CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-438

Chemistry Review(s)

NDA 21-438

InnoPran XL

Propranolol Hydrochloride
Extended-Release Capsules

Reliant Pharmaceuticals, LLC

Stuart Zimmerman
Division of Cardio-Renal Drug products

Chemistry Review Data Sheet

1. NDA 21-438

2. REVIEW # 4:

3. REVIEW DATE: 18-DEC-2002

4. REVIEWER: Stuart Zimmerman, Ph.D.

5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed /Document Date

Original	31-OCT-2001
Amendment	05-APR-2002
Amendment	01-MAY-2002
Amendment	18-JUL-2002
Amendment	31-JUL-2002
Amendment	08-AUG-2002

6. SUBMISSION(S) BEING REVIEWED:

The primary intent of this review is to provide for the evaluation of the applicant's response to the FDA action letter and to include an updated evaluation for the stability data that has been provided and statistically analyzed.

Submission(s) Reviewed /Document Date

Amendment	29-OCT-2002 (updated/revised statistical annalysis)
Amendment	10-OCT-2002 (Revised trade name)
Amendment	30-AUG-2002 (initial 12 mo. statistical analysis)
Amendment	26-AUG-2002 (primary stability data)

7. NAME & ADDRESS OF APPLICANT:

Name: Reliant Pharmaceuticals, LLC

Address: 110 Allen Road, Liberty Corner NJ 07938

Representative: Paulette F. Kosmoski

Telephone: 908-542-4403

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: InnoPran XL
b) Non-Proprietary Name (USAN): Propranolol Hydrochloride
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: Type 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: a non-selective beta-adrenergic receptor blocking agent for the management of essential hypertension

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 80 mg and 120 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x_ Rx ___OTC

15. **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note25]:**

_____SPOTS product – Form Completed

__x__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

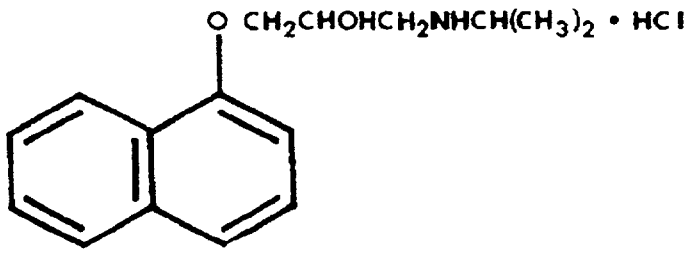
Chemical Name:

(±)-1-(isopropropylamino)-3-(1-naphthyloxy)-2-propanol hydrochloride

Molecular Formula: $C_{16}H_{21}NO_2$ - HCl

Molecular Weight: 295.81

Structural Formula:



17. RELATED/SUPPORTING DOCUMENTS:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II		Propranolol HCl Drug Substance	1	Adequate	Chemistry Review dated 8/7/02	Deficiency response of July 26 2002 is OK
	III			3	Adequate	9/15/00	CR#21
	III			1	Adequate	8/6/02	Certificate of compliance-NDA v. 1.3, p. 04-00629
	III			3	Adequate	2/9/01 and 5/10/99	
	III			3	Adequate	4/3/01	Reviewer P. Maturu
	III			4	Adequate	7/24/02	NDA related Review
	III			3	Adequate	10/12/98	
	III			3	Adequate	4/20/64	See CR#! For NDA 21-283 for detailed reference
	III			3	Adequate	9/27/00	Refer to CR#48
	III			4 (1/2 g.)	Adequate	7/24/02 and 9/3/99(1 g)	NDA related review
	III			7a	Adequate	N/A	Secondary DMF –see DMF [redacted]
	III			7a	Adequate	NA	Secondary DMF –see DMF [redacted]
	IV			7b	Adequate	NA	Compendial excipient
	IV			7b.	Adequate	NA	Compendial excipient
	III			4	Adequate	NA	Based on inspection
	IV			7b.	Adequate	NA	Compendial excipient
	IV			4	Adequate	NA	
	IV			4	Adequate	NA	
	IV			1	Adequate	8/5/02	
	III			7c.	Adequate		[redacted]
	IV			7b.	Adequate	NA	Compendial excipient

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")
7a. This DMF is a nested DMF relating to DMF — and is not directly referenced by the applicant (i.e., LOA). It is considered to be acceptable via supporting information included in the primary DMF —
7b. The article is a compendial excipient controlled by a USP monograph.
7c. —

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

IND [redacted] Historical Review Information (vol. 1.2, p. 04-00017)

DOCUMENT	Serial Number	DESCRIPTION
7/24/2000	002	Provided additional information regarding dissolution rate profile and stability.
7/28/00	003	Provided additional information regarding formulation excipients.
8/16/00	006	Provided initial stability information
11/2/00	008	Provided pharmaceutical documentation for 120 mg strength of drug product, as well as updated information regarding the other two formulations.
2/8/01	009	Stability study data updates and COAs for the drug product.
4/23/01	013	Request for Type C chemistry meeting.

