

MEDICATION

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

SAFETY IN SECONDS

Helping to achieve safe medication use

ISMP SAFETY SIGNAL FOR HYPOTENSION WITH SACUBITRIL/VALSARTAN (ENTRESTO)

Submitted by: Elaine Furmaga, Pharm.D.

Safety Issue

According to a recent issue of the Institute for Safe Medication Practices (ISMP) Quarter-Watch report, a safety signal was noted for hypotension with sacubitril/valsartan for heart failure.¹ With the potential increase in use of sacubitril/valsartan in VA, it is important for providers to be informed of this adverse drug event in the management of patients with heart failure.

Place in Therapy

Sacubitril/valsartan (ENTRESTO) was approved by the U.S. Food and Drug Administration (FDA) in July 2015, to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (New York Heart Association [NYHA] Class II-IV) and reduced ejection fraction.² Heart failure treatment guidelines

recommend use of an angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), or an angiotensin receptor-neprilysin inhibitor (ARNI) such as sacubitril/valsartan, in conjunction with an evidence-based beta-blocker and an aldosterone antagonist in selected patients; and replacement by an ARNI in patients with chronic symptomatic heart failure with reduced ejection fraction (HFrEF) NYHA Class II or III who are tolerating an ACEI or ARB, to further reduce morbidity and mortality.³ With publication of these treatment guidelines, and as providers become more familiar with use of sacubitril/valsartan, it is anticipated that use of this medication will increase in VA.

ISMP QuarterWatch Report

As part of an analysis of the FDA Adverse Event Reporting System (FAERS), it was

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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

- Enoxaparin Sodium Injection: Recall Due to Incorrect Strength Syringe in Blister – 12/28/17- [National PBM Patient Level Recall Communication](#)
- Calcimimetic Therapy in Patients on Dialysis: Risk of Duplicate Therapy and Safety Considerations – 12/26/17 - [National PBM Bulletin](#)

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PULMONOLOGY

[FDA review finds no significant increase in risk of serious asthma outcomes with long-acting beta agonists \(LABAs\) used in combination with inhaled corticosteroids \(ICS\)](#)

12/20/2017

FDA required manufacturers of fixed-dose combination drugs containing an inhaled corticosteroid (ICS) and long-acting beta agonists (LABAs) to conduct several large, randomized, double-blind, active-controlled clinical safety trials to evaluate the risk of serious asthma-related events when using fixed-dose combinations (LABA and ICS) compared to ICS alone in patients with asthma. The studies involved 41,297 patients and looked at a primary safety endpoint of serious asthma-related events (hospitalizations, intubations, and deaths) in addition to a primary efficacy endpoint of asthma exacerbation. The trials were not designed to show that there is no increase in risk with ICS/LABA compared to ICS. Data from three trials conducted in adults and adolescents were combined in a meta-analysis to provide greater precision of the risk of serious asthma-related events with ICS/LABA products. Results show that the use of ICS/LABA in fixed-dose combination does not result in a significant increase in the risk of serious asthma-related events compared to ICS alone (Table 1). Efficacy findings demonstrated that the ICS/LABA combination reduced asthma exacerbations compared to ICS alone (Table 2). This additional information has been added to the ICS/LABA labels and the boxed warning regarding increased risk of asthma-related deaths has been removed.

Table 1. Meta-analysis of Serious Asthma-Related Events in Patients with Asthma 12 Years and Older*

	ICS/LABA (N=17,537)†	ICS (N=17,552)†	ICS/LABA vs. ICS Hazard Ratio (95% CI)‡
Serious asthma-related events§	116	105	1.10 (0.85, 1.44)
Asthma-related deaths	2	0	
Asthma-related intubations	1	2	
Asthma-related hospitalizations	115	105	

* Randomized patients who took at least one dose of study medication.

†Patients could have more than one event. Planned treatment used for analysis.

‡Estimated using a Cox proportional hazards model for time to first event with baseline hazards stratified by each of the three trials.

