ISMP Medication Error Report Analysis

Potential Issues with New Basal Insulin/GLP-1 Fixed Combinations

Hydroxyzine–Hydroxyurea Mix-up

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More Outpatient Oral Cancer Drugs Should Be in Blister Packs

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These medication errors have occurred in health care facilities at least once. They will happen again—perhaps where you work. Through education and alertness of personnel and procedural safeguards, they can be avoided. You should consider publishing accounts of errors in your newsletters and/or presenting them at your inservice training programs.

Your assistance is required to continue this feature. The reports described here were received through the Institute for Safe Medication Practices (ISMP) Medication Errors Reporting Program. Any reports published by ISMP will be anonymous. Comments are also invited; the writers' names will be published if desired. ISMP may be contacted at the address shown below.

Errors, close calls, or hazardous conditions may be reported directly to ISMP through the ISMP Web site (www.ismp.org), by calling 800-FAIL-SAFE, or via e-mail at ismpinfo@ismp.org. ISMP guarantees the confidentiality and security of the information received and respects reporters' wishes as to the level of detail included in publications.

POTENTIAL ISSUES WITH NEW BASAL INSULIN/GLP-1 FIXED COMBINATIONS

Two new fixed-ratio combination insulin/glucagon-like peptide-1 (GLP-1) receptor agonists were approved in November 2016 by the US Food and Drug Administration (FDA). They each combine a basal insulin with a GLP-1 agonist and are administered once daily. Soliqua 100/33, a Sanofi product,

provides 100 units of insulin glargine per mL and 33 mcg of lixisenatide per mL in a 3 mL single-patient-use pen. Novo Nordisk's Xultophy 100/3.6 provides 100 units of insulin degludec per mL and 3.6 mg of liraglutide per mL, also in a 3 mL single-patient-use pen. Soliqua 100/33 and Xultophy 100/3.6 differ from other insulin-containing products and present new potential safety issues.

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Mistaking the Products As Containing Only Insulin

One potential safety issue is that practitioners may mistakenly think that these products contain only insulin. This is one reason why computer system drop-down lists and pharmacy communications about these products should use the ratio expressions (ie, Xultophy 100/3.6 and Soliqua 100/33), which hopefully will help to indicate to users that the product contains 2 different ingredients. The ratio expression is designed to express the ratio of insulin to GLP-1 agonist per mL (eg, Soliqua 100/33 contains 100 units of insulin glargine and 33 mcg of lixisenatide per mL). In contrast to the ratios used for insulin-insulin combination products such as Novo-Log Mix 70/30 (insulin aspart protamine, insulin aspart) or Humalog Mix 50/50 (insulin lispro protamine, insulin lispro), the ratio expressions for Soliqua 100/33 and Xultophy 100/3.6 do not sum up to 100%, which should also help practitioners differentiate them from insulin-only products.

If your system uses generic names, make sure both ingredients are displayed and not truncated. However, keep in mind that the first name practitioners will see is “insulin.” That may contribute to practitioners mistaking these as insulin-only products. Using the brand names, ideally with a hover over presentation of the complete generic names, could reduce the risk of an error. Also, counsel patients when initiating Soliqua 100/33 and Xultophy 100/3.6 so they understand the products contain both insulin and a GLP-1 agonist.

Dosing Is Based on Insulin Units, Not the GLP-1 Agonist Component

Dosing of these products is expressed based on the number of insulin units (the pen dials the dose in insulin units only). The package insert for each product has a table that indicates the amount of GLP-1 agonist per insulin unit, but including the GLP-1 agonist dose is not recommended when prescribing these products. If an order is communicated without the ratio expression (“Soliqua 40 units” or “Xultophy 35 units”), practitioners could think it’s a new insulin product and not recognize that a GLP-1 agonist is contained within. This could lead someone to prescribe a separate GLP-1 agonist to go along with what is thought to be the patient’s only insulin dose.

