

MEDICATION SAFETY IN SECONDS

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

Helping to achieve safe medication use

INSULIN PENS FOR HOME ADMINISTRATION: INCORRECT USE AND RISK OF SEVERE HYPERGLYCEMIA

Submitted by: Paul Fina, Pharm.D., PGY-2 Medication Use Safety Resident

In October 2017, the Institute for Safe Medication Practices (ISMP) National Alert Network (NAN) sent out an alert reporting several cases of patients failing to remove the inner cover of a standard insulin pen needle before injection. The most recent case resulted in a patient's death due to diabetic ketoacidosis. The patient was unaware that she was incorrectly using the pen and not receiving any insulin doses.

Many hospitals use insulin pen needles with a safety mechanism that will automatically recover and lock the insulin needle after removal from the skin in order to prevent inadvertent needle stick injuries and re-use of needles. In addition, needles with this safety feature

may provide benefit to patients with limitations in dexterity or protection to a caregiver administering an injection. NovoFine® Autocover® and BD AutoShield™ are two such products. Using the NovoFine® Autocover® as an example, the structure of the device hides the needle throughout the insulin administration process and thus, the patient will never see it. Removal of the outermost cover of the Autocover® needle reveals a plastic needle shield that envelops the needle. This shield automatically slides back during insulin injection and re-covers the needle after removal from the skin (Figure 1, page 4).

The standard insulin pen needle for at home

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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.

EDITOR-IN-CHIEF

Marie Sales, Pharm.D.
VA Pharmacy Benefits Management Services [PBM] & Center for Medication Safety [VA MedSAFE]; 1st Avenue—1 Block North of Cermak Road | Building 37; Room 139 | Hines, Illinois | 60141; www.pbm.va.gov

NEWSWORTHY... from the pbm

- Diphenoxylate Hydrochloride and Atropine Sulfate Tablets : Recall Due to Possible Sub Potent and Super Potent Tablets – 12/05/17 - [National PBM Patient Level Recall Communication](#)
- Limbrel® Capsules: Recall for Risk of Potential Life-Threatening Adverse Events – 11/30/17; 12/7/17 – Addendum – National PBM Patient Level Recall Communication ***TARGETED to affected sites only***
- Febuxostat (Uloric): FDA Evaluates Risk of Cardiovascular Death – 11/21/17 - [National PBM Bulletin](#)
- Afluria Pre-filled Syringe Label Creates the Potential for Confusion – 11/15/17 - [National PBM Bulletin](#)

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OSTEOARTHRITIS

[Limbrel Capsules by Primus Pharmaceuticals Linked to Potentially Life-Threatening Health Problems](#)

11/21/2017; ***UPDATED 12/18/2017***

The FDA is advising consumers not to use Limbrel because of the risk of drug-induced liver injury and hypersensitivity pneumonitis. Limbrel is a product currently marketed as a medical food product, consisting primarily of a proprietary blend of flavonoid (polyphenol) ingredients with or without a zinc chelate, for the clinical dietary management of the metabolic processes associated with osteoarthritis. Limbrel is supplied in 250 mg and 500 mg capsules:

- Limbrel 250 mg capsules are in two-part turquoise green capsules with a smooth surface bearing the imprint “LIMBREL” on one end and “52001” on the other end (supplied as: NDC # 68040-601-16; Bottle of 60 capsules [250 mg]).
- Limbrel 500 mg capsules are in two-part turquoise green capsules with a smooth surface imprinted with two white stripes on the cap, and bearing the label of “LIMBREL” and “52002” on the body (supplied as: NDC# 68040-602-16; Bottle of 60 capsules [500 mg]).
- Limbrel250 capsules with 50 mg citrated zinc bisglycinate (10 mg elemental zinc) are in two part turquoise green capsules with a smooth surface bearing the imprint “LIMBREL” on one end and “52005” on the other end (supplied as: NDC# 68040-605-16; Bottle of 60 capsules [250/50 mg]).
- Limbrel500 capsules with 50 mg citrated zinc bisglycinate (10 mg elemental zinc) are in two part turquoise green capsules with a smooth surface imprinted with two white stripes on the cap, and bearing the label of “LIMBREL” and “52006” on the body (supplied as: NDC# 68040-606-16; Bottle of 60 capsules [500/50 mg]).

FDA has received a total of 194 adverse event reports regarding Limbrel. Reports consisted of a range of adverse events, including two serious and potentially life-threatening medical conditions: drug-induced liver injury and hypersensitivity pneumonitis. FDA medical experts determined that Limbrel was likely associated with these adverse events in 30 of those cases.