§Events that occurred within 6 months after the first use of study drug or 7 days after the last date of study drug treatment, whichever date was later. A single, blinded, independent adjudication committee determined whether events were asthma-related.

Table 2. Efficacy Results

	Advair (Adult/Adolescent)		Advair (Pediatrics)		Symbicort (Adult/Adolescent)		Dulera (Adult/Adolescent)	
	Advair N=5,834	fluticasone N=5,845	Advair N=3,107	fluticasone N=3,101	Symbicort N=5,846	budesonide N=5,847	Dulera N=5,868	mometasone N=5,861
Patients with exacerbations, n (%)	480 (8)	597 (10)	265 (9)	309 (10)	539 (9.2)	633 (10.8)	708 (12.1)	779 (13.3)
Hazard Ratio (95% CI)	0.79 (0.70, 0.89)		0.86 (0.73, 1.01)		0.84 (0.75, 0.94)		0.89 (0.80, 0.98)	

CONTRAST AGENTS

[FDA warns that gadolinium-based contrast agents \(GBCAs\) are retained in the body; requires new class warnings](#)

12/19/2017

FDA requires a class warning regarding gadolinium retention after an MRI using gadolinium-based contrast agents (GBCAs), as well as actions to minimize risks such as labeling changes, a new patient Medication Guide, and human and animal studies conducted by manufacturers of GBCAs to further assess the safety of these contrast agents. GBCAs are mostly eliminated from the body through the kidneys. However, trace amounts of gadolinium may stay in the body long-term depending on:

- Type of GBCA used (linear GBCAs result in more retention and retention for a longer time than macrocyclic GBCAs); and
- Patient risk factors (i.e., those requiring multiple lifetime doses, pregnant women, children, and patients with

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from the fda

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inflammatory conditions).

Adverse events reported in association with gadolinium retention include a rare condition called nephrogenic systemic fibrosis (NSF) that occurs in a small subgroup of patients with pre-existing kidney failure. Adverse events involving multiple organ systems in patients with normal kidney function have also occurred.

Health care providers should:

- Consider the retention characteristics of each agent when choosing a GBCA, especially for at-risk patients.
- Minimize repeated GBCA imaging studies when possible, particularly closely spaced MRI studies.
- Do not avoid or defer necessary GBCA MRI scans.

RHEUMATOLOGY

[FDA to evaluate increased risk of heart-related death and death from all causes with the gout medicine febuxostat \(Uloric\)](#)

11/15/2017

An additional FDA-required safety study from the manufacturer (after approval) involved over 6,000 patients receiving either febuxostat (Uloric) or allopurinol for the treatment of gout and evaluated combined outcomes of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and urgent cardiovascular revascularization. Early results show no increase in risk of these combined events with febuxostat (Uloric) compared to allopurinol. However, upon evaluation of the outcomes separately, a greater risk of cardiovascular death and death from all causes was found with febuxostat (Uloric) compared to allopurinol. FDA awaits final results from the manufacturer and will report any new information after a comprehensive review. FDA recommends that health care professionals:

- Consider cardiovascular safety findings when prescribing or continuing patients on febuxostat (Uloric).
- Inform patients of the risk of adverse cardiovascular events after initiation of febuxostat (Uloric) therapy due to reports of heart attacks, strokes and cardiovascular deaths seen in clinical studies, but that it is not certain that febuxostat (Uloric) caused these events.

See [National PBM Bulletin](#) entitled “Febuxostat (Uloric): FDA Evaluates Risk of Cardiovascular Death” for more details.

