CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-378

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-378	Submission Date(s): 12/19/01
Brand Name	To be determined
Generic Name	Oxycodone HCl / Ibuprofen Combination
Primary Reviewer	David Lee
Secondary Reviewer	Suresh Doddapaneni
OCPB Division	DPE 2
ORM division	Division of Anesthetic, Critical Care and Addiction Drug Products
Sponsor	Forest Laboratories, Inc.
Relevant NDA(s)	17-463 Motrin® (ibuprofen)
	21-011 Roxicodone™ (oxycodone)
Relevant IND(s)	52,310
Submission Type; Code	505(b)(2); 4 S
Formulation; Strength(s)	Oxycodone / Ibuprofen
	5 mg / 400 mg combination tablet
Proposed Indication	Short term management of acute, moderate to severe pain
Proposed Dosage Regimen	Recommended dose is one 5 mg / 400 mg tablet up to 4 times daily not to exceed 7 days

1 Executive Summary

Forest Laboratories, Inc., has submitted a New Drug Application, NDA 21-378 seeking approval for oxycodone HCl / Ibuprofen combination tablet, 5 mg / 400 mg, for the short-term management of acute, moderate to severe pain.

In the submission, the Applicant stated that this 505(b)(2) submission relies on the Agency's findings of safety and efficacy of Motrin® (ibuprofen) NDA 17-463 and Roxicodone™ (oxycodone HCl) NDA 21-011. The clinical trials essential to this NDA were conducted under IND 52,310. The Applicant stated that they have not licensed the proposed combination tablet to any other sponsor and the product is not marketed nor has an application been filed for its marketing outside the U.S. Both active ingredients are manufactured by —

The Applicant submitted a request for deferral of pediatric studies for patients < 12 years of age. The Applicant submitted a total of six pharmacokinetic/biopharmaceutic studies in healthy subjects under Section 6 of the NDA submission. Additionally, there are two clinical studies (MD-05 and MD3-96-01) which measured both pharmacokinetic parameters and the efficacy endpoints.

Exposure-response (E-R) relationship

The submitted information suggests that there are no apparent E-R relationships between the primary efficacy endpoints and the plasma concentrations of active ingredients, ibuprofen and oxycodone.

Bioequivalence information

The clinical and to-be-marketed formulations were bioequivalent.

In a relative bioequivalence study the Applicant utilized Roxicodone™ 5 mg tablet, which is not an approved drug product, to compare the oxycodone portion of the combination tablet. The data indicated that oxycodone portion of the Applicant's combination tablet is bioequivalent to Roxicodone™ 5 mg tablet.

With respect to utilizing the non-approved Roxicodone™ 5 mg tablet, there is no clinical pharmacology issue, since the currently approved Roxicodone™ 15 mg and 30 mg package insert provided the needed bioequivalence linkage between 5 mg and 15 mg.

Food effect

There were slight changes (less than 30%) in Cmax and AUC of oxycodone after consumption of a high fat breakfast. These changes are probably clinically insignificant.

Multiple dosing

In the Applicant's proposed package insert, it is stated that

"Dosage should not exceed 4 tablets in a 24-hour period for up to 7 days."

In the submission, the Applicant administered the combination tablet every 6 hour for 3 ½ days. There was, as expected based on the elimination half-life of total ibuprofen (T1/2 = 2 hr) and the dosing interval τ = 6 hr), no accumulation of total ibuprofen (and S-ibuprofen) after multiple doses of oxycodone/ibuprofen (5 mg/400 mg) every 6 hours.

There was moderate accumulation of oxycodone after multiple doses of oxycodone/ibuprofen (5 mg/400 mg) every six hours for 3 ½ days, as expected, based on the elimination half life of oxycodone (T1/2 = 3.5 hours) and a dosing interval of 6 hours.

However, the trough concentrations obtained for both ibuprofen and oxycodone indicated that there were no accumulations of total ibuprofen and oxycodone.

From a pharmacokinetic perspective, based on the elimination half-life of oxycodone and ibuprofen, the wording in the proposed package insert seems adequate, i.e., both oxycodone and ibuprofen concentrations reached steady-state after 3 ½ days of administration. However, since there is no E-R relationship, the efficacy due to the combination tablet can not be predicted.

Drug interaction

Drug interaction studies were not studied.

Gender differences

There was no gender differences observed.

Pediatric population

Pharmacokinetic or clinical information is not available in pediatric population. The Applicant has requested a deferral to study the product in pediatric population < 7 years of age. In the current submission approximately 240 pediatric patients between the ages of 13-17 years were exposed to the combination product for the evaluation of safety (approximately 80 of 240 patients were exposed to multiple doses with an average exposure of 4 days in duration. A proposal was made

to the Division on 8/29/01 to conduct a pharmacokinetic study in the pediatric population aged 7 to 12 years old.

