CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-161

SUMMARY REVIEW

ACTING DIVISION DIRECTOR'S REVIEW MEMORANDUM
NDA REVIEW

NDA:	22-161
DRUG:	Regadenoson injection for intravenous administration
TRADENAME:	Lexiscan™
FORMULATION:	Solution in a vial and also presented as pre-filled syringe. The vial contains regadenoson 0.4 mg/5 mL (5 mL volume) and the same strength/volume is contained within the pre-filled syringe. The presented formulation contains regadenoson, phosphate salts, propylene glycol, EDTA and water for injection.
ROUTE:	Intravenous administration "as a rapid (approximately 10 seconds) injection"into a vein.
DOSE:	0.4 mg (fixed dose).
SPONSOR:	CV Therapeutics, Inc.
SUBMITTED:	May 14, 2007
PDUFA DUE DATE:	March 14, 2008
DD MEMO COMPLETED:	March 21, 2008
DD MEMO PREPARERS:	Dwaine Rieves, MD, Acting Division Director Division of Medical Imaging and Hematology Products

OVERALL FINDING:

The review team and I recommend approval of regadenoson for the proposed indication (as a pharmacological stress agent to be used with radionuclide imaging [redacted]. The sponsor has provided persuasive evidence of efficacy and safety. In general, regadenoson appears to perform in a manner very similar to Adenoscan, especially with respect to efficacy. For practical purposes, the major clinical difference between the two products may relate to the bolus dose administration procedure for regadenoson compared to an infusion dose regimen for Adenoscan.

The clinical development program focused almost exclusively upon demonstrating that regadenoson was similar in efficacy to adenosine injection (Adenoscan). The clinical development program somewhat attempted to show that regadenoson may be safer and/or tolerated better than Adenoscan, especially with respect to potentially a lower risk for bronchospasm. However, the studies were not designed sufficiently to make this determination. Indeed, only patients who were judged to be tolerant to a baseline Adenoscan were enrolled in the phase 3 studies (hence, the potentially broad market population was not fully represented in the phase 3 studies).

To support the potential safety of regadenoson among patients with asthma or chronic obstructive pulmonary disease (COPD), the sponsor performed two very small sample size studies in specific patients that focused upon the detection of FEV1 alterations. These two studies, combined with background preclinical data and the totality of clinical data, suggest that regadenoson may be safer than Adenoscan, with respect to bronchospasm. [redacted]

The sponsor is required to conduct a post-marketing clinical study that will provide descriptive summary of the adverse events that occur among patients with airway disease as well as patients with other underlying conditions.

SPONSOR'S PROPOSED INDICATION:

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

Note, the trade name, "Lexican" is the sponsor's proposed trade name; FDA's Proprietary Name Risk Assessment found this trade name acceptable.

RELATED DRUGS:

1. Adenoscan (marketed by Astellas, a company also involved in the development of regadenoson) is generally recognized as the most commonly used pharmacologic stress agent for MPI. Adenoscan is a non-specific adenosine receptor stimulant and acts in multiple organs and tissues, including stimulation of adenosine receptors on blood cells and airway cells. Unlike Adenoscan, regadenoson is relatively selective stimulant of the $A2_A$ receptor (which is thought to be concentrated within coronary arteries).

2. Dipyridamole (injectable) is a drug that is thought to act by blocking adenosine uptake in tissues, effectively increasing local tissue concentrations of adenosine. Hence, Dipyridamole effects are generally regarded as similar to those of Adenoscan.

RELATED REVIEWS:

Clinical:	Ira Krefting, M.D.; Louis Marzella, M.D., Ph.D.
Statistics:	Anthony Mucci, Ph.D, Jyoti Zalkikar, Ph.D.
Chemistry:	Jila Boal, Ph.D., Sharmista Chatterjee, Ph.D.
Microbiology:	Bryan Riley, Ph.D., James McVey, Ph.D.
Pharm-toxicology:	Siham Biade, Ph.D., Adebayo Laniyonu, Ph.D.
Clin Pharmacology:	Christy John, Ph.D, Young Moon Choi, Ph.D.
Project Manager:	Hyon-Zu Lee, Pharm.D
DSI:	Dan-My Chu, PhD, Tejashri Purohit-Sheth, MD
Advisory Committee:	None; regadenoson was not discussed at an advisory committee due to the development program's demonstration of persuasive evidence that it is very similar to Adenoscan, a marketed drug.

