GETTING READY FOR YOUR STRESS TEST

What you should know about your cardiac stress test with Lexiscan® (regadenoson) injection.

Indication
Lexiscan is a prescription drug given through an IV line that increases blood flow through the arteries of the heart during a cardiac nuclear stress test. Lexiscan is given to patients when they are unable to exercise adequately for a stress test.

Important Safety Information
Lexiscan should not be given to patients who have certain abnormal heart rhythms unless they have a pacemaker.
Important Safety Information (Continued)

Lexiscan® (regadenoson) injection can cause serious or fatal cardiac arrest, abnormal heart rhythms or heart attack.

Allergic reactions can occur after Lexiscan injection.
What is coronary artery disease?
The heart is a specialized muscle. Like other muscles in your body, it needs oxygen and nutrients. The coronary (heart) arteries deliver oxygen and nutrients to your heart so that it can effectively pump blood throughout your body. People with heart disease may have 1 or more coronary arteries that have become narrowed or clogged over time by fatty deposits (also called plaques). These can decrease blood flow to the heart. See Figure 1 for an illustration that shows you what a normal (healthy) artery looks like compared with a clogged (unhealthy) artery.

So less blood flow is bad, right?
Exactly. Reduced blood flow may cause chest pain (angina), shortness of breath, and potentially a heart attack. Injured heart muscle can be permanently damaged if the coronary arteries stay blocked for too long. If there is a problem with your heart, it is important to find out about it as soon as possible.

My doctor scheduled me for an MPI test. What is it?
MPI stands for myocardial perfusion imaging. The “myocardium” is your heart muscle. “Perfusion” refers to blood flow. And “imaging” is exactly what it sounds like, taking pictures. So, myocardial perfusion imaging is basically taking pictures of the blood flow to your heart. MPI is also called a cardiac nuclear stress test. It is a commonly used test that provides detailed images that can be used to diagnose and assess coronary artery disease.
Does it hurt?

Except for a small needle (catheter) that will be placed in a vein (IV) in your arm at the start of the test, MPI is a noninvasive test. That means it takes place outside of your body and does not involve surgery of any kind. You will stay awake and alert the entire time.

A small amount of radioactive liquid, called a tracer, will be injected into your bloodstream through the catheter during the MPI test. This tracer helps the doctor see the blood flow to your heart. You probably will not feel any effects from the tracer, which your body eliminates by natural means.

Okay, how do the pictures work? Is there a camera or something?

Yes. A special camera will take pictures of your heart once the tracer moves through your arteries. Depending on the type of test, you may be required to have 2 sets of pictures taken by the camera at 2 different times (either later that day or even the next). These pictures give doctors detailed information about blood flow into your heart. They might see that some areas of your heart are blocked and not getting all the oxygen and nutrients they need. This information will help your doctors decide what steps should be taken next.

So it’s radioactive?

Yes. Remember, radiation is always around us, from computers to wireless technology. Your doctor will make sure this is an appropriate test by looking at the amount of radiation you will be exposed to compared to your risks for heart disease. In many cases, not having this test may present higher risk than having it done.
Important Safety Information (Continued)

Drugs such as Lexiscan® (regadenoson) injection may cause an increase or decrease in blood pressure, especially in patients with certain heart and blood vessel disorders.

Lexiscan can cause breathing difficulties. Before receiving Lexiscan, tell your doctor if you have respiratory diseases, such as COPD (chronic obstructive pulmonary disease) or asthma. Tell your doctor about all medications you use to manage these conditions.
How will the test be monitored?

Your MPI test will be done under the supervision of your heart imaging team, which may consist of a cardiologist, a certified technologist, a radiologist, and/or a registered nurse. In addition to the catheter, electrocardiograph (ECG) leads will be placed on your upper body, and a blood pressure cuff will be used to check your blood pressure. These are all normal monitoring procedures during the test.

What else happens during an MPI test?

To help the tracer move quickly through your body and to your heart, it is necessary to get more blood flowing to your heart. This can often be achieved by walking briskly on a treadmill. This test is known as “exercise stress.” If for any reason you are not able to exercise on the treadmill for your MPI test, your doctor may prescribe a medication that will be given through the catheter to increase blood flow to your heart.

This procedure is called pharmacologic stress, and it’s used millions of times a year to help produce images.

Really? That seems like a lot.

Well, there are any number of reasons why someone may be unable to exercise adequately for an MPI test. Age, obesity, arthritis, diabetes, and even chronic kidney disease can make exercise difficult. If you are unsure of your exercise capability, your doctor may suggest MPI testing with exercise, then switch to pharmacologic stress if deemed necessary and appropriate.

I see. What’s the drug called?

There are a few different pharmacologic stress agents available, but the most commonly used one is called Lexiscan® (regadenoson) injection.
Important Safety Information (Continued)

Lexiscan can increase the risk of seizures. Before receiving Lexiscan, tell your doctor if you have a history of seizures.

Lexiscan can cause stroke, which may be a result of an increase or decrease in blood pressure.

PLEASE SEE ADDITIONAL IMPORTANT SAFETY INFORMATION ON PAGES 16-17.
PLEASE SEE FULL PRESCRIBING INFORMATION AT THE END OF THE DOCUMENT.
Important Safety Information (Continued)

The most common side effects that occurred in clinical trials of Lexiscan were shortness of breath, headache, flushing, chest discomfort or chest pain, dizziness, nausea, abdominal discomfort, a metallic taste in the mouth, and feeling hot. Most common side effects began soon after receiving Lexiscan and went away within 15 minutes except for headache, which resolved in most patients within 30 minutes.
Lexiscan is a prescription drug given through an IV line that increases blood flow through the arteries of the heart during a cardiac nuclear stress test. Lexiscan is given to patients when they are unable to exercise adequately for a stress test.

