

CONSENSUS STATEMENT

Consensus on Initiation and Intensification of Premix Insulin in Type 2 Diabetes Management

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Abstract

Introduction: Premix insulin is the most commonly used insulin preparation in India. The first Indian premix guidelines were developed in 2009 and thereafter were updated in 2013. There is a need to revisit the Indian premix insulin guidelines, in view of emerging evidence and introduction of newer co-formulations.

Objective: The present consensus has been developed to evaluate available premix formulations, examine existing evidence related to premix formulations, and evolve consensus statement of recommendations on the topic.

Methods: A meeting of experts from across India was conducted at Chennai in July 2016. The expert committee evaluated each premix insulin regimen with reference to 1) Current recommendations by various guidelines, 2) Approved pack inserts and 3) Published scientific literature. The information was debated and discussed within the expert group committee, to arrive at seven consensus-based recommendations for initiation and intensification with premix insulin.

Results: Recommendations based on consensus on initiation and intensification of premix insulin in type 2 diabetes mellitus (T2DM) management were developed for the following situations. 1) Initiation of premix insulin co-formulation at diagnosis, 2) Initiation of once daily (OD) premix insulin/co-formulation, 3) Initiation of twice daily (BID) premix insulin/co-formulation 4) Intensification with BID and thrice daily (TID) premix insulin/co-formulation. Three recommendations pertained to the use of premix insulin in other forms of diabetes, or in specific situations: 5) Use of premix insulin in gestational diabetes mellitus 6) Use of premix insulin in type 1 Diabetes Mellitus (T1DM) 7) Premix insulin use during Ramadan

Conclusion: In the setting of high carbohydrate consumption in India, or in patients with predominant post prandial hyperglycemia, premix insulin/co-formulation can offer effective and convenient glycemic control. This paper will help healthcare practitioners initiate and intensify premix insulin effectively.

Introduction

Type 2 diabetes mellitus (T2DM) is associated with significant morbidity and mortality across the globe. It is reported that the developing countries will account for 70% of world diabetic population

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Table 1: Premix formulations

Insulin	Components	Onset of action (minutes)	Peak action (hour)	Duration of action (hour)	Timing of administration
Conventional Premix Formulations					
Biphasic Human Insulin 30/70	Regular human insulin (30%) 30 with NPH (70%)		2-8 hours	Up to 24	To be administered 30 minutes before meals
Analogue Premix Formulations					
Lispro 25/75	Lispro (25%) with protaminated lispro (75%)	15 - 30	1.3	12-24	Should be given within 15 minutes before a meal
Lispro 50/50	Lispro (50%) with protaminated lispro (50%)	15 - 30	0.8 - 4.8	Similar to that of Humulin 50/50	Should be given within 15 minutes before a meal
BIAsp 30/70	Aspart (30%) with protaminated aspart (70%)	10 - 20	1-4	Up to 24	Should generally be given immediately before a meal. When necessary, BIAsp 30 can be given soon after a meal
BIAsp 50/50	Aspart (50%) with protaminated aspart (50%)	10 - 20	1-4	14-24	Should generally be given immediately before a meal. When necessary, BIAsp 50 can be given soon after a meal
Insulin co-formulation					
IDegAsp 30/70	Aspart (30%) and degludec (70%) with preserved pharmacokinetic properties	10 - 20	1.2	>24	At meal time with the main meal(s)

by 2025.¹ India with 69.2 million patients living with T2DM, has the second largest diabetic population in the world. By 2040, the number of individuals living with T2DM is predicted to increase to 123.5 million. The rapidly changing lifestyle and growing urbanisation are some of the most important reasons for this rise in numbers. Diabetes accounts for 14.5% of global all-cause mortality among people with diabetes aged 20 to 79 years.²

Insulin is the oldest and best available treatment option for managing T2DM and maintaining good glycemic control. There are various types of insulin regimens, including basal insulin, basal-bolus, basal plus, premix insulins and prandial insulins. Premix insulin (also termed as biphasic insulin) formulations are the most widely prescribed insulins in India. The preference for premix insulin regimens over other insulins in India may be due to following reasons:

1. Indians with typical Asian Indian Phenotype i.e., higher waist circumference, higher total and visceral fat, hyperinsulinemia and likely insulin resistance respond better to premix insulins.

2. High intake of carbohydrates, resulting in higher glucose excursions after every meal.
3. Several observational studies have demonstrated high baseline post-prandial glucose (PPG) value in T2DM from India vs others.^{3,4}
4. There is often delay in initiation of insulin therapy, resulting in higher risk of failure of basal insulins.
5. Convenience and simplicity with premix insulins, allowing physicians to intensify the treatment with same insulin.

Premix insulin formulations provide a combination of rapid/short-acting and intermediate/long-acting insulins in a fixed ratio, addressing both fasting plasma glucose (FPG) and post-prandial glucose (PPG) in a single injection. It represents 6.8% of total global market and 72.7% of the Indian insulin market.⁵ Premix insulin formulations include both conventional and premix insulin analogues (Table 1). The premix insulins/co-formulation commercially available in India are 1) Biphasic Human Insulin (BHI) (30/70, 50/50): Mixtard® 30, Mixtard® 50, 2) Biphasic insulin aspart (BIAsp) (30/70, 50/50):

NovoMix™ 30, NovoMix™ 50, 3) Biphasic insulin lispro (25/75 and 50/50): Humalog Mix™ 25/75 and 50/50 4) Insulin Degludec/insulin aspart (IDegAsp) 70/30: Ryzodeg™ 70/30). IDegAsp is a soluble co-formulation of a basal insulin with an ultra-long duration of action and a short-acting insulin analogue, containing 70% insulin degludec (IDeg) and 30% insulin aspart (IAsp) in a single injection.

The global and national guidelines and widely accepted and evaluated consensus statements (evaluated by the expert group) included American Diabetes Association Standard of Care 2017 (hence forth referred to as ADA 2017),¹⁰ consensus statement by the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) on the comprehensive T2DM management algorithm-2016 Executive Summary (hence forth referred to as AACE/ACE Consensus statement 2016),¹¹ Global guideline for T2DM IDF (hence forth referred to as IDF 2012 and IDF 2015),^{12,13} Premix insulin initiation and continuation guidelines for management of diabetes in primary care by the Indian National Consensus Group (INCG) and/or Chapter 51 of

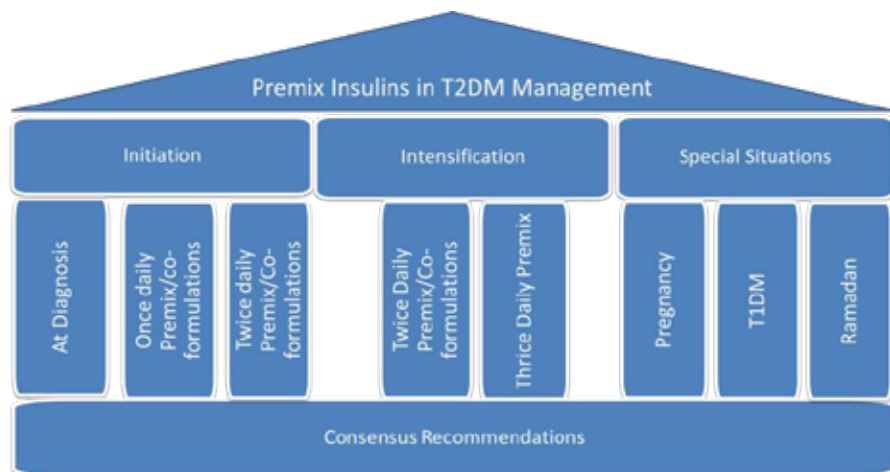


Fig. 1: Consensus meeting: framework for recommendations

INCG-National guidelines on initiation and intensification of insulin therapy with premixed insulin analogues (henceforth written as INCG guidelines),⁸ and Consensus evidence-based guidelines for insulin initiation, optimization and intensification in T2DM, published by Journal of Association of Physicians of India (hence forth referred to as Journal of the Association of Physicians of India [JAPI] 2014 consensus guidelines),¹⁴ Clinical Practice Guidelines, Canadian Diabetes Association, 2013 and 2016 (hence forth referred to as CDA 2013 and CDA 2016),^{15,16} Gestational Diabetes Mellitus by Diabetes in Pregnancy Study Group of India (hence forth referred to as DIPSI, 2006).⁹ Various guidelines recommend the use of premix insulin analogues over human premix insulins for lower risk of hypoglycemia, meal time flexibility and lesser weight gain.^{8,9} The first ever India specific guidelines on premix insulins was drafted and published in 2009. In 2013, India National Consensus Group (INCG) reevaluated the available evidences and published an update in 2013.⁸ While these guidelines are popular among the Indian physicians and often referred in many congresses, there is a growing demand for further update in view of a newer co-formulation being available. In view of this, 15 experts from

