Diabetes Ther (2015) 6:101–111
DOI 10.1007/s13300-015-0106-2

REVIEW

Injectable Coformulations in Diabetology

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Received: February 9, 2015 / Published online: March 24, 2015

ABSTRACT

Coformulations are a novel pharmaceutical development in diabetology. They are composed of two medicinal products, both of which maintain their distinct pharmacokinetic and pharmacodynamic properties. Currently available coformulations include combinations of basal and rapid-acting insulin, and basal and glucagon-like peptide 1 receptor agonists (GLP1RA). This review describes three coformulations which are in advanced stages of development, or are approved in certain markets. We discuss the basic and clinical pharmacology of these drugs, while describing clinical usage of the commercially available insulin degludec aspart (IDegAsp).

Electronic supplementary material The online version of this article (doi:10.1007/s13300-015-0106-2) contains supplementary material, which is available to authorized users.

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Keywords: BEGIN; BOOST; DUAL; GetGoal; Insulin degludec aspart; Insulin degludec liraglutide; Insulin glargine lixisenatide

COFORMULATIONS IN DIABETOLOGY

Fixed dose combination (FDCs) and fixed ratio combinations (FRCs) or fixed proportion combination (FPCs) are an integral and well-accepted part of diabetes care. Oral FDCs are convenient to use and well tolerated in patients, and their efficacy has been well demonstrated [1]. Injectable FRCs or FPCs, such as pre-mixed insulin, are also widely used in diabetes management [1]. These FRCs provide convenient, effective and safe glycemic control. However, the traditionally available FRCs are mixtures of two components which merge with each other in the solution, and may lose their distinct pharmacokinetic and pharmacodynamic profiles [1]. This may lead to limitations in onset of peak or duration of action, and may result in suboptimal efficacy. Recently, injectable coformulations have been developed, which combine two distinct molecules in one formulation. These may be

from the same therapeutic class (e.g., a rapid acting insulin combined with a basal insulin) or from different therapeutic classes (e.g., a basal insulin combined with a glucagon-like peptide 1 receptor agonist [GLP1RA]).

The dictionary defines "formulation" as "the act, process or result of formulating or reducing to a formula" or "a medicinal preparation", and defines coformulation as "the act of packaging more than one drug into one pill" [2]. It must be noted that no injectable coformulations have been described as such until now. The word "injection" when used in terms of drug dosage refers to solution, suspension and emulsion, including those produced from powders or concentrated solutions. Various oral coformulations such as multivitamins, vitamin B complex and certain antibiotics (e.g., co-amoxiclav) are available for intravenous use. Such pharmaceutical advances, however, have not been available in the anti-diabetic segment so far. This is because the challenges of producing and combining biologically engineered molecules, such as insulin and GLP1RA, are infinitely greater than those utilizing synthetic chemical compounds.

In this review, we define injectable pharmaceutical coformulations as preparations, and which also maintain their distinct pharmacological properties. These are distinct from the pre-mixed insulins that have been available over the last 50 years (Table 1).

CLASSIFICATION

In this review, we discuss the following coformulations, which are based on insulin as a common compound. These coformulations may or may not include a GLP1RA.

1. Ultra-long-acting insulin + rapid-acting insulin:
   (a) Insulin degludec aspart (IDegAsp)
2. Insulin + GLP1RA:

Table 1 Coformulation versus pre-mixed preparation

Characteristic	Coformulation	Pre-mixed preparation
Definition	Formulation of two separate components, which maintain distinct identity	Mixture of two components, which are unable to maintain distinct identity
Appearance	Clear	Cloudy
Proportion	Pre-determined	Pre-determined
Pharmacokinetics/ pharmacodynamics	Both components maintain distinct PK/PD profiles	PK/PD profile of both components may merge
Efficacy	Both components achieve efficacy at targeted endpoint	Both components often achieve targeted end points
Scope	Allows coformulation of separate classes of drugs	Does not allow mixing of different classes of drugs
Examples	Insulin degludec + insulin aspart; insulin degludec + liraglutide; insulin glargine + lixisenatide	Biphasic human insulin; biphasic insulin aspart; biphasic insulin lispro

