

# MEDICATION

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

# SAFETY IN SECONDS

## Helping to achieve safe medication use

### SIMILAR ABBREVIATIONS LEAD TO DRUG ERRORS

The continued use of the abbreviation “t-PA” or “TPA” has led to confusion between alteplase (Activase) and tenecteplase (TNKase). Both agents are tissue plasminogen activators. FDA approved alteplase (Activase) in 1987 for acute myocardial infarction, acute ischemic stroke, and pulmonary embolism indications while approval for tenecteplase (TNKase) came in 2000 for use in acute myocardial infarction only. Wrong drug confusion between the two ensues from:

- Similar settings of use in emergency and critical care areas;
- Similar populations (i.e., cardiac);
- Common use of the abbreviation “t-PA” or “TPA” to refer to alteplase (Activase) that sounds similar to “TNK” for tenecteplase (TNKase).

Examples of errors described by ISMP involve wrong drug mix-ups where alteplase (Activase) is ordered by providers as “t-PA”

and nurses assumed that “t-PA” was a shortened form for tenecteplase (TNKase) leading to its inadvertent administration instead of the intended alteplase (Activase). In one instance, a nurse typed “t” into an automated dispensing cabinet because alteplase (Activase) is frequently referred to as “t-PA” or “TPA”, but picked tenecteplase (TNKase) instead. In 2 cases, nurses mistakenly administered tenecteplase (TNKase) to patients instead of the correct alteplase (Activase) (ordered as “t-PA”) due to the assumption that “t-PA” was short-hand for tenecteplase (TNKase). Additionally, in another error, a patient received tenecteplase (TNKase) for an ischemic stroke instead of alteplase (Activase) because of the similarity in abbreviations. The danger of inadvertent administration of tenecteplase (TNKase) instead of alteplase (Activase) for the management of ischemic stroke include suboptimal treatment due to administration of the wrong

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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

- OmniPod Insulin Management System Recall: ADDENDUM – 12/14/2015 - [National PBM Patient Level Recall Communication](#)
- Auvi-Q (epinephrine injection, USP) Recall - Potential Inaccurate Dosage Delivery – 10/30/2015 - [National PBM Patient Level Recall Communication](#)

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# from the fda

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Submitted by Veronica Fassio, Pharm.D., PGY-2 Medication Use Safety Resident

## RADIOLOGY/IMAGING

### [FDA advises of rare cases of underactive thyroid in infants given iodine-containing contrast agents for medical imaging](#)

11/17/2015

FDA reports rare cases of hypothyroidism or transient thyroid suppression in infants following the use of iodinated contrast media (ICM) products for medical imaging procedures. A search of the FDA Adverse Event Reporting System (FAERS) database identified 10 cases between 1969 and early 2014 in infants < 4 months who received ICM products. These infants were either premature or had other serious underlying medication conditions. The rare underactive thyroid events are usually temporary, resolving without treatment and not resulting in any lasting effects. No changes in current prescribing, administration, or monitoring practices have been recommended by the FDA; however, the labels for ICM products will include information about these cases. FDA requires manufacturers of ICM products to investigate this safety issue further and will continue to evaluate and update the public when additional information is available.

## CARDIOLOGY

### [FDA review finds long-term treatment with blood-thinning medicine Plavix \(clopidogrel\) does not change risk of death](#)

11/6/2015

FDA has found long-term treatment with clopidogrel does not increase or decrease the risk for all-cause mortality or the risk for cancer or cancer-related death in a population with, or at risk for, coronary artery disease. The possible risk of death associated with clopidogrel was previously discussed in an [11/16/14 FDA Drug Safety Communication](#), as well as the [VAMedSAFE National PBM Bulletin](#) during the same month. At that time, the FDA was evaluating results from the Dual Antiplatelet Therapy (DAPT) trial in a population of patients implanted with a drug-eluting coronary stent. Data from the DAPT trial showed that treatment with dual antiplatelet therapy for 30 months decreased the risk of heart attacks and clot formation in stents but was associated with an increase in all-cause mortality compared to 12 months of treatment. Higher rates of death were predominantly explained by an increase in deaths from non-cardiovascular causes, primarily cancer and trauma-related. Findings from a meta-analysis conducted by Elmariah et al. concluded that extended DAPT was not associated with a difference in risk for all-cause, cardiovascular, or non-cardiovascular death compared with aspirin or short-term DAPT. Summaries on the DAPT trial and the meta-analysis were mentioned in the [Nov 2014 – Jan 2015 PBM Ez-Minutes Newsletter](#).