RECOMMENDED REGULATORY ACTIONS:

1) Approval:

The sponsor developed the regadenoson clinical program in close collaboration with the Division of Cardiovascular and Renal Products. Regadenoson was transferred to our division in late 2006.

As background, adenosine receptor investigators have identified many categories of adenosine receptors; for example some types are concentrated on mast cells, some on smooth muscle cells, some on neuronal cells, etc. According to the sponsor,

regadenoson was developed because certain studies suggest that it is relatively specific for the $A2_A$ receptor that is concentrated within the coronary artery wall. Hence, regadenoson might not have some of the bronchospastic tendencies, cardiac conduction system problems and peripheral vasodilator tendencies that are characteristics of Adenoscan. Indeed, the Adenoscan label specifically contraindicates use of that drug among certain patients at risk for bronchospastic or conduction system problems.

Stimulation of adenosine receptors (and the $A2_A$ receptor specifically) is thought to cause coronary vasodilation which results in increased perfusion of the heart muscle. However, if patients have fixed coronary obstructions, then the coronary arteries cannot dilate sufficiently and a "coronary steal" syndrome becomes evident on radionuclide myocardial scans as perfusion defects. The defects are regarded as "reversible" if they were not detected on a baseline (non-stress) myocardial perfusion scan.

It is important to note that most stress myocardial perfusion imaging is performed using exercise. For patients who are not capable of exercise, pharmacological stress agents have had a decisive roll in the management of patients with known or suspected coronary artery disease for many years.

The sponsor performed two randomized, double blind clinical studies among patients who had a broad range of risks for coronary artery disease and who were demonstrated to be "tolerant" of a baseline adenosine injection. Both studies were very similar in design. Specifically, patients underwent the baseline rest/stress MPI scanning then (if final eligibility satisfied) they were randomized to undergo either a rest/regadenoson scan or a rest/adenoscan scan. The primary endpoint was a non-inferiority comparison of the extent of "agreement" between reversible perfusion defects on the scans where agreement was a comparison of the:

-number of perfusion defects between the rest/adenoscan baseline scan and repeat rest/adenoscan scan

versus

-number of perfusion defects between the rest/adenoscan baseline scan and rest/regadenoson scan.

The two studies provided very similar results in that the primary endpoints were met and all secondary endpoints that evaluated other aspects of the image "agreements" (such as location of the perfusion defects and ventricular wall motion) also demonstrated a striking similarity between Adenoscan and regadenoson imaging results. The nominal non-inferiority margin was prospectively defined to correlate with a kappa limit of 0.2. However, the robustness of the diagnostic efficacy data is such that the similarity between the two agents appears indisputable.

Safety data were provided from exposure of 1,651 subjects. The controlled data provided persuasive evidence that regadenoson safety was no worse than that of Adenoscan. Unlike the Adenoscan development program, the sponsor performed two clinical studies that suggested regadenoson is tolerated with acceptable adverse events among patients with asthma and COPD. However, both studies signaled the need for close observation (a WARNING in label) when regadenoson is administered to patients with asthma or COPD.

2) Requirement of the sponsor to provide more comprehensive data that characterize the incidence of adverse events when regadenoson is used among a market population with certain underlying conditions:

The sponsor will be required to conduct two single arm, open label clinical studies that will focus upon the detection of adverse events over a 24 hour period following regadenoson administration to at least 3 specific subsets of patients:

-Bronchoconstrictive disease
    -300 patients with asthma
    -300 patients with COPD

-Renal Impairment: 300 patients with moderate (or worse) chronic kidney disease (Stage ≥ 3, GFR < 60 mL/min/1.73 m^2

Eligibility criteria for these studies are anticipated to be minimal, in order to obtain patients representative of the market population.

The asthma and COPD subset expectation is based upon the limited available data in this population (that was excluded from phase 3 studies). The renal subset is based upon the pharmacokinetic findings that suggested patients with moderate (or worse) renal failure may have prolonged regadenoson exposure; this subset also represented a small proportion of the safety database.

3) Pediatric Research Equity Act (PREA) of 2003 expectations:

The sponsor submitted a request for a full pediatric patient waiver (all age groups) to the Division of Cardiovascular and Renal Drug Products. This division granted a full waiver on October 22, 2004. The Pediatric Review Committee re-examined the prior waiver during this review cycle and concurred with full waiver.

