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MEDICATION SAFETYINSECONDS

A MONTHLY PUBLICATION FROM VA MEDSAFE:
VA'S COMPREHENSIVE PHARMACOVIGILANCE CENTER

Helping to achieve safe medication use

SAFETY ISSUES WITH BASAL INSULIN/GLP-1 FIXED COMBINATIONS

According to a recent alert from the Institute for Safe Medication Practices (ISMP), newly-approved basal insulin/glucagon-like peptide-1 (GLP-1) receptor agonist fixed combinations may present potential safety issues. FDA approved 2 fixed-ratio combination products, each available in a 3mL single-patient-use-pen for once-a-day administration:

- Soliqua 100UNIT/33MCG/ML (100 units of insulin glargine per mL and 33 mcg of lixisenatide per mL); and
- Xultophy 100UNIT/3.6MG/ML (100 units of insulin degludec per mL and 3.6 mg of liraglutide per mL).

Confusion may arise from mistaking the products as only containing insulin. Since dosing is based on insulin units, providers may not realize there is a GLP-1 agonist contained within. If this happens, a separate GLP-1 agonist may be prescribed. These combination products are not recommended for use with another GLP-1 agonist-containing product because of the risk of overdose.

To circumvent these safety issues, ISMP recommends:

- When using generic names in computer drop-down lists, display both ingredients in a non-truncated fashion. If a product appears in generic nomenclature with insulin listed first, practitioners may mistake these as insulin-only agents. Including the brand name may reduce the risk of error.
- Use ratio expressions in computerized provider order entry lists to indicate to users that the product contains two ingredients.
- Recognize that there is no direct conversion between these combination products and their single ingredient counterparts. The pen for the fixed-dose combination products will not yield the same dose achievable with the delivery systems for the individual ingredient components.

Within the VA, if a local site creates an entry for these agents within the Drug and Pharmacy Orderable item file, we suggest that VA pharmacy name the Pharmacy Orderable Items as follows:

- **INSULIN GLARGINE/ LIXISENATIDE (SOLIQUA)**
- **INSULIN DEGLUDEC/ LIRAGLUTIDE (XULTOPHY)**

This would appear to providers as below in the medication selection list:

- **INSULIN GLARGINE/ LIXISENATIDE (SOLIQUA) INJ,SOLN**
- **INSULIN DEGLUDEC/ LIRAGLUTIDE (XULTOPHY) INJ,SOLN**

REFERENCE:
Institute for Safe Medication Practices (ISMP). Potential issues with new basal insulin/GLP-1 fixed combinations: New safety challenges? *ISMP Medication Safety Alert! Acute Care* December 2016; 21 (25): 1,5.

IN THIS ISSUE:

VA PHARMACY BENEFITS MANAGEMENT SERVICES (PBM)

PBM maintains VA's national drug formulary, as well as promotes, optimizes, and assists VA practitioners with the safe and appropriate use of all medications.

VA CENTER FOR MEDICATION SAFETY (VA MedSAFE)

VA MedSAFE performs pharmacovigilance activities; tracks adverse drug events (ADEs) using spontaneous and integrated databases; enhances education and communication of ADEs to the field; and promotes medication safety on a national level.

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NEWSWORTHY...

from the pbm

DIRECT-ACTING ANTIVIRAL (DAA) AGENTS AND SAFETY ISSUES

ISMP conducted a review of hepatic safety issues related to DAA use for HCV treatment after an FDA analysis from October 2016 described an increased risk of reactivating hepatitis B virus (HBV) infection in a small group of patients (n=24) treated with DAA medications for HCV infection, which resulted in fulminant hepatitis, hepatic decompensation (n=3), and death (n=2). FDA's findings led to the addition of a boxed warning to the labeling of the newer antivirals, with recommendations for providers to screen and monitor for HBV in all patients initiating DAA therapy. FDA's review was addressed in the Issue 9; Volume 6; October 2016 edition of this newsletter. To follow up on these findings, ISMP further investigated liver-related safety issues reported in patients receiving DAA treatment.

ISMP searched the most recent 12 months (ending June 30, 2016) of data from the FDA Adverse Event Reporting System (FAERS) for terms identifying liver failure in which a DAA was listed as a primary or secondary suspect drug and identified:

- 524 reported cases of liver failure.
  - 55% occurred in males; the median age was 61 years.
  - 31.5% had an outcome of death at the time the report was submitted.
  - 73.7% were reported outside of the US.
- 1,058 reports of severe liver injury that did not progress to liver failure.
  - This refers to "Drug related hepatic disorders – severe events only". However, no information was provided as to the other drugs the patient may have been taking or what the disorder may have been.

This report has several important and notable limitations. No information was reported on patient stage of disease, particularly whether or not these events occurred in patients with known cirrhosis, decompensated cirrhosis, or those who may have been pre- or post-transplant. Additionally, the HBV status of these patients is unknown. As many of the terms used in the search are commonly present in HCV infected patients with advanced disease, particularly those with decompensated cirrhosis, it cannot be determined if these events would have occurred as part of the natural progression of HCV disease itself in the absence of HCV antiviral treatment.

PBM/MedSAFE will be issuing a National PBM Bulletin in February (pending) regarding this safety issue and describing VA's efforts at proactively monitoring adverse outcomes related to DAA use for HCV treatment. While this Bulletin will point out reports of hepatotoxicity associated with DAAs, these agents have been shown to be highly effective in treating HCV infection and, when used appropriately, are safe and easy to take.

