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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

## SAFETY CONSIDERATIONS FOR THE USE OF OVER-THE-COUNTER SODIUM PHOSPHATE PRODUCTS FOR CONSTIPATION

The FDA recently released a Drug Safety Communication warning of potential serious harm with the use of over-the-counter (OTC) sodium phosphate products (including oral solutions and enemas) of more than one dose per 24 hours for constipation.

Review of the FDA Adverse Event Reporting System and medical literature revealed 54 cases of serious adverse events, with most of the cases occurring in older adults or children less than 5 years of age. Serious outcomes were associated with severe dehydration and/or electrolyte disturbances including acute kidney injury, arrhythmias, or death. Fatal outcome was reported in 48% of the adult cases, with 67% of the remaining adult cases considered to be life-threatening. It was reported that the majority of patients with adverse events had one or more of the following risk factors: dehydration, kidney disease, acute colitis, or delayed bowel emptying; or were receiving medications that affect kidney function, including diuretics, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor antagonists (ARBs), and non-steroidal anti-inflammatory drugs (NSAIDs).

The recommended dose of OTC sodium phosphate products (oral solutions or enemas) for the management of constipation is no more than one dose per 24 hours, not to exceed three days of treatment. In the majority of cases reported, serious adverse events occurred in those who received single doses that were greater than the recommended amount, or were administered more frequently than recommended. In the seven adult patients who were treated with an OTC sodium phosphate product according to product labeling yet who experienced a serious adverse event, all had an associated risk factor as indicated above.

The recent FDA Safety Communication includes the following factors that may increase the patient's risk for adverse events if they were to receive higher than the recommended dose of an OTC sodium phosphate product:

- age over 55 years;
- hypovolemia or decreased intravascular volume;
- kidney disease;
- bowel obstruction or inflammation, or decreased bowel transit time;
- use of diuretics, ACEIs, ARBs, or NSAIDs.

Providers are advised to instruct patients on adequate hydration when using OTC sodium phosphate products. It is recommended to evaluate serum electrolytes and kidney function in patients at risk for adverse events, as well as in patients who have retained a rectal dose for more than 30 minutes, are vomiting, or have signs of dehydration.

*(continued on page 2)*

## IN THIS ISSUE:



### 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 fda

## CENTRAL NERVOUS SYSTEM AGENTS

FDA warns of rare risk of long-lasting erections in males taking methylphenidate ADHD medications and has approved label changes

12/17/2013

Data reviewed from the FDA Adverse Event Reporting System (FAERS) and published literature reveal an association between the use of methylphenidate products and priapism. From 1997 through 2012, 15 cases of priapism occurred in association with a methylphenidate product, making it a rare but serious event as some patients required hospitalization and two underwent surgical intervention for shunt placement and needle aspiration of the corpus cavernosum. Patients reporting priapism symptoms ranged in age from 8 to 33 years, with the median at 12.5 years of age. Other drugs used to treat attention deficit hyperactivity disorder (ADHD), such as atomoxetine (Strattera) and amphetamine, have also caused priapism, prompting providers to exercise caution when considering alternate agents.

## NEUROLOGY

FDA warns of serious skin reactions with the anti-seizure drug Onfi (clobazam) and has approved label changes

12/3/2013

FDA has approved revisions to the drug label and Medication Guide for the anti-seizure drug clobazam (Onfi) describing the risk of serious skin reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) that can result in permanent harm and death. Data reviewed from the FDA Adverse Event Reporting System (FAERS) database identified 20 cases of SJS/TEN (6 in the U.S. and 14 abroad), all of which resulted in hospitalization, with one case resulting in blindness and another in death. Nineteen cases reported concomitant use of drugs associated with SJS/TEN (antiepileptic drugs [n=18], beta-lactam antibiotics [n=3], or sulfasalazine [n=2]); however, out of the 17 cases that provided specific timing information, 14 showed a close temporal relationship (within two months) between initiation of clobazam (Onfi) and development of the serious skin reaction. FDA recommends that health care providers should:

- Closely monitor patients taking clobazam (Onfi) for signs or symptoms of SJS/TEN, especially during the first 8 weeks of treatment or when re-introducing therapy.
- Educate patients on the signs and symptoms of serious skin reactions and instruct them to seek immediate medical treatment at the first appearance of a skin rash, blistering or peeling of the skin, sores in the mouth, or hives.
- Discontinue treatment at the first sign of rash, unless not drug-related. Providers should not continue treatment in patients presenting with a serious skin reaction and should consider alternative therapy.
- Consider clobazam (Onfi) as a possible cause when evaluating patients with potentially drug-induced skin reactions in addition to other drugs known to affect the skin.

# Helping to achieve safe medication use

## *SAFETY CONSIDERATIONS FOR THE USE OF OVER-THE-COUNTER SODIUM PHOSPHATE PRODUCTS FOR CONSTIPATION*

*(continued from page 1)*

The information above reiterates safety considerations for use of sodium phosphate/sodium biphosphate enemas as previously addressed. Similar precautions for use are listed; however, it is noted that the recent FDA Safety Communication includes increased risk for adverse events in patients over the age of 55 years (product information includes precautions in patients ≥ 65 years of age). Refer to the following for additional information on contraindications and precautions:

- Sodium Phosphate Sodium Biphosphate Enema, Safety Considerations ;
- Issue 7; Volume 3; July/August 2013.

Efforts at the VISN/local level are encouraged to alert providers to the safety concerns with the use of sodium phosphate products, and to emphasize the dosing recommendations of not more than one dose per 24 hours, and for no more than 3 days, when being used for constipation.