across the country met during Dr. V. Mohan's International Diabetes Update on 30th July, 2016 in Chennai and deliberated on the above subject. The objectives of this meeting were:

- To evaluate the available premix formulations and co-formulation
- Examine the existing evidence related to premix formulations and co-formulation
- Evolve a consensus statement of recommendations on the topic of premix and co-formulation insulins

Methods

The expert group identified seven different clinical situations for the use of premix insulins. These are presented in Figure 1. The group agreed that recommendations would be made on each of these seven situations. 1) Initiation of premix insulin at diagnosis, 2) Initiation of once daily (OD) premix insulin/co-formulation, 3) Initiation of twice daily (BID) premix insulin/co-formulation 4) Intensification with BID premix insulin/co-formulation and T1D premix insulin. Three recommendations pertained to the use of premix insulin in other forms of diabetes, or in specific situations: 5) Use of premix insulin in gestational diabetes mellitus 6) Use of premix insulin in type 1

Diabetes Mellitus (T1DM) 7) Premix insulin use during Ramadan. Each insulin regimen was presented and evaluated based on established guidelines from globally recognised professional bodies as well as those published within India, data from approved pack inserts/ prescribing information for each insulin type and published scientific literature. These evaluations were then factored into the national context based on their clinical practice and common therapeutic practices followed in India. The evaluations were debated and discussed within the expert group committee. The final consensus-based recommendations were proposed and collectively recorded for each insulin regimen in easily implementable steps, without any bias and in an unambiguous language.

Consensus 1: Initiation of Premix Insulin at Diagnosis

Biphasic human insulin 30/70 (BHI 30), biphasic insulin lispro 25 (LisproMix 25), biphasic insulin aspart 30 (BIAsp 30) and IDegAsp are the Premix insulins/ co-formulation currently approved for once/twice daily administration.

Current Place in Guidelines

ADA 2017, INCG 2013 and CDA 2013 guidelines recommend the use of insulin at the time of diagnosis of diabetes. INCG 2013 considered premix insulin as a reasonable option effective in all stages of the disease with the unique advantage of being simple, safe and easy to initiate. Insulin is preferred at diagnosis, if FPG > 250 mg/dL, PPG > 300 mg/dL and HbA1c > 9% or if patient has systemic infection or sepsis, acute myocardial infarction, unstable angina, diabetic ketoacidosis, pregnancy or peri-operative care. The guideline prefers premix insulin analogues over premix human insulins.

Published Scientific Literature

In a systematic review, short-term intensive insulin therapy was

Table 2: Comparison of once daily premix insulin and co-formulation versus once daily insulin glargine for initiation

Trial (Reference)	Objective	Duration of Treatment/Total Number of Enrolled Subjects	Trial arms	Results	
				Efficacy (HbA1c)	Safety (Hypoglycemia)
Open-label, randomized Treat-to-target trial on T2DM patients poorly controlled on Met+ insulin secretagogue for 6 months (Yang et al 2013)	To investigate non inferiority of OD BIAsp 30 to OD IGLar among Chinese and Japanese patients	24 weeks/521	<ul style="list-style-type: none"> • BIAsp 30 (261) • IGLar (260) 	<ul style="list-style-type: none"> • Mean HbA1c reduced by -0.78% with BIAsp 30 and -0.65% with IGLar [ETD: -0.12% (95% CI: -0.25, -0.02) confirming superiority of BIAsp 30 to IGLar] • Proportion of patients achieving HbA1c <7%: 29.1% and 30% with BIAsp 30 and IGLar respectively 	Hypoglycemia event rates (per subject-year): <ul style="list-style-type: none"> • Severe: 0 (BIAsp 30) and 0.01 (IGlar). Similar risk between groups • Nocturnal: 0.84 (BIAsp 30) and 0.55 (IGlar). Similar risk between groups • Documented symptomatic: 3.08 (BIAsp 30) and 2.4 (IGlar)
Multinational, open-labelled, randomized, parallel-group, treat-to-target trial in Insulin-naïve T2DM patients (Strojek et al 2009)	To assess efficacy and safety of BIAsp 30 and IGLar administered OD in subjects with type 2 diabetes	26 weeks/480	<ul style="list-style-type: none"> • BIAsp 30 (239) • IGLar (241) 	<ul style="list-style-type: none"> • Mean HbA1c reduced by -1.41% with BIAsp 30 and -1.25% with IGLar [ETD: -0.16% (95% CI: -0.3, 0.02) confirming non-inferiority of BIAsp 30 to IGLar] • Proportion of patients achieving HbA1c <7%: 44.9% and 45.7% with BIAsp 30 and IGLar respectively 	Hypoglycemia event rates (per subject-year): <ul style="list-style-type: none"> • Severe: 3 episodes in each group • Nocturnal: 1.1 (BIAsp 30) and 0.5 (IGlar); RR: 2.41 (p = 0.003) • Overall: 6.5 (BIAsp 30) and 4.8 (IGlar); RR: 1.41 (p = 0.034)
Multinational, open-labelled, randomized, parallel-group, treat-to-target trial in Insulin-naïve Asian T2DM patients (Kalra et al 2010)	To compare the glycemic efficacy of BIAsp 30 and IGLar as assessed by change from baseline HbA1c	26 weeks/ 155	<ul style="list-style-type: none"> • BIAsp 30 (76) • IGLar (79) 	<ul style="list-style-type: none"> • Mean HbA1c reduced by -1.22% with BIAsp 30 and -0.87% with IGLar [ETD: -0.36% (95% CI: -0.64; -0.07) confirming superiority of BIAsp 30 to IGLar] • Proportion of patients achieving HbA1c <7%: 40.5% and 36.4% with BIAsp 30 and IGLar respectively 	Hypoglycemia event rates (per subject-year): <ul style="list-style-type: none"> • Severe: 1 episode with BIAsp 30 and 3 with IGLar • Nocturnal: 0.9 (BIAsp 30) and 0.9 (IGlar); RR: 0.81 (p = 0.61) • Overall: 6.2 (BIAsp 30) and 4.5 (IGlar); RR: 1.54 (p = 0.15)
Open-label, treat-to-target trial on Insulin-naïve Japanese adults with T2DM (Onishi et al 2013)	To demonstrate the non-inferiority of IDegAsp to IGLar in terms of change from baseline HbA1c	26 weeks/296	<ul style="list-style-type: none"> • IDegAsp (147) • IGLar (149) 	<ul style="list-style-type: none"> • Mean HbA1c reduced by -1.4% with IDegAsp and -1.2% with IGLar [ETD: -0.28% (95% CI: -0.46, -0.10) confirming superiority of IDegAsp to IGLar] • Proportion of patients achieving HbA1c <7%: 59% and 40% with IDegAsp 30 and IGLar respectively 	Hypoglycemia event rates (per subject-year): <ul style="list-style-type: none"> • Severe: No events in either group • Nocturnal confirmed: 0.39 (IDegAsp) and 0.53 (IGlar); RR: 0.75 (p = NS) • Overall confirmed: 1.91 (IDegAsp) and 2.71 (IGlar); RR: 0.75 (p = 0.73)