Providers should continue to monitor patients receiving DAAs for evidence of unexpected consequences and report any adverse reactions with the use of DAA products for treatment of HCV infection by entering the information into CPRS' Allergies/ Adverse Reactions field and/or via local reporting mechanisms. Adverse events should also be reported, as appropriate, to the VA ADERS program and FDA MedWatch (1-800-FDA-1088, fax 1-800-FDA-0178, online at https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm, or by mail).

Moreover, FDA previously communicated recommendations to screen for and assess HBV status and other pertinent hepatic comorbidities before starting treatment of DAAs for HCV infection as their analysis of DAA use in HCV treatment attributed the cause of liver complications to reactivation of HBV infection. For FDA recommendations regarding DAA treatment for HCV infection, please see Issue 9; Volume 6; October 2016.

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1. Institute for Safe Medication Practices (ISMP). New Safety Issues for Hepatitis C Antivirals. *ISMP Quarter Watch: Monitoring FDA Medwatch Reports* January 25, 2017; 2016 Q2: 11-15.
2. FDA Drug Safety Communication: FDA warns about the risk of hepatitis B reactivating in some patients treated with direct-acting antivirals for hepatitis C. http://www.fda.gov/Drugs/DrugSafety/ucm522932.htm . (Accessed October 6, 2016).

Getting the most from our safety surveillance

PROTAMINE ADVERSE REACTION WITH FATAL OUTCOME: LINKED TO PRIOR EXPOSURE TO NPH INSULIN?

Contributed by Vache Sharyan, Pharm.D., MHA, PGY-1 Pharmacy Practice Resident

A report submitted to VA ADERS described a reaction to protamine that occurred in a patient with known NPH insulin exposure. The patient received protamine to reverse the effects of heparin following atrial fibrillation ablation procedure. Unfortunately, the patient suffered profound hypotension with complications including ischemic bowl leading to his death. After investigating this event, it was discovered that the patient was on NPH insulin which carries an increased risk of adverse reaction to protamine according to the manufacturer. No information on rate of administration was documented.

Protamine is indicated for heparin overdose and is also used to neutralize heparin during cardiac and vascular surgeries by ionically binding with heparin to form a stable complex, antagonizing its anticoagulant effects.[1] Some insulin preparations, such as NPH, contain protamine to delay onset, peak, and duration of insulin.[2] Protamine contains a boxed warning that states**:**

"Protamine sulfate can cause severe hypotension, cardiovascular collapse, noncardiogenic pulmonary edema, catastrophic pulmonary vasoconstriction, and pulmonary hypertension. Risk factors include high dose or overdose, rapid administration, repeated doses, previous administration of protamine, and current or previous use of protamine-containing drugs (NPH insulin, protamine zinc insulin, and certain beta-blockers). Allergy to fish, previous vasectomy, and severe left ventricular dysfunction and abnormal preoperative pulmonary hemodynamics also may be risk factors…"[3]

Protamine is a strongly basic protein derived from the sperm of fish from the Salmonidae family. As a non-human protein, protamine can be antigenic, causing production of antiprotamine IgE and IgG antibodies that may lead to an anaphylactic reaction. According product labelling: "Previous exposure to protamine can induce a humoral immune response and predispose susceptible individuals to the development of untoward reactions from the subsequent use of this drug". [3]

Published evidence suggests an increased risk for developing a major protamine reaction in patients using NPH insulin for the treatment of diabetes. Stewart et al conducted a retrospective study of patients who had cardiac catheterization (n=866) and 651 of these patients received protamine for heparin reversal. Of these 651 patients, 8.5% (n=56) had diabetes and 2.3% (n=15) were on NPH insulin. Seven of the patients who received protamine had a major reaction that simulated anaphylaxis, characterized by hypotension and other symptoms that required treatment with catecholamine(s). The incidence of major protamine reaction was 27% (4/15) among those previously exposed to NPH insulin and 0.5% (3/636) among those who had no history of NPH insulin use, $p<0.001$.[4]

These reports suggest a need for screening patients to identify risk factors prior to protamine administration. Recommendations from the manufacturer include:[3]

- The risk to benefit of administration of protamine sulfate should be carefully considered.
- Protamine sulfate should not be given when bleeding occurs without prior heparin use.
- Vasopressors and resuscitation equipment should be immediately available in case of a severe reaction to protamine.
- Protamine sulfate injection should be given by very slow intravenous injection over a 10-minute period in doses not to exceed 50 mg. Too-rapid administration of protamine sulfate can cause severe hypotensive and anaphylactoid reactions. Facilities to treat shock should be available.

In addition, we suggest the following to help protect your patients:

- Have a "time-out" prior to procedure to ensure risks are assessed before use of protamine.
- If possible, minimize use of protamine by using a Z-stitch at the catheter insertion site without having to reverse the heparin.
- Remind staff that sensitization to protamine from NPH use may increase the risk of adverse reaction to protamine.

REFERENCES:

1. Protamine Sulfate. In: Micromdex 2.0. Ann Arbor (MI): Truven Health Analytics, 2016.
2. Triplitt CL, Repas T, Alvarez C. Chapter 57. Diabetes Mellitus. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey L. eds. Pharmacotherapy: A Pathophysiologic Approach, 9e. New York, NY: McGraw-Hill; 2014.
3. Protamine Sulfate [package insert]. Lake Zurich, IL: Fresenius Kabi USA, LLC; 2013.
4. Stewart WJ, McSweeney SM, et al. Increased risk of severe protamine reactions in NPH insulin-dependent diabetics undergoing cardiac catheterization. Circulation. 1984 Nov; 70(5):788-92. ■