PRODUCT MONOGRAPH

SYSTEM WIDE

AN INFORMED BASIS FOR HEALTHCARE PROVIDERS

This Product Monograph provides an overview of Lexiscan in regard to product attributes and risks as well as the impact on potential stakeholders within the health system. When evaluating this information, decision-makers health-system-wide may wish to consider how the risks and attributes explained here affect not only the patient and physician at the point of care but also other members of the healthcare team. As you educate yourself, we encourage you to consider how the information presented here could impact your colleagues, such as ordering physicians, cardiovascular service line (CVSL) managers, and pharmacists.

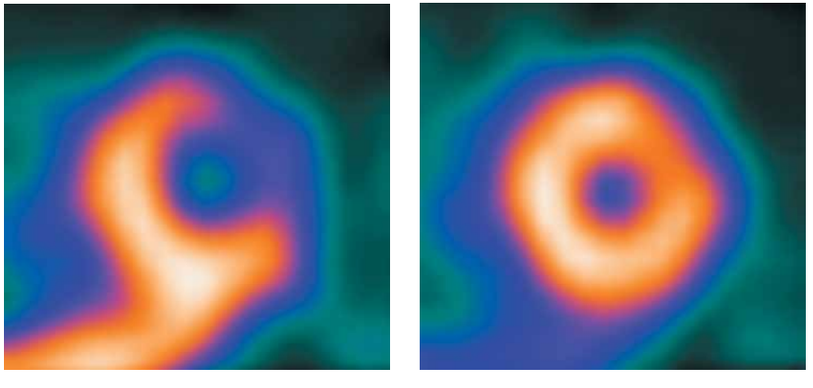
TABLE OF CONTENTS

PLEASE SEE FULL PRESCRIBING INFORMATION AT THE END OF THE DOCUMENT.

BACKGROUND

PHARMACOLOGIC STRESS RADIONUCLIDE MYOCARDIAL PERFUSION IMAGING

FIGURE 1. SPECT MPI IMAGES



Single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) performed during stress and at rest is an established method for diagnosing coronary artery disease (CAD), assessing risk of future cardiac events, and informing treatment decisions.[1]

While exercise is the preferred stress modality for MPI, many patients cannot achieve adequate workload (at least 85% of age-adjusted maximal predicted heart rate and 5 metabolic equivalents).[1,2] For these patients, pharmacologic stress may be used to mimic the effects of exercise on coronary blood flow.

The current ACCF/AHA Guidelines for the Diagnosis and Management of Patients with Stable Ischemic Heart Disease[1] recommend its use in patients with an intermediate- to high-pretest likelihood of CAD who are unable to exercise for[1]:

- Initial diagnosis in patients with suspected stable ischemic heart disease (SIHD)
- Risk assessment in patients with known SIHD
- Patients with SIHD with new or worsening symptoms not consistent with unstable angina
- Follow-up assessment (2 years or longer) in asymptomatic patients with SIHD with prior evidence of silent ischemia or at high risk for recurrent cardiac event, and who have an uninterpretable ECG, are unable to exercise to an adequate workload, or have a history of incomplete coronary revascularization

SYSTEM-WIDE CONSIDERATIONS FOR PHARMACOLOGIC STRESS AGENTS

Although vasodilator pharmacologic stress SPECT MPI is an established method of noninvasive cardiac imaging, there are several logistical and clinical issues that should be considered (see Tables 1 and 2).

TABLE 1. CLINICAL CONSIDERATIONS

How selective is the agent to the adenosine receptor?
Can the agent be used in patients who try but fail to achieve adequate exercise stress?
Is use of the agent supported in patient populations with comorbidities?

TABLE 2. LOGISTICAL CONSIDERATIONS

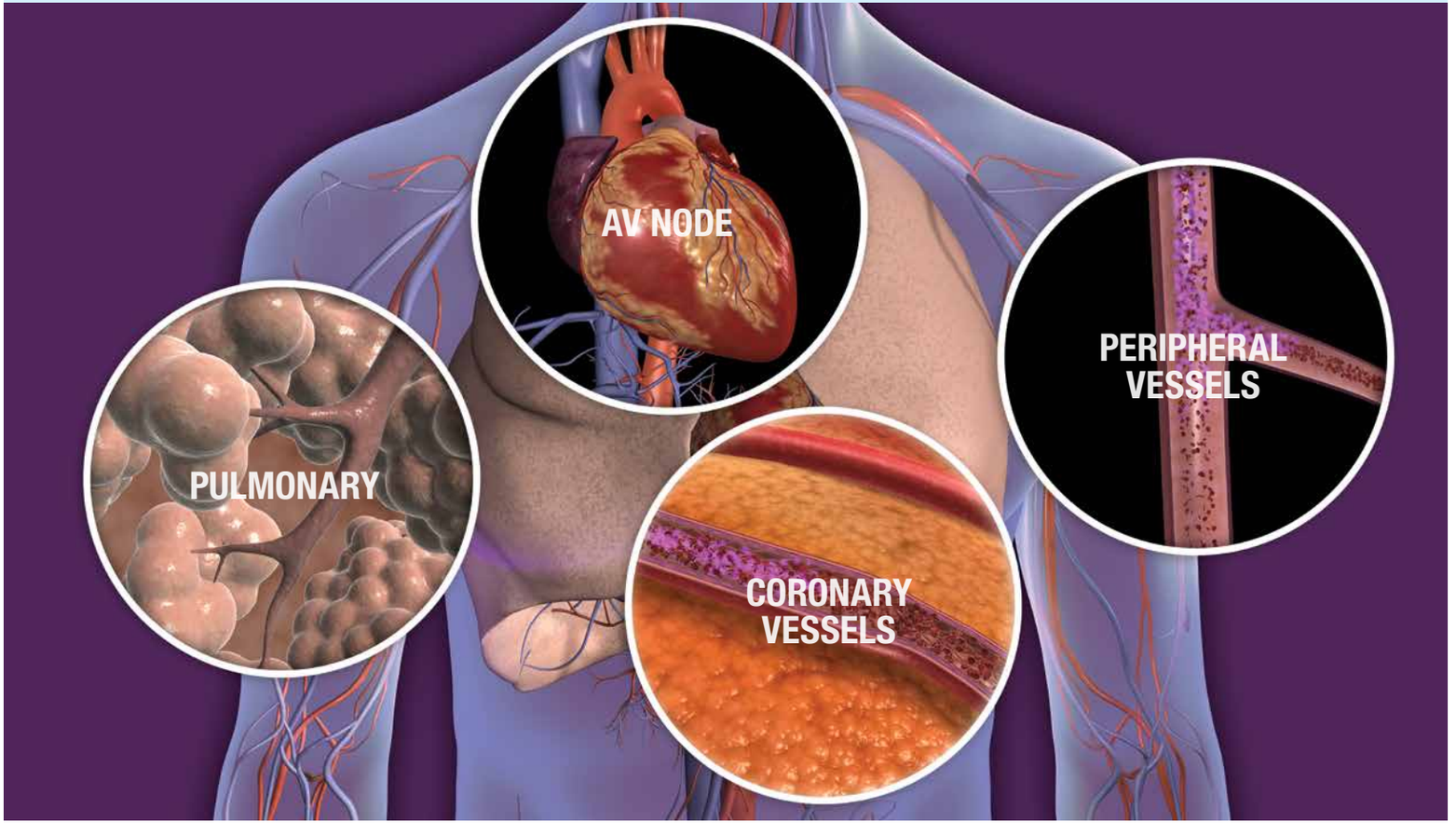
Does the agent require an infusion pump to administer?
What are the storage requirements for the agent?
Are compounding and mixing required to prepare the agent for administration?
Does the agent require weight-based dosing calculation?

These considerations are meaningful to providers at the point of care in the nuclear lab, but they also affect other providers within the institution. Pharmacists are affected by dosing, administration, and storage requirements, whereas ordering physicians should understand the relevance of clinical considerations for their patients with comorbidities or for whom the ability to exercise is uncertain. CVSL managers may wish to consider the implications of clinical and logistical factors on cardiology workflows.