BIAsp 30=Biphasic insulin aspart 30; OD=Once daily; BID=Twice daily; BHI=Biphasic human insulin; BMI=Body mass index; HbA1c=Glycosylated haemoglobin; IDegAsp=Insulin degludec/Insulin aspart; ETD: Estimated treatment difference; IGLar=Insulin Glargine; IGLu= Insulin glulisine; Mix25=25% soluble and 75% protaminated insulin lispro; OAD=Oral anti diabetic drugs; T2DM= Type 2 diabetes mellitus; NS=Not significant

reported to improve the underlying pathophysiology in early T2DM. This meta-analysis of 7 studies showed that intensive insulin therapy leads to an increase in Homeostasis Model Assessment of β -cell function (HOMA-B) and a decrease in Homeostasis model Assessment of Insulin Resistance (HOMA-IR) as compared to baseline data. The glycemic remission was assessed in 4 studies (n=559 participants) and the proportion of participants in drug-free remission was about 66.2%, 58.9%, 46.3% and 42.1% after 3, 6, 12 and 24 months of follow-up, respectively.¹⁷ Currently, there is no published literature on specific role of premix insulin/co-formulation and its impact on beta cell function or remission of diabetes.

Expert Group Recommendation 1: Premix Insulin Initiation at Diagnosis

- In newly diagnosed T2DM patients with symptomatic hyperglycemia and/or metabolic decompensation (glucotoxicity), short-term therapy with premix insulin is recommended.
- Premix insulin analogues are preferred over human premix insulins in view of the lower incidence of major and nocturnal hypoglycemia and flexibility of administration as seen in treatment naïve patients (dose 0.2 to 0.3 U/kg body weight in 2 divided doses).
- IDegAsp may be preferred over premix insulin analogues in view of the lower incidence of overall and nocturnal hypoglycemia and superior fasting plasma control as seen in treatment naïve patients (6U BID).

Consensus 2: Initiation of Once Daily Premix Insulins/Co-formulations

BHI 30/70, 50/50, Lispro Mix 25/75, 50/50, BIASP 30/70, 50/50 and IDegAsp, are the Premix insulins which are currently approved for once daily administration.

Current Place in Guidelines

IDF 2012 recommends initiation of premix insulin OD or BID when first or second line therapies fail to achieve glycemic target of HbA1c < 7%. Doses can be increased by 2 U every 3 days once or biweekly (IDF 2012). As per National Institute for Health and Care Excellence

guideline, OD premix insulin should be considered when HbA1c level is $\geq 9\%$.

INCG 2013 recommends premix insulin OD as an add-on therapy to metformin when HbA1c level is > 7.5% to $\leq 8.5\%$ (failure to reach HbA1c target < 7% after > 3 months of metformin monotherapy). If HbA1c > 7% and FPG > 110 mg/dL, then premix insulin is titrated to achieve FPG < 110 mg/dL. The guideline also recommends initiation with premix insulin therapy at a starting dose of 10 U either before breakfast, if pre-dinner glucose is high or before dinner, if the pre-breakfast glucose is high. The dose should be split when the starting dose is > 30 U.

CDA 2016 recommends initiation of premix insulin at 5-10 U OD or BID (pre-breakfast and/or pre-supper). The doses can be titrated by adding 1-2 U to pre-breakfast and/or pre-supper dose daily until target pre-breakfast and pre-supper blood glucose values are achieved (72-126 mg/dL).

JAPI 2014 recommends premix insulin/co-formulation OD in patients with HbA1c > 9% and high FPG and PPG.

Published Scientific Literature

Three open label randomized studies have shown that OD premix insulin is superior to OD basal insulin in terms of achieving target HbA1c (Table 2).

A systematic review of 28 randomized controlled trials (N=30588) evaluated the effectiveness of insulin analogues to reach the HA1c target of < 7% in T2DM patients. The results reported that higher proportion of patients treated with BIASp 30 achieved the glycemic target than the patients treated with basal insulin (46.5% versus 41.4%).¹⁸

In a 26-week, open-labelled, randomized, parallel group trial which included participants from India as well, the efficacy and safety of OD BIASp 30 was compared to IGLar, both in combination with

metformin and glimepiride in 480 insulin naïve T2DM patients. The results indicated a significantly higher HbA1c reduction with BIASp 30 than insulin glargine (IGlar) (-1.41% versus -1.25%).¹⁹ In a 24-week treat-to-target trial, OD BIASp 30 was compared to OD IGLar in Chinese and Japanese insulin-naïve T2DM patients, who were poorly controlled on Metformin and insulin secretagogues for 6 months. The estimated between-group difference in HbA1c change was -0.12% and BIASp 30 was noninferior to IGLar. However, BIASp 30 provided better coverage of glycemic control post-dinner compared to IGLar group.²⁰ However, a 24-week open-label randomized GALAPAGOS study reported a comparable proportion of insulin-naïve T2DM patients (inadequately controlled on OADs) achieving a HbA1c target < 7% at study end after treatment with OD or BID BIASp 30 and IGLar \pm insulin glulisine (IGlu) OD (55.7% versus 57.6%).²¹

In a phase 3, 26-week, open label, treat-to-target trial, Onishi et al evaluated the efficacy and safety of IDegAsp versus IGLar in Japanese T2DM patients who were inadequately controlled with oral anti-diabetic drugs (OADs). After 26 weeks, IDegAsp was associated with superior glycemic control (7% versus 7.3%) with numerically lower rates of overall confirmed (27%) and nocturnal confirmed hypoglycemia (25%) as compared to IGLar, with similar FPG levels and end of trial insulin doses.²²

Consensus 3: Initiation of Twice Daily Premix Insulins/Co-Formulations

BHI 30/70, 50/50, Lispro Mix 25/75, 50/50, BIASP 30/70, 50/50 and IDegAsp are currently recommended for twice daily administration.

Current Place in Guidelines

IDF 2012 suggests premix insulin BID, particularly for patients with elevated HbA1c and who were already on premix insulin OD.

Expert Group Recommendation 2: Once Daily Premix Insulins/Co-Formulations for Initiation

- It is recommended to initiate insulin early in the course of disease when non-insulin drugs prove inadequate in achieving the desired glycemic goals.
- In the setting of high carbohydrate consumption or in patients with predominant post prandial hyperglycemia, premix insulin analogues could be preferred over basal insulins for insulin initiation (10 U pre-breakfast or pre-dinner).
- In the setting of high carbohydrate consumption or in patients with predominant post prandial hyperglycemia, IDegAsp could be preferred over premix insulin analogues and basal insulins for insulin initiation for achieving recommended glucose targets (10 U pre-breakfast or pre-dinner).
- It is recommended to titrate the dose once/twice a week based on pre-meal value. It is recommended to modify the dose based on the lowest/mean value of the 3 most recent values if available. Frequency of monitoring may be reduced in the maintenance phase.

Recommendation on Titration:

Pre-breakfast/pre-dinner value*(mg/dL)	Pre-dinner/pre-breakfast dose change (Dose adjustment [units])
< 80	-2
80-130	0
131-160	+2
161-180	+4
> 180	+6

*Lowest/mean of the three recent self-measured blood glucose values

Note: For patients initiated on pre-breakfast dose, titrate according to pre-dinner values and vice versa

NICE T2DM guideline 2008 considers premix BID when HbA1c >9%.

