Insulin Degludec/Liraglutide

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Generic Name: Insulin Degludec/Liraglutide
Proprietary Name: Xultophy (Novo Nordisk)
Approval Rating: 4S
Therapeutic Class: Antidiabetics, Insulins, Glucagon-like Peptide 1 (GLP-1) Receptor Agonists
Similar Drugs: Insulin Glargine/Lixisenatide (*Soliqua*)
Sound- or Look-Alike Names: None

Indications

Insulin degludec/liraglutide is US Food and Drug Administration (FDA) approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus inadequately controlled on basal insulin (less than 50 units daily) or liraglutide (less than or equal to 1.8 mg daily).[1] Both insulin degludec and liraglutide are approved to improve glycemic control in patients with diabetes mellitus and are widely used, either alone or in combination with each other or other antidiabetic drugs. Insulin glargine/lixisenatide is similarly approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus inadequately controlled on basal insulin (less than 60 units daily) or lixisenatide.[1,2]

Insulin degludec/liraglutide and insulin glargine/lixisenatide combination products have similar limitations for use:

- Consider other antidiabetic therapies in patients with a history of pancreatitis.
- Not recommended for use in combination with any other product containing the same or another glucagon-like peptide 1 (GLP-1) receptor agonist.
- Not for treatment of type 1 diabetes mellitus or diabetic ketoacidosis.
- Has not been studied in combination with prandial insulin.[1,2]

In addition, insulin glargine/lixisenatide is not recommended for use in patients with gastroparesis.[2]

Clinical Pharmacology

Insulin degludec is a long-acting basal insulin analog that lowers blood glucose by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Liraglutide is a GLP-1 receptor agonist that increases glucose-dependent insulin release, decreases glucagon secretion, and slows gastric emptying.[1]

Pharmacokinetics

The pharmacokinetics of insulin degludec and liraglutide were not affected in a clinically relevant manner when administered as the combination product; a small decrease in the peak concentration of liraglutide was observed.[1,3]

In patients with type 2 diabetes reaching the maximum daily dose (insulin degludec 50 units/liraglutide 1.8 mg), the estimated mean steady-state exposure (area under the curve [$AUC_{0\text{-}24\,h}$]) was 113 h•nmol/L and 1227 h•ng/mL for insulin degludec and liraglutide, respectively. The corresponding maximum concentrations were 5196 pmol/L and 55 ng/mL, respectively. Steady-state concentrations of these agents are reached after 2 to 3 days of daily administration. Both products are extensively bound to plasma proteins (more than 99% and more than 98%, respectively). Degradation of insulin degludec is similar to that of human insulin; all metabolites formed are inactive. Liraglutide is endogenously metabolized in a similar manner to large proteins without a specific organ as a major route of elimination. The half-life is approximately 25 hours for insulin degludec and 13 hours for liraglutide.[1]

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Comparative Efficacy

Indication: Type 2 Diabetes Mellitus

Guidelines

Guideline: Standards of medical care in diabetes—2017
Reference: American Diabetes Association[4,5]
Comments: The choice of antidiabetic drug should be based on a patient-centered approach. The preferred initial pharmacologic agent for treatment of type 2 diabetes is metformin, if not contraindicated and if tolerated. In patients receiving long-term metformin therapy, periodic measurement of B_{12} levels should be considered and supplementation given as needed. Insulin should be considered as initial therapy in patients newly diagnosed with type 2 diabetes who are symptomatic and/or have hemoglobin A_{1c} (HbA_{1c}) 10% or higher and/or blood glucose levels of 300 mg/dL or higher. In patients with established cardiovascular disease, treatment with empagliflozin or liraglutide should be considered.

Guideline: Oral pharmacologic treatment of type 2 diabetes mellitus: A clinical practice guideline update from the American College of Physicians
Reference: American College of Physicians[6]
Comments: If not contraindicated and if tolerated, metformin is the preferred agent for treatment of type 2 diabetes when pharmacologic therapy is needed to improve glycemic control; metformin is for use in addition to lifestyle modifications. The choice to add another antidiabetic drug (eg, sulfonylurea, thiazolidinedione, sodium glucose cotransporter 2 inhibitor, dipeptidyl peptidase 4 [DPP-4] inhibitor) to metformin should be based on a patient-centered approach, taking into consideration the benefits, adverse effects, and costs. The guidelines only evaluated oral drugs and do not mention insulin or GLP-1 receptor agonists.

