

Acute Care

ISMP Medication *Safety Alert!*[®]

Educating the Healthcare Community About Safe Medication Practices

Fluoropyrimidines and routine screening for DPYD genetic variants



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

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. In our July 15, 2021 article, Screening for Dihydropyrimidine Dehydrogenase (DPD) Deficiency in Fluorouracil Patients: Why Not?, and our May 2, 2024 article, Utilizing Pharmacogenomic Testing Can Improve Medication Safety and Prevent Harm, we reinforced our continued support for 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.

continued on page 2 — [DPYD genetic variants](#) >

SAFETY brief



Demonstration IUD inserted vaginally.

A prescriber intended to insert a **MIRENA** (levonorgestrel) intrauterine device (IUD) into a patient at the physician's office. After inserting the device vaginally, the prescriber identified that they had inadvertently inserted a demonstration (demo) **KYLEENA** (levonorgestrel) IUD. Bayer makes both products. Immediately following insertion, the prescriber noticed during documentation that the demo device was used. The prescriber notified the patient of the error, removed the demo device, and inserted the correct Mirena IUD. There was no reported harm.

Prescribers do not insert IUDs frequently in this physician's practice. For educational purposes, demo IUDs were stored on the counter in the procedure room. The IUDs that contain the actual medication were in a locked cabinet also in the procedure room. The Kyleena demo IUD was packaged in a non-sterile, sealed, tear-apart package

(**Figure 1**). The front of the package has a warning, "STOP, NOT FOR USE IN HUMANS," and the back has a warning, "STOP NON-STERILE NOT FOR USE IN HUMANS." Due to how these warning messages are composed and the placement of the "non-sterile" warning on the front of the package, a practitioner could easily mistake the demo for a



Figure 1. Front (left) and back (right) sides of the demo Kyleena IUD, which comes in a non-sterile, sealed, tear-apart package resembling a device that actually contains medication.

continued on page 2 — [SAFETY brief](#) >

> **DPYD genetic variants** — continued from page 1

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 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 Fluoropyrimidines and DPYD](#) 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.

References

- 1) Cordier PY, Nau A, Ciccolini J, et al. 5-FU-induced neurotoxicity in cancer patients with profound DPD deficiency syndrome: a report of two cases. *Cancer Chemother Pharmacol*. 2011;68(3):823-826.
- 2) Kim YA, Chung HC, Choi HJ, Rha SY, Seong JS, Jeung HC. Intermediate dose 5-fluorouracil-induced encephalopathy. *Jpn J Clin Oncol*. 2006;36(1):55-59.
- 3) [National Comprehensive Cancer Network](#). NCCN Clinical Practice Guidelines in Oncology: Colon Cancer. Version 5.2025. Accessed February 5, 2026.
- 4) [Safety Announcement: FDA highlights importance of DPD deficiency discussions with patients prior to capecitabine or 5-FU treatment](#). US Food and Drug Administration. January 24, 2025. Accessed February 5, 2026.
- 5) [Xeloda. Drug safety-related labeling changes](#). US Food and Drug Administration. Accessed February 5, 2026.
- 6) Pratt VM, Cavallari LH, Fulmer ML, et al. DPYD Genotyping Recommendations. *J Mol Diagn*. 2024;26(10):851-863.

To subscribe: www.ismp.org/ext/1367

ISMP Medication **SafetyAlert!** Acute Care (ISSN 1550-6312) © 2026 Institute for Safe Medication Practices (ISMP). All rights reserved. Redistribution and reproduction of this newsletter, including posting on a public-access website, beyond the terms of agreement of your subscription, is prohibited without written permission from ISMP. This is a peer-reviewed publication.

Report medication and vaccine errors to ISMP: Please visit www.ismp.org/report-medication-error or call 1-800-FAIL-SAFE. ISMP guarantees the confidentiality of information received and respects the reporters' wishes regarding the level of detail included in publications.

Editors: Shannon Bertagnoli, PharmD; Ann Shastay, MSN, RN, AOCN; Rita K. Jew, PharmD, MBA, BCPPS, FASHP; Editor Emeritus, Michael R. Cohen, RPh, MS, ScD (hon), DPS (hon), FASHP. ISMP, 3959 Welsh Road, #364, Willow Grove, PA 19090. Email: ismpinfo@ismp.org; Tel: 215-947-7797.

> **SAFETY brief** cont'd from page 1

sterile IUD that contains actual medication. There is also concern with negative warning statements that the practitioner may only see the active action (FOR USE IN HUMANS) and miss the "NOT" in the beginning part of the statement, especially if the label is obstructed, or the statement is separated on to two lines. The practice has since removed demo devices from the office.

Manufacturers should package demo products to look distinctly different than the actual product and should prominently indicate on the label that they are for demonstration purposes only. Only schools, teaching facilities, and staff educators should purchase demo products. Store demo products that are used in simulation training separately in a classroom/training area and away from medication storage areas or patient care areas (e.g., procedure rooms), where they could be mistaken for actual medications. Affix auxiliary labels on all simulation supplies (e.g., For Demonstration Only, Education Only). When demo devices are in use, establish a process for educators to account for every demo device used during training simulations. If you suspect that any training products may have been or were almost administered to a patient, please report it to [ISMP](#), even if the event did not harm the patient.

➔ Special Announcement

Participants needed for study

Doctors, nurses, and pharmacists sometimes confuse drug names that look and sound alike. Researchers at Northwestern University invite you to participate in an online experiment studying drug name confusion errors.

The experiment takes about an hour and pays \$100 upon completion. To participate, you must be a physician, nurse, or pharmacist who has prescribed, transcribed, dispensed, or administered at least one medication in the past year. If interested, email drugname.study@northwestern.edu.