



FDA warns of rare but serious risk of heart attack and death with cardiac nuclear stress test drugs Lexiscan (regadenoson) and Adenoscan (adenosine)

Safety Announcement

[11-20-2013] The U.S. Food and Drug Administration (FDA) is warning health care professionals of the rare but serious risk of heart attack and death with use of the cardiac nuclear stress test agents Lexiscan (regadenoson) and Adenoscan (adenosine). We have approved changes to the drug labels to reflect these serious events and updated our recommendations for use of these agents. Health care professionals should avoid using these drugs in patients with signs or symptoms of unstable angina or cardiovascular instability, as these patients may be at greater risk for serious cardiovascular adverse reactions.

Lexiscan and Adenoscan are FDA approved for use during cardiac nuclear stress tests in patients who cannot exercise adequately. Lexiscan and Adenoscan help identify coronary artery disease. They do this by dilating the arteries of the heart and increasing blood flow to help identify blocks or obstructions in the heart's arteries. Lexiscan and Adenoscan cause blood to flow preferentially to the healthier, unblocked or unobstructed arteries, which can reduce blood flow in the obstructed artery. In some cases, this reduced blood flow can lead to a heart attack, which can be fatal.

The *Warnings & Precautions* section of the Lexiscan and Adenoscan labels previously contained information about the possible risk of heart attack and death with use of these drugs. However, recent reports of serious adverse events in the FDA Adverse Event Reporting System (FAERS) database and the medical literature^{1,2} (see Data Summary) prompted us to approve changes to the drug labels to include updated recommendations for use. Some events occurred in patients with signs or symptoms of acute myocardial ischemia, such as unstable angina or cardiovascular instability. Cardiac resuscitation equipment and trained staff should be available before administering Lexiscan or Adenoscan. At this time, data limitations prevent us from determining if there is a difference in risk of heart attack or death between Lexiscan and Adenoscan.

We recommend that health care professionals and their patients discuss any questions or concerns.

Facts about Lexiscan (regadenoson) and Adenoscan (adenosine)

- Lexiscan or Adenoscan are administered by intravenous injection during a cardiac nuclear stress test to patients who cannot adequately exercise. These drugs dilate

the coronary arteries and increase blood flow so that coronary artery obstructions can be identified.

Additional Information for Patients

- Heart attack and death have occurred in patients who received Lexiscan (regadenoson) or Adenoscan (adenosine) for a cardiac nuclear stress test.
- Tell your health care professional about any heart problems before you have a cardiac nuclear stress test.
- Talk to your health care professional if you have any questions or concerns about having a cardiac nuclear stress test, or about any cardiac nuclear stress test agent, including Lexiscan or Adenoscan.
- Report side effects from Lexiscan or Adenoscan to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of this page.

Additional Information for Health Care Professionals

- Cases of myocardial infarction and death have occurred following the administration of Lexiscan (regadenoson) injection or Adenoscan (adenosine) infusion.
- Both drugs present a risk to patients, especially to those with ongoing cardiac ischemia. Some cases of myocardial infarction and death have occurred in patients with pre-existing unstable angina or cardiovascular instability.
- Screen all nuclear stress test candidates for their suitability to receive Lexiscan or Adenoscan.
- Avoid using these drugs in patients with symptoms or signs of acute myocardial ischemia such as unstable angina or cardiovascular instability; these patients may be at greater risk of serious cardiovascular reactions to Lexiscan or Adenoscan.
- Cardiac resuscitation equipment and trained staff should be readily available before administering Lexiscan or Adenoscan.
- Due to limitations in the currently available data, FDA is unable to discern a difference in risk for acute myocardial infarction or death between Lexiscan and Adenoscan.
- Other cardiac nuclear stress test agents include:
 - intravenous dipyridamole (FDA-approved for use during cardiac stress test)
 - dobutamine (not FDA-approved for use during cardiac stress test)
- Review the updated Lexiscan and Adenoscan labels for the latest recommendations.
- Report adverse events involving Lexiscan or Adenoscan to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of this page.

Data Summary

FDA reviewed the FDA Adverse Event Reporting System (FAERS) database and the medical literature for cases of myocardial infarction (MI) and death from all causes

associated with Lexiscan (regadenoson) and Adenoscan (adenosine). We analyzed FAERS data for Lexiscan from June 24, 2008, to April 10, 2013, and for Adenoscan, from May 18, 1995, to April 10, 2013. The beginning dates correlated with the start of marketing for each drug.

We identified cases of MI and deaths from all causes for both Lexiscan and Adenoscan. The FAERS database contained 26 MI cases and 29 cases of death occurring after Lexiscan administration, and six cases of MI and 27 cases of death following Adenoscan administration. Reports did not always specify when deaths or MIs occurred. When reported, these adverse events tended to occur within 6 hours following Lexiscan or Adenoscan administration. A few deaths occurred when Lexiscan or Adenoscan was administered with exercise stress testing, which is not an FDA approved use of the drugs.

With Lexiscan, the most common adverse events associated with death were cardiac arrest, MI, loss of consciousness, respiratory arrest, electrocardiogram ST segment depression, pulmonary edema, and ventricular fibrillation. With Adenoscan, the most common adverse events associated with death were cardiorespiratory arrest, dyspnea, cardiac arrest, respiratory arrest, and ventricular tachycardia.

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. 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. 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.

Medical Literature Review

A review of the medical literature also identified two case reports of MI associated with Lexiscan.^{1,2} However, published studies from the medical literature have not documented an increased incidence of cardiovascular adverse events with Lexiscan compared to Adenoscan.³⁻⁷

References

1. Shah S, Parra D, Rosenstein RS. Acute myocardial infarction during regadenoson myocardial perfusion imaging. *Pharmacotherapy* 2013;33:90-5.
2. Hsi DH, Marreddy R, Moshiyakhov M, Luft U. Regadenoson induced acute ST-segment elevation myocardial infarction and multivessel coronary thrombosis. *J Nucl Cardiol* 2013;20:481-4.
3. Iskandrian AE, Bateman TM, Belardinelli L, Blackburn B, Cerqueira MD, Hendel RC, et al. Adenosine versus regadenoson comparative evaluation in myocardial

perfusion imaging: results of the ADVANCE phase 3 multicenter international trial. *J Nucl Cardiol* 2007;14:645-58.

4. Thomas GS, Thompson RC, Miyamoto MI, Ip TK, Rice DL, Milikien D, et al. The RegEx trial: a randomized, double-blind, placebo- and active-controlled pilot study combining regadenoson, a selective A_{2A} adenosine agonist, with low-level exercise, in patients undergoing myocardial perfusion imaging. *J Nucl Cardiol* 2009;16:63-72.
5. Cavalcante JL, Barboza J, Ananthasubramaniam K. Regadenoson is a safe and well-tolerated pharmacological stress agent for myocardial perfusion imaging in post-heart transplant patients. *J Nucl Cardiol* 2011;18:628-33.
6. Nair PK, Marroquin OC, Mulukutla SR, Khandhar S, Gulati V, Schindler JT, et al. Clinical utility of regadenoson for assessing fractional flow reserve. *JACC Cardiovasc Interv* 2011;4:1085-92.
7. Arumugham P, Figueredo VM, Patel PB, Morris DL. Comparison of intravenous adenosine and intravenous regadenoson for the measurement of pressure-derived coronary fractional flow reserve. *Euro Intervention* 2013;8:1166-71.