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ISMP Medication Safety Alert!®

Educating the Healthcare Community About Safe Medication Practices

Analysis of Estradiol Transdermal Patch Errors Highlights Safety Gaps – Part I

Problem: Errors associated with estradiol transdermal patches have been reported in clinical practice, identifying several safety concerns related to prescribing, dispensing, and administration. Estradiol transdermal patches are medicated adhesive systems applied to intact skin such as the lower abdomen, hips, and upper buttocks to deliver estrogen continuously into the bloodstream for hormone replacement therapy (HRT) and relief of menopausal symptoms such as night sweats and hot flashes. In **Part I** of our report, we present the types of errors involving estradiol transdermal patches along with identified contributing factors (**Box 1**, page 3). In **Part II** of our report, which will appear in a future newsletter, we will explore how to prevent errors involving estradiol transdermal patches.

Regulatory Changes for Hormone Replacement Therapy Products

Recent regulatory changes and evolving prescribing trends may be contributing to an increased risk or increased occurrence of errors with estradiol patches. The US Food and Drug Administration (FDA) has updated labeling for menopausal HRT, including removal of Boxed Warnings.[1-3] These warnings were originally added following the results from the Women's Health Initiative (WHI), which identified increased risks of cardiovascular disease, breast cancer, and dementia, particularly in older women, with the use of these products. However, evidence suggests that these risks were overgeneralized, especially in women younger than 60 years or within 10 years of menopause.[1,4-7] Updated labeling now supports a more individualized risk-benefit assessment to guide appropriate use of HRT, which may be contributing to increased prescribing.[1-3]

Individualized Treatment

Transdermal drug delivery can vary significantly between patients due to differences in skin permeability, site of application, and external factors such as heat exposure. For instance, applying a patch to different areas of the body or exposure to heating pads or warm environments can alter drug absorption. Because of this variability in absorption, estrogen therapy often needs to be individualized, with some patients responding differently to specific formulations (e.g., patch, cream, oral formulation) or strengths. As a result, switching between patch products is not always straightforward, and presuming interchangeability between products can increase the risk of dosing errors.

Estrogen Patch Availability

As more patients are started on estradiol products, especially in outpatient and community settings, the potential for errors may occur. Differences in product selection, dosing frequency, and patient-specific factors can all contribute. Additionally, increased demand has led to intermittent shortages of estradiol patches, which can complicate dispensing. For example, the American Society of Health-System Pharmacists is tracking supply issues across several manufacturers. At the time of this publication, several manufacturers of estradiol patches report intermittent product availability. These shortages may necessitate product substitutions, increase the risk of incorrect product selection, or result in delays in therapy if changes are not carefully reviewed.

Estradiol patches are available in multiple formulations with different application frequencies, including once-weekly (e.g., **CLIMARA**) and twice-weekly (e.g., **DOTTI**, **VIVELLE-DOT**) products (**Table 1**, page 2). These differences are not always clearly recognized during prescribing or

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SAFETY briefs

Look-Alike Cartons Contribute to Dispensing a Mix of Dosage Forms. In a February 2021 ***SAFETY* brief**, we described an error in which a pharmacy dispensed three **ACTEMRA ACTPEN** (tocilizumab) prefilled pen devices and one **ACTEMRA** prefilled syringe. Actemra is an interleukin-6 (IL-6) receptor antagonist used to treat rheumatoid arthritis and other inflammatory conditions. While there are similarities between these products, the administration instructions differ for the pen and syringe, so there is a risk the patient may not know how to administer the medication if they receive the incorrect device. Fortunately, in this case the patient noticed the error, called the pharmacist, and received education about using the prefilled syringe. Similarities between the products likely contributed to this error.

Figure 1. Actemra ACTPen prefilled pen (left) and Actemra prefilled syringe (right) are available in the same concentrations and similar looking cartons.

Recently, a pharmacist shared with us another incident involving these Actemra products. A patient incorrectly received a mix of Actemra ACTPens and Actemra prefilled syringes. The error was not identified during dispensing or by the patient. It is unknown if the patient used the incorrect product. Pharmacy staff identified an inventory discrepancy and then was able to confirm the patient received a

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dispensing, which can lead to mismatches between the product intended, the product selected, and the directions provided on the pharmacy label.

Table 1. Examples of commercially available estradiol transdermal patches.

