Although the glucagon-like peptide-1 (GLP-1) receptor agonists exenatide (Byetta) and liraglutide (Victoza) and the dipeptidyl peptidase-4 (DPP-4) inhibitors saxagliptin (Onglyza) and sitagliptin (Januvia) have overall favorable safety profiles, some specific concerns have emerged. Pharmacists should be prepared to discuss these concerns with patients in a way that accurately reflects available information without creating undue alarm.

**Pancreatitis**

Postmarketing and clinical trial experience with exenatide, liraglutide, and sitagliptin has included reports of acute pancreatitis, including fatal and nonfatal hemorrhagic or necrotizing pancreatitis. It is not clear whether these cases represent a causal or coincidental relationship between incretin-based agents and pancreatitis. A growing body of data suggests that the incidence of acute pancreatitis is higher in patients with type 2 diabetes regardless of treatment. In addition, a number of common comorbidities of type 2 diabetes—hypertriglyceridemia, obesity, and gallbladder disease in particular—are known risk factors for pancreatitis. Until a causal relationship is ruled out, incretin-based agents should be used with caution, if at all, in patients with a history of pancreatitis or associated risk factors. All patients should be observed carefully for signs and symptoms of pancreatitis when therapy with an incretin-based agent is initiated and whenever doses are increased. Characteristic signs and symptoms include persistent severe abdominal pain, sometimes radiating to the back, which may be accompanied by vomiting. The pain may feel worse after eating. Treatment should be discontinued if pancreatitis is suspected; if pancreatitis is confirmed, therapy should not be restarted.

**What to Tell Patients:**  Pancreatitis (inflammation of the pancreas) is a serious problem that has been reported in a very small number of people who have taken GLP-1 receptor agonists and DPP-4 inhibitors. It is not known yet whether the medications are the cause of this rare problem, because patients with diabetes have a generally greater risk for developing pancreatitis than people without diabetes do. Contact your health care provider right away if you have pain in your stomach area that is severe and will not go away. This pain is different from the feeling of fullness or nausea you may experience during the first few weeks after you start taking exenatide or liraglutide.

**Altered Renal Function**

From April 2005 through October 2008, the U.S. Food and Drug Administration (FDA) received 78 reports of altered renal function (62 cases of acute renal failure and 16 cases of renal insufficiency) that occurred as soon as 3 days and up to 2 years after treatment with exenatide was initiated. Most (95%) of the 78 patients had prior kidney disease or at least one contributory risk factor for altered renal function, including concomitant therapy with medications known to affect renal function or hydration status. More than half (54%) of the patients reported symptoms (e.g., nausea, vomiting, diarrhea) associated with volume depletion; these are common adverse effects of exenatide therapy and may have contributed to the development of altered renal function.

Altered renal function was reversible in many cases with supportive treatment and discontinuation of potentially causative agents. Exenatide was not shown to be directly nephrotoxic in preclinical or clinical studies.

**What to Tell Patients:** A very small number of people who took exenatide developed new or worse problems with kidney function, including kidney failure. Kidney problems are more likely to occur if you have nausea, vomiting, or diarrhea that will not go away, or if you cannot take liquids by mouth. Call your health care provider right away if any of these situations apply to you. Be sure to let your health care provider know if you have or have had kidney problems.

**Thyroid C-Cell Hyperplasia**

The liraglutide prescribing information includes a black box warning about the development of thyroid C-cell tumors in rats and mice. These tumors were more likely to occur at higher doses of liraglutide (especially doses eight times higher than human doses) and with longer treatment duration. Researchers have speculated that sustained GLP-1 receptor activation stimulates release of calcitonin from thyroid C cells, leading to hyperplasia and possible tumor formation.

The relevance of the rodent findings to medullary thyroid cancer in humans remains unclear. Recent data suggest that GLP-1 receptor activation produces C-cell activation and cell proliferation in rodents but not in primates. The FDA has mandated long-term monitoring to assess the possible association between liraglutide and medullary thyroid cancer. Pending these additional data, patients taking liraglutide should be monitored for symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness) and referred to an endocrinologist as needed for evaluation. Liraglutide is contraindicated in patients with a personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2.

**What to Tell Patients:** During the drug testing process, liraglutide caused thyroid gland tumors in rats and mice. Some of these tumors were cancers. It is not known if liraglutide can cause thyroid tumors or a type of thyroid cancer called medullary thyroid cancer in people. Tell your health care provider if you get a lump or swelling in your neck, hoarseness, trouble swallowing, or shortness of breath; these may be symptoms of thyroid cancer.
References


González-Perez A, Schlienger RG, Rodríguez LA. Acute renal failure or renal insufficiency had prior kidney disease or at least one contributory risk factor.


CPE Exam

Communicating With Patients About Safety Concerns

Instructions: The assessment questions printed below allow you to preview the online CPE exam. Please review all of your answers to be sure you have marked the proper letter on the online CPE exam. There is only one correct answer to each question.

1. Which of the following statements about incretin-based agents and pancreatitis is true?
   a. Both the glucagon-like peptide-1 (GLP-1) receptor agonists and the dipeptidyl peptidase-4 (DPP-4) inhibitors have been proven to cause acute pancreatitis.
   b. The incidence of acute pancreatitis appears to be higher in patients with type 2 diabetes regardless of any treatment they receive.
   c. The symptoms of pancreatitis are easily confused with common adverse effects of therapy with exenatide or liraglutide.
   d. All of the above.

2. Evaluating case reports of a possible relationship between exenatide and altered renal function is complicated by which of the following contributing factors?
   a. Almost all of the patients who developed acute renal failure or renal insufficiency had prior kidney disease or at least one contributory risk factor.
   b. Some patients were receiving concomitant therapy with medications known to affect renal function or hydration status.
   c. Many of the patients reported symptoms associated with volume depletion.
   d. All of the above.

3. Which of the following incretin-based agents is known to cause thyroid C-cell tumors in rats and mice?
   a. Exenatide.
   b. Liraglutide.
   c. Sitagliptin.
   d. All of the above.

4. Patients should be advised to contact their health care provider immediately if they develop severe, persistent abdominal pain during therapy with which of the following incretin-based agents?
   a. Exenatide.
   b. Liraglutide.
   c. Sitagliptin.
   d. All of the above.

CPE Instructions

Completing a posttest at www.pharmacist.com/education is as easy as 1-2-3…

1. Go to Online CPE Quick List and click on the title of this activity.

2. Log in. APhA members enter your user name and password. Not an APhA member? Just click “Create one now” to open an account. No fee is required to register.

3. Successfully complete the CPE exam and evaluation form to gain immediate access to your Statement of Credit.

Live step-by-step assistance is available Monday through Friday, 8:30 am to 5:00 pm ET from APhA Member Services at 800-237-APhA (2742) or e-mail InfoCenter@pharmacist.com.