Lexiscan®
(regadenoson) injection
0.4 mg/5 mL

KEY ATTRIBUTES

Selective A<sub>2A</sub> adenosine receptor agent<sup>1</sup>
- At least 10-fold lower affinity for the A<sub>1</sub> receptor
- Weak, if any, affinity for the A<sub>2B</sub> and A<sub>3</sub> receptors

Standard-dose IV injection<sup>1</sup>
- No weight-based dosing calculations

Pharmacologic stress agent in a prefilled syringe<sup>1</sup>
- No drawing up dose from a vial
- No mixing
- Pump-free administration
- No dose adjustments required

Not contraindicated in patients with known or suspected bronchoconstrictive or bronchospastic lung disease<sup>1</sup>
- Adenosine receptor agonists, including Lexiscan<sup>®</sup> (regadenoson) injection, may cause dyspnea, bronchoconstriction, and respiratory compromise. Appropriate bronchodilator therapy and resuscitative measures should be available prior to and following Lexiscan administration

No dose adjustment needed in patients with end-stage renal disease and/or dependent on dialysis<sup>1</sup>

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. Adhere to the recommended duration of injection. As noted in an animal study, longer injection times may increase the duration and magnitude of increase in coronary blood flow. 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.

Atrial Fibrillation/Atrial Flutter
New-onset or recurrent atrial fibrillation with rapid ventricular response and atrial flutter have been reported following Lexiscan injection.

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 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.

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 and following Lexiscan administration.

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

Cerebrovascular Accident (Stroke)
Hemorrhagic and ischemic cerebrovascular accidents have occurred. Hemodynamic effects of Lexiscan including hypotension or hypertension may be associated with these adverse reactions.

PLEASE SEE ADDITIONAL IMPORTANT SAFETY INFORMATION ON PAGE 2.
PLEASE SEE FULL PRESCRIBING INFORMATION AT THE END OF THE DOCUMENT.
PREPARING PATIENTS FOR STRESS MPI WITH LEXISCAN® (REGADENOSON) INJECTION

Discuss prescription and over-the-counter medications
» Instruct to avoid any foods or drugs containing methylxanthines (eg, caffeine, aminophylline, and theophylline) for at least 12 hours prior to the test
» Instruct to withhold dipyridamole for at least 48 hours prior to the test

Per your facility protocol, advise regarding fasting

Discuss history and bronchodilator therapy with those patients who have chronic obstructive pulmonary disease (COPD) or asthma

Question about a history of seizures

Inform patients of the Warnings and Precautions and Patient Counseling Information sections of the package insert

Instruct not to apply creams, lotions, or powders to the chest area the day of the test

Advise to wear comfortable clothing and shoes

IMPORTANT SAFETY INFORMATION (CONTINUED)

ADVERSE REACTIONS
In clinical trials, the most common adverse reactions (≥5%) to Lexiscan were 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 additional adverse reactions have occurred: supraventricular tachyarrhythmias, acute coronary syndrome (ACS), tremor, QTc prolongation, abdominal pain in association with nausea, vomiting, or myalgias, diarrhea, fecal incontinence, wheezing and musculoskeletal pain.

PLEASE SEE ADDITIONAL IMPORTANT SAFETY INFORMATION ON PAGE 1.
PLEASE SEE FULL PRESCRIBING INFORMATION AT THE END OF THE DOCUMENT.

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

**Indications and Usage**
LEXISCAN® injection is for intravenous use only.

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

**Contraindications**
- Do not administer LEXISCAN to patients with:
  - Second- or third-degree AV block.
  - Sinus node dysfunction.