REVIEW COMPONENTS:

Background

Multiple preclinical and clinical background findings suggest that regadenoson should provide the same coronary vasodilator activity of Adenoscan with potentially fewer side effects (such as flushing, dizziness, malaise, etc.). The sponsor's regadenoson development program essentially built upon the concept of similar efficacy to Adenoscan with perhaps less safety concerns.

It is important to note that the development program did not examine the "performance characteristics" of regadenoson in terms of the sensitivity/specificity for the detection of coronary artery disease (where coronary arteriography is the truth standard). Instead, the program was entirely devoted to assessment of the extent of similarity between regadenoson and Adenoscan in terms of coronary vasodilation as manifest on radionuclide scans; that is, the sponsor has not posited that Adenoscan offers any improvement in diagnostic efficacy over Adenoscan (in prior meeting minutes the

sponsor acknowledges that diagnostic efficacy should be the same as Adenoscan). Additionally, performance characteristics are determined in large part by the radionuclide product and image detection equipment, considerations that extend beyond the development of a pharmacologic stress agent that simply purports to be similar to Adenoscan in terms of coronary vasodilation.

Brief Regulatory Timeline

- May 14, 2007 - submission of NDA
- June 26, 2007 - filing meeting, NDA was assigned a standard review
- July 27, 2007 - filing date
- October 29, 2007 - mid-cycle meeting
- March 14, 2008 - PDUFA due date

Clinical Review

The clinical review was performed by Dr. Ira Krefting. Dr. Louis Marzella provided Team Leader/Deputy Division Director expertise to the review and a secondary review. I have examined the clinical reviews and I concur with the major findings, comments and recommendations. The clinical review team recommended approval.

Reiterated below are the major findings from the review of regadenoson clinical data.

Efficacy:

Substantial evidence of safety and efficacy was provided from two clinical studies of similar design, Studies 5132 and 5131. Eligible subjects consisted of patients who underwent a baseline rest/Adenoscan MPI; the enrollment was limited to specific numbers of patients who fit into one of 3 possible categories of perfusion defects (ranging from no defects to five or more defects, where a defect was identified using a typical 17 segment partition of the left ventricle). Randomization occurred following the baseline rest/Adenoscan. A central core/systematic review of images was performed by three evaluators (blinded to clinical data).

The primary endpoint was a comparison of agreement between the scans obtained from the two study groups. Multiple secondary endpoints examined various aspects of the image results, such as "summed stress scores," wall motion comparisons, regional perfusion defects, etc. A "supportive" endpoint consisted of a "tolerability" statistical test that used a step-down procedure in which the first step involved a comparison of the rates of a composite endpoint (in which patients rates their symptoms of flushing, chest pain and dyspnea on a four point scale) followed by a series of individual symptom component comparisons (using the scales).

Since Studies 5131 ad 5131 are essentially the same in design, the primary endpoint results may be summarized for each study, as well as pooled (post-hoc) as shown below.

Table 1. Primary Efficacy Results (agreement of baseline and follow-up scans for reversible ischemia defects) in Phase 3 Studies

Comparison	Study 5131 n = 1113	Study 5132 n = 758	Both Studies n = 1871
Adenosine - Adenosine agreement rate Number of patients (n)	61 ± 3% 372	64 ± 4% 259	62 ± 3% 631
Adenosine - Regadenoson agreement rate	62 ± 2% 741	63 ± 3% 499	63 ± 2% 1240
Rate Difference (R - A) 95% CI	1 ± 4% - 8 to 9%	- 1 ± 5% -11 to 9%	0 ± 3% - 6 to 7%

rates are shown with standard errors

The pre-specified nominal lower bound for the 95% CI was - 13% (which was based upon a clinical estimate of a reasonable correlation coefficient of 0.2). Hence, both studies met the primary endpoint. As shown in extensive analyses by Dr. Mucci, the lead FDA statistician, the submitted data showed success upon the secondary image endpoints, with remarkably similar image findings between Adenoscan and Regadenoson. This extensive correlation of reversible perfusion defects between Adenoscan images and regadenoson images provides solid evidence that regadenoson and Adenoscan are interchangeable, with respect to diagnostic efficacy.

Safety:

Overall, as submitted in the original application, regadenoson was administered to 1,651 subjects who participated in 10 clinical studies, including the two phase 3 studies. The regadenoson dose of 0.4 mg (the proposed market dose) was chosen for final clinical development based upon dose ranging exploratory studies that examined symptoms and a phase 2 study that assessed coronary blood flow. The most important safety information comes from the two phase 3 studies and the two clinical pharmacology studies performed among patients with airway disease (asthma in one, COPD in the other).