How will Lexiscan be given?

Well, you may be lying down on a hospital cart or sitting in a chair when you receive Lexiscan. A nurse or other lab professional will inject Lexiscan, and then the tracer, through the catheter that is already in your arm. You'll feel the effects of the Lexiscan almost immediately.

It’s important to understand that, whether you exercise on a treadmill or receive Lexiscan stress, the goal is the same: to increase blood flow to your heart so the tracer is completely distributed throughout your heart for imaging.

What are the most common side effects with Lexiscan?

The most common side effects that occurred in clinical trials of Lexiscan were shortness of breath, headache, flushing, chest discomfort or chest pain, dizziness, nausea, abdominal discomfort, a metallic taste in the mouth, and feeling hot. Most common side effects began soon after receiving Lexiscan and went away within 15 minutes, except for headache, which resolved in most patients within 30 minutes. You will be monitored before and after administration of Lexiscan for any side effects that require treatment.

Such side effects are expected, so be sure to tell the physician or lab personnel how you’re feeling. Remember, these effects usually go away within minutes. After you receive Lexiscan, you’ll be ready for the images to be taken between 1-2 hours later.
What do I need to do during the imaging part of the test?

For the best possible images of your heart, just do your best to relax and stay still. The goal is to be sure you are as comfortable as possible during the procedure. You may still be feeling the effects of Lexiscan® (regadenoson) injection when you’re ready for the images to be taken. This is expected.

During the imaging part of the test, you’ll rest on your back with your arms above your head. The camera will take images of your heart for about 20 to 40 minutes. It’s very important you’re comfortable so you can be as still as possible for the camera to produce the best images. The camera is large, but don’t worry. It won’t touch your body, and it doesn’t hurt.

Important Safety Information (Continued)

Avoid consuming any caffeine-containing foods and beverages or medicines containing caffeine, aminophylline or theophylline in the 12 hours before your scheduled heart scan.

Ask your doctor if you should stop taking any medications you usually take before the day of the test.
You mentioned that there might be 2 sets of images. How does that work?

One set of images will be taken after the treadmill exercise or after you’ve received pharmacologic stress. You may have another set of images taken while you’re at rest. Comparing these 2 sets of images makes it easier for your doctor to see if any parts of your heart are not getting enough blood.

What happens after the test?

A nuclear cardiologist or radiologist will look at the pictures of your heart to look for areas that might not be getting enough blood. They will discuss the images with the doctor who ordered the test, who may be your cardiologist or your primary care doctor. When you meet with your doctor, you'll discuss the test results and decide what steps to take next. These may include some simple lifestyle changes, new medications, or more testing.

Important Safety Information (Continued)

For women who are nursing, pump and discard breast milk for 10 hours after receiving Lexiscan® (regadenoson) injection.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

PLEASE SEE ADDITIONAL IMPORTANT SAFETY INFORMATION ON PAGES 16-17.
PLEASE SEE FULL PRESCRIBING INFORMATION AT THE END OF THE DOCUMENT.
Which foods, drinks, and medications should I avoid before my test?

DO NOT consume caffeine-containing foods and drinks or medications that contain methylxanthines (e.g., caffeine, aminophylline, or theophylline) in the 12 hours before your scheduled stress test in the event that pharmacologic stress is used. In addition, avoid any prescription medications containing dipyridamole in the 48 hours before your stress test.

See Tables 1-3 for a list of some foods, drinks, and drugs to avoid before the test. Remember, it is only a partial list. Your doctor and pharmacist will know about other products, foods, drinks, and medications you shouldn’t have before your test. Be sure to tell your doctor which over-the-counter (OTC) and prescription drugs you’re currently taking. Your doctor will then give you instructions about those medications.

### TABLE 1: FOODS TO AVOID

<table>
<thead>
<tr>
<th>chocolate candies</th>
</tr>
</thead>
<tbody>
<tr>
<td>chocolate cakes</td>
</tr>
<tr>
<td>brownies</td>
</tr>
<tr>
<td>chocolate pudding</td>
</tr>
<tr>
<td>energy bars</td>
</tr>
<tr>
<td>foods containing guarana</td>
</tr>
</tbody>
</table>

### TABLE 2: DRINKS TO AVOID

<table>
<thead>
<tr>
<th>chocolate milk</th>
</tr>
</thead>
<tbody>
<tr>
<td>hot cocoa</td>
</tr>
<tr>
<td>coffee (brewed, instant, iced, decaf)</td>
</tr>
<tr>
<td>tea (brewed, instant, iced, decaf)</td>
</tr>
<tr>
<td>soda pop (including “caffeine-free”)</td>
</tr>
<tr>
<td>energy drinks</td>
</tr>
<tr>
<td>drinks containing guarana</td>
</tr>
</tbody>
</table>
### TABLE 3: MEDICATIONS TO AVOID