PD pharmacodynamics, *PK* pharmacokinetics

(a) Insulin degludec liraglutide (IDegLira)
(b) Insulin glargine lixisenatide (IGlarLixi)

INSULIN DEGLUDEC AND INSULIN ASPART

Insulin degludec and insulin aspart (IDegAsp) is a novel, soluble coformulation comprising insulin degludec, an ultra-long-acting basal insulin analog, and insulin aspart, a rapid-acting insulin analog. This coformulation is made up of 70% insulin degludec and 30% insulin aspart.

Insulin degludec forms a soluble and stable dihexamer, using phenol and zinc. While zinc is responsible for the formation of hexamers, phenol maintains the molecule in a dihexameric form so that the multihexamers are not formed in the solution. Following injection into the subcutaneous tissue, phenol diffuses away from the formulation leading to the formation of multihexamer chains, which act by causing a slow, continuous and extended release of monomers from the injection site [3]. Insulin degludec has a very long duration of action (>42 h) with four times lower glycemic variability than insulin glargine at steady-state concentration [3]; this translates into a much lower risk of hypoglycemia, especially nocturnal hypoglycemia, as seen in various clinical trials [4].

Pharmacokinetics and Pharmacodynamics

These two insulin analogs have been coformulated in such a manner that they neither interfere with the pharmacokinetics of each other nor cause any change in the mode of action of each other [5]. Receptor affinities of various newer insulins have always been a cause of concern, especially insulin-like growth factor 1 (IGF-1) receptor binding affinity, which could induce mitogenesis and carcinogenicity when at high levels. These properties of insulin degludec [6] and insulin aspart [7] were respectively investigated in vitro, as briefly mentioned in Table 2.

Clinical Trial Program

The efficacy and safety of IDegAsp has been studied in the phase 3 BOOST clinical trial program. These clinical studies were conducted in patients with both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), both as once-daily (OD) and twice-daily (BID) dosing. The endpoints of this trial are summarized in Table 3.

Regulatory Approval Status

IDegAsp has recently received market approval in the European Union, Japan, Mexico, India and Bangladesh for the treatment of T1DM and T2DM.

Posology

As per the IDegAsp label, IDegAsp can be administered OD or BID with main meal(s). In

Table 2 Receptor binding and metabolic and mitogenic properties of insulin aspart and insulin degludec

	Human insulin	Insulin degludec	Insulin aspart
Insulin receptor affinity	100%	13–15%	92%
IGF receptor affinity	100%	2%	81%
Metabolic potency	100%	8–20%	101%
Mitogenic potency	100%	4–14%	58%
Mitogenic/metabolic potency ratio	1	<1	<1

Table 3 Phase 3 trial programs investigating IDegAsp in T1DM and T2DM

Population (*n*)	IDegAsp dosing time	Weeks	Non-inferior HbA1C control	ETD of FPG (mmol/L)	Confirmed hypoglycemia	Nocturnal hypoglycemia
T1DM: IDegAsp OD + IAsp at remaining meals versus IDet (OD/BD) + IAsp at time of meals (548) [9]	Any main meal	26	IDegAsp non-inferior to IDet + IAsp	0.23	9% Lower with IDegAsp (ns)	37% Lower with IDegAsp ($p < 0.05$)
T2DM: IDegAsp OD with major meal versus IGlar OD (Japan) (296) [10]	Any main meal	26	IDegAsp OD decreased HbA1C significantly more than IGlar OD ($p < 0.001$)	0.15	27% Lower with IDegAsp (ns)	25% Lower with IDegAsp (ns)
T2DM: IDegAsp BID versus BiAsp 30 BID (intensify pre-mix 1) (446) [11]	With two major meals	26	IDegAsp non-inferior to BiAsp 30	−1.14 ($p < 0.001$)	32% Lower with IDegAsp ($p = 0.0049$)	73% Lower with IDegAsp ($p < 0.0001$)
T2DM: IDegAsp BID versus BiAsp 30 BID (intensify pre-mix in all) (424) [12]	With two major meals	26	IDegAsp non-inferior to BiAsp 30	−1.06 ($p < 0.001$)	No significant difference	33% Lower with IDegAsp (ns)
T2DM: IDegAsp BID versus BB regimen with OD IDeg with IAsp 2–4 times a day (274) [13]	With two major meals	26	IDegAsp did not achieve non-inferiority	−0.5	19% Lower with IDegAsp BID (ns)	20% Lower with IDegAsp BID (ns)

