

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 |
| Warnings and Precautions, Atrial Fibrillation/Atrial Flutter (5.3) | 07/2014 |
| Warnings and Precautions, Seizure (5.8) | 07/2014 |
| Warnings and Precautions, Cerebrovascular Accident (5.9) | 07/2014 |

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).

DOSAGE 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)

DOSAGE 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)
- Sinoatrial (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)

- Atrial Fibrillation/Atrial Flutter. New-onset or recurrent atrial fibrillation with rapid ventricular response and atrial flutter have been reported (5.3)
- Hypersensitivity, including Anaphylaxis. Anaphylaxis, angioedema, cardiac or respiratory arrest, respiratory distress, decreased oxygen saturation, hypotension, throat tightness, urticaria, and rashes have occurred. Have personnel and resuscitative equipment immediately available (5.4)
- Hypotension. Adenosine receptor agonists, including Lexiscan, induce vasodilation and hypotension. The risk of serious hypotension may be higher in patients with autonomic dysfunction, stenotic valvular heart disease, pericarditis or pericardial effusions, stenotic carotid artery disease with cerebrovascular insufficiency, or hypovolemia (5.5)
- Hypertension. Adenosine receptor agonists, including Lexiscan, may induce clinically significant increases in blood pressure particularly in patients with a history of hypertension and when the MPI includes low level exercise (5.6)
- Bronchoconstriction. Adenosine receptor agonists, including Lexiscan, may induce dyspnea, bronchoconstriction and respiratory compromise in patients with COPD or asthma. Resuscitative measures should be available (5.7)
- Seizure. Lexiscan may lower the seizure threshold. New onset or recurrence of convulsive seizures has occurred. Some seizures are prolonged and require urgent anticonvulsive management. Methylxanthine use is not recommended in patients who experience a seizure in association with Lexiscan (5.8)
- Cerebrovascular Accident (Stroke). Hemorrhagic and ischemic cerebrovascular accidents have occurred (5.9)

ADVERSE REACTIONS

The most common (incidence \geq 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, aminophylline 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)
- Dipyridamole may increase the activity of Lexiscan. When possible, withhold dipyridamole for at least two days prior to Lexiscan administration (7.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised 07/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

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

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Post-Marketing Experience

7 DRUG INTERACTIONS

- 7.1 Effects of Other Drugs on Lexiscan
- 7.2 Effect of Lexiscan on Other Drugs

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*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 post-marketing experience, third-degree heart block and asystole within minutes of Lexiscan administration have occurred [*see Adverse Reactions (6.2)*].

5.3 Atrial Fibrillation/Atrial Flutter

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

5.4 Hypersensitivity, Including Anaphylaxis

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

5.5 Hypotension

Adenosine receptor agonists, including Lexiscan, induce arterial vasodilation and hypotension. In clinical trials, decreased systolic blood pressure (> 35 mm Hg) was observed in 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 post-marketing experience, syncope, transient ischemic attacks and seizures have been observed [*see Adverse Reactions (6.2)*].

5.6 Hypertension

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

5.7 Bronchoconstriction

Adenosine receptor agonists, including Lexiscan, may cause dyspnea, bronchoconstriction, and respiratory compromise. Appropriate bronchodilator therapy and resuscitative measures should be available prior to Lexiscan administration [*see Adverse Reactions (6.1), Clinical Pharmacology (12.2), Overdosage (10) and Patient Counseling Information (17)].*

5.8 Seizure

Lexiscan may lower the seizure threshold. 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.

5.9 Cerebrovascular Accident (Stroke)

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

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

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

During clinical development, 1,651 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%)

| | Lexiscan N = 1,337 | Adenoscan N = 678 |
|--|-------------------------------|------------------------------|
| Dyspnea | 28% | 26% |
| Headache | 26% | 17% |
| Flushing | 16% | 25% |
| Chest Discomfort | 13% | 18% |
| Angina Pectoris or ST Segment Depression | 12% | 18% |
| Dizziness | 8% | 7% |
| Chest Pain | 7% | 10% |
| Nausea | 6% | 6% |
| Abdominal Discomfort | 5% | 2% |
| Dysgeusia | 5% | 7% |
| Feeling Hot | 5% | 8% |

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

| | Lexiscan N / N evaluable (%) | Adenoscan N / N evaluable (%) |
|--|---|--|
| Rhythm or conduction abnormalities [†] | 332/1275 (26%) | 192/645 (30%) |
| Rhythm abnormalities | 260/1275 (20%) | 131/645 (20%) |
| PACs | 86/1274 (7%) | 57/645 (9%) |
| PVCs | 179/1274 (14%) | 79/645 (12%) |
| First-degree AV block (PR prolongation > 220 msec) | 34/1209 (3%) | 43/618 (7%) |
| Second-degree AV block | 1/1209 (0.1%) | 9/618 (1%) |
| AV conduction abnormalities (other than AV blocks) | 1/1209 (0.1%) | 0/618 (0%) |
| Ventricular conduction abnormalities | 64/1152 (6%) | 31/581 (5%) |