ADENOSINE RECEPTOR-MEDIATED PHARMACOLOGIC STRESS

There are 4 types of adenosine receptors—A_1, A_{2A}, A_{2B}, and A_3—located in various tissues throughout the body (see Figure 2).[3] The A_1 and A_2 receptors mediate the known cardiovascular effects of adenosine. Specifically, the A_{2A} adenosine receptor has been shown to mediate coronary vasodilation (see Figure 3).[4]

FIGURE 2. ADENOSINE RECEPTOR DISTRIBUTION



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RECEPTOR AFFINITY

The potency of an agonist is determined in part by its affinity, defined as the attractive force between certain atoms or molecules[5]; in this case, the pharmacologic stress agent and its receptor. A high-affinity agonist binds readily to its receptor and remains bound, eliciting a prolonged response, whereas a low-affinity agonist binds less tightly to its receptor and disassociates quickly, causing a physiologic response that terminates rapidly (see Figure 4).[6]

FIGURE 3. CORONARY ADENOSINE RECEPTORS

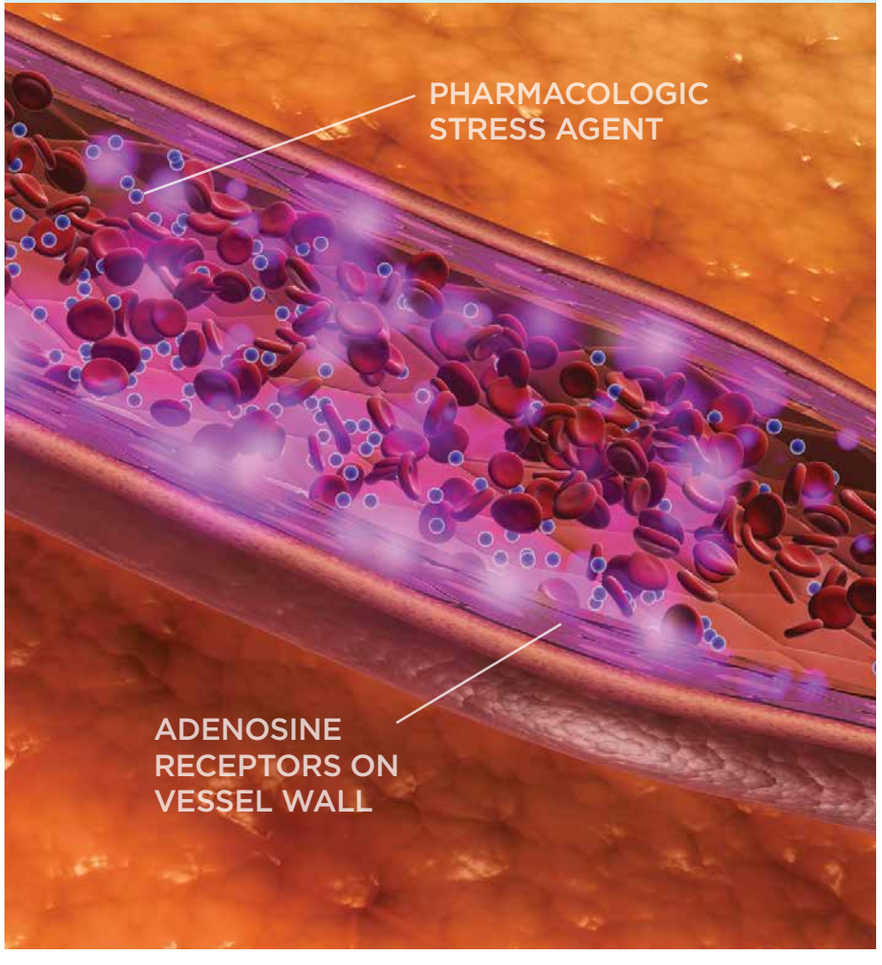
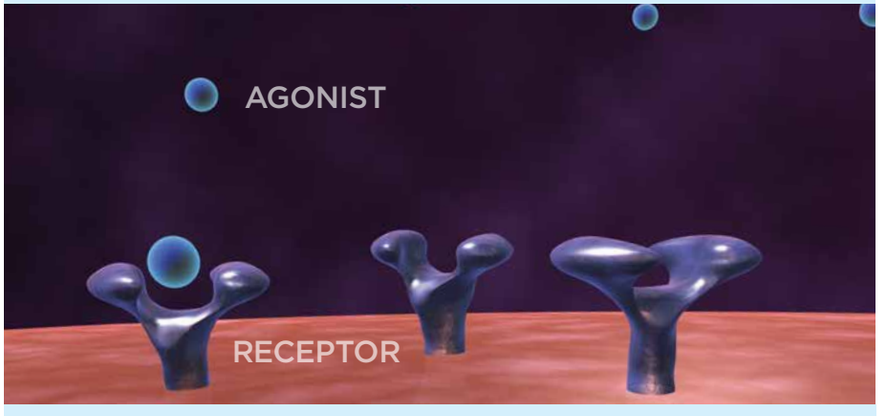
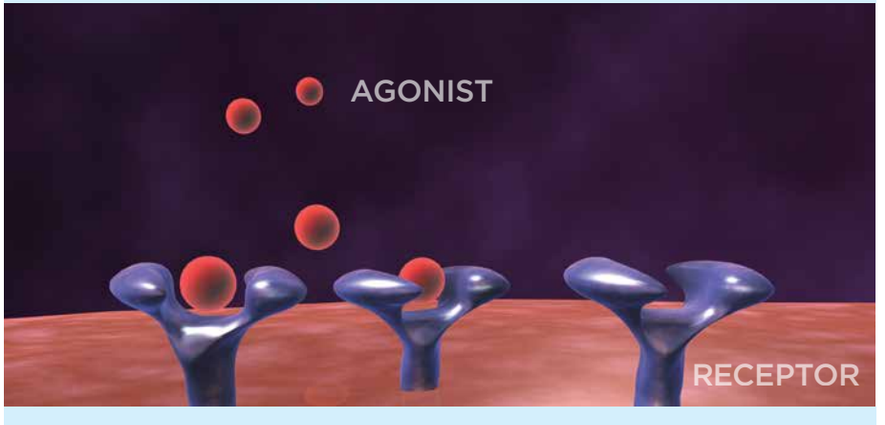


FIGURE 4. RECEPTOR AFFINITY

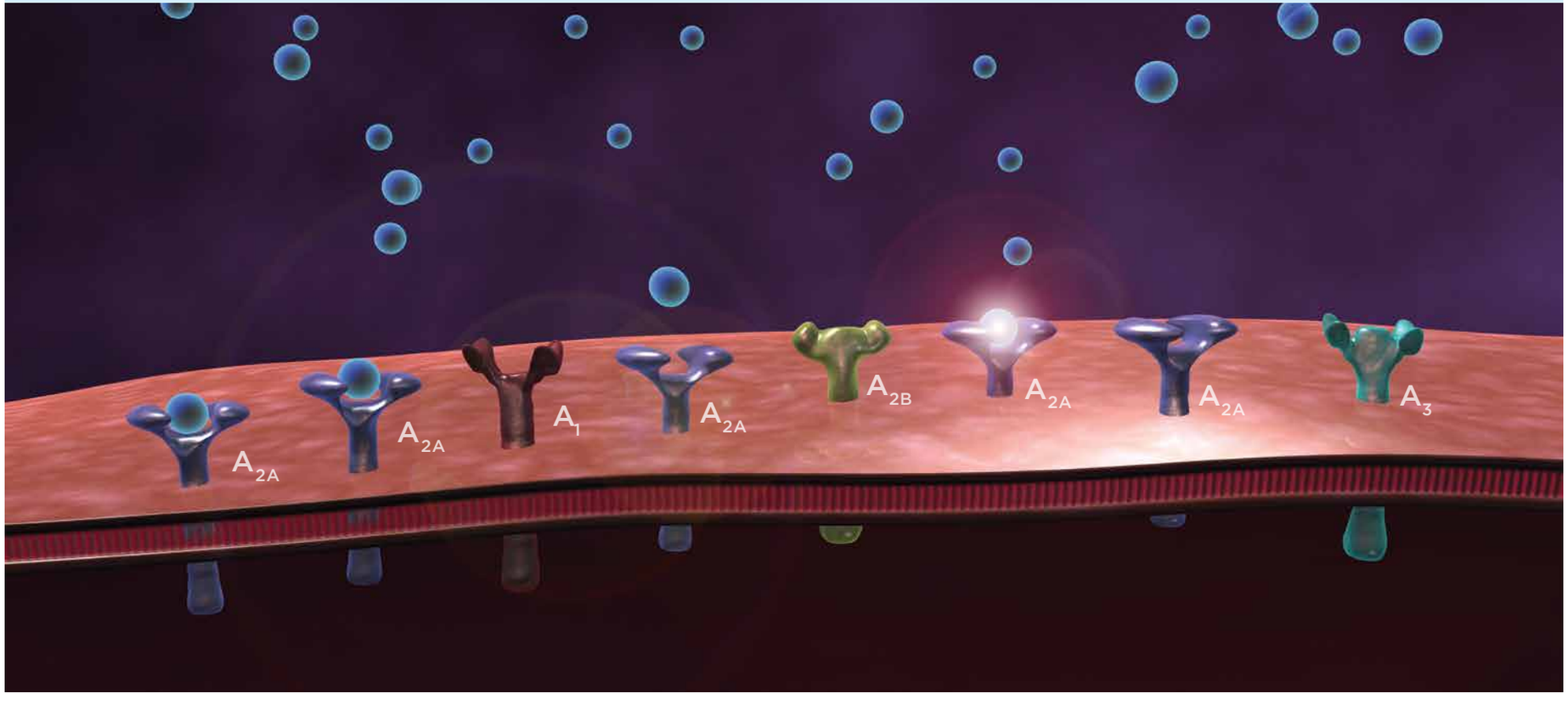


LOW AFFINITY = SHORT DURATION OF EFFECT



HIGH AFFINITY = LONG DURATION OF EFFECT

FIGURE 5. CORONARY A_{2A} RECEPTOR RESERVE[7]



