Drug Class Review Monograph – GPI Class 27 – Anti-diabetics

Review Time Frame: 11/2015 – 04/2017
Previous Class Review: 02/2016

Background:
Antidiabetic drug classes include:

- **Alpha-glucosidase inhibitors**- slow the digestion of carbohydrates and delay glucose absorption, resulting in a smaller and slower rise in blood glucose levels following meals and effectively throughout the day.
- **Amylin analogs**-assist insulin in postprandial glucose control, inhibit glucagon secretion, delay gastric emptying, and signal satiety, suppressing the intake of food.
- **Dipeptidyl peptidase 4 (DPP-4) inhibitors-** inhibit the enzyme DPP-4 and regulate the levels of insulin the body produces after a meal. DPP-4 inhibition results in increased activity of incretins, which inhibits glucagon release. This leads to increased insulin secretion, decreased gastric emptying, and therefore decreased blood sugar levels.
- **Incretin mimetics**- bind to glucagon-like peptide-1 (GLP-1) receptors and stimulate glucose dependent insulin release, therefore acting as antihyperglycemics. Incretin mimetics also suppress appetite and inhibit glucagon secretion. They slow gastric emptying and as a result prevent steep rise in post-prandial blood glucose levels.
- **Insulin**- acts similar to endogenous insulin by regulating the amount of glucose in the blood. Insulin is classified according to how it works in the body (onset, peak, and duration) and whether it is rapid-acting, short-acting, intermediate-acting, long-acting or very long-acting. Insulin is used to treat type 1 diabetes, and it may be used in combination with oral medication in the later stages of type 2 diabetes.
- **Meglitinides**- stimulate the pancreas to release insulin in response to a meal.
- **Biguanides**- inhibit the amount of glucose produced by the liver, increase the insulin-receptor binding, and stimulate tissue uptake of glucose.
- **Sodium-Glucose Co-Transporter 2 (SGLT-2) inhibitors**- lower the renal glucose threshold, resulting in an increased amount being secreted in the urine.
- **Sulfonylureas**- block ATP sensitive potassium channels in beta cells of the islets and reduce the potassium permeability of beta cells. This causes depolarization of the cells and calcium entry into the cell, which causes increased insulin secretion. The insulin released reduces plasma glucose concentrations.
- **Thiazolidinediones**- act as agonists of the peroxisome proliferator-activated receptors-gamma.

New treatment guideline recommendations:

- American Diabetes Association Standards of Medical Care in Diabetes-2017
    - In patients with long-standing suboptimally controlled type 2 diabetes and established atherosclerotic cardiovascular disease, empagliflozin or liraglutide should be considered as they have been shown to reduce cardiovascular and all-cause mortality when added to standard care. Ongoing studies are investigating the cardiovascular benefits of other agents in these drug classes.

Newly approved drugs:

- Approved 02/27/2017: Qtern (dapagliflozin propanediol; saxagliptin) 10 mg/5 mg tablets; anticipated commercial availability unknown.
- Approved 11/21/2016: Xultophy (insulin degludec; liraglutide) 100/3.6 100U/mL and 3.6mg/mL solution for injection; currently commercially available.
- Approved 11/21/2016: Soliqua (insulin glargine; lixisenatide) 100/33 100 U/mL and 33mcg/mL solution for injection; currently commercially available.
- Approved 07/27/2016: Adlyxin (lixisenatide) 0.05 mg/mL, 0.1 mg/mL solution; currently commercially available.

Newly approved formulations:

- Approved 12/09/2016: Synjardy XR (empagliflozin; metformin) 5 mg/1 gm, 10 mg/1 gm, 12.5 mg/1 gm, 25 mg/1 gm extended release tablets; currently commercially available.
- Approved 09/20/2016: Invokamet XR (canagliflozin; metformin) 50 mg/500 mg, 50 mg/1 gm, 150 mg/500 mg, 150 mg/1 gm extended release tablets; currently commercially available.
- Approved 05/27/2016: Jentadueto XR (linagliptin; metformin) 2.5 mg/1000 mg, 5 mg/1000 mg extended release tablets; currently commercially available.
- Approved 12/29/2015: Humulin R U-500 KwikPen; currently commercially available.
- Approved 12/16/2015: Basaglar (insulin glargine) 300 units/3mL (100 units/mL); currently commercially available.

