# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**22-161**

# CROSS DISCIPLINE TEAM LEADER REVIEW

**March 12, 2008**

## DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

### Secondary Clinical Review

| | |
|---|---|
| **NDA** | 22-1161 |
| **Established Name** | Regadenoson |
| **Proposed Trade Name** | Lexiscan |
| **Therapeutic Class** | Diagnostic Radiopharmaceutical<br>Pharmacologic stress agent |
| **Applicant** | CV Therapeutics Inc. |
| **Dosing Regimen** | 400 mcg intravenously as a bolus |
| **Indication** | Pharmacologic stress agent for radionuclide Myocardial Perfusion Imaging (MPI) |
| **Intended Population** | Patients with known or suspected coronary artery disease |
| **Reviewer Name** | Louis Marzella M.D., Ph.D. |

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Recommended regulatory action

The secondary reviewer agrees with the recommendation by Dr. Ira Krefting (primary clinical reviewer) that this NDA be approved provided that final agreement is reached with the Sponsor on the package insert.

Summary of efficacy and safety and labeling implications

Two efficacy studies (CVT 5131 and CVT 5132) demonstrated that regadenoson (400 mcg iv) is not inferior to adenosine (adenoscan at recommended dose) in detecting reversible myocardial perfusion defects (using radionuclide Myocardial Perfusion Imaging) in patients with known or suspected coronary artery disease.

The enrollment criteria targeted patients requiring pharmacologic stress radionuclide MPI (i.e. adults), and excluded patients without a stable medication regimen and without a stable clinical condition.

The most common adverse reactions (>6 %) in the subjects (N= 1651) exposed to regadenoson are dyspnea, headache, flushing, chest discomfort/chest pain, angina/ST segment depression, lightheadedness, nausea/abdominal discomfort. Other important reactions include various cardiac rhythm or conduction abnormalities (26%), increased heart rate (>100 bmp, 22%), decreased systolic and diastolic blood pressure (<90mm Hg, < 50 mm Hg; 2% for each), bronchoconstriction (6/49 study patients with COPD), and worsening migraine headache (one report). No deaths were attributed to regadenoson.

No clinically important changes in hematology or clinical chemistry measurements were noted.

Adenosine receptor agonists interact with a number of receptors in cardiovascular and, pulmonary systems, and can induce severe hemodynamic, respiratory, and conduction disturbances. The alterations in cardiac rhythm, ECG (e.g. ST segment depression), hemodynamic, and respiratory function observed in the clinical trials are the expected extensions of these pharmacologic actions. In the relatively small clinical trial experience, primarily in stable patients, no fatal or serious reactions to regadenoson were observed. However, in clinical use postmarketing, regadenoson will be administered to more seriously ill patients with conditions (e.g. AV conduction abnormalities, low ventricular ejection fraction, bronchospasm) that will increase the risk of serious reactions. Therefore warnings in the label about potential ischemia, heart block, hypotensive and bronchospastic reactions are warranted.

In the efficacy trials, the slowing of AV conduction induced by adenosine dosing appeared to be less pronounced (but was not abrogated) with regadenoson dosing. Moreover, in two studies in approximately 100 patients with COPD or asthma, regadenoson did not induce serious respiratory reactions. These findings suggest a clinically important difference in the safety profile of regadenoson compared to adenosine with respect to potential for slowing of SA and AV nodal conduction and with respect to the potential for inducing bronchospasm; however the findings will have to be supported by further clinical experience. Whereas adenosine is contraindicated in patients with AV or Sinus conduction abnormalities and bronchospastic disorders, regadenoson will be used in these patients with appropriate warnings in the label about the potential risks.

Statistical differences favoring regadenoson over adenosine were noted in the severity or incidence of certain reactions known to be caused by adenosine receptor agonists. The sponsor proposes to [redacted] However, this proposal is not justified. The differences are quantitatively minor. For example the symptom severity score for flushing, chest pain, dyspnea was 0.9 for regadenoson and 1.1 or 1.3 for adenosine using a 4-point scale (0=none, 1=mild, 3=severe). The differences in the incidence of reactions are also inconsistent; for example flushing and chest pain, but not dyspnea are lower with regadenoson. The interpretation is also not straight-forward as symptoms of angina are a potential surrogate for diagnostic performance of the stress agent. These comparisons also do not take into account the increased duration of the reactions with regadenoson compared to the adenosine. Finally the methodology used for the statistical analyses of the differences is not robust.

