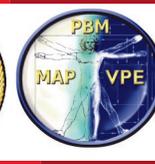




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Medication *safety in seconds*

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

Helping to achieve safe medication use

ZOLPIDEM AND FDA-PROPOSED LOWER DOSES DUE TO IMPAIRED MENTAL ALERTNESS

The Food and Drug Administration (FDA) requires the manufacturers of zolpidem products (brand names Ambien, Ambien CR, Edluar, Zolpimist) to revise product labeling to reflect lower recommended bedtime doses and to warn that higher than recommended doses may more likely impair activities requiring full alertness the next morning, including driving. Pharmacokinetic and driving simulation studies show residual effects impairing functioning when blood levels of zolpidem remain above 50ng/mL the next morning after taking a nighttime dose. The risk appears greater with extended-release formulations and with female patients, due to their slower elimination rate of zolpidem compared to males. If patients' next-morning activities require optimal alertness or involve skilled work (where impairment of performance could pose a danger to themselves or others), providers

should consider discontinuing zolpidem-containing products (or any other sedative hypnotics) or lowering

the dose if patients feel drowsy, dizzy, or experience a lack of concentration the following morning. Providers should also advise patients that impaired performance may still occur ***despite feeling fully awake***. The FDA continues to evaluate the risk of impaired mental alertness with other insomnia drugs, including over-the-counter (OTC) drugs available without a prescription. The VA Center for Medication Safety (VA MedSAFE) will continue to monitor the use of high-dose zolpidem (>10mg daily) within the VA healthcare system, with a focus on utilization in the female

(continued on page 3)



NEWS YOU CAN USE

FROM THE VA NATIONAL PBM: BULLETINS, COMMUNICATIONS, & RECALLS

- Zolpidem and FDA-Proposed Lower Doses Due to Impaired Mental Alertness – 01-16-2013 - [National PBM Communication](#)
- Ondansetron 32mg Single IV Dose Market Withdrawal Due to Cardiac Risks – 12-05-2012 - [National PBM Bulletin](#)



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NEWS YOU CAN USE

FROM THE FOOD AND DRUG ADMINISTRATION (FDA)

CARDIOLOGY

[Pradaxa \(dabigatran etexilate mesylate\) should not be used in patients with mechanical prosthetic heart valves](#)

12/19/2012

Pradaxa (dabigatran etexilate mesylate) is not approved for patients with atrial fibrillation secondary to heart valve problems and should not be used to prevent major thromboembolic events in patients with mechanical heart valves. A clinical trial in Europe (RE-ALIGN) was terminated early because results showed that the Pradaxa treatment arm had significantly more valve thrombosis, stroke, and myocardial infarction in addition to bleeding after valve surgery compared to the warfarin treatment arm. As such, FDA requires Pradaxa labeling to include a contraindication in mechanical heart valve patients. The use of Pradaxa has not been evaluated in patients with bio-prosthetic valves and use cannot be recommended for such patients.

[Important change to heparin container labels to clearly state the total drug strength](#)

12/6/2012

Manufacturers of Heparin Lock Flush Solution, USP and Heparin Sodium Injection, USP will change the way the strength is expressed on the container and carton labels. The revised product labeling, scheduled to go into effect on **May 1, 2013**, will clearly state the total strength of the entire container of the medication followed by how much of the medication exists in 1 milliliter (mL), in order to comply with the USP standards for injectable medications. The new format will help to reduce miscalculations occurring in products containing more than 1 mL and related medication errors.

INFECTIOUS DISEASE

[Serious skin reactions after combination treatment with the Hepatitis C drug Incivek \(telaprevir\), peginterferon alfa, and ribavirin](#)

12/19/2012

FDA has received reports of serious skin reactions, some of which required hospitalization and had fatal outcomes, associated with combination treatment with the Hepatitis C drugs Incivek (telaprevir), peginterferon alfa, and ribavirin. From May 23, 2011, through June 19, 2012, the FDA Adverse Event Reporting System (AERS) reflects:

- 2 cases of toxic epidermal necrolysis (TEN) in Japan resulting in 1 death;
- 92 cases of drug rash with eosinophilia and systemic symptoms (DRESS) associated with 1 death;
- 20 cases of Stevens-Johnson Syndrome (SJS).

Although the Incivek drug label already acknowledges the risk of serious skin reactions, FDA will add a boxed warning stating that Incivek combination treatment must be immediately stopped in patients experiencing a rash with systemic symptoms or a progressive severe rash. Some systemic symptoms and signs may include fever, nausea, diarrhea, mouth sores or ulcers, facial swelling (edema), red or inflamed eyes, or swelling or inflammation of the liver (hepatitis). FDA recommends that:

- *When any of these serious skin reactions occur, it is necessary for healthcare professionals to immediately stop all three components of Incivek combination treatment, and the patient should receive urgent medical care. Consideration should also be given to stopping any other medications that may be associated with serious skin reactions.*
- *Education should be given to patients regarding the signs and symptoms of severe skin reaction and when to seek care.*

Additionally, FDA requires that the Warnings and Precautions section of the Incivek drug label report a higher incidence of anemia with shorter time to onset among patients on Incivek combination treatment compared to those taking peginterferon alfa and ribavirin alone.