BB basal bolus, *BiAsp* biphasic insulin aspart 30/70, *BID* twice daily, *ETD* estimated treatment difference, *FPG* fasting plasma glucose, *HbA1C* glycated hemoglobin, *IAsp* insulin aspart, *IDeg* insulin degludec, *IDegAsp* insulin degludec aspart, *ns* not significant, *IDet* Insulin detemir, *IGlar* insulin glargine, *OD* once daily, *T1DM* type 1 diabetes mellitus, *T2DM* type 2 diabetes mellitus

patients with T2DM, IDegAsp can be administered either alone or with oral anti-diabetic medicinal products and in combination with bolus insulin. In patients with T1DM, IDegAsp is used in combination with short-/rapid-acting insulin with remaining meals. Dose adjustments are recommended to be primarily assessed based on fasting plasma glucose measurements. Flexibility in dosing time of IDegAsp allows for flexibility in the timing of insulin administration, as long as it is administered with main meal(s). If a dose of IDegAsp is missed, patients should not take an extra dose to make up for a missed dose, but can take the missed dose with the next main meal of that day and then resume the usual dosing schedule the following day.

The recommended total daily starting dose for patients with T2DM is 10 unit with the main meal(s), followed by individual dosage adjustments. The recommended starting dose of IDegAsp in patients with T1DM is 60–70% of

the total daily insulin requirements with short-/rapid-acting insulin at the remaining meals, followed by individual dosage adjustments.

Patients with T2DM switching from once-daily basal or pre-mixed insulin therapy can be given unit-to-unit, once-daily IDegAsp at the same total insulin dose as the patient's previous total daily insulin dose. Patients switching from more than once-daily basal or pre-mixed insulin therapy can be converted to unit-to-unit, twice-daily IDegAsp at the same total insulin dose as the patient's previous total daily insulin dose. Patients switching from basal/bolus insulin therapy to IDegAsp will need to convert their dose based on individual needs. In general, patients are initiated on the same number of basal units.

Special Populations

IDegAsp can be used in elderly patients (aged >65 years) and in renal and hepatic impaired patients with intensified glucose monitoring [8]. The insulin dose should be adjusted on an individual basis. The safety and efficacy of IDegAsp in children and adolescents aged under 18 years have not been established, and so this coformulation is not currently approved for use in children.

INSULIN DEGLUDEC AND LIRAGLUTIDE

Insulin degludec and insulin liraglutide (IDegLira) is a fixed-dose, once-daily combination of ultra-long-acting insulin degludec and liraglutide, a GLP1RA. It has been developed for use in patients with T2DM and can be given in a single, daily subcutaneous injection. The use of insulin is often associated with hypoglycemia and weight gain, hence delaying the initiation and intensification of the insulin regimen [14]. When used alongside insulin, GLP1RAs can play an important complimentary role, as their use has been associated with a lower incidence of hypoglycemia and weight loss; this could be due to loss of appetite, as is often seen with the use of GLP1RA [14]. Therefore, when administered together, this combination can be very successful in the management of T2DM. The combined use of basal insulin and GLP1RA analogs has also been jointly recommended by the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) [14].

