CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-161

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-161

NDA APPROVAL

CV Therapeutics, Inc.
Attn: Carol D. Karp
Senior Vice President
Regulatory Affairs, Quality and Drug Safety
3172 Porter Drive
Palo Alto, CA 94303

Dear Ms. Karp:

Please refer to your new drug application (NDA) dated May 14, 2007, received May 16, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (the Act) for Lexiscan™ (Regadenoson Injection).

We acknowledge receipt of your submissions dated August 7 and 22, 2007; September 14, 2007; October 3, 5, and 19, 2007; November 16, 26, and 30, 2007; December 3, 12, 18, 20 and 21, 2007; January 7, 2008; February 18, 27, and 28, 2008; and March 7, 12, 13, 24, 25 and 26, 2008.

This new drug application provides for the use of Lexiscan™ (Regadenoson Injection) for use as a pharmacologic stress agent for radionuclide myocardial perfusion imaging 0.4 mg/5 mL (0.08 mg/mL).

Your application was not referred to an FDA advisory committee for the following reasons. Your product is a member of the class of previously approved pharmacologic agents that includes adenosine injection, is molecularly similar to adenosine, and has a similar purported mechanism of action to adenosine. Your clinical study design included comparisons of your drug's safety and efficacy to adenosine and these comparisons did not raise additional safety concerns for Lexiscan in the indicated patient population.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

We remind you of the following:

1. An expiry period of 30 months is granted for Regadenoson Injection in 5 mL vial and in 5 mL ANSYR Syringe, when stored at controlled room temperature (25°C with excursions in 15° C to 30°C permitted). You may extend the expiration dating period based on the satisfactory accrual of real time data and report it in an annual report.

2. Under section S.2.5 of your NDA, it is stated that process validation and/or evaluation is not applicable to regadenoson drug substance, because it is not sterilized and is not intended to be a sterile drug substance. Please note that the drug substance and the drug product manufacturing processes are expected to be evaluated by manufacturing appropriate batches to demonstrate the validity of the processes at the time of commercialization. You may refer to ICH Q7A and FDA Compliance Policy Guide (CPG) 7132c.08, Sec. 490, 1000, Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients subject to Pre-Market Approval, March, 2004 for details.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling text for the package insert. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 22-161."

CARTON AND CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels and as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005).* Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission **"Final Printed Carton and Container Labels for approved NDA 22-161."** Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric requirement for this application because the necessary studies are impossible or highly impracticable, due to the fact that the number of pediatric patients who undergo radionuclide myocardial perfusion imaging testing is so small.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act to authorize FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)). This provision took effect on March 25, 2008.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) will not be sufficient to assess the signals of serious risk of pulmonary adverse effects in patients with bronchoconstrictive disease following administration of Lexiscan, nor will it be sufficient to assess the signals of serious risk of adverse effects in patients with moderate or worse chronic kidney disease following administration of Lexiscan.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) has not yet been established and is therefore not sufficient to assess these signals of a serious risk.

Finally, we have determined that only clinical trials in which patients with defined underlying risk are carefully evaluated for at least 24 hours following administration of Lexiscan will be sufficient to assess the signals of serious risk of adverse effects.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the Act, to conduct the following postmarketing clinical trials of Lexiscan:

1. A clinical trial to examine the pulmonary adverse effects of a single 0.4mg dose of Lexiscan in approximately 600 patients with a broad severity of bronchoconstrictive disease (300 with asthma, 300 with COPD). Patient follow-up for the detection of adverse reactions will extend over a time period of at least 24 hours following Lexiscan administration.

The timetable you submitted states that you will conduct this trial according to the following timetable:

Protocol Submission:	by October 2008
Trial Start:	by April 2009
Final Report Submission:	by April 2011

2. A clinical trial to examine the serious adverse effects of a single 0.4mg dose of Lexiscan in approximately 300 patients with moderate (or worse) chronic kidney disease (Stage 3 or greater/using NKF GFR definitions). Patient follow-up for the detection of adverse reactions will extend over a time period of at least 24 hours following Lexiscan administration.

The timetable you submitted states that you will conduct this trial according to the following timetable:

Protocol Submission:	by October 2008
Trial Start:	by April 2009
Final Report Submission:	by April 2011

Submit clinical protocols to IND 62, 862 for this product.

Please use the following designators to prominently label all submissions, including supplements, relating to these postmarketing study requirements as appropriate:

- **Required Postmarketing Trial Protocol under 505(o)**
- **Required Postmarketing Trial Final Report under 505(o)**
- **Required Postmarketing Trial Correspondence under 505(o)**

You are required to report periodically to FDA on the status of these studies pursuant to sections 505(o)(3)(E)(ii) and 506B of the Act, as well as 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii). Under section 505(o)(3)(E)(ii), you are also required to periodically report to FDA on the status of any study or trial otherwise undertaken to investigate a safety issue associated with Lexiscan.

Submit chemistry, manufacturing, and controls protocols and all final reports to this NDA. You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

Please submit one market package of the drug product when it is available.

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
HFD-001, Suite 5100
5515 Security Lane
Rockville, MD 20852

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Tiffany Brown, Regulatory Health Project Manager, at (301) 796-1972.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure: Package Insert and Carton/Container Labels

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Richard Pazdur
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