%
DUAL III[41] 2015	T2DM Insulin naïve Uncontrol GLP-1RA + MET ±PIO±SU, 26wks	IDegLira N=292	7.8	-1.3(0.8)	-0.94 (-1.11,-0.78) P<0.001	NA	-2.98 (2.28)	-2.64 (-3.03, -2.25) P<0.001
		GLP-1RA N=146	7.4	-0.3(0.9)		NA	-0.6 (2.74)	
DUAL IV[42] 2015	T2DM Insulin naïve, SU±MET 26wks	IDegLira N=435	7.9	-1.5	-1.02 P<0.001	9.1	-2.6	-2.3 P<0.001
		Pbo N=NA	7.9	-0.5		9.1	-0.3	
DUAL V [43] 2016	T2DM Insulin treated +MET 26wks	IDegLira N=278	8.4(0.9)	-1.81 (1.08)	-0.59 (-0.74, -0.45) P=NA	160.5 (47.5) 159.8 (52) mg/dl	-51 -49.6 mg/dl	-0.15 (-6.28, 5.99) P=0.96
		IGla N=279	8.2(0.9)	-1.13 (0.98)				

Abbreviation: T2DM: Type 2 diabetes mellitus, T1DM: Type 1 diabetes mellitus, IDeg: Insulin degludec 100U, IDegAsp: Insulin degludec/Insulin aspart 70/30, IDegLira: Insulin degludec 100U/ml + Liraglutide 3.6mg/ml, IGla: Insulin glargine 100U, IDet: Insulin Determir, Pbo: Placebo, BiAsp: Biphasic Aspart 70/30, GLP-1RA: Glucagon like peptide 1 receptor agonist, OADs: Oral antidiabetic drugs, MET:Metformin, SU:Sulphonylurea, PIO: Pioglitazone, DPP-4i: DPP-4 inhibitor, NA: Not available

Table 5. Safety of Insulin Degludec on overall hypoglycemia events and nocturnal hypoglycemia

Study	Populatio-n, Duration	Arm	Overall confirmed Hypoglycemia (PYE)	Estimated rate ratio of overall hypoglycemia (95% CI)	Overall nocturnal Hypoglycemia (PYE)	Estimated rate ratio of nocturnal hypoglycemia (95% CI)
BEGIN Once Long[18] 2012	T2DM Insulin naïve, 1year	IDeg 100U N=773	1.52	0.82 (0.64-1.04) P=0.106	0.25	0.64 (0.42-0.98) P=0.038
		IGla 100U N=257	1.85		0.39	
BEGIN Once Long Extension[19] 2013	T2DM Insulin naive 2 years	IDeg 100U N=551	1.72	0.84 (0.68-1.04) P=0.115	0.27	0.57 (0.40-0.81) P=0.002
		IGla 100U N=174	2.05		0.46	

Table 5. Safety of Insulin Degludec on overall hypoglycemia events and nocturnal hypoglycemia

