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MEDICATION SAFETYINSECONDS

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

Helping to achieve safe medication use

SACUBITRIL/VALSARTAN (ENTRESTO) AND SERIOUS OUTCOMES WHEN USED WITH ACE INHIBITORS

According to a recent Institute for Safe Medication Practices (ISMP) alert, FDA has received 55 reports of concomitant use of sacubitril/valsartan (Entresto) and an angiotensin-converting enzyme (ACE) inhibitor, with several cases describing serious outcomes. Hospitalization occurred in eleven patients. Other adverse events reported as a result of this drug interaction include angioedema, hyperkalemia, acute kidney injury, and hypotension.

Sacubitril/valsartan (Entresto) product labelling contraindicates concomitant use with an ACE inhibitor because of the increased risk of angioedema. It was noted that several of the cases had a washout period of less than 36 hours when switching from an ACE inhibitor to sacubitril/valsartan (Entresto), despite these instructions in the product labelling. Also, the manufacturer lists the combined use of sacubitril/valsartan (Entresto) and an ACE inhibitor as a drug interaction due to dual blockade of the renin-angiotensin-aldosterone system from the valsartan component. This may increase the risk of hypotension, acute kidney injury, and hyperkalemia.

Since the primary use of sacubitril/valsartan (Entresto) will be in patients currently receiving treatment with an ACE inhibitor or angiotensin II receptor blocker (ARB), serious events may follow if the ACE inhibitor (or ARB) is not discontinued or if the patient continues taking the previously prescribed ACE inhibitor (or ARB) from their home supply. As such, ISMP recommends that health care professionals:

- Educate patients not to take sacubitril/valsartan (Entresto) together with an ACE inhibitor and inform them of risks associated with concurrent use.

(continued on page 2)

NEWSWORTHY...

from the pbm

- Chlorhexidine Gluconate Safety Issues – 02/07/2017 - National PBM Bulletin

(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

OVER-THE-COUNTER (OTC) AGENTS

FDA warns about rare but serious allergic reactions with the skin antiseptic chlorhexidine gluconate
2/2/2017

FDA is requesting the manufacturers of over-the-counter (OTC) antiseptic products containing chlorhexidine gluconate to add a warning about the risk of serious allergic reactions to the Drug Facts labels. Although rare, serious allergic reactions, including fatal anaphylaxis, can develop within minutes of exposure, and can occur with topical or oral use of the drug. Prescription chlorhexidine gluconate mouthwashes for gingivitis and oral chips used for periodontal disease already contain a warning about the possibility of serious allergic reactions in their labels.

FDA recommends that healthcare professionals:

- Inquire from patients if they have experienced any reaction to the ingredient chlorhexidine gluconate or to antiseptic products containing chlorhexidine gluconate prior to use, such as:
  - Wheezing or difficulty breathing
  - Swelling of the face
  - Hives that can quickly progress to other more serious symptoms
  - Severe rash
  - Shock
- If a patient exhibits an unexplained allergic reaction prior to or during an injection or surgical procedure:
  - check whether chlorhexidine gluconate was used,
  - monitor the reaction carefully,
  - provide immediate respiratory and/or cardiovascular support as needed, and
  - discontinue the use of the drug or medical device containing chlorhexidine gluconate immediately.
- Consider using alternative antiseptics such as povidone-iodine, alcohols, benzalkonium chloride, benzethonium chloride, or parachlorometaxylenol (PCMX) when any previous allergy to chlorhexidine gluconate is documented or suspected.

Further details are available in the National PBM Bulletin issued this month.