**Warnings and Precautions**
- Myocardial Ischemia: Fat-related events have occurred. Avoid use in patients with symptoms or signs of acute myocardial ischemia, for example unstable angina or cardiovascular instability, who may be at greater risk. Cardiac resuscitation equipment and trained staff should be available before administration (5.1).
- Sinusoidal (SA) and Atrioventricular (AV) Nodal Block. Adenosine receptor agonists, including LEXISCAN, can depress the SA and AV nodes and may cause first-, second- or third-degree AV block, or sinus node dysfunction (5.2).
- Atrial Fibrillation/Attral Flutter. New-onset or recurrent atrial fibrillation with rapid ventricular response and atrial flutter have been reported (5.3).
- Hypersensitivity: including anaphylaxis, angioedema, cardiac or respiratory arrest, respiratory distress, decreased oxygen saturation, hypotension, throat tightness, urticaria, and rashes have occurred. Have personnel and resuscitative equipment immediately available (5.4).
- Hypotension. Adenosine receptor agonists, including LEXISCAN, induce vasoconstriction and hypotension. The risk of serious hypotension may be higher in patients with autonomic dysfunction, coronary artery disease, or chronic obstructive pulmonary disease, or prior myocardial infarction (5.5).
- Hypersensitivity, including anaphylaxis, angioedema, cardiac or respiratory arrest, respiratory distress, decreased oxygen saturation, hypotension, throat tightness, urticaria, and rashes have occurred. Have personnel and resuscitative equipment immediately available (5.4).
- Seizure. LEXISCAN may lower the seizure threshold. New onset or recurrence of convulsive seizures has occurred. Some seizures are prolonged and require urgent anticonvulsive management. Methylxanthine use is not recommended in patients who experience a seizure in association with LEXISCAN (5.6).
- Cerebrovascular Accident (Stroke). Hemorrhagic and ischemic cerebrovascular accidents have occurred (5.7).

**Adverse Reactions**
The most commonly reported (>1%) adverse reactions to LEXISCAN are dyspnea, headache, flushing, chest discomfort, dizziness, angina pectoris, chest pain, and nausea (6).

**Drug Interactions**
- Methylxanthines, e.g., caffeine, aminophylline and theophylline, interfere with the activity of LEXISCAN (7, 12).
- Aminophylline may be used to attenuate severe and/or persistent adverse reactions to LEXISCAN (7, 10).
- Dipryidamole may increase the activity of LEXISCAN. When possible, withhold dipryidamole for at least two days prior to LEXISCAN administration (7).

See 17 for PATIENT COUNSELING INFORMATION.
In a randomized, placebo-controlled trial of 999 patients with asthma (n = 532) or stable chronic obstructive pulmonary disease (n = 467), the overall incidence of pre-specified respiratory adverse reactions was greater in the LEXISCAN group compared to the placebo group (p < 0.001). Most respiratory adverse reactions resolved without therapy; a few patients received aminophylline or a short-acting bronchodilator. No differences were observed between treatment arms in the reduction of Income <5% from baseline at two-hours in FEV1 (Table 3).

Table 3 Respiratory Adverse Effects

<table>
<thead>
<tr>
<th>Responder Abnormalities</th>
<th>Asthma Cohort</th>
<th>Chronic Obstructive Pulmonary Disease (COPD) Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LEXISCAN</strong> (N=1,337)</td>
<td><strong>Placebo (N=176)</strong></td>
<td><strong>LEXISCAN</strong> (N=1,337)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>12.9%</td>
<td>2.3%</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 patients 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, dysuria, exercional, and tachypnea.

‡ Change from baseline at 2 hours.

Renal Impairment

In a randomized, placebo-controlled trial of 504 patients (LEXISCAN n=334 and placebo n=170) with a diagnosis or risk factors for coronary artery disease and NKF/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.

Inadequate Exercise Stress

In an open-label, multi-center trial evaluating LEXISCAN administration following inadequate exercise stress, 1,147 patients were randomized into one of two groups. Each group underwent two LEXISCAN stress myocardial perfusion imaging (MPI) procedures. Group 1 received LEXISCAN 3 minutes following inadequate exercise in the first LEXISCAN stress (MPI 1). Group 2 rested 1 hour after inadequate exercise to allow hemodynamics to return to baseline prior to receiving LEXISCAN (MPI 1). Both groups returned for a second stress MPI 1-14 days later and received LEXISCAN without exercise (MPI 2).

