# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPROVAL PACKAGE FOR:

# APPLICATION NUMBER

# 21-438

# Administrative Documents

**Section 13 Patent Information On Any Patent Which Claims the Drug**

Time Sensitive Patent Information pursuant to 21 C.F.R. 314.53 for NDA #21-438

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

| | |
|---|---|
| Trade Name: | To be determined |
| Active Ingredient(s): | Propranolol Hydrochloride |
| Strength(s): | 80mg, 120mg |
| Dosage Form: | Extended release capsules |
| Approval Date: | Not yet approved |

To the best of applicant's knowledge there are currently no existing patents which claim Propranolol Hydrochloride or which claim a method of using Propranolol Hydrochloride for which a claim of patent infringement could reasonably be asserted.

**Section 14 A Patent Certification with Respect to Any Patent Which Claims the Drug**

In the opinion and to the best knowledge of Reliant Pharmaceuticals, LLC there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs.

EXCLUSIVITY SUMMARY for NDA # 21-438 SUPPL #

Trade Name InnoPran XL Generic Name propranolol hydrochloride Extended Release Capsules

Applicant Name Reliant Pharmaceuticals, L.L.C. HFD- 110

Approval Date March 12, 2003

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/_X__/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /__X_/

      If yes, what type(SE1, SE2, etc.)?

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X__/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /_X__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X__/

**IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /_X__/

If yes, NDA # _____ Drug Name

**IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

**IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).**

**PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X__/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 16-418 Inderal (propranolol) Tablets

NDA # 16-419 Inderal (propranolol) Injection

NDA # 18-553 Inderal (propranolol) LA Tablets

Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

**IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.**

**PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /__X_/ NO /___/

**IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X__/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__1__, Study # __3001__

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X__/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # Study 3001

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

| | | |
|---|---|---|
| Investigation #1 | YES /___/ | NO /_X__/ |
| Investigation #2 | YES /___/ | NO /___/ |
| Investigation #3 | YES /___/ | NO /___/ |

If you have answered "yes" for one or more investigations, identify each such investigation and the

the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # [redacted] YES /_X__/ NO /___/ Explain:

Investigation #2

IND # _____ YES /___/ NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X__/

If yes, explain: _____

_____

_____

_____
Signature of Preparer Date
Title: Regulatory Health Project Manager

Signature of Office or Division Director Date

cc:
Archival NDA 21-438
HFD-110/Division File
HFD-110/RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

---

**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
3/17/03 09:17:09 AM

# PEDIATRIC PAGE

## (Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 21-438 Supplement Type (e.g. SE5): _____ Supplement Number:

Stamp Date: November 2, 2001 Action Date: March 12, 2003

HFD-110 Trade and generic names/dosage form: InnoPran XL (propranolol HCl) Extended Release Capsules

Applicant: Reliant Pharmaceuticals, L.L.C. Therapeutic Class: 3S

Indication(s) previously approved:

**Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.**

Number of indications for this application(s): 1

Indication #1: Hypertension

Is there a full waiver for this indication (check one)?

X Yes: Please proceed to Section A.

❑ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

## Section A: Fully Waived Studies

Reason(s) for full waiver:

❑ Products in this class for this indication have been studied/labeled for pediatric population
❑ Disease/condition does not exist in children
❑ Too few children with disease to study
❑ There are safety concerns
X Other: This formulation was developed to treat age-related cardiovascular disease. Numerous different formulations would be require for each age group, which are beyond the capabilities of the sponsor to develop.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

## Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for partial waiver:

❑ Products in this class for this indication have been studied/labeled for pediatric population
❑ Disease/condition does not exist in children
❑ Too few children with disease to study
❑ There are safety concerns
❑ Adult studies ready for approval
❑ Formulation needed
❑ Other: _____

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

## Section C: Deferred Studies

**Age/weight range being deferred:**

**Min _____ kg_____ mo._____ yr._____ Tanner Stage_____**
**Max_____ kg_____ mo._____ yr._____ Tanner Stage_____**

**Reason(s) for deferral:**

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**

**Other:**_____

**Date studies are due (mm/dd/yy):** _____

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

## Section D: Completed Studies

**Age/weight range of completed studies:**

**Min _____ kg_____ mo._____ yr._____ Tanner Stage_____**
**Max_____ kg_____ mo._____ yr._____ Tanner Stage_____**

**Comments:**

*If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**This page was completed by:**

***{See appended electronic signature page}***

_____
**Regulatory Health Project Manager**

**cc: NDA 21-438**
**HFD-960/ Terrie Crescenzi**
**(revised 1-18-02)**

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960**
**301-594-7337**

---

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

---

/s/

---

Melissa Robb
3/14/03 09:54:54 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND [redacted]
NDA 21-438

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

Dear Dr. Rotenberg:

Reference is made to your correspondence dated September 5, 2001 (IND [redacted] requesting a waiver for pediatric studies under 21 CFR 314.55(c).

We have reviewed the information you have submitted and agree that a waiver is justified for propranolol hydrochloride controlled release for hypertension — for the pediatric population.

Accordingly, a waiver for pediatric studies for this application is granted under 21 CFR 314.55 at this time.

If you have questions, please contact:

Ms. Zelda McDonald
Regulatory Project Manager
301-594-5333

Sincerely,

*{See appended electronic signature page}*

/S/

Raymond J. Lipicky, 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.**

---

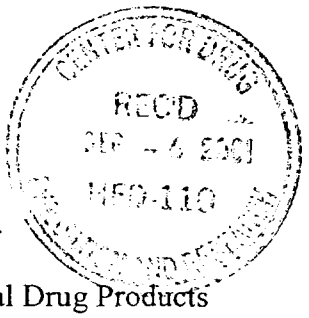
/s/

---

Raymond Lipicky
12/18/01 03:56:14 PM

Reliant
PHARMACEUTICALS

Reliant Pharmaceuticals, LLC
110 Allen Road
Liberty Corner, NJ 07938
908-580-1200
www.ReliantRx.com




September 5, 2001

Raymond Lipicky, M.D.
Director,
Division of Cardio-Renal Drug Products
Woodmont Office Complex 2
1451 Rockville Pike – 5th Floor
Room 5039
Rockville, MD 20852

**RE: — (propranolol hydrochloride) Controlled Release**
**IND No.**
**Amendment No. 021**
**Request for Waiver of Pediatric Studies**

Dear Dr. Lipicky:

The purpose of this communication is to amend the above-mentioned IND. This amendment consists of a request to waiver the conduct of pediatric studies. In accordance with the draft guidance "Recommendations for Complying with the Pediatric Rule (21CFR 314.55 (a) and 601.27 (a)", a Waiver Request Form is attached.