INCG 2013 recommends premix insulin BID as an add-on therapy to Metformin when HbA1c > 8.5% (failure to reach HbA1c target < 7% after 3 months of metformin monotherapy).

JAPI 2014 recommends premix insulin BID to patients already receiving OD regimen, if FPG is persistently high and there is failure to reach target HbA1c.

Published Scientific Literature

Two clinical trials postulated

Expert Group Recommendation 3: Twice Daily Premix Insulins/Co-formulations for Initiation

- It is recommended to initiate twice daily premix analogues over once daily basal insulins to achieve recommended glucose targets.
- Twice daily IDegAsp is recommended over BIAsp 30 in view of lower risk of hypoglycemia and superior fasting glucose control.
- It is recommended to initiate premix insulins/co-formulations at a daily dose of 6 U BID pre-breakfast and pre-dinner in patients taking two large meals.
- It is recommended to titrate the dose once/twice a week based on pre meal value. It is recommended to modify the dose based on the lowest/mean value of the 3 most recent values if available.

Recommendation on Titration:

Pre-breakfast/pre-dinner value*(mg/dL)	Pre-dinner/pre-breakfast dose change Dose adjustment (units)
< 80	-2
80-130	0
131-160	+2
161-180	+4
> 180	+6

*Lowest/mean of the three recent self-measured blood glucose values

Note: For patients initiated on pre-breakfast dose, titrate according to pre-dinner values and vice versa.

that BID premix insulin is superior to OD basal insulin in achieving glycemic targets.^{7,23} A multicentre, open-label, parallel-group, treat-to-target trial in insulin naïve subjects with T2DM reported that BID BIAsp 30 was more effective in achieving HbA1c targets (< 7% [ADA goal]/ ≤ 6.5% [AACE and IDF goal]) than OD IGlax in subjects with HbA1c > 8.5%.⁷ Similar results were reported in another randomized controlled 60-week trial involving 582 patients with or without OAD comparing OD IGlax and BID BIAsp 30.²³ Another multinational, open-label, parallel-group, treat-to-target trial in insulin naïve T2DM patients reported the superiority of BID IDegAsp over BIAsp 30 in terms of FPG control, nocturnal and overall hypoglycaemia.²⁴ An open-label, randomized, single-dose, three-way crossover trial, reported that BIAsp 30 provided significantly better PPG control by

10% than Lispro Mix 25 (16.6 versus 18.9 mmol/L per hour; p<0.05) and by 17% when compared to BHI 30 (16.6 versus 20.1 mmol/L per hour; p<0.001)⁶ (Table 3).

In the 1-2-3 study, 41% of the T2DM participants achieved the glycemic target (HbA1c<7%) after taking OD BIAsp 30 over the period of 16 weeks. The proportion of patients achieving the glycemic target increased after taking BID BIAsp 30 (70%) and TID BIAsp 30 (77%).²⁵

Consensus 4: Intensification with Twice/Thrice Daily Premix Insulins/Co-Formulations

Current Place in Guidelines

Various guidelines recommend intensification of OD premix regimen to BID/TID premix regimen (ADA 2017, IDF 2012, NICE 2009²⁶, CDA 2013, JAPI, INCG).

ADA/EASD 2016 guidelines provide the option of transitioning from basal insulin to BID premix insulin in patients with T2DM who have failed to reach glycemic targets on basal insulin. The guideline recommends to start BID premix insulin as per the previous basal insulin dose and split the total basal dose either as 2:1 (2/3rd of the dose in the morning [AM] and 1/3rd of the dose in the evening [PM]) or 1:1 (½ of the dose in the morning and ½ of the dose in the evening). The doses may be titrated by 1-2 U or 10-15% once or twice weekly until self-measured blood glucose (SMBG) target is reached. In case of hypoglycemia, the corresponding dose can be reduced by 2-4 U or 10-20%. The recently updated ADA 2017 guidelines have further strengthened the importance of twice daily premix insulins following the failure of basal insulin regimen. This regimen is recommended at the same level as basal plus regimen. Similarly, thrice daily administration of premix insulins is recommended at par with basal bolus therapy, when further insulin intensification is necessary. IDF 2012 recommends

Table 3: Twice daily premix insulin/co-formulation for initiation

Trial (Reference)	Objective	Duration of Treatment/Total Number of Enrolled Subjects	Trial arms	Results	
				Efficacy (HbA1C)	Safety (Hypoglycemia)
Multicentre, open-label, parallel-group, treat-to-target insulin naïve subjects with T2DM (INITIATE study Raskin et al 2005)	To compare safety and efficacy of BIAsp 70/30 to IGLar	28 weeks /233	<ul style="list-style-type: none"> • BIAsp30 BD (117) • OD IGLar (116) 	<ul style="list-style-type: none"> • Mean HbA1c reduced by -2.79% with BIAsp 30 and -2.36% with IGLar [p<0.01; BIAsp 30 significantly better than IGLar] • Proportion of patients achieving HbA1c <7%: 66% and 40% with BIAsp 30 and IGLar respectively 	Hypoglycemia event rates (per subject-year): <ul style="list-style-type: none"> • Severe: 1 event with IGLar and none with BIAsp 30 • Overall minor: 3.4 (BIAsp 30) and 0.7 (IGlar) (p< 0.05)
Randomised, open label, parallel group study in Insulin-naïve T2DM (EUROMIX study Kann et al 2006)	To demonstrate the non-inferiority of BIAsp 30 BD to IGLar OD	26 weeks/258	<ul style="list-style-type: none"> • BIAsp 30 BD (128) • IGLar (127) 	<ul style="list-style-type: none"> • Mean HbA1c reduced to 7.5% with BIAsp 30 and 7.9% with IGLar [ETD: -0.5% (95% CI: -0.8, -0.2) p=0.0002] • Proportion of patients achieving HbA1c <7%: 33.1% and 26.2% with BIAsp 30 and IGLar respectively 	Hypoglycemia event rates (per subject-year): <ul style="list-style-type: none"> • Severe: 1 event each with IGLar and BIAsp 30
Multinational, open-label, parallel-group, treat-to-target trial in insulin naïve T2DM patients (Franek et al 2015)	To demonstrate non-inferiority of IDegAsp to BIAps 30 in terms of change from baseline HbA1c	26 weeks/394	<ul style="list-style-type: none"> • BID IDegAsp (197) • BID BIAsp 30 (197) 	<ul style="list-style-type: none"> • Mean HbA1c reduced by -1.71% with IDegAsp and -1.73% with BIAsp 30 [ETD: 0.02% (95% CI: -0.12, 0.17) confirming non-inferiority of IDegAsp to BIAsp 30] 	Hypoglycemia event rates (per PYE): <ul style="list-style-type: none"> • Severe: 0.05 (IDegAsp) and 0.03 (BIAsp 30) • Nocturnal confirmed: 0.63 (IDegAsp) and 2.77 (BIAsp 30); RR: 0.25 (p < 0.001) • Overall confirmed: 5.8 (IDegAsp) and 13.01 (BIAsp 30); RR: 0.46 (p < 0.001)

BIAsp 30=Biphasic insulin aspart 30; BID=Twice daily; BHI=Biphasic human insulin; BMI=Body mass index; HbA1c=Glycosylated haemoglobin; IDegAsp=Insulin degludec/insulin aspart; ETD: Estimated treatment difference; FPG: fasting blood glucose IGLar=Insulin Glargine; IGLu= Insulin glulisine; Mix25=25% soluble and 75% protaminated insulin lispro; OAD=Oral anti diabetic drugs; PPG=post prandial glucose; T2DM=Type 2 diabetes mellitus; PYE: Patient-years of exposure

intensification of the therapy from OD premix insulin to BID/TID to reach targets of HbA1c <7%, FPG <115 mg/dL and PPG <160 mg/dL. CDA 2013 recommends intensification of the therapy from OD premix insulin to BID to reach targets of HbA1c ≤7%, FPG 72-126 mg/dL and PPG 90-180 mg/dL.

