REGADENOSON INJECTION

PRODUCT	DELIVERY SYSTEM	UNIT SIZE	UNITS / BOX	NDC#
Regadenoson Injection	Prefilled Syringe	5 mL	1	76329-3321-0

	WHOLESALER ITEM NUMBERS			
NDC#	AMERISOURCE BERGEN	CARDINAL	MCKESSON	MORRIS & DICKSON
76329-3321-0	10278990	5838743	2802072	271973

For more information,
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REGADENOSON INJECTION

INDICATIONS AND USAGE
Regadenoson Injection is a pharmacologic stress agent indicated for radionuclide myocardial perfusion imaging (MPI) in patients unable to undergo adequate exercise stress.

DOSAGE AND ADMINISTRATION
The recommended dose of Regadenoson Injection 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, when- ever solution and container permit. Do not administer Regadenoson Injection if it contains particulate matter or is discolored.
- Administer Regadenoson Injection 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 Regadenoson Injection.
- 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 Regadenoson Injection.

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

CONTRAINDICATIONS
Do not administer Regadenoson Injection 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)].

WARNINGS AND PRECAUTIONS
Myocardial Ischemia
Fatal and nonfatal myocardial infarction (MI), ventricular arrhythmias, and cardiac arrest have occurred following Regadenoson In- jection. 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 Regadenoson Injection. Cardiac resuscitation equipment and trained staff should be available before administering Regadenoson Injection. 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 Regadenoson Injection oc- cur, consider the use of aminophylline, an adenosine antagonist, to shorten the duration of increased coronary blood flow induced by Regadenoson Injection [see Overdosage (10)].

Sinoatrial and Atrioventricular Nodal Block
Adenosine receptor agonists, including Regadenoson Injection, 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 Regadenoson Injection administration; transient second-degree AV block with one dropped beat was observed in one patient receiving Regadenoson Injection. In post-marketing experience, third-degree heart block and asystole within minutes of Regadenoson Injection administration have occurred [see Adverse Reactions (6.2)].

Atrial Fibrillation/Atrial Flutter
New-onset or recurrent atrial fibrillation with rapid ventricular response and atrial flutter have been reported following Regadenoson Injection [see Adverse Reactions (6.2)].

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

Hypotension
Adenosine receptor agonists, including Regadenoson Injection, 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 Regadenoson Injection 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)].

Hypertension
Administration of adenosine receptor agonists, including Regadenoson Injection, 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 Regadenoson Injection 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)].

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

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

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

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)]

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 Re- gadenoson Injection 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 Phar- macology (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 concentrationtime 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; how- ever, 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 regade- noson. 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.

HOW SUPPLIED/STORAGE AND HANDLING
Regadenoson Injection is supplied as a sterile, preservative-free solution containing 0.08 mg/mL regadenoson in the following package:

- Single-dose 5 mL prefilled syringes with luer-lock fitting (NDC 76329-3321-0; Stock No. 3321).

Store at controlled room temperature, 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F).