This formulation was developed to treat age-related cardiovascular disease. Numerous different formulations would be required for each age group, which are beyond the capabilities of Reliant to develop. We therefore are requesting a waiver for conducting pediatric studies for —

If you have any questions or comments please call the undersigned at (908) 542-4429.

Sincerely,

Robert J. Mandetta
Director,
Regulatory Affairs

RJM/mmc

cc: Zelda McDonald, Project Manager, DCRDP

COPY

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

# INVESTIGATIONAL NEW DRUG APPLICATION (IND)

*(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)*

*Form Approved:* OMB No. 0910-0014.
*Expiration Date: September 30, 2002*
*See OMB Statement on Reverse.*

**NOTE:** No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSOR
Reliant Pharmaceuticals, LLC

2. DATE OF SUBMISSION
05 September 2001

ADDRESS *(Number, Street, City, State and Zip Code)*
110 Allen Road
Liberty Corner, NJ 07938

4. TELEPHONE NUMBER *(Include Area Code)*
908.542.4429

NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*
Propranolol Hydrochloride

6. IND NUMBER *(If previously assigned)*
[redacted]

INDICATION(S) *(Covered by this submission)*
Hypertension,

PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED:
☐ PHASE 1 ☐ PHASE 2 ☐ PHASE 3 ☐ OTHER _____ *(Specify)*

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, DRUG MASTER FILES *(21 CFR Part 314.420)*, AND PRODUCT LICENSE APPLICATIONS (21 CFR Part 601) REFERRED TO IN THIS APPLICATION.

DMF
DMF [redacted]
DMF

***IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.***

SERIAL NUMBER
0 2 1

THIS SUBMISSION CONTAINS THE FOLLOWING: *(Check all that apply)*
☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND) ☐ RESPONSE TO CLINICAL HOLD

| PROTOCOL AMENDMENT(S): | INFORMATION AMENDMENT(S): | IND SAFETY REPORT(S): |
|---|---|---|
| NEW PROTOCOL | ☐ CHEMISTRY/MICROBIOLOGY | ☐ INITIAL WRITTEN REPORT |
| CHANGE IN PROTOCOL | ☐ PHARMACOLOGY/TOXICOLOGY | ☐ FOLLOW-UP TO A WRITTEN REPORT |
| NEW INVESTIGATOR | ☐ CLINICAL | |

RESPONSE TO FDA REQUEST FOR INFORMATION ☐ ANNUAL REPORT ☐ GENERAL CORRESPONDENCE

REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED ☒ OTHER Pediatric Waiver Request *(Specify)*

**CHECK ONLY IF APPLICABLE**

[redacted]

**FOR FDA USE ONLY**

| DDBIND/DGD RECEIPT STAMP | DDR RECEIPT STAMP | DIVISION ASSIGNMENT: |
|---|---|---|
| | CENTER FOR DRUG EVALUATION AND RESEARCH REC'D SEP - 6 2001 HFD-110 | IND NUMBER ASSIGNED: |

# Request for Waiver of Pediatric Studies

**IND No**
**Product:** — (propranolol hydrocloride) Controlled Release
**Sponsor:** Reliant Pharmaceuticals, LLC
**Indication:** Hypertension

1. What age ranges are included in your waiver request? *All*

2. Reason(s) for waiving pediatric studies:

   (a) No meaningful therapeutic benefit over existing treatments **and** is unlikely to be used in a substantial number of pediatric patients.

   (b) Studies are impossible or highly impractical because the number of patients is so small or geographically dispersed.

   (c) The product would be ineffective or unsafe in all pediatric age groups.

   (d) Attempts to develop a pediatric formulation for a specific age group have failed.

   (e) Disease-specific waiver indicated for the treatment of the condition in adults (please check)

| | |
|---|---|
| ___ Alzheimer's Disease | ___ Age-Related Macular Degeneration |
| ___ Prostate Cancer | ___ Breast Cancer |
| ___ Renal Cell Cancer | ___ Non-Germ Cell Ovarian Cancer |
| ___ Hairy Cell Cancer | ___ Pancreatic Cancer, Colorectal Cancer |
| ___ Osteoarthritis | ___ Squamous Cell Cancers of the Oropharynx |
| ___ Uterine Cancer | ___ Basal Cell and Squamous Cell Cancer |
| ___ Endometrial Cancer | ___ Small Cell and Non-Small Cell Lung Cancer |
| ___ Parkinson's Disease | ___ Amyotrophic Lateral Sclerosis |
| ___ Arterioscleroisis | ___ Symptoms of Menopause |
| ___ Infertility | ___ Other (please state and justify) |

3. Justification for waiver (not necessary if category 2(e) is checked):

   *Formulation is for age-related disease, would require numerous formulations for each age group which would be extremely difficult to develop.*

Reliant Pharmaceuticals, LLC
110 Allen Road
Liberty Corner, NJ 07938
908-580-1200
www.ReliantRx.com

## Debarment Certification

Reliant Pharmaceuticals, LLC hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Signature: Keith Rotenberg

Keith Rotenberg, PhD
Vice President, Regulatory
Title: Reliant Pharmaceuticals, LLC

Date: 9/28/01

RHPM Overview of NDA 21-438
InnoPran XL (propranolol HCl) Extended Release 80 and 120 mg Capsules
March 12, 2003

**Sponsor: Reliant Pharmaceuticals**
**Related IND:** [redacted]
**Chemical Type & Therapeutic Potential: 3S**

**Background:**
InnoPran XL is a new, once a day formulation of propranolol hydrochloride (HCL). Propranolol HCl has been widely marketed more than thirty years. InnoPran XL is an oral capsule formulation containing spherical beads allowing delayed release of propranolol HCl. When taken at bedtime, the delayed release beads are intended to attenuate the early morning circadian increases in blood pressure and heart rate.
A pre-NDA telecon was held on August 1, 2001.

