

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-161

LABELING

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 administration

Initial U.S. Approval: 2008

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 vial: Injection solution containing regadenoson 0.4 mg/5 mL (0.08 mg/mL) (3)
- 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

- Fatal cardiac arrest, life threatening ventricular arrhythmias, or myocardial infarction may be induced by pharmacologic stress agents. Cardiac resuscitation equipment and trained staff should be available before administering Lexiscan. (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)
- 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. (5.3)
- Adenosine receptor agonists may induce bronchoconstriction and respiratory compromise in patients with COPD or asthma. Resuscitative measures should be available. (5.4)

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. (1-800-727-7003) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Methylxanthines, e.g., caffeine and theophylline, may interfere with the activity of Lexiscan (7.1)
- 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: 4/2008

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* 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 vial: Injection solution containing regadenoson 0.4 mg/5 mL (0.08 mg/mL).
- 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 cardiac arrest, life threatening ventricular arrhythmias, and myocardial infarction may result from the ischemia induced by pharmacologic stress agents. 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. 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. All episodes of AV block were asymptomatic and did not require intervention.

5.3 Hypotension

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 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.

5.4 Bronchoconstriction

Adenosine receptor agonists may cause bronchoconstriction and respiratory compromise. For patients with known or suspected bronchoconstrictive disease, chronic obstructive pulmonary disease (COPD) or asthma, appropriate bronchodilator therapy and resuscitative measures should be available prior to Lexiscan administration [*see Overdosage (10) and Patient Counseling Information (17.3)*].

The incidence of bronchoconstriction (FEV₁ reduction > 15% from baseline) was assessed in two clinical studies. In a randomized, controlled study of 49 patients with moderate to severe COPD, the rate of bronchoconstriction was 12% and 6%, for the Lexiscan and placebo groups, respectively. In a randomized, controlled study of 48 patients with mild to moderate asthma who had previously been shown to have bronchoconstrictive reactions to adenosine monophosphate, the rate of bronchoconstriction was the same (4%) for both the Lexiscan and placebo groups. In both studies, dyspnea was reported as an adverse reaction in the Lexiscan group (61% for patients with COPD; 34% for patients with asthma) while no subjects in the placebo group experienced dyspnea.

6 ADVERSE REACTIONS

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%)
1 st degree AV block (PR prolongation > 220 msec)	34/1209 (3%)	43/618 (7%)
2 nd 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

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 and may 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

Lexiscan is not known to 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 *Animal Toxicology and Pharmacology* (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%).

10 OVERDOSAGE

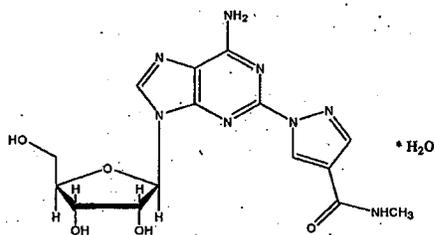
Lexiscan overdose may result in serious reactions [see *Warnings and Precautions* (5)]. In a study of healthy volunteers, symptoms of flushing, dizziness and increased heart rate were assessed as intolerable at Lexiscan doses greater than 0.02 mg/kg.

Aminophylline to Reverse Effects

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



The molecular formula for regadenoson is C₁₅H₁₈N₈O₅ • H₂O 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 vial or 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 ≈ 1.3 μM) for the A_{2A} adenosine receptor, with at least 10-fold lower affinity for the A₁ adenosine receptor (K_i > 16.5 μM), and weak, if any, affinity for the A_{2B} and A₃ 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

A placebo-controlled clinical study assessed the effects of oral caffeine (200 mg) on the regadenoson-induced increase in coronary flow reserve (CFR) using positron emission tomography (PET) with radiolabeled water. Healthy subjects took caffeine 200 mg orally or placebo approximately 2 hours prior to Lexiscan administration. Following Lexiscan administration, the median CFR in caffeinated subjects was 92% of the CFR in non-caffeinated subjects [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 or Adenoscan in Studies 1 and 2 are summarized in Table 3.

Table 3
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%
Diastolic Blood Pressure		
< 50 mm Hg	2%	4%
decrease >25 mm Hg	4%	5%

- **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.

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 ($CL_{Cr} \geq 80$ 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 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 hindlimb 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 1st 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 \geq 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 4).

Table 4
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 packages:

- Single-use 5 mL vials (NDC 0469-6501-05).
- 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.

Marketed by:
Astellas Pharma US, Inc.
Deerfield, IL 60015

Vials Manufactured by:
Baxter Pharmaceutical Solutions LLC
Bloomington, IN 47403

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.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Richard Pazdur
4/10/2008 04:42:07 PM