THE A_{2A} ADENOSINE RECEPTOR RESERVE

Physiologic response to A_{2A} adenosine receptor activation is determined in part by the tissue distribution of the receptor, the ability of a particular agonist to activate the receptor, and the efficiency of coupling of receptor activation to the response.[7]

In the coronary arteries, there is a high density of A_{2A} adenosine receptors called a receptor reserve, and activation of a fraction of receptors is needed to achieve maximal coronary vasodilation (see Figure 5).[7]

INDICATION

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

PLEASE SEE ADDITIONAL IMPORTANT SAFETY INFORMATION THROUGHOUT.
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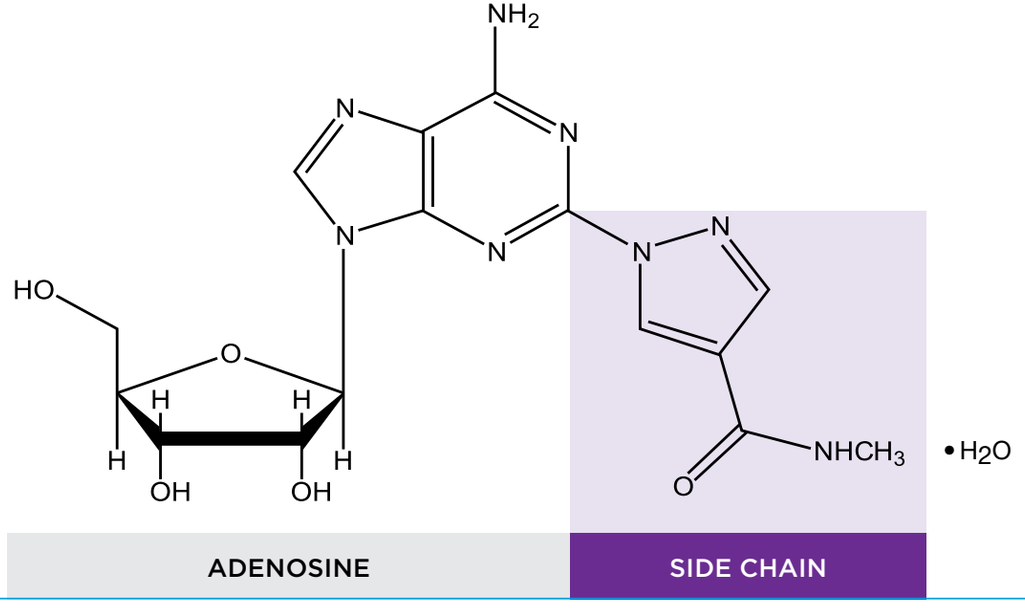
LEXISCAN® (REGADENOSON) INJECTION

Lexiscan is a pharmacologic stress agent indicated for radionuclide MPI in patients unable to undergo adequate exercise stress.[8] Lexiscan is a modified form of the adenosine molecule with an additional side chain (see Figure 6).[3,8] Activation of the A_{2A} adenosine receptor by Lexiscan produces coronary vasodilation and increases coronary blood flow.[8]

FIGURE 6. CHEMICAL STRUCTURE OF LEXISCAN[8]



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.

VISIT LEXISCAN.COM FOR MORE INFORMATION.

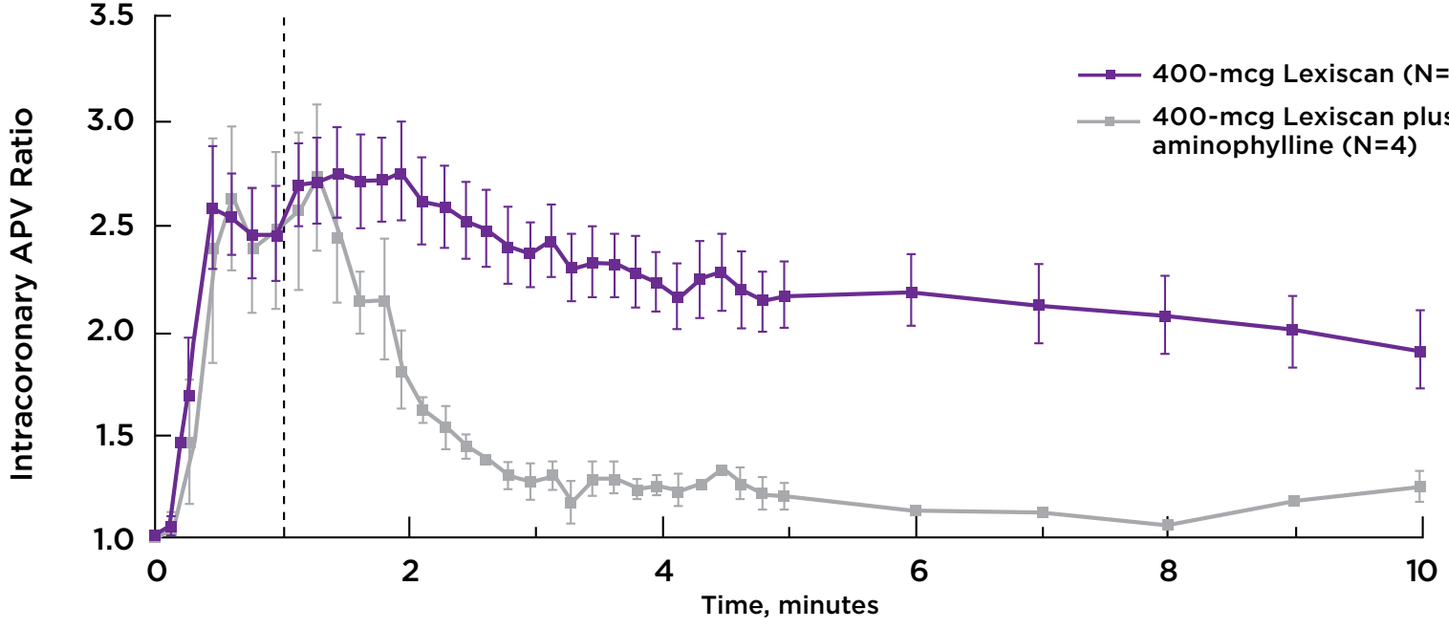
Lexiscan® (regadenoson) injection 0.4 mg/5 mL

CLINICAL PHARMACOLOGY

MECHANISM OF ACTION AND PHARMACODYNAMICS

The affinity of Lexiscan® (regadenoson) injection for the A_{2A} adenosine receptor determines, in part, the duration of coronary vasodilation.[6] Lexiscan is a low-affinity ($K_i \approx 1.3$ μM) A_{2A} adenosine receptor agonist, with at least 10-fold lower affinity for the A_1 adenosine receptor (K_i >16.5 μM), and weak, if any, affinity for the A_{2B} and A_3 adenosine receptors.[8] In the context of the A_{2A} adenosine receptor reserve in the coronary arteries, a selective, low-affinity A_{2A} adenosine receptor agonist like Lexiscan can elicit a full and potent increase in coronary blood flow.[6] The effect of Lexiscan on coronary blood flow (a rapid increase to ≥2.5-fold baseline) is sustained for approximately 2.3 minutes,[9] and decreases to less than twice the baseline level within 10 minutes (see Figure 7).[8,9] Subjects with decompensated congestive heart failure or severe left ventricular dysfunction (ejection fraction <35%) were excluded; therefore, the effects on these patients cannot be concluded from these data.[9] Thus, the combination of low affinity for the A_{2A} adenosine receptor and the presence of a coronary artery A_{2A} adenosine receptor reserve allows Lexiscan to rapidly induce and sustain maximal coronary blood flow to conduct stress radionuclide MPI.[6]

FIGURE 7. LEXISCAN-INDUCED HYPEREMIA[9,a]



Time to near-peak flow velocity: 33 seconds. Mean duration at ≥2.5-fold above baseline: 2.3 minutes.