Study	Populatio-n, Duration	Arm	Overall confirmed Hypoglycemia (PYE)	Estimated rate ratio of overall hypoglycemia (95% CI)	Overall nocturnal Hypoglycemia (PYE)	Estimated rate ratio of nocturnal hypoglycemia (95% CI)
BEGIN Once Asia[20] 2013	T2DM Insulin naïve 26wks	IDeg 100U N=289 IGla 100U N=146	3.0 3.7	0.82 (0.60-1.11) P=0.20	0.8 1.2	0.62 (0.38-1.04) P=0.07
BEGIN FLEX T2 [5] 2012	T2DM Insulin naïve or Insulin treated 26wks	$IDeg_{flex}$ OD N=203 IDeg OD N=204 IGla OD N=203	3.6 3.6 3.5	$IDeg_{flex}$/IDeg: 1.10 (0.79-1.52) P=NS $IDeg_{flex}$/IGla: 1.03 (0.75-1.40) P=NS	0.6 0.6 0.8	$IDeg_{flex}$/ IDeg: 1.18 (0.66-2.12) P=NS $IDeg_{flex}$/IGla: 0.77 (0.44-1.35) P=NS
BEGIN Low Volume [21] 2013	T2DM Insulin naïve 26wks	IDeg 200U N=228 IGla 100U N=229	1.22 1.42	0.86 (0.58-1.28) P=0.46	0.18 0.28	0.64 (0.30-1.37) P=0.25
BEGIN Once Simple [22] 2013	T2DM Insulin naïve 26wks	$IDeg_{Simple}$ N=111 $IDeg_{Stepwise}$ N=111	1.60 1.17 P=0.4273	NA NA	0.21 0.1 P=0.2047	NA
Philis-TA et al.[23] 2013	T2DM Insulin naïve 26wks	IDeg N=225 Sitagliptin N=222	3.07 1.26	3.81 (2.4-6.05) P<0.0001	0.52 0.3	1.93 (0.9-4.1) P=0.09
Kadowaki et al.[24] 2016	T2DM Insulin treated, 26wks	$IDeg_{flex}$100U N=229 $IDeg_{fix}$100U N=229	4.25 3.27	1.33 (0.95-1.86) P=NA	0.69 0.51	1.25 (0.71-2.20) P=NA
Pan C et al. [25] 2016	T2DM Insulin naïve 26wks	IDeg OD 100U N=555 IGla OD 100U N=278	0.85 0.97	0.80 (0.59-1.10) P=NA	0.22 0.24	0.77 (0.43-1.37) P=NA

Table 5. Safety of Insulin Degludec on overall hypoglycemia events and nocturnal hypoglycemia

Study	Populatio-n, Duration	Arm	Overall confirmed Hypoglycemia (PYE)	Estimated rate ratio of overall hypoglycemia (95% CI)	Overall nocturnal Hypoglycemia (PYE)	Estimated rate ratio of nocturnal hypoglycemia (95% CI)
Zinman B et al.[26] 2013 BEGIN Easy (AM)	T2DM Insulin naïve 26wks	$IDeg_{3TW}$ N=229	1.3	1.04 (0.69-1.55) P = 0.8583	0.4	2.12 (1.08-4.16) P = 0.0291
		IGla OD N=230	1.2		0.2	
BEGIN Easy (PM)		$IDeg_{3TW}$ N=233	1.6	1.58 (1.03-2.43) P = 0.0365	0.2	0.60 (0.21-1.69) P = 0.3357
		IGla OD N=234	1.0		0.2	
BEGIN Compare[27] 2014	T2DM Insulin treated 22wks	IDeg 200U N=186	5.17	0.96 (0.67-1.36) P=NA	1.27	0.93 (0.56-1.55) P=NA
		IDeg 100U N=187	5.66		1.7	
BEGIN BB T1[28] 2012	T1DM Insulin treated, 52 wks	IDeg N=472	42.54	1.07 (0.89-1.28) P=0.48	4.41	0.75 (0.59-0.96) P=0.021
		IGla N=157	40.18		5.86	
Davies M et al.[29] 2016	T1DM Insulin treated, 1yr	IDeg OD N=302	37.78	0.95 (0.78-1.17) P=NA	3.38	0.67 (0.51-0.88) P < 0.05
		IDet N=153	39.26		4.81	
BEGIN FLEX T1[30] 2013	T1DM Insulin Treated 26 wks	$IDeg_{forced/flex}$ + IAsp N=164	82.4	$IDeg_{forced/flex}$ vs IGla: 1.03 (0.85-1.26)	6.2	$IDeg_{forced/flex}$ vs IGla: 0.6 (0.44-0.82)
		IDeg+Asp N=165	88.3	$IDeg_{forced/flex}$ vs IDeg: 0.92 (0.76-1.12)	9.6	$IDeg_{forced/flex}$ vs IDeg: 0.63 (0.46-0.86)
		IGla +Asp N=164	79.7		10	
BEGIN BB T2[31] 2012	T2DM Insulin treated 52wks	IDeg 100U N=744	11.09	0.82 (0.69-0.99) P=0.0359	1.39	0.75 (0.58-0.99) P=0.0399
		IGla 100U N=248	13.63		1.84	