NICE 2009 recommends intensification of the therapy from OD premix insulin to BID/TID to reach HbA1c target <7%.

INCG 2013 recommends intensification of premix insulin

therapy from OD to BID, if HbA1c >7% and FPG >110 mg/dL. If a patient on premix insulin (OD/BID) has HbA1c >7%, though the pre-meal blood glucose is within target, intensification to BID or TID should be considered. When the TDD of insulin in an OD regimen nears 40-50 U, the regimen should be intensified to BID and the total premix insulin dose should be split into equal breakfast and pre-dinner doses (50:50). When BID premix insulin is to be intensified to TID, 2-6 U or 10% of total daily BIAsp

30 dose before lunch, which may require down titration of morning dose (-2 U to 4 U) is recommended.

JAPI 2014 recommends premix insulin OD to BID/TID to reach targets of HbA1c ≤7%, FPG <110 mg/dL and PPG <180 mg/dL.

Published Scientific Literature

Various studies have reported BID/TID premix insulins to be similar to basal plus or basal bolus therapies in terms of glycemic control, risk of overall hypoglycemia, insulin dose and weight gain (Table 4).

Table 4: Twice/thrice daily premix insulin/ co-formulation for intensification

Trial (Reference)	Objective	Duration of Treatment/Total Number of Enrolled Subjects	Trial arms	Results	
				Efficacy (HbA1c)	Safety (Hypoglycemia)
Multinational Open-label, trial on Insulin naïve T2DM patients (GALAPAGOS Study Aschner et al 2015)	To demonstrate superiority of insulin glargine (\pm glulisine) Vs premix strategy	weeks/923	<ul style="list-style-type: none"> Premix insulin OD/BID (461) IGlar \pmIGlu (462) 	<ul style="list-style-type: none"> Mean HbA1c reduced by -1.64% with premix insulin and -1.48% with IGlar \pmIGlu [ETD: -0.16% in favour of premix (95% CI: 0.04, 0.27) $p=0.008$] Proportion of patients achieving HbA1c $<7\%$: 52.6% and 43.2% with premix insulin and IGlar \pmIGlu respectively ($p=0.005$), in favour of premix 	Hypoglycemia event rates (per subject-year): <ul style="list-style-type: none"> Severe: 9 events with IGlar \pmIGlu and 15 events with premix insulin Nocturnal symptomatic: 1.07 (IGlar \pmIGlu) and 2.28 (Premix insulin); RR=0.47 ($p < 0.001$) Overall symptomatic: 4.51 (IGlar \pmIGlu) and 8.37 (Premix insulin); RR=0.54 ($p < 0.001$)
Multinational randomized, open-label trial in T2DM patients (Tinahones et al 2015)	To assess non-inferiority, and then superiority, of Biphasic insulin lispro 25 (LM 25) versus insulin glargine once daily and insulin lispro once daily (IGL) in terms of change in HbA1c from baseline	24 weeks/476	<ul style="list-style-type: none"> BID LM25 (236) OD IGlar + OD Lispro (240) 	<ul style="list-style-type: none"> Mean HbA1c reduced by -1.3% with LM25 and -1.08% with IGlar +IGlu [ETD: -0.21% (95% CI: $-0.38, -0.04$) confirming non-inferiority of LM25 to IGL] Proportion of patients achieving HbA1c $<7\%$: 34.5% and 30% with LM25 and IGL respectively ($p=0.359$) 	Hypoglycemia event rates (per subject-year): <ul style="list-style-type: none"> Severe: 0.04 (LM25) and 0.0 (IGL); Similar between groups Nocturnal: 1.54 (LM25) and 1.82 (IGL); Similar between groups Overall symptomatic: 13.07 (LM25) and 16.51 (IGL); RR=0.54 ($p < 0.001$); Similar between groups
Multicentre randomized active-comparator parallel group open-label non-inferiority trial on T2DM patients (Jin et al 2015)	To demonstrate non-inferiority of the basal-prandial insulin treatment vs premixed insulin-based therapy in terms of change from baseline in HbA1c levels	24-weeks/161	<ul style="list-style-type: none"> BIAsp 30 BID (83) IGlar (OD) + IGlu (OD or BID) (78) 	<ul style="list-style-type: none"> Mean HbA1c reduced by -1.04% with BIAsp 30 and -0.94% with IGlar +IGlu [ETD: -0.09% (95% CI: $-0.35, 0.16$) confirming non-inferiority of basal-prandial therapy to premixed insulin therapy] Proportion of patients achieving HbA1c $<7\%$: 29.27% and 33.3% with BIAsp 30 and IGlar +IGlu respectively ($p=0.77$) 	Hypoglycemia events: <ul style="list-style-type: none"> Severe: 1 episode with IGlar +IGlu and BIAsp 30 after dose stabilization Nocturnal symptomatic: 57 and 40 events with BIAsp 30 and IGlar +IGlu after dose stabilization; Similar between groups Overall: 386 and 543 events with BIAsp 30 and IGlar +IGlu after dose stabilization; Similar between groups

Table 4: Twice/thrice daily premix insulin/ co-formulation for intensification

Trial (Reference)	Objective	Duration of Treatment/Total Number of Enrolled Subjects	Trial arms	Results	
				Efficacy (HbA1c)	Safety (Hypoglycemia)
Open-label trial on T2DM patients (LANSCAPE Vora et al 2015)	To test non-inferiority of basal plus regimen with BID premix as assessed HbA1c reduction from baseline	24 weeks/335	<ul style="list-style-type: none"> • BIAsp 30 BID (165) • IGLar + IGlu (OD) (170) 	<ul style="list-style-type: none"> • Mean HbA1c reduced by -1.0% with IGLar +IGlu and -1.22% with BIAsp 30 [ETD: -0.21% (95% CI: UL=0.38) confirming non-inferiority of basal-prandial therapy to premixed insulin therapy] • Proportion of patients achieving HbA1c <7%: 27.9% and 20.6% with BIAsp 30 and IGLar +IGlu respectively (p=0.12) 	<p>Hypoglycemia event rates (per subject-year):</p> <ul style="list-style-type: none"> • Severe: 13 patients with IGLar +IGlu and 9 patients BIAsp 30 experienced severe hypoglycemia • Nocturnal: 3.6 and 5.7 events/patient-year with BIAsp 30 and IGLar +IGlu; RR=1.57 (p=0.019); significantly lesser with BIAsp 30 • Overall: 18.2 and 15.3 events/patient-year (p=0.22); Similar between groups
BID/TID Premix Vs. Basal bolus					
Multinational multicentre, randomized treat-to-target trial on T2DM patients uncontrolled on OADs ± basal insulin. (PREFER Study Liebl et al 2009)	To demonstrate the non-inferiority of BIAsp 30 compared to basal bolus therapy (IDet OD + IAsp at meal times) in terms of HbA1c reduction from baseline	26-week/719	<ul style="list-style-type: none"> • BID BIAsp 30 (178) • OD IDet + TID IAsp (541) 	<ul style="list-style-type: none"> • Mean HbA1c reduced by -1.56% with IDet+IAsp and -1.23% with BIAsp 30 [ETD: -0.23% (95% CI: 0.398, -0.07) confirming superiority of basal-bolus therapy to premixed insulin therapy] • Proportion of patients achieving HbA1c <7%: 60% and 50% with IDet+IAsp and BIAsp 30 respectively 	<p>Hypoglycemia event rates (per subject/week):</p> <ul style="list-style-type: none"> • Severe: 11 episodes with IDet+IAsp and none with BIAsp 30 • Nocturnal: 0.013 and 0.010 with IDet+IAsp and BIAsp 30 respectively; similar between groups • Minor: 0.035 and 0.037 with IDet+IAsp and BIAsp 30 respectively; similar between groups
Multi-country, non-inferiority parallel, prospective, open-label study on insulin naïve T2DM patients (PARADIGM study Bowering et al 2012)	To test non-inferiority of LM25 therapy to IGLar + insulin Lispro therapy In terms of HbA1c reduction	48-week/426	<ul style="list-style-type: none"> • LM 25 ≤TID (214) • IGLar OD + insulin Lispro (ILis) ≤TID (212) 	<ul style="list-style-type: none"> • Mean HbA1c reduced by -1.84% with LM25 and -1.8% with IGLar+ILis [ETD: -0.04% (95% CI: -0.25, 0.17) confirming non-inferiority of LM25 to IGLar + insulin Lispro] • Proportion of patients achieving HbA1c <7%: 40% and 39.1% with LM25 and IGLar+ILis, respectively 	<p>Hypoglycemia event rates (per subject/30 days):</p> <ul style="list-style-type: none"> • Severe: Similar incidence between groups • Nocturnal: 0.67 and 0.85 with LM25 and IGLar+ILis respectively; similar between groups • Overall: 1.71 and 1.96 and 0.037 with LM25 and IGLar+ILis respectively; similar between groups