Studies

Drug: Insulin Degludec/Liraglutide versus Insulin Degludec or Liraglutide
Reference: Gough SC, et al, 2014 (DUAL I trial)[7]
Study Design: Phase 3, randomized, open-label, multicenter study
Study Funding: Novo Nordisk
Patients: 1663 insulin-naive adults (18 years and older) with type 2 diabetes, HbA_{1c} 7% to 10%, and body mass index (BMI) of 40 kg/m^2 or less. Patients had previously been treated with metformin with or without pioglitazone for at least 90 days. Patients were excluded if they had received treatment with GLP-1 receptor agonists, DPP-4 inhibitors, or sulfonylureas within 90 days of screening. Mean patient age was 55 years, mean HbA_{1c} was 8.3%, and mean BMI was 31.2 kg/m^2. Median metformin and pioglitazone dosages were similar among the 3 groups at baseline and did not change during the study. About 83% of patients were receiving metformin at baseline, and 17% were receiving metformin plus pioglitazone.
Intervention: Patients were randomized (2:1:1) to receive a once-daily subcutaneous injection of insulin degludec/liraglutide (n = 834), insulin degludec (n = 414), or liraglutide (n = 415) for 26 weeks. The dose in all 3 groups was adjusted based on glycemic control. Insulin degludec/liraglutide was administered at the same time each day; the dosage regimen was titrated twice weekly to achieve a fasting blood glucose of 72 to 90 mg/dL. Metformin or pioglitazone was continued unchanged, unless documented safety reasons warranted a dosage adjustment.

Results

Primary Endpoint(s)

- The mean reduction in HbA_{1c} was −1.9% with insulin degludec/liraglutide, −1.4% with insulin degludec, and −1.3% with liraglutide at week 26, with insulin degludec/liraglutide meeting criteria for noninferiority to insulin degludec (estimated treatment difference, −0.47% [95% confidence interval, CI, −0.58% to −0.36%]; $P < .001$) and meeting criteria for superiority to liraglutide (estimated treatment difference, −0.64% [95% CI, −0.75% to −0.53%]; $P < .001$). HbA_{1c} at the end of treatment was 6.4% with insulin degludec/liraglutide, 6.9% with insulin degludec, and 7% with liraglutide.

Secondary Endpoint(s)

- Achievement of HbA_{1c} less than 7% at week 26 occurred in 81% of patients with insulin degludec/liraglutide, 65% with insulin degludec, and 60% with liraglutide; the number needed to treat (NNT) was 7 versus insulin degludec and 5 versus liraglutide. The odds ratio (OR) was 2.38 (95% CI, 1.78-3.18; $P < .001$) for insulin degludec/liraglutide versus insulin degludec and 3.26 (95% CI, 2.45-4.33; $P < .001$) for insulin degludec/liraglutide versus liraglutide.
- Achievement of HbA_{1c} less than 6.5% at week 26 occurred in 70% of patients with insulin degludec/liraglutide, 47% with insulin degludec, and 41% with liraglutide; NNT was 5 versus insulin degludec and 4 versus liraglutide. The OR was 2.82 (95% CI, 2.17-3.67; $P < .001$) for insulin degludec/liraglutide versus insulin degludec and 3.98 (95% CI, 3.05-5.18; $P < .001$) for insulin degludec/liraglutide versus liraglutide.
- Insulin degludec/liraglutide therapy was associated with a 0.5-kg weight loss, insulin degludec with a 1.6-kg weight gain, and liraglutide with a 3-kg

weight loss from baseline to week 26; estimated treatment difference was −2.22 kg (95% CI, −2.64 to −1.8; $P < .0001$) between insulin degludec/liraglutide and insulin degludec and +2.44 kg (95% CI, 2.02-2.86; $P < .001$) between insulin degludec/liraglutide and liraglutide.
- Documented symptomatic hypoglycemia occurred in 32% of patients in the insulin degludec/liraglutide group, 39% in the insulin degludec group, and 7% in the liraglutide group.

