

U.S. Pharmacist

PRODUCT INFORMATION GUIDE



Advances in Pharmacologic Stress: Lexiscan® (regadenoson) injection

A Standard-Dose, IV Injection in a Prefilled Syringe

SPECIAL ADVERTISING SECTION

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ADVANCES IN PHARMACOLOGIC STRESS: LEXISCAN® (REGADENOSON) INJECTION



A STANDARD-DOSE, IV INJECTION IN A PREFILLED SYRINGE

Lexiscan is the latest pharmacologic stress agent for use in myocardial perfusion imaging (MPI). The simplified dosing and administration procedure of Lexiscan may help both pharmacies and nuclear cardiology laboratories increase procedural efficiency.

BACKGROUND

ESTABLISHED UTILITY OF MYOCARDIAL PERFUSION IMAGING

MPI with single-photon emission computed tomography (SPECT) is the most commonly performed stress imaging test in the United States.¹ Approximately 7 million MPI procedures were performed in 2008.²

MPI can be a clinically useful and cost-effective part of an overall strategy for coronary artery disease (CAD) testing³ by providing prognostic information that can inform patient management decisions.⁴⁻⁷ MPI can help identify patients at lower risk for cardiac events, and thereby avoid unnecessary invasive procedures,⁴⁻⁶ and can also help identify those higher risk patients who are candidates for invasive cardiac procedures.^{4,7} It is most useful in the evaluation of patients with an intermediate likelihood of angiographically significant CAD as based on age, sex, symptoms, risk factors, and the results of exercise treadmill testing (when available).⁸

The reported sensitivity and specificity of exercise-stress MPI for detecting significant CAD (ie, $\geq 50\%$ stenosis on coronary angiography) have varied widely⁸ but are generally believed to be 90% and 90%, respectively, using technetium-99m (^{99m}Tc)-sestamibi as the radionuclide tracer, and 90% and 80% using thallium-201 (²⁰¹Tl).⁹ Normalcy rates (ie, the rate of normal test results in patients with a very low likelihood of CAD) are in the 80% to 90% range for SPECT MPI with ²⁰¹Tl and generally higher than 90% with ^{99m}Tc-sestamibi.⁹

PHARMACOLOGIC STRESS

While exercise is the preferred method of stress for SPECT MPI,¹⁰ patients must be able to exercise to 85% of their maximal predicted heart rate, or 5 metabolic equivalents (METs), to obtain adequate test results.^{8,10} However, many patients are unable to exercise adequately for MPI due to a variety of reasons, such as certain conditions, physical limitations, and lack of motivation.

When patients are referred for MPI but are unable to exercise to an adequate endpoint, pharmacologic agents that produce certain physiologic effects similar to those of exercise (most importantly, vasodilation) are used. Pharmacologic stress agents are currently used in almost half of all MPI procedures.²

TRADITIONAL PHARMACOLOGIC STRESS AGENTS

AGENTS

For years, the 2 primary agents used for pharmacologic stress were the vasodilators Adenoscan® (adenosine injection) and dipyridamole. Adenoscan, commercially available since 1995,¹¹ had long been the most widely used agent in the US until recently.² Dipyridamole was the first agent approved for pharmacologic stress in MPI, in 1990.¹¹

Another agent, dobutamine, is considered a secondary pharmacologic stress agent.¹⁰ Dobutamine is not actually indicated for use in MPI¹² and is generally used only in patients who require pharmacologic stress but have contraindications to vasodilators—primarily bronchospastic airway disease, such as asthma or chronic obstructive pulmonary disease (COPD).¹⁰

ADENOSCAN AND DIPYRIDAMOLE DOSING AND ADMINISTRATION

Both Adenoscan and dipyridamole require individualized dosing based on patient weight, and timed administration via an infusion pump.^{13,14} Adenoscan is administered in a dose of 140 mcg/kg/min infused over 6 minutes, for a total dose of 0.84 mg/kg.¹³ Dipyridamole is administered in a dose of 0.142 mg/kg/min infused over 4 minutes, for a total dose of 0.57 mg/kg.¹⁴

Because these agents require weight-based dosing, the hospital pharmacy is generally responsible for drawing up and preparing the correct dose for each scheduled MPI procedure. For pharmacies that supply drugs for busy nuclear cardiology laboratories, pharmacologic stress dose preparation can take a great deal of pharmacists' time.

Additionally, a chance of dosing errors exists at several steps in the process. For example, if the wrong patient weight is obtained or communicated, the dose will be incorrect. The potential for dosing errors also exists in preparing the dose and in the laboratory itself, during infusion (eg, pump programming errors or pump failure).