FDA currently requests that the manufacturer cease distribution and immediately initiate a recall of all lots within expiry of any Limbrel product. Preliminary findings of FDA’s investigation recognizes that Limbrel products:

- Are an unapproved new drug.
- Are misbranded drugs because their label is false or misleading.
- Do not meet the definition of a medical food although labeled and marketed as such.
- Pose an ongoing public health risk.

Since the product is labeled and marketed as a medical food, the Food division of the FDA does not have mandatory recall authority over drug products. However, in FDA’s correspondence with the manufacturer, the agency anticipates classifying this as a Class I level recall, representing a serious health hazard which may be life-threatening.

FDA continues to investigate a rise in the number of serious, potentially life-threatening health problems associated with the use of Limbrel in recent months. In the meantime, FDA recommends:

- Patients should immediately stop taking any Limbrel product and contact their provider because of the risk of drug-induced liver injury and hypersensitivity pneumonitis.
- Health care providers who are aware that their patients are taking Limbrel should advise them to stop use.

Last month, PBM issued a targeted **PBM Patient-Level Recall Communication** (to affected sites only; see page 1) to address impacted patients who have received affected product for home use with instructions to discontinue use and return supply. The National Center for Patient Safety (NCPS) also initiated a **VHA Internal Recall** (PRO# 12540) for this product (all strengths) directed to all VHA sites with sequestration actions to remove from use/shelf. Since FDA recommends against continued use of this agent (although the company did not provide a voluntary recall notice) due to risk of life threatening conditions while there is ongoing review, ***PBM suggests no future purchase of the product and having pharmacy ADPACS remove this product from the orderable item and drug file to prevent future prescribing pending final review by FDA (See Table 1, page 4 for Limbrel’s corresponding VA Product Names).*** This should be able to address affected product still available for sale.

This recall is a somber reminder that use of unproven, unapproved agents is not without risk.

REFERENCES:

1. FDA Safety Alerts for Human Medical Products. Limbrel Capsules by Primus Pharmaceuticals: FDA Advisory - Linked to Potentially Life-Threatening Health Problems. <https://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm586111.htm> . (Accessed 11/21/2017).
2. LIMBREL® (flavocoxid, 250 mg and 500 mg) and LIMBREL250® and LIMBREL500® (flavocoxid and citrated zinc bisglycinate, 250 mg/50 mg, 500 mg/50 mg). [package insert]. Scottsdale, AZ: Primus Pharmaceuticals, Inc., 2017.

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Getting the most from our safety surveillance

REDUCING DOSING ADMINISTRATION ERRORS WITH INJECTABLE MEDICATIONS WHERE STRENGTH PER TOTAL VOLUME DIFFERS FROM STRENGTH PER mL

One site reported a medication administration error which resulted in a patient receiving multiple doses (600 mg each) of dupilumab (Dupixent). Dupilumab (Dupixent) is an interleukin-4 receptor alpha antagonist indicated for the treatment of moderate-to-severe atopic dermatitis inadequately controlled with topical prescription therapies or when those therapies are not advisable. Dosing is based on multiples of 300 mg starting with an initial dose of 600 mg (two 300 mg injections in different injection sites), followed by 300 mg given every other week administered by subcutaneous injection. Dupilumab (Dupixent) is available in cartons containing 2 pre-filled syringes either with or without a needle shield. Each pre-filled syringe with or without a needle shield is designed to deliver 300 mg of dupilumab (Dupixent) in 2 mL solution, as marked on the labeling of the syringe and packaging (Figures 1 and 2).

In the case reported, the nurse administering the injection misinterpreted that each syringe contained only 150 mg since the drug name appears in the computer provider order entry system as DUPILUMAB 150MG/ML SYR INJ 2ML. While this is the correct concentration, the syringe contains 2mL, for a total of 300 mg of drug in one syringe. The nurse mistakenly believed there was only 150 mg of drug in a syringe, and thus administered two injections every other week on two occasions (outside of the initial loading dose) to equate to the prescribed dose of 300 mg (the original prescription directions read: "INJECT 300MG UNDER THE SKIN EVERY OTHER WEEK FOR SKIN DISORDER"); however, 600 mg was actually given. The error was discovered by Pharmacy when a request for refill made by Nursing came early. As a result of this incident, the facility began to include the number of syringes to be administered in the dosage instructions to prevent further errors. (Figure 3).