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Statistical analysis the month stability data supports expiry date (bottles).	12/17/02	Dr. Kelly (verbal comments and summary data graphed)
EES	Acceptable	8/29/02	Shirnett Ferguson
Pharm/Tox	N/A		
Biopharm	Revision of dissolution acceptance criteria	8/9/02	Angelica Dorantes
LNC	N/A		
Methods Validation	To be submitted		
DMETS	Acceptable-approved trade name "InnoPran XL"	12/5/02	Scott Dallas
EA	Acceptable (categorical Exclusion)	6/7/02 see review section	Stuart Zimmerman
Microbiology	N/A		

The Chemistry Review for NDA 21-438

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability:

This NDA 21-438 may be approved from the CMC standpoint. All issues identified in the Chemistry Review #3 have been satisfactorily resolved. The newly considered changes evaluated in this review (i.e., concerning in-process controls, and drug product specifications) are considered to be acceptable. All facilities have an acceptable CGMP status. Identified labeling changes as listed in the categorical review item "VI DRAFT LETTER ACTION ITEMS" are to be conveyed to the applicant as included in the labeling revisions to be provided by the project manager. The comment concerning the expiry dates for the drug product should be included in the action letter.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

- The drug product is a once a day capsule formulation that is composed of spherical beads in gelatin capsule shells. The beads allow for a delay effect for drug release for 4- 6 hours followed by a subsequent gradual controlled release of the drug for the duration of the dosing interval. Beads are formulated to a theoretical assay value for the active drug in the total bead matrix on a weight\weight basis. The quantitative composition of each different capsule strength is determined by the particular fill weight for that specific capsule strength. This allows for a common release rate mechanism to operate across all capsule sizes. Two different size gelatin capsules are utilized (i.e., 3 and 2) which are color coded for dosing delineation. Size 3 is for the 80 mg strength, and size 2 is for the 120 mg strength capsule The capsules are packaged in both high density polyethylene bottles having induction seals and child resistant screw caps and in blister packaging configurations.

  The manufacturing process assures that each batch of the drug product can be consistently manufactured to acceptable performance standards. These standards most critically include the unique extended release profile involving a 4 hour delayed release followed by a gradual upward controlled release phase. Also

considered is the fact that chemical impurities and degradation is tightly controlled to very low limits throughout the entire process train - starting with drug substance manufacture.

Valid analytical control methods have been developed that can adequately monitor the critical control attributes to acceptable quality levels. For example, potential impurities and degradants are closely controlled to levels of quantitation of 0.01% relative to active drug abundance. Also, dissolution testing control intervals are designed to appropriately monitor the unique release rate profile for each dosage strength by a common testing approach for all dosage strengths.

Adequate attention was given to the design of the in-process control tests and their respective acceptance criteria for step - by - step monitoring of the performance attributes at each critical unit process operation.

Packaging configurations have been appropriately designed to adequately protect the drug product's performance characteristics against both chemical and functional changes for the shelf-life of the product. Appropriately designed stability studies have been conducted to permit the conclusion that the drug product would be predicted to maintain its unique performance characteristics over the duration of its expiry period which is months for blisters and months for bottles.

- The drug substance is manufactured . procedure. Most of the drug substance chemistry and manufacturing information is in the drug master file (DMF) of the supplier. This DMF has been reviewed. Many deficiencies were identified and conveyed to the DMF holder. The response to these deficiencies has also been reviewed and found to be adequate.

Propranolol Hydrochloride USP is a well known active ingredient that has been marketed for more than 30 years. It is a white, crystalline solid that is readily soluble in water and ethanol. In the USA, it is regulated by a USP monograph. It is also the subject of other monographs such as the EP and BP monographs. It has a retest date of 36 months.

B. Description of How the Drug Product is Intended to be Used

This application for propranolol hydrochloride extended release capsules contains a novel formulation that provides for evening administration by specifying the daily dose to be taken at or around bedtime versus simply once daily. This formulation was designed to release the propranolol in an extended release manner after a controlled 4-hour lag time for the absorption into the gastrointestinal tract At steady state, blood levels of propranolol begin to increase approximately 4 hours after evening administration (taken at or around bedtime) and rise progressively over the early morning hours to reach peak plasma concentrations approximately 14 hours

after dosing These propranolol plasma levels which rise slowly attenuate the rapid increase in blood pressure and heart rate that precedes and follows waking. This increase is associated with the circadian variation in catecholamine secretion and in renin release. The rise in plasma propranolol concentration after dosing parallels the circadian rise in morning blood pressure associated with target organ damage in patients with hypertensive and ischemic cardiovascular disease.

C. Basis for Approvability or Not-Approval Recommendation:

This NDA 21-438 may be approved from the CMC standpoint.

/S/

Stuart Zimmerman, Ph.D.