The most common adverse reactions are similar in type and incidence to those in Table 1 above for both groups. The timing of the administration of LEXISCAN following inadequate exercise did not alter the common adverse reaction profile.

Table 4 shows a comparison of cardiac events of interest for the two groups [see Warnings and Precautions (5.1)]. The cardiac events were numerically higher in Group 1.

Table 4 Cardiac Events of Interest in Inadequate Exercise Stress Study

<table>
<thead>
<tr>
<th>Cardiac Event*</th>
<th>Group 1 / MPI 1</th>
<th>Group 2 / MPI 1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lexiscan</strong> minutes following exercise (N=575)</td>
<td><strong>Lexiscan</strong> minutes following exercise (N=567)</td>
<td></td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>17 (3.0%)</td>
<td>3 (0.5%)</td>
</tr>
<tr>
<td><strong>Atrial Fibrillation/Atrial Flutter</strong></td>
<td>13 (2.3%)</td>
<td>2 (0.4%)</td>
</tr>
<tr>
<td><strong>S1/S2 Elevation (≥ 1 mm)</strong></td>
<td>5 (0.9%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Acute coronary syndrome</strong></td>
<td>1 (0.2%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Myocardial infarction</strong></td>
<td>1 (0.2%)</td>
<td>0</td>
</tr>
</tbody>
</table>

A* clinically significant cardiac event was defined as any of the following events found on the electrocardiogram (ECG) following LEXISCAN administration: ventricular arrhythmias (sustained ventricular tachycardia, ventricular fibrillation, Torse de Points ventricular flutter); S1-S2 depression (≥ 2 mm); S1-S2 elevation (≥ 1 mm); AV block (2:1 AV block, AV Mobitz II, AV Mobitz I >2 seconds), sinuatrial block, atrioventricular block (≥ 3 seconds), sinoatrial arrest >3 seconds in duration.

[See Warnings and Precautions (5.1), (5.2), (5.3), (5.4), (5.5), (5.6), and (5.8)]

Or:

- A Treatment Emergent Adverse Event (TEAE) per the MedDRA SMQ (narrow Scope) for myocardial infarction

- A TEAE preferred term (PT) of angina unstable within 24 hours of regadenoson administration.

6.2 Post-Marketing Experience

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

Cardiovascular

Myocardial infarction, cardiac arrest, ventricular arrhythmias, supraventricular tachyarrhythmias including atrial fibrillation with rapid ventricular response (new-onset or recurrent), atrial flutter, heart block (including third-degree AV block), asystole, marked hypotension, symptomatic hypotension in association with transient ischemic attack, acute coronary syndrome (ACS), seizures and syncope [see Warnings and Precautions (5.1), (5.2), (5.3), (5.4), (5.5) and (5.6)] have been associated with regadenoson. Some events were required to discontinue regadenoson. Some patients experienced hypotension and syncope in association with fluids and angiotensin [see Overdose (10)]. Oligoconcentration shortly after LEXISCAN administration has been reported.

Central Nervous System

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

Gastrointestinal

Abdominal pain, occasionally severe, has been reported a few minutes after LEXISCAN administration, in association with nausea, vomiting, or myalgia. Symptoms of anaphylaxis, 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 (5.4)].
7 DRUG INTERACTIONS

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

7.1 Effects of Other Drugs on LEXISCAN

- Methylxanthines (e.g., caffeine, aminophylline and theophylline) are non-specific adenosine receptor antagonists that interfere with the vasodilation activity of LEXISCAN [see Clinical Pharmacology (12.3) and Patient Counseling Information (17)]. Patients should avoid consumption of any products containing methylxanthines as well as any drugs containing theophylline or aminophylline for at least 12 hours before LEXISCAN administration. Aminophylline may be used to attenuate severe or persistent adverse reactions to LEXISCAN [see Overdosage (10)].
- In clinical studies, LEXISCAN was administered to patients taking other cardioactive drugs (i.e., β-blockers, calcium channel blockers, ACE inhibitors, nitrates, cardiac glycosides, and angiotensin receptor blockers) without reported adverse reactions or apparent effects on efficacy.
- Dipryidamole may change the effects of LEXISCAN. When possible, withhold dipryidamole 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

