

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-331

OTHER REVIEW(S)

NDA 22-331 Jenloga (clonidine hydrochloride) Tablets
RHPM Overview
September 29, 2009

Sponsor: Addrenex Pharmaceuticals, Inc.
Type: 505(b)(2)/3S
Receipt Date: February 19, 2008
Goal Date: September 30, 2009

Action: Approval
Action Date: September 30, 2009

Background

This application requests approval of a new formulation of clonidine tablets. The application was originally submitted on February 19, 2008. The Division issued a Complete Response letter on December 19, 2008.

This is a 505(b)(2) application with Catapres tablets (NDA 17-407) as the RLD. The sponsor conducted two trials to support this application. The first study was a single-dose PK study comparing Jenloga to the approved immediate-release clonidine formulation. The second study was a 28 day, multi-dose study PK/PD study comparing Jenloga to placebo.

The sponsor originally proposed that the new formulation is an "sustained-release" formulation. However, because the dosing schedule for the new formulation is the same as the approved immediate-release formulation, Agency guidelines prevent the use of the "sustained-release" in the official name of the product. The Division proposed using "modified-release" as part of the name to indicate to prescribers that this product is not the same as immediate-release clonidine. This was the official product description used in the CR letter. The LNC later informed the Division that "modified-release" is not an officially recognized dosage form. Therefore, the official product description has been changed to "tablets," while the Dosage and Administration and Description sections use the phrase "modified-release" to describe the product.

The December 19, 2008, CR letter included the following issues that needed to be resolved prior to approval:

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 You may choose to follow the recommendation of the draft guidance "Guidance for Industry, Powder Blends and Finished Dosage Units-Stratified In-Process Dosage Unit Sampling and Assessment."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.
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

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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:

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

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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.

The sponsor submitted a complete response on March 27, 2009. At this time, all issues have been resolved, and this application will be approved.

Division Director's Memo (12/19/08, 9/29/09)

Reviewer: Norman Stockbridge, M.D., Ph.D.

Recommendation: Approval

Summary: Dr. Stockbridge's memo indicates that all outstanding issues have been resolved.

CDTL Review (12/16/08)

Reviewer: Abraham Karkowsky, M.D., Ph.D.

Recommendation: Approval

Summary: All issues noted in Dr. Karkowsky's original CDTL memo have been resolved.

Medical Review (9/22/08)

Reviewer: Akinwale Williams, M.D.

Recommendation: Approval

Summary: Dr. Williams' review indicates that this application should be approved. No new clinical data were submitted in the sponsor's March 30, 2009, resubmission.

Clinical Pharmacology and Biopharmaceutics Review (11/17/08 & 12/17/08)

Reviewer: Divya Menon-Andersen, Ph.D.

Recommendation: Approval

Summary: Dr. Menon-Andersen's reviews indicated that there are no outstanding issues. No clinical pharmacology data were submitted in the sponsor's March 30, 2009, resubmission.

Chemistry Review (3/10/08, 11/12/08, 12/15/08, 9/25/09)

Reviewer: Amit Mitra, Ph.D.

Recommendation: Approval

Summary: Dr. Mitra's 9/25/09 review indicates that all issues described in the CR letter have been resolved. His review notes that the official product name should be JENLOGA (clonidine hydrochloride) Tablets. The Division and the sponsor have both agreed to this proposal.

Dissolution Specifications Review (12/15/08, 9/3/09)

Reviewer: Tapash Ghosh, Ph.D.

Recommendation: Approval

Summary: In response to the Division's CR letter, the sponsor proposed dissolution specifications that were different than those described in the CR letter. Dr. Ghosh tentatively agreed to the sponsor's proposal in February 2009, prior to the sponsor's submission of their complete response. However, after reviewing the official submission, Dr. Ghosh proposed new specifications. During a teleconference on September 24, 2009, ONDQA and the sponsor reached agreement on acceptable dissolution specifications. Dr. Sood's supervisory memo dated 9/25/09 indicates that the agreed-upon specifications should be included in the approval letter.

DSI: There were no inspections of the clinical study sites.

Pediatric Rule: This application was discussed during the September 23, 2009, meeting of the Pediatric Review Committee (PeRC). The Committee agreed to a waiver for children aged 0-5 years, and a deferral for children aged 6-17 years. A Post-Marketing Requirement to conduct the pediatric study will be included in the approval letter.