Comments: This study was conducted in 19 countries (the United States, Australia, Canada, Finland, Germany, Hungary, India, Ireland, Italy, Malaysia, Mexico, Puerto Rico, the Russian Federation, Singapore, Slovakia, South Africa, Spain, Taiwan, Thailand, and the United Kingdom). Of the 1663 patients randomized, 1444 (87%) completed the study. The liraglutide group had the highest withdrawal rate (18%), while 12% of patients withdrew from both the insulin degludec/liraglutide and insulin degludec groups. Gastrointestinal (GI) adverse events were the main cause for study withdrawal in the liraglutide group. A 26-week extension study (total of 52 weeks of treatment) confirmed the initial 26-week results and showed the sustainability of those changes, with no new adverse events or tolerability issues.[8] DUAL II, a trial similar to DUAL I, was a double-blind study comparing insulin degludec/liraglutide plus metformin and insulin degludec plus metformin in 413 patients over 26 weeks. As in DUAL I, the insulin degludec/liraglutide group had better glycemic control than the insulin degludec group.[9] A post hoc analysis used data from DUAL I and DUAL II to determine whether glycemic response to insulin degludec/liraglutide was faster than the response to insulin degludec or liraglutide alone; results show that plasma glucose was reduced to a greater extent with insulin degludec/liraglutide during the first 12 weeks than with each component alone.[10] Another post hoc analysis used data from the DUAL I extension and DUAL II trials to determine whether the combination was consistently effective in patients with type 2 diabetes, regardless of the stage of type 2 diabetes progression; this analysis determined that reduction in HbA_{1c} with insulin degludec/liraglutide was independent of disease duration and previous insulin dose but varied depending on pretrial oral antidiabetic drug treatment.[11]
Limitations: This was an open-label study with a short treatment duration (26 weeks). However, the 26-week extension study helped to overcome the short duration of treatment in the DUAL I study.

Drug: Insulin Degludec/Liraglutide versus Unchanged GLP-1 Receptor Agonist
Reference: Linjawi S, et al, 2016 (DUAL III trial)[12]
Study Design: Phase 3, randomized, open-label, multicenter study
Study Funding: Novo Nordisk
Patients: 438 insulin-naive adults with type 2 diabetes inadequately controlled with a GLP-1 receptor agonist (liraglutide once daily or exenatide twice daily) and oral antidiabetic drugs (metformin alone or in combination with pioglitazone and/or sulfonylurea). Patients were required to have received treatment with the maximum approved or tolerated dose of a GLP-1 or oral antidiabetic drug for at least 90 days before screening. Patients had HbA_{1c} of 7% to 9% and a BMI of 40 kg/m^2 or less. Patients were excluded if they had received oral antidiabetic drugs other than metformin, pioglitazone, and a sulfonylurea, within 90 days of screening. Average baseline characteristics were similar between the 2 study groups (insulin degludec/liraglutide and unchanged GLP-1 receptor agonist): Patient age was approximately 58 years, BMI was approximately 33 kg/m^2, and HbA_{1c} was approximately 7.8%. In the unchanged GLP-1 receptor agonist group, 79.5% of patients were treated with liraglutide once daily and 20.5% received exenatide twice daily. Baseline use of oral antidiabetic drugs was similar in both groups: Approximately 74% received metformin alone, approximately 21% received metformin plus a sulfonylurea, approximately 2.5% received metformin plus pioglitazone, and approximately 2% received metformin plus a sulfonylurea and pioglitazone. Mean duration of treatment with a GLP-1 receptor agonist prior to enrollment was 468.1 days in the insulin degludec/liraglutide group and 498.6 days in the unchanged GLP-1 receptor agonist group. The study was completed by 94.5% of patients in the insulin degludec/liraglutide group and 80.1% of the unchanged GLP-1 receptor agonist group.
Intervention: Patients were randomized 2:1 to receive insulin degludec/liraglutide (n = 292) or unchanged GLP-1 receptor agonist therapy (n = 146). Insulin degludec/liraglutide was dosed once daily, preferably at the same time each day; the dose of insulin degludec/liraglutide was adjusted twice weekly to achieve a fasting plasma glucose of 72 to 90 mg/dL. No changes in dosage regimen were made in the GLP-1 receptor agonist group. Any oral antidiabetic drugs patients were receiving prior to the study were continued unchanged in both groups.

