Therapeutic Class Overview
Insulin and Incretin Mimetic combination agents

INTRODUCTION

- Diabetes is a tremendous burden on the United States (US) healthcare system. In 2013, diabetes was the 7th leading cause of death in the US. More than 29 million people, or 9.3% of the US population, are estimated to have diagnosed or undiagnosed diabetes (Centers for Disease Control [CDC], 2014).
- The classification of diabetes includes four clinical classes: 1) type 1 diabetes mellitus (T1DM) which results from beta-cell (β-cell) destruction, usually leading to absolute insulin deficiency, 2) type 2 diabetes mellitus (T2DM) which results from a progressive insulin secretory defect on the background of insulin resistance, 3) other specific types of diabetes due to other causes, eg, genetic defects in β-cell function, genetic defects in insulin action, diseases of the exocrine pancreas (such as cystic fibrosis), and drug- or chemical-induced (such as in the treatment of human immunodeficiency virus [HIV]/acquired immunodeficiency syndrome [AIDS] or after organ transplantation), and 4) gestational diabetes mellitus (GDM) (diabetes diagnosed during pregnancy that is not clearly overt diabetes) (American Diabetes Association [ADA], 2017).
- The gold standard measure to assess average glycemic exposure in the diagnosis and treatment of T2DM is glycated hemoglobin (HbA1c). HbA1c reflects the average blood glucose (BG) levels over the past 12 weeks including both fasting plasma glucose (FPG) and postprandial plasma glucose (PPG). The exact contributions of PPG and FPG increments to the measure of hyperglycemia and its role in the development of both micro- and macrovascular complications of diabetes remain controversial (Monnier et al, 2011; Monnier et al, 2003).
- Pharmacologic options for T2DM include sulfonylureas (SFUs), biguanides, thiazolidinediones (TZDs), meglitinides (GLNs), alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, amylinomimetics, sodium-glucose cotransporter 2 (SGLT2) inhibitors, combination products, insulin, and glucagon-like peptide-1 (GLP-1) receptor analogs, also referred to as incretin mimetics.
  - Insulin is used as replacement therapy, and there are three basal insulin agents that are Food and Drug Administration (FDA)-approved (insulin detemir [LEVEMIR®], insulin degludec [TRESIBA®], insulin glargine [LANTUS® and TOUJEO®], and follow-on biologic insulin glargine [BASAGLAR®]). As a class of medications, the basal insulins are effective at lowering HbA1c and provide a nearly universal response. In the United Kingdom Prospective Diabetes Study (UKPDS), a reduced risk of microvascular events (eg, neuropathy, retinopathy, and nephropathy) was observed with use; however, insulin products are associated with hypoglycemia and weight gain (ADA, 2017; Prescribing information: BASAGLAR, 2016; LANTUS, 2016; LEVEMIR, 2015; TOUJEO, 2015; TRESIBA, 2015).
  - The GLP-1 receptor agonists (albiglutide [TANZEUM®], dulaglutide [TRULICITY®], exenatide [BYETTA®], exenatide ER [BYDUREON®], liraglutide [VICTOZA®], and lixisenatide [ADLYXIN™]) were developed to mimic the effects of endogenous GLP-1. Due to their extended half-lives, albiglutide, dulaglutide, and exenatide ER are dosed once weekly. Liraglutide and lixisenatide are dosed once daily, while exenatide is dosed twice daily. Of the GLP-1 receptor agonists, liraglutide is the only agent which has been shown to reduce CV and all-cause mortality when added to standard care. As a class of medications, the GLP-1 receptor agonists can cause hypoglycemia but not to the same degree as other oral anti-diabetic agents (OADs) and/or injectable agents. Additionally, they are known to decrease weight gain, increase gastrointestinal (GI)-related adverse events, and have been correlated with pancreatitis and c-cell hyperplasia/medullary thyroid tumors (ADA, 2017; Prescribing information: ADLYXIN, 2016; BYDUREON, 2015; BYETTA, 2015; TANZEUM, 2016; TRULICITY, 2017; VICTOZA, 2016).
- This review will focus on the long-acting insulin and GLP-1 receptor agonist combination products outlined in Table 1 for their respective FDA-approved indications.
- Medispan class: Insulin – Incretin Mimetic Combinations