Considerations for the use of oral sodium phosphate products for bowel preparation are also available at: Oral Sodium Phosphate Products for Bowel Cleansing Formulary Updates .

Providers should report any adverse reactions with the use of sodium phosphate products 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 (1-800-FDA-1088, fax 1-800-FDA 0178, online at *https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm*, or by mail).

*Contributed by: Elaine Furmaga, Pharm.D. and Francine Goodman, Pharm.D., BCPS*

# Getting the most from our safety surveillance

## VA NEPHRON-D RESULTS AND RECOMMENDATIONS ON THE USE OF DUAL RENIN-ANGIOTENSIN SYSTEM BLOCKADE

Results of the VA Cooperative Study, Combination Angiotensin Receptor Blocker and Angiotensin-Converting Enzyme Inhibitor for Treatment of Diabetic Nephropathy (VA NEPHRON-D) were recently published.[1] This trial was terminated early (median follow-up 2.2 years) based on a greater number of observed acute kidney injury events and hyperkalemia in patients receiving combination with an angiotensin II receptor antagonist (ARB) and angiotensin-converting enzyme inhibitor (ACEI) compared to patients treated with an ARB plus placebo. There was no significant difference in the primary composite outcome or secondary renal endpoint between treatment groups.

These results, along with data from clinical trials noting an increase in adverse events without outcome benefit in patients treated with combination renin-angiotensin system (RAS) blockers compared to monotherapy[2-4] and recommendations from Clinical Practice Guidelines in patients with chronic kidney disease (CKD),[5-7] support recommendations as per the National PBM Bulletin entitled Dual Renin-Angiotensin-Aldosterone System Blockade in Diabetic Nephropathy and Increased Adverse Events (February 12, 2013; ***italicized text added since previous publication***) :

- Combination therapy with an ACEI and ARB (or an ACEI or ARB in combination with aliskiren) should not be initiated in patients with: diabetic nephropathy; diabetes and CKD; or nondiabetic kidney disease, if being used for kidney outcomes. *In the rare circumstance where combination therapy is initiated (e.g., in nephrotic syndrome), this should only be done in consultation with Nephrology.*
- For patients already taking an ACEI and an ARB for the potential benefit on kidney outcomes, providers should review treatment for potential discontinuation of either ACEI or ARB, as applicable. *In the rare circumstance where* combination therapy is continued *(e.g., in nephrotic syndrome), this should only be done in consultation with Nephrology*, and it should be documented that the patient has benefited from combination therapy and that there are no current safety concerns.

For patients with concomitant CKD and heart failure with reduced left ventricular ejection fraction who are receiving treatment with an ACEI and ARB, it may be appropriate to consider switching the ARB to an aldosterone antagonist, provided the patient does not have additional safety concerns such as uncorrected hyperkalemia (e.g., potassium > 5.0 mEq/L) or significant kidney impairment (e.g., serum creatinine > 2.5 mg/dL or creatinine clearance < 30 mL/min). Refer to VA PBM clinical guidance on Aldosterone Antagonists (Eplerenone, Spironolactone) in Heart Failure Clinical Recommendations from January 2011 for additional considerations.

Per utilization review, combination therapy with an ACEI and ARB (all diagnoses) has decreased approximately 17% since publication of the National PBM Bulletin (February 2013), and by 26% over the past year (i.e., Q4FY12-Q4FY13). As previously recommended, VISN PBM(s)/P&T Committee(s) should discuss these recommendations for considering discontinuation of either an ACEI or ARB in patients with chronic kidney disease who are receiving combination therapy with both agents, with facilities implementing them upon direction from their VISN Chief Medical Officer and VISN Pharmacist Executive. VA Patient and Provider Letters are available on the PBM INTRAnet at: https://vaww.cmopnational.va.gov/cmop/PBM/default.aspx.


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7. National Kidney Foundation. KDOQI Clinical Practice Guideline for Diabetes and Chronic Kidney Disease: 2012 Update. Am J Kidney Dis 2012;60:850-86.


**VA NEPHRON-D Results Summary** [1]

**Patient population:** Type 2 diabetes mellitus, urinary albumin-to-creatinine ratio ≥ 300 mg/g, and estimated glomerular filtration rate (eGFR) 30 to 89.9 ml/min/1.73m$^2$ body-surface area

**Primary composite outcome:** First occurrence of a change in eGFR (decline of ≥ 30 ml/min/1.73m$^2$ if initial eGFR ≥ 60 ml/min/1.73m$^2$ or decline of > 50% if initial eGFR < 60 ml/min/1.73m$^2$), end-stage renal disease (ESRD), or death

| | Losartan + Lisinopril (N=724) | Losartan + Placebo (N=724) | HR (95% CI) |
|---|---|---|---|
| **Outcome** | | | |
| Primary composite endpoint | 132 (18.2%) | 152 (21.0%) | 0.88 (0.70 to 1.12) |
| Decline eGFR, ESRD | 77 (10.6%) | 101 (14.0%) | 0.78 (0.58 to 1.05) |
| Death | 63 (8.7%) | 60 (8.3%) | 1.04 (0.73 to 1.49) |
| Acute kidney injury[a] | 12.2 | 6.7 | 1.7 (1.3 to 2.2) |
| Hyperkalemia[a] (> 6.0 mmol/L[b]) | 6.3 | 2.6 | 2.8 (1.8 to 4.3) |

[a] Events per 100 person-years; P<0.001 combination vs. monotherapy

[b] or that required an emergency room visit, hospitalization, or dialysis


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