Results

Primary Endpoint(s)

- HbA_{1c} decreased from 7.8% at baseline to 6.4% at week 26 in the insulin degludec/liraglutide group and from 7.7% to 7.4% in the unchanged GLP-1 receptor agonist group. Mean change from baseline to week 26 was 1.3% and 0.3%, respectively. The estimated treatment difference between the 2 groups was −0.94% (95% CI, −1.11% to −0.78%).

Secondary Endpoint(s)

- Achievement of HbA_{1c} less than 7% at week 26 occurred in 75% of patients in the insulin degludec/liraglutide group and in 36% in the unchanged GLP-1 receptor agonist group; NNT was 3. The OR for insulin degludec/liraglutide versus unchanged GLP-1 receptor agonist therapy was 6.84 (95% CI, 4.28-10.94; $P < .001$).
- Achievement of HbA_{1c} 6.5% or less at week 26 occurred in 63% of patients in the insulin degludec/liraglutide group and in 23% in the unchanged GLP-1 receptor agonist group; NNT was 3. The OR for insulin degludec/liraglutide versus unchanged GLP-1 receptor agonist therapy was 7.53 (95% CI, 4.58-12.38; $P < .001$).
- Body weight increased by 2 kg in the insulin degludec/liraglutide group and decreased by 0.8 kg in the unchanged GLP-1 receptor agonist group. The end-of-treatment difference between the 2 groups was 2.89 kg (95% CI, 2.17-3.62; $P < .001$).
- Confirmed hypoglycemia occurred in both groups but was lower in the unchanged GLP-1 receptor agonist group. There were 2.82 episodes of confirmed hypoglycemia per patient-years of exposure in the insulin degludec/liraglutide group and 0.12 episodes per patient-years of exposure in the unchanged GLP-1 receptor agonist group. Only 1 episode of severe hypoglycemia was reported (in the insulin degludec/liraglutide group). The risk of hypoglycemia was increased in both groups if a sulfonylurea was part of the treatment regimen.
- The proportion and rates of other treatment-emergent adverse events and serious adverse events were similar in both groups.

Comments: The study was conducted in Australia, France, Hungary, Slovakia, and the United States. The robustness of the primary outcome was substantiated by 3 sensitivity analyses (repeated measurement analysis, per-protocol analysis, and completer analysis), all of which confirmed superiority of insulin degludec/liraglutide.
Limitations: This was an open-label study with a short treatment duration (26 weeks).

Drug: Insulin Degludec/Liraglutide versus Placebo
Reference: Rodbard HW, et al, 2017 (DUAL IV trial)[13]
Study Design: Phase 3, randomized, double-blind, multicenter study
Study Funding: Novo Nordisk
Patients: 435 adults with type 2 diabetes inadequately controlled with a stable daily dose of sulfonylurea (at least half of the maximum approved dose according to local label) with or without metformin (at least 1500 mg or maximum tolerated dose) for at least 90 days. Patients had a BMI of 40 kg/m^2 or less and were insulin and GLP-1 receptor agonist naive. Patients were excluded if they had received any antidiabetic agent other than sulfonylureas or metformin within 90 days of screening. Average baseline characteristics were similar between the 2 study groups (insulin degludec/liraglutide and placebo): Patient age was approximately 60 years, BMI was approximately 32 kg/m^2, and HbA_{1c} was 6%. At baseline, 10.4% of patients in the insulin degludec/liraglutide group and 11.6% in the placebo group were receiving sulfonylurea therapy; 89.6% and 88.4%, respectively, were receiving sulfonylurea plus metformin therapy. Of the 435 patients randomized, 362 (83.2%) completed the study; the completion rate was 86.9% in the insulin degludec/liraglutide group and 76% in the placebo group.
Intervention: Patients were randomized 2:1 to receive a once-daily subcutaneous injection of insulin degludec/liraglutide or placebo given independently of meals but preferably at the same time each day. The dose of insulin degludec/liraglutide was titrated twice weekly to achieve a fasting blood glucose of 72 to 108 mg/dL. All previously prescribed sulfonylurea and metformin therapy was continued unchanged in both groups.

