Pharmaceutical Approval Update

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Insulin Degludec/Liraglutide (Xultophy 100/3.6)

Manufacturer: Novo Nordisk, Bagsvaerd, Denmark

Date of Approval: November 21, 2016

Indication: Xultophy 100/3.6 is indicated 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).

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The limitations of use include: 1) not recommended as first-line therapy for patients inadequately controlled with diet and exercise, 2) has not been studied in patients with a history of pancreatitis (consider other antidiabetic therapies in patients with a history of pancreatitis), 3) not recommended for use in combination with any other product containing liraglutide or another glucagon-like peptide-1 (GLP-1) receptor agonist, 4) not for treatment of type-1 diabetes mellitus or diabetic ketoacidosis, and 5) has not been studied in combination with prandial insulin.

Drug Class: Antidiabetics, long-acting insulins, GLP-1 agonists

Uniqueness of Drug: Xultophy 100/3.6 is a new combination therapy of insulin degludec (100 units/mL), a long-acting human insulin analogue, and liraglutide (3.6 mg/mL), a GLP-1 receptor agonist. Xultophy 100/3.6 enters into a new class of diabetes treatments that combine a basal insulin and a GLP-1 receptor agonist in a single, once-daily injection.

Warnings and Precautions:

Boxed warning: Risk of thyroid C-cell tumors. Liraglutide, one of the components of Xultophy 100/3.6, causes thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether Xultophy 100/3.6 causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined. Xultophy 100/3.6 is contraindicated in patients with a personal or family history of MTC or in patients with multiple endocrine neoplasia syndrome type-2. Counsel patients regarding the potential risk of MTC and the symptoms of thyroid tumors.

Pancreatitis. Post-marketing reports for liraglutide have included fatal and nonfatal hemorrhagic or necrotizing pancreatitis. Discontinue promptly if pancreatitis is suspected.

Never share a Xultophy 100/3.6 pen. The Xultophy pen must never be shared between patients, even if the needle is changed. Sharing of the pen poses a risk for transmission of blood-borne pathogens.

Hyperglycemia or hypoglycemia with changes in Xultophy 100/3.6 regimen. Changes in regimen may affect glycemic control and predispose patients to hypoglycemia or hyperglycemia. These changes should be made cautiously and only under medical supervision, and the frequency of blood glucose monitoring should be increased.

Overdose due to medication errors. Xultophy 100/3.6 contains two drugs. Instruct patients to check the label before injection because accidental mix-ups with insulin-containing products can occur. Do not exceed the maximum dose or administer with other GLP-1 receptor agonists.

Hypoglycemia. Hypoglycemia is the most common adverse reaction to insulin-containing products and may be life threatening. Increase monitoring with changes to: dosage, coadministered glucose-lowering medications, meal pattern, or physical activity; and in patients with renal impairment or hepatic impairment or hypoglycemia unawareness.

Acute kidney injury (AKI). AKI has been reported post-marketing for liraglutide, usually in association with nausea, vomiting, diarrhea, or dehydration, which may sometimes require hemodialysis. Advise patients of the potential risk of dehydration due to gastrointestinal adverse reactions and take precautions to avoid fluid depletion.

Hypersensitivity and allergic reactions. Severe, life-threatening, generalized allergy, including anaphylaxis, angioedema, bronchospasm, hypotension, and shock, can occur. If a hypersensitivity reaction occurs, discontinue and treat per standard of care.

Hypokalemia. All insulin-containing products cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia. Untreated hypokalemia may cause respiratory paralysis, ventricular arrhythmia, and death. Monitor potassium levels in patients at risk for hypokalemia if indicated (e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations).

Fluid retention and congestive heart failure. Patients treated with insulin-containing products and thiazolidinediones should be observed for signs and symptoms of heart failure; consider dosage reduction or discontinuation if heart failure occurs.

Macrovascular outcomes. There have been no studies establishing conclusive evidence of macrovascular risk reduction with Xultophy 100/3.6.

Dosage and Administration: Therapy with liraglutide or basal insulin should be discontinued before initiation of Xultophy 100/3.6. The recommended starting dosage is 16 units (which contains 16 units of insulin degludec and 0.58 mg of liraglutide) given subcutaneously once daily at the same time each day with or without food. The maximum daily dosage is 50 units (50 units of insulin degludec and 1.8 mg of liraglutide). The Xultophy 100/3.6 pen delivers doses from 10 to 50 units with each injection; each Xultophy 100/3.6 dosage unit contains 1 unit of insulin degludec and 0.036 mg of liraglutide. Use alternative antidiabetic products if patients require a Xultophy

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100/3.6 daily dosage that is persistently below 16 units or greater than 50 units. For titration recommendations, see the full prescribing information. Inject subcutaneously in the thigh, upper arm, or abdomen. Do not administer intravenously, intramuscularly, or by an infusion pump. Do not dilute or mix with any other insulin products or solutions.

