**SAFETY CONSIDERATIONS**

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.

**Myocardial Ischemia:** Fatal and nonfatal myocardial infarction, 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. 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.

**Sinoatrial 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 postmarketing experience, heart block (including third degree), and asystole within minutes of Lexiscan administration have occurred.

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Background

Pharmacologic Stress Radionuclide Myocardial Perfusion Imaging

Single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) performed during stress and at rest is an established method for diagnosing coronary artery disease (CAD), assessing risk of future cardiac events, and informing treatment decisions. While exercise to at least 85% of target heart rate is the preferred method of stress for MPI, many patients cannot exercise adequately due to deconditioning or comorbidities that limit their mobility. For these patients, pharmacologic stress may be used to mimic the effects of exercise on coronary blood flow. The current ACC/AHA/ASNC Guidelines for the Clinical Use of Cardiac Radionuclide Imaging recommend its use in patients with an intermediate- to high-pretest likelihood of CAD who are unable to exercise to:

- Identify the extent, severity, and location of ischemia
- Assess the functional significance of intermediate (25% to 75%) coronary lesions
- Evaluate selected, high-risk patients at 3 to 5 years after revascularization
- Evaluate other high-risk patients (diabetes mellitus or >20% 10-year risk)

Research and Advances in Pharmacologic Stress MPI

While vasodilator pharmacologic stress SPECT MPI is an established method of noninvasive cardiac imaging, there are several logistical and clinical issues that can complicate the procedure. The administration of infused pharmacologic stress agents requires calculation of dose based on patient weight, infusion pump programming, and the coordination of stress infusion with radiotracer injection while monitoring for potential side effects. Researchers continually search for vasodilatory pharmacologic stress agents that are more selective and will simplify the MPI procedure.

Clinical and logistical factors in pharmacologic stress MPI

- Screen for contraindications
- Calculate weight-adjusted dose of agent
- Draw up dose
- Program pump
- Administer continuous infusion
- Monitor for side effects during infusion
- Administer radiotracer based on infusion time or ischemic endpoints
- Monitor patient postprocedure and treat side effects
There are 4 types of adenosine receptors—A1, A2A, A2B, and A3—located in various tissues throughout the body. The A1 and A2 receptors mediate the known cardiovascular effects of adenosine. Specifically, the A2A adenosine receptor has been shown to mediate coronary vasodilation.

Receptor Affinity

The potency of an agonist is determined in part by its affinity, defined as the attractive force between certain atoms or molecules, in this case, the pharmacologic stress agent and its receptor. A high-affinity agonist binds readily to its receptor and remains bound, eliciting a prolonged response, whereas a low-affinity agonist binds less tightly to its receptor and disassociates quickly, causing a physiologic response that terminates rapidly.
The A2A Adenosine Receptor Reserve

Physiologic response to A2A adenosine receptor activation is determined in part by the tissue distribution of the receptor, the ability of a particular agonist to activate the receptor, and the efficiency of coupling of receptor activation to the response.7 In the coronary arteries, there is a high density of A2A adenosine receptors called a receptor reserve, and activation of a fraction of receptors is needed to achieve maximal coronary vasodilation.7

Lexiscan is a pharmacologic stress agent indicated for radionuclide MPI in patients unable to undergo adequate exercise stress.8 Lexiscan is a modified form of the adenosine molecule with an additional side chain.8,9 Activation of the A2A adenosine receptor by Lexiscan produces coronary vasodilation and increases coronary blood flow.8
**MECHANISM OF ACTION**

**A<sub>2A</sub> Adenosine Receptor Affinity**

The affinity of Lexiscan for the A<sub>2A</sub> adenosine receptor determines, in part, the duration of coronary vasodilation. Lexiscan is a low-affinity (K<sub>i</sub> ≈ 1.3 μM) A<sub>2A</sub> adenosine receptor agonist, with at least 10-fold lower affinity for the A<sub>1</sub> adenosine receptor (K<sub>i</sub> > 16.5 μM), and weak, if any, affinity for the A<sub>2B</sub> and A<sub>3</sub> adenosine receptors. In the context of the A<sub>2A</sub> adenosine receptor reserve in the coronary arteries, a selective, low-affinity A<sub>2A</sub> adenosine receptor agonist like Lexiscan can elicit a full and potent increase in coronary blood flow. The effect of Lexiscan on coronary blood flow (a rapid increase to ≥ 2.5-fold baseline) is sustained for approximately 2.3 minutes, and decreases to less than twice the baseline level within 10 minutes. (Subjects with decompensated congestive heart failure or severe left ventricular dysfunction [ejection fraction < 35%] were excluded; therefore, the effects on these patients cannot be concluded from these data.) Thus, the combination of low affinity for the A<sub>2A</sub> adenosine receptor and the presence of a coronary artery A<sub>2A</sub> adenosine receptor reserve allows Lexiscan to rapidly induce and sustain maximal coronary blood flow to conduct stress radionuclide MPI.

---

**Pharmacokinetic Influence**

In healthy subjects, the plasma concentration of Lexiscan reaches a peak 1-4 minutes after injection and parallels the onset of the pharmacodynamic response to produce a rapid increase in blood flow, and then decreases in 3 phases:

- **In the initial phase, the half-life is 2-4 minutes**
- **In the intermediate phase, the plasma concentration of Lexiscan decreases more slowly (half-life of ≈ 30 minutes), coinciding with loss of pharmacodynamic effect**
- **In the final phase, clearance of Lexiscan from the plasma continues to slow (half-life of ≈ 2 hours)**

In addition to receptor affinity, the duration of the pharmacologic effect of Lexiscan is also a function of the concentration at the receptor site over time. For a complete description of the pharmacokinetic profile of Lexiscan, see page 26.

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**SAFETY CONSIDERATIONS**

**Bronchoconstriction:** Adenosine receptor agonists, including Lexiscan, may cause dyspnea, bronchoconstriction and respiratory compromise. Appropriate bronchodilator therapy and resuscitative measures should be available prior to Lexiscan administration.

**Please see important safety information on pages 29 and 30. Please see attached full prescribing information for Lexiscan on pages 33-45.**
DOSING AND ADMINISTRATION

Based on data from phase 2 trials, the recommended intravenous (IV) dose of Lexiscan is 5 mL (0.4 mg). No dose adjustment is needed to account for body weight. In a population pharmacokinetic analysis, body weight and body mass index (BMI) were not found to have a significant effect on the pharmacokinetics of Lexiscan. Lexiscan comes in a prefilled syringe and is administered as a rapid injection (approximately 10 seconds) into a peripheral vein using a 22-gauge or larger catheter or needle. The injection of Lexiscan is immediately followed by a 5-mL saline flush over approximately 10 seconds, and the radiotracer is administered 10-20 seconds after the saline flush.

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</table>
| **LEXISCAN OFFERS PUMP-FREE, STANDARD-DOSE, IV-INJECTION ADMINISTRATION AND FAST PROTOCOLS—**
| STRESS AGENT AND RADIOTRACER ADMINISTERED IN 1 MINUTE. |

SAFETY CONSIDERATIONS

Aminophylline may be administered in doses ranging from 50 mg to 250 mg by slow IV injection (50 mg to 100 mg over 30-60 seconds) to attenuate severe and/or persistent adverse reactions to Lexiscan.

**Dosing and administration of Lexiscan**

- **INJECT LEXISCAN**: (0.4-mg/5-mL IV injection for ≈10 seconds)
- **SALINE FLUSH**: (5 mL over ≈10 seconds)
- **INJECT RADIOTRACER**: (10-20 seconds after flush)

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<th>7</th>
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</tr>
</thead>
</table>
| **DIPYRIDAMOLE**
| (0.142-mg/kg/min IV infusion) |

**Dosing and administration of Adenoscan**

- **INFUSE ADENOSCAN**: (140-mcg/kg/min IV infusion)
- **INJECT THALLIUM-201**

<table>
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<th>6</th>
<th>7</th>
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<th>10</th>
</tr>
</thead>
</table>
| **ADENOSCAN**
| (0.142-mg/kg/min IV infusion) |

**Dosing and administration of dipyridamole**

- **INFUSE DIPYRIDAMOLE**: (0.142-mg/kg/min IV infusion)
- **INJECT THALLIUM-201**: (within 5 minutes of infusion)

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<th>MINUTE</th>
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<th>8</th>
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<th>10</th>
</tr>
</thead>
</table>
| **DIPYRIDAMOLE**
| (0.142-mg/kg/min IV infusion) |

Dosage information and administration schedule for dipyridamole is based on package insert, Irvine, CA: Sicor Pharmaceuticals, Inc. No other comparison is implied.

PLEASE SEE IMPORTANT SAFETY INFORMATION ON PAGES 29 AND 30. PLEASE SEE ATTACHED FULL PRESCRIBING INFORMATION FOR LEXISCAN AND ADENOSCAN ON PAGES 33-53.