Recommended postmarketing actions

The secondary reviewer agrees with the recommendation by Dr. Krefting that a clinical safety study of regadenoson is needed. An approach to be considered would be to establish a registry to collect data on serious adverse reactions focusing on hypotension (and end-organ ischemic damage), hypertension, arrhythmias, AV conduction abnormalities, and respiratory compromise. The patient populations of interest are patients scheduled for a stress MPI who have bronchospasm, rhythm or conduction

abnormalities, or myocardial dysfunction including abnormal ventricular ejection fraction. The follow up period for this study should be at least 24 hours after regadenoson dosing. In addition the sponsor should summarize spontaneous reports of these reactions and propose an appropriate frequency for summarizing and reporting the safety data from the registry study and the data from the spontaneous reports (using time and product usage milestones).

Review procedure

The secondary reviewer read the FDA's primary clinical and statistical reviews, and evaluated the Sponsor's clinical study reports and selected biopharmaceutic and toxicology study reports. The secondary reviewer also evaluated the package insert for regadenoson and other competing products and reviewed the AERS safety profile of adenoscan.

CMC and microbiology

No findings relevant to the clinical review were noted.

Toxicology

The principal finding of potential clinical importance was the development of cardiomyopathy induced by regadenoson in rats (see below for details). In clinical studies no evidence of acute MI by symptoms or ECG studies was observed. In a few patients cardiac enzymes were measured and no elevations were found. The consensus view of the review team is that there is no evidence that at clinically applicable doses regadenoson induces myocardial injury.

*Cardiomyopathy*

Regadenoson induced acute (day 2 post-dosing) focal, isolated cardiac myocyte necrosis and mononuclear cell inflammation in rats following single dose administration at doses higher than human doses. These cardiomyopathic changes were classified as minimal in severity. The proportion of affected male rats increased with the dose of regadenoson (1 of 5 rats at 0.08 mg/kg, 2/5 at 0.2 mg/kg, and 5/5 at 0.8 mg/kg) 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 mg/kg and 0.8 mg/kg, respectively. The drug-induced changes were reversible (no cardiomyopathy was noted in rats sacrificed 15 days following single administration of regadenoson) and were not cumulative (not observed with repeat dosing). The mechanism of the cardiomyopathy induced by regadenoson was not elucidated in the Sponsor's studies but was associated with the hypotensive effects of regadenoson. Profound hypotension induced by vasoactive drugs is known to cause cardiomyopathy in rats (see Dr. Yanli Ouyang's toxicology review for detailed analyses).

Pharmacology

*Pharmacodynamics*

Pharmacologic Stress Agents (psa) are used in the detection and functional characterization of ischemic heart disease. Radiopharmaceuticals used for the diagnosis of coronary artery disease (CAD) distribute proportionally to myocardial blood flow. In

an MPI study, images are obtained at rest and under conditions that increase coronary blood flow such as exercise or the administration of a pharmacologic stress agent such as coronary vasodilators. In patients with CAD an increase in blood flow in normal coronaries due to vasodilatation, and a relative decrease of blood flow in stenotic arteries is visualized with radionuclides.

Regadenoson is an $A_{2A}$-AdoR agonist (activities: coronary and systemic arterial vasodilatation with decreased BP, and sympathomimetic effects including increased heart rate), and has low affinity for the $A_1$-AdoR (activity: slowing AV nodal conduction), and the $A_{2B}$-AdoRs (activity: bronchospasm from mast cell activation).

*Pharmacokinetics*
A three-compartment model best described the concentration-time profile of regadenoson after rapid intravenous injection. The initial half-life was 2 to 4 minutes, the intermediate half-life was approximately 30 minutes, and the terminal half-life was approximately 2 hours. The central volume of distribution was weakly correlated with body weight, and clearance was not correlated with body weight. This provided the rationale for non-weight-adjusted dosing.

