

Community/Ambulatory Care

ISMP Medication Safety Alert!®

Educating the Healthcare Community About Safe Medication Practices

Fluoropyrimidines and routine screening for DPYD genetic variants

PROBLEM: A hospital recently reported that over a three-week period two patients experienced seizures following administration of injectable fluorouracil. The first patient experienced seizures after two separate injections were administered, approximately two weeks apart. The second patient experienced multiple seizures, with the first occurring within 30 hours after exposure. While the first patient had prior exposure to fluorouracil, the second patient was treatment naïve. At the reporting organization, routine screening for dihydropyrimidine dehydrogenase (DPD) deficiency was not standard practice prior to initiating fluoropyrimidine therapy, therefore, both patients had not undergone testing. Although we are not certain of the cause of the seizures or other contributing factors, neurotoxicity, including seizures, has been reported with fluorouracil administration, and patients with reduced DPD activity are at increased risk.^{1,2} “DPYD is the gene that encodes the DPD enzyme. Genetic variants of DPYD are known to affect the risk of severe toxicity and drug exposure in patients receiving fluoropyrimidines.”³

DPYD Screening

ISMP is aware of several reports of patients who suffered severe toxicities or even death from fluorouracil or **XELODA** (capecitabine), an oral prodrug that is metabolized to fluorouracil. Both are fluoropyrimidine chemotherapy drugs. We continue to support universal screening of this deficiency prior to fluorouracil administration.

In January 2025, the US Food and Drug Administration (FDA) issued a [safety announcement](#) to increase awareness of recent updates to the product labeling of fluorouracil and capecitabine related to risks associated with DPD deficiency. FDA emphasized that all healthcare providers should be aware of the risks, inform patients prior to treatment about the potential for serious and life-threatening toxicities, and discuss testing options for DPD deficiency with their patients.⁴

In addition, the latest version of the National Comprehensive Cancer Network’s (NCCN’s) Colon Cancer guidelines, released in October 2025, now recommends considering testing for DPYD genetic variants prior to initiating fluoropyrimidine therapy. The NCCN panel endorses identifying patients at the greatest risk for severe fluoropyrimidine toxicity, emphasizing that discussion of DPYD genetic variant testing should occur with patients prior to fluoropyrimidine therapy, and should be considered within the context of the patient’s individual circumstances.³

In March 2024, the fluorouracil prescribing information was updated to include a warning regarding the increased risk of serious or fatal adverse reactions in patients with low or absent DPD activity, and to consider testing for genetic variants of DPYD prior to initiating fluorouracil to reduce the risk of serious adverse reactions if the patient’s clinical status permits and based on clinical judgment. Furthermore, in October 2025, FDA added a Boxed Warning for Xeloda that includes the statement, “Test patients for genetic variants of DPYD prior to initiating Xeloda unless immediate treatment is necessary.”⁵ However, fluorouracil does not have the same Boxed Warning, which ISMP advocates for FDA to consider adding.

SAFE PRACTICE RECOMMENDATIONS: To enhance patient safety when using fluoropyrimidines, several key considerations should be integrated into practice.

Gather a multidisciplinary team. Create a team with representatives from pharmacy, oncology, clinical laboratory, and other relevant departments to oversee fluoropyrimidine safety and conduct

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SAFETY briefs



Risk of mix-ups among the Pedia-Lax line of products.

The C.B. Fleet Company markets a number of products within the Pedia-Lax line of products. These include a magnesium hydroxide laxative, docusate sodium stool softener, glycerin suppository, and sodium phosphates enema. The use of the same brand name (e.g., Pedia-Lax) across different over-the-counter (OTC) products is referred to as “brand-name extension,” a practice to reuse a well-known proprietary name to introduce a new product that may contain an active ingredient different from the active ingredient in the original product. However, brand-name extension OTC products have been associated with patient and practitioner confusion about the product’s ingredients, strength, and concentration, which has contributed to errors. A pharmacist recently reported an error that involved the Pedia-Lax family of products.

A family member asked the pharmacy to order Pedia-Lax for her child. Since the pharmacist was familiar with the Pedia-Lax glycerin suppositories, they placed the order for the suppositories. After the product arrived in the pharmacy, the patient’s family came back to pick it up. It was discovered that the wrong Pedia-Lax product had been ordered.