Product	Strength		Application Frequency
Alora	■ 0.025 mg/24 hr		Twice weekly
Dotti	■ 0.025 mg/24 hr ■ 0.0375 mg/24 hr ■ 0.05 mg/24 hr	■ 0.075 mg/24 hr ■ 0.1 mg/24 hr	Twice weekly
Lyllana	■ 0.025 mg/24 hr ■ 0.0375 mg/24 hr ■ 0.05 mg/24 hr	■ 0.075 mg/24 hr ■ 0.1 mg/24 hr	Twice weekly
Minivelle	■ 0.025 mg/24 hr ■ 0.0375 mg/24 hr ■ 0.05 mg/24 hr	■ 0.075 mg/24 hr ■ 0.1 mg/24 hr	Twice weekly
Vivelle-Dot	■ 0.025 mg/24 hr ■ 0.0375 mg/24 hr ■ 0.05 mg/24 hr	■ 0.075 mg/24 hr ■ 0.1 mg/24 hr	Twice weekly
Generic products	■ 0.025 mg/24 hr ■ 0.0375 mg/24 hr ■ 0.05 mg/24 hr	■ 0.075 mg/24 hr ■ 0.1 mg/24 hr	Twice weekly
Climara	■ 0.025 mg/24 hr ■ 0.0375 mg/24 hr ■ 0.05 mg/24 hr	■ 0.06 mg/24 hr ■ 0.075 mg/24 hr ■ 0.1 mg/24 hr	Once weekly
Menostar	■ 14 mcg/24 hr		Once weekly
Generic products	■ 0.025 mg/24 hr ■ 0.0375 mg/24 hr ■ 0.05 mg/24 hr	■ 0.06 mg/24 hr ■ 0.075 mg/24 hr ■ 0.1 mg/24 hr	Once weekly

Error Analysis

We analyzed estradiol patch-related cases reported to the California Medication Error Reporting (CAMER) program between June 30, 2025, and March 25, 2026, as well as errors reported to the ISMP National Medication Errors Reporting Program (ISMP MERP). Common issues included mismatches between product selection and directions, incorrect strength selection, failure to clarify discrepancies, and system-level limitations that contributed to errors during prescribing and dispensing. Similar safety concerns have been previously described in our March 2021 article, Analysis of Transdermal Medication Patch Errors Uncovers a "Patchwork" of Safety Challenges.

Errors in the Frequency of Patch Application or Removal

Errors involving how often estradiol patches should be applied were commonly identified. These errors are often related to differences between available formulations, as some products are intended for once-weekly use, while others are for twice-weekly use, and confusion between formulations can lead to incorrect frequency of administration.

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mix of pens and syringes. The reporter noted that the similar looking packaging (**Figure 1**, page 1), storage of the products near each other in the refrigerator, and a lack of scanning each carton during the dispensing process contributed to the event.

The reporter also identified that a similar error risk exists with the **AJOVY** (fremanezumab-vfrm) 225 mg/1.5 mL prefilled syringe and the Ajovy 225 mg/1.5 mL prefilled autoinjector. Ajovy is a calcitonin gene-related peptide antagonist approved for the preventive treatment of migraine in adults and preventive treatment of episodic migraine in pediatric patients 6 to 17 years of age and who weigh 45 kg or more. The cartons for both products look similar, using the same color scheme for the drug name and concentration (**Figure 2**). The manufacturer, Teva, does include on the principal display panels drawings of the devices included. However, the differences between these drawings may not catch the attention of practitioners as the drug name is much more prominent than the device used for administration, and parts of each of the device images are covered by the same blue bubble that says "225 mg/1.5 mL."

Figure 2. Ajovy prefilled syringes (top) and autoinjector (bottom) are available in the same concentrations and similar looking cartons.

To reduce the risk of errors, print and affix a label to each package dispensed. Scan each carton's barcode during production instead of scanning just one carton once or one carton multiple times. If your pharmacy dispensing software does not provide the ability to scan multiple containers for a prescription, request that the vendor provide this functionality. We advocate for this functionality in Best Practice 2 in the ISMP Targeted Medication Safety Best Practices for Community Pharmacy.

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In one case, a once-weekly estradiol patch was prescribed with directions to apply the patch twice weekly. The discrepancy was not identified during verification and persisted until the patient returned for a refill. This reflects a breakdown in confirming that the directions match the product selected.

In another safety report, similar to the one described above, a new prescription for a once-weekly estradiol patch included directions to apply one patch twice weekly. The prescription was verified as written, and the patient received two cartons of patches. Although the patient recognized the discrepancy and self-corrected the frequency, the mismatch between product selection and dosing instructions was not identified during verification. This highlights the importance of reconciling the written prescription with the chosen product during the final pharmacist verification step.

A third case involved an electronic prescription that was transmitted for a twice-weekly estradiol patch, but the directions were incorrect and directed the patient to "apply one patch twice daily." The error was recognized after the patient picked up the medication and the prescriber updated the instructions; however, the revised directions did not match the product selected, as the patch remained a twice-weekly formulation while the instructions were changed to once-weekly use. This case highlights how errors with electronic prescribing (e-prescribing), along with mismatches between the product and directions, persist if they are not caught and corrected.

Dose Confusion and Strength Selection Errors

Dose confusion was also seen with estradiol patches, particularly when multiple strengths were active on the patient's profile. While labeling may contribute, many errors were related to how information was interpreted and verified during dispensing.

In one case, a patient had active prescriptions for two strengths of Dotti (0.0375 mg/24 hr and 0.075 mg/24 hr). When contacted, the patient was unsure which strength she had been using and requested whichever had been dispensed previously. Due to misinterpretation and not verifying the intended dose, the lower strength was refilled instead of the higher strength that the patient should have been using. This case reflects how incomplete clarification of the intended dose with the prescriber can lead to selection errors.