*Metabolism*
Regadenoson is excreted approximately equally between urine and bile, and almost entirely as unchanged drug. Regadenoson does not inhibit the major cytochrome P450 enzymes.

*Drug interactions*
*Caffeine*. Study CVT 5123 measured the ratio of myocardial blood flow (MBF) after regadenoson administration to the resting MBF (coronary flow reserve, CFR) in the presence and absence of caffeine (1–2 standard cups of coffee 2 hours before the regadenoson stress test). The study provided an assessment of the effect of caffeine on the regadenoson-induced stress response. The data showed with 95% confidence that any CFR reduction associated with caffeine intake is not greater than 20%.

*Aminophylline*. With the introduction of aminophylline, coronary flow was sustained above 2-times baseline for only one-tenth the time of that observed in subjects who had not received aminophylline, and returned to near-baseline levels within approximately 2 minutes after administration of aminophylline.

Clinical studies: dose selection
In study CVT 5111, the maximal tolerated dose when administered to subjects in the supine position was determined to be 20 mcg/kg. The observed $C_{max}$ concentrations at this dose level ranged from 69 to 134 ng/mL (mean 102 ng/mL).

Study 5121 identified a dose (300 mcg) that increased the average peak velocity of CBF > 2-times baseline for at least 2 minutes, and maximum (3.1-fold baseline) within 2 minutes, with CBF returning to < 2-fold baseline within 10 minutes. The study also established the antagonistic effects of aminophylline. The time course of a patient's

increase in HR parallels the time course for the increase in CBF. Doses 400 mcg and above were chosen for further study due to less variability in CBF effects.

Two doses of regadenoson (400 mcg and 500 mcg) were evaluated in study CVT 5122. The images produced by each of the two doses were comparable to the respective initial adenosine images and reversible perfusion defects were apparent in 89% and 82% of patients in the 400 mcg and 500 mcg regadenoson dose groups. Overall, 83% of patients in the 500 mcg group and 61% of patients in the 400 mcg group had at least one adverse event. Given the similar diagnostic performance of the two doses of regadenoson and the suggestion of lower reactions with the 400 mcg dose, the 400 mcg dose was chosen for study in phase 3.

Clinical studies: efficacy

The secondary reviewer agrees with the assessment by FDA's clinical reviewer and statistical reviewer that regadenoson is efficacious.

*Study design, primary endpoint*

The Sponsor conducted two identically designed multinational studies (CVT 5131 and CVT 5132) with identical primary endpoints (**Table 1**). Most of the patients enrolled in the studies were North Americans; South Americans and Europeans also participated.

**Table 1. Efficacy trials**

| Study Number and Efficacy Populations | Study Design | Primary Endpoint |
|---|---|---|
| CVT 5131<br>Dosed: 1231 Reg: 820 Ado: 411<br>Efficacy[1]: 1113 Reg: 741 Ado: 372<br>Efficacy[2]: 1213 Reg: 807 Ado: 406<br><br>CVT 5132<br>Dosed: 787 Reg: 519 Ado: 268<br>Efficacy[1]: 758 Reg: 499 Ado: 259<br>Efficacy[2]: 773 Reg: 508 Ado: 265 | Double-blind, multicenter, double-dummy, randomized trials in patients referred for a pharmacologic stress MPI study. Patients had a stress scan with adenosine[3] (active comparator) and were randomized 2:1 to a second stress scan with regadenoson or adenosine. Images were read by three blinded-independent readers. | Strength of agreement between regadenoson and adenosine MPI is not inferior to the strength of agreement between two sequential adenosine MPIs. The measure of agreement was based on the median count across 3 readers of the number of segments showing reversible perfusion defects[4] using a 17-segment model. The LL of the 95% CI for the difference in the two agreement rates was pre-specified as –13.3%. |

[1] primary analysis population: dosed with blinded study medication; initial and randomized studies scored by the readers; if enrolled after closure of randomization to patients with adenosine MPI with <2 segments with reversible defects, also had randomized MPI with at least 2 segments with reversible defects.

