Insulin degludec / liraglutide (Xultophy®) New Drug Update

December 2016

<table>
<thead>
<tr>
<th><strong>Drug Name:</strong></th>
<th>Insulin degludec / liraglutide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trade Name (Manufacturer):</strong></td>
<td>Xultophy (Novo Nordisk)</td>
</tr>
<tr>
<td><strong>Form:</strong></td>
<td>Subcutaneous injection</td>
</tr>
<tr>
<td><strong>Strength:</strong></td>
<td>Insulin degludec 100 units and liraglutide 3.6 mg per mL solution in a 3 mL prefilled multi-dose pen</td>
</tr>
<tr>
<td><strong>FDA Approval:</strong></td>
<td>November 21, 2016</td>
</tr>
<tr>
<td><strong>Market Availability:</strong></td>
<td>Anticipated first half of 2017</td>
</tr>
<tr>
<td><strong>FDA Approval Classification:</strong></td>
<td>Standard Review</td>
</tr>
<tr>
<td><strong>Classification:</strong></td>
<td>Specific Therapeutic Class (HIC3): Antihyperglycemics, Insulin, Long Acting-GLP-1 Receptor agonist (C4X)</td>
</tr>
</tbody>
</table>

**INDICATION**

Xultophy, a fixed-dose combination of insulin degludec (Tresiba®) and the GLP-1 agonist, liraglutide (Victoza®) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) who are not controlled on basal insulin (< 50 units daily) or liraglutide (≤ to 1.8 mg daily).

Limitations of use:
- Not recommended as first-line therapy in patients not controlled on diet and exercise
- Not for treatment of type 1 diabetes or diabetic ketoacidosis
- Not recommended in combination with other products containing a GLP-1 agonist, including liraglutide
- Not studied in combination with prandial insulin

**CONTRAINDICATIONS/WARNINGS**

Contraindications include use during episodes of hypoglycemia and use in patients with a hypersensitivity to any component of the product.

In animal studies, liraglutide was associated with malignant thyroid C-cell tumors. Postmarketing cases of medullary thyroid carcinoma (MTC) were reported; causality was not determined. Use of insulin degludec/liraglutide is contraindicated in patients with a personal or family history of MTC and in patients with multiple endocrine neoplasia syndrome type 2 (MEN 2).

Cases of pancreatitis were reported postmarketing in patients treated with liraglutide, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. Insulin degludec/liraglutide should be discontinued in patients with suspected pancreatitis and therapy should not be restarted if pancreatitis is confirmed. Alternative antidiabetic therapies should be considered in patients with a history of pancreatitis.
Acute renal failure and worsening of chronic renal failure has been reported postmarketing in patients treated with liraglutide. Patients should be aware of the potential risk of dehydration, particularly due to gastrointestinal side effects.

A risk evaluation and mitigation strategy (REMS) was approved for insulin degludec/liraglutide to mitigate the potential risk of MTC and acute pancreatitis. It includes a communication plan to healthcare providers and professional societies and submission of assessments to the FDA for up to 7 years.

As with other insulin-containing products, insulin degludec/liraglutide, can lead to hypokalemia. Potassium levels should be monitored in at risk patients.

Liraglutide slows gastric emptying. Insulin degludec/liraglutide has not studied in patients with gastroparesis.

Patients may develop antibodies against insulin degludec and/or liraglutide however, this occurrence has not been associated with reduced efficacy of insulin degludec/liraglutide.

Concomitant use with a thiazolidinedione (TZD) can lead to dose-related fluid retention, which can in turn exacerbate heart failure (HF). Patients with HF should be monitored appropriately.

**DRUG INTERACTIONS**

Liraglutide-containing products delay gastric emptying which has the potential to impact the absorption of concomitantly administered oral medications. Although, in clinical studies liraglutide had no relevant affect on the absorption of tested orally administered medications, caution should be used with coadministration of insulin degludec/liraglutide with oral agents.

Dose reductions or increases of insulin degludec/liraglutide may be necessary with concurrent use of medications that affect glucose metabolism.