**Division Director's Memo**
In his review dated August 30, 2002, Dr. Throckmorton stated that an approvable action should be taken for the NDA for the drug to be used as an antihypertensive at 80 and 120 mg given once daily at night.

**Medical Review**
In her review dated May 1, 2002, Dr. Gordon stated that the one clinical efficacy trial in hypertensive patients found that InnoPran XL, in doses of 80 mg to 640 mg, taken once daily, lowered sitting diastolic and systolic blood pressure compared to placebo. There was a small dose response for blood pressure lowering effects and a more prominent one for heart rate lowering effects. The 640 mg dose had higher adverse event rates and discontinuations.
Dr. Gordon stated that she had reviewed the **Financial Disclosure** section of the application.
Dr. Gordon did not make a recommendation as to approvability or labeling changes.

**Secondary Medical Review**
In his memo dated, August 29, 2002, Dr. Karkowsky recommended that the application not be approved because the only study submitted for the treatment of hypertension is inadequate to conclude that InnoPran XL affords blood pressure control during the entire dosing interval. He believes an approval recommendation sets a poor precedent for other drugs, engineered to deliver drug only after long lag. In addition, the labeling of InnoPran XL would of necessity rely on non-trough blood pressure effects since no "true" trough measurements are available.

**Statistics**
In his review dated May 8, 2002, Dr. Wang agreed with the Sponsor's efficacy conclusions. He noted that there was only one efficacy study and primary endpoint did not have a very small p-value, therefore, it might not be enough to represent a wide-ranging population.

**Biopharmaceutics**
In her review dated August 9, 2002, Dr. Dorantes stated that the sponsor has provided appropriate information to satisfy the clinical pharmacology and biopharmaceutic requirements for an ER-product and NDA 21-438 for InnoPran XL Capsules is acceptable, provided that her dissolution and labeling comments are addressed (see page 6 of her review).

**Pharmacology**

In his review dated November 22, 2002, Dr. Resnick made some recommendations to be included in the labeling. He also noted as this is a 505(b)(2) application, no evidence of safety from new in vitro or in vivo studies nor a formal pharm/tox review are required.

**Chemistry**
In his review dated August 16, 2002, Dr. Zimmerman stated that this NDA is approvable from a CMC standpoint pending the satisfactory completion of the inspection of a new stability testing facility. The deficiencies and comments on pages 31 and 32 of his review should be conveyed to the sponsor in the action letter.

In his review dated December 20, 2002, Dr. Zimmerman stated there were no deficiencies noted. The comments to be placed in the action letter re: stability data and validation of regulatory methods can be found on page 36 of the review.

Environmental Assessment: The sponsor requested and qualifies for a categorical exclusion.

Trade Name Review: In their trade name review dated July 12, 2002, DMETS found the proprietary name, ——— acceptable. On December 12, 2002, DMETS found the proprietary name on InnoPran XL acceptable and acknowledged the withdrawal of the name ———

EER: Acceptable August 29, 2002

Methods Validation: Submitted but not validated by FDA labs yet.

**Advisory Committee Meeting**
No meeting held.

**PM Summary**

To my knowledge, there are no issues that might prevent action on this NDA.

/S/

Melissa Robb, RHPM

---

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

---

/s/

---

Melissa Robb
3/14/03 09:44:45 AM
CSO

CSO Overview of NDA 21-438
— . (propranolol HCl) Extended Release 80,120 Capsules
August 29, 2002

**Sponsor: Reliant Pharmaceuticals**
**Related IND:** [redacted]
**Chemical Type & Therapeutic Potential: 3S**

**Background:**
— is a new, once a day formulation of propranolol hydrochloride (HCL). Propranolol HCl has been widely marketed more than thirty years. — is an oral capsule formulation containing spherical beads allowing delayed release of propranolol HCl. When taken at bedtime, the delayed release beads are intended to atenuate the early morning circadian increases in blood pressure and heart rate.
A pre-NDA telecon was held on August 1, 2001.

**Medical Review**
In her review dated May 1, 2002, Dr. Gordon stated that the one clinical efficacy trial in hypertensive patients found that — in doses of 80 mg to 640 mg, taken once daily, lowered sitting diastolic and systolic blood pressure compared to placebo. There was a small dose response for blood pressure lowering effects and a more prominent one for heart rate lowering effects. The 640 mg dose had higher adverse event rates and discontinuations.
Dr. Gordon stated that she had reviewed the **Financial Disclosure** section of the application.
Dr. Gordon did not make a recommendation as to approvability or labeling changes.

**Secondary Medical Review**
In his memo dated, August 29, 2002, Dr. Karkowsky recommended that the application not be approved because the only study submitted for the treatment of hypertension is inadequate to conclude that — affords blood pressure control during the entire dosing interval. He believes an approval recommendation sets a poor precedent for other drugs, engineered to deliver drug only after long lag. In addition, the labeling of — would of necessity rely on non-trough blood pressure effects since no "true" trough measurements are available.

**Statistics**
In his review dated May 8, 2002, Dr. Wang agreed with the Sponsor's efficacy conclusions. He noted that there was only one efficacy study and primary endpoint did not have a very small p-value, therefore, it might not be enough to represent a wide-ranging population.