LEXISCAN® (REGADENOSON) INJECTION

SELECTIVE A_{2A} ADENOSINE RECEPTOR AGONIST

Lexiscan is the latest vasodilator to be approved, in 2008, for use in MPI¹⁵ and has overtaken Adenoscan as the most widely used agent in the US.² The active ingredient in Lexiscan, regadenoson, is a variant of the adenosine molecule (Figure 1).^{13,15}

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

All 3 vasodilators work through the activation of adenosine receptors in the coronary arteries.¹³⁻¹⁵ There are 4 types of adenosine receptors—A₁, A_{2A}, A_{2B}, and A₃.¹⁶ The A_{2A} receptor mediates coronary vasodilation.¹⁷ Because the coronary arteries contain a relatively high density of A_{2A} adenosine receptors—a receptor reserve—an agonist with a relatively low affinity for the A_{2A} receptor can still elicit a full and potent increase in intracoronary blood flow.¹⁶

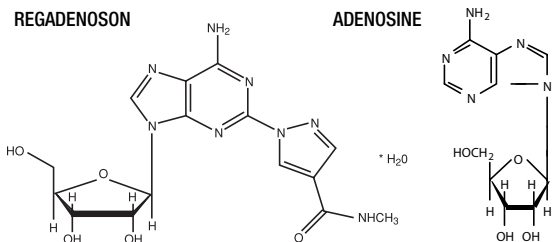
Adenoscan directly but nonselectively binds to and activates adenosine receptors.¹³ Dipyridamole indirectly activates adenosine receptors by inhibiting the reuptake of endogenous adenosine¹⁴; therefore, the various receptors are activated nonselectively.

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Figure 1. Molecular Structure of Regadenoson and Adenosine^{13,15}



Lexiscan is the first selective A_{2A} adenosine receptor agonist. Lexiscan has a low affinity for the A_{2A} adenosine receptor, with at least a 10-fold lower affinity for the A_1 receptor and weak if any affinity for the A_{2B} and A_3 receptors.¹⁵ A_1 receptor agonism has been shown to affect AV node conduction,¹⁸ and A_{2B} and A_3 receptors have been implicated in the pathophysiology of bronchoconstriction in susceptible patients, such as those with asthma.^{15,19,20}

LEXISCAN DOSING AND ADMINISTRATION

Unlike the other vasodilators, Lexiscan is provided in a prefilled syringe and administered as a standard dose for all patients, regardless of their weight.¹⁵ **A fixed dose helps to reduce the chances of dosing errors.**²¹ The prefilled syringe also allows for storage in the laboratory or automated drug dispenser. In facilities where regulations require pharmacologic stress agents to be kept in the pharmacy, the standard-dose prefilled syringe facilitates and expedites the process of filling orders.

Lexiscan is administered as an intravenous injection over approximately 10 seconds,¹⁵ which can further simplify pharmacologic stress protocols by eliminating the need for an infusion pump and eliminating the chance of pump programming errors.

Figure 2 shows the administration protocols for the 3 vasodilators.

SAFETY CONSIDERATIONS

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

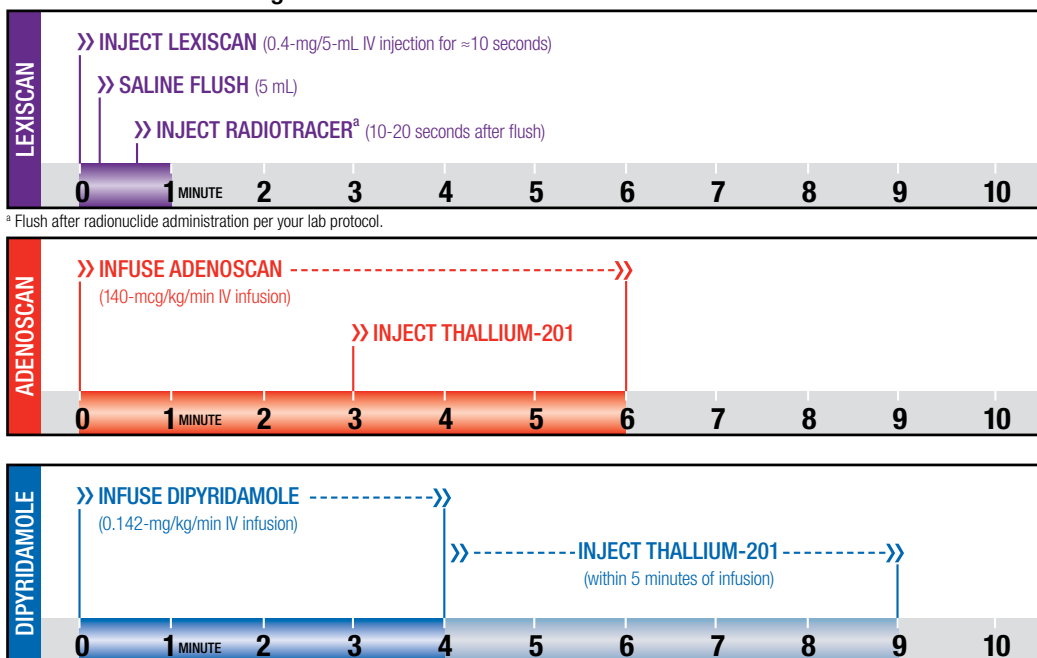
Fatal cardiac arrest, life-threatening ventricular arrhythmias, and myocardial infarction may result from the ischemia induced by pharmacologic stress agents. Cardiac resuscitation equipment and trained staff should be available before administering Lexiscan.