<table>
<thead>
<tr>
<th>OTC drugs containing caffeine</th>
<th>Prescription drugs containing caffeine</th>
<th>Prescription drugs containing dipyridamole (withhold for 48 hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anacin® (aspirin, caffeine)</td>
<td>Cafergot® (ergotamine tartrate, caffeine)</td>
<td></td>
</tr>
<tr>
<td>Excedrin® (acetaminophen, aspirin, caffeine)</td>
<td>Esgic® (butalbital, acetaminophen, caffeine)</td>
<td>Aggrenox® (aspirin, dipyridamole)</td>
</tr>
<tr>
<td>Vivarin® (caffeine)</td>
<td>Fioricet® (butalbital, acetaminophen, caffeine)</td>
<td>Persantine® (dipyridamole)</td>
</tr>
<tr>
<td>NoDoz® (caffeine)</td>
<td>Fiorinal® (butalbital, aspirin, caffeine)</td>
<td>Prescription drugs containing theophylline</td>
</tr>
</tbody>
</table>

Elixophylline® (theophylline)  
Theo-24® (theophylline)
Indication

Lexiscan® (regadenoson) injection is a prescription drug given through an IV line that increases blood flow through the arteries of the heart during a cardiac nuclear stress test. Lexiscan is given to patients when they are unable to exercise adequately for a stress test.

Important Safety Information

Lexiscan should not be given to patients who have certain abnormal heart rhythms unless they have a pacemaker.

Lexiscan can cause serious or fatal cardiac arrest, abnormal heart rhythms or heart attack.

Allergic reactions can occur after Lexiscan injection.

Drugs such as Lexiscan may cause an increase or decrease in blood pressure, especially in patients with certain heart and blood vessel disorders.
Important Safety Information (Continued)

Lexiscan can cause breathing difficulties. Before receiving Lexiscan, tell your doctor if you have respiratory diseases, such as COPD (chronic obstructive pulmonary disease) or asthma. Tell your doctor about all medications you use to manage these conditions.

Lexiscan can increase the risk of seizures. Before receiving Lexiscan, tell your doctor if you have a history of seizures.

Lexiscan can cause stroke, which may be a result of an increase or decrease in blood pressure.

The most common side effects that occurred in clinical trials of Lexiscan were shortness of breath, headache, flushing, chest discomfort or chest pain, dizziness, nausea, abdominal discomfort, a metallic taste in the mouth, and feeling hot. Most common side effects began soon after receiving Lexiscan and went away within 15 minutes except for headache, which resolved in most patients within 30 minutes.

Avoid consuming any caffeine-containing foods and beverages or medicines containing caffeine, aminophylline or theophylline in the 12 hours before your scheduled heart scan.

Ask your doctor if you should stop taking any medications you usually take before the day of the test.

For women who are nursing, pump and discard breast milk for 10 hours after receiving Lexiscan.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.
We hope this brochure has helped you get a better understanding of your cardiac nuclear stress test with Lexiscan® (regadenoson) injection.

For more tips on how to prepare for your test, see page 19, which you can print, fill out, and bring with you on the day of your appointment.

Important Safety Information (Continued)

Lexiscan should not be given to patients who have certain abnormal heart rhythms unless they have a pacemaker.

PLEASE SEE ADDITIONAL IMPORTANT SAFETY INFORMATION ON PAGES 16-17.
PLEASE SEE FULL PRESCRIBING INFORMATION AT THE END OF THE DOCUMENT.
Okay, I think I understand the test. So what should I do to prepare for it?

Glad you asked! Be sure to read and understand the following steps to take **BEFORE** the day of your test:

- Ask your doctor if you should follow any dietary restrictions before your test
- Ask your doctor if you should stop taking any medications you usually take before the day of the test
- If you have diabetes and use insulin or oral diabetes medications, ask your doctor for special instructions
- Tell your doctor if you have a history of wheezing, asthma, or chronic lung disease
- Tell your doctor if you have a history of seizures

**Methylxanthines interfere with the activity of pharmacologic stress agents.** DO NOT consume foods, drinks, or medications that contain methylxanthines (eg, caffeine, aminophylline, or theophylline) for **at least 12 hours before the test in the event that a pharmacologic stress agent will be administered**; one easy way to remember this is: “**12 hours or less, no pharm stress.**” Some medications containing certain ingredients should also be avoided; see the tables on pages 14 and 15 for products you should avoid.

- DO NOT apply creams, lotions, or powder to your chest area on the day of the test
- Wear comfortable clothing and shoes
The information in this booklet is only a starting point. Be sure to talk with your doctor. If you have questions, please talk with all of your healthcare providers.

Presented by:

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Lexiscan was developed in collaboration with Gilead Palo Alto, Inc. (formerly CV Therapeutics, Inc.).

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Lexiscan® (regadenoson) injection for intravenous use

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LEXISCAN® safely and effectively. See full prescribing information for LEXISCAN®. LEXISCAN® (regadenoson) injection for intravenous use

Initial U.S. Approval: 2008

Dosage and Administration (2)  5/2018

INDICATIONS AND USAGE

LEXISCAN® is a pharmacologic stress agent indicated for radionuclide myocardial perfusion imaging (MPI) in patients unable to undergo adequate exercise stress (1).

DOSE AND ADMINISTRATION

The recommended dose of LEXISCAN is 5 mL (0.4 mg regadenoson) administered as an intravenous injection within 10 seconds; followed immediately by saline flush and radiopharmaceutical (2).

DOSE FORMS AND STRENGTHS

Injection: Single-dose pre-filled syringe: 0.4 mg/5 mL (0.08 mg/mL) (3).

CONTRAINDICATIONS

Do not administer LEXISCAN to patients with:

• Second- or third-degree AV block, or

• sinus node dysfunction

unless the patients have a functioning artificial pacemaker (4).

WARNINGS AND PRECAUTIONS

• Myocardial Ischemia. Fatal cardiac events have occurred. Avoid use in patients with symptoms or signs of acute myocardial ischemia, for example unstable angina or cardiovascular instability, who may be at greater risk. Cardiac resuscitation equipment and trained staff should be available before administration (5.1).