[a]The effects of Lexiscan (400-mcg, ≤10-second IV bolus, N=8) alone or followed 1 minute later by aminophylline (100-mg slow IV bolus, N=4) on average peak velocity (APV) of intracoronary blood flow were studied in patients with mild to moderate stable ischemic heart disease and nonobstructive coronary artery stenosis (≤70% stenosis in any vessel).[9]

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PHARMACOKINETICS

In healthy subjects, the plasma concentration of Lexiscan reaches the peak 1-4 minutes after injection and parallels the onset of the pharmacodynamic response to produce a rapid increase in blood flow, and then it decreases in 3 phases[8,10]:

In the initial phase, the half-life is 2-4 minutes[8]

In the intermediate phase, the plasma concentration of Lexiscan decreases more slowly (average half-life of ≈30 minutes), coinciding with loss of pharmacodynamic effect[8]

In the final phase, there is a decline in Lexiscan plasma concentration (half-life of ≈2 hours)[8]

In addition to receptor affinity, the duration of the pharmacologic effect of Lexiscan is also a function of the concentration at the receptor site over time. For a complete description of the pharmacokinetic profile of Lexiscan, see page 29.

IMPORTANT SAFETY INFORMATION (CONTINUED)

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.

VISIT LEXISCAN.COM FOR MORE INFORMATION.

Lexiscan® (regadenoson) injection 0.4 mg/5 mL

DOSING AND ADMINISTRATION

Based on data from phase 2 trials,[9,11] the recommended intravenous (IV) dose of Lexiscan is 5 mL (0.4 mg).[8] No dose adjustment is needed to account for body weight. In a population pharmacokinetic analysis, body weight and body mass index (BMI) were not found to have a significant effect on the pharmacokinetics of Lexiscan.[10] Lexiscan comes in a prefilled syringe and is administered as an IV injection within 10 seconds into a peripheral vein using a 22-gauge or larger catheter or needle.[8] The injection of Lexiscan is immediately followed by a 5-mL saline flush over approximately 10 seconds,[12] and the radiotracer is administered 10-20 seconds after the saline flush.[8]

SELECT SAFETY INFORMATION

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

FIGURE 8. DOSING AND ADMINISTRATION ATTRIBUTES

NO
weight-based calculations

NO
vial draw-up needed with prefilled syringe

NO
pump required

LEXISCAN OFFERS PUMP-FREE, STANDARD-DOSE, IV-INJECTION ADMINISTRATION WITH STRESS AGENT AND RADIOTRACER ADMINISTERED IN 1 MINUTE.

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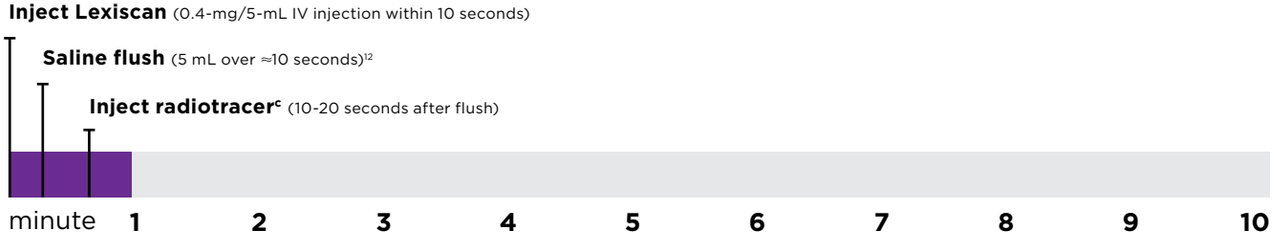
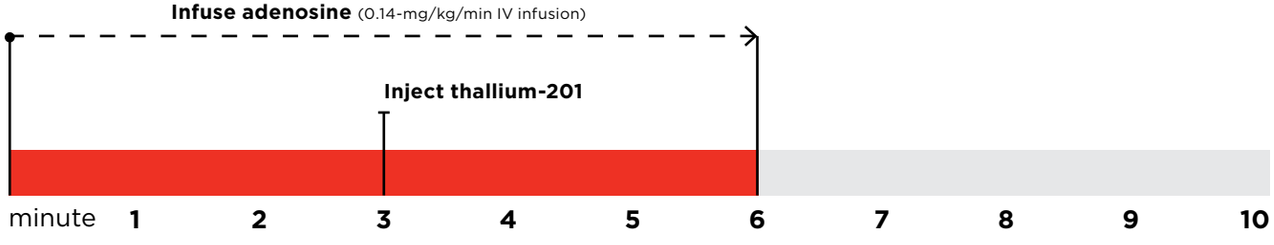
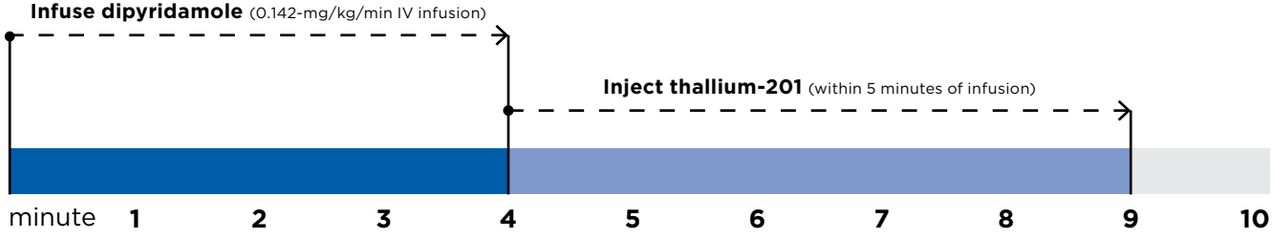
DOSING AND ADMINISTRATION OF LEXISCAN® (REGADENOSON) INJECTION[8,a,b]



DOSING AND ADMINISTRATION OF ADENOSINE[13,d]



DOSING AND ADMINISTRATION OF DIPYRIDAMOLE INJECTION[14,d]



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.[8]

[a]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.

[b]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.

[c]Flush after radionuclide administration per your lab protocol.

[d]Dosage and administration information for adenosine and dipyridamole is for informational purposes only. **No efficacy or safety comparison is implied**.

IMPORTANT SAFETY INFORMATION (CONTINUED)

WARNINGS AND PRECAUTIONS

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.

VISIT LEXISCAN.COM FOR MORE INFORMATION.

Lexiscan® (regadenoson) injection 0.4 mg/5 mL

CLINICAL EFFICACY

IMAGING STUDIES

ADVANCE MPI PIVOTAL TRIALS

The efficacy and safety of Lexiscan injection were determined relative to Adenoscan in 2 randomized, double-blind studies (**AD**enoscan **V**ersus reg**A**denoso**N** **C**omparative **E**valuation for **M**yocardial **P**erfusion **I**maging [ADVANCE MPI 1 and 2]) in 2015 patients referred for pharmacologic stress MPI.[8,15,16] The efficacy, safety, and tolerability of Adenoscan and Lexiscan were also compared in subgroup analyses based on patient age, gender, BMI, and a history of diabetes mellitus (DM).[15]

All patients underwent a baseline Adenoscan gated SPECT MPI (6-minute infusion of 0.14 mg/kg/min).[8] Patients were then randomized 2:1 to a Lexiscan MPI or Adenoscan MPI using the same protocol as the baseline scan.[8,16] The primary objective of the studies was to demonstrate noninferiority in the strength of agreement between sequential Adenoscan and Lexiscan images, and the strength of agreement between 2 sequential Adenoscan images for detecting the extent of reversible perfusion defects.[15,16] Image assessment was performed by 3 independent expert readers who were blinded to treatment assignment.[15,16] A total of 1871 patients had images considered valid for the primary efficacy evaluation.[8,15] Baseline demographics were not significantly different between the 2 groups.[15] The agreement rates in studies 1 and 2, respectively, were 62% and 63% for Lexiscan vs baseline Adenoscan, and 61% and 64% for Adenoscan vs baseline Adenoscan, representing a nonsignificant difference of 1% (see Table 3).[8] Agreement rates were similar regardless of patient age, gender, BMI, or history of DM.[15] Thus, the ADVANCE MPI trials demonstrated that Lexiscan was similar to Adenoscan for assessing the presence and extent of reversible perfusion defects.[8,15,16]

TABLE 3. AGREEMENT RATES FOR DETECTING THE EXTENT OF REVERSIBLE PERFUSION DEFECTS[8]

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

All patients underwent initial baseline Adenoscan imaging and then were randomized to a second imaging procedure with either Lexiscan (0.4 mg) or Adenoscan (140 mcg/kg/min). Using the 17-segment model, average agreement rates were determined between the baseline and randomized scans by 3 independent, blinded readers. Data were studied from 2 randomized, double-blind, multicenter studies of 2015 patients with known or suspected coronary artery disease who were indicated for pharmacologic stress MPI. Of those patients, 1871 had images considered valid for the primary efficacy study (Lexiscan: n=1240; Adenoscan: n=631).[8,15]