Getting the most from our safety surveillance

DIRECT ORAL ANTICOAGULANTS (DOACs): SAFETY UPDATES IN VA

Submitted by: Lisa Longo, Pharm.D., BCPS

The VA Center for Medication Safety (VA MedSAFE) continues to conduct serial drug safety surveillance on the direct oral anticoagulants (DOACs) through our drug utilization evaluation safety surveillance program. The VA MedSAFE DOAC analysis has evolved since the introduction of dabigatran into the VA system in late 2010 and now includes data on dabigatran, rivaroxaban, and apixaban (edoxaban has not yet been incorporated due to low exposure in the VA system to date). Specific adverse outcomes of interest such as gastrointestinal (GI) bleeding, intracranial hemorrhage (ICH), stroke, and all-cause mortality are evaluated in a new user cohort of patients with a diagnosis of atrial fibrillation and using detailed statistical methodology to account for bias and confounding. Results are shared with administration and formulary decision makers semi-annually. In addition to our standard surveillance where DOACs are compared to warfarin as a reference agent, DOACs were compared to each other in the latest report based on a request from the Na-

tional Formulary Committee.

The latest surveillance analysis covers the timeframe of 11/1/10 through 9/30/17. Nearly 150,000 patients were included in the analysis. A brief summary of the results are as follows:

DOACs vs. WARFARIN:

- **Dabigatran** – Dabigatran is associated with significantly less ICH, GI bleeding, and all-cause mortality versus warfarin. There was a favorable trend for reduction in stroke compared to warfarin, but the difference was not statistically significant.
- **Rivaroxaban** – Rivaroxaban is associated with significantly less ICH, GI bleeding, and all-cause mortality versus warfarin. There was a favorable trend for reduction in stroke compared to warfarin, but the difference was not statistically

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Getting the most from our safety surveillance

DIRECT ORAL ANTICOAGULANTS (DOACs): SAFETY UPDATES IN VA

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significant.

- **Apixaban** – Apixaban was associated with significantly less GI bleeding versus warfarin. The risk of ICH, all-cause mortality, and stroke was similar with apixaban versus warfarin (hazard ratio less than but close to 1).

DOAC vs. DOAC:

- **Dabigatran vs. apixaban** – To date, dabigatran appears to be associated with significantly less ICH and all-cause mortality compared to apixaban. The risk of GI bleed appears to be significantly higher with dabigatran versus apixaban. The risk of stroke with dabigatran does not appear to be significantly different.
- **Rivaroxaban vs. apixaban** – To date, rivaroxaban appears to be associated with significantly less ICH compared to apixaban, but appears to have a significantly higher risk of GI bleed compared to apixaban. The risk of all-cause mortality and stroke appear to be similar between the two agents.
- **Rivaroxaban vs. dabigatran** – To date, dabigatran appears to be associated with significantly less all-cause mortality

compared to rivaroxaban. Risk of GI bleed, ICH, and stroke appear to be similar between the two agents.

Limitations: Even though rigorous methods are used to adjust for potential confounding variables, it is likely that a channeling effect is being observed based on prescribing patterns from the criteria for use (CFU). Per the PBM CFU, patients selected for dabigatran are likely younger with less renal impairment and bleeding risk factors. Patients receiving apixaban are likely older with more risk factors for bleeding.

Conclusions: In summary, outcomes with DOACs appear similar-to-favorable compared to warfarin in our Veteran population based on the outcomes evaluated and use according to PBM Criteria for Use. Although analyses are ongoing, some differences between DOACs are noted, though a channeling effect may be contributory. Additional analyses of MI with DOACs will be conducted in 2018.

REFERENCE:
Internal data.

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noted that sacubitril/valsartan was one of 66 medications with 1,000 or more adverse drug event (ADE) reports in 2017 Q1. According to the report, there were 1,684 adverse event reports of a hypotension-related event, with symptoms ranging from dizziness to blackouts, some requiring hospitalization. It was noted that the events were reported in older patients, with a median age of 70 years. Two-thirds of the cases were not considered severe; however, there were 69 deaths reported.¹

It has been noted that adverse events with sacubitril/valsartan have been largely underestimated due to the design of the pivotal clinical trial (described below), which may not accurately reflect clinical practice.