**Biopharmaceutics**
In her review dated August 9, 2002, Dr. Dorantes stated that the sponsor has provided appropriate information to satisfy the clinical pharmacology and biopharmaceutic requirements for an ER-product and NDA 21-438 for — Capsules is acceptable, provided that her dissolution and labeling comments are addressed (see page 6 of her review).

**Pharmacology**
Not applicable since this is a 505(b)(2) application.

**Chemistry**
In his review dated August 16, 2002, Dr. Zimmerman stated that this NDA is approvable from a CMC standpoint pending the satisfactory completion of the inspection of a new stability testing facility. The deficiencies and comments on pages 31 and 32 of his review should be conveyed to the sponsor in the action letter.

Environmental Assessment: The sponsor requested and qualifies for a categorical exclusion.

Trade Name Review: In their trade name review dated July 12, 2002, DMETS found the proprietary name, ——, acceptable.

EER: Acceptable August 29, 2002

Methods Validation: Submitted but not validated by FDA labs yet.

**Advisory Committee Meeting**
No meeting held.

CSO Summary

To my knowledge, there are no issues that might prevent action on this NDA.

/S/

Zelda McDonald, CSO

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

## DIVISION OF CARDIO-RENAL DRUG PRODUCTS
## FOOD AND DRUG ADMINISTRATION

*US Mail address:*
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852



| | |
|---|---|
| **Transmitted to FAX Number:** | 908-542-4460 |
| **Attention:** | **Mr. Bob Mandetta** |
| **Company Name:** | **Reliant Pharmaceuticals** |
| **Phone:** | 908-542-4429 |
| **Subject:** | **Confirmation of 12/12/02 Teleconference** |
| **Date:** | 11/6/02 |
| **Pages including this sheet:** | 2 |
| **From:** | **Melissa Robb** |
| **Phone:** | **301-594-5313** |
| **Fax:** | **301-594-5494** |

**PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!**

********** -COMM. JOURNAL- ********** DATE NOV-06-2002 ***** TIME 13:24 *********

MODE = MEMORY TRANSMISSION START=NOV-06 13:23 END=NOV-06 13:24

FILE NO.=482

| STN NO. | COMM. | ONE-TOUCH/ ABBR NO. | STATION NAME/TEL NO. | PAGES | DURATION |
|---|---|---|---|---|---|
| 001 | OK | # | 919085424460 | 002/002 | 00:00:34 |

-FDA,CDER,OND,ODEI,DCRDP -

********** -CARDIO RENAL - ***** - 301 594 5494- **********

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS**
**FOOD AND DRUG ADMINISTRATION**

***US Mail address:***
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852



| | |
|---|---|
| **Transmitted to FAX Number:** | 908-542-4460 |
| **Attention:** | **Mr. Bob Mandetta** |
| **Company Name:** | **Reliant Pharmaceuticals** |
| **Phone:** | 908-542-4429 |
| **Subject:** | **Confirmation of 12/12/02 Teleconference** |
| **Date:** | 11/6/02 |
| **Pages including this sheet:** | 2 |
| **From:** | **Melissa Robb** |
| **Phone:** | **301-594-5313** |
| **Fax:** | **301-594-5494** |

**PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!**

Confirmation of Teleconference

| | |
|---|---|
| Drug: | Propanolol Hydrochloride Extended Release Capsules, 80 mg and 120 mg |
| NDA: | 21-438 |
| Sponsor: | Reliant Pharmaceuticals |
| Date Requested: | November 1, 2002 |
| Date Confirmation Faxed: | November 6, 2002 |
| | |
| Teleconference Date: | December 12, 2002 |
| Teleconference Time: | 12:30 pm |

FDA Participants:

| | |
|---|---|
| Douglas Throckmorton, M.D. | Director, Division of Cardio-Renal Drug Products, HFD-110 |
| Abraham Karkowsky, M.D., Ph.D. | Medical Team Leader, HFD-110 |
| Maryann Gordon, M.D. | Medical Officer, HFD-110 |
| James Hung, Ph.D. | Team Leader, Statistics, HFD-710 |
| Angelica Dorantes, Ph.D. | Pharmacokineticist, HFD-860 |
| Stuart Zimmerman, Ph.D. | Chemist, HFD-110 |
| Melissa Robb | Regulatory Health Project Manager, HFD-110 |

---

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

---

/s/

---

Melissa Robb
11/6/02 01:38:56 PM
CSO

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS**
**FOOD AND DRUG ADMINISTRATION**

*US Mail address:*
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852



| | |
|---|---|
| **Transmitted to FAX Number:** | 908-542-4460 |
| **Attention:** | **Mr. Bob Mandetta** |
| **Company Name:** | **Reliant Pharmaceuticals** |
| **Phone:** | 908-542-4429 |
| **Subject:** | **Teleconference Minutes 12/19/02** |
| **Date:** | 1/2/03 |
| **Pages including this sheet:** | 3 |
| **From:** | **Melissa Robb** |
| **Phone:** | **301-594-5313** |
| **Fax:** | **301-594-5494** |

**PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!**

Teleconference Minutes
December 19, 2002

| | |
|---|---|
| NDA# | 21-438 |
| Drug: | InnoPran XL (propanolol hydrochloride extended release) Capsules |
| Sponsor: | Reliant Pharmaceuticals |
| Subject: | Status of Review |

FDA Participants:

| | |
|---|---|
| Douglas C. Throckmorton, M.D. | Director, Division of Cardio-Renal Drug Products, HFD-110 |
| Melissa Robb | Regulatory Health Project Manager, HFD-110 |

Reliant Participants:

| | |
|---|---|
| Keith Rothenberg, Ph.D. | Sr. Vice President, R&D |
| Robert Mandetta | Director, Regulatory |
| Paulette Kosmoski | Director, Regulatory CMC |
| George Bobotas | Vice President, Scientific Affairs |
| Kathleen Murtaugh | Sr. Product Manager |
| Jim Misner | Director, Cardiovascular Marketing |

**Background:**

Reliant Pharmaceuticals submitted an original NDA 505(b)(2) dated October 31, 2002. On August 30, 2002 the Agency issued an approvable letter for this NDA. In this approvable letter, the Agency requested Final Printed Labeling for the drug. It requested labeling to be "essentially identical in content" to the labeling included in Reliant's July 31, 2002 submission. In addition, the Agency noted some recommendations and request for the labeling. Finally, the approvable letter identified deficiencies in the chemistry and clinical pharmacology sections of the application. These deficiencies were to be addressed prior to this issuance of an approval letter.