Chemist Name/Date: Stuart Zimmerman, 12/18/02
ChemistryTeamLeaderName/Date: Kastui Srinivasachar, 12/20/02
ProjectManagerName/Date: Melissa Robb, 12/20/02

Redacted 26

pages of trade

secret and/or

confidential

commercial

information

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

/s/

Stuart Zimmerman
12/20/02 03:33:55 PM
CHEMIST

Kasturi Srinivasachar
12/20/02 03:50:46 PM
CHEMIST

NDA 21-438

Propranolol Hydrochloride
Extended-Release Capsules

Reliant Pharmaceuticals, LLC

Stuart Zimmerman
Division of Cardio-Renal Drug products

Chemistry Review Data Sheet

1. NDA 21-438

2. REVIEW # 3:

3. REVIEW DATE: 29-AUG-2002

4. REVIEWER: Stuart Zimmerman, Ph.D.

5. PREVIOUS DOCUMENTS:

Submission(s) Reviewed /Document Date

Original	31-OCT-2001
Amendment	05-APR-2002
Amendment	01-MAY-2002
Amendment	18-JUL-2002
Amendment	31-JUL-2002
Amendment	08-AUG-2002

6. SUBMISSION(S) BEING REVIEWED:

The primary intent of this review is to provide an update of the status of the inspection of the —— facility that was outstanding and to provide for changes in the labeling that have resulted from the deletion of the 160 mg dosage strength capsule based on clinical evaluation.

Submission / Document Date
Amendment * 16-AUG-2002

* (not reviewed since it falls outside the period allowed for additional recommendations to be included in the action letter.)

7. NAME & ADDRESS OF APPLICANT:

Chemistry Review Data Sheet

Name: Reliant Pharmaceuticals, LLC

Address: 110 Allen Road, Liberty Corner NJ 07938

Representative: Paulette F. Kosmoski

Telephone: 908-542-4403

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: ——
b) Non-Proprietary Name (USAN): Propranolol Hydrochloride
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: Type 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: a non-selective beta-adrenergic receptor blocking agent for the management of essential hypertension

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 80 mg and 120 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x Rx ___OTC

15. **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note25]:**

_____SPOTS product – Form Completed

__x__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

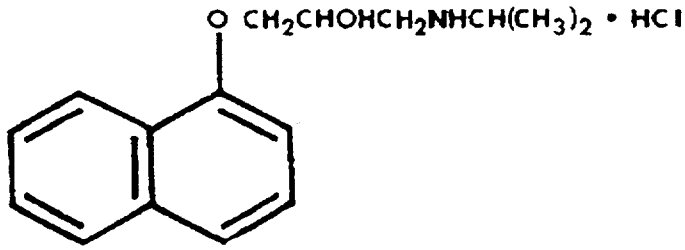
Chemical Name:

(±)-1-(isopropropylamino)-3-(1-naphthyloxy)-2-propanol hydrochloride

Molecular Formula: $C_{16}H_{21}NO_2$ - HCl

Molecular Weight: 295.81

Structural Formula:



17. RELATED/SUPPORTING DOCUMENTS:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II		Propranolol HCl Drug Substance	1	Adequate	Chemistry Review dated 8/7/02	Deficiency response of July 26 2002 is OK
	III			3	Adequate	9/15/00	CR#21
	III			1	Adequate	8/6/02	Certificate of compliance- NDA v. 1.3. p. 04-00629
	III			3	Adequate	2/9/01 and 5/10/99	
	III			3	Adequate	4/3/01	Reviewer P. Maturu
	III			4	Adequate	7/24/02	NDA related Review
	III			3	Adequate	10/12/98	
	III			3	Adequate	4/20/64	See CR#! For NDA 21-283 for detailed reference
	III			3	Adequate	9/27/00	Refer to CR#48
	III			4 (1/2 g.)	Adequate	7/24/02 and 9/3/99(1 g)	NDA related review
	III			7a	Adequate	N/A	Secondary DMF –see DMF
	III			7a	Adequate	NA	Secondary DMF –see DMF
	IV			7b	Adequate	NA	Compendial excipient
	IV			7b.	Adequate	NA	Compendial excipient
	III			4	Adequate	NA	Based on inspection
	IV			7b.	Adequate	NA	Compendial excipient
	IV			4	Adequate	NA	
	IV			4	Adequate	NA	
	IV			1	Adequate	8/5/02	
	III			7c.	Adequate		
	IV			7b.	Adequate	NA	Compendial excipient

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")
7a. This DMF is a nested DMF relating to DMF — and is not directly referenced by the applicant (i.e., LOA). It is considered to be acceptable via supporting information included in the primary DMF —
7b. The article is a compendial excipient controlled by a USP monograph.
7c.