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
SOLIQUA™ 100/33 (insulin glargine/lixisenatide)	Sanofi-Aventis	11/21/2016	-
XULTOPHY® 100/3.6 (insulin degludec/liraglutide)	Novo Nordisk	11/21/2016	-

(DRUGS@FDA, 2017)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	SOLIQUA (insulin glargine/ lixisenatide)	XULTOPHY (insulin degludec/ liraglutide)
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM inadequately controlled on:		
Basal insulin (<60 U daily) or lixisenatide	✔	--
Basal insulin (<50 U daily) or liraglutide (≤1.8 mg daily)	--	✔
Limitations of Use		
Not recommended as first-line therapy for patients inadequately controlled on diet and exercise.	--	✔
Has not been studied in patients with a history of unexplained pancreatitis. Other antidiabetic therapies should be considered in patients with a history of pancreatitis.	✔	✔
Not recommended for use in combination with any other product containing another GLP-1 receptor agonist.	✔	✔
Not for treatment of T1DM or diabetic ketoacidosis.	✔	✔
Not recommended for use in patients with gastroparesis.	✔	--
Has not been studied in combination with prandial insulin.	✔	✔

(Prescribing information: SOLIQUA, 2016; XULTOPHY, 2016)

NOTE: Information on indications, mechanism of action, pharmacokinetics, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Overview

- XULTOPHY, a combination of insulin degludec 100 U/mL and liraglutide 3.6 mg/mL, and SOLIQUA, a combination of insulin glargine 100 U/mL and lixisenatide 33 mcg/mL, have been approved for use in patients with T2DM who are inadequately controlled on basal insulin, or a GLP-1 receptor agonist (specifically liraglutide or lixisenatide, respectively). Insulin degludec/liraglutide reduced HbA1c more than its individual components when added to either metformin, pioglitazone, or a SFU. When added to metformin, insulin glargine/lixisenatide reduced HbA1c significantly more than insulin glargine alone. Insulin glargine/lixisenatide and insulin degludec/liraglutide are not FDA-approved for use in patients previously uncontrolled on OADs; therefore, these trials have been excluded from this review unless addressing comparative data in a class not addressed elsewhere.

SOLIQUA (insulin glargine/lixisenatide)

- The efficacy and safety of insulin glargine/lixisenatide were evaluated over 30 weeks in two Phase 3, active-comparator (AC), open-label (OL), randomized controlled trials (RCTs), titled the LIXILAN trials:
  - o T2DM patients uncontrolled on basal insulin: The LIXILAN-L trial was a two-treatment arm study in 731 T2DM patients. At baseline, patients were receiving basal insulin for at least six months at stable daily doses of 15 to 40 U ± OADs. Patients who had an insulin glargine daily dose of 20 to 50 U were randomized to either insulin glargine/lixisenatide 100/33 (N=366) or insulin glargine 100 U/mL (N=365). The maximum dose of insulin glargine allowed in the trial was 60 U for both groups. For the primary endpoint, HbA1c reduction after 30 weeks of treatment, the least square mean difference (LSMD) between insulin glargine/lixisenatide and insulin glargine was statistically significant favoring combination therapy over monotherapy (LSMD, −0.5%; 95% confidence interval [CI], −0.6 to −0.4; P<0.0001) (Aroda et al, 2016; FDA briefing document [SOLIQUA], 2016; FDA summary review [SOLIQUA], 2016).
  - o Comparative data vs. GLP-1 receptor agonists: The LIXILAN-O trial was a three-treatment arm study in 1,167 patients with T2DM who were inadequately controlled on metformin ± OADs. Patients who met HbA1c goals based on prior therapy were then randomized to either insulin glargine/lixisenatide 100/33 (N=468), insulin glargine 100