Commentary: The approval of Xultophy 100/3.6 is based on efficacy and safety data from the DUAL clinical trials. In three DUAL trials involving 1,393 adults with type-2 diabetes, patients who were inadequately controlled on liraglutide or basal insulin therapy and switched to Xultophy 100/3.6 achieved reductions in hemoglobin A1c (HbA_{1c}). For adults uncontrolled on basal insulin, Xultophy 100/3.6 demonstrated significant reductions in HbA_{1c} from baseline of 1.67% and 1.94%. The most common adverse events seen during the trials included nasopharyngitis, headache, nausea, diarrhea, increased lipase, and upper respiratory tract infection.

Sources: Novo Nordisk, Xultophy 100/3.6 prescribing information

Rucaparib (Rubraca)

Manufacturer: Clovis Oncology, Inc., Boulder, Colorado

Date of Approval: December 19, 2016

Indication: The Food and Drug Administration (FDA) approved rucaparib as monotherapy for the treatment of patients with advanced ovarian cancer associated with deleterious *BRCA* mutation (germline and/or somatic) who have been treated with two or more chemotherapies and selected for therapy based on an FDA-approved companion diagnostic.

Drug Class: Antineoplastics, poly (ADP-ribose) polymerase (PARP) inhibitors

Uniqueness of Drug: Rucaparib is a PARP inhibitor approved by the FDA under its accelerated approval program. The drug also had a breakthrough therapy designation, priority review status, and orphan drug designation.

Warnings and Precautions:

Myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML). MDS/AML occurred in patients exposed to rucaparib, including one fatal event of AML. Complete blood count testing should be monitored at baseline and monthly thereafter. Discontinue rucaparib if MDS/AML is confirmed.

Embryo-fetal toxicity. Rucaparib can cause fetal harm. Advise women of reproductive potential to use effective contraception during treatment and for six months following the last dose of rucaparib.

Dosage and Administration: The recommended dose of rucaparib is 600 mg taken orally twice daily with or without food. Continue treatment until disease progression or unacceptable toxicity. If a patient misses a dose of rucaparib, instruct the patient to take the next dose at its scheduled time. Vomited doses should not be replaced.

To manage adverse reactions, consider interruption of treatment or dose reduction. Three dose adjustments may be made. After the staring dose of 600 mg twice daily, the first, second and third dose reductions should be to 500 mg twice daily, 400 mg twice daily, and 300 mg twice daily, respectively.

Commentary: The safety and efficacy of rucaparib were studied in two single-arm clinical trials involving 106 participants with *BRCA*-mutated advanced ovarian cancer who had been treated with two or more chemotherapy regimens. *BRCA* mutations were confirmed in 96% of tested trial participants with available tumor tissue using the FoundationFocus CDx_{BRCA} companion diagnostic (Foundation Medicine, Inc.). Fifty-four percent of the participants who received rucaparib in the trials experienced complete or partial shrinkage of their tumors lasting a median of 9.2 months. Common side effects of rucaparib include nausea, fatigue, vomiting, and anemia.

Sources: Clovis Oncology, Inc., Rubraca prescribing information

Nusinersen (Spinraza)

Manufacturer: Biogen, Inc., Cambridge, Massachusetts

Date of Approval: December 23, 2016

Indication: The Food and Drug Administration (FDA) approved nusinersen for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients.

Drug Class: Neurologics

Uniqueness of Drug: Nusinersen is the first and only treatment approved in the U.S. for SMA, a rare and often fatal genetic disease in infants and toddlers that is marked by progressive debilitating muscle weakness. It is an injection administered into the fluid surrounding the spinal cord. The FDA granted this application a fast-track designation and priority review. The drug also received an orphan drug designation.

Warnings and Precautions:

Thrombocytopenia and coagulation abnormalities. Patients may be at increased risk of bleeding complications because of the risk of thrombocytopenia and coagulation abnormalities associated with nusinersen. Perform a platelet count and coagulation laboratory testing at baseline and prior to each dose.

Renal toxicity. Renal toxicity, including potentially fatal glomerulonephritis, has been observed after administration of some antisense oligonucleotides. Conduct quantitative spot urine protein testing (preferably using a first morning urine specimen) at baseline and prior to each dose. For urinary protein concentration greater than 0.2 g/L, consider repeat testing and further evaluation.

Dosage and Administration: Nusinersen is administered intrathecally by a health care professional experienced in performing lumbar punctures. The recommended dosage is 12 mg (5 mL) per administration. Initiate treatment with four loading doses. The first three loading doses should be administered at 14-day intervals. The fourth loading dose should be administered 30 days after the third dose. A maintenance dose should be administered once every four months thereafter.

At baseline and prior to each dose, obtain a platelet count, coagulation laboratory testing, and quantitative spot urine protein testing.

Commentary: The approval of nusinersen was based on positive results from multiple clinical studies in more than 170 patients. The most common side effects included upper and lower respiratory tract infections, complete or partial collapse of a lung or lobe of a lung, constipation, headache, back pain, and postlumbar puncture syndrome.

Sources: Biogen, Inc., Spinraza prescribing information ■