CENTRAL NERVOUS SYSTEM

[Warning against use of Xyrem \(sodium oxybate\) with alcohol or drugs causing respiratory depression](#)

12/17/2012

FDA evaluated reports of mortality ensuing from sodium oxybate (Xyrem®) use submitted to their Adverse Event Reporting System (AERS) as well as manufacturer (Jazz Pharmaceuticals) data and found that deaths occurred in:

- Patients concomitantly taking one or more CNS depressant medications (i.e., neuroleptics, benzodiazepines, opioids, sedating antidepressants or antipsychotics, general anesthetics and muscle relaxants);
- Patients who have concomitantly ingested alcohol;
- Patients on doses exceeding those recommended or who have gone through a more rapid dose titration than recommended;
- Patients taking sodium oxybate (Xyrem®) for unapproved uses such as fibromyalgia, insomnia, or migraine;
- Patients with concomitant illnesses (i.e., depression and substance abuse) predisposing to the CNS and respiratory depressant effects of sodium oxybate (Xyrem®).

These findings have led to pending revisions to the product label, including a new contraindication regarding the use of sodium oxybate (Xyrem®) with alcohol; recommendations on dose reduction or discontinuation in patients concomitantly using sodium oxybate (Xyrem®) with a CNS depressant; and a restriction limiting use of sodium oxybate (Xyrem®) to patients enrolled in the Xyrem® Success program.

Getting the most from our safety surveillance



VACCINE ADVERSE EVENTS: REPORTING TO ARTS, VA ADERS, AND FDA/CDC VAERS

VA monitors safety associated with vaccines through provider- and patient-reported adverse drug events (ADE) entered into two spontaneous ADE reporting systems currently active in the VA:

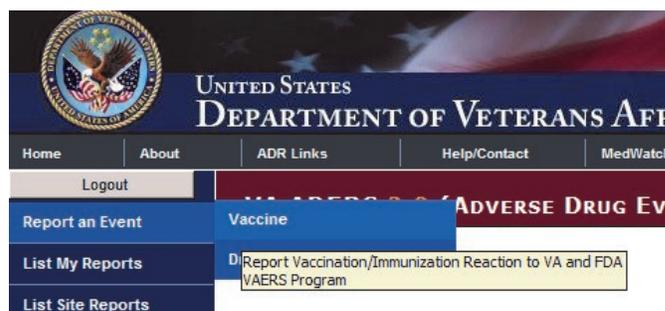
- the Allergy/Adverse Reaction Tracking System (ARTS) Package, which resides in the Computerized Patient Record System (CPRS). This system allows order checks to fire based on previous reactions when a potentially offensive agent (vaccine or drug) is ordered for the patient.
- the VA Adverse Drug Event Reporting System (VA ADERS), VA's web-based national reporting system for medication, vaccination, and biologic product adverse events.

Reporting adverse events related to vaccinations contributes to VA's surveillance and safety initiatives by helping to identify an overall known set of possible reactions or events potentially related to a particular vaccine in order to provide healthcare staff with safety information needed to optimize the outcomes of patients receiving the vaccination. Events commonly reported to VA ADERS for vaccinations include rash, pyrexia, pruritus, and erythema. Other reaction symptoms have been reported, and events of interest may be followed up by VA Center for Medication Safety (VA MedSAFE) staff and potentially staff from the Vaccine Adverse Event Reporting System (VAERS) program office, for further evaluation and action, if needed.

VA encourages ALL providers to report ANY adverse event (regardless of severity) seen with vaccinations into the ARTS system first and foremost, since it directly impacts patient care activities. All adverse events related to vaccines must also be

reported by facilities to VA ADERS, and through VA ADERS, to the Vaccine Adverse Event Reporting System (VAERS), which is the national vaccine safety surveillance program co-sponsored by the Center for Disease Control (CDC) and the Food and Drug Administration (FDA). VA ADERS allows reporters to enter vaccine events using a form identical to the VAERS report form, which providers can use for direct submission (electronically or via fax) from VA ADERS to the VAERS program office for national surveillance and safety review.

To report a suspected adverse event to a vaccine, select "Report an Event", and then click on "Vaccine" from the Home screen of the VA ADERS application.



After completing the report, the application allows you to review the report (List My Report), and once complete, you may fax to the VAERS program.

REFERENCES

VAERS: Vaccine Adverse Event Reporting System <http://vaers.hhs.gov/index>.

Helping to achieve safe medication use

ZOLPIDEM AND FDA-PROPOSED LOWER DOSES DUE TO IMPAIRED MENTAL ALERTNESS

(continued from page 1)

Veteran population (currently in progress) due to the higher risk of experiencing next-morning residual effects residing in women. For more information, please visit:

- **Zolpidem and FDA-Proposed Lower Doses Due To Impaired Mental Alertness - National PBM Communication**
<http://www.pbm.va.gov/VACenterForMedicationSafety-BulletinsAndNewsAlerts.aspx>

- **FDA Drug Safety Communication: Risk of next-morning impairment after use of insomnia drugs; FDA requires lower recommended doses for certain drugs containing zolpidem (Ambien, Ambien CR, Edluar, and Zolpimist).**
<http://www.fda.gov/Drugs/DrugSafety/ucm334033.htm>

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FDA Drug Safety Communication: Risk of next-morning impairment after use of insomnia drugs; FDA requires lower recommended doses for certain drugs containing zolpidem (Ambien, Ambien CR, Edluar, and Zolpimist). <http://www.fda.gov/Drugs/DrugSafety/ucm334033.htm>.