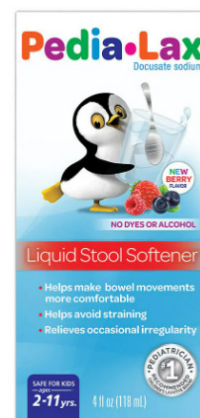


Figure 1. Carton of Pedia-Lax docusate liquid stool softener uses the same stylized brand name and design elements (e.g., image of the penguin) as other products in the Pedia-Lax family of products.

In addition to sharing the name Pedia-Lax, the medication cartons contain design elements that may also contribute to confusion. Each carton prominently displays the Pedia-Lax name in rainbow colors at the

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a comprehensive review of current testing protocols, comparing them to established guidelines to identify gaps in current practice.

Establish DPYD testing guidelines. Develop guidelines that clearly define DPYD testing criteria, provide instructions for interpreting results, and outline appropriate clinical action that includes a system to track patients initiating fluoropyrimidine treatment. For additional information, please refer to the [DPYD Genotyping Recommendations](#)⁶ which aim to promote consistency in DPYD genetic variant testing across clinical laboratories.

Utilize clinical decision support. Integrate the [Clinical Pharmacogenetics Implementation Consortium \(CPIC\) Guideline for DPYD and Fluoropyrimidines](#) into the electronic health record (EHR) to alert prescribers and recommend DPYD genetic variant testing before ordering fluorouracil or capecitabine. Integrate testing results with clinical decision support (e.g., alerts for contraindications, dose adjustments) directly into the EHR workflow.

Educate staff. Educate staff about your organization's guidelines and how to interpret test results and adjust or hold the fluoropyrimidine dose when needed.

Inform patients. Engage in shared decision-making with patients by reviewing their DPYD genetic variant test results before initiating therapy and explaining the implications on their treatment plan. Provide patients with detailed documentation of their test results and emphasize the importance of sharing this information with all healthcare professionals involved in their care.

Antidote availability. Ensure uridine triacetate, the antidote for fluoropyrimidine overdose or toxicity, is readily available and included in order sets that contain fluoropyrimidine drugs to ensure appropriate doses and timing for both adult and pediatric patients, should signs and symptoms of an overdose/toxicity present themselves.

Written by Kara Jensen, PharmD, BCPS; 2025-2026 ISMP Safe Medication Management Fellow, supported by the US Army

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Worth repeating...



Another mix-up involving metOLazone and methotrexate

A pharmacy recently shared that a number of factors contributed to a patient receiving metOLazone, a thiazide diuretic, instead of the prescribed chemotherapeutic agent methotrexate. An electronic prescription for methotrexate 2.5 mg was sent to the pharmacy with the directions to take 8 tablets by mouth once weekly. However, the prescription was filled as metOLazone 2.5 mg with the same directions. During verification, the pharmacist determined that the dose of metOLazone (eight 2.5 mg tablets or 20 mg) to be clinically appropriate based on the patient's profile and tertiary references. When the patient requested a refill, the error was discovered

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top of the primary display panel. The principal display panels also include an image of a penguin, either holding the dosage form (e.g., liquid in a glass) of the product (**Figure 1**, page 1) or nothing at all in the case of the carton containing the sodium phosphates enema. While the cartons include a description of the product (e.g., chewable laxative, liquid stool softener), not all caregivers may understand the differences. Also, the generic names may be much less prominent than the Pedia-Lax name. The use of the same brand name and imagery across the product line may cause confusion for caregivers and contribute to medication errors.

The US Food and Drug Administration should not allow brand-name extensions of OTC products. Also, the generic name should be displayed prominently. Pharmacies should closely examine new products before they are sold and evaluate how and where these products are placed on OTC shelves in order to minimize confusion for patients when they are selecting products on their own.



Dose confusion with Hemlibra leads to overdose.

A pediatric patient was prescribed **HEMLIBRA** (emicizumab), a factor IXa- and factor X-directed antibody indicated for prophylaxis against bleeding episodes in patients with hemophilia A. The drug is intended for use under the guidance of a healthcare provider. However, after proper training, a patient may self-inject, or the patient's caregiver may administer Hemlibra, if a healthcare provider determines that it is appropriate. In this case, the patient's parent was preparing 33 mg (or 0.22 mL) of Hemlibra to administer subcutaneously to the child. However, they became confused about how much Hemlibra should be drawn up into the parenteral syringe. They contacted the specialty pharmacy and began a conversation with the on-call answering service. Before the answering service could direct the call to the appropriate person, the parent became confused and frustrated. They disconnected from the call and administered a dose. Unfortunately, they drew up the entire contents of a vial (0.4 mL or 60 mg) into a syringe and administered it, almost double the prescribed dose.