Newly approved generics:

- Approved 04/01/2016: Avandaryl (rosiglitazone maleate/glimepiride) 4 mg/1 mg, 4 mg/2 mg, 4 mg/4gm, 8 mg/2 mg, 8 mg/8 mg tablets; anticipated commercial availability unknown.

Discontinued drugs:

- None identified

FDA Safety Alerts/black box warnings:

- 12/12/2016: FDA Drug Safety Communication: Updated FDA review concludes that use of type 2 diabetes medicine pioglitazone may be linked to an increased risk of bladder cancer (see page 4 for full detail).
- 06/14/2016: FDA Drug Safety Communication: FDA strengthens kidney warnings for diabetes medicines canagliflozin (Invokana, Invokamet) and dapagliflozin (Farxiga, Xigduo XR) (see page 4 for full detail).
- 05/18/2016: FDA Drug Safety Communication: Interim clinical trial results find increased risk of leg and foot amputations, mostly affecting the toes, with the diabetes medicine canagliflozin (Invokana, Invokamet); FDA to investigate (see page 5 for full detail).
- 04/08/2016: FDA Drug Safety Communication: FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function (see page 6 for full detail).

- 04/05/2016: FDA Drug Safety Communication: FDA adds warnings about heart failure risk to labels of type 2 diabetes medicines containing saxagliptin and alogliptin (see page 7 for full detail).
- 12/16/2015: FDA Drug Safety Communication: FDA eliminates the Risk Evaluation and Mitigation Strategy (REMS) for rosiglitazone-containing diabetes medicines (see page 8 for full detail).
- 12/04/2015: FDA Drug Safety Communication: FDA revises labels of SGLT2 inhibitors for diabetes to include warnings about too much acid in the blood and serious urinary tract infections (see page 9 for full detail).

Pipeline alerts:
Agents pending FDA approval include:
- Victoza (liraglutide): reduction of risk of cardiovascular events in patients with diabetes mellitus; PDUFA: 08/25/2017
- Exenatide continuous delivery: treatment of type 2 diabetes mellitus; PDUFA: 09/21/2017
- Insulin aspart fast acting: treatment of type 1 and type 2 diabetes mellitus; PDUFA: 09/29/2017
- Ertugliflozin/ metformin: treatment of type 2 diabetes mellitus; PDUFA: 12/01/2017
- Ertugliflozin: treatment of type 2 diabetes mellitus; PDUFA: 12/01/2017
- Ertugliflozin/ sitagliptin: treatment of type 2 diabetes mellitus; PDUFA: 12/01/2017
- Semaglutide: treatment of type 2 diabetes mellitus in adults; PDUFA: 12/05/2017
- Insulin lispro (biosimilar of Humalog); PDUFA: 01/01/2018

References:

1. Dungan K, DeSantis A. Dipeptidyl peptidase 4 (DPP-4) inhibitors for the treatment of type 2 diabetes mellitus. Nathan DM. (Ed), UpToDate. Waltham MA. Accessed May 2017.
2. McCulloch DK. Sulfonylureas and Meglitinides in the treatment of diabetes mellitus. Nathan DM. (Ed), UpToDate. Waltham, MA. Accessed May 2017
3. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2017. URL: http://www.clinicalpharmacology-ip.com/. Accessed May 2017.
4. American Diabetes Association. Standards of medical care in diabetes—2017. Diabetes Care. 2017; 40(suppl 1): S1-S135.
5. US Food and Drug Administration. WWW.FDA.GOV. Accessed May 2017.
6. https://www.drugs.com/. Accessed May 2017.
7. Envolve Pharmacy Solutions internal pipeline database. Accessed May 2017.