Although the above example describes an instance concerning one particular injectable medication, the type of dosing administration error that took place is not drug-specific and may occur with other single- and multiple-dose injectable drug products (i.e., heparin). According to studies, half of all harmful medication errors transpire during drug administration, of which two-thirds involve injectable drugs. Multiple manipulations and steps potentially required to prepare injectable medications for administration could introduce risk for errors and patient harm. One such complexity involves translating drug concentration into dose based on strength, volume, and other considerations. The "Strength and Total Volume for Single- and Multiple-Dose Injectable Drug Products" section of United States Pharmacopeia (USP) General Chapter <1> requires that labels display strength per total volume as the primary expression followed by strength per mL in parentheses. Availability of both values on labeling can minimize the potential for confusion when determining dose.

Recommendations to reduce the potential for similar dosing administration errors with injectable medications include:

- Educate ALL staff involved with ordering, dispensing, preparation, and administration of injectable drugs on the potential for misinterpreting drug concentration (strength per total

volume versus strength per mL) when determining dose.

- Engage nursing staff in educational efforts. Consider including information in newsletters, e-mail announcements, computer screen banners, and other forms of communication your medical center may use (such as daily bulletins).
- Consider independent double checks during the dispensing and administration phases to verify appropriate dose.
- Review processes for computerized provider order entry systems and labeling (i.e., quick orders, drug menus, dispensing labels, etc.) to ensure language is consistent with current standard of strength per total volume presentation.

REFERENCES:

1. Internal data.
2. DUPIXENT® (dupilumab) [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc.; March 2017.
3. Grissinger M. Reducing Errors with Injectable Medications. *P&T* 2010; 35 (8): 428,451.
4. *United States Pharmacopeia and National Formulary* (USP 31-NF 26). Rockville, MD: United States Pharmacopeial Convention; 2008. http://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/generalChapterInjections.pdf. Accessed November 20, 2017.

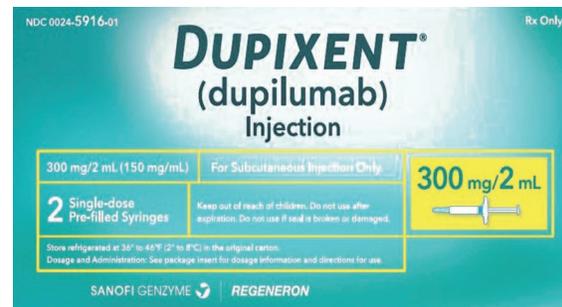


Figure 1. Product packaging with both strength per total volume and strength per mL represented.



Figure 2. Pre-filled syringe delivering 300 mg of dupilumab (Dupixent) in 2 mL solution as per label.

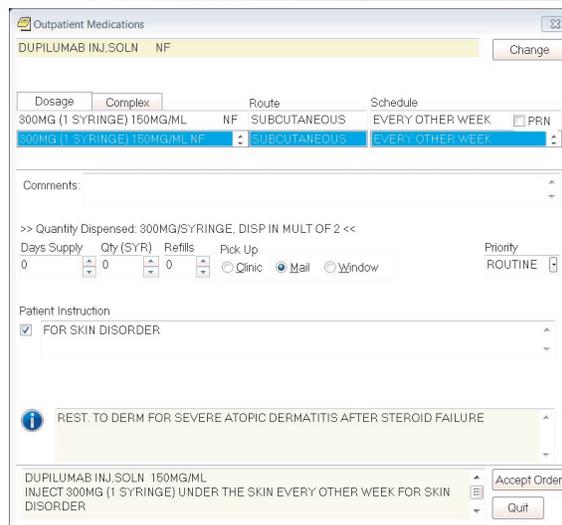


Figure 3. As a process improvement, the facility began to include the number of syringes to be administered in the dosage instructions to prevent errors in the future.

Helping to achieve safe medication use

INSULIN PENS FOR HOME ADMINISTRATION: INCORRECT USE AND RISK OF SEVERE HYPERGLYCEMIA

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use has a similar look and administration process to the safety pen needle, but requires an extra step to expose the needle for insulin delivery. The standard pen needle also has an outer cover, but instead of a plastic shield that covers the needle and automatically retracts during use, there is an inner needle cover that must be manually removed prior to insulin injection to allow the administration of insulin (Figure 2). Failing to remove this inner needle cover will result in a failed injection and no insulin delivery.

Awareness of the difference between standard insulin pen needles and safety pen needles as well as instruction on the proper technique for each device would help to reduce errors in administration. ISMP recommends several steps to prevent incorrect pen needle use:

- Educate all patients that receive an insulin pen on how to use it properly. Tailor patient training to the type of needle that they will be using at home and require patients to

demonstrate how to use an insulin pen during the education session.