PARADIGM-HF

FDA approval of sacubitril/valsartan was based on the pivotal Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial. Results from PARADIGM-HF demonstrated a statistically significant reduction in the composite pri-

mary outcome (death from cardiovascular causes or first hospitalization for heart failure) with sacubitril/valsartan compared to the ACEI enalapril (21.8% vs. 26.5%, respectively; HR 0.80, 95% CI 0.73 to 0.87; P<0.001).⁴

Patients enrolled in PARADIGM-HF were previously receiving treatment with an ACEI or ARB, and were excluded if they experienced unacceptable side effects during treatment with an ACEI or ARB. Patients were also excluded if they had symptomatic hypotension, systolic blood pressure < 100 mm Hg at screening or 95 mm Hg at randomization. During the run-in period of the trial, patients were treated with the enalapril 10 mg twice daily for 2 weeks; it is noted that approximately 10.5% of patients discontinued treatment at this point (5.6% due to an adverse event; 0.6% due to abnormal laboratory or other test result). If no intolerable side effects, the ACEI was discontinued and treatment was subsequently initiated with sacubitril/valsartan for 4 to 6 weeks (reported in the trial as starting at 100 mg twice daily, then increased to 200 mg twice daily); with approximately 10.4% of patients discontinuing treatment at this

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point (5.8% due to an adverse event; 0.6% due to abnormal laboratory or other test result).

Warnings and Precautions: Hypotension

Per the product information for sacubitril/valsartan, hypotension was reported as an adverse event in 18% of patients treated with sacubitril/valsartan compared to 12% of patients receiving treatment with enalapril, with hypotension reported as a serious adverse event in approximately 1.5% of patients in both treatment groups. It is also noted that patients who are volume and/or salt-depleted are at increased risk for developing hypotension with sacubitril/valsartan.²

Symptomatic hypotension was reported in 14.0% of patients receiving sacubitril/valsartan vs. 9.2% of patients in the enalapril treatment group (P<0.001); symptomatic hypotension with a systolic blood pressure < 90 mm Hg occurred in 2.7% of patients on sacubitril/valsartan and 1.4% patients on enalapril (P<0.001) in the clinical trial.⁴

According to the ISMP QuarterWatch Report, if the hypotension-related symptoms are included as noted per the FDA medical reviewer, the rate would increase to 24.4%; with a further increase to 29.5% if patients with treatment-related hypotension during the study run-in period are included.¹

VA Adverse Drug Event Reporting System (VA ADERS)

The following are reports submitted to VA ADERS for hypotension or dizziness for sacubitril/valsartan by quarter (Q) for the respective Fiscal Year (FY). See Table 1.

Summary

The ISMP QuarterWatch report concluded that approximately 1

in 4 patients started on sacubitril/valsartan may experience a hypotension-related adverse event; a risk which appears to have been underestimated due to the careful selection of patients in the published clinical trial supporting FDA drug approval of this agent.

Providers should take into consideration the patient's risk (e.g., older patients, baseline blood pressure, volume and/or salt depletion, tolerability of previous treatment with an ACEI or ARB) for hypotension or hypotension-related events when initiating and monitoring treatment with sacubitril/valsartan. Patients should be informed of the risk for low blood pressure and associated symptoms, and instructed to report any adverse events to their healthcare provider. It is recommended that providers report any ADEs that occur with sacubitril/valsartan per local VA protocols.

Sacubitril/valsartan is listed on the VA National Formulary, with Prior-Authorization at the Facility level (PA-F), according to [VA Criteria for Use](#).

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2. ENTRESTO™ (sacubitril and valsartan) tablets [prescribing information]. East Hanover, NJ: Novartis. Nov 2017.
3. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation 2017;136(6):e137-e161.
4. McMurray JJV, Packer M, Desai AS, et al., for the PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371:993-1004. ■

Table 1. VA ADERS reports for hypotension or dizziness for sacubitril/valsartan by quarter (Q) for the respective Fiscal Year (FY).

Symptom	Severity	Q2 FY16	Q3 FY16	Q4 FY16	Q1 FY17	Q2 FY17	Q3 FY17	Q4 FY17	Q1 FY18	Grand Totals
Hypotension	Mild	1		2	2		2	2	2	11
Dizziness	Mild				2	1	1	1		5
Hypotension	Moderate	1				1	2	1		5
Dizziness	Moderate					1				1