• Sinusoidal (SA) and Atrioventricular (AV) Nodal Block. Adenosine receptor agonists, including LEXISCAN, can depress AV nodes and may cause first-, second- or third-degree AV block, or sinus bradycardia (5.2).

• Atrial Fibrillation/Atrial Flutter. New-onset or recurrent atrial fibrillation with rapid ventricular response and atrial flutter have been reported (5.3).

• Hypersensitivity, including anaphylaxis, angioedema, cardiac or respiratory arrest, respiratory distress, decreased oxygen saturation, hypotension, throat tightness, urticaria, and rashes have occurred. Have personnel and resuscitative equipment immediately available (5.4).

• Hypotension. Adenosine receptor agonists, including LEXISCAN, induce vasodilation and hypotension. The risk of serious hypotension may be higher in patients with autonomic dysfunction, systolic or diastolic blood pressure (COPD) or asthma. Resuscitative measures should be available (5.5).

• Hypertension. Adenosine receptor agonists, including LEXISCAN, may induce clinically significant increases in blood pressure particularly in patients with a history of hypertension and when the MPI includes low level exercise (5.6).

• Bronchocostriction. Adenosine receptor agonists, including LEXISCAN, may induce dyspnea, bronchoconstriction and respiratory compromise in patients with chronic obstructive pulmonary disease (COPD) or asthma. Resuscitative measures should be available (5.7).

• Seizure. LEXISCAN may lower the seizure threshold. New onset or recurrence of convulsive seizures has occurred. Some seizures are prolonged and require urgent anticonvulsive management. Methylxanthine use is not recommended in patients who experience a seizure in association with LEXISCAN (5.8).

• Cerebrovascular Accident (Stroke). Hemorrhagic and ischemic cerebrovascular accidents have occurred (5.9).

ADVERSE REACTIONS

The most common (incidence ≥ 5%) adverse reactions to LEXISCAN are dyspnea, headache, flushing, chest discomfort, dizziness, angina pectoris, chest pain, and nausea (6).

See 17 for PATIENT COUNSELING INFORMATION.

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4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

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5.3 Atrial Fibrillation/Atrial Flutter

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

LEXISCAN® (regadenoson) injection is a pharmacologic stress agent indicated for radionuclide myocardial perfusion imaging (MPI) in patients unable to undergo adequate exercise stress.

2 DOSAGE AND ADMINISTRATION

The recommended dose of LEXISCAN is 5 mL (0.4 mg regadenoson) administered as an intravenous injection within 10 seconds.

• Patients should be instructed to avoid consumption of any products containing methylxanthines, including caffeinated coffee, tea or other caffeinated beverages, caffeinated drug products, aminophylline and theophylline for at least 12 hours before a scheduled radionuclide MPI [see Drug Interactions (7.1) and Clinical Pharmacology (12.2)].

• Patients and drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not administer LEXISCAN if it contains particulate matter or is discolored. Administer LEXISCAN as an intravenous injection within 10 seconds into a peripheral vein using a 22 gauge or larger catheter or needle.

• Administer a 5 mL saline flush immediately after the injection of LEXISCAN.

• Administer the radionuclide myocardial perfusion imaging agent 10–20 seconds after the saline flush. The radionuclide may be injected directly into the same catheter as LEXISCAN.

3 DOSAGE FORMS AND STRENGTHS

• Single-dose pre-filled syringe: clear, colorless solution containing regadenoson 0.4 mg/5 mL (0.08 mg/mL).

4 CONTRAINDICATIONS

Do not administer LEXISCAN to patients with:

• Second- or third-degree AV block, or

• sinus node dysfunction

unless these patients have a functioning artificial pacemaker [see Warnings and Precautions (5.2)].

5 WARNINGS AND PRECAUTIONS

5.1 Myocardial Ischemia

Fatal and nonfatal myocardial infarction (MI), ventricular arrhythmias, and cardiac arrest have occurred following LEXISCAN injection. Avoid use in patients with symptoms or signs of acute myocardial ischemia, for example unstable angina or cardiovascular instability; these patients may be at greater risk of serious cardiovascular reactions to LEXISCAN. Cardiac resuscitation equipment and trained staff should be available before administering LEXISCAN. Adhere to recommendations in duration of injection [see Dosage and Administration (2)]. As noted in an animal study, longer injection times may increase the duration and magnitude of increase in coronary blood flow [see Clinical Pharmacology (12.2)]. If serious reactions to LEXISCAN occur, consider the use of aminophylline, an adenosine antagonist, to shorten the duration of increased coronary blood flow induced by LEXISCAN [see Overdosage (10)].

5.2 Sinusoidal and Atrioventricular Nodal Block

Adenosine receptor agonists, including LEXISCAN, can depress the SA and AV nodes and may cause first-, second- or third-degree AV block, or sinus bradycardia requiring intervention. In clinical trials first-degree AV block (PR prolongation > 200 msec) developed in 8% of patients within 2 hours of LEXISCAN administration; transient second-degree AV block with one dropped beat was observed in one patient receiving LEXISCAN. In post-marketing experience, third-degree heart block and asystole within minutes of LEXISCAN administration have occurred [see Adverse Reactions (6.2)].

5.3 Atrial Fibrillation/Atrial Flutter

New-onset or recurrent atrial fibrillation with rapid ventricular response and atrial flutter have been reported following LEXISCAN injection [see Adverse Reactions (6.2)].