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.

Adenosine receptor agonists, including Lexiscan, induce arterial vasodilation and hypotension. In postmarketing experience, syncope, transient ischemic attacks, and seizures have been observed. 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.

Adenosine receptor agonists, including Lexiscan, may result in clinically significant increases in blood pressure in some patients. When it occurred in clinical trials, increased blood pressure was observed within minutes of Lexiscan administration, and in most cases, resolved within 10 to 15 minutes. In some cases, blood pressure increases were observed 45 minutes following Lexiscan administration. 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.

Figure 2. Vasodilator Administration Protocols¹³⁻¹⁵



Dosage information and administration schedule for dipyrindamole is based on package insert dated December 2007, Bedford Laboratories, Bedford, OH. No other comparison is implied.

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COMPLIANCE WITH STANDARDS AND GUIDELINES

The simplified dosing and administration provided by Lexiscan® (regadenoson) injection may help facilitate compliance with various professional standards, regulations, and guidelines. For example, the Joint Commission Standards, which serve as the basis for the Intersocietal Commission for the Accreditation of Nuclear Medicine Laboratories (ICANL) accreditation program, define the minimal requirements for nuclear laboratories to provide high-quality care.²² Standard MM.05.01.11 ensures that facilities dispense medications safely.²³ An element of performance under this standard indicates that²³:

“Medications are dispensed in the most ready-to-administer forms commercially available, and, if feasible, in unit doses that have been repackaged by the pharmacy or licensed repackager.”

Provided in a **standard-dose, prefilled syringe**, Lexiscan is the only ready-to-administer pharmacologic stress agent commercially available.

Likewise, USP General Chapter 797 contains a number of recommendations that are applicable to the preparation of pharmacologic stress agents, including²⁴:

For drugs prepared for administration, compounding personnel *“are responsible for ensuring that CSPs [compounded sterile preparations] are accurately identified, measured, diluted, and mixed and are correctly purified, sterilized, packaged, sealed, labeled, stored, dispensed, and distributed. These performance responsibilities include maintaining appropriate cleanliness conditions and providing labeling and supplementary instructions for the proper clinical administration of CSPs.”*

Because Lexiscan is ready-to-administer from a prefilled syringe, it requires no compounding or mixing, thereby eliminating concerns and responsibilities associated with such activities.

LEXISCAN CLINICAL TRIAL DATA

Lexiscan has been extensively studied in 2 identical double-blind, randomized, active-comparator, double-dummy phase 3 trials (ADVANCE MPI 1 and 2; N=2015) designed to demonstrate the noninferiority of Lexiscan to Adenoscan® (adenosine injection) for the detection of reversible myocardial perfusion defects.^{15,25,26} All patients had an

initial Adenoscan study and were then randomized to either a Lexiscan (Adenoscan-Lexiscan) or a second Adenoscan (Adenoscan-Adenoscan) study in a 2-to-1 ratio.^{15,25}

Efficacy: Agreement Rates—The blinded images were scored independently by 3 expert readers.²⁵ Of the 2015 study subjects, 1871 had images considered valid for efficacy analysis, including 1294 men (69%) and 577 women (31%).^{15,25}

Agreement rates between the Adenoscan-Lexiscan and Adenoscan-Adenoscan groups were almost identical, demonstrating that Lexiscan is similar to Adenoscan in assessing the extent of reversible perfusion abnormalities.^{15,25,27} Lexiscan and Adenoscan agreement rates were also similar for detecting the presence or absence of reversible perfusion defects,²⁵ image quality,²⁵⁻²⁷ and detecting defect type (ie, none, reversible, fixed, or mixed).²⁶