U/mL (N=466), or lixisenatide (N=233). The maximum dose of insulin glargine allowed in the trial was 60 U. For the primary endpoint, insulin glargine/lixisenatide required a non-inferior HbA1c reduction over 30 weeks compared to insulin glargine (non-inferiority upper margin of 0.3%). Both co-primary hypotheses were required to be established before the step-down testing procedure for the secondary efficacy endpoints, which included a test of superiority of insulin glargine/lixisenatide over insulin glargine. After 30 weeks of treatment, the LSMD in HbA1c reduction met non-inferiority compared to insulin glargine (LSMD, −0.3%; 95% CI, −0.4 to −0.2; P<0.0001) and also demonstrated superiority for the endpoint (P<0.0001). At week 30, the LSMD between insulin glargine/lixisenatide and lixisenatide was also statistically different for the primary endpoint (LSMD, −0.8%; 95% CI, −0.9 to −0.7; P<0.0001) (Rosenstock et al, 2016; FDA briefing document [SOLIQUA], 2016; FDA summary review [SOLIQUA], 2016).

- Weight and hypoglycemic events: Treatment with insulin glargine/lixisenatide was associated with mean weight losses of up to 0.7 kg from baseline across the aforementioned trials. Hypoglycemic rates were comparable for insulin glargine/lixisenatide and insulin glargine; however, a fewer proportion of lixisenatide-treated patients experienced documented symptomatic hypoglycemic events compared to insulin glargine/lixisenatide (6.4% vs. 25.6%, respectively) (Aroda et al, 2016**;** Rosenstock, et al, 2016; FDA summary review [SOLIQUA], 2016).

XULTOPHY (insulin degludec/liraglutide)

- The efficacy and safety of insulin degludec/liraglutide were evaluated over 26 weeks in nine Phase 3, parallel-group, AC, RCTs, titled the DUAL trials (XULTOPHY dossier, 2016). Currently, results from DUAL I through V are available, and DUAL VII through IX are on-going; therefore, results are not available. The DUAL I and IV trials were conducted in patients uncontrolled while administered OADs, and since insulin degludec/liraglutide is not FDA-approved for use in patients previously uncontrolled on OADs, these trials have been excluded from this review:
  - T2DM patients uncontrolled on basal insulin and OADs:
    - The DUAL II trial was a two-treatment arm, double-blinded (DB) study in 413 T2DM patients which compared insulin degludec/liraglutide (N=207) to insulin degludec (N=206). Prior to randomization, uncontrolled patients were receiving basal insulin (20 to 40 U) and metformin ± OADs. The maximum dose of insulin degludec allowed in the trial was 50 U, and the maximum allowed dose of liraglutide was 1.8 mg. HbA1c reduction from baseline after 26 weeks of treatment, the primary endpoint, was 1.9% for insulin degludec/liraglutide and 0.9% for insulin degludec. The estimated treatment difference (ETD) for HbA1c statistically favored combination injectable therapy over monotherapy (ETD, −1.1%; 95% CI, −1.3 to −0.8; P<0.0001) (Buse et al, 2014).
    - The DUAL V trial was a two-treatment arm, OL, non-inferiority study in 557 T2DM patients which compared insulin degludec/liraglutide (N=278) to insulin glargine (N=279) and metformin. Prior to randomization, uncontrolled patients were receiving insulin glargine (20 to 50 U) and metformin. The trial maximum dose of insulin degludec/liraglutide was 50 U of insulin degludec and 1.8 mg of liraglutide; there was no maximum dose for insulin glargine. For the primary endpoint, an upper bound of the 95% CI <0.3% was required for non-inferiority, which was achieved. The HbA1c reduction from baseline after 26 weeks of treatment was -1.8% for insulin degludec/liraglutide and -1.1% for insulin glargine. The ETD for HbA1c statistically favored combination injectable therapy over monotherapy (ETD, −0.59%; 95% CI, −0.74 to −0.45; P<0.001 for non-inferiority) (Lingvay et al, 2016).
  - T2DM patients uncontrolled on GLP-1 receptor agonists: The DUAL III trial was a two-treatment arm, OL study in 438 T2DM patients which compared insulin degludec/liraglutide (N=292) to the currently administered maximum dose of GLP-1 receptor agonist (N=146) and metformin ± OAD therapy. Prior to randomization, patients were receiving maximum doses of liraglutide once daily or exenatide twice daily, according to the local labeling, and metformin ± OADs. Internationally-approved doses of GLP-1 receptor agonists do not match FDA-approved doses. The trial maximum dose of insulin degludec/liraglutide was 50 U of insulin degludec and 1.8 mg of liraglutide. HbA1c reduction from baseline after 26 weeks of treatment, the primary endpoint, was 1.4% for insulin degludec/liraglutide and 0.3% for unchanged doses of GLP-1 receptor agonists. The ETD for HbA1c statistically favored combination injectable therapy over monotherapy (ETD, −0.94%; 95% CI, −1.1 to −0.8; P<0.001) (Linjawi et al, 2017).
  - Weight and hypoglycemic events: Treatment with insulin degludec/liraglutide was associated with mean weight losses of up to 2.7 kg and weight gain of 2 kg from baseline across the aforementioned trials. Hypoglycemia rates with insulin degludec/liraglutide were comparable to insulin degludec. However compared to GLP-1 receptor agonists, the estimated rate ratio (ERR) was 25.36 (95% CI, 10.63 to 60.51; P<0.001), demonstrating a statistically significantly higher rate of hypoglycemic episodes in the insulin degludec/liraglutide group vs. the GLP-1 receptor agonist group. Conversely, the ERR favored insulin degludec/liraglutide over insulin glargine, demonstrating a statistically significantly higher rate of hypoglycemic episodes in the insulin glargine group (ERR, 0.43; 95% CI, 0.3 to 0.61; P<0.001) (Buse et al, 2014; Lingvay et al, 2016; Linjawi et al, 2017; XULTOPHY dossier, 2016).