[2] secondary analysis population

[3] adenoscan (abbreviation Ado) was the adenosine comparator (0.14 mg/kg/min intravenously over 6 min)

[4] median count of the number of segments with reversible defects among the three readers was categorized as follows: 0–1 segments with reversible perfusion defects = no ischemia; 2–4 segments with reversible perfusion defects = small to moderate ischemia; 5–17 segments with reversible perfusion defects = large ischemia.

*Patient population*

Enrollment criteria targeted patients requiring pharmacologic stress radionuclide MPI (i.e. adults), while excluding patients without a stable medication regimen and without a stable clinical condition (ostensibly out of concern for the risks posed by the adenosine comparator).

The following conditions were grounds for exclusion: 2nd or 3rd degree AV block, or sick sinus syndrome (without functioning artificial pacemaker), or serious uncontrolled ventricular arrhythmia; known or suspected bronchoconstrictive and bronchospastic lung disease (e.g., asthma with wheezing); resting heart rate < 50 bpm or > 100 bpm; systolic blood pressure < 100 mm Hg; susceptibility to symptomatic hypotension, or uncontrolled hypertension.

In addition, patients whose clinical status changed significantly between the time of the initial adenosine scan and the randomized scan, and those whose initial adenosine images were not of at least good quality, were not randomized because their inclusion would have confounded the image comparison. Randomization to the three categories of ischemia extent was monitored and each study discontinued randomization of patients in the 'no ischemia' category before study completion in order to adhere to the protocol-specified requirements to limit the number of patients in this category.

The requirement for a stable regimen and clinical condition in the clinical studies raises concerns about unappreciated risks if regadenoson is used in more unstable patients post approval.

*Patient demographics and disposition*
The majority of patients were elderly Caucasian men (median age of 66 yr), who were overweight and had a history of angina or CAD. Patients who received regadenoson had a history of cardiac intervention (50% with bypass, angioplasty, or stenting), MI (40%), arrhythmias (34%), and COPD (5%). The majority (69%) of patients receiving regadenoson had a Diamond and Forrester estimated pretest probability of CAD > 90%. The results of the initial study showed that 68% of patients had 0-1 myocardial segments with reversible defects, 23% had 2–4 segments, and 8% had ≥ 5 segments with reversible defects. There were no important differences between the patients randomized to adenosine and those randomized to regadenoson.

A total of 1,651 subjects received regadenoson (by intravenous bolus injection) in the course of the clinical development program, including 1,339 in the Phase 3 trials. Twenty-three patients were prematurely withdrawn from these studies, primarily because of scheduling conflicts, and 1,995 patients completed the randomized phase of the study. Of these, 1,986 patients had their MPI images read at the [redacted] and were included in the full efficacy analysis set. The primary efficacy analysis excluded patients whose randomized MPI scans were read by the study site as having 'no ischemia' after enrollment was closed to patients in the 'no ischemia' category. As a result, a total of 115 patients (100 in CVT 5131 and 15 in CVT 5132) were excluded from the primary analysis. Thus, 1,871 patients were included in the primary analysis; 631 received adenosine and 1,240 received regadenoson (see **Tables 1** and **2**).

**Table 2. Patient disposition**

| | adenosine | regadenoson |
|---|---|---|
| Numbers enrolled in study 5131 and 5132 | 683 | 1350 |
| Completing | 670 | 1325 |
| Termination | 9 (1%) | 14 (1%) |
| Adverse event | 0 | 2 (<1%) |
| Other | 9 (1%) | 12 (1%) |
| Secondary analysis | 671 | 1415 |
| Primary analysis | 631 | 1240 |

A total of 1,451 patients received the initial adenosine dose but did not receive blinded study drug. The majority (n = 1100) of these patients were not eligible for randomization because their initial adenosine studies were assessed at the sites as showing 0–1 reversible segments. Other reasons for not proceeding to randomized dosing are listed in **Table 3.**