Abbreviations: CI: confidence interval; IGla: Insulin Glargine 100U, IDeg: Insulin degludec 100U, IDegfix: Insulin degludec with fixed dose scheme; IDegflex: Insulin degludec with flexible dose scheme; IDegforced-flex, insulin degludec with forced-flexible scheme; IDet, Insulin detemir; NA, not available; NS: not significant; BBT1: Basal Bolus Type 1; BB T2: Basal Bolus Type 2, IDegSimple: IDeg simple algorithm with dose adjustment based on one pre-breakfast self-monitoring blood glucose measurement(SMBG), IDegStepwise: IDeg stepwise algorithm with dose adjustment based on three consecutive pre-breakfast SMBG values, Sitagliptin: Sitagliptin 100mg OD, PYE: Episode per patient per year

Table 6. Safety of IDegAsp and IDegLira in overall confirmed hypoglycemia and nocturnal hypoglycemia

Study	Population Duration	Arm	Overall Hypoglycemia (PYE)	Estimated ratio of overall hypoglycemia (95% CI)	Overall nocturnal Hypoglycemia (PYE)	Estimated ratio of nocturnal hypoglycemia (95% CI)
Fulcher GR et al.[33] 2014	T2DM Insulin treated ±OADs 26wks	IDegAsp N=224 BiAsp 30 N=222	9.72 13.96	0.68 (0.52-0.89) P=0.0049	0.74 2.53	0.27 (0.18-0.41) P<0.0001
Onishi Y etal.[34] 2013	T2DM Japanese Insulin naïve, Discontinue SU, DPP4i 26wk	IDegAsp N=147 IGla N=149	1.91 2.71	0.73 (0.5-1.08) P=NS	0.39 0.53	0.75 (0.34-1.64) P=NS
Kaneko S et al. BOOST Asia[35] 2015	T2DM Asian Insulin treated +MET 26wks	IDegAsp N=280 BiAsp 30 N=142	9.6 9.5	1.00 (0.76-1.32) P=NS	1.1 1.6	0.67 (0.43-1.06) P=NS
Hirsch IB et al.[45] 2012	T1DM Insulin treated 26wks	IDegAsp N=366 IDet N=182	39.17 44.34	0.91 (0.76-1.09) P=NS	3.71 5.72	0.63 (0.49-0.81) P<0.05
BEGIN ADD TO GLP-[36] 2016	T2DM Insulin naïve+ MET±SU, DPP4i,exenatide 26wks	IDeg+Lira N=174 IDeg+Pbo N=172	0.57 0.12	4.67 (2.07-10.56) P=0.0002	0.05 0.03	1.75 (0.24-12.71) P=NS
BEGIN VICTOZA ADD-ON[37] 2014	T2DM Insulin treated +MET ±DPP4i 26wks	IDeg+Lira N=88 IDeg+Asp N=89	1 8.15	0.13 (0.08-0.21) P<0.0001	0.17 1.11	0.14 (0.05-0.40) P=0.0002
DUAL I [38] 2014	T2DM Insulin naïve + MET, PIO 26wks	IDegLira N=825 IDeg N=412 Lira N=412	1.8 2.6 0.2	IDegLira vs Lira: 7.61 (5.17-11.21) P<0.0001 IDegLira vs IDeg: 0.68 (0.53-0.87) P=0.0023	0.2 0.3 0.03	NA

Table 6. Safety of IDegAsp and IDegLira in overall confirmed hypoglycemia and nocturnal hypoglycemia