Cardiovascular (CV) outcomes

- A number of key CV studies have been conducted with insulin glargine, insulin degludec, liraglutide, and lixisenatide; of these, only liraglutide has demonstrated CV-positive outcomes. Studies with adequate power have not been conducted with the long-acting insulin and GLP-1 receptor agonist combination products.
  - The ORIGIN trial was a randomized trial without blinding conducted in 12,612 patients with CV risk factors plus impaired fasting glucose, impaired glucose tolerance, or T2DM. Patients were randomized to receive insulin glargine or standard of care therapy, which included continuing their pre-existing glycemic control regimen. CV risk factors at baseline included previous myocardial infarction (MI), stroke, angina, or coronary, carotid, or peripheral arterial revascularization. After a median 6.2 year follow-up, no significant difference in the co-primary endpoints of nonfatal MI, nonfatal stroke, or death from CV causes, and these events plus revascularization or hospitalization for heart failure (HF), were observed. The rates of incident CV outcomes were similar in the insulin glargine and standard care groups: 2.94 and 2.85 per 100 person-years, respectively, for the first co-primary outcome (hazard ratio [HR], 1.02; 95% CI, 0.94 to 1.11; P=0.63) and 5.52 and 5.28 per 100 person-years, respectively, for the second co-primary outcome (HR, 1.04; 95% CI, 0.97 to 1.11; P=0.27) (Gerstein et al, 2012).
  - A multi-center (MC), DB, randomized, placebo-controlled (PC) trial (ELIXA trial; N=6,068) was conducted to evaluate the long-term effects of lixisenatide vs. placebo on CV outcomes in patients with T2DM who had a recent acute coronary syndrome event within 180 days of screening. The primary endpoint was a composite of the first occurrence of any of the following: death from CV causes, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina. The median follow-up was 25 months. It was found that the primary endpoint event occurred in 13.4% of patients in the lixisenatide group and 13.2% in the placebo group (HR, 1.02; 95% CI, 0.89 to 1.17), which demonstrated non-inferiority of lixisenatide to placebo (P<0.001), but did not demonstrate superiority (P=0.81). The rates of the individual CV components of the primary endpoint were similar between the lixisenatide and placebo groups (Pfeffer et al, 2015).
  - A MC, DB, randomized, PC trial (LEADER trial; N=9,340) was conducted to evaluate the long-term effects of liraglutide vs. placebo on CV outcomes in patients with T2DM and high CV risk. The median follow-up was 3.8 years. It was found that the primary composite outcome (CV death, non-fatal MI, or non-fatal stroke) occurred in fewer patients in the liraglutide group (13%) vs. the placebo group (14.9%) (HR, 0.87; 95% CI, 0.78 to 0.97; P<0.001 for noninferiority; P=0.01 for superiority). Fewer patients died from CV causes in the liraglutide group (4.7%) vs. the placebo group (6%) (HR, 0.78; 95% CI, 0.66 to 0.93; P=0.007). The rate of death from any cause was lower in the liraglutide group (8.2%) vs. the placebo group (9.6%) (HR, 0.85; 95% CI, 0.74 to 0.97; P=0.02).The rates of nonfatal MI, nonfatal stroke, and hospitalization for heart failure were nonsignificantly lower in the liraglutide group than in the placebo group (Marso et al, 2016).
  - In 2015, insulin degludec was FDA-approved based on interim data from the DEVOTE trial which assessed CV risk; however, the full results of the DEVOTE trial are anticipated to be available in 2017 (Novo Nordisk press release [DEVOTE], 2016).
- According to reputable guidelines, the combination of both a GLP-1 receptor agonist and a basal insulin is generally reserved for third- or fourth-line treatment in patients who are inadequately controlled after a trial and failure of other agents. Combination insulin therapy may be initiated in patients with an HbA1c ≥10%, BG ≥300 mg/dL, or in patients who are markedly symptomatic; if HbA1c is not controlled, then combination injectable therapy may be considered (ADA, 2017; Garber et al, 2017).