VISIT WWW.LEXISCAN.COM FOR MORE INFORMATION.
CLINICAL EFFICACY

Imaging Studies

The efficacy and safety of Lexiscan were determined relative to Adenoscan® (adenosine injection) in 2 randomized, double-blind studies (ADenoscan Versus regAdenoscan Comparative Evaluation for Myocardial Perfusion Imaging [ADVANCE MPI 1 and 2]) in 2015 patients referred for pharmacologic stress MPI.8,16,17 The efficacy, safety, and tolerability of Adenoscan and Lexiscan were also compared in subgroup analyses based on patient age, gender, BMI, and a history of diabetes mellitus (DM).8,16

All patients underwent a baseline Adenoscan gated SPECT MPI (6-minute infusion of 0.14 mg/kg/min).8 Patients were then randomized 2:1 to a Lexiscan MPI or Adenoscan MPI using the same protocol as the baseline scan.8,17 The primary objective of the studies was to demonstrate noninferiority in the strength of agreement between sequential Adenoscan and Lexiscan images, and the strength of agreement between 2 sequential Adenoscan images for detecting the extent of reversible perfusion defects.16,17 Image assessment was performed by 3 independent expert readers who were blinded to treatment assignment.16,17

A total of 1871 patients had images considered valid for the primary efficacy evaluation.8,16 Baseline demographics were not significantly different between the 2 groups.16 The agreement rates in studies 1 and 2, respectively, were 62% and 63% for Lexiscan vs baseline Adenoscan and 61% and 64% for Adenoscan vs baseline Adenoscan, representing a nonsignificant difference of 1% (Figure 1).8 Agreement rates were similar regardless of patient age, gender, BMI, or history of DM.8,16 Thus, the ADVANCE MPI trials demonstrated that Lexiscan was similar to Adenoscan for assessing the presence and extent of reversible perfusion defects.8,16,17

Overall, and for each patient subgroup, Lexiscan was also similar to Adenoscan for (1) detecting the presence or absence of any perfusion defect,16 (2) image quality,16 (3) detecting defect type,13,17 and (4) side-by-side comparisons (Figure 2).13

SAFETY CONSIDERATIONS

Hypotension: Adenosine receptor agonists, including Lexiscan, induce arterial vasodilation and hypotension. The risk of serious hypotension may be higher in patients with autonomic dysfunction, hypovolemia, left main coronary artery stenosis, stenotic valvular heart disease, pericarditis or pericardial effusions, or stenotic carotid artery disease with cerebrovascular insufficiency. In postmarketing experience, transient ischemic attacks, seizures and syncope have been observed.
Hypotension

Adenosine receptor agonists, including Lexiscan, induce arterial vasodilation and hypotension. In clinical trials, decreased systolic blood pressure (>35 mm Hg) was observed in 7% of patients and decreased diastolic blood pressure (>25 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, stenotic valvular heart disease, pericarditis or pericardial effusions, or stenotic carotid artery disease with cerebrovascular insufficiency. In postmarketing experience, syncope, transient ischemic attacks, and seizures have been observed.

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. 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.

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.

Warnings and Precautions

Myocardial Ischemia

Fatal and nonfatal myocardial infarction, 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. 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.

Sinoatrial (SA) and Atioventricular (AV) 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 >220 msec) developed in 3% 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 postmarketing experience, third degree heart block and asystole within minutes of Lexiscan administration have occurred.

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. Have personnel and resuscitative equipment immediately available.

Hypotension

Myocardial Ischemia

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. 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.

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Warnings and Precautions (cont.)

Bronchoconstriction

Adenosine receptor agonists, including Lexiscan, may cause dyspnea, bronchoconstriction, and respiratory compromise. Appropriate bronchodilator therapy and resuscitative measures should be available prior to Lexiscan administration.

In a randomized, placebo-controlled clinical trial of 999 subjects with a diagnosis or risk factors for CAD and concurrent asthma (n=532) or stable chronic obstructive pulmonary disease (COPD; n=467), the incidence of bronchoconstriction (FEV₁ reduction >15% from baseline) 2 hours post-baseline was not statistically significantly different for Lexiscan compared with placebo: 1.1% (Lexiscan) and 2.9% (placebo) for the asthma cohort and 4.2% (Lexiscan) and 5.4% (placebo) for the COPD cohort.

Randomized patients were stratified by respiratory disease: 532 asthma (356 Lexiscan and 176 placebo) and 467 COPD (316 Lexiscan and 151 placebo). Asthma severity was categorized using the National Heart, Lung, and Blood Institute (NHLBI) step guide for therapy and COPD severity was defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria. All patients were instructed to continue their respiratory medications as prescribed prior to administration of Lexiscan. Physicians were not required to administer short-acting bronchodilators prior to the administration of Lexiscan.

The overall incidence of prespecified respiratory adverse events in the respiratory safety study was statistically significantly greater with Lexiscan compared with placebo. Moderate (2.5%) or severe (<1%) respiratory reactions were observed more frequently in the Lexiscan group compared to placebo. Most respiratory adverse reactions resolved without therapy. Short-acting bronchodilators were used by <2% of patients at the time of the selected respiratory adverse event in both groups and respiratory cohorts.

In subjects who experienced a >15% decrease in FEV₁, from baseline to the 2-hour post-baseline assessment, no subjects who received placebo or any subject in the asthma cohort reported a selected respiratory adverse event up to 1 day after study drug administration. In the COPD cohort, 2 subjects reported dyspnea within 2 hours after Lexiscan administration, 2 subjects reported dyspnea within 1 day after Lexiscan administration, and 1 subject reported wheezing within 1 day after receiving Lexiscan. Only 2 subjects receiving Lexiscan in the COPD group were given aminophylline for treatment of bradycardia (n=1) and dyspnea (n=1).

Incidence of prespecified respiratory treatment-emergent adverse events in the respiratory safety study

<table>
<thead>
<tr>
<th></th>
<th>Asthma Cohort</th>
<th>COPD Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lexiscan</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>(N=356)</td>
<td>(N=176)</td>
</tr>
<tr>
<td>Overall prespecified respiratory adverse event</td>
<td>12.9%&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.3%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>10.7%&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.1%</td>
</tr>
<tr>
<td>Wheezing</td>
<td>3.1%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Obstructive airways disorder</td>
<td>0.3%</td>
<td>-</td>
</tr>
<tr>
<td>Dyspnea exertional</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tachypnea</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>a</sup> Subjects may have reported more than 1 type of adverse event. Adverse events were collected up to 24 hours following drug administration.

<sup>b</sup> P<0.001 vs placebo.

<sup>c</sup> P<0.0001 vs placebo.

- = event not observed for this cohort.

DURING SELECTED RESPIRATORY ADVERSE EVENTS, THERE WAS NO DIFFERENCE IN THE USE OF SHORT-ACTING β₂-ADRENERGIC RECEPTOR AGONISTS BETWEEN THE LEXISCAN AND PLACEBO GROUPS WITHIN 2 HOURS AND WITHIN 24 HOURS OF STUDY DRUG ADMINISTRATION

SAFETY CONSIDERATIONS

Bronchoconstriction: Adenosine receptor agonists, including Lexiscan, may cause dyspnea, bronchoconstriction and respiratory compromise. Appropriate bronchodilator therapy and resuscitative measures should be available prior to Lexiscan administration.
FEV1 is the volume of air that can be forcibly exhaled in 1 second after taking a deep breath—a measure of pulmonary function used to evaluate patients with bronchoconstrictive disease. The percentage of subjects experiencing a >15% decrease in FEV1 at 2 hours post-baseline was not statistically significantly different between the Lexiscan and placebo groups in the asthma or COPD cohorts. The change in FEV1 with Lexiscan or placebo was not affected by baseline disease severity in either the asthma or the COPD cohort.

### Incidence of bronchoconstriction at 2 hours after Lexiscan or placebo administration in patients with asthma

<table>
<thead>
<tr>
<th>Asthma cohort by asthma step classifications</th>
<th>Lexiscan</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall frequency</td>
<td>4/351 (1.1%)</td>
<td>5/174 (2.9%)</td>
</tr>
<tr>
<td><strong>Step</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Asthma medications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 SABA PRN</td>
<td>2/107 (1.9%)</td>
<td>0/47 (0%)</td>
</tr>
<tr>
<td>2 Low-dose ICS or Any of the following:</td>
<td>1/33 (3.0%)</td>
<td>0/27 (0%)</td>
</tr>
<tr>
<td>cromolyn, LTRA, nedocromil, theophylline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Low-dose ICS + LABA, or Medium-dose ICS, or</td>
<td>1/49 (2.0%)</td>
<td>3/31 (9.7%)</td>
</tr>
<tr>
<td>Low-dose ICS + either LTRA, theophylline, or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>zileuton</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 Medium-dose ICS + LABA or Medium-dose ICS +</td>
<td>0/64 (0%)</td>
<td>0/23 (0%)</td>
</tr>
<tr>
<td>either LTRA, theophylline, or zileuton</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 High-dose ICS + LABA (patients may be using</td>
<td>0/44 (0%)</td>
<td>1/25 (4.0%)</td>
</tr>
<tr>
<td>omalizumab)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 High-dose ICS + LABA + oral steroids</td>
<td>-</td>
<td>1/2 (50%)</td>
</tr>
<tr>
<td>(patients may be using omalizumab)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unable to classify</td>
<td>0/34 (0%)</td>
<td>0/19 (0%)</td>
</tr>
</tbody>
</table>

### Incidence of bronchoconstriction at 2 hours after Lexiscan or placebo administration in patients with COPD

<table>
<thead>
<tr>
<th>COPD Cohort by COPD Severity</th>
<th>Lexiscan</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall frequency</td>
<td>13/313 (4.2%)</td>
<td>8/147 (5.4%)</td>
</tr>
<tr>
<td><strong>Stage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>I</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>FEV1/FVC &lt;0.70</td>
<td>0/43 (0%)</td>
</tr>
<tr>
<td>FEV1 ≥80% predicted</td>
<td>1/20 (5.0%)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>FEV1/FVC &lt;0.70</td>
<td>9/148 (6.1%)</td>
</tr>
<tr>
<td>50% ≤ FEV1 &lt;80% predicted</td>
<td>1/72 (1.4%)</td>
<td></td>
</tr>
<tr>
<td><strong>Stage III</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>FEV1/FVC &lt;0.70</td>
<td>2/60 (3.3%)</td>
</tr>
<tr>
<td>30% ≤ FEV1 &lt;50% predicted</td>
<td>2/28 (7.1%)</td>
<td></td>
</tr>
<tr>
<td>Very Severe</td>
<td>FEV1/FVC &lt;0.70</td>
<td>0/4 (0%)</td>
</tr>
<tr>
<td>FEV1 &lt;30% predicted or FEV1 &lt;50%</td>
<td>1/2 (50%)</td>
<td></td>
</tr>
<tr>
<td>predicted plus chronic respiratory failure</td>
<td>2/58 (3.4%)</td>
<td></td>
</tr>
<tr>
<td>Not calculated</td>
<td>3/25 (12.0%)</td>
<td></td>
</tr>
</tbody>
</table>