Risk Summary

There is no available data on LEXISCAN use in pregnant women to inform a drug-associated risk. In animal reproduction studies, adverse developmental outcomes were observed with the administration of regadenoson to pregnant rats and rabbits during organogenesis only at doses that produced maternal toxicity (see Data). In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

Data

Animal Data

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

8.2 Lactation

Risk Summary

There is no information on the presence of regadenoson in human milk, the effects on breastfed infants of exposure to regadenoson and breast milk. Because of the potential for serious cardiac reactions in the breastfed infant, advise the nursing mother to pump and discard breast milk for at least two days prior to LEXISCAN administration.

8.3 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.4 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 incidence of hypotension (2% vs. ≤ 1%).

8.5 Renal Impairment

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

10 OVERDOSAGE

LEXISCAN overdosage may result in serious reactions [see Warnings and Precautions (5.1)]. In a study of healthy volunteers, symptoms of flushing, dizziness and increased heart rate were observed after a single intravenous dose of LEXISCAN. In this dose. At higher doses, 12 and 20 times the MRHD, maternal toxicity occurred along with increased embryo-fetal loss and fetal malformations.

11 DESCRIPTION

Regadenoson is an A2A adenosine receptor agonist that is a coronary vasodilator [see Clinical Pharmacology (12.3)]. Regadenoson is chemically described as adenine, 2-[4-[(methylamino)carbonyl]-1H-pyrrolo[1-3-y]yl]-3,4-dihydroxy benzoic acid. Its empirical formula is: C17H17N3O7. 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 3.2 and 7.7.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Regadenoson is a low affinity agonist (K<sub>i</sub> ≈ 1.3 µM) for the A<sub>2A</sub> adenosine receptor, 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. Activation of the A<sub>2A</sub> adenosine receptor by regadenoson produces coronary vasodilation and increases coronary blood flow (CBF).

12.2 Pharmacodynamics

Coronary Blood Flow

LEXISCAN increases a rapid increase in CBF which is sustained for a short duration. In patients undergoing coronary angiography, pulsed-wave Doppler ultrasonography was used to measure the average peak velocity (APV) of coronary blood flow before injection and up to 30 minutes after administration of regadenoson (0.4 mg, intravenously). Mean APV increased to greater than 115 mm Hg for at least 10 minutes. The time to maximum hemodynamic effect was 97±14 seconds (n=6) and 221±20 seconds (n=4), respectively, for the 10 second and 30 second injections. The peaks effect (i.e., maximal increase) on CBF after the 10 second and 30 second injections were 217±15% and 297±33% above baseline, respectively. The times to peak effect on CBF were 17.2±2 seconds and 27.1±6 seconds, respectively.

12.3 Myocardial Uptake

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 duration of injection

A study in dogs compared the effects of intravenous injection of 2.5 µg/kg regadenoson (in 10 mL) over 10 seconds and 30 seconds on CBF. The duration of a two-fold increase in CBF was 9±14 seconds (n=6) and 221±20 seconds (n=4), respectively, for the 10 second and 30 second injections. The peak effects (i.e., maximal increase) on CBF after the 10 second and 30 second injections were 217±15% and 297±33% above baseline, respectively. The times to peak effect on CBF were 17.2±2 seconds and 27.1±6 seconds, respectively.

Effect of Adenosine A1 Antagonists

Aminophylline (100 mg, administered by slow intravenous injection over 60 seconds) injected 1 minute after 0.4 mg LEXISCAN in patients undergoing cardiac catheterization, was used 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)].