(FDA Drug Safety Communication, continued from page 2)

FDA Drug Safety Communication: Updated FDA review concludes that use of type 2 diabetes medicine pioglitazone may be linked to an increased risk of bladder cancer
[12/12/2016]
As a result of an updated review, the U.S. Food and Drug Administration (FDA) has concluded that use of the type 2 diabetes medicine pioglitazone (Actos, Actoplus Met, Actoplus Met XR, Duetact, Oseni) may be linked to an increased risk of bladder cancer. The labels of pioglitazone-containing medicines already contain warnings about this risk, and we have now approved label updates to describe the additional studies we reviewed.

We alerted the public about the possible risk of bladder cancer in September 2010 and June 2011 based on interim results from a 10-year epidemiologic study. We changed the labels of pioglitazone-containing medicines in August 2011 to include warnings about this risk, and required the manufacturer to modify and continue the 10-year study.

Pioglitazone is approved to improve blood sugar control, along with diet and exercise, in adults with type 2 diabetes. Pioglitazone works by increasing the body's sensitivity to insulin, a natural hormone that helps control blood sugar levels. Untreated, type 2 diabetes can lead to serious problems, including blindness, nerve and kidney damage, and heart disease.

Health care professionals should not use pioglitazone in patients with active bladder cancer, and should carefully consider the benefits and risks before using pioglitazone in patients with a history of bladder cancer.

Patients should contact their health care professionals if they experience any of the following signs or symptoms after starting pioglitazone, as these may be due to bladder cancer:
- Blood or a red color in the urine
- New or worsening urge to urinate
- Pain when urinating

We reviewed additional published studies evaluating the risk of bladder cancer in patients treated with pioglitazone. Results varied among the reviewed studies. For instance, the 10-year epidemiologic study did not find an increased risk of bladder cancer with pioglitazone use, whereas another study did.[2] In addition, a randomized controlled trial found an increased risk during the trial period; however the risk did not persist when patients were followed after the trial was completed. Furthermore, findings of these and other reviewed studies conflicted about whether the duration of use and/or total dose over time of pioglitazone influenced the risk of bladder cancer. We also previously communicated in 2010 that bladder tumors were seen with pioglitazone exposure in animal studies. Overall, the data suggest that pioglitazone use may be linked to an increased risk of bladder cancer.

FDA Drug Safety Communication: FDA strengthens kidney warnings for diabetes medicines canagliflozin (Invokana, Invokamet) and dapagliflozin (Farxiga, Xigduo XR)
[06/14/2016]

The U.S. Food and Drug Administration (FDA) has strengthened the existing warning about the risk of acute kidney injury for the type 2 diabetes medicines canagliflozin (Invokana, Invokamet) and dapagliflozin (Farxiga, Xigduo XR). Based on recent reports, we have revised the warnings in the drug labels to include information about acute kidney injury and added recommendations to minimize this risk.

Patients should seek medical attention immediately if they experience signs and symptoms of acute kidney injury. This is a serious condition in which the kidneys suddenly stop working, causing dangerous levels of wastes to build up in the body. Signs and symptoms of acute kidney injury may include decreased urine or swelling in the legs or feet. Patients should not stop taking their medicine without first talking to their health care professionals. Doing so can lead to uncontrolled blood sugar levels that can be harmful.

Health care professionals should consider factors that may predispose patients to acute kidney injury prior to starting them on canagliflozin or dapagliflozin. These include decreased blood volume; chronic kidney insufficiency; congestive heart failure; and taking other medications such as diuretics, blood pressure medicines called angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), and nonsteroidal anti-inflammatory drugs (NSAIDs). Assess kidney function prior to starting canagliflozin or dapagliflozin and monitor periodically thereafter. If acute kidney injury occurs, promptly discontinue the drug and treat the kidney impairment.

Canagliflozin and dapagliflozin are prescription medicines used with diet and exercise to help lower blood sugar in adults with type 2 diabetes. They belong to a class of drugs called sodium-glucose cotransporter-2 (SGLT2) inhibitors. Canagliflozin and dapagliflozin lower blood sugar by causing the kidneys to remove sugar from the body through the urine. Untreated, type 2 diabetes can lead to serious problems, including blindness, nerve and kidney damage, and heart disease.

