

Drugs

Micro-bubble Contrast Agents (marketed as Definity (Perflutren Lipid Microsphere) Injectable Suspension and Optison (Perflutren Protein-Type A Microspheres for Injection) - Healthcare Professional Sheet text version

FDA ALERT [10/2007, UPDATED 7/17/2008]: FDA is issuing this alert to update healthcare professionals about changes that were made to the *Boxed Warning, Warnings, and Contraindications* sections of the prescribing information for micro-bubble contrast agents in May and June, 2008. The revised *Boxed Warning and Warnings* continue to highlight the risk of serious cardiopulmonary reactions during or within 30 minutes following the administration of these products and recommend that high risk patients with pulmonary hypertension or unstable cardiopulmonary conditions be closely monitored during and for at least 30 minutes post administration of these contrast agents. Concurrent with these labeling changes, FDA required that manufacturers of micro-bubble contrast agents conduct clinical studies to more thoroughly assess the risks for serious cardiopulmonary reactions.

Several of the *Contraindications* that were added to the labeling in October, 2007 were removed because FDA determined that, in some patients, the benefits from the diagnostic information that could be obtained through the use of Definity or Optison may outweigh the risk for serious cardiopulmonary reactions, even among some patients at particularly high risk for these reactions. The *Contraindications* that were removed include: 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.

These changes reflect conclusions of FDA reviews related to information received following the addition of new contraindications and warnings to the labeling for these products in October 2007.

This information reflects FDA's current analysis of data available to FDA concerning this drug. FDA intends to update this when additional information or analyses become available.

Adverse reactions or quality problems experienced with the use of this Product may

be reported to the FDA's MedWatch Adverse Event Reporting program either online, by regular mail or by fax, using the contact information at the bottom of this sheet.

Considerations

The revised labeling for this class of products includes the following information and recommendations for physicians who administer micro-bubble contrast agents to improve the quality of echocardiograms:

- Serious cardiopulmonary reactions, including fatalities, have occurred during or within 30 minutes following administration of a micro-bubble contrast agent.
- Patients with pulmonary hypertension or unstable cardiopulmonary conditions should have their vital signs and cutaneous oxygen saturation monitored during and for at least 30 minutes following the administration of a micro-bubble contrast agent.

Information for the Patient

- Tell the physician performing the echocardiogram if you:
 - have a congenital heart defect
 - have a heart or lung condition that has recently gotten worse
 - have a condition that has caused high blood pressure in the blood vessels going to your lungs
 - have ever had a reaction to a drug given to you during an echocardiogram

Data Summary

Changes to the labeling for Definity and Optison were made in October 2007 following the receipt of postmarket reports of serious adverse events as well as new animal data that suggested the products may cause transient but marked pulmonary hypertension. The labeling changes included addition of a boxed warning to highlight a risk for serious cardiopulmonary reactions, a recommendation to monitor all patients for at least 30 minutes following administration of the products, and new contraindications for use of the products in patients with certain cardiopulmonary conditions.

Following the labeling changes, the FDA was informed by physicians that the diagnostic information that could be provided by using Definity or Optison may, in certain situations, justify the risk for serious cardiopulmonary reactions, even in those patients at high risk for these reactions and in some patients for whom the use of these products was contraindicated. FDA reviewed published reports of hemodynamic measurements from patients undergoing heart surgery and/or congestive heart failure evaluation that suggested that these products might not

carry as great a risk for pulmonary hypertension as was previously thought.

Following the review of the published reports and consideration of what we heard from physicians, FDA determined that the labeling for these products should be changed to reflect our current thinking. Coincident with the changes to be made to the *Boxed Warning*, *Warnings* and *Contraindications* in May and June, 2008, FDA exercised its authority under the Food and Drug Administration Amendments Act of 2007 to require the manufacturers of micro-bubble contrast agents to conduct new clinical studies to more thoroughly assess the risks for serious cardiopulmonary reactions. Two of the studies will obtain pulmonary hemodynamic data from patients receiving the products; the other two studies will use existing patient databases to assess the risks for use of the products among critically ill patients.

Since the time the Information for Healthcare Professionals sheet was posted in October 2007, FDA has received postmarket reports of five deaths following the administration of Definity; no deaths were reported for Optison. All patients who died following the administration of Definity had severe underlying medical conditions. Three of the deaths were associated with cardiac arrest that occurred within 30 minutes following Definity administration. Most patients had multiple co-morbidities.

Also following the 2007 posting, FDA received approximately 60 reports of serious non-fatal reactions following Definity administration. The reported reactions generally occurred in a pattern similar to those previously reported. There were no additional reports of serious non-fatal reactions following Optison administration.

The revised labeling for the micro-bubble contrast agents emphasizes the need for intensive monitoring of patients with pulmonary hypertension or unstable cardiopulmonary conditions during and following administration of the products and continues to emphasize the need to observe all patients closely during and following administration of Definity or Optison. Below is a summary of the labeling changes made in May and June, 2008:

Boxed Warning and ***Warnings*** specifically recommend intensive monitoring for patients with pulmonary hypertension or unstable cardiopulmonary conditions and close observation of patients without these underlying conditions.

Boxed Warning identifies a risk for serious cardiopulmonary reactions and the ***Warnings*** section also identifies a risk for serious cardiopulmonary reactions that have occurred during or within 30 minutes following administration of the products. Patients with pulmonary hypertension or unstable cardiopulmonary conditions should be monitored with vital sign measurements, electrocardiography and cutaneous oxygen saturation during and for at least 30 minutes after administration of the products. All other patients should be observed closely during and following

administration of the products. Resuscitation equipment and trained personnel should always be readily available during the drug administration and monitoring period.

Contraindications currently state that the products are contraindicated among 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.

The following *Contraindications* were removed from the labeling:

- worsening or clinically unstable congestive heart failure,
- acute myocardial infarction or acute coronary syndromes,
- serious ventricular arrhythmias or high risk for arrhythmias due to prolongation of the QT interval,
- respiratory failure,
- severe emphysema,
- pulmonary emboli or other conditions that cause pulmonary hypertension.

Micro-bubble ultrasound contrast agents are a sterile suspension of perflutren gas microspheres that are indicated for use in certain patients with suboptimal echocardiograms. These products are used to opacify the left ventricular chamber and to improve the delineation of the left ventricular endocardial border.

Definity and Optison are the only micro-bubble products approved for use in the United States. FDA approved Optison in 1997. The manufacturer of Optison voluntarily temporarily suspended marketing the product in 2005 but resumed marketing in 2007. Definity has been marketed since FDA approval in 2001.

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