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SACUBITRIL/VALSARTAN (ENTRESTO) AND SERIOUS OUTCOMES WHEN USED WITH ACE INHIBITORS

(continued from page 1)

- Review patients' medication regimens for any ACE inhibitor use. If a patient is taking an ACE inhibitor, discontinue the ACE inhibitor and instruct the patient to stop its use. Allow for a 36-hour washout period before initiating sacubitril/valsartan (Entresto).
- Conduct a thorough medication reconciliation (on admission and at discharge) for current or prior ACE inhibitor or ARB use to ensure that patients who are prescribed sacubitril/valsartan (Entresto) upon discharge do not restart these other medications at home.
- Create order entry system alerts against the concomitant use of sacubitril/valsartan (Entresto) and ACE inhibitors when both agents have been prescribed for the same patient. If possible, enable the alert to continue for 36 hours after sacubitril/valsartan (Entresto) or the ACE inhibitor have been discontinued. (*Note - VA's provider order entry system in the Computerized Patient Record System [CPRS] already has its own order check process for sacubitril/valsartan [Entresto]: a Critical drug-drug interaction order check (alert) in the case of a concomitant ACE inhibitor or a Duplicate therapy order check (alert) in the case of a concomitant ARB*).

Within VA, concomitant use of sacubitril/valsartan (Entresto) and an ACE inhibitor or ARB along with associated safety issues is currently monitored by PBM/MedSAFE.

REFERENCES:

1. Institute for Safe Medication Practices (ISMP). Concomitant use of Entresto and ACE inhibitors can lead to serious outcomes. *ISMP Medication Safety Alert! Acute Care* January 2017; 22 (1): 3-4.
2. Entresto (sacubitril/valsartan) [package insert]. East Hanover, NJ: Novartis Pharmaceutical Corporation; Aug 2015.

Getting the most from our safety surveillance

PROTAMINE ADVERSE REACTION WITH FATAL OUTCOME AND POSSIBLE LINK TO PRIOR EXPOSURE TO NPH INSULIN – REPONSE TO FIELD INQUIRIES

Last month's issue (Issue 1; Volume 7; January 2017) included an article describing a patient who experienced a fatal adverse reaction to protamine that may have been linked to prior exposure to NPH insulin and recommended certain measures to take in order to mitigate future risk. This sparked feedback from the field on whether the combination of protamine and NPH insulin should be included as a drug-drug interaction in the clinical drug interaction package used to generate alerts to providers at the point of computer order entry triggered by the order of either of these agents. However, the co-administration of protamine and NPH insulin is not listed as a drug interaction in the product labeling.

According to the FDA, drug-drug interactions occur when two or more drugs react with each other. This can either increase or decrease the action of either or both drugs or cause unexpected side effects. On the contrary, in the aforementioned case, prior exposure to NPH insulin may have induced protamine reactions via an immunologic process as opposed to a drug interaction.

Evidence suggests that in protamine insulin dependent diabetics, the increased risk of serious reactions associated with intravenous protamine ensue from antibody-mediated mechanisms. This happens because protamine is a non-human protein and may act as an antigen stimulating the production of specific anti-protamine IgE and IgG antibodies, which mediate anaphylactic reactions. Because NPH insulin contains protamine (neural protamine Hagedon), NPH insulin dependent diabetic patients may develop sensitivity to protamine, putting them at higher risk of life-threatening reactions to protamine.

PBM suggests not adding the combination of protamine to the drug interaction package utilized by the computerized order entry system because:

- The manufacturer does not identify protamine and insulin as a drug interaction in the product labeling.
- Humorally mediated immune responses to protamine are likely the cause of the increased risk of reaction to the intravenous protamine in the previously reported case of the patient who had protamine insulin dependent diabetes.

Alternative methods of awareness may include:

- Educating staff that sensitization to protamine from previous NPH use may increase the risk of adverse reaction to protamine.
- Add a short reminder using the DRUG TEXT feature of VistA associated with the corresponding protamine entries in the Pharmacy Orderable Item file #50.7 (less than 74 characters). As blue line text, this reminder displays as information-only and does not become part of that order (i.e. suggested DRUG TEXT SUCH AS: *Prior NPH use may increase risk of protamine reaction*).
- Create a clinical reminder order check (CROC) for ANY protamine order that provides the same message from above.
- Create a clinical reminder order check for a protamine order on a patient whose chart shows any history of NPH use (or history of diabetes, which may imply previous use of NPH) to provide the message.

REFERENCE:

Protamine Sulfate [package insert]. Lake Zurich, IL: Fresenius Kabi USA, LLC; 2013. ■