### Incidence of bronchoconstriction at 2 hours after Lexiscan or placebo administration in patients with asthma

<table>
<thead>
<tr>
<th>Asthma Cohort by FEV1 Baseline Value</th>
<th>Lexiscan</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60% predicted</td>
<td>0/18 (0%)</td>
<td>0/9 (0%)</td>
</tr>
<tr>
<td>≥60% to ≤80% predicted</td>
<td>3/151 (2.0%)</td>
<td>2/66 (3.0%)</td>
</tr>
<tr>
<td>&gt;80% predicted</td>
<td>1/182 (0.5%)</td>
<td>3/90 (3.0%)</td>
</tr>
</tbody>
</table>

### Incidence of bronchoconstriction at 2 hours after Lexiscan or placebo administration in patients with COPD

<table>
<thead>
<tr>
<th>COPD Cohort by FEV1 Baseline Value</th>
<th>Lexiscan</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60%</td>
<td>10/195 (5.1%)</td>
<td>5/86 (5.8%)</td>
</tr>
<tr>
<td>≥60% to ≤80% predicted</td>
<td>3/94 (3.2%)</td>
<td>3/55 (5.5%)</td>
</tr>
<tr>
<td>&gt;80% predicted</td>
<td>0/24 (0%)</td>
<td>0/6 (0%)</td>
</tr>
</tbody>
</table>

### SAFETY CONSIDERATIONS

**Bronchoconstriction:** Adenosine receptor agonists, including Lexiscan, may cause dyspnea, bronchoconstriction and respiratory compromise. Appropriate bronchodilator therapy and resuscitative measures should be available prior to Lexiscan administration.

**FEV1** is the volume of air that can be forcibly exhaled in 1 second after taking a deep breath—a measure of pulmonary function used to evaluate patients with bronchoconstrictive disease. The percentage of subjects experiencing a >15% decrease in FEV1 at 2 hours post-baseline was not statistically significantly different between the Lexiscan and placebo groups in the asthma or COPD cohorts. The change in FEV1, with Lexiscan or placebo was not affected by baseline disease severity in either the asthma or the COPD cohort.

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Visit the Lexiscan website for more information.

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Please see important safety information on pages 29 and 30. Please see attached full prescribing information for Lexiscan on pages 33-45.
Renal Impairment Safety Study

The safety of Lexiscan was assessed in a randomized, placebo-controlled clinical trial of 504 subjects (Lexiscan n=334 and placebo n=170) with a diagnosis or risk factors for CAD and NKF K/DOQI stage 3 or stage 4 renal impairment (GFR 15-59 mL/min/1.73 m²). In this study, the frequency of treatment-emergent adverse events was greater with Lexiscan compared with placebo (62.6% vs 21.2%, respectively, P<.001). No serious adverse events were reported through the 24-hour follow-up period.

### Incidence of treatment-emergent adverse events ≥5% in the renal impairment safety study

<table>
<thead>
<tr>
<th>Stage 3 Renal Impairment</th>
<th>Stage 4 Renal Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lexiscan (N=267)</td>
<td>Placebo (N=145)</td>
</tr>
<tr>
<td>Lexiscan (N=47)</td>
<td>Placebo (N=25)</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>182 (63.4%)</td>
</tr>
<tr>
<td>Headache</td>
<td>70 (24.4%)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>54 (18.8%)</td>
</tr>
<tr>
<td>Chest discomfort</td>
<td>44 (15.3%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>42 (14.6%)</td>
</tr>
<tr>
<td>Angina pectoris or ST-segment depression</td>
<td>30 (10.5%)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>28 (9.8%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>16 (5.7%)</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>10 (3.8%)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>8 (2.8%)</td>
</tr>
<tr>
<td>Feeling hot</td>
<td>6 (2.2%)</td>
</tr>
</tbody>
</table>

Aminophylline Use in Clinical Trials of Lexiscan

Studies on the safety of Lexiscan show that the use of aminophylline to treat serious and/or persistent adverse reactions to Lexiscan aligns with the safety data from the ADVANCE MPI pivotal clinical trials. Aminophylline may be administered in doses ranging from 50 mg to 250 mg by slow IV injection (50 mg to 100 mg over 30-60 seconds) to attenuate severe and/or persistent adverse reactions to Lexiscan.
Hemodynamic Effects

In phase 3 trials, the majority of patients experienced an increase in heart rate and a decrease in blood pressure after administration of Lexiscan. Adenosine receptor agonists including Lexiscan induce arterial vasodilation and hypotension. Decreased systolic blood pressure (>35 mm Hg) was observed in 7% of patients and decreased diastolic blood pressure (>25 mm Hg) was observed in 4% of patients within 45 minutes of Lexiscan administration. Compared with Adenoscan (adenosine injection), the effect of Lexiscan on heart rate and blood pressure had a more rapid onset and a slower return to baseline.

<table>
<thead>
<tr>
<th>Vital Sign Parameter</th>
<th>Lexiscan (N=1337)</th>
<th>Adenoscan (N=678)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heart rate</strong></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><strong>Systolic blood pressure</strong></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>≥200 mm Hg</td>
<td>1.9%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Increase ≥50 mm Hg</td>
<td>0.7%</td>
<td>0.8%</td>
</tr>
<tr>
<td>≥180 mm Hg and increase of ≥20 mm Hg from baseline</td>
<td>4.6%</td>
<td>3.2%</td>
</tr>
<tr>
<td><strong>Diastolic blood pressure</strong></td>
<td></td>
<td></td>
</tr>
<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 ≥50 mm Hg</td>
<td>0.5%</td>
<td>1.1%</td>
</tr>
</tbody>
</table>

Effect of Caffeine

Ingestion of caffeine decreases the ability to detect reversible ischemic defects. A placebo-controlled, parallel group clinical study assessed the effects of oral caffeine (200 mg, 400 mg, and placebo) on the number of reversible defects observed with Lexiscan SPECT MPI. Patients with known or suspected myocardial ischemia recommended for MPI received a baseline rest/stress MPI followed by a second stress MPI. Patients received caffeine or placebo approximately 90 minutes prior to completing the second Lexiscan stress MPI. Following caffeine administration, the mean number of reversible defects identified was reduced by approximately 60%; the mean change in the number of reversible defects detected from the baseline Lexiscan stress scan was 0.12 for the placebo group, –0.61 for the 200 mg caffeine group, and –0.62 for the 400 mg caffeine group. The changes observed in the caffeine groups were statistically significantly different than the change observed in the placebo group, indicating that reversible ischemic defects will be less detectable if caffeine is ingested prior to MPI with Lexiscan.

METHYLXANTHINES (EG, CAFFEINE AND THEOPHYLLINE) ARE NONSPECIFIC ADENOSINE RECEPTOR ANTAGONISTS WHICH INTERFERE WITH THE VASODILATORY ACTIVITY OF LEXISCAN

PATIENTS SHOULD BE INSTRUCTED TO AVOID CONSUMPTION OF ANY PRODUCTS CONTAINING METHYLXANTHINES FOR AT LEAST 12 HOURS BEFORE A SCHEDULED RADIONUCLIDE MPI, INCLUDING:
- COFFEE
- TEA OR OTHER CAFFEINATED BEVERAGES
- CAFFEINE-CONTAINING DRUGS
- THEOPHYLLINE
PHARMACOKINETICS

Clearance

Clearance increases with increasing body weight. Age, gender, and race appear to have minimal effects on the pharmacokinetics of Lexiscan, which supports standard-dose, rapid-injection administration for all patients.

Metabolism and Excretion

Preclinical studies indicate that metabolism of Lexiscan does not play a major role in the elimination of the drug. While the metabolism of regadenoson is unknown in humans, the majority of Lexiscan dose (57%) is excreted unchanged in the urine. The average plasma renal clearance is around 450 mL/min, which is in excess of the glomerular filtration rate. This indicates that renal tubular secretion plays a role in regadenoson elimination.

Renally Impaired Patients

The disposition of a 400-mcg bolus dose of Lexiscan was studied in 18 subjects with various degrees of renal impairment (creatinine clearance [Clcr] <30-79 mL/min) and in 6 healthy subjects (Clcr >80 mL/min). With increasing renal impairment, the fraction of Lexiscan excreted unchanged in urine and the renal clearance decreased, and the elimination half-life increased compared with healthy subjects. The maximum observed plasma concentrations, as well as volume of distribution estimates, were similar across the groups.

Drug Interactions

No formal pharmacokinetic drug interaction studies have been conducted with Lexiscan. Lexiscan has been administered to patients taking other cardioactive drugs, including ß-blockers, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, nitrates, cardiac glycosides, and angiotensin receptor blockers, without any reports of adverse reactions or apparent effects on efficacy. The potential for enhanced effects of Lexiscan in the presence of other coronary vasodilators (such as dipyridamole) has not been assessed, and dipyridamole should be withheld for at least 2 days prior to administering Lexiscan.

How Supplied and Storage Requirements

Lexiscan is supplied as a sterile, preservative-free solution of 0.08-mg/mL regadenoson in a prefilled plastic Ansyr® syringe with luer-lock fitting (NDC 0469-6501-89). Lexiscan should be stored at a controlled room temperature, 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F).

Support Services

There are a number of support services available to assist customers who are interested in trying Lexiscan.

To set up a Lexiscan inservice, please contact Customer Service at 1-800-888-7704.
For general questions and product information, please contact Medical Communications at 1-800-727-7003.
For questions about reimbursement, please visit www.astellasaccess.com or call 1-800-477-6472.
You can find more information about Lexiscan and Astellas Pharma US, Inc. by visiting www.lexiscan.com or www.us.astellas.com.
LEXISCAN IS A STANDARD-DOSE, IV-INJECTION PHARMACOLOGIC STRESS AGENT INDICATED FOR RADIONUCLIDE MPI IN PATIENTS UNABLE TO UNDERGO ADEQUATE EXERCISE STRESS.