**COMMON ADVERSE EFFECTS**

The most common adverse event reported in clinical trials with insulin degludec/liraglutide was hypoglycemia. In clinical trials, severe hypoglycemia was reported in zero to 0.5% of patients.

Other common adverse reactions occurring in ≥ 5% of patients treated with insulin degludec/liraglutide include nasopharyngitis (9.6%), headache (9.1%), nausea (7.8%), diarrhea (7.5%), increased lipase (6.7%), and upper respiratory tract infection (5.7%).

Weight gain of 2 kg has been reported in clinical studies with insulin degludec/liraglutide.

Gastrointestinal adverse reaction may occur when initiating insulin degludec/liraglutide therapy.

Mild injection site reaction may occur with insulin degludec/liraglutide. As with other subcutaneous (SC) insulins, lipoatrophy or lipohypertrophy can also occur at injection sites.

**SPECIAL POPULATIONS**

**Pregnancy**

There are no available data with insulin degludec, liraglutide, or their combination in pregnant women to inform a drug associated risk for major birth defects and miscarriage.
**Pediatrics**

Safety and effectiveness in pediatric patients have not been established.

**Geriatrics**

No overall differences have been observed in elderly (≥ 65 years) or very elderly (≥ 75 years) patients compared to the overall population, but individual sensitivity cannot be ruled out.

**Hepatic Impairment**

Insulin degludec/liraglutide has not been studied in patients with hepatic impairment. There is limited data on use of liraglutide in this population. No clinically relevant impact on the pharmacokinetics of insulin degludec was identified in patients with hepatic impairment.

**Renal Impairment**

There is limited data on the use of insulin degludec/liraglutide in patients with mild and moderate renal impairment; additional glucose monitoring and dose adjustments may be required. Insulin degludec/liraglutide has not been studied in patients with severe renal impairment.

**DOSAGES**

Discontinue therapy with liraglutide or basal insulin prior to starting insulin degludec/liraglutide.

Recommended starting dose of insulin degludec/liraglutide is 16 units SC once daily (16 units insulin degludec and 0.58 mg liraglutide)

Administer at the same time each day with or without food.

Dosage can be titrated in 2 unit increments every 3 to 4 days as-needed. Maximum dose is 50 units (50 units insulin degludec and 1.8mg liraglutide)

Prefilled pen delivers from 10 to 50 units in a single injection. In patients who require < 16 units or > 50 units, an alternative antidiabetic product should be prescribed.

The product labeling provides a table with the units insulin degludec and mg of liraglutide in each dose of the combination product.

If a dose is missed, therapy should be resumed with the next scheduled dose at the prescribed dosage. If more than 3 days have elapsed since the last dose, restart dosage at 16 units to lessen gastrointestinal side effects.

Do not split the dose or mix with other insulins.
CLINICAL TRIALS\textsuperscript{2,3} 

A literature search was conducted using “liraglutide” and “insulin degludec” and “iDegLira”

Three pivotal 26-week, phase 3 trials evaluated the efficacy and safety of the fixed-combination of insulin degludec/liraglutide in 1,393 patients with T2DM. Study 1, 2, and 3 switched patients from liraglutide, any basal insulin, or insulin glargine U-100 to the fixed-dose combination insulin degludec/liraglutide, respectively. Dosages for the combination product and the basal-insulin comparators were titrated based on fasting plasma glucose (FPG) of 72 to 90 mg/dL.

Study 1 was an open-label study that randomized patients who were inadequately controlled on liraglutide and metformin alone or in combination with pioglitazone, sulfonylurea or both. OADs were continued at pre-trial doses. Patients received insulin degludec/liraglutide (starting dose of 16 units) or liraglutide (median dose was 1.7 mg). Baseline HbA1c was 7.8% in each group. The dose of the combination product was 44 units at trial end. At 26-weeks, change in HbA1c was -1.31% in the combination group compared to -0.36% in the liraglutide group. Percent of patients that achieved HbA1c < 7% was 74.6% and 30.2%, respectively. At study end, mean FPG was lower with the combination than with liraglutide (112 versus 153 mg/dL).

