

MEDICATION

A MONTHLY PUBLICATION FROM VA MEDSAFE:  
VA'S COMPREHENSIVE PHARMACOVIGILANCE CENTER**SAFETY IN SECONDS**

# Helping to achieve safe medication use

## **THYROTROPIN ALFA FOR INJECTION (THYROGEN®) AND POTENTIAL CONTAMINATION WITH TRACE AMOUNTS OF VANCOMYCIN HCL**

The manufacturer of thyrotropin alfa for injection (Thyrogen®) has issued a Dear Health Care Provider letter alerting physicians to the potential for inadvertent patient exposure to trace amounts of vancomycin during the delivery of parenteral thyrotropin alfa for injection (Thyrogen®). The third party manufacturing facility that fills thyrotropin alfa for injection (Thyrogen®) also handles vancomycin hydrochloride (HCl), leading to the contamination of some lots of the thyroid stimulating hormone. Lot numbers E1089 to E4023 of thyrotropin alfa for injection (Thyrogen®) have been identified as affected, with the amount of vancomycin HCl estimated to represent less than 1/100,000 of the vancomycin HCl therapeutic dose. This may pose a safety risk in patients with a known hypersensitivity to vancomycin, and as such, the manufacturer

warns that thyrotropin alfa for injection (Thyrogen®) should not be administered to these patients. The manufacturer recommends that for patients who may have received affected lots:

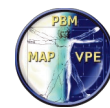
- *Patients should be questioned about known hypersensitivity to vancomycin HCl.*
- *Thyrotropin alfa for injection (Thyrogen®) should not be administered if a history of hypersensitivity to vancomycin HCl is identified.*
- *Thyroxine withdrawal is an alternative method for preparing patients for diagnostic radioiodine imaging or treatment.*

**REFERENCE:**

Thyrogen® (thyrotropin alfa for injection) Dear Health Care Provider Letter. Cambridge, MA: Genzyme Corporation; December 2014.

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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.

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NEWSWORTHY...

# from the pbm

- DAPT Trial and Risk of Non-Cardiovascular Death – 12/17/14 - [National PBM Bulletin](#)
- Dimethyl Fumarate (Tecfidera) and PML Resulting in Death – 11/07/14 – [National PBM Bulletin](#)

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# from the fda

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## MENTAL HEALTH

[FDA reporting mental health drug ziprasidone \(Geodon\) associated with rare but potentially fatal skin reactions](#)  
12/11/2014

FDA reviewed six worldwide cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) temporally associated with ziprasidone use (onset of symptoms 11-30 days after initiation) reported to the FDA Adverse Event Reporting System (FAERS). Hospitalization occurred in all cases and no deaths were reported. FDA required the manufacturer of ziprasidone (marketed under the brand name, Geodon, and its generics) to add a new warning for DRESS to the *Warnings and Precautions* section of the drug labels for the capsule, oral suspension, and injection formulations. DRESS is a serious skin reaction that can spread to other parts of the body and has a mortality rate of up to 10%. Management of DRESS consists of early recognition of the syndrome, discontinuation of the offending agent as soon as possible, supportive care, and in cases with extensive organ involvement, treatment with systemic corticosteroids.

Provider should be aware that:

- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) appears to occur within the first month of therapy.
- DRESS consists of three or more of the following:
  - \* cutaneous reaction (such as rash or exfoliative dermatitis)
  - \* eosinophilia
  - \* fever
  - \* lymphadenopathy, and
  - \* one or more systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, pericarditis, and pancreatitis.

Clinicians should consider:

- Explaining the signs and symptoms of severe skin reactions to pertinent patients and telling them when to seek immediate care. **This is especially important when initiating ziprasidone.**
- Stopping ziprasidone treatment immediately if DRESS is suspected.
- Counseling all patients receiving ziprasidone to contact their providers in the event of any new rash, although DRESS is not known to occur beyond 4 weeks of therapy with ziprasidone.

## NEUROLOGY

[FDA warns about case of rare brain infection PML with MS drug Tecfidera \(dimethyl fumarate\)](#)  
11/25/2014

A death following development of progressive multifocal leukoencephalopathy (PML) in a patient with multiple sclerosis (MS) treated with dimethyl fumarate (Tecfidera) has been reported by the manufacturer to the FDA. The patient participated in the placebo arm of the DEFINE trial and joined the ENDORSE extension study receiving dimethyl fumarate (Tecfidera) in a dose-blinded manner twice or three times daily. The patient had no prior immunosuppression with natalizumab (Tysabri); had 4.5 years exposure to dimethyl fumarate (Tecfidera); and had Grade 3 lymphopenia ( $> 0.2 \times 10^9/L$  and  $< 0.5 \times 10^9/L$ ) for 3.5 years. The patient displayed symptoms of relapse in July 2014. Imaging and CSF analysis at that time indicated potential PML; however a final diagnosis was not made. The patient expired from aspiration pneumonia. Information describing this case of PML is being added to the drug label.