As a selective A<sub>2A</sub> adenosine receptor agonist, Lexiscan rapidly and reversibly increases coronary blood flow for a length of time sufficient for MPI. Lexiscan is administered as a single, standard dose, IV injection (approximately 10 seconds), regardless of patient weight, thus eliminating the need for infusion pumps and weight-based dose calculations. Clinical trials have demonstrated that the image agreement rate and quality with Lexiscan MPI are similar to those of Adenoscan® (adenosine injection).

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

IMPORTANT SAFETY INFORMATION

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.

WARNINGS AND PRECAUTIONS
Myocardial Ischemia
Fatal and nonfatal myocardial infarction, 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. 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.

Sinoatrial 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 postmarketing experience, heart block (including third degree), and asystole within minutes of Lexiscan administration have occurred.

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.

Hypotension
Adenosine receptor agonists, including Lexiscan, induce arterial vasodilation and hypotension. The risk of serious hypotension may be higher in patients with autonomic dysfunction, hypovolemia, left main coronary artery stenosis, stenotic valvar heart disease, pericarditis or pericardial effusions, or stenotic carotid artery disease with cerebrovascular insufficiency. In postmarketing experience, transient ischemic attacks, seizures and syncope have been observed.

Hypertension
Adenosine receptor agonists, including Lexiscan, may result in clinically significant increases in blood pressure in some patients. In postmarketing experience, cases of potentially clinically significant hypertension have been reported, particularly in patients with underlying hypertension and when low-level exercise was included in the MPI.

Bronchoconstriction
Adenosine receptor agonists, including Lexiscan, may cause dyspnea, bronchoconstriction and respiratory compromise. Appropriate bronchodilator therapy and resuscitative measures should be available prior to Lexiscan administration.

ADVERSE REACTIONS
The most common adverse reactions (≥5%) to Lexiscan are dyspnea, headache, flushing, chest discomfort, angina pectoris or ST-segment depression, dizziness, chest pain, nausea, abdominal discomfort, dysgeusia, and feeling hot. Most adverse reactions began soon after dosing, and generally resolved within approximately 15 minutes, except for headache, which resolved in most patients within 30 minutes. Aminophylline was used as a reversal agent in 3% of patients.

In postmarketing experience, the following adverse reactions have occurred: myocardial infarction, cardiac arrest, ventricular arrhythmias, supraventricular tachyarrhythmias including atrial fibrillation or flutter, heart block, astylole, marked hypertension, hypotension, seizure, syncope, QTc prolongation, tremor, abdominal pain in association with nausea, vomiting, or myalgias, diarrhea, fecal incontinence, wheezing and musculoskeletal pain.
INDICATION

Intravenous Adenoscan® (adenosine injection) is indicated as an adjunct to thallium-201 myocardial perfusion scintigraphy in patients unable to exercise adequately.

IMPORTANT SAFETY INFORMATION

Adenoscan is contraindicated in patients with second- or third-degree AV block, unless these patients have a functioning pacemaker, sinus node disease, and known or suspected bronchoconstrictive or bronchospastic lung disease.

Fatal and nonfatal cardiac arrest, sustained ventricular tachycardia (requiring resuscitation), and myocardial infarction have occurred following Adenoscan infusion. 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 Adenoscan. Appropriate resuscitative measures should be available.

Adenoscan is a potent peripheral vasodilator and can cause significant hypotension. The risk of hypotension may be higher in patients with cardiac or cerebrovascular insufficiency.

Adenoscan exerts a direct depressant effect on the SA and AV nodes and has the potential to cause first-, second- or third-degree AV block, or sinus bradycardia.

Increases in systolic and diastolic pressure have been observed. Adenosine receptor agonists, including Adenoscan, may cause bronchoconstriction and respiratory compromise.

Atrial fibrillation has been reported in patients with Adenoscan infusion and may last from a few seconds to hours, however, patients spontaneously converted to normal sinus rhythm.

Most common adverse reactions (>5%) to Adenoscan are flushing, chest discomfort, dyspnea, headache, discomfort of the throat, neck, or jaw, gastrointestinal discomfort, and lightheadedness/dizziness. Side effects with Adenoscan usually resolve quickly when the infusion is discontinued, although delayed or persistent effects have been observed.

REFERENCES


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

-----------------------------RECENT MAJOR CHANGES-----------------------------
Warnings and Precautions, Myocardial ischemia (5.1) 10/2013

-----------------------------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) by
  rapid intravenous injection; followed immediately by saline flush and
  radiopharmaceutical (2).

-----------------------------DOSE FORMS AND STRENGTHS-----------------------------

• Single-use pre-filled syringe: Injection solution containing regadenoson
  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)

• Sinusatral (SA) and Atrioventricular (AV) 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 (5.2).

• Hypersensitivity, including Anaphylaxis. 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 (5.3).

• Hypotension. Adenosine receptor agonists, including Lexiscan, induce
  vasodilation and hypotension. The risk of serious hypotension may be
  higher in patients with autonomic dysfunction, stenotic valvular heart
  disease, pericarditis or pericardial effusions, stenotic carotid artery
  disease with cerebrovascular insufficiency, or hypovolemia (5.4).

• 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 (5.5).

• Bronchoconstriction. Adenosine receptor agonists, including Lexiscan,
  may induce dyspnea, bronchoconstriction and respiratory compromise in
  patients with COPD or asthma. Resuscitative measures should be
  available (5.6).

-----------------------------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).

To report SUSPECTED ADVERSE REACTIONS, contact Astellas
Pharma US, Inc. at 1-800-727-7003 or FDA at 1-800-FDA-1088 or
www.fda.gov/medwatch

-----------------------------DRUG INTERACTIONS-----------------------------

• Methylxanthines, e.g., caffeine and theophylline, interfere with the
  activity of Lexiscan (7.1, 12.2).

• Aminophylline may be used to attenuate severe and/or persistent adverse
  reactions to Lexiscan (7.1, 10).

• Diprydamole may increase the activity of Lexiscan. When possible,
  withhold diprydamole for at least two days prior to Lexiscan
  administration (7.1).

See 17 for PATIENT COUNSELING INFORMATION

10/2013

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2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
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  5.2 Sinusatral and Atrioventricular Nodal Block
  5.3 Hypersensitivity, including Anaphylaxis
  5.4 Hypotension
  5.5 Hypertension
  5.6 Bronchoconstriction
6 AVERSE REACTIONS
  6.1 Clinical Trials Experience
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7 DRUG INTERACTIONS
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  7.2 Effect of Lexiscan on Other Drugs
8 USE IN SPECIFIC POPULATIONS
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9 OVERDOSAGE
10 DESCRIPTION
11 CLINICAL PHARMACOLOGY
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12 NONCLINICAL TOXICOLOGY
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14 CLINICAL STUDIES
15 HOW SUPPLIED/STORAGE AND HANDLING
16 PATIENT COUNSELING INFORMATION
  17.1 Methylxanthine Consumption
  17.2 Common Reactions
  17.3 Patients with COPD or Asthma
*Sections or subsections omitted from the full prescribing information are not
listed
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 intravenous dose of Lexiscan is 5 mL (0.4 mg regadenoson)
• Administer Lexiscan as a rapid (approximately 10 seconds) injection 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.
NOTE: Parenteral 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.

3 DOSAGE FORMS AND STRENGTHS
• Single-use pre-filled syringe: Injection 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, 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. 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 Sinoatrial 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 > 220 msec) developed in 3% 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 postmarketing experience, third degree heart block and asystole within minutes of Lexiscan administration have occurred [see Adverse Reactions (6.2)].

5.3 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.

5.4 Hypotension
Adenosine receptor agonists, including Lexiscan, induce arterial vasodilation and hypotension. In clinical trials, decreased systolic blood pressure (> 35 mm Hg) was observed in 7% of patients and decreased diastolic blood pressure (> 25 mm Hg) was observed in 4% of patients within 45 min of Lexiscan administration. The risk of serious hypotension may be higher in patients with autonomic dysfunction, hypovolemia, left main coronary artery stenosis, stenotic valvular heart disease, pericarditis or pericardial effusions, or stenotic carotid artery disease with cerebrovascular insufficiency. In postmarketing experience, syncope, transient ischemic attacks and seizures have been observed [see Adverse Reactions (6.2)].

5.5 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)].

5.6 Bronchoconstriction
Adenosine receptor agonists, including Lexiscan, may cause dyspnea, bronchoconstriction, and respiratory compromise. Appropriate bronchodilator therapy and resuscitative measures should be available prior to Lexiscan administration [see Adverse Reactions (6.1), Clinical Pharmacology (12.2), Overdosage (10) and Patient Counseling Information (17.3)].

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)]
- Hypersensitivity, Including Anaphylaxis [see Warnings and Precautions (5.3)]
- Hypotension [see Warnings and Precautions (5.4)]
• Hypertension [see Warnings and Precautions (5.5)]
• Bronchoconstriction [see Warnings and Precautions (5.6)]

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 subjects were exposed to Lexiscan, with most receiving 0.4 mg as a rapid (≤10 seconds) intravenous injection. Most of these subjects received Lexiscan in two clinical studies that enrolled patients who had no history of bronchospastic lung disease as well as no history of a cardiac conduction block of greater than first-degree AV block, except for patients with functioning artificial pacemakers. 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 66 years), 70% male and primarily Caucasian (76% Caucasian, 7% African American, 9% Hispanic, 5% Asian). Table 1 shows the most frequently reported adverse reactions.

