

## FDA Issues Warning on Regadenoson and Adenosine

The U.S. Food and Drug Administration (FDA) issued a warning on November 20 regarding potential health risks associated with the cardiac nuclear stress test agents regadenoson and adenosine (Lexiscan and Adenoscan, respectively). The agency approved changes to the drug labels to reflect risk of adverse cardiac events, including heart attack and death, and updated its recommendations for use of the 2 agents.

### New Recommendations

The FDA is now urging health care providers to avoid the use of Lexiscan and Adenoscan in patients showing signs or symptoms of acute myocardial ischemia including unstable cardiovascular function or angina. These patients may be at increased risk of myocardial infarction and potential death.

Both radiopharmaceuticals are designed to dilate the heart's arteries and boost the flow of blood, which is increased in viable blood vessels, but this process may lead to a natural decrease in blood flow through already compromised and vulnerable stenotic and atherosclerotic arteries. In severe cases, this decrease in blood circulation to the heart can lead to a fatal heart attack, cardiac arrest, and/or other major events. The FDA recommends that health care providers perform comprehensive screening of nuclear stress test patients to gauge the safety of Lexiscan or Adenoscan administration. Cardiac resuscitation equipment and trained staff should be available before patients are given Lexiscan or Adenoscan. Clinicians are also encouraged to consider alternative imaging agents for high-risk patients. These include dipyridamole, which is FDA approved, and dobutamine, which has not yet been approved for this application.

### FDA Labeling Addresses Risks

Approved changes in Lexiscan and Adenoscan labeling include updated recommendations for clinical use. The FDA has issued a summation of adverse events based on an analysis of relevant data from June 24, 2008, to April 10, 2013, as well as a review of published instances of myocardial infarction associated with the 2 radiopharmaceuticals. The period of data review reflects the initiation of postapproval marketing for both drugs. A total of 26 cases of myocardial infarction and 29 deaths were reported for Lexiscan, and 6 cases of myocardial infarction and 27

fatalities were associated with administration of Adenoscan. Details of myocardial infarction and death were not always reported, but documented events tended to occur within 6 hours after injection. Deaths associated with Lexiscan were most commonly reported as resulting from myocardial infarction, cardiac or respiratory arrest, loss of consciousness, pulmonary edema, and ventricular fibrillation, among other potential effects. For Adenoscan, death was associated with many of the same indications, such as cardiorespiratory arrest, as well as dyspnea and ventricular tachycardia. The review summary also indicated that some of these adverse events may have resulted from off-label use during exercise stress testing.

"The number of postmarketing reports is subject to change over time, and may not reflect the true proportion of cases associated with either Lexiscan or Adenoscan," FDA officials stated in the report. "Many factors can influence whether adverse effects are reported, particularly the length of time a drug has been marketed, whether or not the adverse effect is described in the drug label, and the amount of publicity about an event or safety concern."

In addition to clinical reports, a review of the medical literature revealed 2 cases of Lexiscan-related myocardial infarction. The report did not differentiate risks of adverse effects between Lexiscan and Adenoscan. "Specifically for Lexiscan and Adenoscan, the analysis is complicated by differences in the number of patient exposures and in underlying cardiac risk factors that can influence choice of drug, and for Adenoscan, by its longer time on the market," noted FDA officials.

The FDA has set up a system through which health care providers can report on their own experiences with the tests. Reports of adverse events specifically related to Lexiscan or Adenoscan can be submitted to MedWatch, an adverse event reporting program and safety resource provided by the FDA. Contact MedWatch by telephone at 1-800-FDA-1088 or by fax at 1-800-FDA-0178. Clinicians can access the program online at [www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm](http://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm) or by mail via the postage-paid FDA form 3500, which can be obtained online at [www.fda.gov/MedWatch/getforms.htm](http://www.fda.gov/MedWatch/getforms.htm). Forms can be mailed to MedWatch, 5600 Fishers Lane, Rockville, MD, 20852-9787.