CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-378

CHEMISTRY REVIEW(S)

CHEMISTRY REVIEW

Chemistry Assessment Section

NDA 21-378

COMBUNOX
(Oxycodone HCl and Ibuprofen) Tablets

Forest Laboratories, Inc.
Harborside Financial Center
Plaza 3- Suite 602
Jersey City, NJ 07311

Danae D. Christodoulou, Ph.D.
Division of Anesthetics, Critical Care, and Addiction Drug Products (DACCADP)- HFD-170

[redacted] [redacted]

CHEMISTRY REVIEW

Chemistry Assessment Section

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[redacted] CHEMISTRY REVIEW

Chemistry Assessment Section

Chemistry Review Data Sheet

1. NDA 21-378

2. REVIEW #: 2

3. REVIEW DATE: November 19, 2004

4. REVIEWER: Danae D. Christodoulou, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND 52310	January 3, 1997
Original NDA submission	December 19, 2001
CMC Review # 1	October 4, 2002
AE Letter	October 18, 2002

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Resubmission 000 (AZ)	May 27, 2004
Amendment 000 (BC)	June 2, 2004
Amendment 000 (BC)	November 2, 2004

7. NAME & ADDRESS OF APPLICANT:

[redacted] [redacted]

CHEMISTRY REVIEW

Chemistry Assessment Section

Name:	Forest Laboratories Inc.
Address:	Harborside Financial Center Plaza 3- Suite 602 Jersey City, NJ 07311
Representative:	Michael K. Olchaskey, Pharm.D. Associate Director, Regulatory Affairs
Telephone:	201-386-2142

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Combunox
b) Non-Proprietary Name (USAN): (Oxycodone HCl and Ibuprofen) tablet
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 4
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505b2 Application based on the following Listed Drugs:

Motrin® (Ibuprofen) NDA # 17, 463 and
Roxicodone™ (Oxycodone HCl) NDA # 21, 011

10. PHARMACOL. CATEGORY: Short term management of acute, moderate to severe pain with a combination of opioid analgesic oxycodone and non-steroidal anti-inflammatory drug (NSAID) ibuprofen

11. DOSAGE FORM: Coated tablets

12. STRENGTH/POTENCY: Oxycodone HCl, 5-mg and Ibuprofen, 400-mg

13. ROUTE OF ADMINISTRATION: Oral

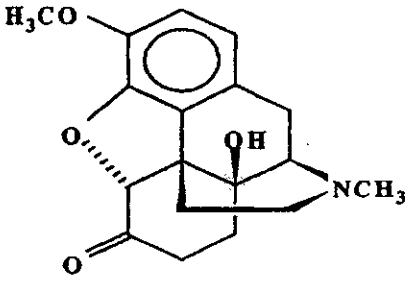
14. Rx/OTC DISPENSED: _x__Rx ___OTC

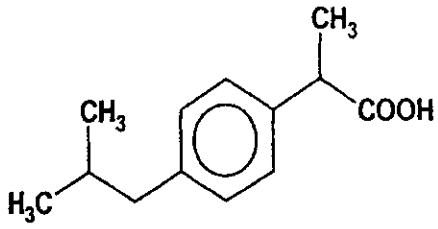
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___x__Not a SPOTS product

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





Oxycodone HCl: 4, 5α-Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride. $C_{18}H_{21}NO_4HCl$. Mol. Wt. 351.82 (USP)

Ibuprofen: (±)-2-(p-isobutylphenyl) propionic acid. $C_{13}H_{18}O_2$. Mol. Wt. 206.28 (USP)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
–	II			1	Adequate	11/19/04	D. Christodoulou
–	II			1	Adequate	11/19/04	D. Christodoulou
–	II			3, 4	Adequate	11/6/2003	S. Dhanesar