On October 10, 2002, Reliant submitted revised draft labeling and per the Agency's request, on October 28, 2002, Reliant resubmitted draft labeling in the format the Agency requested. Also on October 10, 2002, Reliant withdrew the name of ——— as a trade name and requested InnoPran XL (first choice), or ——— to be considered by the Agency. The name InnoPran XL was approved for use. A submission dated October 29, 2002 was received by the Division, from Reliant, which stated it included responses to all Chemistry and Clinical Pharmacology deficiencies cited in the approvable letter from the Agency. On November 26, 2002, Reliant submitted copies of all articles cited in the Clinical Pharmacology sections of the proposed labeling as requested by the Agency. On December 12, 2002, the Division and Reliant had a teleconference to discuss submitted proposed labeling.

**Teleconference:**

Dr. Throckmorton informed Reliant that the clinical pharmacology reviews on the submitted data are still under review. Therefore, no final revised labeling will be available to Reliant this week. Currently, at least three reviewers are going over the articles and proposed labeling.

Reliant updated Dr. Throckmorton on the status of the outstanding chemistry issues. Dr. Zimmerman has been supplied with the requested stability data. Reliant stated that Dr. Zimmerman had notified them that a statistician, who believed the data was acceptable, had also reviewed this data. Reliant stated that Dr. Zimmerman had told them that the Division was leaning towards granting them an — expiration date on the bottles and a — expiration date on the blister packs. In addition, Reliant was told by Dr. Zimmerman, that the Division would continue to review stability data as submitted and extend the expiration date as data are reviewed to support that extension.

Dr. Throckmorton encouraged the sponsor to submit to the Division any available data to support the approval of — dose. This should be assigned to Dr. Karkowsky for review.

The sponsor inquired about a statement in the PHARMACOKINETICS section regarding the relative bioavailability of InnoPran XL as related to Inderal LA. Dr. Throckmorton encouraged Reliant to submit an alternative suggested sentence, as the Division was not pleased with the statement in the proposed labeling. The Division would evaluate all suggestions.

Dr. Throckmorton concluded stating he could not give a specific response date, but it probably would not be before the end of the month. Dr. Throckmorton informed Reliant he would discuss the status again with them next week, through the Project Manager.

Signature, minutes preparer: /S/

Concurrence Chair: _____

Drafted: 12/19/02 Finaled: 1/2/03

RD:
Throckmorton 1/2/03

---

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

---

/s/

---

Melissa Robb
1/2/03 02:37:26 PM
CSO
Signed by Dr. Throckmorton 1/2/03; Faxed 1/2/03

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS**
**FOOD AND DRUG ADMINISTRATION**

***US Mail address:***
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852



| | |
|---|---|
| **Transmitted to FAX Number:** | 908-542-4460 |
| **Attention:** | **Mr. Bob Mandetta** |
| **Company Name:** | **Reliant Pharmaceuticals** |
| **Phone:** | 908-542-4429 |
| **Subject:** | **Teleconference Minutes 12/19/02** |
| **Date:** | 1/2/03 |
| **Pages including this sheet:** | 3 |
| **From:** | **Melissa Robb** |
| **Phone:** | **301-594-5313** |
| **Fax:** | **301-594-5494** |

**PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!**

Teleconference Minutes

| | |
|---|---|
| Telecon Date: | August 29, 2002 |
| NDA: | 21-438 |
| Drug: | —— (propranolol HCl) Extended Release Capsules |
| Sponsor: | Reliant Pharmaceuticals |
| Our Request Type: | Guidance |
| Classification: | C |
| Telecon Chair: | Douglas C. Throckmorton, M.D. |
| Telecon Recorder: | Zelda McDonald |
| External Participant Lead: | Keith Rotenberg, Ph.D. |

FDA:

| | |
|---|---|
| Douglas C. Throckmorton, M.D. | Director, Div. Cardio-Renal Drug Products, HFD-110 |
| Patrick Marroum, Ph.D. | Team Leader, Biopharmaceutics, HFD-860 |
| Zelda McDonald | Regulatory Project Manager, HFD-110 |

Reliant Pharmaceuticals:

| | |
|---|---|
| Neil Manowitz, Ph.D. | Director, Clinical Development |
| Douglas Kling, M.D. | Clinical |
| Keith Rotenberg, Ph.D. | Vice President, Regulatory Affairs |
| Robert Mandetta | Director, Regulatory Affairs |
| George Bobotas, Ph.D. | Product Development |

**Background**

—— is a new, once a day formulation of propranolol hydrochloride (HCL). Propranolol HCl has been widely marketed more than thirty years. —— is an oral capsule formulation containing spherical beads allowing delayed release of propranolol HCl. The Division requested this teleconference to discuss the pending NDA.

**Telecon:**

Dr. Throckmorton stated that he planned to issue an approvable letter tomorrow (August 30, 2002). The action will be approvable because there are other issues that need to be addressed, including coming to an agreement on final printed labeling. He noted that the eventual approval would be for only the 80 and 120 mg strengths. In addition, the indication would be for hypertension only. There were not sufficient data submitted to support ——.