From March 2013, when canagliflozin was approved, to October 2015, FDA received reports of 101 confirmable cases of acute kidney injury, some requiring hospitalization and dialysis, with canagliflozin or dapagliflozin use. This number includes only reports submitted to FDA, so there are likely additional cases about which we are unaware. In approximately half of the cases, the events of acute kidney injury occurred within 1 month of starting the drug, and most patients improved after stopping it. Some cases occurred in patients who were younger than 65 years. Some patients were dehydrated, had low blood pressure, or were taking other medicines that can affect the kidneys.

FDA Drug Safety Communication: Interim clinical trial results find increased risk of leg and foot amputations, mostly affecting the toes, with the diabetes medicine canagliflozin (Invokana, Invokamet); FDA to investigate
[05/18/2016]
The U.S. Food and Drug Administration (FDA) is alerting the public about interim safety results from an ongoing clinical trial that found an increase in leg and foot amputations, mostly affecting the toes, in patients treated with the diabetes medicine canagliflozin (Invokana, Invokamet). We have not determined whether canagliflozin increases the risk of leg and foot amputations. We are

currently investigating this new safety issue and will update the public when we have more information.

Patients should not stop or change their diabetes medicines without first talking to their health care professional. Doing so can lead to uncontrolled blood sugar levels that can be harmful. Over time, this can cause serious problems, including blindness, nerve and kidney damage, and heart disease. Patients taking canagliflozin should notify their health care professionals right away if they notice any new pain or tenderness, sores or ulcers, or infections in their legs or feet.

Health care professionals should follow the recommendations in the canagliflozin drug labels. Monitor patients for the signs and symptoms described above and advise patients to seek medical advice if they experience them.
Canagliflozin is a prescription medicine used with diet and exercise to lower blood sugar in adults with type 2 diabetes. It belongs to a class of drugs called sodium-glucose cotransporter-2 (SGLT2) inhibitors. Canagliflozin lowers blood sugar by causing the kidneys to remove sugar from the body through the urine. It is available as a single-ingredient product under the brand name Invokana and also in combination with the diabetes medicine metformin under the brand name Invokamet.

In the ongoing Canagliflozin Cardiovascular Assessment Study (CANVAS) clinical trial, the trial's independent data monitoring committee (IDMC) identified an increased risk of leg and foot amputations. The amputations occurred about twice as often in patients treated with canagliflozin compared to patients treated with placebo, which is an inactive treatment. An interim analysis showed that over a year's time, the risks of amputation for patients in the trial were equivalent to:

- 7 out of every 1,000 patients treated with 100 mg daily of canagliflozin
- 5 out of every 1,000 patients treated with 300 mg daily of canagliflozin
- 3 out of every 1,000 patients treated with placebo

Patients in the CANVAS trial have been followed for an average of 4.5 years to date. The IDMC has recommended, based on an overall assessment, that the CANVAS trial continue. The IDMC has also reported that a second, similar trial evaluating canagliflozin, the CANVAS-R trial, has not shown the same risks of increased leg and foot amputations to date. Patients in the CANVAS-R trial have been followed for an average of 9 months.

FDA Drug Safety Communication: FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kidney function
[04/08/2016]
The U.S. Food and Drug Administration (FDA) is requiring labeling changes regarding the recommendations for metformin-containing medicines for diabetes to expand metformin's use in certain patients with reduced kidney function. The current labeling strongly recommends against use of metformin in some patients whose kidneys do not work normally. We were asked to review numerous medical studies regarding the safety of metformin use in patients with mild to moderate impairment in kidney function, and to change the measure of kidney function in the metformin drug labeling that is used to determine whether a patient can receive metformin. We

have concluded our review, and are requiring changes to the labeling of all metformin-containing medicines to reflect this new information.

Health care professionals should follow the latest recommendations when prescribing metformin-containing medicines to patients with impaired kidney function. Patients should talk to their health care professionals if they have any questions or concerns about taking metformin.