The FDA conducted a separate meta-analysis including the DAPT trial and several large clinical trials assessing long-term treatment (12 months or longer) with clopidogrel and aspirin. The FDA determined that long-term use of dual antiplatelet therapy with clopidogrel plus aspirin does not increase or decrease overall risk of death in patients with, or at risk for, heart disease in comparison to short-term treatment (6 months or less), or even aspirin alone. FDA also found no apparent increase in cancer-related adverse events or cancer-related deaths with long-term compared to short-term clopidogrel plus aspirin. Of note, the FDA meta-analysis included 12 out of the 14 trials from the Elmariah meta-analysis; however, the FDA performed different statistical methods than those used by Elmariah. More information on which trials were assessed and the FDA's data summary are available in the FDA Drug Safety Communication (see references below).

	Number of patients included	Long-term clopidogrel plus aspirin	Short term clopidogrel plus aspirin or aspirin alone	Mantel Haenszel Risk Difference, 95% CI
Overall incidence of death	56,799	6.7%	6.6%	0.04%, (-0.35% - 0.44%)
Incidence of cancer adverse events	37,835	4.2%	4.0%	0.19%, (-0.20% - 0.59%)
Incidence of cancer death	40,855	0.9%	1.1%	-0.14%, (-0.33% - 0.06%)

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# from the fda

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FDA emphasizes that patients should not stop taking clopidogrel or other antiplatelet medicines without discussing with a health care provider. Health care providers should consider the benefits and risks of available antiplatelet medicines before starting treatment and inform patients about the increased risk of bleeding and bruising when taking clopidogrel. Please see the [VA Clinical Guidance](#) for further prescribing information on clopidogrel.

## REFERENCES

1. FDA Drug Safety Communication: FDA review finds long-term treatment with blood-thinning medicine Plavix (clopidogrel) does not change risk of death. 2014 Nov 6. <http://www.fda.gov/Drugs/DrugSafety/ucm471286.htm>
2. Mauri L, Kereiakes DJ, Yeh RW, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med*. 2014 Nov 16.
3. Elmariah S, Mauri L, Doros G, et al. Extended duration dual antiplatelet therapy and mortality: a systematic review and meta-analysis. *Lancet* 2014; 2014 Nov 16.

## NEUROLOGY

[FDA review found no increased cardiovascular risks with Parkinson's disease drug entacapone](#)  
10/26/2015

FDA has found no clear evidence associating the Parkinson's disease drug entacapone with an increased risk of cardiovascular events (heart attack, stroke, and cardiovascular death). Entacapone can be found in the combination product Stalevo (with carbidopa/levodopa) and in the single-ingredient product Comtan. The possible cardiovascular risk associated with entacapone was previously discussed [8/20/2010 in an FDA Drug Safety Communication](#). At that time, the FDA was evaluating clinical trial data suggesting entacapone's association with a small increased risk of cardiovascular events compared to carbidopa/levodopa. This data consisted of results from a clinical trial called Stalevo Reduction in Dyskinesia Evaluation in Parkinson's disease (STRIDE-PD)<sup>1</sup> and an FDA conducted meta-analysis of 15 clinical trials including STRIDE-PD. Of note, the clinical trials assessed were not specifically designed to assess cardiovascular risk, the patients had pre-existing risk factors for cardiovascular disease, and the follow-up duration was < 6 months. Furthermore, a statistically significant increased risk for cardiovascular events and entacapone was only noticed when the STRIDE-PD trial was included in the meta-analysis. Since carbidopa and levodopa have been used extensively in these studies with no associated cardiovascular risk, this led to the concern that the entacapone component in Stalevo influenced cardiovascular risk because the comparison drugs do not contain this ingredient. But because of the limitations, the FDA did not conclude that Stalevo increases cardiovascular risk and they pursued ongoing review.

The FDA reviewed two observational studies. The first study<sup>2</sup> was by Novartis, manufacturer of Stalevo, which used data from a commercial insurance database and assessed the potential risk for MI in patients 18-64 years old. A second study was by Graham et al.<sup>3</sup> which used the Medicare database to assess the risk of MI, stroke, and death (follow-up duration < and > 6 months) in a population age >65. Neither study found a cardiovascular risk association with entacapone. A limitation to the manufacturer study was that few patients in either group had an MI, making it difficult to assess association. Based on these two studies, the FDA concluded that the results from the STRIDE-PD and meta-analysis were chance findings; there is no evidence for an increased cardiovascular risk associated with entacapone and the drug label will remain unchanged. Providers should continue to report any adverse reactions by entering the information into CPRS' Allergies/ Adverse Reactions field and/or via local reporting mechanisms. Adverse events should also be reported, as appropriate, to the VA ADERS program and FDA MedWatch (phone: 1-800-FDA-1088; fax: 1-800-FDA-0178; online at: <https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm>, or by mail).