Dr. Marroum stated that the letter would recommend different dissolution specifications. In addition, the Clinical Pharmacology section of the labeling needs to be rewritten. It should be updated with information from the literature (refereed Journals) that includes: drug/drug interactions, Cytochrome P450 information, whether it is a PGP substrate or inhibitor, the effects of propranolol on age, gender, and hepatic and/or renal impairment. There is also a Guidance available on the FDA Web site that provides format and language suggestions. Reliant was encouraged to discuss the revisions with the Biopharm reviewers at the Agency.

Dr. Throckmorton stated that although Reliant had modeled the —— labeling after the Inderal LA labeling, that is a very dated label, and we will propose significant changes to its content and format, and will be asking Reliant to make proposals in these regards. The Division

Division plans to talk with the Sponsor of Inderal LA labeling regarding needed changes as that labeling is old and should be revised. Dr. Throckmorton asked Reliant to submit a written proposal for the labeling. An electronic version would be preferable.

Reliant asked if the Division foresaw an approval action within the next two months. Dr. Throckmorton said the Division would have to look at the revised labeling before speculating as to how long it would take. He noted that the Division would like to act as soon as possible

Reliant said they would get back to the Division as soon as they could after receipt of the approvable letter and had time to look it over.

Signature minutes preparer: 9/6/02

Concurrence, Chair: 9.6.02

Drafted: 9/5/02 Finaled: 9/6/02

RD:
Throckmorton 9/6/02
Marroum 9/5/02

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS**
**FOOD AND DRUG ADMINISTRATION**

*US Mail address:*
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852



| | |
|---|---|
| **Transmitted to FAX Number:** | 908-542-9405 |
| **Attention:** | **Mr. Robert J. Mandetta** |
| **Company Name:** | Reliant Pharmaceuticals |
| **Phone:** | 908-542-4429 |
| **Subject:** | Minutes of 8/29/02 Telecon |
| **Date:** | 9/6/02 |
| **Pages including this sheet:** | 3 |
| **From:** | **Zelda McDonald** |
| **Phone:** | **301-594-5333** |
| **Fax:** | **301-594-5494** |

You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes (as reflected in the minutes).

PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!

********** -COMM. JOURNAL- ********** DATE SEP-06-2002 ***** TIME 08:46 ********

MODE = MEMORY TRANSMISSION START=SEP-06 08:45 END=SEP-06 08:46

FILE NO.=765

| STN NO. | COMM. | ONE-TOUCH/ ABBR NO. | STATION NAME/TEL NO. | PAGES | DURATION |
|---|---|---|---|---|---|
| 001 | OK | a | 919085429405 | 003/003 | 00:00:54 |

-FDA,CDER,OND,ODEI,DCRDP -

********** -CARDIO RENAL - ***** - 301 594 5494- **********


**DIVISION OF CARDIO-RENAL DRUG PRODUCTS**
**FOOD AND DRUG ADMINISTRATION**

*US Mail address:*
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852




| | |
|---|---|
| **Transmitted to FAX Number:** | 908-542-9405 |
| **Attention:** | **Mr. Robert J. Mandetta** |
| **Company Name:** | Reliant Pharmaceuticals |
| **Phone:** | 908-542-4429 |
| **Subject:** | Minutes of 8/29/02 Telecon |
| **Date:** | 9/6/02 |
| **Pages including this sheet:** | 3 |


**From:** **Zelda McDonald**
**Phone:** **301-594-5333**
**Fax:** **301-594-5494**


You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes (as reflected in the minutes).

PLEASE LET ME KNOW YOU RECEIVED THIS. THANKS!

**Record/Minutes of December 17, 2001 Filing Meeting**

NDA Number and Drug Name: 21-438 —— (propranolol hydrochloride) Extended Release Capsule
Related IND: [redacted]

Indication: Hypertension —

Sponsor: Reliant Pharmaceuticals

Therapeutic Classification: 3S

Date of Application: October 31, 2001

Date of Receipt: November 2, 2001

User Fee Goal: September 2, 2001 (10 month)

User Fee Status: Paid

Submission Complete As Required Under 21 CFR 314.50? YES

Patent Information Included? YES – Filed as 505(b)(2)

Exclusivity Requested? NO

Debarment Statement Included? YES

Pediatric Rule addressed? NO – Requested waiver in 9/5/01 submission # 021, IND [redacted]
Waived in December 18, 2001 letter.

Financial Disclosure addressed? YES

Pre-NDA Meeting(s)? YES

**BACKGROUND**

— is a new, once a day formulation of propranolol hydrochloride (HCL). Propranolol HCl has been widely marketed more than thirty years. —— is an oral capsule formulation containing spherical beads allowing both an immediate and delayed release of propranolol HCl. When taken at bedtime, this combination of immediate and delayed release beads is intended to atenuate the early morning circadian increases in blood pressure and heart rate.

Attendees:

| | |
|---|---|
| Douglas Throckmorton, M.D. | Deputy Director, HFD-110 |
| Norman Stockbridge, M.D., Ph.D. | Team Leader, Medical, HFD-110 |
| Maryann Gordon, M.D. | Medical Officer, HFD-110 |
| Thomas Marciniak, M.D. | Medical Officer, HFD-110 |
| James Hung, Ph.D. | Team Leader, Statistics, HFD-710 |
| Patrick Marroum, Ph.D. | Team Leader, Biopharmaceutics, HFD-860 |
| Angelica Dorantes, Ph.D. | Pharmacokineticist, HFD-860 |
| Stuart Zimmerman, Ph.D. | Chemist, HFD-810 |
| Antoine El Hage, Ph.D. | Supervisory Pharmacologist, Div. Scientific Invest.,HFD-45 |
| Natalia Morgenstern | Chief, Project Management Staff, HFD-110 |
| Zelda McDonald | Regulatory Health Project Manager. HFD-110 |

Assigned Reviewers:

| DISCIPLINE | REVIEWER | Expected Review Completion Date |
|---|---|---|
| Medical: | Maryann Gordon | July 1, 2002 |
| Sec. Medical: | Abraham Karkowsky | |
| Pharmacology: | NA – 505(b)(2) | |
| Chemist: | Stuart Zimmerman | July 1, 2002 |
| Env. Assessment: | NA | |
| Statistician: | James Hung | July 1, 2002 |
| Biopharmaceuticist: | Angelica Dorantes | July 1, 2002 |
| Microbiologist: | NA | |
| DSI: | NA | |
| Project Manager: | Zelda McDonald | |

**CHEMISTRY -**

Did firm request categorical exclusion for environmental assessment? YES

EIR package transmitted? YES

Trade Name Review Requested? NO – —— ) is not a tradename. It is an internal designator for Reliant's circadian formulation of propranolol. Reliant expects to submit a tradename early next year.