Study	Population Duration	Arm	Overall Hypoglycemia (PYE)	Estimated ratio of overall hypoglycemia (95% CI)	Overall nocturnal Hypoglycemia (PYE)	Estimated ratio of nocturnal hypoglycemia (95% CI)
DUAL I extension[39] 2015	T2DM Insulin naïve + MET, PIO 52wks	IDegLira N=833	1.767	IDegLira vs IDeg: 0.63 (0.5-0.79) P<0.0001	0.223	IDegLira vs Lira: 11.99 (4.85-29.63) P<0.0001
		IDeg N=413	2.791		0.366	
		Lira N=414	0.191	IDegLira vs Lira: 8.52 (6.09-11.93) P<0.0001	0.018	IDegLira vs IDeg: 0.68 (0.44-1.06) P=0.09
DUAL II[40] 2014	T2DM Insulin treated +MET, ±SU 26wks	IDegLira N=199	1.5	0.66 (0.39-1.13)	0.22	0.81 (0.35-1.90)
		IDeg N=199	2.6	P=NS	0.32	P=NS
DUAL III[41] 2015	T2DM Insulin naïve Uncontrol GLP-1+ MET±PIO±SU 26wks	IDegLira N=292	2.82	25.4 (10.6-60.5)	NA	NA
		GLP-1 RA N=146	0.12	P<0.001	NA	
DUAL IV[42] 2015	T2DM Insulin naïve +SU ± MET 26wks	IDegLira +OADs N=435	3.5	3.74 P < 0.001	NA	NA
		Pbo +OAD N=NA	1.4		NA	NA
DUAL V[43] 2016	T2DM Insulin treated +MET 26wks	IDegLira N=278	2.23	0.43 (0.30-0.61)	0.22	0.17 (0.10-0.31)
		IGla $_{2TW}$ N=279	5.05	P < 0.001	1.23	P < 0.001

Abbreviation: T2DM: Type 2 diabetes mellitus, T1DM: Type 1 diabetes mellitus, IDeg: Insulin degludec 100U, IDegAsp: Insulin degludec/Insulin aspart 70/30, IDegLira: Insulin degludec 100U/ml + Liraglutide 3.6mg/ml, IGla: Insulin glargine 100U, IDet: Insulin Determir, Pbo: Placebo, BiAsp: Biphasic Aspart 70/30, GLP-1RA: Glucagon like peptide 1 receptor agonist, OADs: Oral antidiabetic drugs, MET:Metformin, SU:Sulphonylurea, PIO: Pioglitazone, DPP-4i: DPP-4 inhibitor, NA: Not available, PYE: Episode per patient per year

6.1.3. Insulin degludec and Liraglutide (IDegLira)

Five 26 weeks, phase 3 trials (DUAL-I, II, III, IV and V) were conducted in T2DM. Add on IDegLira was associated with lower incidence of overall hypoglycemia and nocturnal hypoglycemia than add on IDeg in both insulin naïve patients or insulin experienced patients who are ongoing IGla.[38-43] The data are summarized in **Table 6**.

6.2. Cardiovascular Safety

According to US FDA 2008 Cardiovascular Risk Guidance recommendation, a pre-specified meta-analysis of major adverse cardiovascular events (MACE) in phase 3 trials was carried out. In 16 clinical trials involving 8918 participants, 80 patients experienced treatment emergent MACE [53 patients in IDeg or Insulin degludec/Insulin Aspart (IDegAsp) group and 27 patients in comparator groups]. The incidence was observed in IDeg or IDegAsp group more than in comparator group [the incidence rate: 1.48 events per 100 patient-year of exposure (PYE) in patients treated with IDeg or IDegAsp vs 1.44 events per 100 PYE in patients treated with comparator basal insulins]. The DEVOTE (NCT 01959529) trial which is aiming to enroll 75,00 T2DM patients at high cardiovascular risk (age ≥ 50 years with a history of cardiovascular disease or diabetic nephropathy or age ≥ 60 years with cardiovascular risk factors) is expected to be available in 2018.[46]

7. Starting dose, dose adjustment and switching therapy

7.1. Insulin Degludec (IDeg)[47-48]

For T2DM insulin naïve patients, the recommended starting dose for IDeg is 10U once daily. In T1DM insulin naive patients, 0.2-0.4 U/kg of body weight can be calculated as initial total daily insulin dose and approximately 1/3 to 1/2 of total daily insulin dose should be administered as basal insulin for IDeg. The remainder is administered as short acting insulin and divided between each daily meal. The recommended day between dose increases is 3-4 days. The treat-to-target goal and insulin dose adjustment are based around an individual's pre-breakfast FPG (or self-monitoring plasma glucose) level. A calculated mean FPG from 2 preceding days can be compared to desired glycemic goals and insulin dose can be adjusted up or down by 2 units.