In study 2, insulin degludec/liraglutide was compared to insulin degludec as add-on to metformin (n=348). Basal insulin, sulfonylureas, and glinides were discontinued at randomization. Each study drug was started at a dose of 16 units and the maximum dose was 50 units. Baseline HbA1c were 8.7% for the combination group and 8.8% for the insulin degludec group. At week 26, change in HbA1c was -1.94% for the combination group and -1.05% for the insulin degludec group, the difference was statistically significant. Percentage of patients that achieved HbA1c < 7% was 57.3% in the combination group and 22.6% in the insulin degludec group. In addition, mean FPG at study end was lower with the combination product than insulin degludec (110 versus 118 mg/dL). The final dose of insulin in each group was 46 units; this study was designed to show the benefit of liraglutide component on glycemic lowering.

Study 3 compared insulin degludec/liraglutide with insulin glargine U-100, both given once daily as add-on to metformin, in patients (n=557) inadequately controlled on insulin glargine U-100 and metformin. Starting doses were 16 units and 32 units for the combination and insulin glargine, respectively. Baseline HbA1c were 8.4% in the combination group and 8.2% in the insulin glargine group. At 26 weeks, average dose for the combination was 41 units and for insulin, glargine was 66 units. HbA1c changed by -1.67% for the combination and -1.16% for insulin glargine. Percentage of patients that achieved HbA1c < 7% was 68.3% in the combination group compared to 46.2% in the insulin glargine group. Mean change in FPG was similar between groups.

In general, across the studies insulin degludec/liraglutide was associated with weight gain when compared to a GLP-1 agonist or placebo (3 kg and 1.7 kg, respectively). It also caused numerically less weight gain when compared to insulin.
OTHER DRUGS USED FOR CONDITION

According to the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) 2016 Comprehensive Type 2 Diabetes Management Algorithm, treatment recommendations include metformin, GLP-1 receptor agonists, dipeptidyl peptase-4 inhibitors, sodium glucose co-transporter 2 inhibitors, thiazolidinediones, insulin, coleselvam, bromocriptine, sulfonylureas, and alpha glucosidase inhibitors. 4

PLACE IN THERAPY

In patients with T2DM, dual- and triple-therapy is appropriate when HbA1c is 7.5% or greater. Insulin degludec/liraglutide targets both FPG and postprandial glucose. In clinical trials, the combination product resulted in significantly greater decrease in HbA1c (approximately an additional 1%) and FPG when compared to either component. Insulin degludec/liraglutide is an option for patients who are not controlled with basal insulin (< 50 units daily) or liraglutide (≤ to 1.8 mg daily). Combining antidiabetic medication in a single dosage form can reduce injection burden, but this may be at the cost of dosing flexibility.

In addition, the LEADER trial reported positive cardiovascular outcomes with liraglutide, a component of insulin degludec/liraglutide (Xultophy). 5 As comparison, the GLP-1 agonist, lixisenatide (Adlyxin™), demonstrated a neutral effect on cardiovascular outcomes when compared to placebo (ELIXA study) 6.

SUGGESTED UTILIZATION MANAGEMENT

<table>
<thead>
<tr>
<th>Anticipated Therapeutic Class Review (TCR) Placement</th>
<th>Hypoglycemics, Incretin Mimetics/Enhancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Edit</td>
<td>• Age ≥ 18 years</td>
</tr>
<tr>
<td></td>
<td>• Diagnosis of type 2 diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>• Trial and failure of liraglutide or basal insulin</td>
</tr>
<tr>
<td></td>
<td>• If non-preferred, trial and failure of preferred GLP-1 receptor agonists and insulin</td>
</tr>
<tr>
<td>Quantity Limit</td>
<td>5 pens (1 carton) / 30 days</td>
</tr>
<tr>
<td>Duration of Approval</td>
<td>1 year</td>
</tr>
<tr>
<td>Drug to Disease Hard Edit</td>
<td>• Type 1 diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>• Diabetic ketoacidosis</td>
</tr>
<tr>
<td></td>
<td>• Pancreatitis</td>
</tr>
<tr>
<td></td>
<td>• Gastroparesis</td>
</tr>
</tbody>
</table>

REFERENCES