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Press Release

Hikma launches Regadenoson Injection in prefilled syringe

London, 17 April 2023 – Hikma Pharmaceuticals PLC (Hikma), the multinational pharmaceutical company, has launched Regadenoson Injection, in prefilled syringe (PFS) form. The product has been launched in the US in a 0.4mg/5mL dose. Regadenoson injection is a pharmacologic stress agent indicated for radionuclide myocardial perfusion imaging (MPI) in patients unable to undergo adequate exercise stress.

According to IQVIA, US sales of Regadenoson Injection, 0.4mg/5mL were approximately $668 million in the 12 months ending February 2023.

Hikma is a top three supplier of generic injectable medicines by volume in the US[1], with a growing portfolio of more than 130 products. We are continuously expanding our portfolio of essential medicines and introducing new dosage forms that enhance patient care.

- ENDS -

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About Hikma
(LSE: HIK) (NASDAQ Dubai: HIK) (OTC: HKMPY) (rated BBB-/stable S&P and BBB-/stable Fitch)

Hikma helps put better health within reach every day for millions of people around the world. For more than 40 years, we've been creating high-quality medicines and making them accessible to the people who need them. Headquartered in the UK, we are a global company with a local presence across the North America, the Middle East and North Africa (MENA) and Europe, and we use our unique insight and expertise to transform cutting-edge science into innovative solutions that transform people's lives. We're committed to our customers, and the people they care for, and by thinking creatively and acting practically, we provide them with a broad range of branded and non-branded generic medicines. Together, our 8,800 colleagues are helping to shape a healthier world that enriches all our communities. We are a leading licensing partner, and through our venture capital arm, are helping bring innovative health technologies to people around the world. For more information, please visit: www.hikma.com

[1] Source: IQVIA MAT February 2023, generic injectable volumes by eaches, excluding branded generics and Becton Dickinson

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This product has been approved for marketing in the United States by the US FDA. This product approval does not confer the right on Hikma, or any other party, to market this product outside the United States.

Important Safety Information for Regadenoson Injection, 0.4mg/5mL:

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 & PRECAUTIONS

- **Myocardial Ischemia –** Fatal and nonfatal myocardial infarction (MI), ventricular arrhythmias, and cardiac arrest have occurred following regadenoson 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 regadenoson injection. Cardiac resuscitation equipment and trained staff should be available before administering regadenoson injection. 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 regadenoson injection occur, consider the use of aminophylline, an adenosine antagonist, to shorten the duration of increased coronary blood flow induced by regadenoson injection.
- **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.
- **Atrial Fibrillation/Atrial Flutter –** New-onset or recurrent atrial fibrillation with rapid ventricular response and atrial flutter have been reported following regadenoson 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 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.
- **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. 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.
- **Bronchoconstriction –** Adenosine receptor agonists, including regadenoson injection, may cause dyspnea, bronchoconstriction, and respiratory compromise. Appropriate bronchodilator therapy and resuscitative measures should be available prior to and following regadenoson injection administration.
- **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.

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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)*]

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 regadenoson injection, with most receiving 0.4 mg as a rapid (≤ 10 seconds) intravenous injection. Most of these patients received regadenoson injection 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 regadenoson injection (N = 1,337) or adenosine injection (N = 678). The population was 26 to 93 years of age (median 66 years), 70% male and primarily Caucasian (76% Caucasian, 7% African American, 9% Hispanic, 5% Asian). Table 1 of the package insert shows the most frequently reported adverse reactions.

Overall, any adverse reaction occurred at similar rates between the study groups (80% for the regadenoson injection group and 83% for the adenosine injection group). Aminophylline was used to treat the reactions in 3% of patients in the regadenoson injection group and 2% of patients in the adenosine injection 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.

ECG Abnormalities

The frequency of rhythm or conduction abnormalities following regadenoson injection or adenosine injection is shown in Table 2 of the package insert.