Switching to IDeg from other once daily basal insulin dose can usually be done on a 1:1 basis. Dose should be reduced by 20% if transitioning from a twice daily basal schedule and also depending upon individual glycemic response. When switching from a once-daily basal insulin, dose reduction can also be considered if the patients have low HbA1C. FPG should be closely monitored before, during and in the weeks following a switch to IDeg. When switching patients from other basal insulin to IDeg, it is necessary to manage a brief period between the loss of previous basal insulin's effect and attainment of steady state with IDeg. During this period, patients may observe higher blood glucose values of 3-5 days following the switch to IDeg and this should be discussed with patient prior to the switch. Dose and timing adjustment of concurrent short or rapid-acting insulin analogues or other glucose-lowering treatment may be required.

7.2. Insulin Degludec/Insulin Aspart (IDegAsp)[49]

IDegAsp can be administered once or twice daily with any main meal. The starting dose for T2DM, insulin naïve patients is 10U once daily. For insulin naïve T1DM patients, the starting dose of Ryzodeg® is approximately 1/3 to 1/2 of total daily insulin dose. The remainder of total daily insulin dose can be administered as a short- or rapid- acting insulin divided between each daily meal. In general, 0.2 to 0.4 units of insulin unit/kg of body weight can be used to calculate as initial total daily insulin dose.

For switching therapy, for both T1DM and T2DM, if the patient is transferred from only once or twice daily basal insulin, start Ryzodeg® 70/30 at the same unit dose and injection schedule. For patients switching from once-daily basal insulin to once daily, Ryzodeg® 70/30, monitor blood glucose after starting therapy due to the

rapid-acting insulin component. If switch from multiple daily regimen which include both basal and short- or rapid- acting insulin at meal time, start Ryzodeg® 70/30 once daily with main meal at same unit dose as basal insulin and continue short- or rapid- acting insulin at same dose for meals not covered by Ryzodeg® 70/30. If the patient use once or twice daily premix or self-mix insulin, start with the same unit dose and injection schedule and if the patients also using short or rapid-acting insulin at mealtimes, continue the short- or rapid- acting insulin at the same dose for meals not covered by Ryzodeg® 70/30.

7.3. Insulin degludec/Liraglutide (IDegLira)[50-51]

IDegLira is available in market as Xultophy® which contains IDeg 100 U/ml and liraglutide 3.6 mg/ml. One dose step contains 1U of IDeg and 0.036 mg of liraglutide. The maximum daily dose step is 50 dose steps (IDeg 50 U/liraglutide 1.8mg). For switching therapy, if the patient is not transferred from GLP-1 receptor agonist or basal insulin, the recommended starting dose is 10 U/0.36 mg once daily. If the patient is switched from GLP-1 receptor agonist or basal insulin, starting dose is 16 U/0.6 mg once daily and this starting dose should not be exceeded. When the patient is transferred from once weekly administered long-acting GLP-1 receptor agonist, initiate IDegLira at the same time as the next scheduled dose of long–acting GLP-1 receptor agonist. IDegLira can be added to existing oral anti-diabetic drugs (OADs) therapy; however, dose reduction for concomitantly administered sulphonylurea should be considered. IDegLira is not recommended in moderate or severe renal impairment, ESRD (end stage renal disease) and clinical experience in patients with hepatic impairment is currently too limited to recommend its use in these patients. Although pharmacokinetics of IDeg is not significantly affected by renal or hepatic impairment, liraglutide exposure was reduced in renal or hepatic impairment compared with healthy individuals.

Conclusion

All things considered, for both T1DM and T2DM, IDeg lead to tight glycemic control with reduction of mean HbA1C % and reduce rate of hypoglycemic events, particularly nocturnal hypoglycemia. In special population including renal and hepatic impairment, there is no specific dosage adjustment for these populations. However, glucose monitoring should be intensified and dosage should be titrated according to individual requirement in these populations. IDeg, with its unique pharmacodynamic properties, by offering basal insulin with flexible dosing schedule, it can increase the patient's adherence and improve glycemic outcome.

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