Fixed Ratios of Insulin to GLP-1 Agonist

Both Soliqua 100/33 and Xultophy 100/3.6 may be used at doses containing less than the currently approved doses for the single ingredient GLP-1

component. For example, the Soliqua 100/33 starting dose is 15 units per day, which contains 5 mcg of lixisenatide. However, the recommended starting dose for single ingredient lixisenatide (Adlyxin) is 10 mcg daily. Converting between these products and the individual ingredients can be problematic since the dosing is not the same. For example, if a hospital stocks only Xultophy 100/3.6, the pen will not provide the same dose achievable with the individual ingredient components (eg, insulin degludec pens and liraglutide pen).

Not Recommended for Concurrent Use with Other Products Containing GLP-1 Agonists

These products are not recommended for use in combination with any other product containing a GLP-1 agonist because of the risk of overdose. The package insert recommends using alternative anti-diabetic products if patients require a Soliqua 100/33 daily dosage below 15 units or over 60 units. For Xultophy 100/3.6, use alternative antidiabetic products if patients persistently require less than 16 units or more than 50 units.

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HYDROXYZINE-HYDROXYUREA MIX-UP

A pharmacist intended to enter an order for liquid hydrOXYzine 25 mg every 6 hours on a scheduled basis for itching (not prn), but accidentally chose liquid hydroxyurea from an order system drop-down list. Liquid hydroxyurea is an institutionally compounded product of 100 mg/mL, while hydrOXYzine is commercially available as 10 mg/5 mL. The hospital required that the purpose be included for “as needed” orders (prn) but not scheduled doses, so that information was not added to the instructions. Also, there was no dose range checking for hydroxyurea, so a 25 mg dose didn’t signal an alert. The order was verified by another pharmacist and then dispensed and administered for 48 hours until medical staff questioned why the patient was receiving hydroxyurea.

There was no apparent harm to the patient with this error, but it certainly was a concern to the hospital because it could have had serious consequences. Such an error could result in a patient with itching being deprived from receiving helpful therapy, as happened here. For a patient with sickle cell disease or one who needed the cytotoxic agent for oncologic

use, this error would have caused them to miss a critically needed dose.

The reporting hospital is considering the use of tall man letters for hydroxyurea. We've recommended tall man letters for hydrOXYzine for some time but have not made any recommendations for hydroxyurea. One problem with using tall man letters for hydroxyurea is that the first 7 letters of each name are identical. It's not until the 8th letter that tall man letter characters would appear (eg, hydroxyUREA). Depending on how brand and generic names are displayed, the final letters of the drug name may be overlooked during drug selection, which apparently happened here. Although hydroxyurea liquid is a pharmacy-compounded product, it may make sense to primarily identify the drug as HYDREA or DROXIA, brand names for currently available commercial hydroxyurea capsule products. Also, some hospitals strive to include a purpose for medications whether scheduled or prn (eg, why would hydroxyurea be used for itching). That may have helped prevent this error.

CONCOMITANT USE OF ENTRESTO AND ACE INHIBITORS CAN LEAD TO SERIOUS OUTCOMES

Entresto (sacubitril/valsartan) is an angiotensin II receptor-neprilysin inhibitor (ARNI) used to reduce the risk of cardiovascular death and hospitalization in patients with chronic heart failure and reduced ejection fraction. It contains the angiotensin II receptor blocker (ARB) valsartan and the neprilysin inhibitor sacubitril. Entresto is contraindicated with concomitant use of angiotensin converting enzyme (ACE) inhibitors because the inhibition of neprilysin from the sacubitril component in Entresto combined with an ACE inhibitor increases the risk of angioedema.¹ Also, the dual renin-angiotensin-aldosterone system blockade that occurs when valsartan is combined with ACE inhibitors increases the risk of hypotension, acute kidney injury, and hyperkalemia. Thus, Entresto should not be administered within 36 hours of switching from or to an ACE inhibitor. Still, the FDA has received 55 cases reporting concomitant use of Entresto and an ACE inhibitor, with several cases describing serious outcomes.

The cases submitted to FDA describe patients who were taking an ACE inhibitor and were prescribed Entresto and patients who started taking Entresto in the hospital and inadvertently restarted their ACE inhibitor after discharge. Several cases described a washout period of less than 36 hours when switching from an ACE inhibitor to Entresto. Eleven patients were hospitalized. The most common

adverse events reported due to this drug interaction were angioedema, hyperkalemia, acute kidney injury, and hypotension.