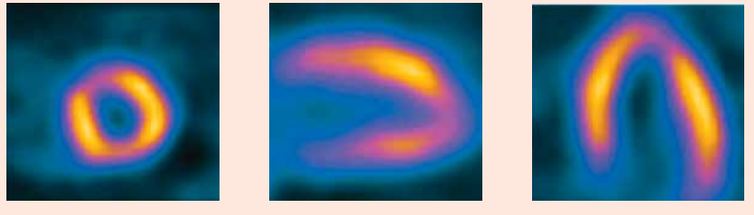
Overall, and for each patient subgroup, Lexiscan was also similar to Adenoscan for (1) detecting the presence or absence of any perfusion defect,[15] (2) image quality,[15] (3) detecting defect type,[16] and (4) side-by-side comparisons (Figure 9).[16]

ADVANCE MPI PIVOTAL TRIALS (CONTINUED)

FIGURE 9. SAME-PATIENT COMPARISON OF SPECT MPI IMAGES OBTAINED DURING LEXISCAN AND ADENOSCAN STRESS

LEXISCAN® (REGADENOSON) INJECTION STRESS IN SPECT MPI

ADENOSCAN® (ADENOSINE) INJECTION STRESS IN SPECT MPI



Scan images provided by Manuel D. Cerqueira, MD.

EXERRT

The efficacy and safety of Lexiscan following inadequate exercise stress compared to Lexiscan administered at rest were evaluated in an open-label randomized, multicenter, noninferiority study (**EXE**rcise to **R**egadenoson in **R**ecovery **T**rial [EXERRT]). Adequate exercise was defined as ≥85% maximum predicted heart rate and 5 metabolic equivalents. Patients who failed to achieve adequate exercise stress were randomized into 1 of 2 groups. Group 1 received Lexiscan 3 minutes following inadequate exercise, and Group 2 rested 1 hour after inadequate exercise to allow hemodynamics to return to baseline prior to receiving Lexiscan. SPECT MPI was performed 60-90 minutes after Lexiscan administration in each group (MPI 1). Patients in both groups returned 1-14 days later to undergo a second stress MPI with Lexiscan without exercise (MPI 2).[8]

Of the 1147 patients randomized, a total of 1073 patients received Lexiscan and had interpretable SPECT scans at all visits; 538 in Group 1 and 535 in Group 2. Images from MPI 1 and MPI 2 were compared for presence or absence of perfusion defects. The level of agreement between the MPI 1 and MPI 2 reads in Group 1 was similar to the level of agreement between MPI 1 and MPI 2 reads in Group 2. However, 2 patients receiving Lexiscan 3 minutes following inadequate exercise experienced a serious cardiac adverse reaction. No serious cardiac adverse reactions occurred in patients receiving Lexiscan 1 hour following inadequate exercise.[8]

IMPORTANT SAFETY INFORMATION (CONTINUED)

WARNINGS AND PRECAUTIONS

Atrial Fibrillation/Atrial Flutter

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

VISIT LEXISCAN.COM FOR MORE INFORMATION.

Lexiscan® (regadenoson) injection 0.4 mg/5 mL

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

CONTRAINDICATIONS[8]

Do not administer Lexiscan® (regadenoson) injection to patients with second- or third-degree AV block or sinus node dysfunction unless these patients have a functioning artificial pacemaker.

WARNINGS AND PRECAUTIONS[8]

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 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 1 dropped beat was observed in 1 patient receiving Lexiscan. In postmarketing experience, third-degree heart block 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. Have personnel and resuscitative equipment immediately available.

Hypotension

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

Hypertension

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.

TABLE 4. RHYTHM OR CONDUCTION ABNORMALITIES[a] IN ADVANCE MPI 1 AND 2[8]

	Lexiscan® (regadenoson) injection n/N eva luable (%)	Adenoscan® (adenosine) injection n/N evaluable (%)
Rhythm or conduction abnormalities[b]	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%)

AV = atrioventricular; PACs = premature atrial contractions; PVCs = premature ventricular contractions.

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

Most increases resolved within 10 to 15 minutes, but in some cases, increases were observed at 45 minutes following administration. In postmarketing experience, cases of potentially clinically significant hypertension have been reported, particularly 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.

IMPORTANT SAFETY INFORMATION (CONTINUED)

WARNINGS AND PRECAUTIONS

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.

VISIT LEXISCAN.COM FOR MORE INFORMATION.

Lexiscan® (regadenoson) injection 0.4 mg/5 mL

IMPORTANT SAFETY INFORMATION (CONTINUED)

WARNINGS AND PRECAUTIONS[8]

Seizure

Lexiscan® (regadenoson) injection 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.

BRONCHOCONSTRICTIVE DISEASE SAFETY STUDY[8,17]

In a randomized, placebo-controlled clinical trial of 999 patients with a diagnosis or risk factors for CAD and concurrent asthma (n=532) or stable chronic obstructive pulmonary disease (COPD; n=467), the incidence of bronchoconstriction (FEV_1 reduction >15% from baseline) 2 hours postbaseline was not statistically significantly different for Lexiscan compared with placebo: 1.1% (Lexiscan) and 2.9% (placebo) for the asthma cohort, and 4.2% (Lexiscan) and 5.4% (placebo) for the COPD cohort.

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

The overall incidence of prespecified respiratory adverse events in the respiratory safety study was statistically significantly greater with Lexiscan compared with placebo (see Table 5).[8] Moderate (2.5%) or severe (<1%) respiratory reactions were observed more frequently in the Lexiscan group compared with placebo.[8] Most respiratory adverse reactions resolved without therapy.[8] Short-acting bronchodilators were used by <2% of patients at the time of the selected respiratory adverse event in both groups and respiratory cohorts.[17]

In patients who experienced a >15% decrease in FEV_1 from baseline to the 2-hour postbaseline assessment, no patients who received placebo nor any patients in the asthma cohort reported a selected respiratory adverse event up to 1 day after study drug administration.[17] In the COPD cohort, 2 patients reported dyspnea within 2 hours after Lexiscan administration, 2 patients reported dyspnea within 1 day after Lexiscan administration, and 1 patient reported wheezing within 1 day after receiving Lexiscan.[17] Only 2 patients receiving Lexiscan in the COPD group were given aminophylline for treatment of bradycardia (n=1) and dyspnea (n=1).[17]

PLEASE SEE ADDITIONAL IMPORTANT SAFETY INFORMATION THROUGHOUT.
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TABLE 5. INCIDENCE OF PRESPECIFIED RESPIRATORY TREATMENT-EMERGENT ADVERSE EVENTS IN THE RESPIRATORY SAFETY STUDY[8,12]

	Asthma Cohort		COPD Cohort	
	Lexiscan (N=356)	Placebo (N=176)	Lexiscan (N=316)	Placebo (N=151)
Overall prespecified respiratory adverse event[a]	12.9%[b]	2.3%	19.0%[b]	4.0%
Dyspnea	10.7%[b]	1.1%	18.0%[b]	2.6%
Wheezing	3.1%	1.1%	0.9%	0.7%
Obstructive airways disorder	0.3%	0%	-	-
Dyspnea exertional	-	-	0%	0.7%
Tachypnea	-	-	0.3%	0%

- = event not observed for this cohort.
[a]Patients may have reported more than 1 type of adverse event. Adverse events were collected up to 24 hours following drug administration.
[b]*P*<0.0001 vs placebo.

During selected respiratory adverse events, there was no difference in the use of short-acting ß$_2$-adrenergic receptor agonists between the Lexiscan® (regadenoson) injection and placebo groups within 2 hours and within 24 hours of study drug administration.[17]

IMPORTANT SAFETY INFORMATION (CONTINUED)

WARNINGS AND PRECAUTIONS

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.