Rationale

Many studies combining basal insulin analogs with GLP1RA have shown synergistic beneficial effects of these therapies with better safety profiles.

In a 26-week randomized, open-label study of patients with poorly controlled T2DM, addition of liraglutide to metformin treatment followed by intensification with basal insulin (insulin detemir [IDet]) showed that 61% of participants completing the run-in achieved glycated hemoglobin (HbA1C) levels of <7% (mean change −1.3%) compared with liraglutide alone [15]. At 26 weeks, HbA1C further decreased by 0.5% with IDet versus a 0.02% increase without IDet (estimated treatment difference −0.52; 95% confidence interval [CI] −0.68 to −0.36; $p < 0.0001$). At week 26, HbA1C levels of <7% were achieved in 43% of patients taking IDet versus 17% patients not taking IDet. Sustained weight loss was observed during the study; however, there were higher rates of minor hypoglycemia in patients treated with IDet compared to without IDet (9.2 versus 1.3%, $p = 0.004$) [15].

The efficacy and safety of adding long-acting GLP1RA liraglutide OD versus adding short-acting insulin aspart (IAsp) OD to long-acting insulin degludec (IDeg) OD + metformin in subjects with T2DM was first investigated in the BEGIN: VICTOZA ADD-ON trial [16]. Eligible subjects completing 104 weeks of treatment with IDeg + metformin in preceding trials were randomized to intensify treatment by adding either liraglutide or IAsp OD, on top of IDeg + metformin if their HbA1C was ≥7% (≥53 mmol/mol). After 104 weeks, a third arm was included to evaluate the durability of IDeg to maintain glycemic control over an additional 26 weeks comprising non-randomized subjects with HbA1C of <7.0%. The results showed that IDegLira reduced HbA1C (−0.74% points) significantly more than IDegAsp (−0.39% points; $p = 0.0024$). 49.4% of subjects in the IDegLira arm and only 7.2% in the IDegAsp arm achieved HbA1C of <7% without confirmed hypoglycemia or severe hypoglycemia, and without weight gain ($p < 0.0001$). IDegLira subjects had significantly less confirmed and nocturnal confirmed hypoglycemia, and significantly greater weight loss (−2.8 kg) versus IDegAsp (+0.9 kg; $p < 0.0001$) [16].

Pharmacokinetics and Pharmacodynamics

IDeg is a basal insulin with an ultra-long duration of action that forms soluble multi-hexamers at the injection site following subcutaneous administration and a half-life of 24 h [17]. Liraglutide is a human GLP1RA with 97% homology. The peptide precursor of liraglutide is produced using recombinant DNA technology in yeast (Saccharomyces cerevisiae). In a dose escalation study in healthy subjects, five consecutive dose levels (1.25, 5.0, 7.5, 10.0 and 12.5 μg/kg) of liraglutide were given subcutaneously on day 1 and days 5 to 11. A steady state was observed after three doses and the half-life was determined to be 12.6 ± 1.1 h [18].

Phase 3 Clinical Trial Program

The *DU*al *A*ction of *L*iraglutide and Insulin Degludec in Type 2 Diabetes (DUAL) trial includes two phase 3a trials encompassing around 2000 people with T2DM. It was designed to study the efficacy and safety of combined use of insulin degludec and liraglutide. All treatments in both the trials were given subcutaneously and could be given at any time of day, provided the chosen time was used consistently every day.

The main features and the study results of both the DUAL programs (I and II) are shown in Table 4.

Regulatory Approval Status

IDegLira has been given market authorization by the European Medical Agency (EMA), which is valid throughout the EU [21].