	III	3, 4	Adequate	4/5/2002 7/25/2000 9/21/2003	D. Lewis G. Gillsangha J. Boal
		1	Adequate	10/04/02	R Harapanhalli
	IV	3, 4	Adequate	4/30/02 6/6/02	B Rogers J Boal
	IV	3	Adequate	7/30/97 4/29/02	C Bertha R Frackewich
	IV	3	Adequate	7/13/99 2/28/01	T. Oliver S. Zuk
	IV	3, 4	Adequate	9/24/01	J Salemme
	IV	3, 4	Adequate	8/17/2000	S Zimmerman
	IV	3, 4	Adequate	9/17/2001 11/15/2004	D. Kline M. Heimann
	IV	3, 4	Adequate	4/29/2002	R Frankewich
	IV	3, 4	Adequate	5/4/96 9/9/98 5/2/02	C Bertha K Srinvasachar E. Chickale
	IV	3, 4	Adequate	6/13/02	J Boal

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CHEMISTRY REVIEW

Chemistry Assessment Section

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not consulted since the real-time 36-month stability data update was adequate and no further statistical analysis was deemed necessary.	N/A	N/A
EES	Acceptable	11/15/04	Office of Compliance
Pharm/Tox	Recommended for approval, provided: the sponsor commits to completing Segment I and III reproductive toxicology studies previously agreed to; continues to work with the Division and DMF holder regarding the risks associated with — — and any other detected impurities with structural alerts for mutagenicity or reduce the limits of any genotoxic impurities to acceptable levels.	11/12/04	Mamata De, Ph.D.
Biopharm	The dissolution specification should be tightened from Q = — , at — , to Q = — in 30 minutes. No new information since the first review cycle; recommendation for approval.	09/13/02 11/15/04	David Lee, Ph.D.
LNC	Not consulted as the two drug substances are not NCEs and they have USAN names and the dosage form is conventional.	N/A	N/A
Methods Validation	Not requested since the test methods are conventional in nature and do not qualify for any of the seven criteria described in the ONDC interim policy on methods validation.	N/A	N/A
DMETS	The proposed tradename	9/1/04	N. Roselle

	"COMBUNOX" is acceptable.		
EA	Not applicable. Categorical exclusion claimed and is deemed adequate.	N/A	N/A
Microbiology	Not applicable as this is solid oral dosage form and there are no apparent microbiological issues	N/A	N/A

APPEARS THIS WAY
ON ORIGINAL

Chemistry Assessment Section

The Chemistry Review for NDA 21-378

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Responses to the chemistry deficiencies noted in the approvable letter dated October 18, 2002 are adequate. The Office of Compliance deemed the facilities acceptable from cGMP compliance. All DMFs are adequate to support the NDA. Therefore, the NDA is recommended for approval.

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

Sodium Starch Glycolate, NF:
The limits for bulk density, tap density and particle size distribution have not been established. Based on the analysis of at least five additional batches of Sodium Starch Glycolate, NF, applicant should establish the limits for bulk density, tap density and particle size distribution and report in the NDA Annual Report.

II. Summary of Chemistry Assessments

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

The drug product is a fixed combination immediate-release tablet form for oral administration containing an opioid analgesic oxycodone HCl (5-mg) and a nonsteroidal anti-inflammatory (NSAID) agent ibuprofen (400-mg) indicated for the short term management of acute, moderate to severe pain. It is a white to off-white capsule shaped, film-coated tablet, with "F" bisect "P" on one side and "5400" on the other side. The weights of the core and film-coated tablets are — 1 618 mg respectively. Inactive ingredients include sodiums starch glycolate, microcrystalline cellulose, colloidal silicon dioxide, stearic acid, calcium stearate, — polydextrose, triacetin, polyethylene glycol 8000, povidone, — and Opadry Y-22-7719 white. The product is packaged in 30-count, 100-count, and 500-count HDPE bottles and in unit dose blisters (4 X 25).
The two drug substances, ibuprofen and oxycodone HCl are well known in the literature and are both individually approved in the United States. They are both highly soluble and — The commercial drug product is made by a — The clinical batches were made by —

— and subsequently a PK/BE study was conducted to demonstrate the equivalency of the two processes and also the two formulations.

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

One to four times a day orally. The drug product is a capsule-shaped coated tabet.