**Table 3. Patients terminating prematurely before randomized study drug**

| Total number in study 5131 and 5132 | 1451 |
|---|---|
| Primary reason | |
| Assessed as having 0–1 reversible defects | 1100 |
| Failed to meet other additional qualifying criteria | 35 |
| Adverse event | 49 |
| Inappropriate enrollment | 5 |
| Noncompliance | 26 |
| Elective withdrawal | 149 |
| Lost to follow-up | 13 |
| Death | 1 |
| Other | 72 |

*Primary efficacy outcome*

In the primary analysis, both studies demonstrated non-inferiority of regadenoson to adenosine by comparing image to image agreement rates. For two successive scans using adenosine and for an adenosine scan followed by a regadenoson scan, the lower limit of the 95% confidence interval for the regadenoson – adenosine difference in agreement rates was above the prespecified non-inferiority margin of -13.3% (see **Table 4**).

**Table 4. Agreement of initial adenosine and randomized drug with respect to ischemia size category (median across readers)**

| | CVT 5131 | CVT 5132 |
|---|---|---|
| Adenosine – Adenosine agreement rate (± SE) | 61 ± 3% | 64 ± 4% |
| Adenosine – Regadenoson agreement rate (± SE) | 62 ± 2% | 63 ± 3% |
| Rate Difference (Regadenoson – Adenosine) (± SE)<br>95% Confidence Interval | 1 ± 4%<br>−7.5, 9.2% | −1 ± 5%<br>−11.2, 8.7% |

*Secondary efficacy outcomes*

The choice of a measure of agreement between two MPI studies, (the first with adenosine followed by adenosine, the second with adenosine followed by regadenoson) as the primary efficacy endpoint is based on the long clinical experience with adenosine stress MPI for the diagnosis of CAD. Nevertheless a measure of agreement of two MPI studies is not as clear a demonstration of clinical utility as the assessment of sensitivity and specificity of the test agent and its comparator in diagnosis of CAD relative to a coronary arteriography truth standard. Nevertheless subgroup analyses in the few patients undergoing coronary angiography (280 patients in CVT 5131 and 119 in CVT 5132) did not suggest that regadenoson underperformed adenosine. Regadenoson showed a sensitivity of 86% and a specificity of 39%, compared to 82% and 50%, respectively, for adenosine.

Various other secondary outcomes were also supportive of the efficacy of regadenoson including agreement with respect to diagnostic category (patient diagnosis). For the individual studies and combined analysis, overall average agreement rate by diagnostic categories of 'normal,' 'ischemia,' 'ischemia + scar,' or 'scar' and average agreement by coronary artery territory were similar for both stress agents. For both stress agents, wall motion abnormalities were similar in location and severity between the initial and randomized scan. The performance of regadenoson did not appear to be affected by the radionuclide ($^{201}$Tl or $^{99m}$Tc (sestamibi or tetrofosmin)) used for MPI.

For both stress agents, women had lower MPI agreement rates than men when $\geq$ 2 segments of ischemia were noted on the initial scan. For regadenoson and adenosine, agreement rates appeared to be similar for subgroups defined by age (< 65, $\geq$65 yr), BMI ($\leq$30, > 30 kg/m$^2$), diabetes (+/-), LVEF (< 35%, $\geq$35%), and ethnicity.

In conclusion, studies CVT 5131 and CVT 5132 demonstrate that regadenoson (400 mcg administered as an intravenous bolus) in conjunction with SPECT MPI is not inferior to adenosine MPI in detecting reversible myocardial perfusion defects in patients with known or suspected coronary artery disease.

Clinical studies: safety including special populations

Safety data included assessment of changes in physical exams, vital signs, ECGs, clinical laboratory assessments, and the collection of AE and concomitant medication information. Blood samples for clinical laboratory measurements were obtained at 24 hours after dosing in CVT 5111, whereas the termination samples were obtained at 1–3 hours after dosing (a relatively short time period) for studies CVT 5121, CVT 5122, CVT 5123, CVT 5131, and CVT 5132. AEs were obtained until the follow-up contact 2–18 days after the last visit. Reactions expected due to the pharmacology of regadenoson (arrhythmias, AV conduction abnormalities, hemodynamic changes such as tachycardia, hypotension, or hypertension, respiratory alterations such as bronchoconstriction) were examined and potential interactions with vasoactive medications such as nitroglycerin and beta blockers were explored.