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Lexiscan® (regadenoson) injection 0.4 mg/5 mL

TABLE 6. INCIDENCE OF BRONCHOCONSTRICTION[a] AT 2 HOURS AFTER LEXISCAN® (REGADENOSON) INJECTION OR PLACEBO ADMINISTRATION IN PATIENTS WITH ASTHMA[17]

ASTHMA COHORT BY ASTHMA STEP CLASSIFICATION		Lexiscan[b]	Placebo
OVERALL FREQUENCY		4/351 (1.1%)	5/174 (2.9%)
Step	**Asthma medications**		
1	SABA PRN	2/107 (1.9%)	0/47 (0%)
2	Low-dose ICS or any of the following: cromolyn, LTRA, nedocromil, theophylline	1/33 (3.0%)	0/27 (0%)
3	Low-dose ICS + LABA, or medium-dose ICS, or low-dose ICS + either LTRA, theophylline, or zileuton	1/49 (2.0%)	3/31 (9.7%)
4	Medium-dose ICS + LABA or medium-dose ICS + either LTRA, theophylline, or zileuton	0/84 (0%)	0/23 (0%)
5	High-dose ICS + LABA	0/44 (0%)	1/25 (4.0%)
6	High-dose ICS + LABA + oral steroids	-	1/2 (50.0%)
	Unable to classify	0/34 (0%)	0/19 (0%)

ASTHMA COHORT BY FEV_1 BASELINE VALUE[12]	Lexiscan[b]	Placebo
<60% predicted	0/18 (0%)	0/9 (0%)
≥60% to ≤80% predicted	3/151 (2.0%)	2/66 (3.0%)
>80% predicted	1/182 (0.5%)	3/99 (3.0%)

[a]Bronchoconstriction was defined as an FEV_1 reduction >15% from baseline.
[b]*P*=NS for all comparisons of Lexiscan vs placebo (Cochran-Mantel-Haenszel).
ICS=inhaled corticosteroid; LABA=long-acting β_2-agonist; LTRA=leukotriene receptor antagonist; PRN=when needed; SABA=short-acting β_2-agonist.

IMPORTANT SAFETY INFORMATION (CONTINUED)

WARNINGS AND PRECAUTIONS

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.

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TABLE 7. INCIDENCE OF BRONCHOCONSTRICTION[a] AT 2 HOURS AFTER LEXISCAN OR PLACEBO ADMINISTRATION IN PATIENTS WITH COPD[17]

COPD COHORT BY COPD SEVERITY		Lexiscan[b]	Placebo
OVERALL FREQUENCY		13/313 (4.2%)	8/147 (5.4%)
Stage I Mild	FEV_1/FVC <0.70 FEV_1 ≥80% predicted	0/43 (0%)	1/20 (5.0%)
Stage II Moderate	FEV_1/FVC <0.70 50% ≤ FEV_1 <80% predicted	9/148 (6.1%)	1/72 (1.4%)
Stage III Severe	FEV_1/FVC <0.70 30% ≤ FEV_1 <50% predicted	2/60 (3.3%)	2/28 (7.1%)
Stage IV Very Severe	FEV_1/FVC <0.70 FEV_1 <30% predicted or FEV_1 <50% predicted plus chronic respiratory failure	0/4 (0%)	1/2 (50.0%)
	Not calculated	2/58 (3.4%)	3/25 (12.0%)

COPD COHORT BY FEV_1 BASELINE VALUE[12]	Lexiscan[b]	Placebo
<60% predicted	10/195 (5.1%)	5/86 (5.8%)
≥60% to ≤80% predicted	3/94 (3.2%)	3/55 (5.5%)
>80% predicted	0/24 (0%)	0/6 (0%)

FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity, the amount of air that can be forcibly exhaled after taking the deepest breath possible.
[a]Bronchoconstriction was defined as an FEV_1 reduction >15% from baseline.
[b]*P* = NS for all comparisons of Lexiscan vs placebo (Cochran-Mantel-Haenszel).

FEV_1 is the volume of air that can be forcibly exhaled in 1 second after taking a deep breath—a measure of pulmonary function used to evaluate patients with bronchoconstrictive disease. The percentage of patients experiencing a >15% decrease in FEV_1 at 2 hours postbaseline was not statistically significantly different between the Lexiscan and placebo groups in the asthma or COPD cohorts.[8] The change in FEV_1 with Lexiscan or placebo was not affected by baseline disease severity in either the asthma or the COPD cohort.[17]

ADVERSE REACTIONS

ADVANCE MPI PIVOTAL TRIALS

In the ADVANCE MPI phase 3 clinical trials, 2015 patients were included in the safety analysis.[8,15] The rate of adverse reactions was similar with Lexiscan® (regadenoson) injection and Adenoscan® (adenosine) injection (80% vs 83%).[8] Most adverse reactions had an onset soon after dosing that resolved within 15 minutes of dosing; headache, if present, resolved within 30 minutes of dosing.[8] Aminophylline was used to treat adverse reactions in 3% of Lexiscan patients and 2% of Adenoscan patients.[8]

TABLE 8. ADVERSE REACTIONS WITH INCIDENCE ≥5% IN PHASE 3 CLINICAL TRIALS[8]

	Lexiscan, % (N=1337)	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

Patients should be informed prior to Lexiscan administration that shortness of breath, headache, and flushing are the most common reactions experienced during a Lexiscan MPI.[8] Lexiscan overdosage may result in serious reactions.[8] 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).[8] Methylxanthine use is not recommended in patients who experience a seizure in association with Lexiscan administration.[8]

EXERRT

Safety analysis was performed in 1142 patients who participated in the EXERRT trial. The most common adverse events were similar in type and incidence to those seen in pivotal trials (see Table 8) and the timing of Lexiscan administration following inadequate exercise did not alter the common adverse reaction profile. Table 9 presents a comparison of cardiac events of interest for the 2 groups with the overall rate of cardiac events being higher in Group 1 (3%) compared with Group 2 (0.5%).[8]

TABLE 9. CARDIAC EVENTS OF INTEREST IN INADEQUATE EXERCISE STRESS STUDY[8]

	Group 1 / MPI 1 Lexiscan 3 minutes following exercise (N=575)	Group 2 / MPI 1 Lexiscan 1 hour following exercise (N=567)
Cardiac Event[a]	**17 (3.0%)**	**3 (0.5%)**
Holter/12-Lead ECG Abnormality		
ST-T Depression (≥2 mm)	13 (2.3%)	2 (0.4%)
ST-T Elevation (≥1 mm)	3 (0.5%)	1 (0.2%)
Acute coronary syndrome	1 (0.2%)	0
Myocardial infarction	1 (0.2%)	0

[a]A clinically significant cardiac event was defined as any of the following events found on the Holter ECG/12-lead ECG within 1 hour after regadenoson administration: ventricular arrhythmias (sustained ventricular tachycardia, ventricular fibrillation, Torsade de Pointes, ventricular flutter); ST-T depression (≥2 mm); ST-T elevation (≥1 mm); AV block (2:1 AV block, AV Mobitz I, AV Mobitz II, complete heart block); sinus arrest >3 seconds in duration
Or
- Treatment Emergent Adverse Event (TEAE) per the MedDRA SMQ (narrow Scope) for myocardial infarction

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

IMPORTANT SAFETY INFORMATION (CONTINUED)

WARNINGS AND PRECAUTIONS

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.

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Lexiscan® (regadenoson) injection 0.4 mg/5 mL

RENAL IMPAIRMENT SAFETY STUDY

The safety of Lexiscan was assessed in a randomized, placebo-controlled clinical trial of 504 patients (Lexiscan n=334 and placebo n=170) with a diagnosis or risk factors for CAD and NKF K/DOQI stage 3 or stage 4 renal impairment (GFR 15-59 mL/min/1.73 m^2).[8] In this study, the frequency of treatment-emergent adverse events was greater with Lexiscan compared with placebo (62.6% vs 21.2%, respectively, *P*<0.0001; see Table 10).[18] No serious adverse events were reported through the 24-hour follow-up period.[8]

TABLE 10. INCIDENCE OF TREATMENT-EMERGENT ADVERSE EVENTS ≥5% IN THE RENAL IMPAIRMENT SAFETY STUDY[18]

	Stage 3 Renal Impairment		Stage 4 Renal Impairment	
	Lexiscan (N=287)	Placebo (N=145)	Lexiscan (N=47)	Placebo (N=25)
Any adverse event	182 (63.4%)	30 (20.7%)	27 (57.4%)	6 (24.0%)
Headache	70 (24.4%)	11 (7.6%)	13 (27.7%)	1 (4.0%)
Dyspnea	54 (18.8%)	1 (0.7%)	10 (21.3%)	0
Chest discomfort	44 (15.3%)	1 (0.7%)	5 (10.6%)	0
Nausea	42 (14.6%)	1 (0.7%)	7 (14.9%)	1 (4.0%)
Dizziness	30 (10.5%)	1 (0.7%)	2 (4.3%)	0
Flushing	38 (13.2%)	3 (2.1%)	2 (4.3%)	0
Dysgeusia	14 (4.9%)	4 (2.8%)	4 (8.5%)	2 (8.0%)

AMINOPHYLLINE USE IN CLINICAL TRIALS OF LEXISCAN® (REGADENOSON) INJECTION

Studies on the safety of Lexiscan show that the use of aminophylline to treat serious and/or persistent adverse reactions to Lexiscan aligns with the safety data from the ADVANCE MPI pivotal clinical trials (see Table 11).[8,17,18]

TABLE 11. USE OF AMINOPHYLLINE IN SUBJECTS RECEIVING LEXISCAN IN LARGE CLINICAL TRIALS[8,17,18]

	Subjects Receiving Lexiscan	Subjects Experiencing an Adverse Event	Aminophylline Use
ADVANCE MPI 1 and 2	1337	80%	3%
Respiratory Safety Study	356 (asthma) 316 (COPD)	66% (asthma) 61.1% (COPD)	0% (asthma) 0.6% (COPD)
Renal Impairment Safety Study	334	62.6%	0.3%

IMPORTANT SAFETY INFORMATION (CONTINUED)

WARNINGS AND PRECAUTIONS

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.