C. Basis for Approvability or Not-Approval Recommendation

The NDA was submitted under 505(b) (2) and according to the applicant, it relied on Agency's evaluation of the safety and efficacy of Motrin® (NDA# 17,463) and Roxicodone™ (NDA # 21,011). Review of the first cycle of the NDA identified 31 CMC deficiencies, included in the Approvable Letter of October 18, 2002, with the recommendation for approvable action for CMC. The NDA resubmission was a Complete Response to the CMC deficiencies and the current CMC recommendation is Approval, based on "adequate" CMC, "acceptable" cGMP recommendation from the Office of Compliance dated November 15, 2004 and adequate DMF updates.
The drug substance (Oxycodone HCl) specification for — , a potential genotoxic impurity, has been tightened to an interim specification of NMT — by — on April 2, 2004. The firm agreed to continue discussions with the division about tightening the levels of this impurity and any other potential genotoxic impurities or structural alerts for mutagenicity. The firm provided 36-month real time stability data according to ICH guidelines to support that — the data are consistent with the interim specification of — in the Therefore, a specification for — the d was not deemed necessary. The safety of the levels of — in the drug substance and drug product have been evaluated also by the Toxicology Division. The only significant degradant identified in the drug product is —

specification of "NMT ' was acceptable based on 36-month real stability data and the Toxicology Division's recommendation. Other critical aspects for the performance of the drug product was the tightening of the dissolution specification to Q = , at 30 minutes [USP Apparatus 1, Basket, 100 rpm, pH = 7.2 phosphate buffer] recommended during the first cycle of review.
The 36-month real time stability data support a 36-month expiration dating for COMBUNOX. All proposed commercial packaging configurations were supported by the stability data. The proposed physicians blister packs are larger in count size (25 versus 10 in stability studies) but their configuration was justified as being equivalent in representing the stability. Other critical aspects of CMC such as excipient specifications with potential to affect performance of the drug product, packaging considerations, and justification for categorical exclusion from environmental assessment have been adequately addressed. One

supplier was withdrawn from the NDA. The Office of Compliance recommendation dated November 15, 2004 was "Acceptable". All DMF updates were deemed adequate to support the NDA. Therefore, from CMC perspective, the NDA is recommended for approval.

APPEARS THIS WAY
ON ORIGINAL

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Danae D. Christodoulou Ph.D./November 17, 2004
R. Harapanhalli, Ph.D./
L. Basham-Cruz/

C. CC Block

cc: Orig. NDA 21-378
HFD-170/NDA Division File
HFD-170/Chemist/DChristodoulou
HFD-170/MO/RRoca
HFD-170/Pharmacologist/Mamata De
HFD-170/CSO/LBasham-Cruz
R/D Init by: R. Harapanhalli, Ph.D.
filename: c:/data/mydocs/21378R2a.doc

46 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

____ § 552(b)(5) Draft Labeling

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

/s/

Danae Christodoulou
11/19/04 04:28:40 PM
CHEMIST

Ravi Harapanhalli
11/19/04 04:42:53 PM
CHEMIST
AP with an agreement

NDA 21-378

Oxycodone HCl/Ibuprofen Tablets
(No Brand name)

Forest Laboratories, Inc.
Harborside Financial Center
Plaza 3- Suite 602
Jersey City, NJ 07311

Ravi S. Harapanhalli, Ph.D.
Division of Anesthetics, Critical Care, and Addiction Drug Products (DACCADP)- HFD-170

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-378

2. REVIEW #: 1

3. REVIEW DATE: October 04, 2002

4. REVIEWER: Ravi S. Harapanhalli, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND 52310	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original NDA 000	December 19, 2001

7. NAME & ADDRESS OF APPLICANT:

Name:	Forest Laboratories Inc.
Address:	Harborside Financial Center Plaza 3- Suite 602 Jersey City, NJ 07311
Representative:	M. Daniel Gordin, Ph.D. Associate Director, Regulatory Affairs
Telephone:	770-534-8239

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None proposed
b) Non-Proprietary Name (USAN): Oxycodone HCl/Ibuprofen
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505B2 Application based on the following Listed Drugs:

Motrin® (Ibuprofen) NDA # 17, 463 and
Roxicodone™ (Oxycodone HCl) NDA # 21, 011

10. PHARMACOL. CATEGORY: Short term management of acute, moderate to severe pain with a combination of opioid analgesic oxycodone and non-steroidal anti-inflammatory drug (NSAID) ibuprofen