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

IND [redacted] Historical Review Information (vol. 1.2, p. 04-00017)

DOCUMENT	Serial Number	DESCRIPTION
7/24/2000	002	Provided additional information regarding dissolution rate profile and stability.
7/28/00	003	Provided additional information regarding formulation excipients.
8/16/00	006	Provided initial stability information
11/2/00	008	Provided pharmaceutical documentation for 120 mg strength of drug product, as well as updated information regarding the other two formulations.
2/8/01	009	Stability study data updates and COAs for the drug product.
4/23/01	013	Request for Type C chemistry meeting.

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	The statistical analysis the stability data will be provided in a future submission.	N/A	N/A
EES	Acceptable	8/29/02	Shirnett Ferguson
Pharm/Tox	N/A		
Biopharm	Revision of dissolution acceptance criteria	8/9/02	Angelica Dorantes
LNC	N/A		
Methods Validation	To be submitted		
DMETS	Acceptable-approved trade name "	7/12/02	Hye-Joo Kim
EA	Acceptable (categorical Exclusion)	6/7/02 see review section	Stuart Zimmerman
Microbiology	N/A		

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-438

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability:

This NDA 21-438 is considered to be approvable from the CMC standpoint. The overall recommendation from the Office of Compliance is acceptable as provided by the report on August 29, 2002. The remaining deficiencies and comments concerning in-process controls, drug product specifications, labeling and the expiration dating period for the drug product, as listed in categorical item "VI DRAFT DEFICIENCY ISSUES AND COMMENTS" should be conveyed to the applicant in the action letter for this NDA.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

- The drug substance is manufactured
procedure. Most of the drug substance chemistry and manufacturing information is in the drug master file (DMF) of the supplier. This DMF has been reviewed. Many deficiencies were identified and conveyed to the DMF holder. The response to these deficiencies has also been reviewed and found to be adequate.

  Propranolol Hydrochloride USP is a well known active ingredient that has been marketed for more than 30 years. It is a white, crystalline solid that is readily soluble in water and ethanol. In the USA, it is regulated by a USP monograph. It is also the subject of other monographs such as the EP and BP monographs. It has a retest date of 36 months.

- The drug product is a once a day capsule formulation that is composed of spherical beads in gelatin capsule shells. The beads allow for a delay effect for drug release for 4- 6 hours followed by a subsequent gradual controlled release of the drug for the duration of the dosing interval. Beads are formulated to a theoretical assay value for the active drug in the total bead matrix on a weight\weight basis. The quantitative composition of each different capsule strength is determined by the particular fill weight for that specific capsule strength. This allows for a common

release rate mechanism to operate across all capsule sizes. Two different size gelatin capsules are utilized (i.e., 3 and 2) which are color coded for dosing delineation. Size 3 is for the 80 mg strength, and size 2 is for the 120 mg strength capsule The capsules are packaged in both high density polyethylene bottles having induction seals and child resistant screw caps and in blister packaging configurations.

The manufacturing process assures that each batch of the drug product can be consistently manufactured to acceptable performance standards. These standards most critically include the unique extended release profile involving a 4 hour delayed release followed by a gradual upward controlled release phase. Also considered is the fact that chemical impurities and degradation is tightly controlled to very low limits throughout the entire process train - starting with drug substance manufacture.

Valid analytical control methods have been developed that can adequately monitor the critical control attributes to acceptable quality levels. For example, potential impurities and degradants are closely controlled to levels of quantitation of 0.01% relative to active drug abundance. Also, dissolution testing control intervals are designed to appropriately monitor the unique release rate profile for each dosage strength by a common testing approach for all dosage strengths.

Adequate attention was given to the design of the in-process control tests and their respective acceptance criteria for step - by - step monitoring of the performance attributes at each critical unit process operation.

Packaging configurations have been appropriately designed to adequately protect the drug product's performance characteristics against both chemical and functional changes for the shelf-life of the product. Appropriately designed stability studies have been conducted to permit the conclusion that the drug product would be predicted to maintain its unique performance characteristics over the duration of its expiry period. However, only months of real time primary stability data has been submitted. An expiration date of only months can be permitted at this time taking into account both primary and supporting data.

B. Description of How the Drug Product is Intended to be Used

This application for propranolol hydrochloride extended release capsules contains a novel formulation that provides a for evening administration by specifying the daily dose to be taken at or around bedtime versus simply once daily. This formulation was designed to release the propranolol in an extended release manner after a controlled 4-hour lag time for the absorption into the gastrointestinal tract At steady state, blood levels of propranolol begin to increase approximately 4 hours after evening administration (taken at or around bedtime) and rise progressively over the

early morning hours to reach peak plasma concentrations approximately 14 hours after dosing These propranolol plasma levels which rise slowly attenuate the rapid increase in blood pressure and heart rate that precedes and follows waking. This increase is associated with the circadian variation in catecholamine secretion and in renin release. The rise in plasma propranolol concentration after dosing parallels the circadian rise in morning blood pressure associated with target organ damage in patients with hypertensive and ischemic cardiovascular disease

C. Basis for Approvability or Not-Approval Recommendation:

This NDA is approvable from the CMC standpoint. Many of the deficiencies cited in the Chemistry Review #1 have been satisfactorily resolved. The remaining deficiencies/comments pertaining to in-process controls, specifications for the drug product, labeling and the expiration date, as listed in categorical review item "VI DRAFT DEFICIENCY ISSUES AND COMMENTS" should be conveyed to the applicant in the action letter for this NDA.