The two phase 3 studies (which provide regadenoson exposure information from 1,337 subjects and Adenoscan exposure information from 678 subjects) were designed to enroll only subjects who were assessed as suitable for an Adenoscan injection. Hence, patients with contraindications to Adenoscan were excluded from the studies (second or third degree AV block, sinus node dysfunction—if a pacemaker was not in place; known or suspected bronchospastic lung disease). Nevertheless, the enrolled subjects had a relatively extensive history of co-morbidities, including prior coronary bypass or coronary procedures (50%) or prior myocardial infarction (40%). The patients were older (median 66 years) and predominantly male (70%). Most subjects had near normal renal function; only 16% had moderate to severe renal impairment.

In the two phase 3 studies, the rates of adverse events (80% vs 83%) and serious adverse events (1% vs 2%) were similar between the regadenoson groups and the Adenoscan groups. Three deaths occurred following regadenoson administration (all many days following the drug administration) and two deaths occurred among Adenoscan administration. While the serious adverse events generally appeared unrelated to the drugs (with the single exception of a migraine headache exacerbation), several adverse events appeared temporarily related to the drugs. Most of these events

were mild to moderate severity and tended to last longer following regadenoson exposure than following Adenoscan exposure. The adverse reactions that occurred in ≥ 5% of subjects are shown in table 2.

Table 2. Adverse reactions in the phase 3 studies (frequency ≥ 5%)

Reaction	Regadenoson 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%

In general, the pattern of adverse events appears slightly different between regadenoson and Adenoscan, with less flushing and chest discomfort among regadenoson-exposed patients but more headaches. Notably, dyspnea adverse events occurred at similar rates between the two groups. The similarity in adverse reaction profile between the two drugs is exemplified by the use of aminophylline (to treat symptoms); aminophylline was administered to 3% of the regadenoson-exposed subjects and 2% of the Adenoscan-exposed subjects.

The protocols for the phase 3 studies identified safety and tolerability as secondary objectives and the statistical analytical plan outlined a relatively complex plan for analysis of symptoms that consisted of step-down (in an attempt to control multiplicity) statistical comparisons of:

-the rates and severity of spontaneously reported symptoms that occurred within 30 minutes of study drug administration; an overall comparison of symptom incidence/severity was to be calculated with scores assigned as 0 = none, 1 = mild, 2 = moderate, 3 = severe; a total "symptom score" was to be calculated for the composite of flushing chest pain and dyspnea. Importantly, the severity of symptoms was assigned by the site investigator (not the subject).

-responses to two questions; at 30 minutes after the study drug administration, subjects were asked to rate the overall tolerability of the procedure on a 4 point scale (1 = comfortable and 4 = extremely uncomfortable); they were also asked to rate how the procedure compared to the initial adenoscan procedure on a 5 point scale (1 = much better and 5 = much worse). The distribution of the responses was to be displayed and compared using the average of the scores between the two groups.

The sponsor requested [redacted]
Notably, in the meeting minutes from July, 2002, FDA noted that [redacted]

Shown below are the results from the phase 3 composite symptom/severity score (flushing, chest pain, dyspnea; the summed score integrates the rate and severity assessment by the investigator); subsequently shown are the rates of pre-specified symptoms as well as the results of the tolerability questionnaire.

Table 3. Phase 3 summed symptom score (flushing, chest pain, dyspnea)

Study 5131		Study 5132	
Regadenoson n = 820	Adenoscan n = 411	Regadenoson n = 517	Adenoscan n = 267
0.9 ± 0.03	1.3 ± 0.06	0.9 ± 0.05	1.1 ± 0.08
$p < 0.05$		$p < 0.05$	

Table 4. Rates of pre-defined adverse event symptoms

Symptom	Study 5131		Study 5132	
	Regadenoson n = 820	Adenoscan n = 411	Regadenoson n = 517	Adenoscan n = 267
Flushing*	22%	35%	20%	29%
Chest pain*	29%	44%	26%	35%
Dyspnea	29%	30%	25%	18%
Flushing, chest pain or dyspnea	59%	72%	55%	61%
Throat, neck or jaw pain*	7%	13%	6%	12%
Headache*	23%	16%	28%	15%
GI discomfort	21%	16%	19%	11%
Lightheadedness/dizziness	8%	8%	6%	3%