SAFETY SUMMARY

- Contraindications:
  - All agents in class are contraindicated in patients with hypersensitivity to any component of the products and during episodes of hypoglycemia.
  - XULTOPHY (insulin degludec/liraglutide) is also contraindicated in and has a boxed warning for patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
- Boxed warnings:
  - Due to the liraglutide component of XULTOPHY, there is a boxed warning and a warning and precaution associated with thyroid C-cell tumors in rats and mice. It is unknown if they cause thyroid C-cell tumors including MTC in humans.
- Warnings/Precautions:
  - Warnings and precautions for the class are consistent with each individual agent and include pancreatitis, serious hypersensitivity reactions/allergic reactions, hypoglycemia or hyperglycemia, the potential for overdose due to medication errors, acute kidney injury, hypokalemia, the potential for fluid retention and HF with use of TZDs, and

the lack of clinical studies showing macrovascular risk reductions. Prefilled pens should never be shared between patients (even if the needle is changed) due to the risk of transmission of blood-borne pathogens.
  - Additional warnings and precautions for SOLIQUA include immunogenicity risks associated with the development of antibodies to insulin glargine and lixisenatide resulting in a loss of glycemic control.
- Adverse events:
  - The most common adverse reactions reported with these agents include nausea, nasopharyngitis, diarrhea, headache, and upper respiratory tract infection.
  - Additional common adverse reactions include hypoglycemia and allergic reactions with SOLIQUA and increased lipase reports with XULTOPHY.
- Drug Interactions:
  - The GLP-1 receptor agonist components may cause delayed gastric emptying of oral medications. Certain medications may require administration 1 hour before (ie, antibiotics, acetaminophen, oral contraceptives, or other medications dependent on threshold concentrations for efficacy) or 11 hours after (ie, oral contraceptives) administration of the GLP-1 receptor agonist.
  - Monitor use closely when administered concomitantly with other medications that may affect glucose metabolism.
  - Antiadrenergic medications (ie, beta blockers, clonidine, guanethidine, and reserpine) may mask the signs and symptoms of hypoglycemia.
- Risk Evaluation and Mitigation Strategy (REMS) programs:
  - As with other liraglutide-containing products, there is a REMS program for XULTOPHY, which includes a communication plan for alerting healthcare professionals about the risk of acute pancreatitis (including necrotizing pancreatitis) and the potential risk of MTC (REMS@FDA, 2017).