- Ensure that patients understand to remove both caps if using standard insulin pen with non-safety needles.
- Pharmacy staff should verify that patients can properly administer insulin whenever insulin pens and needles are dispensed. Inform patients that there are several different types of insulin pen needles and to contact their pharmacy if the pen needle is different than what they expect or have been taught to use.
- Instruct patients to contact their provider if blood glucose levels are elevated. Review the insulin injection technique with patients if faulty technique is suspected to contribute to uncontrolled glucose levels.

REFERENCE:

NAN ALERT. Severe hypoglycemia in patients incorrectly using insulin pens at home. National Coordinating Council on Medication Error Reporting and Prevention (NCCMERP); October 12, 2017.

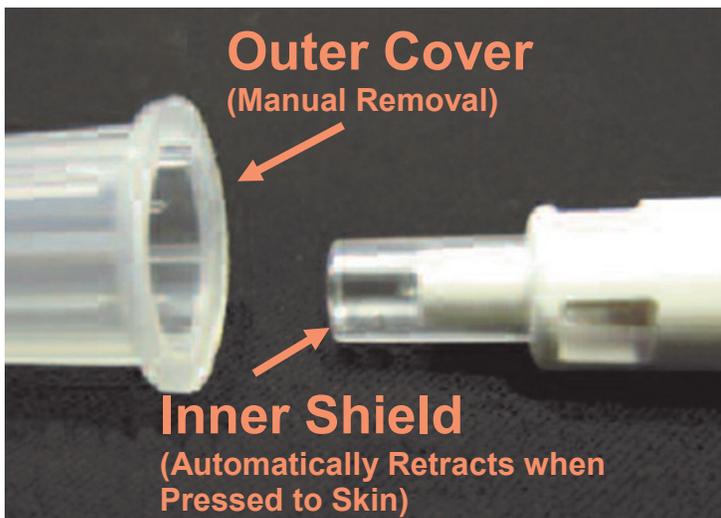


Figure 1. Safety Pen Needle (as pictured in ISMP's NAN Alert). After manual removal of the outer cover, this device has an inner needle shield that automatically retracts upon injection, then recovers and locks over the needle when withdrawn from the skin.

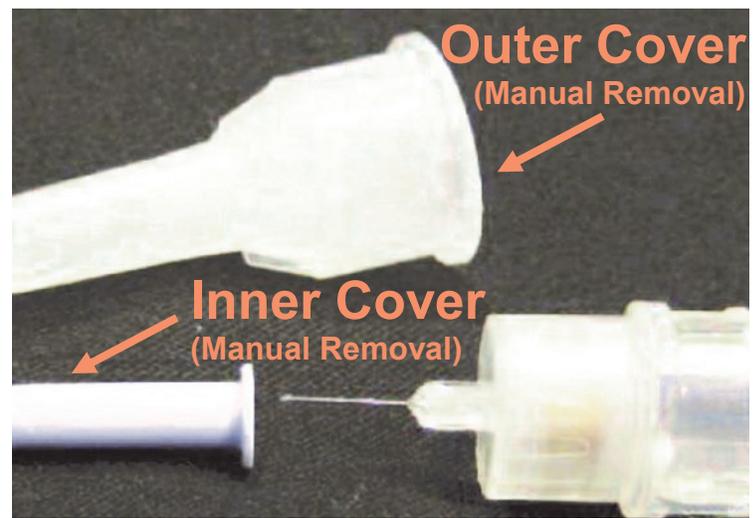


Figure 2. Standard Pen Needle (as pictured in ISMP's NAN Alert). This device has both an outer cover and inner needle cover that must be manually removed prior to injection.

from the fda

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PRODUCT DESCRIPTION	NDC	VA PRODUCT NAME
LIMBREL 250mg (without zinc) Bottle of 60 capsules (250 mg)	68040-601-16	FLAVOCOXID 250MG CAP,ORAL
LIMBREL 500mg (without zinc) Bottle of 60 capsules (500 mg)	68040-602-16	FLAVOCOXID 500MG CAP,ORAL
LIMBREL250 (with zinc) Bottle of 60 capsules (250/50 mg)	68040-605-16	BAICALIN,CATECHIN 250MG/CITRATED ZINC 50MG CAP,ORAL
LIMBREL500 (with zinc) Bottle of 60 capsules (500/50 mg)	68040-606-16	BAICALIN,CATECHIN 500MG/CITRATED ZINC 50MG CAP,ORAL

Table 1. Limbrel's corresponding VA Product Names are listed in the last column on the right. Local site listings may vary according to how the product is entered with respect to local name. ■