Table 4: Twice/thrice daily premix insulin/ co-formulation for intensification

Trial (Reference)	Objective	Duration of Treatment/Total Number of Enrolled Subjects	Trial arms	Results	
				Efficacy (HbA1c)	Safety (Hypoglycemia)
Multinational, open-label, randomized, parallel-arm treat-to-target trial on T2DM patients not controlled by OADs (Malek et al 2015)	To demonstrate the non-inferiority of stepwise insulin intensification of basal-bolus insulin analogues to BIAsp30 in reduction in HbA1c from baseline	50-week/403	<ul style="list-style-type: none"> BIAsp 30 (1-2-3) (203) IDet + IAsp (1-2-3) (200) 	<ul style="list-style-type: none"> Mean HbA1c reduced to 7.4% with IDet + IAsp and 7.3% BIAsp1-2-3 [ETD: 0.1% (95% CI: -0.1, 0.3) confirming non-inferiority of IDet+IAsp to BIAsp 30 Proportion of patients achieving HbA1c <7%: 40.3% and 44.9% with IDet+IAsp and BIAsp 30 respectively 	Hypoglycemia event numbers: <ul style="list-style-type: none"> Major: 37 and 36 with IDet+IAsp and BIAsp 30 respectively Nocturnal: 90 and 88 with IDet+IAsp and BIAsp 30 respectively Overall: 725 and 651 with IDet+IAsp and BIAsp 30 respectively
Multinational Open-label, treat-to-target trial on T2DM patients ≥18 years of age inadequately controlled OD or BID pre- or self-mixed insulin with or without OADs (Fulcher et al 2014)	To demonstrate non-inferiority of IDegAsp to BIAsp 30 in terms of change in HbA1c	26-week/447	<ul style="list-style-type: none"> BID IDegAsp (224) BID BIAsp 30 (223) 	<ul style="list-style-type: none"> Mean HbA1c reduced to 7.1% with both IDegAsp and BIAsp 30 [ETD: -0.03% [95%CI -0.18, 0.13]) confirming non-inferiority of IDegAsp to BIAsp 30 Proportion of patients achieving HbA1c <7%: 50.4% and 48.6% with IDegAsp and BIAsp 30, respectively 	Hypoglycemia event rates (per patient-year of exposure): <ul style="list-style-type: none"> Severe: 0.09 and 0.25 with IDegAsp and BIAsp 30 respectively; similar between the groups Nocturnal confirmed: 0.74 and 2.53 with IDegAsp and BIAsp 30 respectively; RR: 0.27 (p<0.0001) Overall confirmed: 9.72 and 13.96 with IDegAsp and BIAsp 30 respectively; RR: 0.68 (p=0.0049)
Open label, treat to target trial in insulin experienced T2DM patients (Rodbard et al 2015)	To demonstrate the non-inferiority of IDegAsp compared to basal bolus therapy for change in HbA1c from baseline	26 weeks/274	<ul style="list-style-type: none"> IDegAsp BID (138) IDeg OD + IAsp (2-4 times daily) (136) 	<ul style="list-style-type: none"> Mean HbA1c reduced by -1.31% with IDegAsp and -1.50% IDeg+IAsp [ETD: 0.18% [95%CI -0.04, 0.41]) not confirming non-inferiority of IDegAsp to IDeg + IAsp Proportion of patients achieving HbA1c <7%: 56.5% and 59.6% with IDegAsp and IDeg + IAsp, respectively (similar between groups) 	Hypoglycemia event rates (per patient-year of exposure): <ul style="list-style-type: none"> Severe: 0.47 and 0.24 with IDegAsp and IDeg + IAsp respectively Nocturnal confirmed: 1.2 and 1.6 with IDegAsp and IDeg + IAsp 30 respectively; RR: 0.8 (p=NS) Overall confirmed: 11.6 and 13.6 with IDegAsp and IDeg + IAsp 30 respectively; RR: 0.81 (p=NS)

BIAsp 30=Biphasic insulin aspart 30; BID=Twice daily; BHI=Biphasic human insulin; BMI=Body mass index; HbA1c=Glycosylated haemoglobin; IDet:Insulin Detemir; IDegAsp=Insulin Degludec/insulin Aspart ETD: Estimated treatment difference; IGlargin=Insulin Glargine; IGlu= Insulin glulisine; IAsp=Insulin aspart; ITT=intent to treat; Mix25/ LM25=25% soluble and 75% protaminated insulin lispro; OAD=Oral anti diabetic drugs; SMBG Self-Monitoring of Blood Glucose T2DM= Type 2 diabetes mellitus

In a recent meta-analysis, based on 13 randomized control trials (RCTs) on T2DM patients (≥18 years old), the efficacy and safety of basal

bolus (including basal plus) was compared with premixed insulin (≤3 injections/day).²⁸ The mean HbA1c decrease from baseline is

comparable for both the treatment groups (basal bolus and premixed groups; -1.56%, and -1.47% respectively, p = 0.13). Further, the

Expert Group Recommendation 4: Twice/thrice Daily Premix Insulins/Co- Formulations for Intensification

- Twice daily premix analogue provide comparable glycemic control and safety versus basal plus strategy with the additional benefit of simplicity (one device vs 2 devices).
- When intensifying premix analogue therapy from once daily to twice daily, split the once daily dose into equal breakfast and dinner doses and titrate further.
- When intensifying premix analogue from twice daily to thrice daily, consider adding 2–6 U or 10% of total daily premix insulin dose before lunch which may require down titration of morning dose (-2 to 4 U).
- Premix insulin analogue thrice daily is comparable to basal bolus regimen, and offers more convenience as an option for intensive insulin therapy.
- IDegAsp twice daily is comparable to basal bolus regimen and offers for a convenient alternative to intensive insulin therapy.
- Twice daily IDegAsp can be recommended over premix analogues in view of superior fasting glucose control and lower risk of major and nocturnal hypoglycemia.
- Twice daily IDegAsp can be recommended over premix analogues for patients where basal insulin analogue is inadequate for superior fasting glucose control.
- The recommended target for titration is pre-meal value of 80-130 mg/dL, pre-breakfast dose if titrated based on pre-dinner values and vice-versa.