Lexiscan was as efficacious as Adenoscan in detecting ischemia regardless of age, gender, body mass index, and diabetic status.²⁵

Safety Profile: Adverse Events (AEs)—In the phase 3 clinical trials, overall AE rates were similar for Lexiscan and Adenoscan (80% vs 83%, respectively).¹⁵ Aminophylline was used to treat reactions in 3% of patients with Lexiscan and in 2% with Adenoscan.¹⁵ Most adverse reactions began soon after dosing and generally resolved within approximately 15 minutes, except for headache, which usually resolved within 30 minutes. Individual AE rates are shown in Table 1.¹⁵ In postmarketing experience, abdominal pain in association with nausea, vomiting, or myalgias, and diarrhea, fecal incontinence, and musculoskeletal pain, have occurred.

SAFETY CONSIDERATIONS

Adenosine receptor agonists, including Lexiscan, may cause bronchoconstriction and respiratory compromise. For patients with known or suspected bronchoconstrictive disease, chronic obstructive pulmonary disease (COPD), or asthma, appropriate bronchodilator therapy and resuscitative measures should be available prior to Lexiscan administration.

Lexiscan overdosage may result in serious reactions. Aminophylline was used as a reversal agent in 3% of patients.

Table 1. Pooled Adverse Reactions (Incidence ≥5%) in the ADVANCE MPI 1 and 2 Trials¹⁵

	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

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PATIENTS WITH BRONCHOCONSTRICTIVE DISEASE

The incidence of bronchoconstriction (FEV₁ reduction >15% from baseline) after Lexiscan administration in patients with COPD or asthma was assessed in 2 small, randomized, double-blind, placebo-controlled, crossover studies.^{15,28,29} One study included 49 subjects with moderate (n=38) or severe (n=11) COPD, 47% of whom also had asthma; 37% reported dyspnea during their daily activities.²⁸ Short-acting bronchodilators were withheld for 8 hours prior to Lexiscan administration.²⁸ The other study included 48 subjects with mild (n=24) or moderate (n=24) asthma.²⁹ Short-acting bronchodilators were withheld for >6 hours, and long-acting bronchodilators and methylxanthines for >24 hours, before Lexiscan administration.²⁹

In the COPD study, the rates of bronchoconstrictive response were 12% and 6% in the Lexiscan and placebo groups, respectively ($P=.31$).²⁸ In the asthma study, 4% of patients in each group (ie, Lexiscan and placebo) had a bronchoconstrictive response.²⁹ In both studies, dyspnea was reported in the Lexiscan group (61% for patients with COPD; 34% for patients with asthma), while no subjects in the placebo group experienced dyspnea.¹⁵ Adenosine receptor agonists, including Lexiscan, may cause bronchoconstriction and respiratory compromise. For patients with known or suspected bronchoconstrictive disease, chronic obstructive pulmonary disease (COPD), or asthma, appropriate bronchodilator therapy and resuscitative measures should be available prior to Lexiscan administration.

CAFFEINE AND LEXISCAN STRESS TESTING

Methylxanthines, including caffeine, are nonspecific adenosine receptor antagonists and may interfere with the vasodilation activity of Lexiscan.¹⁵ Therefore, patients should avoid consumption of any products containing methylxanthines for at least 12 hours before Lexiscan administration.

The effects of caffeine on Lexiscan-induced myocardial blood flow (MBF) were assessed in a double-blind, randomized, placebo-controlled crossover study of 41 healthy volunteers.³⁰ Subjects received either a 200-mg caffeine capsule—a dose corresponding to 2 cups of coffee—on Day 1 and placebo on Day 2 (after a washout period of 2-14 days), or the inverse after refraining from methylxanthine-containing products for

at least 24 hours. MBF was measured 2 hours after capsule ingestion by PET with ¹⁵O-labeled water at rest and immediately after intravenous administration of Lexiscan.³⁰

MBF was not significantly different between caffeine and placebo at rest (1.13 ± 0.04 mL/min/g vs 1.06 ± 0.05 mL/min/g) or after Lexiscan stress (2.98 ± 0.14 mL/min/g vs 3.05 ± 0.14 mL/min/g). Lexiscan-induced coronary flow reserve (CFR) was comparable with and without caffeine (2.75 ± 0.16 vs 2.97 ± 0.16 , $P=NS$). Any CFR reduction associated with caffeine intake was <20%.³⁰

CONCLUSIONS

Stress MPI with SPECT is an established and useful testing modality for appropriate patients undergoing cardiac assessment. Exercise is the preferred method of stress for MPI, but many patients are unable to exercise to an adequate endpoint. Pharmacologic stress is an effective option for these patients. The traditional pharmacologic stress agents, Adenoscan and dipyridamole, require individualized, weight-based dosing and infusion-pump administration over several minutes.