Metformin-containing medicines are available by prescription only and are used along with diet and exercise to lower blood sugar levels in patients with type 2 diabetes. When untreated, type 2 diabetes can lead to serious problems, including blindness, nerve and kidney damage, and heart disease. Metformin-containing medicines are available as single-ingredient products and also in combination with other drugs used to treat diabetes. The current drug labeling strongly recommends against metformin use in some patients whose kidneys do not work normally because use of metformin in these patients can increase the risk of developing a serious and potentially deadly condition called lactic acidosis, in which too much lactic acid builds up in the blood.

We have concluded from the review of studies published in the medical literature that metformin can be used safely in patients with mild impairment in kidney function and in some patients with moderate impairment in kidney function. We are requiring changes to the metformin labeling to reflect this new information and provide specific recommendations on the drug's use in patients with mild to moderate kidney impairment. We are also recommending that the measure of kidney function used to determine whether a patient can receive metformin be changed from one based on a single laboratory parameter (blood creatinine concentration) to one that provides a better estimate of kidney function in patients with kidney disease (i.e., glomerular filtration rate estimating equation (eGFR)).

FDA Drug Safety Communication: FDA adds warnings about heart failure risk to labels of type 2 diabetes medicines containing saxagliptin and alogliptin
[04/05/2016]
A U.S. Food and Drug Administration (FDA) safety review has found that type 2 diabetes medicines containing saxagliptin and alogliptin may increase the risk of heart failure, particularly in patients who already have heart or kidney disease. Heart failure can result in the heart not being able to pump enough blood to meet the body's needs. As a result, we are adding new warnings to the drug labels about this safety issue.

Saxagliptin and alogliptin are part of the class of dipeptidyl peptidase-4 (DPP-4) inhibitor drugs, which are used with diet and exercise to lower blood sugar in adults with type 2 diabetes. Untreated, type 2 diabetes can lead to serious health problems, including blindness, nerve and kidney damage, and heart disease. Patients taking these medicines should contact their health care professionals right away if they develop signs and symptoms of heart failure such as:

- Unusual shortness of breath during daily activities
- Trouble breathing when lying down
- Tiredness, weakness, or fatigue
- Weight gain with swelling in the ankles, feet, legs, or stomach

Patients should not stop taking their medicine without first talking to their health care professionals.

Health care professionals should consider discontinuing the medicine in patients who develop heart failure and monitor their diabetes control. If a patient's blood sugar level is not well-controlled with their current treatment, other diabetes medicines may be required.
We evaluated two large clinical trials conducted in patients with heart disease. These clinical trials were also discussed at the FDA Endocrinologic and Metabolic Drugs Advisory Committee meeting in April 2015. Each trial showed that more patients who received saxagliptin- or alogliptin-containing medicines were hospitalized for heart failure compared to patients who received an inactive treatment called a placebo. In the saxagliptin trial, 3.5% of patients who received the drug were hospitalized for heart failure versus 2.8% of patients who received a placebo. This is the same as 35 out of every 1,000 patients compared to 28 out of every 1,000 patients. Risk factors included a history of heart failure or kidney impairment. In the alogliptin trial, 3.9% of alogliptin-treated patients were hospitalized for heart failure versus 3.3% in the placebo group. This is the same as 39 out of every 1,000 patients compared to 33 out of every 1,000 patients. As a result, we have added new *Warnings and Precautions* to the labels of medicines that contain saxagliptin or alogliptin to inform of the potential increased risk of heart failure.

FDA Drug Safety Communication: FDA eliminates the Risk Evaluation and Mitigation Strategy (REMS) for rosiglitazone-containing diabetes medicines
[12/16/2015]
The U.S. Food and Drug Administration (FDA) is eliminating the Risk Evaluation and Mitigation Strategy (REMS) for rosiglitazone-containing type 2 diabetes medicines, which are approved as Avandia, Avandamet, Avandaryl, and generics. The REMS is no longer necessary to ensure that the benefits of rosiglitazone medicines outweigh their risks.

Type 2 diabetes is a disease that can lead to serious complications such as kidney failure, blindness, and premature death. Rosiglitazone can be used along with diet and exercise to control blood sugar in adults with the disease.

