

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-331

OTHER ACTION LETTER(s)



NDA 22-331

COMPLETE RESPONSE

Addrenex Pharmaceuticals, Inc.
Attention: Moise A. Khayrallah, Ph.D.
President & CEO
4825 Creekstone Drive, Suite 100
Durham, NC 27703

Dear Dr. Khayrallah:

Please refer to your new drug application (NDA) dated February 15, 2008, received February 19, 2008, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Sympres (clonidine hydrochloride), 0.1 mg Modified-Release Tablets.

We acknowledge receipt of your amendments dated May 15, August 15, 28, September 10, 24, November 5, 6, and 7, 2008.

We also acknowledge receipt of your amendment dated December 4, 2008, which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed the review of your application, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

1. Since Sympres tablets contain only — of clonidine hydrochloride, adopt a blend uniformity specification for the final blend to assure that the whole blend is uniform with respect to clonidine hydrochloride. You may choose to follow the recommendation of the draft guidance "Guidance for Industry, Powder Blends and Finished Dosage Units-Stratified In-Process Dosage Unit Sampling and Assessment."
2. Complement the identity test by HPLC retention time method with a second identification test with a justified acceptance criterion as recommended in ICH-Q6A. Include the analytical method with methods validation and a revised specification sheet for the drug product.
3. Provide stability data with hardness and friability values in support of in-process hardness and friability acceptance criteria. Revise the specification sheet with justified hardness and friability specification if the hardness and friability values are out of range of the in-process specifications.

b(4)

4. In your validation report, identify by relative retention time each degradation product found during the forced degradation study. Provide the amount of each degradation product found in the forced degradation study. Provide the mass balance information in the forced degradation experiment. If known degradation products are found, provide the chemical names of those degradants and the quality of the reference standards used to identify them.
5. Report all degradation products above 0.1%, as recommended by ICH-Q3B. The degradation products should include each specified and unspecified degradation product, and total degradation products. Submit the specification sheet with revised related substances acceptance criteria. Include the analytical method and its validation.
6. Submit the revised specification sheet with microbial limits specification.
7. Provide intermediate precision results of percentage dissolved from tablets at all time points with different operators, different equipment and different days.
8. Revise your post approval stability commitment to include in the stability program at least one annual batch each year in each marketed container/closure system manufactured at the commercial manufacturing site under long-term storage conditions following the currently approved stability protocol.
9. Revise your dissolution specification as follows:

pH	% Released			
	2.0	7.0	7.0	7.0
Time (hr)	1	4	8	16
Reviewer's proposed Spec	—	—	—	—

b(4)

10. Submit the revised drug product specification, revised raw material specification or batch records, as committed in your cover letter, dated 7-NOV-2008.

PEDIATRIC RESEARCH EQUITY ACT (PREA)

11. All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We acknowledge your request for a waiver of these studies. However, we do not agree that your arguments support a waiver. Therefore, you must submit a proposal for conducting the required pediatric studies.

LABELING

12. We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(1)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>.

FACILITY INSPECTIONS

During a recent inspection of the UPM Pharmaceuticals manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit

your meeting request as described in the FDA Guidance for Industry *Formal Meetings With Sponsors and Applicants for PDUFA Products*, February, 2000 (<http://www.fda.gov/cder/guidance/2125fnl.htm>).

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, please call Russell Fortney, Regulatory Project Manager, at (301) 796-1068.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Norman Stockbridge
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