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and corrected. The pharmacy identified that the high stress environment, high prescription volume, look- and sound-alike similarities of metOLazone and methotrexate, and distractions from various sources (e.g., patient questions, employee questions, incoming phone calls, doctor messages) contributed to the mix-up. Also, only three letters are required to be entered into the pharmacy software to search for a drug name. This may have contributed to the event as a search for “met” displays methotrexate, metOLazone, and methylphenidate.

While this error did not result in reported patient harm, a mix-up of these drugs in which methotrexate is dispensed in error can end in tragedy. We have written multiple times about mix-ups between these. For example, in the **Safety brief**, Methotrexate-MetOLazone Mix-ups, published in June 2016, a hospital nurse called in eight discharge medications to a pharmacy. Unfortunately, one of the telephone prescriptions was transcribed incorrectly at the pharmacy as methotrexate 2.5 mg daily instead of metOLazone 2.5 mg. Subsequently, the patient died as a result of the error. In the November 2019 article, Another Patient Dies After Receiving Methotrexate Instead of MetOLazone, we shared the story in which a pharmacy sent the wrong prescription to an assisted living facility. Unfortunately, the error was not discovered, and the facility staff administered methotrexate to the patient. The patient experienced severe pain and discomfort and died about one month after daily doses of methotrexate were administered.

To reduce the risk of mix-ups between these drugs and prevent severe patient harm, it is **Worth repeating** the strategies that can reduce these errors. Software system vendors should develop and implement a dynamic search function, an algorithm that allows users to enter the exact number of characters to get only one unique drug name to appear on the screen when searching for medication names. If a dynamic search function is not available, consider requiring entry of a minimum of the first five letters of the drug name. ISMP also recommends using tall man letters for metOLazone to help differentiate it from methotrexate and employing a hard stop in prescribing and dispensing software to prevent methotrexate from being entered as a daily dose without an appropriate cancer indication.

Design pharmacy space and workflow to minimize distractions, especially during data entry, filling, and pharmacist verification. Borrow a concept from the airline industry and create a “sterile cockpit” at each workstation to minimize unnecessary distractions and interruptions. Explore ways to build additional redundancies in your dispensing process. For example, investigate whether your pharmacy software will allow for two separate pharmacist verification steps: 1) pharmacist verification of the data entry and clinical information before the pharmacy label is printed, and 2) pharmacist verification of the completed prescription. Prior to dispensing methotrexate to any patient, verification of the dose, frequency, and indication is required. Similarly, prior to administering methotrexate, nurses should verify the patient has an appropriate indication for the medication, dose, and frequency.

Patient education is also required. This provides an opportunity for the pharmacist to recognize an error if the wrong drug is being dispensed. Consider establishing a system to ensure review of all methotrexate prescriptions that have been dispensed within the past 24 hours. For additional strategies to prevent errors involving the inadvertent daily dosing of oral methotrexate, please see Best Practice 3 in the [ISMP Targeted Medication Safety Best Practices for Community Pharmacy](#).

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Multiple preparation steps and supplies are needed to prepare and administer a dose of Hemlibra. For example, for the patient's dose described above, the caregiver would need the vial of medication, alcohol swabs, a 1 mL parenteral syringe, a transfer needle, and an injection needle. Without proper training and experience, working with the multiple items could cause anxiety and confusion for a caregiver. In addition, maintenance doses of Hemlibra may be administered once a week, once every 2 weeks, or once every 4 weeks. This means there may be a long period of time in between when caregivers prepare doses, which can contribute to anxiety and confusion the next time they administer a dose. Thus, it is critical that the prescriber and/or specialty pharmacy provide training and confirm, via return demonstration, the caregiver's ability to prepare and administer the product properly and safely. If this cannot be done, a healthcare practitioner should administer the medication.

The reporter indicated that the parent also may not have understood the directions printed on the prescription label. **The pharmacy prescription label's main purpose is to support the patient or caregiver to use the medication correctly and safely.** It is important for both prescribers and pharmacy staff to provide directions that are easily understood by patients and caregivers. To help accomplish this, the patient directions should only include the unit of measure the patient or caregiver will need to measure the correct amount of medication to administer the specific dose. For example, in the case above, the instructions could read “Inject 0.22 mL subcutaneously in the morning once a week.” Ensure the dosing instructions on the prescription label match the dose marking(s) on the provided dosing device. Do not use multiple units of measure or combine both the dosage unit and the volume (e.g., 33 mg [0.22 mL]) on the prescription label as this can cause confusion for the caregiver or patient.

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