## REFERENCES

1. Stocchi F, Rascol O, Kieburtz K, Poewe W, Jankovic J, Tolosa E, Barone P, Lang AE, Olanow CW. Initiating levodopa/carbidopa therapy with and without entacapone in early Parkinson disease: the STRIDE-PD study. *Ann Neurol* 2010 Jul; 68(1):18-27.
2. Final Study Report, "The risk of incident myocardial infarction in Parkinson's disease patients with add-on entacapone to levodopa/DDCI compared to other add-on Parkinson's disease therapy without entacapone". A retrospective cohort study using data from MarketScanTM; February 2014.
3. Graham DJ, Williams JR, Hsueh YH, Calia K, Levenson M, Pinheiro SP, MaCurdy TE, Shih D, Worrall C, Kelman JA. Cardiovascular and mortality risks in Parkinson's disease patients treated with entacapone. *Mov Disord* 2013; 28:490-497.

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## INFECTIOUS DISEASES

### [FDA warns of serious liver injury risk with hepatitis C treatments Viekira Pak and Technivie](#)

10/22/2015

FDA has released an alert warning of serious liver injury (i.e., hepatic decompensation and hepatic failure) particularly in patients with cirrhosis taking Viekira Pak or Technivie. Viekira Pak consists of ombitasvir, paritaprevir, and ritonavir tablets plus dasabuvir tablets (approved December 2014) and Technivie consists of ombitasvir, paritaprevir and ritonavir (approved July 2015). This alert is based on cases reported to the FDA Adverse Event Reporting System (FAERS) database and the manufacturer AbbVie. Out of a total of 26 assessable cases, 10 experienced hepatic failure leading to transplantations and death; 16 experienced a range of liver dysfunction.

Findings for the cases reviewed include:

- Liver injury occurred within 1 to 4 weeks of starting treatment in most cases.
- Transaminase elevation was not a predominant presentation for the advanced liver disease patients.
- For some patients, there was a temporal association between starting and discontinuing the medication leading to the presentation and resolution of symptoms.
- More serious outcomes occurred in patients taking Viekira Pak with advanced cirrhosis prior to treatment.
- Some events occurred in patients where use was contraindicated or not recommended.

In light of this information, the FDA is requiring the manufacturer to include serious liver injury adverse events to the drug labels. The FDA also emphasizes that Viekira Pak is contraindicated in moderate and severe hepatic impairment (Child-Pugh Class B & C) while Technivie is not indicated for patients with cirrhosis.

FDA recommends:

- Patients should not stop taking these medications before discussing with their health care providers.
- Health care professionals are advised to discuss the risks of hepatic decompensation and hepatic failure and the need for close monitoring for patients with cirrhosis already being treated on Viekira Pak or Technivie.
- Below is guidance from the FDA for when to discontinue these medications.
  - Consider discontinuing if alanine aminotransferase (ALT) levels remain persistently greater than 10 times the upper limit of normal (ULN).
  - Discontinue in the presence of decompensated cirrhosis with or without increased levels of bilirubin and/or transaminases.
  - Discontinue if ALT elevation is accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or international normalized ration (INR).

Providers should continue to report any adverse reactions with the use of hepatitis C medications by entering the information into CPRS' Allergies/ Adverse Reactions field and/or via local reporting mechanisms. When entering a report, please include base-line liver status (e.g., Child-Pugh Class; ALT; bilirubin levels; clinical signs and symptoms of hepatic decompensation such as ascites, hepatic encephalopathy, and variceal hemorrhage; presence or absence of cirrhosis). Adverse events should also be reported, as appropriate, to the VA ADERS program and FDA MedWatch. MedWatch reports can be completed and faxed to the FDA through VA ADERS ([https://vaww.cmop.med.va.gov/MedSafe\\_Portal/](https://vaww.cmop.med.va.gov/MedSafe_Portal/) select VA ADERS Launch). For more information on reporting to the FDA, access <https://www.accessdata.fda.gov/scripts/medwatch/medwatch->

## ANTIDOTES

### [FDA requires drug interaction studies with potassium-lowering drug Kayexalate \(sodium polystyrene sulfonate\)](#)

10/22/2015

The FDA is requiring that the manufacturer of Kayexalate (Concordia Pharmaceuticals) conduct studies to assess the potential for drug-binding interactions with other medications. The cation-exchange resin Kayexalate

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(sodium polystyrene sulfonate), also available as the branded generics Kionex and SPS, treats hyperkalemia by binding to potassium in the large intestine so it can be removed from the body. The package insert includes the drug-binding interactions with lithium and thyroxine, where Kayexalate may decrease their absorption. However, no extensive studies were completed to assess for additional drug-binding interactions with Kayexalate.