Overall, any adverse reaction occurred at similar rates between the study groups (80% for the Lexiscan group and 83% for the Adenoscan group). Aminophylline was used to treat the reactions in 3% of patients in the Lexiscan group and 2% of patients in the Adenoscan group. Most adverse reactions began soon after dosing, and generally resolved within approximately 15 minutes, except for headache which resolved in most patients within 30 minutes.

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

<table>
<thead>
<tr>
<th></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>
</tr>
<tr>
<td>Nausea</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Abdominal Discomfort</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>5%</td>
<td>7%</td>
</tr>
<tr>
<td>Feeling Hot</td>
<td>5%</td>
<td>8%</td>
</tr>
</tbody>
</table>

ECG Abnormalities

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>Condition</th>
<th>Lexiscan N / N evaluable (%)</th>
<th>Adenoscan N / N evaluable (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhythm or conduction abnormalities †</td>
<td>332/1275 (26%)</td>
<td>192/645 (30%)</td>
</tr>
<tr>
<td>Rhythm abnormalities</td>
<td>260/1275 (20%)</td>
<td>131/645 (20%)</td>
</tr>
<tr>
<td>PACs</td>
<td>86/1274 (7%)</td>
<td>57/645 (9%)</td>
</tr>
<tr>
<td>PVCs</td>
<td>179/1274 (14%)</td>
<td>79/645 (12%)</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%)</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 (6%)</td>
<td>31/581 (5%)</td>
</tr>
</tbody>
</table>

* 12-lead ECGs were recorded before and for up to 2 hrs after dosing
† includes rhythm abnormalities (PACs, PVCs, atrial fibrillation/flutter, wandering atrial pacemaker, supraventricular or ventricular arrhythmia) or conduction abnormalities, including AV block

Respiratory Abnormalities
In a randomized, placebo-controlled trial (Study 3) of 999 subjects with asthma (n= 532) or stable chronic obstructive pulmonary disease (n=467), the overall incidence of pre-specific 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 subjects 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).

Table 3 Respiratory Adverse Effects in Study 3*

<table>
<thead>
<tr>
<th></th>
<th>Asthma Cohort</th>
<th>COPD Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lexiscan (N=356)</td>
<td>Placebo (N=176)</td>
</tr>
<tr>
<td>Overall Pre-specified Respiratory Adverse Reaction †</td>
<td>12.9%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>10.7%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Wheezing</td>
<td>3.1%</td>
<td>1.1%</td>
</tr>
<tr>
<td>FEV₁ reduction &gt;15% ‡</td>
<td>1.1%</td>
<td>2.9%</td>
</tr>
</tbody>
</table>

*All subjects continued the use of their respiratory medications as prescribed prior to administration of Lexiscan.
† Patients may have reported more than one type of adverse reaction. Adverse reactions were collected up to 24 hours following drug administration. Pre-specified respiratory adverse reactions included dyspnea, wheezing, obstructive airway disorder, dyspnea exertional, and tachypnea.
‡ Change from baseline at 2 hours

Renal Impairment
In a randomized, placebo-controlled trial of 504 subjects (Lexiscan n=334 and placebo n=170) with a diagnosis or risk factors for coronary artery disease and NKFK/DOQI Stage III or IV renal impairment (defined as GFR 15-59 mL/min/1.73 m²), no serious adverse events were reported through the 24-hour follow-up period.

6.2 Post-Marketing Experience
Cardiovascular
Myocardial infarction, cardiac arrest, ventricular arrhythmias, supraventricular tachyarrhythmias including atrial fibrillation or flutter, heart block (including third degree block), asystole, marked hypertension, symptomatic
hypotension in association with transient ischemic attack, seizures and syncope [see Warnings and Precautions (5.1)] have been reported. Some events required intervention with fluids and/or aminophylline. QTc prolongation shortly after Lexiscan administration has been reported.

Central Nervous System
Tremor, seizure (particularly with a history of seizure)

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, rashes have occurred and have required treatment including resuscitation [see Warnings and Precautions (5.3)].

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.

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 Lexiscan exposure.

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 and theophylline) are non-specific adenosine receptor antagonists that interfere with the vasodilation activity of Lexiscan [see Clinical Pharmacology (12.2) and Patient Counseling Information (17.1)]. Patients should avoid consumption of any products containing methylxanthines as well as any drugs containing theophylline 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 angiotensin receptor blockers) without reported adverse reactions or apparent effects on efficacy.
- Dipyridamole may change the effects of Lexiscan. When possible, withhold dipyridamole 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, CYP2C8, 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
Pregnancy Category C:
There are no adequate well-controlled studies with Lexiscan in pregnant women. Lexiscan should be used during pregnancy only if the potential benefit to the patient justifies the potential risk to the fetus. 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 significant ossification delays in fore- and hind limb phalanges and metatarsals; however, maternal toxicity also occurred at these doses. Skeletal variations were increased in all treated groups. In rabbits, there were no Teratogenic effects in offspring at regadenoson doses 4 times the MRHD, although signs of maternal toxicity occurred at this dose. At regadenoson doses equivalent to 12 and 20 times the MRHD, maternal toxicity occurred along with increased embryo-fetal loss and fetal malformations. It is not clear whether malformations that occurred at maternally toxic doses of regadenoson in both animal species were due to fetal drug effects or only to the maternal toxic effects. Because animals received repeated doses of regadenoson, their exposure was significantly higher than that achieved with the standard single dose administered to humans [see Nonclinical Toxicology (13.2)].

8.3 Nursing Mothers
It is not known whether Lexiscan is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions from Lexiscan in nursing infants, the decision to interrupt nursing after administration of Lexiscan or not to administer Lexiscan, should take into account the importance of the drug to the mother. Based on the pharmacokinetics of Lexiscan, it should be cleared 10 hours after administration. Therefore, nursing women may consider interrupting nursing for 10 hours after administration.

8.4 Pediatric Use
Safety and effectiveness in pediatric patients (<18 years of age) 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
Lexiscan was assessed in a randomized, placebo-controlled trial of patients with NKF/DOQI Stage III or IV renal impairment (defined as a GFR 15-59 mL/min/1.73 m²). No serious adverse events were reported through the 24-hour follow-up period [see Adverse Reactions (6.1)].

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
Aminophylline may be administered in doses ranging from 50 mg to 250 mg by slow intravenous injection (50 mg to 100 mg over 30–60 seconds) to attenuate severe and/or persistent adverse reactions to Lexiscan.

11 DESCRIPTION
Regadenoson is an $A_{2A}$ adenosine receptor agonist that is a coronary vasodilator [see Clinical Pharmacology (12.1)]. Regadenoson is chemically described as adenosine, 2-[(methylamino)carbonyl]-1H-pyrazol-1-yl]-, monohydrate. Its structural formula is:

![Structural formula of regadenoson]

The molecular formula for regadenoson is $C_{13}H_{18}N_{6}O_{5}\cdot H_{2}O$ and its molecular weight is 408.37. Lexiscan is a sterile, nonpyrogenic solution for intravenous injection. The solution is clear and colorless. Each 1 mL in the 5 mL pre-filled syringe contains 0.084 mg of regadenoson monohydrate, corresponding to 0.08 mg regadenoson on an anhydrous basis, 10.9 mg dibasic sodium phosphate dihydrate or 8.7 mg dibasic sodium phosphate anhydrous, 5.4 mg monobasic sodium phosphate monohydrate, 150 mg propylene glycol, 1 mg edetate disodium dihydrate, and Water for Injection, with pH between 6.3 and 7.7.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Regadenoson is a low affinity agonist ($K_i \approx 1.3 \mu M$) for the $A_{2A}$ adenosine receptor, with at least 10-fold lower affinity for the $A_1$ adenosine receptor ($K_i > 16.5 \mu M$), and weak, if any, affinity for the $A_{2B}$ and $A_3$ adenosine receptors. Activation of the $A_{2A}$ adenosine receptor by regadenoson produces coronary vasodilation and increases coronary blood flow (CBF).

12.2 Pharmacodynamics
Coronary Blood Flow
Lexiscan causes a rapid increase in CBF which is sustained for a short duration. In patients undergoing coronary catheterization, pulsed-wave Doppler ultrasonography was used to measure the average peak velocity (APV) of coronary blood flow before and up to 30 minutes after administration of regadenoson (0.4 mg, intravenously). Mean APV increased to greater than twice baseline by 30 seconds and decreased to less than twice the baseline level within 10 minutes [see Clinical Pharmacology (12.3)].

Myocardial uptake of the radiopharmaceutical is proportional to CBF. Because Lexiscan increases blood flow in normal coronary arteries with little or no increase in stenotic arteries, Lexiscan causes relatively less uptake of the radiopharmaceutical in vascular territories supplied by stenotic arteries. MPI intensity after Lexiscan administration is therefore greater in areas perfused by normal relative to stenosed arteries.

Effect of Aminophylline
Aminophylline (100 mg, administered by slow iv injection over 60 seconds) injected 1 minute after 0.4 mg Lexiscan in subjects undergoing cardiac catheterization, was shown to shorten the duration of the coronary blood flow response to Lexiscan as measured by pulsed-wave Doppler ultrasonography [see Overdosage (10)].
Effect of Caffeine
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 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. Following caffeine administration (200 or 400 mg), the mean number of reversible defects identified was reduced by approximately 60%. This decrease was statistically significant. [see Drug Interactions (7.1) and Patient Counseling Information (17.1)].

Hemodynamic Effects
In clinical studies, the majority of patients had an increase in heart rate and a decrease in blood pressure within 45 minutes after administration of Lexiscan. Maximum hemodynamic changes after Lexiscan and Adenoscan in Studies 1 and 2 are summarized in Table 4.