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Lexiscan® (regadenoson) injection 0.4 mg/5 mL

PHARMACODYNAMICS

HEMODYNAMIC EFFECTS

ADVANCE MPI PIVOTAL TRIALS

In phase 3 trials, the majority of patients experienced an increase in heart rate and a decrease in blood pressure after administration of Lexiscan® (regadenoson) injection.[8] Adenosine receptor agonists including Lexiscan induce arterial vasodilation and hypotension.[8] Decreased systolic blood pressure (>35 mm Hg) was observed in 7% of patients, and decreased diastolic blood pressure (>25 mm Hg) was observed in 4% of patients within 45 minutes of Lexiscan administration.[8] Compared with Adenoscan® (adenosine) injection, the effect of Lexiscan on heart rate and blood pressure had a more rapid onset and a slower return to baseline (see Table 12).[8]

TABLE 12. HEMODYNAMIC EFFECTS[8]

Vital Sign Parameter	Lexiscan (N=1337)	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%
≥115 mm Hg	0.9%	0.9%
Increase ≥30 mm Hg	0.5%	1.1%

IMPORTANT SAFETY INFORMATION (CONTINUED)

WARNINGS AND PRECAUTIONS

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.

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EXERRT

In a clinical trial of patients unable to achieve adequate exercise stress, hemodynamic effects differed between patients receiving Lexiscan 3 minutes following inadequate exercise compared with patients receiving Lexiscan at rest. Heart rates >100 bpm were reported more frequently in patients receiving Lexiscan following inadequate exercise (44%) as was a decrease in systolic blood pressure (>35 mm Hg) (29%). The changes were not associated with any clinically significant adverse reaction. Maximum hemodynamic changes are presented in Table 13.[8]

TABLE 13. HEMODYNAMIC EFFECTS IN INADEQUATE EXERCISE STRESS STUDY[8]

Vital Sign Parameter	Group 1/MPI 1 Lexiscan 3 minutes following exercise (N=575)	Group 2/MPI 1 Lexiscan 1 hour following exercise (N=567)
Heart rate		
>100 bpm	44%	31%
Increase >40 bpm	5%	16%
Systolic blood pressure		
<90 mm Hg	2%	4%
Decrease >35 mm Hg	29%	10%
≥200 mm Hg	0.9%	0.4%
Increase ≥50 mm Hg	2%	0.4%
≥180 mm Hg and increase of ≥20 mm Hg from baseline	5%	2%
Diastolic blood pressure		
<50 mm Hg	3%	3%
Decrease >25 mm Hg	6%	5%
≥115 mm Hg	0.7%	0.4%
Increase ≥30 mm Hg	2%	1%

EFFECT OF METHYLXANTHINES

A multicenter, double-blind, randomized clinical study assessed the effects of oral caffeine (200 mg, 400 mg, and placebo) on the number of reversible defects observed with Lexiscan SPECT MPI. Patients with known or suspected myocardial ischemia recommended for MPI received a baseline rest/stress MPI followed by a second stress MPI. Patients received caffeine or placebo approximately 90 minutes prior to completing the second Lexiscan stress MPI. Overall, 207 patients completed the study (caffeine 200 mg, n=70; caffeine 400 mg, n=71; placebo, n=66).[19]

Following caffeine administration, the mean number of reversible defects identified was reduced by approximately 60%; the mean change in the number of reversible defects detected from the baseline Lexiscan stress scan was 0.12 3 0.981 for the placebo group, –0.61 3 1.097 for the 200 mg caffeine group, and –0.62 3 1.367 for the 400 mg caffeine group. The changes observed in the caffeine groups were statistically significantly different than the change observed in the placebo group (*P*<0.001), indicating that reversible ischemic defects will be less detectible if caffeine is ingested prior to MPI with Lexiscan.[19]

FIGURE 10. EFFECT OF METHYLXANTHINES

NO
coffee, tea, or other caffeinated beverages

NO
caffeine-containing drugs

NO
theophylline or aminophylline

Methylxanthines (eg, caffeine, aminophylline, and theophylline) are nonspecific adenosine receptor antagonists, which interfere with the vasodilatory activity of Lexiscan® (regadenoson) injection and should be avoided for at least 12 hours prior to radionuclide MPI testing[8]

Question patients about a history of seizures

PHARMACOKINETICS

CLEARANCE

Clearance increases with increasing body weight.[8] Age, gender, and race appear to have minimal effects on the pharmacokinetics of Lexiscan, which supports standard-dose, IV-injection administration for all patients.[8,10]

METABOLISM AND EXCRETION[8]

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

RENALLY IMPAIRED PATIENTS

The disposition of Lexiscan was studied in 18 subjects with various degrees of renal impairment (creatinine clearance [CLcr] <30-79 mL/min) and in 6 healthy subjects (CLcr ≥80 mL/min).[8,20] With increasing renal impairment, the fraction of Lexiscan excreted unchanged in urine and the renal clearance decreased, and the elimination half-life increased compared with healthy subjects.[8,20]

The maximum observed plasma concentrations, as well as volume of distribution estimates, were similar across the groups. Plasma concentration-time profiles were not significantly altered early after dosing when most pharmacologic effects and clinically meaningful effects on coronary blood flow are observed.[8,20] In addition, adverse reactions and heart rate responses were similar across all levels of renal function.[20]

No dose adjustment of Lexiscan is needed in patients with renal impairment, including patients with end-stage renal disease (ESRD) and/or dependent on dialysis. Of note, the pharmacokinetics of Lexiscan in patients with ESRD on dialysis have not been assessed; however, in an *in vitro* study, regadenoson was found to be dialyzable.[8]

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.[8]

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.

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Lexiscan® (regadenoson) injection 0.4 mg/5 mL

GERIATRIC PATIENTS[8]

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

DRUG INTERACTIONS[8]

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

Methylxanthines (eg, caffeine, aminophylline, and theophylline) are nonspecific adenosine receptor antagonists that interfere with the vasodilation activity of Lexiscan. 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.

HOW SUPPLIED AND STORAGE REQUIREMENTS[8]

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

SUPPORT SERVICES

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

To set up a Lexiscan inservice, please contact Customer Service at **1-800-888-7704**.

For general questions and product information, please contact Medical Communications at **1-800-727-7003**.

For questions about reimbursement, please visit **LexiscanSupportSolutions.com** or call **1-800-477-6472**.

You can find more information about Lexiscan and Astellas Pharma US, Inc., by visiting **Lexiscan.com** or **us.astellas.com.**

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SUMMARY

LEXISCAN® (REGADENOSON) INJECTION IS A STANDARD-DOSE, IV INJECTION PHARMACOLOGIC STRESS AGENT INDICATED FOR RADIONUCLIDE MPI IN PATIENTS UNABLE TO UNDERGO ADEQUATE EXERCISE STRESS[8]

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

[a]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.

IMPORTANT SAFETY INFORMATION (CONTINUED)

ADVERSE REACTIONS

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.

VISIT LEXISCAN.COM FOR MORE INFORMATION.

Lexiscan®
(regadenoson) injection
0.4 mg/5 mL

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Lexiscan®
(regadenoson) injection

astellas

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 ----------

Dosage and Administration (2) 5/2018
Warnings and Precautions, Myocardial Ischemia (5.1) 5/2018

---------- INDICATIONS AND USAGE ----------

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

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

---------- DOSAGE FORMS AND STRENGTHS ----------

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

---------- CONTRAINDICATIONS ----------

Do not administer LEXISCAN to patients with:

- Second- or third-degree AV block, or
- sinus node dysfunction

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

---------- WARNINGS AND PRECAUTIONS ----------

- Myocardial Ischemia. Fatal cardiac events have occurred. Avoid use in patients with symptoms or signs of acute myocardial ischemia, for example unstable angina or cardiovascular instability, who may be at greater risk. Cardiac resuscitation equipment and trained staff should be available before administration (5.1).
- 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, 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 chronic obstructive pulmonary disease (COPD) or asthma. Resuscitative measures should be available (5.7).
- Seizure. LEXISCAN may lower the seizure threshold. New onset or recurrence of convulsive seizures has occurred. Some seizures are prolonged and require urgent anticonvulsive management. Methylxanthine use is not recommended in patients who experience a seizure in association with LEXISCAN (5.8).
- Cerebrovascular Accident (Stroke). Hemorrhagic and ischemic cerebrovascular accidents have occurred (5.9).