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 5.

Table 5 Hemodynamic Effects in Studies 1 and 2

<table>
<thead>
<tr>
<th>Vital Sign Parameter</th>
<th>LEXISCAN</th>
<th>ADENOSCAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 100 bpm</td>
<td>22%</td>
<td>13%</td>
</tr>
<tr>
<td>Increase &gt; 40 bpm</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Systolic Blood Pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 90 mm Hg</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Decrease &gt; 35 mm Hg</td>
<td>7%</td>
<td>8%</td>
</tr>
<tr>
<td>≥ 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>0.9%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Diastolic Blood Pressure</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>

Hemodynamic Effects Following Inadequate Exercise

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

Table 6 Hemodynamic Effects in Inadequate Exercise Stress Study

<table>
<thead>
<tr>
<th>Vital Sign Parameter</th>
<th>Group 1 / MPI 3 minutes following exercise (N=1075)</th>
<th>Group 2 / MPI 3 minutes following exercise (N=967)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 100 bpm</td>
<td>44%</td>
<td>31%</td>
</tr>
<tr>
<td>Increase &gt; 40 bpm</td>
<td>5%</td>
<td>16%</td>
</tr>
<tr>
<td>Systolic Blood Pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 90 mm Hg</td>
<td>2%</td>
<td>4%</td>
</tr>
<tr>
<td>Decrease &gt; 35 mm Hg</td>
<td>9%</td>
<td>10%</td>
</tr>
<tr>
<td>≥ 200 mm Hg</td>
<td>0.9%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Increase ≥ 50 mm Hg</td>
<td>2%</td>
<td>0.4%</td>
</tr>
<tr>
<td>≥ 180 mm Hg and increase of</td>
<td>5%</td>
<td>2%</td>
</tr>
</tbody>
</table>
concentration with a half-life of approximately 2 hours with loss of the pharmacodynamic effect. The terminal phase consists of a decline in plasma nature and best characterized by 3-compartment model. The maximal plasma concentration 12.3 Pharmacokinetics adverse reactions (dyspnea, wheezing) was greater with LEXISCAN compared to placebo. In a randomized, placebo-controlled clinical trial of 999 patients 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. Mucociliary and respiratory tract effects were observed more frequently in the LEXISCAN group compared to placebo [see Adverse Reactions (6.1)].

12.3 Pharmacokinetics

In healthy subjects, 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 the loss of the pharmacodynamic effect. The terminal phase 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.

Specific Populations

Renally Impaired Patients: The disposition of regadenoson was studied in 18 patients with various degrees of renal function and in 6 healthy subjects. Increasing renal impairment, from CrCl = 40–100 mL/min to 0–30 mL/min, did not affect regadenoson terminal clearance (CrCl = 40–100 mL/min). However, the maximal observed plasma concentrations as well as volume of distribution estimates were similar across the groups. The plasma concentration-time profiles were not significantly altered in the early stages after dosing when renal pharmacokinetic 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 have not been assessed; however, in in vitro study regadenoson was found to be dialyzable (CrCl = 30–50 mL/min) to total renal impairment (CrCl = 10–50 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 volunteers (CrCl = > 90 mL/min). However, the maximal observed plasma concentrations as well as volume of distribution estimates were similar across the groups. The plasma concentration-time profiles were not significantly altered in the early stages after dosing when renal pharmacokinetic effects are observed. No dose adjustment is needed in patients with hematocrit (5.1), (5.3), (5.5), (5.6) and (5.9) Toxicity

Cardiovascular

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 0.88, 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-dose 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, vessel constriction, inflammation, a thrombus and necrosis, with inflammation and thrombus persisting through day 8 (last observation day). Perivascular administration of LEXISCAN to rabbits resulted in hemorrhage, inflammation, postural 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.