A decrease in lymphocyte counts is an identified risk of dimethyl fumarate (Tecfidera). Severe, prolonged lymphopenia is a known risk factor for PML. As detailed in the VA PBM [Dimethyl Fumarate \(Tecfidera\) Criteria for Use Update March 2014](#):

- Before initiating treatment with dimethyl fumarate (Tecfidera), a recent complete blood count (CBC) (i.e. within 6 months) should be available.
- A lymphocyte count below  $500/\mu L$  (equal to less than  $0.5 \times 10^9/L$ ) is an exclusion criteria for initiating

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# from the fda

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therapy with dimethyl fumarate (Tecfidera).

- Dimethyl fumarate (Tecfidera) should be held if the WBC falls below 2000/  $\mu$ L or the lymphocyte count is below 500/ $\mu$ L and permanently discontinued if the WBC did not increase to over 2000/  $\mu$ L or if the lymphocyte count did not increase to over 500/ $\mu$ L after 4 weeks of withholding therapy.
- Patients should have a CBC with differential monitored on a quarterly basis.

## CARDIOLOGY

[FDA reviews long-term antiplatelet therapy as preliminary trial data shows benefits but a higher risk of non-cardiovascular death](#)

11/16/2014

A recent safety announcement from the Food and Drug Administration (FDA) describes findings from the Dual Antiplatelet Therapy (DAPT) trial which suggest that extending treatment with a thienopyridine and aspirin compared to aspirin alone beyond 1 year after percutaneous coronary intervention with drug-eluting stent placement reduced the risk of stent thrombosis and ischemic events, but was associated with an increase in bleeding events and non-cardiovascular death. FDA continues to examine these preliminary trial findings as well as other available data and has not yet reached any conclusions. FDA recommends that:

- Benefits of clopidogrel (Plavix) and prasugrel (Effient) therapy continue to outweigh their potential risks when used for approved indications.
- Patients should continue to take these drugs as directed to prevent ischemic events.
- Health care providers should not change the way they prescribe these drugs at this time.

Current VA guidance for use of clopidogrel (Plavix) or prasugrel (Effient) is available at: <http://www.pbm.va.gov/clinicalguidance/criteriaforuse.asp>. PBM is reviewing VA's dual antiplatelet guidance and will obtain input from the Cardiology Field Advisory Committee to provide further recommendations for VA in the near future.

## Getting the most from our safety surveillance

### DABIGATRAN SAFETY SURVEILLANCE

The Department of Veterans Affairs Center for Medication Safety (VAMedSAFE) continues to conduct serial drug safety surveillance on the target specific oral anticoagulants through our drug utilization evaluation safety surveillance program. Specific adverse outcomes of interest such as gastrointestinal (GI) bleeding, intracranial hemorrhage, stroke, and myocardial infarction are evaluated using VA's automated integrated databases. A multivariate regression analysis is conducted to assess risks and adjusted for pertinent covariates. Results are shared with administration and formulary decision makers semi-annually. In addition to our standard surveillance, a more detailed review using propensity matched analysis was recently conducted on dabigatran to assess VA's safety profile on the GI bleeding adverse event based on recent safety warnings.

The VA semi-annual analysis compares dabigatran to warfarin as a reference agent. The results of the overall analysis and the subgroup analysis to date have consistently shown minimal to no difference in GI bleeding in Veteran patients between dabigatran and warfarin (Overall Hazard Ratio [HR] = 0.8 with

95% Confidence Interval [CI] {0.71, 0.99}) as well as the subgroup analysis in elderly patients  $\geq 80$  years of age (HR = 0.8, 95% CI [0.6, 1.1]). The adjusted risk of intracranial hemorrhage is lower with dabigatran compared to warfarin (HR = 0.4, 95% CI [0.2, 0.7]), which is consistent with findings from pivotal clinical trials. The detailed analysis using matched propensity scoring methodology as well as a more specific algorithm for GI bleeding had similar results with a HR of approximately 0.9 and not different from warfarin.

Based on the regular surveillance, the subgroup analysis of patients 80 years and older, and the more detailed propensity matched analysis, the risk of GI bleeding in the VA population utilizing dabigatran to date is not greater than warfarin, although this may still, in part, be attributable to selective criteria regarding dabigatran. Consistent with findings from clinical trials, the adjusted risk of intracranial hemorrhage with dabigatran is lower than with warfarin in VA patients.

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