5.4 Hypersensitivity, Including Anaphylaxis

Anaphylaxis, angioedema, cardiac or respiratory arrest, respiratory distress, decreased oxygen saturation, hypotension, throat tightness, urticaria and rashes have occurred. In clinical trials, hypersensitivity reactions were reported in fewer than 1 percent of patients [see Adverse Reactions (6.1)]. Have personnel and resuscitative equipment immediately available.

5.5 Hypotension

Adenosine receptor agonists, including LEXISCAN, induce arterial vasodilation and hypotension. In clinical trials, decreased systolic blood pressure (> 35 mm Hg) was observed in 4% of patients within 45 minutes of LEXISCAN administration. The risk of serious hypotension may be higher in patients with autonomic dysfunction, hypovolemia, left main coronary artery stenosis, spinal or collateral arterial disease with cerebrovascular insufficiency, in post-marketing experience, syncope, transient ischemic attacks and seizures have been observed [see Adverse Reactions (6.2)].
5.6 Hypertension

Administration of adenosine receptor agonists, including LEXISCAN, may result in clinically significant increases in blood pressure in some patients. Among patients who experienced an increase in blood pressure in clinical trials, the increase was observed within minutes of LEXISCAN administration. Most increases resolved within 10 to 15 minutes, but in some cases, increases were observed at 45 minutes following administration [see Clinical Pharmacology (12.2)]. In post-marketing experience, cases of potentially clinically significant hypertension have been reported particularly with underlying hypertension and when low-level exercise was included in the MPI [see Adverse Reactions (6.2)].

5.7 Bronchoconstriction

Adenosine receptor agonists, including LEXISCAN, may cause dyspnea, bronchoconstriction, and respiratory compromise. Appropriate bronchodilator therapy and resuscitative measures should be available prior to and following LEXISCAN administration [see Warnings and Precautions (5.9) and (6.1)]. Overdosage should be available prior to and following LEXISCAN administration [see Warnings and Precautions (5.8)].

5.8 Seizure

LEXISCAN may lower the seizure threshold; obtain a seizure history. New-onset or recurrence of convulsive seizures has occurred following LEXISCAN injection. Some seizures are prolonged and require emergent anticonvulsive management. Aminophylline may increase the risk of seizures associated with LEXISCAN injection. Methyldihthazine use is not recommended in patients who experience a seizure in association with LEXISCAN administration.

5.9 Cerebrovascular Accident (Stroke)

Hemorrhagic and ischemic cerebrovascular accidents have occurred. Hemodynamic effects of LEXISCAN including hypotension or hypertension may be associated with these adverse reactions [see Warnings and Precautions (5.5) and (5.6)].

6. ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling.

- Myocardial Ischemia [see Warnings and Precautions (5.1)]
- Sinoatrial and Atrioventricular Nodal Block [see Warnings and Precautions (5.2)]
- Atrial Fibrillation/Atrial Flutter [see Warnings and Precautions (5.3)]
- Hypersensitivity, including Anaphylaxis [see Warnings and Precautions (5.4)]
- Hypotension [see Warnings and Precautions (5.5)]
- Hypertension [see Warnings and Precautions (5.6)]
- Bronchoconstriction [see Warnings and Precautions (5.7)]
- Seizure [see Warnings and Precautions (5.8)]
- Cerebrovascular Accident (Stroke) [see Warnings and Precautions (5.9)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

During clinical development, 1,651 patients were exposed to LEXISCAN, with most receiving 0.4 mg as a rapid (≤ 10 seconds) intravenous injection. Most of these patients received LEXISCAN in two clinical studies that enrolled patients who had no history of bronchospastic disease. In these studies (Studies 1 and 2), 2,015 patients underwent myocardial perfusion imaging after administration of LEXISCAN (N = 1,337) or ADENOSCAN (N = 678). The population was 26–93 years of age (median 68 years), 76% male and primarily Caucasian (76% Caucasian, 7% African American, 9% Hispanic, 5% Asian). Table 1 shows the most frequently reported adverse reactions.

Table 1 Adverse Reactions in Studies 1 and 2 Pooled (Frequency ≥ 5%)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>LEXISCAN N = 1,337</th>
<th>ADENOSCAN N = 678</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>28%</td>
<td>26%</td>
</tr>
<tr>
<td>Headache</td>
<td>26%</td>
<td>17%</td>
</tr>
<tr>
<td>Flushing</td>
<td>16%</td>
<td>25%</td>
</tr>
<tr>
<td>Chest Discomfort</td>
<td>13%</td>
<td>18%</td>
</tr>
<tr>
<td>Angina Pectoris or ST Segment Depression</td>
<td>12%</td>
<td>18%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>8%</td>
<td>7%</td>
</tr>
<tr>
<td>Chest Pain</td>
<td>7%</td>
<td>10%</td>
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<tr>
<td>Nausea</td>
<td>6%</td>
<td>6%</td>
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<tr>
<td>Abdominal Discomfort</td>
<td>5%</td>
<td>2%</td>
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<tr>
<td>Dysuria</td>
<td>5%</td>
<td>7%</td>
</tr>
<tr>
<td>Feeling Hot</td>
<td>5%</td>
<td>8%</td>
</tr>
</tbody>
</table>

The frequency of rhythm or conduction abnormalities following LEXISCAN or ADENOSCAN is shown in Table 2 [see Warnings and Precautions (5.2)].