Only one SAE was attributed to regadenoson: the exacerbation of an ongoing migraine headache. Two patients receiving regadenoson died: one from complications following abdominal surgery for metastatic carcinoid tumors, and one from complications of a

catheterization procedure not specified by the protocol. Neither of these deaths was attributed to regadenoson.

The most frequent adverse reactions induced by regadenoson are shown in **Table 5.** Overall, the incidence of adverse reactions induced by regadenoson was not importantly different from that of adenosine. The duration of these AEs, although in general short (most resolved within 16 minutes after dosing), was slightly longer after regadenoson. ECG findings also tended to persist slightly longer after regadenoson than after adenosine.

**Table 5. Adverse reactions in studies CVT 5131 and 5132 pooled (frequency ≥ 5%)**

| | **Regadenoson (0.4 mg iv injection over ≤ 10 sec) N = 1,337** |
|---|---|
| Nervous System Disorders | |
| Headache | 26% |
| Dizziness | 8% |
| Dysgeusia | 5% |
| Respiratory, Thoracic and Mediastinal Disorders | |
| Dyspnea | 28% |
| Vascular Disorders | |
| Flushing | 16% |
| General Disorders and Administrative Site Conditions | |
| Chest Discomfort | 13% |
| Chest Pain | 7% |
| Feeling Hot | 5% |
| Cardiac Disorders | |
| Angina Pectoris or ST Segment Depression | 12% |
| Gastrointestinal Disorders | |
| Nausea | 6% |
| Abdominal Discomfort | 5% |

Aminophylline was used to reverse the adverse effects of regadenoson when deemed appropriate by the investigator; 3% of regadenoson patients and 2% of adenosine patients received aminophylline in the Phase 3 studies. The AEs for which aminophylline was given in regadenoson patients (angina, headache, ECG ST segment depression, and chest pain) resolved without further treatment.

No clinically significant changes in hematology or clinical chemistry laboratory values occurred following regadenoson dosing; however the sampling interval was relatively short.

Because the primary efficacy analyses demonstrated non-inferiority of image agreement, hypotheses related to severity and incidence of specific adverse reactions after regadenoson and after adenosine were tested in a pre-specified order, each at the 5% level of significance. Formal testing continued until the first non-significant result. **Table 6**

shows the incidence of selected AEs by study after regadenoson and adenosine. It cannot be concluded that there is an important difference favoring regadenoson in these reactions. With respect to the first comparison (step 1), the clinical importance of a minimal change in a "mild" summed severity score for flushing, chest pain and dyspnea favoring regadenoson cannot be considered clinically important. This initial difference is also not fully consistent as examined in repeated other comparisons (step 2). The incidence of flushing, chest pain or dyspnea favored regadenoson (nominal P <0.5) in only study 5131, dyspnea did not favor regadenoson in either study. Finally the incidence of other symptoms induced by adenosine agonists such as headache, gastrointestinal discomfort and lightheadedness does not favor regadenoson. Confounding due to intake of caffeine (demonstrable levels were found in a number of patients) was not taken into account. This analysis also does not take into account the duration of symptoms (tends to be longer after regadenoson).