14.4 Interactions

Agreement between LEXISCAN and ADENOSCAN 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 (CAD). Patients were randomized to treatment with either LEXISCAN or ADENOSCAN. 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 68 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 malignancy, and the presence of a hematoma or a heart transplant were excluded. A number of patients took cardiovascular medications on the day of the scan, including β-blockers (18%), calcium channel blockers (9%), and nitrates (6%). In the general population, 88% of patients had 0–1 segments showing reversible defects on the initial scan, 24% had 2–4 segments, and 9% had ≥ 5 segments. 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 LEXISCAN 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 LEXISCAN image was calculated by determining how frequently the patients assigned to each initial LEXISCAN 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 7).

Table 7 Agreement Rates in Studies 1 and 2

<table>
<thead>
<tr>
<th>Study</th>
<th>ADENOSCAN – ADENOSCAN Agreement Rate (± SE)</th>
<th>LEXISCAN – ADENOSCAN Agreement Rate (± SE)</th>
<th>Rate Difference (LEXISCAN – ADENOSCAN)</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>61 ± 3%</td>
<td>64 ± 4%</td>
<td>3 ± 4%</td>
<td>-6.5, 13.5</td>
</tr>
<tr>
<td>Study 2</td>
<td>62 ± 2%</td>
<td>63 ± 3%</td>
<td>1 ± 4%</td>
<td>-5.9, 13.9</td>
</tr>
</tbody>
</table>

Use of LEXISCAN in Patients with Inadequate Exercise Stress

The efficacy and safety of LEXISCAN administered 3 minutes (Group 1) or 1 hour (Group 2) following inadequate exercise stress were evaluated in an open-label randomized, multi-center, parallel-group study. Adequate exercise was defined as ≥ 35% maximum predicted heart rate and ≥ 5 METS. SPECT MPI was performed 60-90 minutes after LEXISCAN administration in Group 1 and 90-120 minutes after LEXISCAN administration in Group 2. Patients enrolled 1-14 days later to undergo a second stress MPI with LEXISCAN without exercise (MPI 2). All patients were referred for evaluation of coronary artery disease. Of the 1,147 patients randomized, a total of 1,073 patients received LEXISCAN and had interpretable SPECT images at all visits; 538 in Group 1 and 535 in Group 2. The median age of the patients was 62 years (range 28 to 90 years) and included 633 (69%) men and 440 (41%) women. Images from MPI 1 and MPI 2 for the groups were compared for presence or absence of myocardial ischemia. The level of agreement between the MPI 1 and MPI 2 readings in Group 1 was similar to the level of agreement between MPI 1 and MPI 2 readings in Group 2. However, two patients receiving LEXISCAN 3 minutes following inadequate exercise exercise a serious cardiac adverse reaction. No serious cardiac adverse reactions occurred in patients receiving LEXISCAN 1 hour following inadequate exercise stress [see Adverse Reactions (6.1), Clinical Pharmacology (12.2)].

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-dose 5 mL, pre-filled plastic Ansary® 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

Dispensing Information

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

Cardiovascular

Advise patients that they may be at increased risk of fatal and nonfatal heart attacks, abnormal heart rhythms, cardiac arrest, significant increase or decrease in blood pressure, or cerebrovascular accidents (stroke) with the use of LEXISCAN [see Warnings and Precautions (5.1), (5.3), (5.5), (5.6) and (5.9)].

Hypersensitivity

Inform patients that allergic reactions have been reported with LEXISCAN. Advise patients how to recognize such a reaction and when to seek medical attention [see Warnings and Precautions (5.4)].

Respiratory

Advise patients with COPD or asthma about the need for administration of pre- and post-study bronchodilator therapy and to call their clinician if they experience any shortness of breath or difficulty breathing following an MPI study with LEXISCAN [see Warnings and Precautions (5.7)].

Seizures

Advise patients that they may be at increased risk of seizures. Question patients about a history of seizures [see Warnings and Precautions (5.8)].

Lactation

Advise a woman to pump and discard breast milk for 10 hours after LEXISCAN administration [see Use in Specific Populations (8.2)].

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