B. Reviewer's Signature /S/

Stuart Zimmerman, Ph.D.

C. Endorsement Block

Chemist Name/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

D. CC Block

Redacted 7

pages of trade

secret and/or

confidential

commercial

information

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

/s/

Stuart Zimmerman
8/30/02 10:20:22 AM
CHEMIST

Kasturi Srinivasachar
8/30/02 01:49:06 PM
CHEMIST

NDA 21-438

Propranolol Hydrochloride Extended-Release Capsules

Reliant Pharmaceuticals, LLC

Stuart Zimmerman
Division of Cardio-Renal Drug products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-438

2. REVIEW # 2:

3. REVIEW DATE: 15-AUG-2002

4. REVIEWER: Stuart Zimmerman, Ph.D.

5. PREVIOUS DOCUMENTS:
   Original 31-OCT-2002
   Amendment 05-APR-2002
   Amendment 01-MAY-2002
   Amendment 18-JUL-2002

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	/Document Date
Amendment	08-AUG-2002
Amendment	31-JUL-2002

7. NAME & ADDRESS OF APPLICANT:

Name:	Reliant Pharmaceuticals, LLC
Address:	110 Allen Road, Liberty Corner NJ 07938
Representative:	Paulette F. Kosmoski
Telephone:	908-542-4403

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: —
b) Non-Proprietary Name (USAN): Propranolol Hydrochloride
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: Type 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: a non-selective beta-adrenergic receptor blocking agent for the management of essential hypertension

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 80 mg, 120 mg, —

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x_ Rx ___OTC

15. **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note26]:**

_____SPOTS product – Form Completed

__x__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

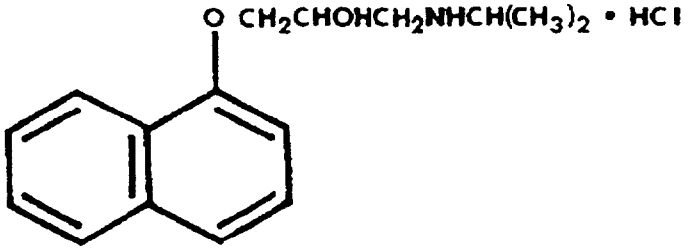
Chemical Name:

(±)-1-(isopropropylamino)-3-(1-naphthyloxy)-2-propanol hydrochloride

Molecular Formula: $C_{16}H_{21}NO_2$ - HCl

Molecular Weight: 295.81

Structural Formula:



17. RELATED/SUPPORTING DOCUMENTS:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II		Propranolol HCl Drug Substance	1	Adequate	Chemistry Review dated 8/7/02	Deficiency response of July 26 2002 is OK
	III			3	Adequate	9/15/00	CR#21
	III			1	Adequate	8/6/02	Certificate of compliance- NDA v. 1.3, p. 04-00629
	III			3	Adequate	2/9/01 and 5/10/99	
	III			3	Adequate	4/3/01	Reviewer P. Maturu
	III			4	Adequate	7/24/02	NDA related Review
	III			3	Adequate	10/12/98	
	III			3	Adequate	4/20/64	See CR#! For NDA 21-283 for detailed reference
	III			3	Adequate	9/27/00	Refer to CR#48
	III			4 (1/2 g.)	Adequate	7/24/02 and 9/3/99(1 g)	NDA related review
	III			7a	Adequate	N/A	Secondary DMF –see DMF —
	III			7a	Adequate	NA	Secondary DMF –see DMF —
	IV			7b	Adequate	NA	Compendial excipient
	IV			7b.	Adequate	NA	Compendial excipient
	III			4	Adequate	NA	Based on inspection
	IV			7b.	Adequate	NA	Compendial excipient
	IV			4	Adequate	NA	
	IV			4	Adequate	NA	
	IV			1	Adequate	8/5/02	
	III			7c.	Adequate		
	IV			7b.	Adequate	NA	Compendial excipient

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")
7a. This DMF is a nested DMF relating to DMF — and is not directly referenced by the applicant (i.e., LOA). It is considered to be acceptable via supporting information included in the primary DMF —
7b. The article is a compendial excipient controlled by a USP monograph.
7c.

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

IND ( ) Historial Review Information (vol. 1.2, p. 04-00017)

DOCUMENT	Serial Number	DESCRIPTION
7/24/2000	002	Provided additional information regarding dissolution rate profile and stability.
7/28/00	003	Provided additional information regarding formulation excipients.
8/16/00	006	Provided initial stability information
11/2/00	008	Provided pharmaceutical documentation for 120 mg strength of drug product, as well as updated information regarding the other two formulations.
2/8/01	009	Stability study data updates and COAs for the drug product.
4/23/01	013	Request for Type C chemistry meeting.