Table 2 Rhythm or Conduction Abnormalities in Studies 1 and 2

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>LEXISCAN N = 1,337</th>
<th>ADENOSCAN N = 678</th>
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</thead>
<tbody>
<tr>
<td>Sinus Bradycardia</td>
<td>332/1275 (26%)</td>
<td>192/645 (30%)</td>
</tr>
<tr>
<td>Sinus Arrhythmia</td>
<td>260/1275 (20%)</td>
<td>131/645 (20%)</td>
</tr>
<tr>
<td>PACs</td>
<td>68/1274 (5.1%)</td>
<td>57/645 (9%)</td>
</tr>
<tr>
<td>PVCs</td>
<td>17/1274 (1.4%)</td>
<td>2/645 (0.4%)</td>
</tr>
<tr>
<td>First-degree AV block (PR prolongation &gt; 220 msec)</td>
<td>34/1209 (3%)</td>
<td>43/618 (7%)</td>
</tr>
<tr>
<td>Second-degree AV block</td>
<td>1/1209 (0.1%)</td>
<td>9/618 (1.5%)</td>
</tr>
<tr>
<td>AV conduction abnormalities (other than AV blocks)</td>
<td>1/1209 (0.1%)</td>
<td>0/618 (0%)</td>
</tr>
<tr>
<td>Ventricular conduction abnormalities</td>
<td>64/1152 (5.6%)</td>
<td>31/581 (5.3%)</td>
</tr>
</tbody>
</table>

+ 12-lead ECGs were recorded before and for up to 2 hours after dosing.
+ Includes rhythm abnormalities (PACs, PVCs, atrial fibrillation/flutter, wandering atrial pacemaker, supraventricular or ventricular arrhythmias) or conduction abnormalities, including AV block.

6.2 Post-Marketing Experience

The following adverse reactions have been reported from worldwide marketing experience with regadenoson. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiovascular

Myocardial infarction, cardiac arrest, ventricular arrhythmias, supraventricular tachyarhythmias including atrial fibrillation with rapid ventricular response (new-onset or recurrent), atrial flutter, heart block (including third-degree block), asystole, marked hypertension, symptomatic hypotension in association with transient ischemic attack, acute coronary syndrome (ACS), seizures and syncope [see Warnings and Precautions (5.1), (5.2), (5.3), (5.5), (5.6) and (5.8)], have been reported. Some events required intervention with fluids and/or aminophylline [see Overdosage (10)]. QTc prolongation shortly after LEXISCAN administration has been reported.

Central Nervous System

Fremor, seizure, transient ischemic attack, and cerebrovascular accident including intracranial hemorrhage [see Warnings and Precautions (5.8) and (5.9)].

Gastrointestinal

Abdominal pain, occasionally severe, has been reported a few minutes after LEXISCAN administration, in association with nausea, vomiting, or myalgias; administration of aminophylline, an adenosine antagonist, appeared to lessen the pain. Diarrhea and fecal incontinence have also been reported following LEXISCAN administration.

Hypersensitivity

Anaphylaxis, angioedema, cardiac or respiratory arrest, respiratory distress, decreased oxygen saturation, hypotension, throat tightness, urticaria, rash have occurred and have required treatment including resuscitation [see Warnings and Precautions (5.4)].

Table 3 Respiratory Adverse Effects

<table>
<thead>
<tr>
<th>Asthma Cohort</th>
<th>Chronic Obstructive Pulmonary Disease (COPD) Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEXISCAN</td>
<td>Placebo</td>
</tr>
<tr>
<td>N = 356</td>
<td>N = 176</td>
</tr>
<tr>
<td>Dypnea</td>
<td>12.9%</td>
</tr>
<tr>
<td>10.7%</td>
<td>12.3%</td>
</tr>
<tr>
<td>13.8%</td>
<td>19.0%</td>
</tr>
<tr>
<td>18.0%</td>
<td>4.0%</td>
</tr>
</tbody>
</table>

Table 4 Cardiac Events of Interest in Inadequate Exercise Stress Study

<table>
<thead>
<tr>
<th>Group 1 / MPI 1</th>
<th>Group 2 / MPI 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEXISCAN 3 minutes following exercise</td>
<td>LEXISCAN 1 hour following exercise</td>
</tr>
<tr>
<td>Cardiac Event *</td>
<td>Placebo (N=575)</td>
</tr>
<tr>
<td>Holter/12-Lead ECG Abnormality</td>
<td>17 (3.0%)</td>
</tr>
<tr>
<td>ST-T Depression (≥ 2 mm)</td>
<td>13 (2.3%)</td>
</tr>
<tr>
<td>ST-T Elevation (≥ 2 mm)</td>
<td>3 (0.5%)</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1 (0.2%)</td>
</tr>
</tbody>
</table>

* A clinically significant cardiac event was defined as any of the following events found on the Holter/12-lead ECG within one hour after regadenoson administration: ventricular arrhythmias (sustained ventricular tachycardia, ventricular tachypalpitation, torsades de Points, ventricular flutter); ST-T depression (≥ 2 mm); ST-T elevation (≥ 2 mm); AV block (2:1 AV block, AV Mobitz I, AV Mobitz II, complete heart block); sinus arrest > 3 seconds in duration or:

- a Treatment Emergent Adverse Event (TEAE) per the MedDRA SMG (narrow Scope) for myocardial infarction
- or a TEAE preferred term (PT) of angina unstable within 24 hours of regadenoson administration.