The sponsor has submitted a Proposed Pediatric Study Request. The Division plans to issue a Written Request for the proposed study. The proposed Written Request will be discussed at a PeRC meeting scheduled for December 2, 2009.

Labeling: The labeling is similar to the most recently approved label for Catapres (tablet), with modifications to describe the clinical program for the current application, formulation-related differences, and the change to the PLR format.

Tradename: The sponsor originally called their product CLONICEL during the development program. Although this name appears throughout the application, it was never officially submitted to the Agency for consideration. The sponsor initially proposed CLONIBID as the official tradename. However, because it contains "BID" (a reference to a dosing schedule) as part of the name, DMEPA rejected this proposal. The sponsor then proposed SYMPRES as the tradename. DMEPA accepted this proposal, and this was the name that was used in the Division's December 19, 2008, CR letter. However, on May 21, 2009, the sponsor submitted a request to change the tradename to JENLOGA. This request was subsequently approved by DMEPA, and is the currently approved tradename.

Advisory Committee: N/A



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: September 18, 2009

To: Norman Stockbridge, MD, Director
Division of Cardiovascular and Renal Products

Through: Carlos M. Mena-Grillasca, RPh, Acting Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

From: LaToya Shenee Toombs, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name: Jenloga (Clonidine Hydrochloride) Extended-release Tablets
0.1 mg

Application Type/Number: NDA 22-331

Applicant: Addrenex Pharmaceuticals, Inc.

OSE RCM #: 2009-1066

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1 INTRODUCTION

This review is written in response to a request from the Division of Cardiovascular and Renal Products for a review of the revised Jenloga label in response to the Division of Medication Error Prevention and Analysis' previous comments to the Applicant.

2 MATERIALS REVIEWED

The Applicant provided revised labels on September 8, 2009. We also evaluated the recommendations pertaining to the previous revision in OSE RCM# 2009-1066 dated August 28, 2009.

3 DISCUSSION

The proposed container labels submitted use the term "modified-release tablets" to describe the finished dosage form for the proposed product. Modified-release is not an official USP dosage form designation. Thus, the Office of New Drug Quality Assessment (ONDQA) and CDER Labeling and Nomenclature Committee (LNC) recommended that "tablets" be used to express the finished dosage form of this product rather than modified-release. However, there is some concern from the clinical team that labeling the product as "tablets" infers that the proposed product can be substituted on a mg-per-mg basis when in this case such substitution is not appropriate.

According to Dr. Stockbridge's December 12, 2008 Memorandum to the File, it appears that there are C_{max} differences between the proposed product as compared to other clonidine tablet products currently marketed and these differences will mean that both blood pressure and adverse effect profiles are likely to be different. If substitution between the proposed product and the currently marketed product occurs re-titration, of the dose will be required. In order to avoid inappropriate substitution the clinical team would like some distinction in the established name and they believe "modified release" is the best choice.

The clinical team's concern has merit however; DMEPA does not believe that revising the established name to "modified-release" will fully address this concern. Although "modified-release" may provide some information to practitioners that Jenloga is different from currently marketed Clonidine products it is not a recognized USP dosage form and thus not defined. It may not communicate to practitioners that there may be clinical differences (e.g., adverse events and blood pressure) and should not be substituted for other Clonidine tablets on a mg-per-mg bases. We believe additional information is needed on the labels and labeling to convey this information. As such we provide recommendations in Section 4, which may help minimize potential for inappropriate substitution.

4 RECOMMENDATIONS

All of DMEPA's recommendations from our August 28, 2009 review have been addressed, except for the recommendation pertaining to the dosage form. However, we defer the final disposition on the dosage form to LNC/ONDQA and the Division of Cardiovascular and Renal Products. In addition, DMEPA recommends the following container label and insert labeling statements be implemented regardless of the final disposition on the dosage form to help minimize the potential for inappropriate substitution between Jenloga and currently marketed

Clonidine tablets.