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	The statistical analysis the of stability data has not yet provided to FDA)		
EES	Pending — inspection		
Pharm/Tox	N/A		
Biopharm	Revision of dissolution acceptance criteria	8/9/02	Angelica Dorantes
LNC	N/A		
Methods Validation	To be submitted		
DMETS	Acceptable-approved trade name ' ——	7/12/02	Hye-Joo Kim
EA	Acceptable (categorical Exclusion)	6/7/02 see review section	Stuart Zimmerman
Microbiology	N/A		

The Chemistry Review for NDA 21-438

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability:

This NDA 21-438 is considered to be approvable from the CMC standpoint pending the satisfactory completion of the inspection of a new stability testing facility. The remaining deficiencies and comments concerning in-process controls, drug product specifications, labeling and the expiration dating period for the drug product, as listed on page 31 and 32, should be conveyed to the applicant in the action letter for this NDA.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

- The drug substance is manufactured as a procedure. Most of the drug substance chemistry and manufacturing information is in the drug master file (DMF) of the supplier. This DMF has been reviewed. Many deficiencies were identified and conveyed to the DMF holder. The response to these deficiencies has also been reviewed and found to be adequate.

  Propranolol Hydrochloride USP is a well known active ingredient that has been marketed for more than 30 years. It is a white, crystalline solid that is readily soluble in water and ethanol. In the USA, it is regulated by a USP monograph. It is also the subject of other monographs such as the EP and BP monographs. It has a retest date of 36 months.

  The drug product is a once a day capsule formulation that is composed of spherical beads in gelatin capsule shells. The beads allow for a delay effect for drug release for 4- 6 hours followed by a subsequent gradual controlled release of the drug for the duration of the dosing interval. Beads are formulated to a theoretical assay value for the active drug in the total bead matrix on a weight\weight basis. The quantitative composition of each different capsule strength is determined by the particular fill weight for that specific capsule strength. This allows for a common release rate mechanism to operate across all capsule sizes. Three different size gelatin capsules are utilized (i.e., 3, 2) which are color coded for dosing

delineation. Size 3 is for the 80 mg strength, size 2 is for the 120 mg capsule The capsules are packaged in both high density polyethylene bottles having induction seals and child resistant screw caps and in blister packaging configurations.

The manufacturing process assures that each batch of the drug product can be consistently manufactured to acceptable performance standards. These standards most critically include the unique extended release profile involving a 4 hour delayed release followed by a gradual upward controlled release phase. Also considered is the fact that chemical impurities and degradation is tightly controlled to very low limits throughout the entire process train - starting with drug substance manufacture.

Valid analytical control methods have been developed that can adequately monitor the critical control attributes to acceptable quality levels. For example, potential impurities and degradants are closely controlled to levels of quantitation of 0.01% relative to active drug abundance. Also, dissolution testing control intervals are designed to appropriately monitor the unique release rate profile for each dosage strength by a common testing approach for all dosage strengths.

Adequate attention was given to the design of the in-process control tests and their respective acceptance criteria for step - by - step monitoring of the performance attributes at each critical unit process operation.

Packaging configurations have been appropriately designed to adequately protect the drug product's performance characteristics against both chemical and functional) changes for the shelf-life of the product. Appropriately designed stability studies have been conducted to permit the conclusion that the drug product would be predicted to maintain its unique performance characteristics over the duration of its expiry period. However, only months of real time primary stability data has been submitted. An expiration date of only months can be permitted at this time taking into account both primary and supporting data.

B. Description of How the Drug Product is Intended to be Used

This application for propranolol hydrochloride extended release capsules contains a novel formulation that provides a for evening administration by specifying the daily dose to be taken at or around bedtime versus simply once daily. This formulation was designed to release the propranolol in an extended release manner after a controlled 4-hour lag time for the absorption into the gastrointestinal tract At steady state, blood levels of propranolol begin to increase approximately 4 hours after evening administration (taken at or around bedtime) and rise progressively over the early morning hours to reach peak plasma concentrations approximately 14 hours after dosing These propranolol plasma levels which rise slowly attenuate the rapid

increase in blood pressure and heart rate that precedes and follows waking. This increase is associated with the circadian variation in catecholamine secretion and in renin release. The rise in plasma propranolol concentration after dosing parallels the circadian rise in morning blood pressure associated with target organ damage in patients with hypertensive and ischemic cardiovascular disease

C. Basis for Approvability or Not-Approval Recommendation:

This NDA is approvable from the CMC standpoint provided the overall cGMP status recommendation from the Office of Compliance is "acceptable". Many of the deficiencies cited in the Chemistry Review #1 have been satisfactorily resolved. The remaining deficiencies/comments pertaining to in-process controls, specifications for the drug product, labeling and the expiration date, as listed (p.31-32), should be included in the action letter for this NDA.