INSULIN GLARGINE AND LIXISENATIDE

Lixisenatide is a new selective once-daily GLP1RA in development for the treatment of T2DM [22]. In a 13-week, phase II study, the optimal dose of lixisenatide was found to be 20 μg OD. At this dose, significant improvements in HbA1C versus placebo were observed, with a good efficacy/tolerability ratio [22]. Lixisenatide has demonstrated dose-dependent improvements in post-meal glucose levels and suppression of postprandial glucagon secretion in patients with T2DM insufficiently controlled

Table 4 DUAL I and DUAL II clinical trial program

Population	Number of weeks	Non-inferior HbA1C	Other important points regarding confirmed hypoglycemia and weight change
DUAL I: T2DM: IDegLira OD versus insulin degludec OD versus liraglutide OD ($n = 1663$) [19]	26	Mean HbA1C decreased by 1.9% with IDegLira, by 1.4% with insulin degludec, and by 1.3% with liraglutide. IDegLira was non-inferior to insulin degludec ($p < 0.0001$) and superior to liraglutide, ($p < 0.0001$)	36% Of patients on IDegLira, 14% of patients on insulin degludec and 52% of patients on liraglutide achieved HbA1C levels of <7% without any weight gain and hypoglycemia Number of confirmed hypoglycemic events per patient year was 1.8 for IDegLira, 2.6 for insulin degludec and 0.2 for liraglutide
DUAL II: T2DM: IDegLira OD + metformin versus IDeg OD + metformin ($n = 413$) [20]	26	Superior HbA1C reduction with IDegLira by 1.9% versus 0.9% by insulin degludec ($p < 0.0001$)	Mean weight change of 2.7 kg with IDegLira versus no weight change with insulin degludec, ($p < 0.0001$) Comparable incidence of confirmed hypoglycemia was seen in 24% of patients on IDegLira versus 25% of patients on insulin degludec

HbA1C glycated hemoglobin, *IDegLira* insulin degludec liraglutide, *OD* once daily

with metformin, as well as pharmacodynamic effects consistent with a glucose-dependent effect on insulin secretion and suggested improvements in β-cell function [23].

Clinical Trial Program

A phase 3 clinical trial program named GetGoal, which included 10 clinical trials, has been carried out to establish the safety and efficacy of insulin glargine and lixisenatide combination for the management of patients of T2DM. Table 5 summaries a few important trials of GetGoal program.

CONCLUSION

IDegAsp is the first soluble coformulation with both the basal and bolus insulin components available with the pharmacokinetic profile well retained unlike the previously available biphasic insulin preparations. Also, no re-suspension is required before using IDegAsp, unlike other biphasic insulin preparations. This coformulation has shown non-inferiority in HbA1C control in comparison to the currently available basal and pre-mixed insulins both as OD dosing and BID dosing with lower risk of hypoglycemia. It is anticipated to offer clinical advantage over currently available pre-mixed insulin suspensions.

GLP1RAs have been designed to restore and maintain incretin glucagon-like peptide 1 levels and attenuate postprandial plasma glucose excursions. Currently, four GLP1RAs are available for the treatment of T2DM: exenatide BID; a long-acting formulation, once weekly; liraglutide OD; and prandial lixisenatide OD.