**Table 4** Hemodynamic Effects in Studies 1 and 2

<table>
<thead>
<tr>
<th>Vital Sign Parameter</th>
<th>Lexiscan N = 1,337</th>
<th>Adenoscan N = 678</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heart Rate</strong></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><strong>Systolic Blood Pressure</strong></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>≥ 200 mm Hg</td>
<td>1.9%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Increase ≥ 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></td>
<td></td>
</tr>
<tr>
<td><strong>Diastolic Blood Pressure</strong></td>
<td></td>
<td></td>
</tr>
<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 ≥ 30 mm Hg</td>
<td>0.5%</td>
<td>1.1%</td>
</tr>
</tbody>
</table>

Respiratory Effects
The A2B and A3 adenosine receptors have been implicated in the pathophysiology of bronchoconstriction in susceptible individuals (i.e., asthmatics). In *in vitro* studies, regadenoson has not been shown to have appreciable binding affinity for the A2B and A3 adenosine receptors.

In a randomized, placebo-controlled clinical trial (Study 3) of 999 subjects with a diagnosis, or risk factors for, coronary artery disease and concurrent asthma or COPD, the incidence of respiratory adverse reactions (dyspnea, wheezing) was greater with Lexiscan compared to placebo. Moderate (2.5%) or severe (<1%) respiratory reactions were observed more frequently in the Lexiscan group compared to placebo [see Adverse Reactions (6.1)].

**12.3 Pharmacokinetics**
In healthy volunteers, the regadenoson plasma concentration-time profile is multi-exponential in nature and best characterized by 3-compartment model. The maximal plasma concentration of regadenoson is achieved within 1 to 4 minutes after injection of Lexiscan and parallels the onset of the pharmacodynamic response. The half-life of this initial phase is approximately 2 to 4 minutes. An intermediate phase follows, with a half-life on average of
30 minutes coinciding with loss of the pharmacodynamic effect. The terminal phase consists of a decline in plasma concentration with a half-life of approximately 2 hours [see Clinical Pharmacology (12.2)]. Within the dose range of 0.3–20 μg/kg in healthy subjects, clearance, terminal half-life or volume of distribution do not appear dependent upon the dose.

A population pharmacokinetic analysis including data from subjects and patients demonstrated that regadenoson clearance decreases in parallel with a reduction in creatinine clearance and clearance increases with increased body weight. Age, gender, and race have minimal effects on the pharmacokinetics of regadenoson.

Special Populations

Renally Impaired Patients: The disposition of regadenoson was studied in 18 subjects with various degrees of renal function and in 6 healthy subjects. With increasing renal impairment, from mild (CLcr 50 to < 80 mL/min) to moderate (CLcr 30 to < 50 mL/min) to severe renal impairment (CLcr < 30 mL/min), the fraction of regadenoson excreted unchanged in urine and the renal clearance decreased, resulting in increased elimination half-lives and AUC values compared to healthy subjects (CLcr ≥ 80 mL/min). However, the maximum observed plasma concentrations as well as volumes of distribution estimates were similar across the groups. The plasma concentration-time profiles were not significantly altered in the early stages after dosing when most pharmacologic effects are observed. No dose adjustment is needed in patients with renal impairment.

Patients with End Stage Renal Disease: The pharmacokinetics of regadenoson in patients on dialysis has not been assessed.

Hepatically Impaired Patients: The influence of hepatic impairment on the pharmacokinetics of regadenoson has not been evaluated. Because greater than 55% of the dose is excreted in the urine as unchanged drug and factors that decrease clearance do not affect the plasma concentration in the early stages after dosing when clinically meaningful pharmacologic effects are observed, no dose adjustment is needed in patients with hepatic impairment.

Geriatric Patients: Based on a population pharmacokinetic analysis, age has a minor influence on the pharmacokinetics of regadenoson. No dose adjustment is needed in elderly patients.

Metabolism

The metabolism of regadenoson is unknown in humans. Incubation with rat, dog, and human liver microsomes as well as human hepatocytes produced no detectable metabolites of regadenoson.

Excretion

In healthy volunteers, 57% of the regadenoson dose is excreted unchanged in the urine (range 19–77%), with an average plasma renal clearance around 450 mL/min, i.e., in excess of the glomerular filtration rate. This indicates that renal tubular secretion plays a role in regadenoson elimination.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Regadenoson was negative in the Ames bacterial mutation assay, chromosomal aberration assay in Chinese hamster ovary (CHO) cells, and mouse bone marrow micronucleus assay.

Long-term animal studies have not been conducted to evaluate Lexiscan's carcinogenic potential or potential effects on fertility.
13.2 Animal Toxicology and/or Pharmacology

Reproductive Toxicology Studies

Reproduction studies were conducted in rabbits and rats using doses of Lexiscan that were 2 to 20 times (rats) and 4 to 20 times (rabbits) the maximum recommended human dose (MRHD), based on body surface area comparison.

When administered to rabbits during organogenesis, regadenoson caused maternal toxicity including tachypnea, soft, liquid or scant feces, and localized alopecia in all treated groups, and caused reduction in body weight and feed consumption at 0.3 and 0.5 mg/kg/day (12 and 20 X MRHD, respectively). At regadenoson doses equivalent to 12 and 20 times the MRHD, maternal toxicity occurred along with decreased number of live fetuses, reduced fetal body weight, and occurrence of fetal variations and malformations. At regadenoson doses equivalent to 20 times the MRHD, resorptions were increased and fetal body weights reduced. Fetal malformations included microphthalmia (1/116 at 20 X MRHD), interrelated vertebrae/rib alterations (2/145 and 2/116 each at 12 and 20 X MRHD), and misaligned caudal vertebrae (3/145 at 12 X MRHD). Fetal toxicity was only observed at maternally toxic doses. The no effect dose level for fetal toxicity is 0.1 mg/kg (4 X MRHD). A no effect dose level was not identified for maternal toxicity.

When regadenoson was administered to pregnant rats during the period of major organogenesis, 4/25 rats from the 1.0 mg/kg/day group (20 X MRHD) and 1/25 rats from the 0.8 mg/kg (16 X MRHD) group died immediately following the first dose of regadenoson. All dams had decreased motor activity and one was gasping post-dosing. At doses ≥ 0.5 mg/kg (10 X MRHD), maternal toxicity included decreased motor activity, increased limb extension, excess salivation, and reduction in body weight and feed consumption. At doses ≥ 0.5 mg/kg, fetal body weights were significantly reduced and significant ossification delays were observed in fore- and hind limb phalanges and metatarsals. Skeletal malformations included delayed ossification of the skull (1/167), and hemivertebra present at a thoracic vertebra (1/167), observed at 16-20 X MRHD, and small arches of a lumbar and sacral vertebrae (1/174) observed at 2 X MRHD. The no effect dose level for maternal toxicity is 0.1 mg/kg/day (2 X MRHD).

Cardiomyopathy

Minimal cardiomyopathy (myocyte necrosis and inflammation) was observed in rats following single dose administration of regadenoson. Increased incidence of minimal cardiomyopathy was observed on day 2 in males at doses of 0.08, 0.2 and 0.8 mg/kg (1/5, 2/5, and 5/5) and in females (2/5) at 0.8 mg/kg. In a separate study in male rats, the mean arterial pressure was decreased by 30 to 50% of baseline values for up to 90 minutes at regadenoson doses of 0.2 and 0.8 mg/kg, respectively. No cardiomyopathy was noted in rats sacrificed 15 days following single administration of regadenoson. The mechanism of the cardiomyopathy induced by regadenoson was not elucidated in this study but was associated with the hypotensive effects of regadenoson. Profound hypotension induced by vasoactive drugs is known to cause cardiomyopathy in rats.

Local Irritation

Intravenous administration of Lexiscan to rabbits resulted in perivascular hemorrhage, vein vasculitis, inflammation, thrombosis and necrosis, with inflammation and thrombosis persisting through day 8 (last observation day). Perivascular administration of Lexiscan to rabbits resulted in hemorrhage, inflammation, pustule formation and epidermal hyperplasia, which persisted through day 8 except for the hemorrhage which resolved. Subcutaneous administration of Lexiscan to rabbits resulted in hemorrhage, acute inflammation, and necrosis; on day 8 muscle fiber regeneration was observed.

14 CLINICAL STUDIES

The efficacy and safety of Lexiscan were determined relative to Adenoscan in two randomized, double-blind studies (Studies 1 and 2) in 2,015 patients with known or suspected coronary artery disease who were indicated for pharmacologic stress MPI. A total of 1,871 of these patients had images considered valid for the primary efficacy evaluation, including 1,294 (69%) men and 577 (31%) women with a median age of 66 years (range 26–
93 years of age. 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 radionuclide 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 as that 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%), CABG, PTCA or stenting (51%), angina (63%), and history of myocardial infarction (41%) or arrhythmia (33%); other medical history 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 heart transplant were excluded. A number of patients took cardioactive medications on the day of the scan, including β-blockers (18%), calcium channel blockers (9%), and nitrates (6%). In the pooled study population, 68% of patients had 0–1 segments showing reversible defects on the initial scan, 24% had 2–4 segments, and 9% had ≥ 5 segments.

Image Agreement

Comparison of the images obtained with Lexiscan to those obtained with Adenoscan was performed as follows. Using the 17-segment model, the number of segments showing a reversible perfusion defect was calculated for the initial Adenoscan study and for the randomized study obtained using Lexiscan or Adenoscan. The agreement rate for the image obtained with Lexiscan or Adenoscan relative to the initial Adenoscan image was calculated by determining how frequently the patients assigned to each initial Adenoscan category (0–1, 2–4, 5–17 reversible segments) were placed in the same category with the randomized scan. The agreement rates for Lexiscan and Adenoscan were calculated as the average of the agreement rates across the three categories determined by the initial scan. Studies 1 and 2 each demonstrated that Lexiscan is similar to Adenoscan in assessing the extent of reversible perfusion abnormalities (Table 5).