Recommendation on Titration:

Pre-breakfast/pre-dinner value*(mg/dL)	Pre-dinner/pre-breakfast dose change Dose adjustment (units)
< 80	-2
80-130	0
131-160	+2
161-180	+4
> 180	+6

*Lowest/mean of the three recent self-measured blood glucose values

Note: For patients initiated on pre-breakfast dose, titrate according to pre-dinner values and vice versa

study group analysed 9 RCTs and reported no significant difference in event rate of overall hypoglycemia (12.1 Vs. 12.2 episodes per patient per year with mean difference 0.16) and body weight gain (2.4

kg Vs. 2.2 kg with mean difference of 0.21) The analysis of daily insulin dose based on two RCTs in the same study reported mean difference to be -0.54U/day and -0.02U/day favouring premixed insulin group.²⁸ The authors suggested basal bolus insulin therapy up to 4 injections/day as the intensification of basal plus and T1D premix as the intensification of BID premix insulin analogues is similar. Since premix analogue insulins (up to 3 injections per day) have been established to be non-inferior to basal-bolus insulin therapy (up to 4 injections per day) in terms of efficacy, weight and overall hypoglycemia, it was anticipated that the these options would be suggested after basal insulin insufficiency as a revision in ADA Standards of Medical Care in Diabetes 2017.²⁹ Highlighting this much anticipated change has now been updated in the ADA Standards of Medical care 2017.

In a 26-week, randomized, open-label, multinational, treat-to-target trial, IDegAsp was found to be superior to BIAsp30 in T2DM patients inadequately controlled with OD/BID pre/self-mixed insulin with/without OADs in terms of significantly lower FPG levels (estimated treatment difference [ETD] -20.52 mg/dL mmol/L [95% CI -27.56 to -13.69], $p < 0.001$) and mean daily insulin dose (estimated rate ratio 0.89 [95% CI 0.83–0.96], $p = 0.002$). Additionally, fewer confirmed, nocturnal confirmed, and severe hypoglycemia episodes were reported in IDegAsp group compared with BIAsp 30 group.³⁰

In a randomized, open-label, treat-to-target, phase III non inferiority study of BID IDegAsp with basal bolus insulin therapy (IDeg once daily administered with IAsp 2–4 times daily) in type 2 diabetes previously treated with basal insulin with/without OADs reported comparable reduction in HbA1c with both treatment groups and numerically lower overall and nocturnal confirmed hypoglycemia

with IDegAsp in comparison to basal bolus therapy.³¹

Consensus 5: Premix Insulins In Gestational Diabetes

Premix insulins BHI 30 and BIAsp30 have been reported to provide tight glycemic control with fewer injections in women with GDM.

Current Place in Guidelines

As per DIPSI guidelines 2006 for Indian GDM patients, combination of short acting insulin and intermediate acting insulins was suggested for GDM patients in morning and evening. In this regimen, 2/3rd of the total daily dose (TDD) of insulin is given in the morning and 1/3rd in the evening. For each combination, 1/3rd of the dose should be regular insulin and 2/3rd should be intermediate acting insulin. If a patient continues to have fasting hyperglycemia, the intermediate acting insulin should be given at bedtime instead of before dinner. Use of premix insulin analogues in pregnancy should be individualized and physician-based.

Published Scientific Literature

BIAsp 30 was reported to be safe during pregnancy and allows considerable flexibility in the meal time insulin dosing without disturbing patient's routine life pattern.⁹

In a single-center, randomized, open-label, parallel group trial, the efficacy and safety of 6 U of BIAsp 30 (Group A) was compared with 6 U of BHI 30 (Group B) in 323 patients with GDM. Both the groups were comparable in terms of glycemic (FPG and PPG) levels, rates of hypoglycemia, adverse events and neonatal macrosomia. Patients in Group A had significantly lower mean total insulin dose at the end of the study compared to Group B patients, indicating a lower dose requirement by Group A patients to achieve the similar degree of glycemic control. Hence, BIAsp 30 was considered as non-inferior to BHI 30, producing similar glycemic

Expert Group Recommendation 5: Premix Insulins in Gestational Diabetes

- Though prandial insulins are used most often in women with GDM, premix analogues may be recommended in patients with high fasting plasma glucose values.
- Premix insulin analogues are:
 - Generally, more effective than human premix insulin in lowering postprandial glucose levels.
 - Have overall safety and efficacy profiles comparable to those of human premix insulin.
- BIAsp can be initiated at 6 U OD before breakfast and titrated to achieve FPG 90-120 mg/dL and mean plasma glucose not less than 86 mg/dL.
- Twice daily BIAsp can be considered based on individual requirements.

and neonatal outcomes and was well-tolerated during pregnancy.³²

Consensus 6: Premix Insulins In Type 1 Diabetes Mellitus

Premix insulin formulations BIAsp 30, LisproMix 25 and IDegAsp are recommended for achieving the glycemic control in patients with type 1 diabetes mellitus (T1DM).

Published Scientific Literature

In a 26-week, multicentre, open-label, two-arm, parallel study, the efficacy and safety of OD IDegAsp + mealtime IAsp was compared to OD IDet + mealtime IAsp in T1DM patients aged >18 years. A total of 548 patients with T1DM were randomized 2:1 to IDegAsp or IDet + IAsp. Non-inferiority for IDegAsp versus IDet was confirmed; A1C improved by 0.75% with IDegAsp and 0.70% with IDet to 7.6% in both groups (estimated treatment difference IDegAsp - IDet: -0.05% [95% CI -0.18 to 0.08]). There was no statistically significant difference between IDegAsp and IDet + IAsp in the rates of severe hypoglycemia (0.33 and 0.42 episodes/patient-year, respectively) or overall confirmed (plasma glucose, 56 mg/dL) hypoglycemia (39.17 and 44.34 episodes/patient-year, respectively). Nocturnal confirmed hypoglycemia rate was 37% lower with IDegAsp than IDet (3.71 vs.

5.72 episodes/patient-year, $P < 0.05$).³³

Expert Group Recommendation 6: Premix Insulins in T1DM

- In T1DM patients aged more than 18 years where basal bolus is not feasible, biphasic insulin analogues are preferred over human premix insulins in view of their safety profile.
- In T1DM patients aged more than 18 years where basal bolus is not feasible, IDegAsp based regimen provides similar efficacy as compared to basal bolus therapy.

Consensus 7: Premix Insulins During Ramadan

Current Place in Guidelines

IDF 2016 recommended the use of premix analogues over biphasic human insulin due in view of the lower incidence of hypoglycemia. In case of OD dosing, the normal dose should be taken at iftar. For BD dosing, the normal dose should be taken at iftar and suhur dose should be reduced by 25–50%. For T1D dosing, an afternoon dose should be omitted and iftar and suhur doses to be adjusted based on the FBG levels.³⁴

SAFES guidelines also recommend premix analogues in patients with diabetes during Ramadan owing to its multiple advantages of safety and flexibility. The guideline also recommends that if a patient is already on premix insulin, the usual morning dose should be used at the sunset meal and the usual evening dose should be halved at predawn meal.³⁵

Published Scientific Literature

Premix insulins are more convenient for T2DM patients since they require fewer injections than basal-bolus regimens (Table 5). In an open-label randomised trial, the effects of LisproMix25 and BHI 30/70 was compared during Ramadan in terms of glycemic control. Patients treated with insulin lispro Mix25 had lower overall glycemia than patients on BHI 30/70. However, there was no difference in the number of hypoglycemic episodes between treatments³⁶. A regimen of

insulin lispro Mix50 in the evening and regular human insulin with NPH (30:70) in the morning was compared with regular human insulin with NPH (30:70) given twice daily during Ramadan in a small observational study. Switching the evening meal dose to insulin lispro Mix50 significantly improved glycemic control without increasing the incidence of hypoglycemic events³⁷. A new regimen in which 40% of the daily insulin dose was given as IDet at suhoor and 60% was given as NovoMix70 before iftar was assessed in another randomised study. The new regimen was found to be non-inferior to standard care with a significantly lower hypoglycemic event rate³⁸. A prospective observational study in Indonesia found that BIAsp significantly reduced all glycemic indices following Ramadan without an increase in body weight or risk of hypoglycemia; however, there were no significant changes in body weight or body mass index (BMI).³⁹

Expert Group Recommendation 7: Premix Insulins during Ramadan

- It is recommended to use premix analogues over human premix during Ramadan in view of improved safety and flexibility of dosing.
- Patients on once daily premix insulin/co-formulations need not modify dose but have to administer the dose at the time of breaking the fast.
- Patients on twice daily premix insulin/co-formulations should take usual pre-dinner dose at night meal and reduce morning dose by 25-50%.

