CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-438

Approval Letter(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-438

Reliant Pharmaceuticals, LLC
Attention: Keith S. Rotenberg, Ph.D.
110 Allen Road
Liberty Corner, NJ 07938

Dear Dr. Rotenberg:

Please refer to your new drug application (NDA) dated October 31, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for InnoPran XL (propranolol hydrochloride) Extended Release 80 and 120 mg Capsules.

We acknowledge receipt of your submissions dated January 9, August 30, September 4, October 1, 10 (two), 22, 28 and 29 and November 26, 2002; January 29 and March 4, 2003.

The November 26, 2002 submission constituted a complete response to our August 30, 2002 action letter.

This new drug application provides for the use of InnoPran XL (propranolol hydrochloride) Extended Release 80 and 120 mg Capsules for Hypertension.

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 agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the submitted labeling (package insert submitted March 4, 2003 and immediate container labels submitted March 4, 2203). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

At the time of the next printing, please make the following changes:

Package Insert

1. In the **DESCRIPTION** section, delete the second sentence of the third paragraph, ——

   ——

2. In the **DESCRIPTION** section, change the second sentence of the first paragraph from:

   —

   ——

   To:

   InnoPran XL is available as 80 mg and 120 mg capsules which contain sustained-release beads.

3. In the **DESCRIPTION** section, change the wording of the last sentence of the third paragraph from —— " to "120 mg."

4. In the **PHARMACOKINETICS AND DRUG METABOLISM/Drug Interactions/***Interactions with Substrates, Inhibitors or Inducers of Cytochrome P-450 Enzymes* subsection, please change the word —— ` to "affect".

5. In the **PHARMACOKINETICS AND DRUG METABOLISM/Drug Interactions** section, reorder the subheadings under *Non-Cardiovascular Drugs* so that they are in alphabetical order.

6. In the **PHARMACOKINETICS AND DRUG METABOLISM/Drug Interactions/***Non-Cardiovascular Drugs/Anti-Ulcer Drugs* section, delete the words "——" in the second paragraph from:

7. Correct spelling error in the section title, **PHARMACODYNAMICS AND CLINICAL EFFECTS.**

8. In the **PHARMACOKINETICS AND DRUG METABOLISM/Special Populations/Race** section, change "——" to "Whites" in the last sentence.

9. In the **PRECAUTIONS/Drug Interactions** section, reorder the subheadings under **Cardiovascular Drugs** so that they are in alphabetical order.

10. In the **PRECAUTIONS/Drug Interactions** section, reorder the subheadings under **Non-Cardiovascular Drugs** so that they are in alphabetical order.

11. In the **PRECAUTIONS/Carcinogenesis, Mutagenesis, Impairment of Fertility** section and **PRECAUTIONS/Pregnancy: Pregnancy Category C** section, change "——" to "propranolol HCl" wherever it occurs.

Container labeling

1. Revise immediate container labels so the boldness in type is consistent across dosage strengths and labeling provisions. It is noted that on certain 120 mg strength labeling text is relatively faint.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-438.**" Approval of this submission by FDA is not required before the labeling is used.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Cardio-Renal Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

Your stability data supports an expiration date of —months for the drug product packaged in blister configurations and —months for the drug product packaged in the —— bottles.

Reference to the —— information should be deleted with appropriate revision of the stability protocol.

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

If you have any questions, please call:

Ms. Melissa Robb
Regulatory Health Project Manager
(301) 594-5313

Sincerely,

{See appended electronic signature page}

/s/

Douglas C. Throckmorton, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Doug Throckmorton
3/12/03 12:55:05 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-438

Approvable Letter (S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-438

Reliant Pharmaceuticals, LLC
Attention: Keith S. Rotenberg, Ph.D.
110 Allen Road
Liberty Corner, NJ 07938

Dear Dr. Rotenberg:

Please refer to your new drug application (NDA) dated October 31, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for — (propranolol HCl) Extended Release 80 and 120 mg Capsules.

We acknowledge receipt of your submissions dated December 19 and November 26, 2002; February 4 and 20, April 5, May 1 (two), July 18 and 31 and August 8, 23 (two) and 26, 2002.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling (FPL) for the drug. The labeling should be essentially identical in content to the enclosed labeling for the package insert and the carton and container labels included in your July 31, 2002 submission. In addition, we have the following recommendations and requests:

Clinical:

Hypertension

The unique properties of the release of propranolol from — make it necessary for us to focus heavily on the clinical data obtained with this specific formulation, and then look for support from the wealth of other available data on other propranolol-containing formulations. Based on the clinical studies you have submitted, — is approvable for the treatment of hypertension at doses of 80 and 120 mg. First, when the effects of multiple doses of — in mild-to-moderate hypertension were examined in study 3003, we are convinced that there is persistent antihypertensive effect for these two doses during the full 24 hour dosing interval. However, regarding the dose-response effects of — there were no additional blood pressure effects at doses greater than 120 mg daily. Based on an analysis of the blood pressure effect using two-way ANCOVA (with treatment center and baseline value as the covariates), the changes in placebo-subtracted seated diastolic blood pressure effects in the afternoon were –3.6, –5.5, –3.4, and –4.4 mm Hg for the 80, 120, 160 and 640 mg respectively. These results are consistent with the results you reported to the Agency using an alternate statistical analysis and to results obtained using changes in systolic blood pressure. As you pointed out in your fax of August 23, 2002, — does reduce mean resting heart rate in a dose-related manner (–3.2, –4.8, –6.8 and –7.8 beats per minute for the 80, 120, 160 and 640 mg doses, respectively, by our analysis). This suggests that doses of — >120 mg have the increased potential to cause symptoms related to bradycardia without any greater effect to lower blood pressure.

An additional comment needs to be made about your focus on the antihypertensive effects of — in the morning. Despite the epidemiological data associating an increased risk of cardiac events with hypertension during this time, there are no data demonstrating that a pharmacological reduction in

blood pressure during this time period ('preventing the early-morning rise') is associated with any specific clinical benefit. Hence, to include such data in the label would be to invite a false claim of benefit.

Chemistry:

1. The drug product appearance specifications should also be revised to reflect current changes (e.g., use of the code name, "RD201", to replace the trade name) and to use the terminology of "segmented bands" to define the imprinted dosage strength markings. The "How Supplied" section of the package insert should be appropriately revised.

2. Relocate the net quantity to the bottom of the container label and decrease its font size to prevent confusion with the strength.

Please note that the submitted stability data support a — expiration date for the drug product.

Clinical Pharmacology:

1. The following dissolution method is acceptable: USP apparatus 2 at 50 rpm; 700 ml of 0.1 N HCl for 2 hours, then pH change to 6.8 with an additional 200 ml of phosphate buffer.

   The proposed dissolution specifications are inadequate and should be revised as follows:

   2 hours NMT — %
   4 hours NMT — %
   6 hours — %
   10 hours — %
   20 hours NLT — %

2. In-process dissolution specification should be revised for your TSR beads to match the changes recommended for your capsules as well as corresponding changes for related control provisions (e.g., worksheets, stability protocols, etc.).

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL, ten of which individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

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

If you have any questions, call Ms. Zelda McDonald, Regulatory Health Project Manager, at (301) 594-5333.

Sincerely,

{See appended electronic signature page}

/S/

Douglas C.Throckmorton M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Doug Throckmorton
8/30/02 06:14:33 PM

6 pages redacted from this section of the approval package consisted of draft labeling