The most recently approved pharmacologic stress agent, Lexiscan, is supplied in a prefilled syringe and administered as a standard dose, regardless of patient weight, via intravenous injection over 10 seconds. The simplified administration protocol of Lexiscan and the convenience of a prefilled syringe may help both pharmacies and nuclear cardiology laboratories increase efficiency while maintaining efficacy, safety, and imaging quality.

SAFETY CONSIDERATIONS

The most common adverse reactions ($\geq 5\%$) to Lexiscan are dyspnea, headache, flushing, chest discomfort, angina pectoris or ST-segment depression, dizziness, chest pain, nausea, abdominal discomfort, dysgeusia, and feeling hot. Most adverse reactions began soon after dosing, and generally resolved within approximately 15 minutes, except for headache, which resolved in most patients within 30 minutes.

In postmarketing experience, abdominal pain in association with nausea, vomiting, or myalgias, and diarrhea, fecal incontinence, musculoskeletal pain, and tremor have occurred.

LEXISCAN REIMBURSEMENT

Payment for Lexiscan through Medicare in both physician office and hospital outpatient sites of service will be based on ASP + 6%. The HCPCS code for Lexiscan is J2785. For more information or assistance with reimbursement, contact Astellas Reimbursement ServicesSM at 1-866-283-8483, or visit www.AstellasReimbursement.com.

LEXISCAN FORMULARY KIT

The 2010 Lexiscan Formulary Kit contains many useful resources, including:



Product Information

- Dosing and administration brochure
- Product monograph
- Highlighted prescribing information
- Trade FAQ sheet

Reimbursement/Ordering

- Astellas reimbursement services summary
- Trade sell sheet

Clinical Support

- Bibliography of Lexiscan-related journal articles
- Iskandrian journal article (2007)
- Cerqueira journal article (2008)

CD-ROM

- Full kit contents
- Lexiscan clinical presentation

To obtain a Lexiscan Formulary Kit, visit www.lexiscan.com or contact your Astellas representative.

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

IMPORTANT SAFETY INFORMATION

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.

Fatal cardiac arrest, life-threatening ventricular arrhythmias, and myocardial infarction may result from the ischemia induced by pharmacologic stress agents. Cardiac resuscitation equipment and trained staff should be available before administering Lexiscan.

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.

Adenosine receptor agonists, including Lexiscan, induce arterial vasodilation and hypotension. In postmarketing experience, syncope, transient ischemic attacks, and seizures have been observed. 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.

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

IMPORTANT SAFETY INFORMATION

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

Fatal cardiac arrest, sustained ventricular tachycardia (requiring resuscitation), and nonfatal myocardial infarction have been reported coincident with Adenoscan infusion. Patients with unstable angina may be at greater risk. Appropriate resuscitative measures should be available.

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

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Adenosine receptor agonists, including Lexiscan, may result in clinically significant increases in blood pressure in some patients. When it occurred in clinical trials, increased blood pressure was observed within minutes of Lexiscan administration, and in most cases, resolved within 10 to 15 minutes. In some cases, blood pressure increases were observed 45 minutes following Lexiscan administration. 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.

Adenosine receptor agonists, including Lexiscan, may cause bronchoconstriction and respiratory compromise. For patients with known or suspected bronchoconstrictive disease, chronic obstructive pulmonary disease (COPD), or asthma, appropriate bronchodilator therapy and resuscitative measures should be available prior to Lexiscan administration.

Lexiscan overdosage may result in serious reactions. Aminophylline was used as a reversal agent in 3% of patients.

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

In postmarketing experience, abdominal pain in association with nausea, vomiting, or myalgias, and diarrhea, fecal incontinence, musculoskeletal pain, and tremor have occurred.

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

Increases in systolic and diastolic pressure have been observed.

Adenosine receptor agonists, including Adenoscan, may cause bronchoconstriction and respiratory compromise.

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

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

For information about Lexiscan or to obtain a formulary kit, visit www.lexiscan.com.

For additional published literature and clinical data, call Astellas Medical Information at 1-800-727-7003.

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