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 regadenoson injection 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 FEV1 (Table 3 of the package insert).

Renal Impairment

In a randomized, placebo-controlled trial of 504 patients (regadenoson injection 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 to 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 regadenoson injection administration following inadequate exercise stress, 1,147 patients were randomized into one of two groups. Each group underwent two regadenoson injection stress myocardial perfusion imaging (MPI) procedures. Group 1 received regadenoson injection 3 minutes following inadequate exercise in the first regadenoson injection stress (MPI 1). Group 2 rested 1 hour after inadequate exercise to allow hemodynamics to return to baseline prior to receiving regadenoson injection (MPI 1). Both groups returned for a second stress MPI 1 to 14 days later and received regadenoson injection without exercise (MPI 2).

The most common adverse reactions are similar in type and incidence to those in Table 1 of the package insert for both Groups. The timing of the administration of regadenoson injection following inadequate exercise did not alter the common adverse reaction profile. Table 4 of the package insert 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.

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 have been reported. Some events required intervention with fluids and/or aminophylline. QTc prolongation shortly after regadenoson injection administration has been reported.

Central Nervous System
Tremor, seizure, transient ischemic attack, and cerebrovascular accident including intracranial hemorrhage.

Gastrointestinal
Abdominal pain, occasionally severe, has been reported a few minutes after regadenoson injection 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 regadenoson injection 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.

Musculoskeletal
Musculoskeletal pain has occurred, typically 10 to 20 minutes after regadenoson injection 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 regadenoson injection administration.

DRUG INTERACTIONS

No formal pharmacokinetic drug interaction studies have been conducted with regadenoson injection.

Effects of Other Drugs on Regadenoson Injection
- Methylxanthines (e.g., caffeine, aminophylline and theophylline) are non-specific adenosine receptor antagonists that interfere with the vasodilation activity of regadenoson injection. Patients should avoid consumption of any products containing methylxanthines as well as any drugs containing theophylline or aminophylline for at least 12 hours before regadenoson injection administration. Aminophylline may be used to attenuate severe or persistent adverse reactions to regadenoson injection.
- In clinical studies, regadenoson injection 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 regadenoson injection. When possible, withhold dipyridamole for at least two days prior to regadenoson injection administration.

Effect of Regadenoson Injection 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.

USE IN SPECIFIC POPULATIONS

Pregnancy
Risk Summary
There are no available data on regadenoson injection 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 to 4% and 15 to 20%, respectively.

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 regadenoson injection.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

Geriatric Use
Of the 1,337 patients receiving regadenoson injection 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%).

Renal Impairment
No dose adjustment is needed in patients with renal impairment including patients with end stage renal disease and/or dependent on dialysis.

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.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever 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 to 20 seconds after the saline flush. The radionuclide may be injected directly into the same catheter as regadenoson injection.

OVERDOSAGE

Regadenoson injection overdosage may result in serious reactions. In a study of healthy volunteers, symptoms of flushing, dizziness and increased heart rate were assessed as intolerable at regadenoson injection 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 to 60 seconds). Methylxanthine use is not recommended in patients who experience a seizure in association with regadenoson injection administration.

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.

HOW SUPPLIED/STORAGE AND HANDLING

Regadenoson Injection is supplied as a sterile, clear, colorless preservative-free solution containing 0.08 mg/mL regadenoson in the following package:

- Single-dose 0.4 mg/5 mL pre-filled plastic syringes with luer-lock fitting (NDC 0641-6253-01).

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature]. Discard unused portion.

ENDING INFORMATION

Patient Counseling Information should be shared with the patient prior to administration.
For additional information, please refer to the Package Insert for full prescribing information, available on www.hikma.com.

To report SUSPECTED ADVERSE REACTIONS, contact Hikma Pharmaceuticals USA Inc. at 1-877-845-0689 or FDA at 1-800 FDA-1088 or www.fda.gov/medwatch.

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