11. DOSAGE FORM: Coated tablets

12. STRENGTH/POTENCY: Oxycodone HCl, 5-mg/Ibuprofen, 400-mg

13. ROUTE OF ADMINISTRATION: Oral

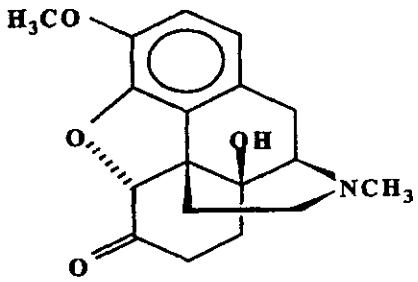
14. Rx/OTC DISPENSED: _x__Rx ___OTC

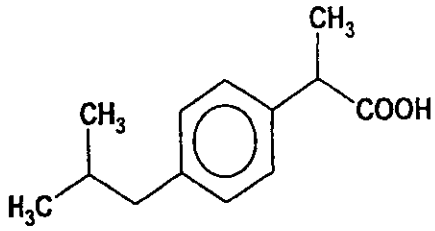
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:

_____SPOTS product – Form Completed

___x___Not a SPOTS product

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





Oxycodone HCl: 4, 5α-Epoxy-14-hydroxy-3-methoxy-17-methylmorphinan-6-one hydrochloride. $C_{18}H_{21}NO_4HCl$. Mol. Wt. 351.82 (USP)

Ibuprofen: (±)-2-(p-isobutylphenyl) propionic acid. $C_{13}H_{18}O_2$. Mol. Wt. 206.28 (USP)

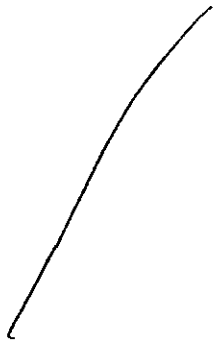
17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
–	II			1	Inadequate	10/02/02	Specs should be updated
–	II			1	Inadequate	10/07/02	R. Harapanhalli
–	III			3, 4	Adequate	4/5/2002 7/25/2000	D Lewis G Gillsangha
–				1	Adequate	10/04/02	R Harapanhalli
–	IV			3, 4	Adequate	4/30/02 6/6/02	B Rogers J Boal
–	IV			3	Adequate	7/30/97 4/29/02	C Bertha R Frackewich
–	IV			3	Adequate	7/13/99	Tom Oliver
–	IV			3, 4	Adequate	9/24/01	J Salemme

Chemistry Review Data Sheet

~	IV
~	IV
~	IV
~	IV
~	IV



3, 4	Adequate	8/17/2000	S Zimmerman
3, 4	Adequate	9/17/2001	D. Kline
3, 4	Adequate	4/29/2002	R Frankewich
3, 4	Adequate	5/4/96 9/9/98	C Bertha K Srinvasachar
3, 4	Adequate	6/13/02	J Boal

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not consulted as the NDA is approvable from CMC and an updated stability data will be requested.	N/A	N/A
EES*	Acceptable	10/17/02	Office of Compliance
Pharm/Tox	Recommended that impurities be limited to NMT ~ o or tox qualification data be provided. Also recommended that genotox studies be carried out on a mutagenic structural alert ~	10/02/02	Tim McGovern, Ph.D.
Biopharm	The dissolution specification should be tightened from Q = ~ at ~ o Q = ~.	09/13/02	David Lee, Ph.D. See Biopharm review dated 09/13/02 in the DFS

	in 30 minutes.		
LNC	Not consulted as the two drug substances are not NCEs and they have USAN names	N/A	N/A
Methods Validation	Not requested at this time since the specifications need to be revised.	N/A	N/A
ODS	Not requested as no tradename is proposed in the NDA.	N/A	N/A
EA	Not applicable. Categorical exclusion claimed	N/A	N/A
Microbiology	Not applicable as this is solid oral dosage form and there are no apparent microbiological issues	N/A	N/A

*

listed in the DMF — ıot listed in NDA but requested by the reviewer) were also found to be acceptable by the Office of Compliance on 10/17/02. Therefore, all related facilities to NDA 21378 were deemed acceptable by OC.

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-378

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable pending satisfactory resolution of CMC deficiencies and comments listed at the end of the review.