**Table 6. Adverse reactions**

| | CVT 5131 | | CVT 5131 | |
|---|---|---|---|---|
| Symptom | regadenoson | adenosine | regadenoson | Adenosine |
| **STEP 1** | | | | |
| Summed score: flushing, chest pain, dyspnea | 0.9 ± 0.03* | 1.3 ± 0.06 | 0.9 ± 0.05* | 1.1 ± 0.08 |
| **STEP 2** | | | | |
| Flushing | 21.7* | 34.5 | 20.1* | 29.2 |
| Chest pain | 28.5* | 43.6 | 26.3* | 35.2 |
| Dyspnea | 29.3 | 30.4 | 24.8 | 18.4 |
| Flushing, chest pain, or dyspnea | 58.8* | 72 | 54.7 | 61 |
| Throat, neck or jaw pain | 7.3* | 13.1 | 6* | 11.6 |
| Headache | 23.3 | 16.1 | 27.7 | 15.4 |
| Gastrointestinal discomfort | 20.5 | 16.1 | 19.1 | 10.9 |
| Lightheadedness/dizziness | 8.2 | 8 | 6 | 3 |

In the efficacy trials, the slowing of AV conduction induced by adenosine dosing appeared to be less pronounced (but was not abrogated) with regadenoson dosing (**Table 7**). Regadenoson did not appear to affect the QTc interval (after taking into account the increased HR induced by regadenoson).

**Table 7. AV conduction effects of regadenoson**

| | regadenoson | adenosine |
|---|---|---|
| 1st degree AV block | 2.8% | 7% |
| 2nd degree AV block | 0.1% | 1.5% |

Regadenoson has a variable effect on SBP and DBP, with the majority of patients showing transient decreases (**Table 8**); however some patients showed a slight increase after dosing. A concentration-dependent increase in HR was observed in all clinical studies with regadenoson. Onset is rapid, and the maximum effect is typically observed within 1 to 2 minutes after drug administration.

**Table 8. Hemodynamic effects of regadenoson**

| | | |
|---|---|---|
| **Maximum Values** | | |
| Heart Rate | > 100 bpm | 22% |
| **Minimum Values** | | |
| Systolic Blood Pressure | < 90 mm Hg | 2% |
| Diastolic Blood Pressure | < 50 mm Hg | 2% |
| **Maximum Changes** | | |
| Heart Rate | Increase > 40 bpm | 5% |
| Systolic Blood Pressure | Decrease > 35 mm Hg | 7% |
| Diastolic Blood Pressure | Decrease > 25 mm Hg | 4% |

*Special Populations*

Studies of regadenoson in patients with asthma and COPD did not show major safety signals.

*COPD*

Regadenoson (0.4 mg, intravenously) was evaluated in a randomized, double-blind, placebo-controlled, cross-over study (CVT 5125) in 38 subjects with moderate and 11 subjects with severe COPD. The incidence of a bronchoconstrictive response, defined as a 15% reduction in $FEV_1$ from baseline, was 12% for regadenoson and 6% for placebo. None of the patients required treatment for the events.

*Asthma*

Regadenoson (0.4 mg, intravenously) was evaluated in a randomized, double-blind, placebo-controlled, cross-over study (CVT 5124) in 24 subjects with mild and 24 subjects with moderate asthma who were responsive to challenge with adenosine monophosphate. The incidence of a bronchoconstrictive response, defined as a 15% reduction in $FEV_1$ from baseline, was the same after both regadenoson and placebo (4%). These $FEV_1$ reductions were not associated with any respiratory adverse events and did not require treatment.

*Renal insufficiency*

In study CVT 5112, subjects with varying degrees of renal insufficiency received a 400 mcg iv dose of regadenoson. Total clearance (CL) of regadenoson was reduced in parallel with the reduction in renal function; however, $C_{max}$ and PK parameters associated with distribution showed only minor differences between the groups.

*Regadenoson with low level exercise*

CVT 5126 was an exploratory study of regadenoson with low level exercise (defined in the study protocol as submaximal treadmill exercise for 4 minutes on a 0% incline at a rate of 1.7 miles per hour). No safety signals were identified.

In conclusion, the secondary reviewer agrees with Dr. Krefting's assessment that regadenoson has an acceptable safety profile. The slowing of AV conduction induced by adenosine dosing appeared to be less pronounced (but was not abrogated) with regadenoson dosing. Regadenoson did not cause serious respiratory reactions in patients with asthma or COPD. These findings suggest a clinically important difference in the safety profile of regadenoson compared to adenosine with respect to potential for slowing of SA and AV nodal conduction and with respect to the potential for inducing bronchospasm.

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