In 2013, we required removal of the prescribing and dispensing restrictions for rosiglitazone medicines after determining that data did not demonstrate an increased risk of heart attack with rosiglitazone medicines compared to the standard type 2 diabetes medicines metformin and sulfonylurea. We also required the drug manufacturers to provide educational training to health care professionals about the current state of knowledge regarding the heart risks of rosiglitazone medicines. Manufacturers have since fulfilled these requirements.

We have continued monitoring these medicines and identified no new pertinent safety information. As a result, we have determined the REMS is no longer necessary to ensure that the benefits of rosiglitazone medicines outweigh their risks. We will update the public if any new information becomes available

Drug Safety Communication: FDA revises labels of SGLT2 inhibitors for diabetes to include warnings about too much acid in the blood and serious urinary tract infections
[12/04/2015]
A U.S. Food and Drug Administration (FDA) safety review has resulted in adding warnings to the labels of a specific class of type 2 diabetes medicines called sodium-glucose cotransporter-2 (SGLT2) inhibitors about the risks of too much acid in the blood and of serious urinary tract infections. Both conditions can result in hospitalization.

Patients should stop taking their SGLT2 inhibitor and seek medical attention immediately if they have any symptoms of ketoacidosis, a serious condition in which the body produces high levels of blood acids called ketones. Symptoms of ketoacidosis include nausea, vomiting, abdominal pain, tiredness, and trouble breathing. Patients should also be alert for signs and symptoms of a urinary tract infection, such as a feeling of burning when urinating or the need to urinate often or right away; pain in the lower part of the stomach area or pelvis; fever; or blood in the urine. Contact a health care professional if you experience any of these symptoms.
Health care professionals should assess for ketoacidosis and urinary tract infections in patients taking SGLT2 inhibitors who present with suggestive symptoms. Ketoacidosis associated with the use of SGLT2 inhibitors can occur even if the blood sugar level is not very high. If ketoacidosis is suspected, the SGLT2 inhibitor should be discontinued and treatment instituted promptly.

SGLT2 inhibitors are a class of prescription medicines that are FDA-approved for use with diet and exercise to lower blood sugar in adults with type 2 diabetes. When untreated, type 2 diabetes can lead to serious problems, including blindness, nerve and kidney damage, and heart disease. Medicines in the SGLT2 inhibitor class include canagliflozin, dapagliflozin, and empagliflozin (see section on List of FDA-approved SGLT2 Inhibitors for Type 2 Diabetes). SGLT2 inhibitors are not FDA-approved for use in patients with type 1 diabetes.
We issued a Drug Safety Communication in May 2015 warning about the risk of ketoacidosis with SGLT2 inhibitors and alerting that we would continue to evaluate this safety issue. Our review of the FDA Adverse Event Reporting System (FAERS) database from March 2013 to May 2015 identified 73 cases of ketoacidosis in patients with type 1 or type 2 diabetes treated with SGLT2 inhibitors (see Data Summary). FAERS includes only reports submitted to FDA, so there are likely additional cases about which we are unaware. All patients required hospitalization or treatment in an emergency department. In many cases, ketoacidosis was not immediately recognized because the blood glucose levels were below those typically expected for diabetic ketoacidosis. As a result, treatment of the ketoacidosis was delayed in some cases.

We also identified 19 cases of life-threatening blood infections (urosepsis) and kidney infections (pyelonephritis) that started as urinary tract infections with the SGLT2 inhibitors reported to FAERS from March 2013 through October 2014. All 19 patients were hospitalized, and a few required admission to an intensive care unit or dialysis in order to treat kidney failure.

As a result, we have added new *Warnings and Precautions* to the labels of all SGLT2 inhibitors to describe these two safety issues, and to provide prescribing and monitoring recommendations. We are also requiring manufacturers of SGLT2 inhibitors to conduct a required postmarketing study. This required enhanced pharmacovigilance study requests that

manufacturers perform analyses of spontaneous postmarketing reports of ketoacidosis in patients treated with SGLT2 inhibitors, including specialized follow-up to collect additional information, for a period of 5 years.

We urge health care professionals and patients to report side effects involving SGLT2 inhibitors to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of the page.