NATIONAL PBM ALERT

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DEPARTMENT OF VETERANS AFFAIRS - VETERANS HEALTH ADMINISTRATION (VHA)
PHARMACY BENEFITS MANAGEMENT SERVICES (PBM), MEDICAL ADVISORY PANEL (MAP), AND
CENTER FOR MEDICATION SAFETY PSCI (VA MEDSAFE)

MICRO-BUBBLE CONTRAST AGENTS (DEFINITY® [PERFLUTREN LIPID MICROSPHERE] INJECTABLE SUSPENSION AND OPTISON® [PERFLUTREN PROTEIN-TYPE A MICROSPHERES] FOR INJECTION): RISK OF CARDIOPULMONARY REACTIONS AND CHANGES TO PACKAGE LABELING

I. ISSUE

The Food and Drug Administration (FDA) has released an alert to inform healthcare providers of updated package labeling including boxed warnings of an increased risk of cardiopulmonary reactions with Definity® and Optison® micro-bubble contrast agents. [1] Definity® and Optison® are injectable suspensions of perflutren microspheres for enhancement of imaging the left ventricle in suboptimal echocardiograms.

II. BACKGROUND

In October 2007, FDA issued information for healthcare professionals regarding reports of deaths and serious cardiopulmonary reactions in patients administered micro-bubble contrast agents. Four out of eleven deaths resulted from cardiac arrest and occurred within thirty minutes after the administration of the contrast agent. Serious, non-fatal reactions (199 reports) were also reported to have transpired during this time period.

III. DISCUSSION

Labeling changes consist of a boxed warning in addition to other warnings highlighting the risk for serious cardiopulmonary reactions, an increased need for intensive or close monitoring during and after administration of the agents, and caution in patients with concomitant conditions (previously listed as contraindications to receiving the agent) that increase their risk for a cardiopulmonary event (i.e., worsening or clinically unstable congestive heart failure, acute myocardial infarction or acute coronary syndromes, serious ventricular arrhythmias or high risk of arrhythmias due to prolongation of the QT interval, respiratory failure, severe emphysema, pulmonary emboli or other conditions that cause pulmonary hypertension.). [2, 3]

IV. VA MEDSAFE RECOMMENDATIONS *reinforce those of the FDA and include*:

- Providers must intensively monitor patients with pulmonary hypertension or unstable cardiopulmonary conditions during and for at least 30 minutes after administration of the products with respect to:
    - Vital Signs
    - Electrocardiography
    - Cutaneous oxygen saturation
- Close observation of patients without these underlying conditions is recommended.
- Always have cardiopulmonary resuscitation personnel and equipment readily available prior to Definity® and Optison® administration and monitor for acute reactions. [2, 3]
- Providers should consider the potential benefit and risks to each individual patient before utilizing a micro-bubble contrast agent.
- ***Contraindications*** currently list patients with either known hypersensitivity to the products or have fixed right-to-left, bi-directional cardiac shunts or transient right-to-left shunts. The ***Contraindications*** section also notes that the products are not for intra-arterial injection.
- Further information regarding this safety issue can be accessed via the following link: http://www.fda.gov/medwatch/safety/2007/safety07.htm#bubble.

V. REFERENCES

1. Food and Drug Administration (FDA) Alert. 07/17/2008. http://www.fda.gov/medwatch/safety/2007/safety07.htm#bubble.
2. Food and Drug Administration (FDA) Label and Approval History. Accessed 07/17/2008. http://www.fda.gov/cder/foi/label/2008/021064s009lbl.pdf.
3. Food and Drug Administration (FDA) Label and Approval History. Accessed 07/17/2008. http://www.fda.gov/cder/foi/label/2008/020899s011lbl.pdf.