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
SOLIQUA (insulin glargine/ lixisenatide)	Prefilled pen (100 U and 33 mcg/mL): 3 mL prefilled pen in packages of 5 pens, with each pen delivering 46 possible dosages ranging from 15 U/5 mcg to 60 U/20 mcg	Initial (*previously treated with lixisenatide or <30 U of basal insulin*): 15 U (15 U of insulin glargine and 5 mcg of lixisenatide) SC once daily; Initial (*previously treated with 30 to 60 U of basal insulin*): 30 U (30 U of insulin glargine and 10 mcg of lixisenatide) SC once daily; Maximum: 60 U (60 U of insulin glargine and 20 mcg of lixisenatide) SC once daily	Titrate or taper doses by 2 to 4 U every week based on metabolic needs, BG monitoring, and glycemic control. For patients who require daily doses below 15 U or over 60 U, an alternative antidiabetic agent should be prescribed.	Discontinue GLP-1 receptor agonist or a basal insulin prior to therapy initiation. Inject in the abdomen, thigh, or upper arm. Administer within 1 hour before the first meal of the day, preferably the same meal each day. After first use, pens should be discarded after 14 days.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
XULTOPHY (insulin degludec/ liraglutide)	Prefilled pen (100 U and 3.6 mg/mL): 3 mL prefilled pen in packages of 5 pens, with each pen delivering 41 possible dosages ranging from 10 U/0.36 mg to 50 U/1.8 mg	Initial: 16 U (16 U of insulin glargine and 0.58 mg of liraglutide) SC once daily; Maximum: 50 U (50 U of insulin glargine and 1.8 mg of liraglutide) SC once daily	Titrate or taper doses by 2 U every 3 to 4 days based on metabolic needs, BG monitoring, and glycemic control. The dosage may be temporarily down titrated to below 16 U (ie, 10 to 15 U); however, an alternative therapy should be used if patients require persistent dosages below 16 U. For patients who require daily doses below 16 U or over 50 U, an alternative antidiabetic agent should be prescribed.	Discontinue GLP-1 receptor agonist or a basal insulin prior to therapy initiation. Inject in the abdomen, thigh, or upper arm. Administer at the same time every day with or without food. After first use, pens should be discarded after 21 days.

Abbreviations: BG = blood glucose; GLP-1 = glucagon-like peptide; SC = subcutaneously; U = unit

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
SOLIQUA* (insulin glargine/ lixisenatide)	Of the patients treated with SOLIQUA, a total of 25.2% were ≥65 years of age, and 4% were ≥75 years of age. No overall differences in efficacy and safety have been observed in older patients, but greater sensitivity in some older individuals cannot be ruled out. Hypoglycemia	Safety and efficacy have not been established.	The effect of renal impairment on SOLIQUA has not been studied. *Insulin glargine*: Increased levels of insulin have been observed in renal failure. *Lixisenatide*: Mild and moderate renal impairment require no dose adjustment. Only five patients with severe impairment have been exposed; therefore,	The effect of hepatic impairment on SOLIQUA has not been studied; however, monitoring should be intensified.	Category C† was assigned to insulin glargine mono-therapy previously. No well-controlled studies with SOLIQUA have been conducted in pregnancy; use only if the potential benefit outweighs the risk. Endogen-ous insulin is present in human milk. Lixisenatide is present in the milk of animal models.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
	may be difficult to detect in the elderly.		use should be closely monitored for GI AE and changes in renal function. SOLIQUA is not recommended in ESRD.		An assessment of the risks and benefits should be considered prior to nursing.
XULTOPHY* (insulin degludec/ liraglutide)	Of the patients treated with XULTOPHY, a total of 19.9% were ≥65 years of age, and 2.8% were ≥75 years of age. No overall differences in efficacy and safety have been observed in older patients, but greater sensitivity in some older individuals cannot be ruled out. Hypoglycemia may be difficult to detect in the elderly.	Safety and efficacy have not been established.	There is limited mild to moderate renal impairment experience with XULTOPHY, and no severe impairment experience. *Insulin degludec*: There are no clinically relevant PK differences in renal impairment. *Liraglutide*: This drug was evaluated in a 26-week study of moderate renal impairment patients. There is limited experience in severe impairment or ESRD. Post-marketing reports of acute or worsening chronic renal failure have been reported.	The effect of hepatic impairment on XULTOPHY has not been studied. *Insulin degludec*: There are no clinically relevant PK differences in hepatic impairment. *Liraglutide*: There is limited experience in patients with mild to severe hepatic impairment.	No well-controlled studies with XULTOPHY have been conducted in pregnancy; use only if the potential benefit outweighs the risk. Insulin degludec and liraglutide are present in the milk of animal models. An assessment of the risks and benefits should be considered prior to nursing.