<table>
<thead>
<tr>
<th>Table 5 Agreement Rates in Studies 1 and 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Study 1</strong></td>
</tr>
<tr>
<td>Adenoscan – Adenoscan Agreement Rate (± SE)</td>
</tr>
<tr>
<td>Adenoscan – Lexiscan Agreement Rate (± SE)</td>
</tr>
<tr>
<td>Rate Difference (Lexiscan – Adenoscan) (± SE)</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
</tr>
<tr>
<td><strong>Study 2</strong></td>
</tr>
<tr>
<td>Adenoscan – Adenoscan Agreement Rate (± SE)</td>
</tr>
<tr>
<td>Adenoscan – Lexiscan Agreement Rate (± SE)</td>
</tr>
<tr>
<td>Rate Difference (Lexiscan – Adenoscan) (± SE)</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
</tr>
</tbody>
</table>

16 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-use 5 mL pre-filled plastic Ansyr® syringes with luer-lock fitting (NDC 0469-6501-89).

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

17 PATIENT COUNSELING INFORMATION

17.1 Methylxanthine Consumption

Patients should be instructed to avoid consumption of any products containing methylxanthines, including caffeinated coffee, tea or other caffeinated beverages, caffeine-containing drug products, and theophylline for at least 12 hours before a scheduled radionuclide MPI.
17.2 Common Reactions

Prior to Lexiscan administration, patients should be informed of the most common reactions (such as shortness of breath, headache and flushing) that have been reported in association with Lexiscan during MPI.

17.3 Patients with COPD or Asthma

Patients with COPD or asthma should be informed to discuss their respiratory history and administration of pre- and post-study bronchodilator therapy with their clinician before scheduling an MPI study with Lexiscan.

Rx Only

Marketed by:
Astellas Pharma US, Inc.
Northbrook, IL 60062

Syringes Manufactured by:
Hospira, Inc.
Lake Forest, IL 60045 USA

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Revised: October 2013
13G036-1-LEX-WPI
ADENOSCAN®
(adenosine injection)

FOR INTRAVENOUS INFUSION ONLY

DESCRIPTION

Adenosine is an endogenous nucleoside occurring in all cells of the body. It is chemically 6-amino-9-beta-D-ribofuranosyl-9-H-purine and has the following structural formula:

\[
\begin{align*}
\text{C}_{10}\text{H}_{13}\text{N}_{5}\text{O}_4 & \quad 267.24 \\
\text{Adenosine is a white crystalline powder. It is soluble in water and practically insoluble in alcohol. Solubility increases by warming and lowering the pH of the solution. Each Adenocan vial contains a sterile, non-pyrogenic solution of adenosine 3 mg/mL and sodium chloride 9 mg/mL in Water for Injection, q.s. The pH of the solution is between 4.5 and 7.5.}
\end{align*}
\]

CLINICAL PHARMACOLOGY

Mechanism of Action

Adenosine is a potent vasodilator in most vascular beds, except in renal afferent arterioles and hepatic veins where it produces vasoconstriction. Adenosine is thought to exert its pharmacological effects through activation of purine receptors (cell-surface A_1 and A_2 adenosine receptors). Although the exact mechanism by which adenosine receptor activation relaxes vascular smooth muscle is not known, there is evidence to support both inhibition of the slow inward calcium current reducing calcium uptake, and activation of adenylate cyclase through A_2 receptors in smooth muscle cells. Adenosine may also lessen vascular tone by modulating sympathetic neurotransmission. The intracellular uptake of adenosine is mediated by a specific transmembrane nucleoside transport system. Once inside the cell, adenosine is rapidly phosphorylated by adenosine kinase to adenosine monophosphate, or deaminated by adenosine deaminase to inosine. These intracellular metabolites of adenosine are not vasoactive. Myocardial uptake of thallium-201 is directly proportional to coronary blood flow. Since Adenoscan significantly increases blood flow in normal coronary arteries with little or no
increase in stenotic arteries, Adenoscan causes relatively less thallium-201 uptake in vascular territories supplied by stenotic coronary arteries i.e., a greater difference is seen after Adenoscan between areas served by normal and areas served by stenotic vessels than is seen prior to Adenoscan.

**Hemodynamics**
Adenosine produces a direct negative chronotropic, dromotropic and inotropic effect on the heart, presumably due to $A_1$-receptor agonism, and produces peripheral vasodilation, presumably due to $A_2$-receptor agonism. The net effect of Adenoscan in humans is typically a mild to moderate reduction in systolic, diastolic and mean arterial blood pressure associated with a reflex increase in heart rate. Rarely, significant hypotension and tachycardia have been observed.

**Pharmacokinetics**
Intravenously administered adenosine is rapidly cleared from the circulation via cellular uptake, primarily by erythrocytes and vascular endothelial cells. This process involves a specific transmembrane nucleoside carrier system that is reversible, nonconcentrative, and bidirectionally symmetrical. Intracellular adenosine is rapidly metabolized either via phosphorylation to adenosine monophosphate by adenosine kinase, or via deamination to inosine by adenosine deaminase in the cytosol. Since adenosine kinase has a lower $K_m$ and $V_{max}$ than adenosine deaminase, deamination plays a significant role only when cytosolic adenosine saturates the phosphorylation pathway. Inosine formed by deamination of adenosine can leave the cell intact or can be degraded to hypoxanthine, xanthine, and ultimately uric acid. Adenosine monophosphate formed by phosphorylation of adenosine is incorporated into the high-energy phosphate pool. While extracellular adenosine is primarily cleared by cellular uptake with a half-life of less than 10 seconds in whole blood, excessive amounts may be deaminated by an ecto-form of adenosine deaminase. As Adenoscan requires no hepatic or renal function for its activation or inactivation, hepatic and renal failure would not be expected to alter its effectiveness or tolerability.

**Clinical Trials**
In two crossover comparative studies involving 319 subjects who could exercise (including 106 healthy volunteers and 213 patients with known or suspected coronary disease), Adenoscan and exercise thallium images were compared by blinded observers. The images were concordant for the presence of perfusion defects in 85.5% of cases by global analysis (patient by patient) and up to 93% of cases based on vascular territories. In these two studies, 193 patients also had recent coronary arteriography for comparison (healthy volunteers were not catheterized). The sensitivity (true positive Adenoscan divided by the number of patients with positive (abnormal) angiography) for detecting angiographically significant disease ($\geq$50% reduction in the luminal diameter of at least one major vessel) was 64% for Adenoscan and 64% for exercise testing, while the specificity (true negative divided by the number of patients with negative angiograms) was 54% for Adenoscan and 65% for exercise testing. The 95% confidence limits for Adenoscan sensitivity were 56% to 78% and for specificity were 37% to 71%. Intracoronary Doppler flow catheter studies have demonstrated that a dose of intravenous Adenoscan of 140 mcg/kg/min produces maximum coronary hyperemia (relative to intracoronary papaverine) in approximately 95% of cases within two to three minutes of the onset of the infusion. Coronary blood flow velocity returns to basal levels within one to two minutes of discontinuing the Adenoscan infusion.

**INDICATIONS AND USAGE**
Intravenous Adenoscan is indicated as an adjunct to thallium-201 myocardial perfusion scintigraphy in patients unable to exercise adequately (See WARNINGS).
CONTRAINDICATIONS
Intravenous Adenoscan (adenosine injection) should not be administered to individuals with:
1. Second- or third-degree AV block (except in patients with a functioning artificial pacemaker).
2. Sinus node disease, such as sick sinus syndrome or symptomatic bradycardia (except in patients with a functioning artificial pacemaker).
3. Known or suspected bronchoconstrictive or bronchospastic lung disease (e.g., asthma).
4. Known hypersensitivity to adenosine.

WARNINGS
Fatal Cardiac Arrest, Ventricular Arrhythmias, and Myocardial Infarction
Fatal and nonfatal cardiac arrest, sustained ventricular tachycardia (requiring resuscitation), and myocardial infarction have occurred following Adenoscan infusion. 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 Adenoscan. Appropriate resuscitative measures should be available.

Sinoatrial and Atrioventricular Nodal Block
Adenoscan (adenosine injection) exerts a direct depressant effect on the SA and AV nodes and has the potential to cause first-, second- or third-degree AV block, or sinus bradycardia. Approximately 6.3% of patients develop AV block with Adenoscan, including first-degree (2.9%), second-degree (2.6%), and third-degree (0.8%) heart block. Adenoscan can cause sinus bradycardia. Adenoscan should be used with caution in patients with pre-existing first-degree AV block or bundle branch block and should be avoided in patients with high-grade AV block or sinus node dysfunction (except in patients with a functioning artificial pacemaker). Adenoscan should be discontinued in any patient who develops persistent or symptomatic high-grade AV block. Sinus pause has been rarely observed with adenosine infusions.

Hypotension
Adenoscan (adenosine injection) is a potent peripheral vasodilator and can cause significant hypotension. Patients with an intact baroreceptor reflex mechanism are able to maintain blood pressure and tissue perfusion in response to Adenoscan by increasing heart rate and cardiac output. However, Adenoscan should be used with caution in patients with autonomic dysfunction, stenotic valvular heart disease, pericarditis or pericardial effusions, stenotic carotid artery disease with cerebrovascular insufficiency, or uncorrected hypovolemia, due to the risk of hypotensive complications in these patients. Adenoscan should be discontinued in any patient who develops persistent or symptomatic hypotension.

Hypertension
Increases in systolic and diastolic pressure have been observed (as great as 140 mm Hg systolic in one case) concomitant with Adenoscan infusion; most increases resolved spontaneously within several minutes, but in some cases, hypertension lasted for several hours.

Bronchoconstriction
Adenoscan (adenosine injection) is a respiratory stimulant (probably through activation of carotid body chemoreceptors) and intravenous administration in man has been shown to increase minute ventilation (Ve) and reduce arterial PCO₂ causing respiratory alkalosis. Approximately 28% of
patients experience breathlessness (dyspnea) or an urge to breathe deeply with Adenoscan. These respiratory complaints are transient and only rarely require intervention.