Entresto is used to lessen morbidity and mortality and replaces an ACE inhibitor or ARB in patients with chronic symptomatic heart failure (NYHA class II or III) with a reduced ejection fraction (HFrEF) who tolerate an ACE inhibitor or ARB.² Due to the previous standard of care, many patients starting Entresto are already taking ACE inhibitors. This could lead to serious adverse events if the ACE inhibitor is not discontinued or if the patient continues taking the previously prescribed ACE inhibitor at home. These errors may be related to the lack of familiarity with Entresto. But since approval in 2015, the drug's use has increased. It was added in the updated 2016 heart failure guidelines published by the American College of Cardiology (ACC), the American Heart Association (AHA), and the Heart Failure Society of America (HFSA). The new guidelines recommend either an ACE inhibitor, an ARB, or an ARNI (eg, Entresto) for patients with chronic HFrEF, but not in combination (Table 1).

Please consider the following recommendations to help prevent the concomitant use of Entresto and ACE inhibitors.

Table 1. ACE inhibitors/ARBs to avoid with Entresto

ACE inhibitors	ARBs
Benazepril (LOTENSIN)	Candesartan (ATACAND)
Captopril	
Enalapril (VASOTEC)	Eprosartan (TEVETEN)
Enalaprilat	
Lisinopril (PRINIVIL, ZESTRIL)	Irbesartan (AVAPRO)
Moexipril (UNIVASC)	Losartan (COZAAR)
Perindopril (ACEON)	Olmesartan (BENICAR)
Quinapril (ACCUPRIL)	
Ramipril (ALTACE)	Telmisartan (MICARDIS)
Trandolapril (MAVIK)	Valsartan (DIOVAN)

Note: ACE = angiotensin converting enzyme; ARBs = angiotensin II receptor blockers.

For Prescribers, Pharmacists, and Nurses

- Prior to prescribing Entresto, ensure that patients are not already taking an ACE inhibitor. For patients taking an ACE inhibitor, ensure that it is stopped and allow for a 36-hour washout period

prior to starting Entresto.

- Work with information technology (IT) staff to create and/or enable order entry system alerts to warn against the concomitant use of Entresto and ACE inhibitors when both of these drugs have been prescribed for the patient. If possible, configure the alert to continue for 36 hours after Entresto or the ACE inhibitor has been discontinued.
- Before dispensing or administering Entresto, review patients' medication regimens. If ACE inhibitors are listed, ensure that patients have discontinued the ACE inhibitor and wait 36 hours before starting Entresto.
- Educate patients about the importance of not taking Entresto and ACE inhibitors together.
- Conduct a thorough medication reconciliation (on admission and at discharge) to ensure that patients who are prescribed Entresto, but were taking an ACE inhibitor or ARB in the past, do not restart it upon discharge from the hospital.

For Insurers

- Create alerts to warn against the concomitant use of Entresto and ACE inhibitors when claims are submitted for both drugs.

REFERENCES

1. Entresto [package insert]. Novartis Pharmaceuticals Corporation. East Hanover, NJ; August 2015. www.ismp.org/sc?id=2848
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MORE OUTPATIENT ORAL CANCER DRUGS SHOULD BE IN BLISTER PACKS

Certain oral cancer drugs would benefit from safer packaging, such as child-resistant blister packs. We've asked the FDA to give this more consideration.

Our medication safety colleagues at *Prescrire*, a French publication, recently wrote about a 30-month-old child who swallowed 8 tablets of mercaptopurine 50 mg (400 mg). The drug was prescribed for his 7-year-old sister with acute lymphoblastic leukemia. The child initially suffered liver cell damage, but this resolved within 12 days and there were no permanent sequelae. It was learned that the tablets were dispensed in a prescription bottle with a child-proof cap. It is unknown how the drug was accessed by the child. However, improperly replaced caps are a well-known problem with bottles.

Incidents like this one are a reminder that child-resistant blister packaging that meets the requirements of the Poison Prevention Packaging Act can help reduce the risk of poisoning, as can keeping all medications out of the reach and sight of children. Dispensing certain drugs in blister packs that also serve as calendar packs can improve adherence in addition to preventing errors. ■