Results

Primary Endpoint(s)

- HbA_{1c} decreased from 7.9% to 6.4% in the insulin degludec/liraglutide group and from 7.9% to 7.4% in the placebo group. The estimated treatment difference was −1.02% (95% CI, −1.18% to −0.87%; $P < .001$).

Secondary Endpoint(s)

- Achievement of HbA_{1c} less than 7% at week 26 occurred in 79.2% of patients in the insulin degludec/liraglutide group and in 28.8% in the placebo group; NNT was 2. The OR for insulin degludec/liraglutide versus placebo was 11.95 (95% CI, 7.22-19.77; $P < .001$).
- Achievement of HbA_{1c} less than 6.5% at week 26 occurred in 64% of patients in the insulin degludec/liraglutide group and in 12.3% in the placebo group; NNT was 2. The OR for insulin degludec/liraglutide versus placebo was 16.36 (95% CI, 9.05-29.56; $P < .001$).
- Body weight increased by 0.5 kg in the insulin degludec/liraglutide group and decreased by 1 kg in the placebo group; the end-of-treatment difference between the 2 groups was 1.48 kg (95% CI, 0.9-2.06; $P < .001$).
- Confirmed hypoglycemia occurred in 41.7% of patients in the insulin degludec/liraglutide group and in 17.1% of the placebo group. There were 3.52 episodes of confirmed hypoglycemia per patient-years of

exposure in the insulin degludec/liraglutide group and 1.35 episodes per patient-years of exposure in the placebo group. Only 2 episodes of severe hypoglycemia were reported, both in the insulin degludec/liraglutide group.

Comments: The study drug and placebo were added to preexisting treatment with a sulfonylurea with or without metformin. The goal of this study was to determine the safety and efficacy of insulin degludec/liraglutide in insulin-naive patients with type 2 diabetes inadequately controlled on sulfonylurea therapy (glibenclamide, gliclazide, glimepiride, and glipizide) with or without metformin. The study was conducted in Bulgaria, Canada, Germany, India, Israel, Turkey, and the United States. The rate of hypoglycemia was higher in DUAL IV compared with DUAL I, DUAL II, and DUAL III; however, all patients were receiving a sulfonylurea in DUAL IV, and previous studies have shown a higher risk of hypoglycemia when liraglutide or other GLP-1 receptor agonists were combined with sulfonylurea therapy.
Limitations: The study had a short treatment duration (26 weeks).

Contraindications, Warnings, and Precautions

Contraindications

Insulin degludec/liraglutide is contraindicated in patients with hypersensitivity to insulin degludec, liraglutide, or any component of the formulation.[1] Insulin degludec/liraglutide is contraindicated during episodes of hypoglycemia.[1] Insulin degludec/liraglutide is also contraindicated in patients with a personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2; this is a boxed warning and contraindication that was required for several GLP-1 receptor agonists based on animal data.[1]

Warnings and Precautions

Anaphylaxis and serious hypersensitivity reactions, including angioedema, may occur with insulin degludec/liraglutide. Patients with a history of these reactions with use of other GLP-1 receptor agonists may be at risk for similar reactions. Use of insulin degludec/liraglutide is contraindicated in patients with a previous hypersensitivity reaction to insulin degludec, liraglutide, or any excipients of these products. If a hypersensitivity reaction occurs, insulin degludec/liraglutide therapy should be discontinued.[1]

Acute pancreatitis, including fatal and nonfatal hemorrhagic or necrotizing pancreatitis, has been reported with GLP-1 receptor agonists. Insulin degludec/liraglutide is not recommended for patients with a history of pancreatitis. If signs or symptoms associated with pancreatitis develop, insulin degludec/liraglutide therapy should be discontinued and appropriate management initiated. If pancreatitis is confirmed, it is recommended that insulin degludec/liraglutide therapy not be restarted.[1]