Table 5 GetGoal clinical trial program

Study design (*n*)	Weeks	Non-inferior HbA1C	Other important points regarding confirmed hypoglycemia and weight change
GetGoal Duo 1 [24]: double-blind, parallel group trial in which patients not achieving target HbA1C of <7% with insulin glargine were given lixisenatide or placebo as add on therapy (446)	24	Adding lixisenatide to insulin glargine further reduced HbA1C by 0.71% versus 0.40% with placebo ($p < 0.0001$) More participants attained HbA1C 7% with lixisenatide (56% versus 39%; $p < 0.0001$)	Lixisenatide reduced 2 h PPG more than placebo ($p < 0.0001$) Lixisenatide had a favorable effect on body weight (−0.89 kg compared to placebo; $p = 0.0012$) Nausea, vomiting, and symptomatic hypoglycemia (3.3 mmol/L) were more common with lixisenatide
GetGoal-M [25]: double-blind placebo-controlled study where the patients were randomized to receive injections of lixisenatide in the morning, lixisenatide in the evening, placebo in the morning, or placebo in the evening (680)	24	From a baseline HbA1C of 8.1%, administration of lixisenatide led to a decrease of −0.9% (morning injection) and −0.8% (evening injection) versus −0.4% with placebo (primary end point) at 24 weeks	Mild and transient nausea and vomiting were the most commonly reported and only notable treatment emergent adverse events Hypoglycemia frequency was slightly higher in the lixisenatide groups versus placebo, but remained low with no cases of severe hypoglycemia
GetGoal-L [26]: efficacy and safety of lixisenatide as an add-on therapy to basal insulin was investigated in patients inadequately controlled on a combination of basal insulin ± metformin (495)	24	Lixisenatide significantly reduced HbA1C by −0.7 ± 0.1% versus −0.4 ± 0.1% with placebo at 24 weeks ($p = 0.0002$) and increased the proportion of patients achieving HbA1C <7% (28.0% versus 12.0% for placebo; $p < 0.0001$)	Lixisenatide reduced body weight compared with placebo ($p < 0.0001$). A decrease in insulin dose at study end was seen with lixisenatide compared with placebo (−5.6 versus −1.9 U; $p = 0.012$) Incidence of symptomatic hypoglycemia was comparable (27.7% for lixisenatide versus 21.6% for placebo), whereas four cases of severe hypoglycemia occurred in the lixisenatide group compared to none in the placebo group

Table 5 continued

Study design (*n*)	Weeks	Non-inferior HbA1C	Other important points regarding confirmed hypoglycemia and weight change
GetGoal-L-Asia [27]: adults previously treated and inadequately controlled with basal insulin ± sulfonylurea and were randomized on lixisenatide or placebo (311)	24	Lixisenatide significantly improved HbA1C by −0.88% compared to placebo ($p < 0.0001$) and more patients treated with lixisenatide achieved HbA1C of <7% compared to placebo (35.6% versus 5.2%; $p < 0.0001$)	There was a trend in weight decreases in patients treated with lixisenatide, with no statistically significant differences between lixisenatide and placebo Symptomatic hypoglycemia was similar in patients not receiving sulfonylureas, but was more frequent with lixisenatide versus placebo (32.6 versus 28.3%)

PPG postprandial plasma glucose

Table 6 Comparison of IDegLira and IGlarLixi

	IDegLira	IGlarLixi
Components	Combination of insulin degludec (basal insulin with a half-life of 25 h and duration of action >42 h), and liraglutide (GLP1RA analog with half-life of 13 h and OD dosing)	Combination of insulin glargine (basal insulin with a half-life of 12.5 h and duration of action 24 h), and lixisenatide (a short acting GLP1RA analog with a half-life of 2.6 h and OD dosing)
Phase 3 program	Completed	Completed
Approval status	Approved by European Medical Agency for the European Market	Not yet approved

GLP1RA glucagon-like peptide 1 receptor agonist, *IDegLira* insulin degludec and liraglutide, *IGlarLixi* insulin glargine and lixisenatide

Multiple studies are being conducted to establish the efficacy and safety of combining basal insulin to GLP1R agonists, and these combinations can provide additional glycemic control by reducing both fasting plasma glucose and, to a lesser extent, postprandial plasma glucose excursions, in addition to promoting weight loss and a low rate of hypoglycemia. Table 6 gives a summarized comparison of IDegLira and IGlarLixi.

ACKNOWLEDGMENTS

No funding or sponsorship was received for this study or publication of this article. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

Conflict of interest. S. Kalra has been on speaker's bureau of Novo Nordisk A/S, Sanofi Aventis and Boerhinger Ingelheim. Y. Gupta declares no conflict of interest.

Compliance with ethics guidelines. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

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