B. Reviewer's Signature /S/

C. Endorsement Block

Chemist Name/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

D. CC Block

Redacted 20

pages of trade

secret and/or

confidential

commercial

information

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

/s/

Stuart Zimmerman
8/16/02 09:29:59 AM
CHEMIST

Kasturi Srinivasachar
8/16/02 10:01:01 AM
CHEMIST

NDA 21-438

Propranolol Hydrochloride Extended-Release Capsules

Reliant Pharmaceuticals, LLC

Stuart Zimmerman
Division of Cardio-Renal Drug products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-438

2. REVIEW # 1:

3. REVIEW DATE: 14-AUG-2002

4. REVIEWER: Stuart Zimmerman, Ph.D.

5. PREVIOUS DOCUMENTS: None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed /Document Date	
Original Submission:	31-OCT-2001
Amendment	05-APR-2002
Amendment	01-MAY-2002
Amendment	18-JUL-2002

7. NAME & ADDRESS OF APPLICANT:

Name:	Reliant Pharmaceuticals, LLC
Address:	110 Allen Road, Liberty Corner NJ 07938
Representative:	Paulette F. Kosmoski
Telephone:	908-542-4403

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: ——

b) Non-Proprietary Name (USAN): Propranolol Hydrochloride Extended Release Capsules
c) Code Name/# (ONDC only):
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: Type 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: a non-selective beta-adrenergic receptor blocking agent for the management of essential hypertension

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 80 mg, 120 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x Rx ___OTC

15. **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note26]:**

_____SPOTS product – Form Completed

__x__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

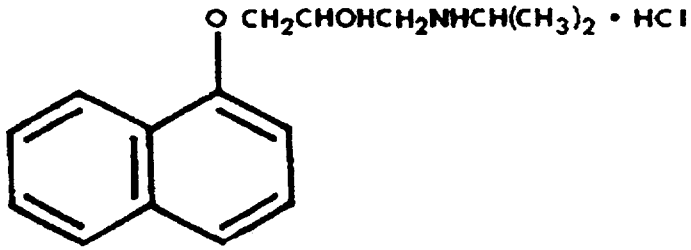
Chemical Name:

(±)-1-(isopropropylamino)-3-(1-naphthyloxy)-2-propanol hydrochloride

Molecular Formula: $C_{16}H_{21}NO_2$ - HCl

Molecular Weight: 295.81

Structural Formula:



17. RELATED/SUPPORTING DOCUMENTS:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II		Propranolol HCl Drug Substance	1	Adequate	Chemistry Review dated 8/7/02	Deficiency response of July 26 2002 is OK
	III			3	Adequate	9/15/00	CR#21
	III			1	Adequate	8/6/02	Certificate of compliance-NDA v. 1.3, p. 04-00629
	III			3	Adequate	2/9/01 and 5/10/99	
	III			3	Adequate	4/3/01	Reviewer P. Maturu
	III			4	Adequate	7/24/02	NDA related Review
	III			3	Adequate	10/12/98	
	III			3	Adequate	4/20/64	See CR=! For NDA 21-283 for detailed reference
	III			3	Adequate	9/27/00	Refer to CR#48
	III			4 (1/2 g.)	Adequate	7/24/02 and 9/3/99(1 g)	NDA related review
	III			7a	Adequate	N/A	Secondary DMF –see DMF
	III			7a	Adequate	NA	Secondary DMF –see DMF
	IV			7b	Adequate	NA	Compendial excipient
	IV			7b.	Adequate	NA	Compendial excipient
	III			4	Adequate	NA	Based on inspection
	IV			7b.	Adequate	NA	Compendial excipient
	IV			4	Adequate	NA	
	IV			4	Adequate	NA	
	IV			1	Adequate	8/5/02	
	III			7c.	Adequate		
	IV			7b.	Adequate	NA	Compendial excipient

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")
7a. This DMF is a nested DMF relating to DMF [redacted] and is not directly referenced by the applicant (i.e., LOA). It is considered to be acceptable via supporting information included in the primary DMF [redacted]
7b. The article is a compendial excipient controlled by a USP monograph.
7c. [redacted]

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

IND [redacted] Historical Review Information (vol. 1.2, p. 04-00017)

DOCUMENT	Serial Number	DESCRIPTION
7/24/2000	002	Provided additional information regarding dissolution rate profile and stability.
7/28/00	003	Provided additional information regarding formulation excipients.
8/16/00	006	Provided initial stability information
11/2/00	008	Provided pharmaceutical documentation for 120 mg strength of drug product, as well as updated information regarding the other two formulations.
2/8/01	009	Stability study data updates and COAs for the drug product.
4/23/01	013	Request for Type C chemistry meeting.