FDA's extensive review of another potassium-lowering drug Veltassa (patiromer) showed drug-drug interactions occurring in about half of the medications tested with Veltassa which led to a warning in the product label to not take other orally administered medications within 6 hours of taking Veltassa. As a result FDA is requiring the manufacturer of Kayexalate to further examine the potential for this agent to bind to other oral medications. If findings confirm additional significant drug-binding interactions, the drug label will be updated to include this information. At this time, the FDA is recommending to consider separating Kayexalate dosing from other oral medications (e.g., antibiotics, antihypertensive agents, blood thinners, antacids, laxatives) by at least 6 hours. Health care professionals should also monitor blood levels or clinical response to other medications as needed or appropriate.

## Helping to achieve safe medication use

### **SIMILAR ABBREVIATIONS LEAD TO DRUG ERRORS**

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drug as well as risk of overdose since alteplase (Activase) has a higher dose requirement than the maximum of tenecteplase (TNKase). In the acute myocardial infarction indication for which both agents are approved, the recommended total dose of alteplase (Activase) is based on patient weight, not to exceed 100 milligrams (mg) while the recommended total dose of tenecteplase (TNKase) should not exceed 50 mg and is also based on patient weight. Therefore, unintentional administration of tenecteplase (TNKase) instead of alteplase (Activase) at the dosing recommendations of alteplase (Activase) may increase the risk for bleeding as well as associated hospitalizations and deaths.

The abbreviations "t-PA", "TPA" and "TNK" appear on the Drug Name Abbreviations section of the [ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations](#). ISMP further recommends:

- *Never use abbreviations for drug names.*
- *Do not use the abbreviation "TPA" and refer to all three tissue plasminogen activators by their brand names (Activase, TNKase, Retavase), established/generic names (alteplase, tenecteplase, reteplase), or both in all verbal and written communications.*
- *Do not use "TNK" as an abbreviation for TNKase.*
- *Remove the abbreviation "TPA" and "TNK" from all standardized order sets, computerized provider order entry screens, and treatment protocols to avoid confusion.*
- *Since Activase, but not TNKase or Retavase, is approved for use in the management of ischemic stroke and pulmonary*

*embolism, prescribers should state the indication on prescription orders to help ensure the correct drug is ordered and dispensed.*

- *Consider the use of alerts for TNKase in electronic prescriber order entry systems and/or automatic dispensing cabinets (e.g., "Warning: Frequently confused with Activase [alteplase], verify the correct drug for the appropriate indication").*

Within the VA, pharmacy can take the following steps inside the computerized drug-order entry system to reduce potential error with these similar names:

- Add a short descriptor (less than 30 characters) to "Display Restriction/Guidelines" when ordering Tenecteplase (i.e., "Frequently confused with Activase[alteplase], verify appropriate drug is ordered"). As blue line text, this descriptor displays as dialog and does not become part of order but alerts providers about possible confusion when ordering TNKase (tenecteplase).
- A second message can be added in the "Quantity Dispensed" section in the middle of the order screen to reiterate the caution.

#### REFERENCES:

1. Institute for Safe Medication Practices. FDA Advise-ERR: Avoid using the error-prone abbreviation, TPA. *ISMP Medication Safety Alert! Acute Care*. 20(19): 1, 4-5. September 24, 2015.
2. Activase® (Alteplase) product package insert. South San Francisco, CA: Genentech, Inc.; February 2015.
3. TNKase® (Tenecteplase) product package insert. South San Francisco, CA: Genentech, Inc.; May 2011.

# Getting the most from our safety surveillance

## **ATTENTION PHARMACISTS: SOLICITATION FOR MEDICATION UTILIZATION EVALUATION (MUE) - HYPOLYCEMIA IN THE COMMUNITY LIVING CENTER SETTING**

*Submitted by Muriel Burk, Pharm.D.*

PBM/VAMedSAFE, in collaboration with the Office of Geriatrics and Extended Care (GEC), is planning a multi-site national Medication Utilization Evaluation (MUE) titled “Evaluation of Hypoglycemic Events in the Community Living Center Setting.” The objective of this MUE is to examine hypoglycemic events in Veterans who are prescribed anti-diabetic agents while residing in VHA CLCs. Specifically, the project aims to determine how hypoglycemic events are identified and documented and to obtain an initial estimate of the prevalence of hypoglycemic events in this population and setting. For identified hypo-

glycemic events, associated individual (e.g., sociodemographic and health variables) and system-level (e.g., transitions in care) factors will be examined. The project has been approved as QA/QI by the Hines IRB. Individual sites will need to comply with local requirements for review and approval of QA/QI initiatives.

We are looking for 5 more sites (total of 20 sites) to participate in this MUE. If interested, please contact Muriel Burk at [Muriel.Burk@va.gov](mailto:Muriel.Burk@va.gov). ■