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

The NDA is being recommended "Approvable" from the stand point of CMC. The applicant should address all the listed CMC deficiencies and comments. Recommendations on Phase 4 commitments, agreements etc., if any, will be made at the time of approval.

II. Summary of Chemistry Assessments

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

The drug product is a fixed combination immediate-release tablet form for oral administration containing an opioid analgesic oxycodone HCl (5-mg) and a nonsteroidal anti-inflammatory (NSAID) agent ibuprofen (400-mg) indicated for the short term management of acute, moderate to severe pain. It is a white to off-white capsule shaped, film-coated tablet, with "F" bisect "P" on one side and "5400" on the other side. The weights of the core and film-coated tablets are , 618 mg respectively. Inactive ingredients include sodiums starch glycolate, microcrystalline cellulose, colloidal silicon dioxide, stearic acid, calcium stearate. , polydextrose, triacetin, polyethylene glycol 8000, povidone, , and Opadry Y-22-7719 white. The product is packaged in 30-count, 100-count, and 500-count HDPE bottles and in unit dose blisters (4 X 25).

The two drug substances, ibuprofen and oxycodone HCl are well known in the literature and are both individually approved in the United States. They are both highly soluble and . The commercial drug product is made by a The clinical batches were made by and subsequently a PK/BE study was conducted to demonstrate the equivalency of the two processes and also the two formulations.

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

One to four times a day orally. The drug product is a capsule-shaped coated tabet.

C. Basis for Approvability or Not-Approval Recommendation

The NDA was submitted under 505(b) (2) and according to the applicant, it relied on Agency's evaluation of the safety and efficacy of Motrin® (NDA# 17,463) and Roxicodone™ (NDA # 21,011). The NDA is deficient in major areas of CMC. The acceptance specifications of oxycodone HCl and ibuprofen — , are inadequate in limiting the impurities and in assuring the safety. The proposed limits on impurities are high and should be tightened significantly or supporting safety qualification data should be provided. — and a potential genotoxic agent, specified at — should be supported by adequate in vitro genotoxicity testing studies, else it should be limited to — . The specifications on impurities should be revised to bring additional clarity in the description of the individual and total impurities. — impurity in — should be specified in — and also method validation data on this should be provided to the NDA. Additional physical controls such as bulk density, tapped density, and particle size distribution should be established for the — Without such additional controls, the consistency and performance of the drug product can not be assured from batch to batch. The drug product dissolution specification should be tightened to reflect its immediate-release nature and to reflect the observed data at product release and through stability period. An additional specification of should be established for the drug product to ensure its consistent performance and adequacy of its packaging throughout the expiration dating period. The analytical methods should be revised by including quantitation and detection limits for the impurities so that they can be deemed adequate for regulatory purpose. The environmental assessment section should be revised by including projected sales in the next five years and the environmental introduction calculations (EIC) to justify claimed exclusion. The Office of Compliance in their pre-approval inspections found the facilities acceptable for compliance with cGMPs. The drug product does not have a brand name. The applicant should clarify if they intend to propose a brand name. Lastly, the two referenced DMFs DMF — and DMF — were deemed inadequate to support the NDA. The two DMFs should therefore be adequately amended to support the NDA.

The deficiencies are fixable within a reasonable time. Therefore, the NDA is "approvable" pending adequate resolution of the CMC issues listed at the end of the review.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

R. S. Harapanhalli, Ph.D./October 7, 2002
Dale Koble, Ph.D./
Kim Compton/

C. CC Block

cc: Orig. NDA 21-378
HFD-170/NDA Division File
HFD-170/chemist/Harapanhalli
HFD-170/MO/Comfort Shaun.
HFD-170/Pharmacologist/DMellon
HFD-170/CSO/Lbasham-Cruz
R/D Init by: Dale Koble, Ph.D.
filename: c:/data/mydocs/NDAs/21378.000.doc

56 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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

/s/

Ravi Harapanhalli
10/17/02 02:35:15 PM
CHEMIST

CMC review is updated with today's information from OC regarding acceptable status of all four facilities listed in the DMF 7890. All related facilities are deemed acceptable by OC.

Dale Koble
10/17/02 02:42:12 PM
CHEMIST