6.3 Respiratory Adverse Reactions

In a randomized, placebo-controlled trial of 999 patients with asthma (n = 532) or stable chronic obstructive pulmonary disease (n = 467), the overall incidence of pre-specified respiratory adverse reactions was greater in the LEXISCAN group compared to the placebo group (p < 0.001). Most respiratory adverse reactions resolved without therapy; a few patients received aminophylline or a short-acting bronchodilator. No differences were observed between treatment arms in the reduction of >15% from baseline at two-hours in FEV1 (Table 3).
Musculoskeletal
Musculoskeletal pain has occurred, typically 10-20 minutes after LEXISCAN administration; the pain was occasionally severe, localized in the arms and lower back and extended to the buttocks and lower legs bilaterally. Administration of aminophylline appeared to lessen the pain.

Respiratory
Respiratory arrest, dyspnea and wheezing have been reported following LEXISCAN administration.

7 DRUG INTERACTIONS

No formal pharmacokinetic drug interaction studies have been conducted with LEXISCAN.

7.1 Effects of Other Drugs on LEXISCAN

- Methylxanthines (e.g., caffeine, aminophylline and theophylline) are non-specific adenosine receptor antagonists that interfere with the vasodilatory activity of LEXISCAN [see Clinical Pharmacology (12.2) and Patient Counseling Information (17)]. Patients should avoid consumption of any products containing methylxanthines as well as any drugs containing theophylline or aminophylline for at least 12 hours before LEXISCAN administration. Aminophylline may be used to attenuate severe or persistent adverse reactions to LEXISCAN [see Overdosage (10)].

- In clinical studies, LEXISCAN was administered to patients taking other cardioactive drugs (i.e., β-blockers, calcium channel blockers, ACE inhibitors, nitrates, cardiac glycosides, and angioedema receptor blockers) without reported adverse reactions or apparent effects on efficacy.

- Dipryridamole may change the pharmacokinetics of LEXISCAN. We have not studied possible, withhold dipryridamole for at least two days prior to LEXISCAN administration.

7.2 Effect of LEXISCAN on Other Drugs

Regadenoson does not inhibit the metabolism of substrates for CYP1A2, CYP3A4, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 in human liver microsomes, indicating that it is unlikely to alter the pharmacokinetics of drugs metabolized by these cytochrome P450 enzymes.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on LEXISCAN use in pregnant women to inform a drug-associated risk. In animal reproduction studies, adverse developmental outcomes were observed with the administration of regadenoson to pregnant rats and rabbits during organogenesis only at doses that produced maternal toxicity (see Data).

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. Data

Animal Data

Reproductive studies in rats showed that regadenoson doses 10 and 20 times the maximum recommended human dose (MRHD) based on body surface area caused reduced fetal body weights and reduced fetal body weights and delays in fore- and hind limb phalanges and metatarsals; maternal toxicity also occurred at these doses. Skeletal variations were increased in all treated groups. In rabbits, maternal toxicity occurred at regadenoson doses administered during organogenesis 4-8 times the MRHD; however, there were no teratogenic effects in offspring at this dose. At higher doses, 12 and 20 times the MRHD, maternal toxicity occurred along with increased embryo-fetal loss and fetal malformations.

8.2 Lactation

Risk Summary

There is no information on the presence of regadenoson in human milk, the effects on the breastfed infant, or the effects on milk production. Because of the potential risk of serious cardiac reactions in the nursing infant, advise the nursing mother to pump and discard breast milk for 10 hours after administration of LEXISCAN.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the 1,337 patients receiving LEXISCAN in Studies 1 and 2, 56% were 65 years of age and over and 24% were 75 years of age and over. Older patients (≥75 years of age) had a similar adverse event profile compared to younger patients (<65 years of age), but had a higher incidence of hypotension (2% vs. ≤1%).

8.6 Renal Impairment

No dose adjustment is needed in patients with renal impairment including patients with end stage renal disease and/or dependent on dialysis [see Pharmacokinetics (12.3)].

10 OVERDOSAGE

LEXISCAN overdosage may result in serious reactions [see Warnings and Precautions (5)]. In a study of healthy volunteers, symptoms of flushing, dizziness and increased heart rate were assessed as intolerable at LEXISCAN doses greater than 0.02 mg/kg. Aminophylline to Reverse Effects

Methylxanthines, such as caffeine, aminophylline, and theophylline, are competitive inhibitors of adenosine receptors.

Effect of duration of injection

In a clinical study, LEXISCAN was administered for MPI following inadequate exercise stress. Ingestion of caffeine decreases the ability to detect reversible ischemic defects. In a placebo-controlled, parallel group clinical study, patients with known or suspected myocardial ischemia who received a baseline rest/stress MPI followed by a second stress MPI. Patients received caffeine or placebo 90 minutes before the second LEXISCAN stress MPI. The decrease was statistically significant [see Drug Interactions (7.1) and Patient Counseling Information (17)].

Adverse reactions. Maximum hemodynamic changes after LEXISCAN and ADENOSCAN in Studies 1 and 2 are summarized in Table 5.