4.1 INSERT LABELING

Add a statement such as “When prescribing and dispensing, do not substitute a Jenloga prescription for other clonidine tablets. Differences exist in the...of Jenloga compared to other clonidine tablets that may require re-titration if substitution occurs”

4.2 CONTAINER LABEL

Add a statement to the principal display panel such as “Do not substitute Jenloga for other clonidine tablets.”

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 ✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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/s/

Latoya S TOOMBS
09/18/2009

DENISE P TOYER
09/18/2009

CAROL A HOLQUIST
09/18/2009



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: August 28, 2009

To: Norman Stockbridge, MD, Director
Division of Cardiovascular and Renal Products

Through: Carlos M. Mena-Grillasca, RPh, Acting Team Leader
Denise Toyer, PharmD, Deputy Director
Division of Medication Error Prevention and Analysis

From: LaToya Shenee' Toombs, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis

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0.1 mg

Application Type/Number: NDA 22-331

Applicant/sponsor: Addrenex Pharmaceuticals, Inc.

OSE RCM #: 2009-1066

1 INTRODUCTION

This review was written in response to a request from the Division of Cardiovascular and Renal Products to evaluate the container labels and insert labeling for the product Jenloga (NDA 22-331), for areas that could lead to medication errors.

2 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis used Failure Mode and Effects Analysis (FMEA)¹ in our evaluation of the Jenloga container labels and insert labeling received May 22, 2009 (see Appendix A).

3 RECOMMENDATIONS

Our evaluation of the proposed container labels and insert labeling noted areas of needed improvement in order to minimize the potential for medication errors. We provide recommendations on the insert labeling in Section 3.1 *Comments to the Division* for discussion during the labeling meetings. Section 3.2 *Comments to the Applicant* contains our recommendations for the container label. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

3.1 COMMENTS TO THE DIVISION

A. GENERAL COMMENTS

1. DMEPA concurs with the Office of New Drug Quality Assessment (ONDQA) Chemistry review (submitted 11/12/2008) recommending the established name be presented as, "(Clonidine hydrochloride) extended-release tablets".

B. FULL PRESCRIBING INFORMATION

1. DOSAGE AND ADMINISTRATION

a) DMEPA notes instructions for conversion from the clonidine immediate-release product to the clonidine extended-release formulation are not included in this section. Include this information as it is pertinent for patients switching from the immediate-release to the extended-release formulation.

b) DMEPA notes the frequency of administration recommendations are ambiguous. (e.g. divided doses, morning and bedtime). The frequency of administration for this product is considered to be twice daily. Therefore we recommend the frequency of administration be presented as, "twice daily at morning and bedtime". Consider revising the statement, "Doses should be taken at morning and bedtime", to read, "Doses should be taken twice daily at morning and bedtime." In addition, add the statement, "If morning and bedtime doses are not equal, then the bedtime dose should be the larger of the two doses."

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Modify the HIGHLIGHTS OF PRESCRIBING INFORMATION Dosage and Administration section and PATIENT COUNSELING INFORMATION Dosing section (15.1), to be consistent with the above recommendations.

2. DOSAGE FORMS AND STRENGTHS

The Applicant indicates that the tablets are available as, "...white, round, non-scored, standard convex with debossing on one side" tablets. The term "debossing" is a general description. Modify the statement to include the description of the debossed imprints.

3. HOW SUPPLIED/STORAGE AND HANDLING

See comment B.2.

3.2 COMMENTS TO THE APPLICANT

A. General Comments (All Labels)

1. Revise the dosage form to read, "Extended-release Tablets".
2. Delete the statement, _____ ' from the Usual Dosage statement. The dosing range for this product is 0.1 mg to 0.6 mg per day. A daily dose of 0.3 mg or higher will require more than one tablet _____ and would render the statement inaccurate. Revise to state, "Usual Dosage: See package insert for dosage information."
3. Increase the prominence of the strength (i.e. 0.1 mg). Consider relocating to the area immediately below the dosage form. For example:

Extended-Release Tablets
0.1 mg
4. The black text color over the blue shaded background is difficult to read. Change the color hue of the shaded background to increase the contrast with the black text.
5. Revise the proprietary name to read in title case font (i.e. Jenloga). As currently presented, with all-CAPS, it is difficult to read.

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 Trade Secret / Confidential (b4)

 ✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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/s/

Latoya S TOOMBS
08/28/2009

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