Box 1. Identified factors contributing to errors involving estrogen transdermal patches.

- Differences in dosing frequency between once-weekly and twice-weekly formulations
- Multiple active prescriptions for different strengths
- Similar product names and labeling
- Increased prescribing following regulatory changes
- Drug shortages leading to substitutions and workflow disruptions
- System limitations in electronic prescribing and dispensing software
- Reliance on system defaults without adequate verification
- Incomplete communication among prescribers, pharmacists, and patients

In another case that happened in a mail-order pharmacy, a patient requested a lower patch strength; however, a higher strength was dispensed after a drug utilization review alert was misinterpreted. The lower strength prescription was discontinued without confirming the intended dose with the patient. This case highlights how miscommunication, combined with gaps in verification, can contribute to incorrect dosing decisions. When uncertainty exists, prescriptions should be clarified with the prescriber.

In a separate case reported to the ISMP MERP, a prescription for Lyllana 0.05 mg/24 hr patch was mistakenly entered into the pharmacy dispensing software as an estradiol 0.075 mg/24 hr patch. A

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Ideally, pharmacy computer systems will prompt or require each product's barcode to be scanned. Apply an auxiliary label or circle the dosage form on these cartons when received from the supplier to differentiate the autoinjector devices from the prefilled syringes. The reporter shared that they have separated these products in the refrigerator. If you do this, make sure to notify staff where the products have been moved.

PRN Prescriptions Need Reasons and Dosing Parameters. A patient presented to the emergency department (ED) after ingesting an unintentional overdose of colchicine, which was being used to treat acute flare-ups associated with gout. The patient was prescribed colchicine 0.6 mg tablets with the directions to "Take 2 tablets by mouth for 1 dose then 1 tablet 1 hour later as needed for gout flare." According to records from the ED, the patient took an initial dose in the morning and then another tablet every hour for the next 10 hours. After taking the 11th dose, the patient began having profuse, watery diarrhea. They contacted Poison Control, who advised them to go to the ED for evaluation. The patient was later admitted to the intensive care unit (ICU).

Typical dosing of oral colchicine is 1.2 mg at the first sign of a flare, followed by 0.6 mg after 1 hour. The maximum total dose on day one should not exceed 1.8 mg. In this case, the patient took more than 7 mg total in less than 12 hours, a significant overdose.

All "as needed" or PRN medication prescriptions should include the indication and specific dosing parameters for the drug. This should include the frequency at which the medication can be taken and the maximum amount of medication that can be taken in a given time frame (e.g., 24 hours). Both prescribers and pharmacists should provide patients with clear, specific directions both verbally and in writing. They should also discuss with the patient what to do if the treatment is ineffective and when to follow up with the prescriber. When counseling a patient, use the teach-back method to verify that they understand the information and will be able to use the drug correctly.

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0.075 mg/24 hr patch was dispensed to the patient twice. The error was noted on the second refill of the prescription. The patient did not report any adverse effects.

Errors Related to System Defaults and Dispensing

In several cases, pharmacy dispensing software–driven processes contributed to errors when they were not carefully reviewed during dispensing. These issues often occurred when the software automatically selected a product or quantity, and the discrepancy was not identified during verification.

In one case, a prescription for estradiol transdermal patches included a prescriber note specifying "no generic;" however, the medication was processed and dispensed as a generic product. Although the instruction was present in the prescription, it was not acted upon during processing, and the medication was shipped to the patient as entered. This case illustrates the importance of prescribers optimizing the use of Dispense as Written (DAW) codes and pharmacists fully reviewing prescription notes rather than relying on default system processing.

In another case, a patient received an estradiol patch from a different manufacturer than the one dispensed previously. The original prescription included a note to keep the same manufacturer, but this was not carried out during processing. Instead, the system selected a different available product, and the change was not caught during verification.

In a third case, a patient reported receiving 11 estradiol patches from a mail-order pharmacy instead of the expected 12. A review of the order showed that the system defaulted to a quantity of 11 patches for an 83-day supply after the prescription was processed through the online portal. This discrepancy was not identified during dispensing and was only recognized after the patient received the medication. The issue was later attributed to a system-related error that was corrected after the event. This case highlights how system-generated quantities can lead to errors if they are not reviewed prior to dispensing.

Wrong Drug Errors

Practitioners have also submitted reports of wrong drug errors to the ISMP MERP. Recently, a patient was ordered a combination HRT twice-weekly patch containing estradiol 0.05 mg and norethindrone 0.14 mg per day. The directions were "Apply 1 patch twice a week by transdermal route, for HRT." However, the pharmacy dispensed Dotti 0.05 mg/24 hr patches, which only contain estradiol. The patient developed dysfunctional uterine bleeding, requiring follow-up with a specialist and consultation for surgical intervention.

Conclusion

In **Part II** of our report, we will provide recommendations to help address errors involving estradiol transdermal patches. In preparation, we would love to hear from organizations that have been working to prevent these types of errors. Please send a message to: medicationsafety@ecri.org, if you would like to contribute to the dialogue on this important issue.

References appear in the right column >

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