Abbreviations: AE = adverse event; ESRD = end stage renal disease; GI = gastrointestinal; PK = pharmacokinetic
*Lixisenatide and liraglutide slow gastric emptying. Patients with gastroparesis were excluded from trials; therefore, agents are generally not recommended in cases of severe gastroparesis.
†Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

CONCLUSION

- Insulin glargine/lixisenatide (SOLIQUA) and insulin degludec/liraglutide (XULTOPHY) are long-acting insulin and incretin-based antidiabetic combination therapies that are FDA-approved as adjunctive therapy to diet and exercise in adult T2DM patients who are uncontrolled on a basal insulin or lixisenatide and liraglutide, respectively. The indication for both agents has dose limitations: XULTOPHY is indicated for patients uncontrolled on <50 U daily of a basal insulin or ≤1.8 mg daily of liraglutide, and SOLIQUA is indicated for patients uncontrolled on <60 U daily of a basal insulin. Neither agent is FDA-approved for use in T2DM patients who are uncontrolled on OADs.
- The medications are administered through a fixed ratio pen. SOLIQUA may be administered in doses of 15 to 60 U of insulin glargine and 5 to 20 mcg of lixisenatide, while XULTOPHY may be administered in doses of 10 to 50 U of insulin degludec and 0.36 to 1.3 mcg of liraglutide SC once daily depending on prior treatment and dosages.

Individualized dosing is recommended based on metabolic needs, BG monitoring, glycemic control, type of diabetes, and prior insulin use of the patient.

- The insulin and incretin mimetic combination agents have been studied in combination with metformin, SFU, pioglitazone, and GLN. In studies, SOLIQUA demonstrated HbA1c reductions ranging from 0.3 to 0.5% versus insulin glargine and 0.8% versus lixisenatide. XULTOPHY demonstrated estimated treatment differences in HbA1c reductions of 1% versus insulin degludec monotherapy, 0.6% versus insulin glargine monotherapy, and 0.9% versus a GLP-1 receptor agonist (eg, liraglutide or exenatide twice daily). Across trials, XULTOPHY and SOLIQUA were associated with both weight losses and gains. Hypoglycemia rates are mostly similar to those observed within the basal insulin monotherapy arms; however, the GLP-1 receptor agonists were associated with less hypoglycemic events (Aroda et al, 2016**;** FDA summary review [SOLIQUA], 2016; Buse et al, 2014; Lingvay et al, 2016; Linjawi et al, 2017; Rosenstock, et al 2016). Several CV outcomes trials have been conducted in patients with T2DM who were administered basal insulin monotherapy or GLP-1 receptor agonist monotherapy. Of these trials, the only trial which demonstrated a reduced CV risk was the LEADER trial, which compared liraglutide to placebo (Gerstein et al, 2012; Marso et al, 2016; Pfeffer et al, 2015).
- Overall, the safety profiles of the insulin and incretin mimetic combination agents are similar. A few differences are that XULTOPHY has a boxed warning regarding the risk of thyroid C-cell tumors and is contraindicated in patients with a history of MTC or MEN 2. There is also a REMS program for XULTOPHY which includes a communication plan for alerting healthcare professionals about the risk of acute pancreatitis and the potential risk of MTC. Other key warnings for these drugs include increased risks of pancreatitis, hypoglycemia or hyperglycemia, the potential for overdose due to medication errors, acute kidney injury, hypokalemia, and the potential for fluid retention and HF with use of TZDs. SOLIQUA has an additional warning and precaution regarding immunogenicity risks associated with the development of antibodies which may result in the loss of glycemic control. Common adverse reactions include GI effects (eg, nausea, diarrhea, etc), nasopharyngitis, headache, and upper respiratory tract infection.
- According to current clinical guidelines, metformin remains the cornerstone of most T2DM treatment regimens. Combination injection therapy (including the combination of a GLP-1 receptor agonist and a basal insulin) is generally reserved for third- or fourth-line treatment in patients who are inadequately controlled after a trial and failure of other agents. Combination injection therapy may be initiated in severely uncontrolled T2DM patients who present with an HbA1c ≥10%, BG ≥300 mg/dL, or in those who are markedly symptomatic at baseline (ADA 2017; Garber et al, 2017; Inzucchi et al, 2015).

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