Conclusion

Appropriate management of glycemic levels in patients with T2DM is important in delaying long-term complications associated with this disease. The principal factors important in optimal glycemic control include choice of an appropriate insulin regimen and timing of initiation and intensification/optimisation of insulin therapy. Premix insulin formulations are the most widely prescribed insulins in India due to typical Indian phenotype, high

Table 5: Premix Insulin during Ramadan

Trial (Reference)	Objective	Duration of Treatment/Total Number of Enrolled Subjects	Trial arms	Results	
				Efficacy (HbA1c)	Safety (Hypoglycemia)
Multicenter, open-label observational study in Indonesian people with T2DM before, during, and after Ramadan fasting in routine clinical practice. (Soewondo et al 2009).	To assess the efficacy and safety of BIAsp30 before, during and after Ramadan fasting	152	BIAsp 30	<ul style="list-style-type: none"> Mean HbA1c reduced by 0.9% with BIAsp 30 treatment (p<0.05) 	Hypoglycemia (Times): <ul style="list-style-type: none"> Severe: None at pre-Ramadan, Ramadan, and end-of-study evaluation Nocturnal minor: reduced from 0.722 at baseline to 0.277 at end-of-study (p=NS) Daytime minor: 1.065 at baseline to 0.546 at end-of-study (p=NS)
Multicentre, Open label, controlled, cluster randomised non-inferiority study comparing IDet + BIAsp 70 to standard of care during Ramadan fast in insulin treated T2DM patients (Shehadeh et al 2015)	To compare non-inferiority of IDet + BIAsp 70 treatment to standard of care in terms of 4-point SMBG during days 23–30 of treatment.	245	<ul style="list-style-type: none"> IDet at predawn meal (40% of total daily insulin dose) + BIAsp 70 at sunset meal (60% of total daily insulin dose) (127) Standard of care (128) 	<ul style="list-style-type: none"> Mean 4 point-SMBG during days 23-30 of treatment was 155mg/dl and 159mg/dl with intervention and control arms confirming non-inferiority of IDet + BIAsp 70 treatment to standard of care 	<ul style="list-style-type: none"> Hypoglycemia event rate was lower with IDet + BIAsp 70 treatment compared to standard of care (0.00 vs. 0.01 respectively, p ≤ 0.001)
Multicentre, open-label, randomised, crossover study in patients with T2DM who wish to fast during Ramadan (Mattoo et al 2003)	To compare the average daily BG control and PPG control post morning and evening meals between LisproMix 25 and BHI 30/70 in T2DM patients during Ramadan	151	<ul style="list-style-type: none"> LisproMix25 switched to BHI 30 (72) BHI 30 switched to LisproMix25 (72) 	<ul style="list-style-type: none"> Significantly lower PPG excursion with insulin LisproMix25 (3.4± 2.9 mmol/l) compared to BHI 30/70 (4.0+/-3.2 mmol/l, P=0.007) The average daily BG control was better with LisproMix 25 vs BHI 30 (9.5± 2.4 mmol/l Vs. 10.1± 2.5 mmol/l respectively) (P=0.004) 	Hypoglycemia event rate (per patient/ 14 days): <ul style="list-style-type: none"> 0.4 for both lispro Mix25 and and BHI 30; similar between groups
Observational study in Muslim patients with T2DM on treatment with BHI 30 BID who wish to fast during Ramadan (Hui et al 2010)	To compare HbA1c, hypoglycaemia risk and weight gain between BHI 30 + Humalog Mix 50 and BHI 30 BID in insulin experienced T2DM patients	2 weeks before Ramadan to 10 days after the last dose of Ramadan/ 52	<ul style="list-style-type: none"> BHI 30 + Humalog Mix 50 (Group 1; n=26) BHI 30 BID (Group 2; n=26) 	<ul style="list-style-type: none"> Mean HbA1c reduced by -0.48% with Group 1 and increased by +0.28% with Group 2 [ETD: 0.4% (95% CI: 0.19, 0.62) p=0.0004]. Thus, group 1 reduced HbA1c significantly better than group 2 	Hypoglycemia mean events <ul style="list-style-type: none"> Reduced by 0.04 and increased by 0.15 with group 1 and group 2 respectively, during Ramadan compared with before Ramadan; Similar risk between groups (p = 0.36)

BIAsp=Biphasic insulin aspart; BID=Twice daily; BHI=Biphasic human insulin; BMI=Body mass index; HbA1c=Glycosylated haemoglobin; IDet:Insulin Detemir IDegAsp=Insulin degludec/ insulin aspart; ETD: Estimated treatment difference; IGlar=Insulin Glargine; IGLu= Insulin glulisine; LisproMix25=25% soluble and 75% protaminated insulin lispro; SMBG Self-Monitoring of Blood Glucose T2DM= Type 2 diabetes mellitus; BG=Blood glucose; OD: Once daily; PPG: Post-prandial glucose

carbohydrate intake and high PPG levels There is a need to update premix guidelines with respect to newer evidence and

newer co-formulations. The recommendations put forth are based on the existing established guidelines and published evidence.

The recommendations presented in this paper can be further simplified as follows:

- In the setting of high

carbohydrate consumption or in patients with predominant post prandial hyperglycemia like in India, IDegAsp could be preferred over premix insulin analogues and basal insulins for insulin initiation, to achieve recommended glucose targets without increasing the risk of overall and nocturnal hyperglycemia.

- Twice daily IDegAsp is recommended over BIAsp 30 in view of lower risk of hypoglycemia and superior fasting glucose control. It is also recommended where premix/basal insulin analogues are considered inadequate for superior fasting glucose control.
- Both premix insulin analogues thrice daily and IDegAsp twice daily are comparable to basal bolus regimen and offers a convenient alternative to intensive insulin therapy.
- When intensifying premix analogue therapy from once daily to twice daily, the once daily dose should be split into equal breakfast and dinner doses and titrated further. When intensifying premix analogue from twice daily to thrice daily, consider adding 2–6 U or 10% of total daily premix insulin dose before lunch. This may require down titration of morning dose.
- Premixed insulin analogues are more effective than human premix insulin in lowering PPG levels in patients with GDM.
- IDegAsp based regimen provides similar efficacy versus basal bolus therapy in T1DM patients aged > 18 years where basal bolus regimen is not feasible.
- Premix insulin analogues are recommended over human premix insulin during Ramadan in view of their safety and flexibility.

The strength of the current

consensus is that it is evidence based, and concordant with globally acceptable guidelines. It includes evidence based discussion of modern insulin coformulation, and covers the complete spectrum of premix insulin use in various clinical presentations of diabetes, including type 1 diabetes, type 2 diabetes, GDM and symptomatic hyperglycemia.

We hope that these consensus recommendations will be a useful reference tool for physicians and that their impact will be validated through observational research, involving large number of physicians and in the setting of routine outpatient care of T2DM in India.

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