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A (No statistical analysis of stability yet provided to FDA)		
EES	Pending — inspection		
Pharm/Tox	N/A		
Biopharm	Revision of dissolution acceptance criteria	8/9/02	Angelica Dorantes
LNC	N/A		
Methods Validation	To be submitted		
DMETS	Acceptable-approved trade name —	7/12/02	Hye-Joo Kim
EA	Acceptable (categorical Exclusion)	6/7/02 see review section	Stuart Zimmerman
Microbiology	N/A		

The Chemistry Review for NDA 21-438

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability:
A final recommendation of approvability cannot be given at this time since the inspection of a packaging/stability testing facility is still pending. There are also other review deficiencies that must be resolved - see page 71and 72 of this review for details.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable
N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

- The drug substance is manufactured . procedure. Most of the drug substance chemistry and manufacturing information is in the drug master file (DMF) of the supplier. This DMF has been reviewed. Many deficiencies were identified and conveyed to the DMF holder. The response to these deficiencies has also been reviewed and found to be adequate.

  Propranolol Hydrochloride USP is a well known active ingredient that has been marketed for more than 30 years. It is a white, crystalline solid that is readily soluble in water and ethanol. In the USA, it is regulated by a USP monograph. It is also the subject of other monographs such as the EP and BP monographs. It has a retest date of 36 months.

  The drug product is a once a day capsule formulation that is composed of spherical beads in gelatin capsule shells. The beads allow for a delay effect for drug release for 4- 6 hours followed by a subsequent gradual controlled release of the drug for the duration of the dosing interval. Beads are formulated to a theoretical assay value for the active drug in the total bead matrix on a weight\weight basis. The quantitative composition of each different capsule strength is determined by the particular fill weight for that specific capsule strength. This allows for a common release rate mechanism to operate across all capsule sizes. Three different size gelatin capsules are utilized (i.e., 3, 2 ·) which are color coded for dosing delineation. Size 3 is for the 80 mg strength, size 2 is for the 120 mg capsule The capsules are packaged in both high density polyethylene bottles having induction seals and child resistant screw caps and in blister packaging configurations.

The manufacturing process assures that each batch of the drug product can be consistently manufactured to acceptable performance standards. These standards most critically include the unique extended release profile involving a 4 hour delayed release followed by a gradual upward controlled release phase. Also considered is the fact that chemical impurities and degradation is tightly controlled to very low limits throughout the entire process train - starting with drug substance manufacture.

Valid analytical control methods have been developed that can adequately monitor the critical control attributes to acceptable quality levels. For example, potential impurities and degradants are closely controlled to levels of quantitation of 0.01% relative to active drug abundance. Also, dissolution testing control intervals are designed to appropriately monitor the unique release rate profile for each dosage strength by a common testing approach for all dosage strengths.

Adequate attention was given to the design of the in-process control tests and their respective acceptance criteria for step - by - step monitoring of the performance attributes at each critical unit process operation.

Packaging configurations have been appropriately designed to adequately protect the drug product's performance characteristics against both chemical and functional changes for the shelf-life of the product.
Appropriately designed stability studies have been conducted to permit the conclusion that the drug product would be predicted to maintain its unique performance characteristics over the duration of its expiry period. However, only months of real time primary stability data has been submitted. An expiration date of only months can be permitted at this time taking into account both primary and supporting data.

B. Description of How the Drug Product is Intended to be Used

This application for propranolol hydrochloride extended release capsules contains a novel formulation that provides a for evening administration by specifying the daily dose to be taken at or around bedtime versus simply once daily. This formulation was designed to release the propranolol in an extended release manner after a controlled 4-hour lag time for the absorption into the gastrointestinal tract. At steady state, blood levels of propranolol begin to increase approximately 4 hours after evening administration (taken at or around bedtime) and rise progressively over the early morning hours to reach peak plasma concentrations approximately 14 hours after dosing. These propranolol plasma levels which rise slowly attenuate the rapid increase in blood pressure and heart rate that precedes and follows waking. This increase is associated with the circadian variation in catecholamine secretion and in renin release. The rise in plasma propranolol concentration after dosing parallels the circadian rise in morning blood pressure associated with target organ

damage in patients with hypertensive and ischemic cardiovascular disease

C. Basis for Approvability or Not-Approval Recommendation:

A recommendation can only be given after the Office of Compliance has provided an overall cGMP status for all facilities submitted for inspection. The review issues identified in the list of deficiencies (p. 71 and 72)also need to be resolved.

D. Reviewer's Signature

E. Endorsement Block

Chemist: Stuart Zimmerman / August 13, 2002
ChemistryTeam Leader : Kasturi Srinivasachar / August 13, 2002
ProjectManager: Zelda McDonald / August 13, 2002

F. CC Block

Redacted 60

pages of trade

secret and/or

confidential

commercial

information

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

/s/

Stuart Zimmerman
8/16/02 09:42:52 AM
CHEMIST

Kasturi Srinivasachar
8/16/02 09:53:56 AM
CHEMIST