Adenosine administered by inhalation has been reported to cause bronchoconstriction in asthmatic patients, presumably due to mast cell degranulation and histamine release. These effects have not been observed in normal subjects. Adenoscan has been administered to a limited number of patients with asthma and mild to moderate exacerbation of their symptoms has been reported. Respiratory compromise has occurred during adenosine infusion in patients with obstructive pulmonary disease. Adenoscan should be used with caution in patients with obstructive lung disease not associated with bronchoconstriction (e.g., emphysema, bronchitis, etc.) and should be avoided in patients with bronchoconstriction or bronchospasm (e.g., asthma). Adenoscan should be discontinued in any patient who develops severe respiratory difficulties.

Atrial fibrillation
Atrial fibrillation has been reported in patients (with and without a history of atrial fibrillation) undergoing myocardial perfusion imaging with adenosine infusion. In these cases, atrial fibrillation began 1.5 to 3 minutes after initiation of adenosine, lasted for 15 seconds to 6 hours, and spontaneously converted to normal sinus rhythm.

PRECAUTIONS
Drug interactions
Intravenous Adenoscan (adenosine injection) has been given with other cardioactive drugs (such as beta adrenergic blocking agents, cardiac glycosides, and calcium channel blockers) without apparent adverse interactions, but its effectiveness with these agents has not been systematically evaluated. Because of the potential for additive or synergistic depressant effects on the SA and AV nodes, however, Adenoscan should be used with caution in the presence of these agents.

The vasoactive effects of Adenoscan are inhibited by adenosine receptor antagonists, such as methylxanthines (e.g., caffeine and theophylline). The safety and efficacy of Adenoscan in the presence of these agents has not been systematically evaluated.

The vasoactive effects of Adenoscan are potentiated by nucleoside transport inhibitors, such as dipyridamole. The safety and efficacy of Adenoscan in the presence of dipyridamole has not been systematically evaluated.

Whenever possible, drugs that might inhibit or augment the effects of adenosine should be withheld for at least five half-lives prior to the use of Adenoscan.

Carcinogenesis, mutagenesis, impairment of fertility
Studies in animals have not been performed to evaluate the carcinogenic potential of Adenoscan (adenosine injection). Adenosine was negative for genotoxic potential in the Salmonella (Ames Test) and Mammalian Microsome Assay.

Adenosine, however, like other nucleosides at millimolar concentrations present for several doubling times of cells in culture, is known to produce a variety of chromosomal alterations. Fertility studies in animals have not been conducted with adenosine.

Pregnancy Category C
Animal reproduction studies have not been conducted with adenosine; nor have studies been performed in pregnant women. Because it is not known whether Adenoscan can cause fetal harm when administered to pregnant women, Adenoscan should be used during pregnancy only if clearly needed.
**Pediatric use**
The safety and effectiveness of Adenoscan in patients less than 18 years of age have not been established.

**Geriatric use**
Clinical studies of Adenoscan did not include sufficient numbers of subjects aged younger than 65 years to determine whether they respond differently. Other reported experience has not revealed clinically relevant differences of the response of elderly in comparison to younger patients. Greater sensitivity of some older individuals, however, cannot be ruled out.

**ADVERSE REACTIONS**
The following reactions with an incidence of at least 1% were reported with intravenous Adenoscan among 1421 patients enrolled in controlled and uncontrolled U.S. clinical trials. Despite the short half-life of adenosine, 10.6% of the side effects occurred not with the infusion of Adenoscan but several hours after the infusion terminated. Also, 8.4% of the side effects that began coincident with the infusion persisted for up to 24 hours after the infusion was complete. In many cases, it is not possible to know whether these late adverse events are the result of Adenoscan infusion.

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flushing</td>
<td>44%</td>
</tr>
<tr>
<td>Chest discomfort</td>
<td>40%</td>
</tr>
<tr>
<td>Dyspnea or urge to breathe deeply</td>
<td>28%</td>
</tr>
<tr>
<td>Headache</td>
<td>18%</td>
</tr>
<tr>
<td>Throat, neck or jaw discomfort</td>
<td>15%</td>
</tr>
<tr>
<td>Gastrointestinal discomfort</td>
<td>13%</td>
</tr>
<tr>
<td>Lightheadedness/dizziness</td>
<td>12%</td>
</tr>
<tr>
<td>Upper extremity discomfort</td>
<td>4%</td>
</tr>
<tr>
<td>ST segment depression</td>
<td>3%</td>
</tr>
<tr>
<td>First-degree AV block</td>
<td>3%</td>
</tr>
<tr>
<td>Second-degree AV block</td>
<td>3%</td>
</tr>
<tr>
<td>Paresthesis</td>
<td>2%</td>
</tr>
<tr>
<td>Hypotension</td>
<td>2%</td>
</tr>
<tr>
<td>Nervousness</td>
<td>2%</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>1%</td>
</tr>
</tbody>
</table>

Adverse experiences of any severity reported in less than 1% of patients include:

**Body as a Whole**
Back discomfort; lower extremity discomfort; weakness

**Cardiovascular System**
Nonfatal myocardial infarction; life-threatening ventricular arrhythmia; third-degree AV block; bradycardia; palpitation; sinus exit block; sinus pause; sweating; T-wave changes; hypertension (systolic blood pressure > 200 mm Hg)

**Central Nervous System**
Drowsiness; emotional instability; tremors
Genital/Urinary System
Vaginal pressure; urgency

Respiratory System
Cough

Special Senses
Blurred vision; dry mouth; ear discomfort; metallic taste; nasal congestion; scotomas; tongue discomfort

Post Marketing Experience (see WARNINGS)
The following adverse events have been reported from marketing experience with Adenoscan. Because these events are reported voluntarily from a population of uncertain size, are associated with concomitant diseases and multiple drug therapies and surgical procedures, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these events in labeling are typically based on one or more of the following factors: (1) seriousness of the event, (2) frequency of the reporting, (3) strength of causal connection to the drug, or a combination of these factors.

Body as a Whole
Injection site reaction

Cardiovascular System
Fatal and nonfatal cardiac arrest, myocardial infarction, ventricular arrhythmia

Central Nervous System
Seizure activity, including tonic clonic (grand mal) seizures, and loss of consciousness

Digestive
Nausea and vomiting

Respiratory
Respiratory arrest, throat tightness

OVERDOSAGE
The half-life of adenosine is less than 10 seconds and side effects of Adenoscan (when they occur) usually resolve quickly when the infusion is discontinued, although delayed or persistent effects have been observed. Methylxanthines, such as caffeine and theophylline, are competitive adenosine receptor antagonists and theophylline has been used to effectively terminate persistent side effects. In controlled U.S. clinical trials, theophylline (50-125 mg slow intravenous injection) was needed to abort Adenoscan side effects in less than 2% of patients.

DOSAGE AND ADMINISTRATION
For intravenous infusion only.
Adenoscan should be given as a continuous peripheral intravenous infusion. The recommended intravenous dose for adults is 140 mcg/kg/min infused for six minutes (total dose of 0.84 mg/kg). The required dose of thallium-201 should be injected at the midpoint of the Adenoscan infusion (i.e., after the first three minutes of Adenoscan). Thallium-201 is physically compatible with Adenoscan and may be injected directly into the Adenoscan infusion set. The injection should be as close to the venous access as possible to prevent an inadvertent increase in the dose of Adenoscan (the contents of the IV tubing) being administered. There are no data on the safety or efficacy of alternative Adenoscan infusion protocols. The safety and efficacy of Adenoscan administered by the intracoronary route have not been established. The following Adenoscan infusion nomogram may be used to determine the appropriate infusion rate corrected for total body weight:

<table>
<thead>
<tr>
<th>Patient Weight kg</th>
<th>lbs</th>
<th>Infusion Rate mL/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>45</td>
<td>99</td>
<td>2.1</td>
</tr>
<tr>
<td>50</td>
<td>110</td>
<td>2.3</td>
</tr>
<tr>
<td>55</td>
<td>121</td>
<td>2.6</td>
</tr>
<tr>
<td>60</td>
<td>132</td>
<td>2.8</td>
</tr>
<tr>
<td>65</td>
<td>143</td>
<td>3.0</td>
</tr>
<tr>
<td>70</td>
<td>154</td>
<td>3.3</td>
</tr>
<tr>
<td>75</td>
<td>165</td>
<td>3.5</td>
</tr>
<tr>
<td>80</td>
<td>176</td>
<td>3.8</td>
</tr>
<tr>
<td>85</td>
<td>187</td>
<td>4.0</td>
</tr>
<tr>
<td>90</td>
<td>198</td>
<td>4.2</td>
</tr>
</tbody>
</table>

This nomogram was derived from the following general formula:

\[
\frac{0.140 \text{ (mg/kg/min)} \times \text{total body weight (kg)}}{\text{Adenoscan concentration (3 mg/mL)}} = \text{Infusion rate (mL/min)}
\]

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.
HOW SUPPLIED

Adenoscan (adenosine injection) is supplied as 20 mL and 30 mL vials of sterile, nonpyrogenic solution in normal saline.

<table>
<thead>
<tr>
<th>NDC</th>
<th>Product Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0469-0871-20</td>
<td>87120</td>
<td>60 mg/20 mL (3 mg/mL) in a 20 mL single-dose, flip-top glass vial, packaged individually and in packages of ten.</td>
</tr>
<tr>
<td>0469-0871-30</td>
<td>87130</td>
<td>90 mg/30 mL (3 mg/mL) in a 30 mL single-dose, flip-top glass vial, packaged individually and in packages of ten.</td>
</tr>
</tbody>
</table>

Store at controlled room temperature 15º-30ºC (59º-86ºF)
Do not refrigerate as crystallization may occur. If crystallization has occurred, dissolve crystals by warming to room temperature. The solution must be clear at the time of use.
Contains no preservative. Discard unused portion.

Rx only

Product of Germany

Marketed by:
Astellas Pharma US, Inc.
Northbrook, IL 60062 USA

Manufactured by:
Hospira, Inc.
Lake Forest, IL 60045 USA

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