Hypoglycemia or hyperglycemia may occur with changes in a diabetes control regimen. When adjustments are made in insulin degludec/liraglutide dose, the frequency of blood glucose monitoring should be increased. Adjustments in the dose of concomitant oral antidiabetic treatment may be needed.[1] Hypoglycemia is the most common adverse reaction associated with insulin-containing products. The risk of hypoglycemia increases with intensity of glycemic control. Other factors that may increase the risk of hypoglycemia include changes in meal pattern or composition, changes in level of physical activity, changes in coadministered medication, or renal/hepatic impairment.[1]

Hypokalemia may occur with any insulin product. Potassium levels should be monitored in patients at risk for hypokalemia.[1]

Acute kidney injury and worsening of chronic renal failure have been reported with use of GLP-1 receptor agonists. Renal function should be monitored when therapy is initiated or the dose of insulin degludec/liraglutide is increased, especially in patients with renal impairment and in those reporting severe GI reactions.[1]

If insulin degludec/liraglutide is used concomitantly with peroxisome proliferator–activated receptor-gamma agonists (eg, thiazolidinediones), fluid retention and heart failure may occur.[1]

Patients may develop antibodies to insulin or liraglutide. Monitoring for antibodies is not recommended, but if the patient fails to achieve targeted glycemic control or develops worsening glycemic control, significant injection-site reactions, or allergic reactions, alternative antidiabetic therapy should be considered.[1]

The impact of insulin degludec/liraglutide on macrovascular risk reduction has not been established.[1]

Thyroid C-cell tumors have been observed in rats and mice exposed to liraglutide. It is unknown whether insulin degludec/liraglutide causes thyroid C-cell tumors, including medullary thyroid carcinoma.[1]

Insulin degludec/liraglutide pens should not be shared between patients.[1]

The safety of liraglutide use during pregnancy has not been fully established; based on animal reproduction studies, there may be risks to the fetus associated with exposure to liraglutide. Insulin degludec/liraglutide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.[1]

There are no data regarding the presence of liraglutide or insulin degludec in human milk or their effects on breastfeeding infants or milk production. Insulin degludec and liraglutide are present in the milk of lactating rats.[1]

Safety and effectiveness have not been established in pediatric patients.[1]

No adjustments in dose are required for elderly patients; however, hypoglycemia may be difficult to recognize in this population. Initial therapy for an elderly patient should be conservative to minimize the risk of hypoglycemic reactions.[1]

Dosage adjustments may be required in patients with renal impairment. Liraglutide should be used with caution in patients with impaired renal function because of the risk of acute kidney injury or worsening of chronic renal failure.[1]

Liraglutide slows gastric emptying. It has not been evaluated in patients with preexisting gastroparesis.[1]

The warnings and precautions in insulin degludec/liraglutide product labeling are similar to those of insulin glargine/lixisenatide.[1,2] One exception is regarding the risk of thyroid C-cell tumors in the insulin degludec/liraglutide product labeling.

Adverse Reactions

Adverse reactions commonly associated with insulin degludec/liraglutide therapy include nasopharyngitis (9.6%), headache (9.1%), nausea (7.8%), diarrhea (7.5%), increased lipase (6.7%), and upper respiratory tract infection (5.7%). Severe symptomatic hypoglycemia occurred in 0% to 0.5% of patients in clinical trials. Other adverse reactions included GI adverse reactions (eg, vomiting, constipation, dyspepsia, gastritis, abdominal pain, flatulence, gastroesophageal reflux disease, abdominal distension, decreased appetite), cholelithiasis, cholecystitis, lipodystrophy at the injection site, injection-site reactions, peripheral edema, and weight gain.[1]

Similar adverse reactions have been reported with insulin glargine/lixisenatide.[2]

Drug Interactions

Concomitant use of medications that can affect glucose metabolism requires careful monitoring for impact on glycemic control; appropriate dosage adjustments should be made, if necessary.[1]

The liraglutide component of insulin degludec/liraglutide may delay gastric emptying and therefore may reduce the rate of absorption of orally administered medications.[1]

The drug interactions addressed in insulin degludec/liraglutide product labeling are similar to those with insulin glargine/lixisenatide.[1,2]

Recommended Monitoring

The frequency of blood glucose monitoring should be increased after any change in dose or after the addition of other antidiabetic drugs or drugs known to alter blood glucose levels.[1]