**DSI** – Per Dr. Lipicky, site inspections are not needed.

**REGULATORY REQUIREMENTS/ORGANIZATION –**
The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

Conclusion: Everyone agreed the application could be filed.

Zelda McDonald
Project Manager, HFD-110

---

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

---

/s/

---

Zelda McDonald
2/6/02 10:43:47 AM

Teleconference Minutes

| | |
|---|---|
| Telecon Date: | August 1, 2001 |
| IND: | [redacted] |
| Drug: | — (propranolol HCl) |
| Sponsor: | Reliant Pharmaceuticals |
| Date Requested: | June 20, 2001 |
| Date Confirmation Faxed: | June 28, 2001 |
| Type: | Pre-NDA |
| Classification: | B |

| | |
|---|---|
| Telecon Chair: | Norman Stockbridge, M.D., Ph.D. |
| Telecon Recorder: | Zelda McDonald |
| External Participant Lead: | Robert Mandetta |

FDA:

| | |
|---|---|
| Norman Stockbridge, M.D, Ph.D. | Medical Team Leader, HFD-110 |
| Hasmukh Patel, Ph.D. | Deputy Director, Div. of New Drug Chemistry I, HFD-810 |
| Kasturi Srinivasachar, Ph.D. | Team Leader, HFD-810 |
| Stuart Zimmerman, Ph.D. | Chemist, HFD-810 |
| Angelica Dorantes, Ph.D. | Pharmacokineticist, HFD-860 |
| Zelda McDonald | Regulatory Project Manager, HFD-110 |

Reliant Pharmaceuticals:

| | |
|---|---|
| George Bobotas, Ph.D. | Vice President, Scientific Affairs |
| Paulette Kosmoski | Director, Regulatory CMC |
| Robert Mandetta | Director, Regulatory Affairs |
| Neil Manowitz, Ph.D. | Director, Clinical Development |
| Keith Rotenberg, Ph.D. | Vice President, Regulatory Affairs |

Eurand America:

| | |
|---|---|
| Bhanu Balasubramaniam | Regulatory Specialist |
| Phillip Percel | Formulation Group Leader |

**Background**

— is a new once a day formulation of propranolol hydrochloride (HCl) of spherical beads. Originally, this oral capsule formulation contained two types of beads (immediate and delayed/sustained release), however, it has been reformulated to one bead. When taken in the evening, the sustained release propranolol beads are intended to attenuate the early morning circadian increases in blood pressure and heart rate. Reliant requested this Pre-NDA teleconference to update the Division on issues that arose in the June 4, 2001 guidance meeting.

**Telecon:**
Discussion Points/Agreements Reached:

1. Since the safety and efficacy of the active moiety is well documented, the submission will consists of a single efficacy and safety study (N=420) and several bioavailability/pharmacokinetic studies. As discussed previously, Reliant agreed to include in the table of contents headings for ISS and ISE but not to include the traditional contents of these sections. The ISE will refer back to the final study report of the efficacy study and the ISS will consist of a few tables of adverse events from the studies. The single efficacy and safety study will provide a detailed analysis of this study. Please confirm that this is acceptable.

   - The Division agreed.

2. Data and analyses are available electronically. Reliant proposes to provide the labeling in a word file and the data and the analyses in version 5 SAS transport format. Is this acceptable?

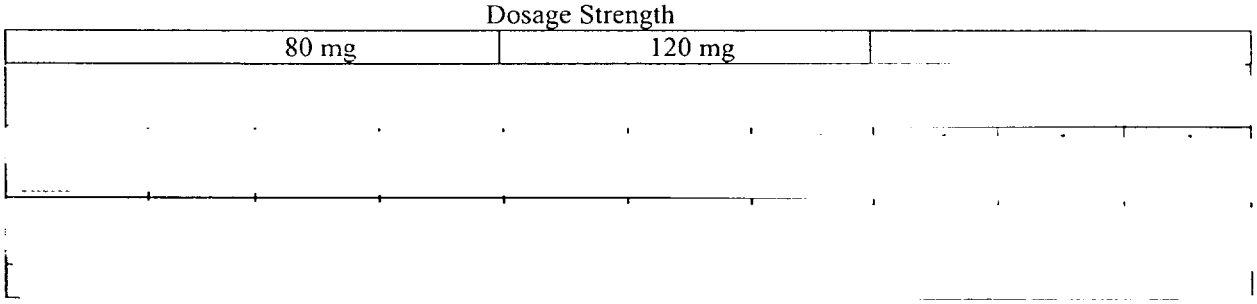
   - The Division agreed.

3. Reliant proposes to provide only paper copies of CRFs and SAEs, deaths and dropouts. Is this acceptable?

   - The Division agreed.

4. At the June 4th chemistry meeting, proposed stability study designs were presented for consideration. FDA tentatively agreed to a matrixing/bracketing design for the number of batches with suggested modification. Subsequently, the [redacted] foil blister has been deleted, therefore, the stability program has been modified to reflect this change. The primary NDA study will reflect a full testing program of all package presentations. Is the design of the revised primary NDA stability study acceptable to the Division?

PRIMARY STABILITY PROGRAM (MATRIX/BRACKETING DESIGN)
Total of 30 batches
Dosage Strength




Blank spaces = not available presentation
- not placed on stability

   - The Division agreed.