*$p < 0.05$ in both studies

Table 5. Subject responses on a five point scale to the question that asked how the second procedure was tolerated compared to the baseline Adenoscan procedure (1 = much better; 5 = much worse)

Study 5131		Study 5132	
Regadenoson n = 816	Adenoscan n = 411	Regadenoson n = 517	Adenoscan n = 267
2.1 ± 0.04	2.6 ± 0.05	2.3 ± 0.05	2.6 ± 0.065
$p < 0.05$		$p < 0.05$	

The response to the question that related to how subjects felt (using a 4 point scale) after the second procedure revealed findings similar to those shown in Table 5. Notably, the differences between the scores/responses for the two groups were incremental (not dramatic) and the clinical significance of these incremental changes is unclear.

Overall, within the phase 3 studies, the rates of adverse events were similar between the two groups, the use of aminophylline to treat symptoms was similar between the groups and, of the eight pre-defined symptoms identified for tracking, only four appeared to occur at lower rates in the regadenoson group. The summed symptom score for the composite of chest pain, flushing and dyspnea is of unclear clinical meaningfulness since data verifying the clinical meaningfulness of incremental changes in this summed symptom score are not available; additionally, the occurrence of the dyspnea (a symptom of potentially greater clinical importance than flushing) was similar between the

two study groups. Together, these data do not support a conclusion that regadenoson has been demonstrated to be "better tolerated" than Adenoscan and the data do not support claims of fewer/less severe symptoms with regadenoson.

Since regadenoson is administered as a fixed dose (0.4 mg), one of the concerns is the possibility of more adverse events among lower weight subjects. However, exploratory analyses did not show a weight-related effect upon adverse event rates.

Statistical Review:

The statistical review was performed by Dr. Anthony Mucci, lead statistician for the NDA. The findings from her review were secondarily reviewed by Dr. Jyoti Zalkikar, Biometric Team Leader.

I have read Dr. Mucci's statistical review report and I concur with his major statistical analyses, findings and comments. Dr. Mucci's review includes multiple exploratory analyses which support the robustness of the diagnostic efficacy outcomes.

Clinical Pharmacology and Biopharmaceuticals (OCPB) Review

The clinical pharmacology and biopharmaceutical review was performed by Dr. Christy John. The findings from the review were secondarily reviewed by Dr. Young Moon Choi, Team Leader.

I have read the clinical pharmacology review report and I concur with the observations and comments.

Chemistry and Microbiology

The Chemistry review was performed mainly by Drs. Jilia Boal and Sharmista Chatterjee. The chemists regarded the manufacturing as sufficient to support approval.

Dr. Bryan Riley (with Dr. James McVey) provided a microbiology review that recommended approval.

Pharamcology/Toxicology

The pharmacology/toxicology review was performed by Dr. Siham Biade and was secondarily reviewed by Dr. Adebayo Laniyonu.

During the review cycle, concern was raised when a "bridging study" in rats raised a question of whether or not histopathological changes of myocardial inflammation were associated with the "to-be marketed" formulation of the drug. Notably, the "to-be marketed" formulation of the product was tested in the phase 3 studies as well as other studies that assessed cardiac enzymes following regadenoson administration. The ultimate conclusion from the review of the rat bridging study was that the detected myocardial inflammation did not have clinical relevance (since the occurrence was not at clinically relevant doses--due to the marked hypotension the drug prompted in rats) and cardiac enzyme data from humans did not disclose any evidence of myocardial injury.

Pediatric Safety and Efficacy

As previously noted, a waiver has been granted.

Proposed Labeling

The label has been developed based upon discussions with the sponsor. The regadenoson label importantly differs from the Adenoscan label in that regadenoson is not contraindicated for use in patients with known or suspected bronchospastic lung disease (a WARNING is provided in the regadenoson label).

DMETS/DDMAC reviews

DMETS and DDMAC (Denise Baugh, PharmD and Sean Bradley) provided a review of the proposed patient prescribing information and proposed product name. Concerns from these reviews were incorporated into the product labeling discussions.

Division of Scientific Investigation (DSI)

Dr. Dan-My Chu provided a report of the FDA inspectional findings that pertained to the phase 3 studies. These inspections revealed some findings that were referred to the review team for assessment as to their clinical and data significance. The inspectional findings were determined to be acceptable and the data integrity assessed as sufficient.

Financial Disclosure

As noted in Dr. Krefting's review, the sponsor has submitted required financial disclosure information and the information is acceptable.

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/s/

Rafel Rieves
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