<table>
<thead>
<tr>
<th>Vital Sign Parameter</th>
<th>LEXISCAN N = 1,337</th>
<th>ADENOSCAN N = 678</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 100 bpm</td>
<td>22%</td>
<td>13%</td>
</tr>
<tr>
<td>Increase &gt; 40 bpm</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Systolic Blood Pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 90 mm Hg</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Decrease &gt; 35 mm Hg</td>
<td>7%</td>
<td>8%</td>
</tr>
<tr>
<td>&gt; 20 mm Hg</td>
<td>1.9%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Increase &gt; 50 mm Hg</td>
<td>0.7%</td>
<td>0.8%</td>
</tr>
<tr>
<td>≥ 180 mm Hg and increase of</td>
<td>4.6%</td>
<td>3.2%</td>
</tr>
<tr>
<td>20 mm Hg from baseline</td>
<td>0.5%</td>
<td>1.1%</td>
</tr>
</tbody>
</table>

Diastolic Blood Pressure

<table>
<thead>
<tr>
<th>Vital Sign Parameter</th>
<th>LEXISCAN N = 1,337</th>
<th>ADENOSCAN N = 678</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50 mm Hg</td>
<td>2%</td>
<td>4%</td>
</tr>
<tr>
<td>Decrease &gt; 25 mm Hg</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>≥ 115 mm Hg</td>
<td>0.9%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Increase &gt; 30 mm Hg</td>
<td>0.5%</td>
<td>1.1%</td>
</tr>
</tbody>
</table>

Hemodynamic Effects Following Inadequate Exercise

In a clinical study, LEXISCAN was administered for MPI following inadequate exercise stress. More patients with LEXISCAN administration three minutes following inadequate exercise stress had an increase in heart rate and a decrease in systolic blood pressure compared with LEXISCAN administered at rest. The changes were not associated with any clinically significant adverse reactions. Maximum hemodynamic changes are presented in Table 6.

<table>
<thead>
<tr>
<th>Vital Sign Parameter</th>
<th>LEXISCAN 3 minutes following exercise (N=90)</th>
<th>LEXISCAN 1 hour following exercise (N=363)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 100 bpm</td>
<td>44%</td>
<td>31%</td>
</tr>
<tr>
<td>Increase &gt; 40 bpm</td>
<td>5%</td>
<td>16%</td>
</tr>
<tr>
<td>Systolic Blood Pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 90 mm Hg</td>
<td>2%</td>
<td>4%</td>
</tr>
<tr>
<td>Decrease &gt; 35 mm Hg</td>
<td>29%</td>
<td>10%</td>
</tr>
<tr>
<td>≥ 200 mm Hg</td>
<td>0.9%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Increase ≥ 50 mm Hg</td>
<td>2%</td>
<td>0.4%</td>
</tr>
<tr>
<td>≥ 180 mm Hg and increase of</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td>20 mm Hg from baseline</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Each patient received an initial stress scan using ADENOSCAN (6-minute infusion using a dose of 0.14 mg/kg/min, without exercise) with a radioisotope gated SPECT imaging protocol. After the initial scan, patients were randomized to either LEXISCAN or ADENOSCAN, and received a second stress scan with the same radionuclide imaging protocol that was used for the initial scan. The median time between scans was 7 days (range of 1–104 days).

The most common cardiovascular histories included hypertension (81%), CAGB, PTCA or stenting (51%), angina (63%), and history of myocardial infarction (41%) or arrhythmia (33%); overall, 75% of this study included diabetes (32%) and COPD (5%). Patients with a recent history of serious uncontrolled ventricular arrhythmia, myocardial infarction, or unstable angina, a history of greater than first-degree AV block, or with symptomatic bradycardia, sick sinus syndrome, or a history of any other serious arrhythmia were not eligible for participation. Adequate exercise was defined as ≥ 85% maximum predicted heart rate or ≥ 5 METS. Spect MPI was performed 60–90 minutes after LEXISCAN administration in all patients after an initial stress scan (MPI 1). Patients returned 1–14 days later to undergo a second stress MPI with LEXISCAN without exercise (MPI 2).

All patients were referred for evaluation of coronary artery disease. Of the 1,147 patients randomized, a total of 1,073 patients received LEXISCAN and had interpretable SPECT scans at all visits; 538 in Group 1 and 535 in Group 2. The median age of the patients was 62 years (range 28 to 90 years) and included 633 (59%) men and 440 (41%) women. Images from MPI 1 and MPI 2 for the two groups were compared for presence or absence of perfusion defects. The level of agreement between the MPI 1 and the MPI 2 reads in Group 1 was similar to the level of agreement between MPI 1 and MPI 2 reads in Group 2. However, two patients receiving LEXISCAN 3 minutes following inadequate exercise experienced a serious cardiac adverse reaction. No serious cardiac adverse reactions occurred in patients receiving LEXISCAN 1 hour following inadequate exercise stress [see Adverse Reactions (6.1), Clinical Pharmacology (12.2)].

17 PATIENT COUNSELING INFORMATION

Drug Interaction

Patients should be instructed to avoid consumption of any products containing methylxanthines, including decaffeinated coffee, tea or other caffeinated beverages, caffeine-containing drug products, aminophylline and theophylline for at least 12 hours before a scheduled radionuclide MPI [see Warnings and Precautions (5.8) and Clinical Pharmacology (12.2)].

18 HOW SUPPLIED/STORAGE AND HANDLING

LEXISCAN is supplied as a sterile, preservative-free solution containing 0.08 mg/mL regadenoson in the following package:

• Single-dose 5 mL pre-filled plastic Ansyr® syringes with luer-lock fitting

Store at controlled room temperature, 25°C (77°F); excursions permitted to 15° to 30°C (59° – 86°F).

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Use of LEXISCAN in Patients with Inadequate Exercise Stress

The efficacy and safety of LEXISCAN administered 3 minutes (Group 1) or 1 hour (Group 2) following inadequate exercise stress were evaluated in an open-label, randomized, multi-center, non-inferiority study. Adequate exercise was defined as ≥ 85% maximum predicted heart rate and ≥ 5 METS. SPECT MPI was performed 60-90 minutes after LEXISCAN administration in all patients after an initial stress scan (MPI 1). Patients returned 1-14 days later to undergo a second stress MPI with LEXISCAN without exercise (MPI 2).

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