5. As a result of the same meeting noted above, the release and stability specifications for the drug product are under revision as recommended by FDA. Reliant now has a better definition of the specifications, e.g., a second identity test, IR, has been added, the — specs have been tightened to not more than — ppm and the modified impurities are based on actual data: — Specified, —unspecified, — ; total impurities.

   - The Division could not comment on actual specifications until the application has been submitted and reviewed. Right now, it looks as if Reliant is following the Division's recommendations. The Division noted that the limits need to be based on actual data which are not yet available for review by FDA.

6. Reliant proposed to extend the approved expiration dating period with updated stability data generated in accordance with the stability protocol on the registration batches and to report this change in the annual report. Is this approach and filing category acceptable to the FDA?

   - The Division stated that full shelf-life data from 3 production scale batches would be needed in order to extend the expiration dating period in an annual report. Extension of the expiration dating period based on full shelf-life data from pilot scale batches used in the primary stability studies requires a prior approval supplement.

7. At the time of NDA submission, —months supportive stability data under ICH conditions will be available for 2 batches of each strength of pilot scale production, in · — (total of 6 batches). The batches were packaged in blister and plastic bottle, single configuration presentations.

   Due to unforeseen and unanticipated circumstances there was a delay in the initiation of the primary stability studies. As a result, a stability database of months of real time and accelerated, site specific data under ICH conditions will be available. In concordance with the Division's recommendations, further accumulated data updates from the ongoing primary and supportive stability studies will be submitted before or up to 6 months into the review period.

   - The Division stated that the expiration date granted will depend on the amount of data that is submitted during the review period.

8. The inclusion of executed batch records with supportive documentation for the stability batches of the 3 strengths of — represents an inordinate amount of documentation to the NDA (total of 6 batches). Reliant proposes the incorporation of a single executed batch record with complete supporting documentation representative of the — strength drug product stability batch, as the 3 strengths come from a common bead blend. Is this approach acceptable to the FDA?

   - The Division agreed.

Reliant asked how many desk copies of the NDA would be needed.

- The Division said none would be needed if Reliant will provide the summary documents and the texts of the study reports in PDF form with supporting electronic data.

- The Division also stated that the Biopharmaceutics group has a proposal for a format for written reports that would be helpful to them (attached).

Dr. Zimmerman stated that he had a few suggestions/recommendations that could be discussed in a subsequent telephone call if Reliant was interested. Reliant stated they would contact Dr. Zimmerman.

Signature minutes preparer: _____

Concurrence, Chair: _____

Drafted: 8/7/01 Finaled: 8/20/01

RD:

| | |
|---|---|
| Stockbridge | 8/9/01 |
| Patel | 8/20/01 |
| Srinivasachar | 8/8/01 |
| Zimmerman | 8/8/01 |
| Dorantes | 8/7/01 |

**REVIEWER COMMENTS:**

1. It is recommended that the "Human Pharmacokinetics and Bioavailability" section (Item 6) of the NDA be organized as follows:

- Overall Summary (including an integrated summary of all studies, summary tables/figures and overall conclusions).

- Background Information

- Drug Formulation Information (including investigational and to-be-marketed formulations).

- *In-Vitro* Testing Methodology.

- Analytical Methodology (including assay validation data for parent drug and major active metabolites)

- Protein Binding Information (including *in vitro* and *in* vivo data)

- Bioavailability Information
- Bioavailability (absolute and/or relative)
- Food Effect

- Bioequivalence Information
- Bioequivalence (clinical formulation vs. to-be-marketed formulation and/or possible dosage strength bioequivalence)

- Pharmacokinetic Information
- Healthy subjects (single and multiple dose)
- Target population (single and multiple dose)
- Dose proportionality (covering the dosage range recommended in the labeling)

- Proposed Labeling

**NOTE:** Where information is lacking it should be so stated,

2. It is recommended that for each one of the individual studies provided in the NDA, the sponsor include an abbreviated summary. The following format is recommended.

**RECOMMENDED FORMAT FOR THE PREPARATION OF THE ABBREVIATED SUMMARY**

Title of Trial:

Investigator(s)/Center(s):

Trial Period:

Objectives:

Design:

Subjects: - Target or healthy population  Number of subjects: enrolled
completed
evaluated

Criteria for inclusion (trial population):

Test product, dose and mode of administration, batch and formulation No.:

Reference therapy, dose and mode of administration, batch and formulation Nos.:

Duration of treatment;

Analytical method(s)/Analytical center(s):

Statistical methods:

Results:

- Pharmacokinetics: Mean PK parameters/profile (including table(s) and/or figure(s), if appropriate)
- Adverse experiences and safety monitoring

Conclusions:

3. It is recommended that in addition of the hard copy, the overall intergated summary and the abbreviated summary of each individual study included in section 6 of the NDA be also submitted in electronic format (diskette) as a Microsoft Word file(s).

4. It is recommended that an electronic copy of the proposed labeling be submitted as a Microsoft Word file. The following format is recommended for the pharmacokinetic section of the labeling.

**RECOMMENDED FORMAT FOR THE PREPARATION OF THE PHARMACOKINETIC SECTION OF THE LABELING**

The *Pharmacokinetics portion* of the *Clinical Pharmacology section* of the package insert should present information for — Extended release Capsules under the subheadings of *Absorption, Distribution, Metabolism, and Excretion.* Following this, there should be a section with the heading *Special Populations,* where pharmacokinetic information under the subheadings of *Geriatric, Pediatric, Gender, Race, Renal Insufficiency, Hepatic Impairment* should be included. A section with the heading *Drug-Drug Interactions* is needed. Where relevant information is lacking it should be so stated.

On August 1, 2001 during the Pre-NDA teleconference, the sponsor was informed of OCPB's preferred format for the "Human Pharmacokinetics and Bioavailability" section of the NDA.

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

/s/
---
Zelda McDonald
8/27/01 11:15:08 AM
CSO