* 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-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 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*

| | Asthma Cohort | | COPD Cohort | |
|---|---------------------|--------------------|---------------------|--------------------|
| | Lexiscan (N=356) | Placebo (N=176) | Lexiscan (N=316) | Placebo (N=151) |
| Overall Pre-specified Respiratory Adverse Reaction [†] | 12.9% | 2.3% | 19.0% | 4.0% |
| Dyspnea | 10.7% | 1.1% | 18.0% | 2.6% |
| Wheezing | 3.1% | 1.1% | 0.9% | 0.7% |
| FEV ₁ reduction >15% [‡] | 1.1% | 2.9% | 4.2% | 5.4% |

*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 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.

6.2 Post-Marketing Experience

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 block), asystole, marked hypertension, symptomatic hypotension in association with transient ischemic attack, seizures and syncope [see *Warnings and Precautions (5.1), (5.2), (5.3), (5.5), (5.6) and (5.8)*] have been reported. Some events required intervention with fluids and/or aminophylline [see *Overdosage (10)*]. QTc prolongation shortly after Lexiscan administration has been reported.

Central Nervous System

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

Gastrointestinal

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

Hypersensitivity

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

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, aminophylline 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)*]. 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.
- 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. $\leq 1\%$).

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

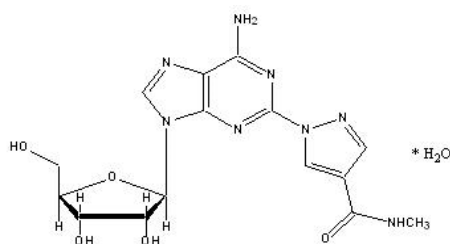
Lexiscan overdose may result in serious reactions [see *Warnings and Precautions (5)*]. In a study of healthy volunteers, symptoms of flushing, dizziness and increased heart rate were assessed as intolerable at Lexiscan doses greater than 0.02 mg/kg.

Aminophylline to Reverse Effects

Methylxanthines, such as caffeine, aminophylline, and theophylline, are competitive adenosine receptor antagonists and aminophylline has been used to terminate persistent pharmacodynamic 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). Methylxanthine use is not recommended in patients who experience a seizure in association with Lexiscan administration.

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-[4-[(methylamino)carbonyl]-1*H*-pyrazol-1-yl]-, monohydrate. Its structural formula is:



The molecular formula for regadenoson is $C_{15}H_{18}N_8O_5 \cdot H_2O$ 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)].

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

| Vital Sign Parameter | Lexiscan N = 1,337 | Adenoscan N = 678 |
|---|-------------------------------|------------------------------|
| Heart Rate | | |
| > 100 bpm | 22% | 13% |
| Increase > 40 bpm | 5% | 3% |
| Systolic Blood Pressure | | |
| < 90 mm Hg | 2% | 3% |
| Decrease > 35 mm Hg | 7% | 8% |
| ≥ 200 mm Hg | 1.9% | 1.9% |
| Increase ≥ 50 mm Hg | 0.7% | 0.8% |
| ≥ 180 mm Hg and increase of ≥ 20 mm Hg from baseline | 4.6% | 3.2% |
| Diastolic Blood Pressure | | |
| < 50 mm Hg | 2% | 4% |
| Decrease > 25 mm Hg | 4% | 5% |

| Vital Sign Parameter | Lexiscan N = 1,337 | Adenoscan N = 678 |
|----------------------|-----------------------|----------------------|
| ≥ 115 mm Hg | 0.9% | 0.9% |
| Increase ≥ 30 mm Hg | 0.5% | 1.1% |

Respiratory Effects

The A_{2B} 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 A_{2B} 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 (CL_{cr} 50 to < 80 mL/min) to moderate (CL_{cr} 30 to < 50 mL/min) to severe renal impairment (CL_{cr} < 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 (CL_{cr} ≥ 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 5 Agreement Rates in Studies 1 and 2

| | Study 1 | Study 2 |
|--|----------------|----------------|
| Adenoscan – Adenoscan Agreement Rate (\pm SE) | 61 \pm 3% | 64 \pm 4% |
| Adenoscan – Lexiscan Agreement Rate (\pm SE) | 62 \pm 2% | 63 \pm 3% |
| Rate Difference (Lexiscan – Adenoscan) (\pm SE) | 1 \pm 4% | -1 \pm 5% |
| 95% Confidence Interval | -7.5, 9.2% | -11.2, 8.7% |

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

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, hypersensitivity reactions, seizures, bronchoconstriction, or cerebrovascular accidents (stroke) with the use of Lexiscan [see *Warnings and Precautions* (5.1), (5.3), (5.4), (5.5), (5.6), (5.8) and (5.9)].

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

Question patients about a history of seizures.

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.

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

Only Lexiscan is the trademark of Astellas US, LLC. Other trademarks listed belong to their respective owners.

Revised: July 2014

14B008-LEX