---------- ADVERSE REACTIONS ----------

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

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: 5/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

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

- Patients should be instructed to avoid consumption of any products containing methylxanthines, including caffeinated coffee, tea or other caffeinated beverages, caffeine-containing drug products, aminophylline and theophylline for at least 12 hours before a scheduled radionuclide MPI [*see Drug Interactions (7.1) and Clinical Pharmacology (12.2)*].
- 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.
- Administer LEXISCAN as an intravenous injection within 10 seconds into a peripheral vein using a 22 gauge or larger catheter or needle.
- Administer a 5 mL saline flush immediately after the injection of LEXISCAN.
- Administer the radionuclide myocardial perfusion imaging agent 10–20 seconds after the saline flush. The radionuclide may be injected directly into the same catheter as LEXISCAN.

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

Do not administer LEXISCAN to patients with:

- Second- or third-degree AV block, or
- sinus node dysfunction

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

5 WARNINGS AND PRECAUTIONS

5.1 Myocardial Ischemia

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

5.2 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 [s*ee 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 minutes of LEXISCAN administration. The risk of serious hypotension may be higher in patients with autonomic dysfunction, hypovolemia, left main coronary artery stenosis, stenotic valvular heart disease, pericarditis or pericardial effusions, or stenotic carotid artery disease with cerebrovascular insufficiency. In post-marketing experience, syncope, transient ischemic attacks and seizures have been observed [*see Adverse Reactions (6.2)*].

5.6 Hypertension

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

5.7 Bronchoconstriction

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

5.8 Seizure

LEXISCAN may lower the seizure threshold; obtain a seizure history. New-onset or recurrence of convulsive seizures has occurred following LEXISCAN injection. Some seizures are prolonged and require emergent anticonvulsive management. Aminophylline may increase the risk of seizures associated with LEXISCAN injection. 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 patients were exposed to LEXISCAN, with most receiving 0.4 mg as a rapid (≤ 10 seconds) intravenous injection. Most of these patients received LEXISCAN in two clinical studies that enrolled patients who had no history of bronchospastic 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 hours 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 of 999 patients with asthma (n = 532) or stable chronic obstructive pulmonary disease (n = 467), the overall incidence of pre-specified respiratory adverse reactions was greater in the LEXISCAN group compared to the placebo group ($p < 0.001$). Most respiratory adverse reactions resolved without therapy; a few patients received aminophylline or a short-acting bronchodilator. No differences were observed between treatment arms in the reduction of >15% from baseline at two-hours in FEV_1 (Table 3).

Table 3 Respiratory Adverse Effects*

	Asthma Cohort		Chronic Obstructive Pulmonary Disease (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 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, dyspnea exertional, 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 NKFK/DOQI Stage III or IV renal impairment (defined as GFR 15-59 mL/min/1.73 m^2), 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

	Group 1 / MPI 1 LEXISCAN 3 minutes following exercise (N=575)	Group 2 / MPI 1 LEXISCAN 1 hour following exercise (N=567)
Cardiac Event*	17 (3.0%)	3 (0.5%)
Holter/12-Lead ECG Abnormality		
ST-T Depression (≥ 2 mm)	13 (2.3%)	2 (0.4%)
ST-T Elevation (≥ 1 mm)	3 (0.5%)	1 (0.2%)
Acute coronary syndrome	1 (0.2%)	0
Myocardial infarction	1 (0.2%)	0

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

Or

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

Or

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

Central Nervous System

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.

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

Risk Summary

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

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

Data

Animal Data

Reproductive studies in rats showed that regadenoson doses 10 and 20 times the maximum recommended human dose (MRHD) based on body surface area caused reduced fetal body weights and significant ossification delays in fore- and hind limb phalanges and metatarsals; maternal toxicity also occurred at these doses. Skeletal variations were increased in all treated groups. In rabbits, maternal toxicity occurred at regadenoson doses administered during organogenesis 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 the breastfed infant, or the effects on milk production. Because of the potential risk of serious cardiac reactions in the breastfed infant, advise the nursing mother to pump and discard breast milk for 10 hours after administration of LEXISCAN.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

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

8.6 Renal Impairment

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

10 OVERDOSAGE

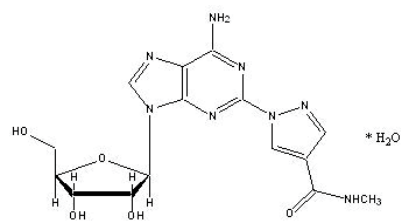
LEXISCAN overdosage may result in serious reactions [*see Warnings and Precautions (5)*]. In a study of healthy volunteers, symptoms of flushing, dizziness and increased heart rate were assessed as intolerable at LEXISCAN doses greater than 0.02 mg/kg.

Aminophylline to Reverse Effects

Methylxanthines, such as caffeine, aminophylline, and theophylline, are competitive 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 [*see Warnings and Precautions (5.8)*].

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 $C_{15}H_{18}N_8O_5 \bullet H_2O$ 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 ($K_i \approx 1.3$ μM) for the A_{2A} adenosine receptor, with at least 10-fold lower affinity for the A_1 adenosine receptor ($K_i > 16.5$ μM), 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 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 97±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 seconds and 27±6 seconds, respectively.

Effect of Aminophylline

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 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 5.

Table 5 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%
≥ 115 mm Hg	0.9%	0.9%
Increase ≥ 30 mm Hg	0.5%	1.1%

Hemodynamic Effects Following Inadequate Exercise

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

Table 6 Hemodynamic Effects in Inadequate Exercise Stress Study

Vital Sign Parameter	Group 1 / MPI 1 LEXISCAN 3 minutes following exercise (N=575)	Group 2 / MPI 1 LEXISCAN 1 hour following exercise (N=567)
Heart Rate		
> 100 bpm	44%	31%
Increase > 40 bpm	5%	16%
Systolic Blood Pressure		
< 90 mm Hg	2%	4%
Decrease > 35 mm Hg	29%	10%
≥ 200 mm Hg	0.9%	0.4%
Increase ≥ 50 mm Hg	2%	0.4%
≥ 180 mm Hg and increase of ≥ 20 mm Hg from baseline	5%	2%

Table 6 continued

Diastolic Blood Pressure		
< 50 mm Hg	3%	3%
Decrease > 25 mm Hg	6%	5%
≥ 115 mm Hg	0.7%	0.4%
Increase ≥ 30 mm Hg	2%	1%

Respiratory Effects

The A_{2B} and A_3 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 A_3 adenosine receptors.

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. 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 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 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.

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

Patients with End Stage Renal Disease: The pharmacokinetics of regadenoson in patients on dialysis has not been assessed; however, in an *in vitro* study regadenoson was found to be dialyzable.

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

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

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 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.

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 7).

Table 7 Agreement Rates in Studies 1 and 2

	Study 1	**Study 2**
ADENOSCAN – ADENOSCAN Agreement Rate (± SE)	61 ± 3%	64 ± 4%
ADENOSCAN – LEXISCAN Agreement Rate (± SE)	62 ± 2%	63 ± 3%
Rate Difference (LEXISCAN – ADENOSCAN) (± SE)	1 ± 4%	-1 ± 5%
95% Confidence Interval	-7.5, 9.2%	-11.2, 8.7%

Use of LEXISCAN in Patients with Inadequate Exercise Stress

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

All patients were referred for evaluation of coronary artery disease. Of the 1,147 patients randomized, a total of 1,073 patients received LEXISCAN and had interpretable SPECT scans at all visits; 538 in Group 1 and 535 in Group 2. The median age of the patients was 62 years (range 28 to 90 years) and included 633 (59%) men and 440 (41%) women.

Images from MPI 1 and MPI 2 for the two groups were compared for presence or absence of perfusion defects. The level of agreement between the MPI 1 and the MPI 2 reads in Group 1 was similar to the level of agreement between MPI 1 and MPI 2 reads in Group 2. However, two patients receiving LEXISCAN 3 minutes following inadequate exercise experienced a serious cardiac adverse reaction. No serious cardiac adverse reactions occurred in patients receiving LEXISCAN 1 hour following inadequate exercise stress [*see Adverse Reactions (6.1), Clinical Pharmacology (12.2)*].

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 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

Drug Interaction

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 [*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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