Potassium levels should be monitored in patients at risk for hypokalemia.[1]

The monitoring recommendations regarding blood glucose and potassium for insulin degludec/liraglutide are similar to those for insulin glargine/lixisenatide.[1,2]

Dosing

Prior to administration of the first dose of insulin degludec/liraglutide, previous liraglutide and basal insulin therapy must be discontinued. The starting dose of insulin degludec/liraglutide is determined by the patient's previous basal insulin or liraglutide dose. If the patient was previously receiving less than 30 units of basal insulin or was receiving liraglutide, the starting dosage of the combination product is 16 units (insulin degludec 16 units/liraglutide 0.58 mg) given subcutaneously once daily.[1]

Dosage titration should occur at 3- to 4-day intervals in increments of 2 units, based on the patient's metabolic needs, blood glucose monitoring results, and glycemic control goal. Dosage adjustments may be needed to minimize the risk of hypoglycemia or hyperglycemia in cases of change in patient's physical activity, meal patterns, or renal or hepatic function; during acute illness; or when used with other medications.[1]

If a dose of insulin degludec/liraglutide is missed, the patient should resume the prescribed once-daily regimen with the next scheduled dose. If more than 3 days have elapsed since the last dose, therapy should be reinitiated at the starting dose.[1]

The insulin degludec/liraglutide combination should be injected subcutaneously once daily. The maximum daily dosage is 50 units (insulin degludec 50 units/liraglutide 1.8 mg). The pens are designed to deliver insulin degludec doses of 10 to 50 units with each injection. If the patient requires a persistent daily dosage of insulin degludec below 16 units or above 50 units, alternative products should be prescribed; the ability of the pen to deliver 10 units of insulin degludec is intended for temporary dosing during down-titration, not for continuous therapy.[1]

Insulin degludec/liraglutide is for subcutaneous administration in the thigh, upper arm, or abdomen. Rotate injection sites within the same region from one injection to the next to reduce the risk of lipodystrophy. Insulin degludec/liraglutide should not be administered intravenously, intramuscularly, or by an infusion pump; nor should it be diluted or mixed with any other insulin products or solutions.[1]

Both insulin degludec/liraglutide and insulin glargine/lixisenatide are for administration subcutaneously once daily.[1,2]

Product Availability

Insulin degludec/liraglutide was approved by the FDA on November 21, 2016.[14] It is available as a 3-mL single-patient-use pen injector. Each pen contains insulin degludec 100 units/mL and liraglutide 3.6 mg/mL. The product is distributed in

packages containing 5 pens, but needles are not included; a new *NovoFine* or *NovoTwist* needle is needed.[1]

Prior to first use, the pen should be stored in the refrigerator at 2°C to 8°C (36°F-46°F). Freezing should be avoided; if contents freeze, the pen should be discarded. After first use, the pen can be stored at room temperature (15°C-30°C [59°F-86°F]) but must be discarded after 21 days. The pens should be protected from light. The needle should be removed after each use. New needles (eg, *NovoFine* or *NovoTwist* needles) should be used for each injection.[1]

Drug Safety/Risk Evaluation and Mitigation Strategy (REMS)

A communication plan REMS is required for insulin degludec/liraglutide.[1,14]

Conclusion

Insulin degludec/liraglutide is a combination of a long-acting basal insulin and a GLP-1 receptor agonist approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus inadequately controlled on basal insulin (less than 50 units daily) or liraglutide (less than or equal to 1.8 mg daily). A factor influencing the decision to add the combination agent to the formulary will be whether the individual ingredients are already on the formulary. This convenient combination produces better glucose lowering and related changes in laboratory values than either agent alone and is more convenient for patient use because it requires 1 injection instead of 2 separate injections. There are no head-to-head comparison studies with insulin degludec/liraglutide and insulin glargine/lixisenatide (another long-acting insulin/GLP-1 receptor agonist combination). The role of various diabetes drugs in the treatment of patients with established cardiovascular disease also needs to be considered; 2017 treatment guidelines indicate that empagliflozin or liraglutide therapy should be considered for these patients.

Declaration of Conflicting Interests

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