Comment on dissolution methodology

The Applicant proposed the following specification for oxycodone/ibuprofen tablet:

USP basket method at 100 RPM in 500 mL of pH 7.2 phosphate buffer at 37°C. The release is Q — at (

The Applicant's proposal of using USP basket method is acceptable. However the submitted data displayed that Q — at 30 minutes is achievable. Therefore it is recommended that specification be Q — at 30 minutes for the combination drug product. This recommendation will be finalized upon consultation with CMC reviewer.

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation II (OCPB/DPE-II) has reviewed NDA 21-378 (oxycodone HCl/Ibuprofen) submitted on December 19, 2001. The Applicant utilized Roxicodone™ 5 mg as a reference product, which is not an approved drug product, in the relative bioavailability study.

The information contained in the NDA is acceptable, even though the Applicant used non-approved Roxicodone™ 5 mg, since the currently approved Roxicodone™ 15 mg and 30 mg package insert provided the needed bioequivalence linkage between 5 mg and 15 mg.

1.2 Comment to the Applicant

A. The submitted dissolution data indicated that Q — at 30 minutes is achievable. Therefore it is recommended that new specification be set at Q — at 30 minutes for the combination drug product.

2 Table of Contents

3 Summary of CPB Findings

Oxycodone

1. After single dose administration of 5 mg/400 mg tablet under fasted condition, Cmax and AUC_{∞} values ranged from 9.8 to 11.7 ng/mL and 51.4 to 60.6 ng.hr/mL, respectively, in healthy volunteers.
2. The terminal half-life ranged from 3.1 to 3.7 hours.
3. After single dose administration, peak concentrations are reached around 1.3 to 2.1 hours post administration.
4. Dose proportionality was observed for Cmax and AUC values after single doses of 5 mg/ 400 mg and 10 mg/ 400 mg tablets. It is noted that the Applicant is not seeking approval for the 10 mg/ 400 mg tablet.
5. Following a standardized high-fat breakfast, Cmax and AUC values increased 16.2 % and 19.7 %, respectively, after single dose administration.
6. After oral administration of 5 mg/ 400 mg tablet q.i.d. for 3.5 days, Cmax increased approximately 50-65%. However, trough concentrations did not change after 3.5 days of combination tablet administration.
7. No gender differences were observed.
8. After single dose administration, less than 4% of the administered dose was excreted unchanged in urine.
9. After single dose administration of 5 mg / 400 mg, bioequivalence was established (both Cmax and AUC_{∞}) for clinical and to-be-marketed formulations.
10. Drug-drug interaction studies were not conducted.
11. The Applicant submitted a deferral to study the combination tablet in pediatric population.

Ibuprofen

1. After single dose administration of 5 mg/400 mg tablet under fasted condition, Cmax and AUC_{∞} values ranged from 18.5 to 34.3 µg/mL and 86.5 to 134.3 µg.hr/mL, respectively, in healthy volunteers.
2. The terminal half-life ranged from 1.8 to 2.6 hours.
3. After single dose administration, peak concentrations are reached around 1.6 to 3.1 hours post administration.
4. Following a standardized high-fat breakfast, Cmax and AUC values decreased 16 % and 5.2 %, respectively, after single dose administration.
5. After oral administration of 5 mg/ 400 mg tablet q.i.d. for 3.5 days, no accumulation was observed.
6. No gender differences were observed.
7. After single dose administration, less than 0.2% of the administered dose was excreted unchanged in urine.
8. After single dose administration of 5 mg / 400 mg, bioequivalence was established (both Cmax and AUC_{∞}) for clinical and to-be-marketed formulations.
9. Drug-drug interaction studies were not conducted.
10. The Applicant submitted a deferral to study the combination tablet in pediatric population.

4 QBR

4.1 General Attributes

What is the pharmacological class for both oxycodone and ibuprofen?

Oxycodone HCl is a centrally acting semi-synthetic opioid analgesic. Ibuprofen is a nonsteroidal anti-inflammatory drug with analgesic and antipyretic properties. The therapeutic value of combination analgesic products, according to the Applicant, is that they overcome the "ceiling" effect of traditional analgesics like aspirin or acetaminophen in patients for whom satisfactory pain relief is otherwise not possible.

What is the combination tablet composition?

Composition of oxycodone/ibuprofen Tablets:

Strength	Oxycodone/ Ibuprofen 5 mg/400 mg	Oxycodone/ Ibuprofen mg/200 mg (Forest)	Oxycodone/Ibuprofen 5 mg/400 mg (Forest)		Oxycodone/Ibuprofen 10 mg/400 mg (Forest)	Oxycodone/Ibuprofen 5 mg/400 mg (Forest)	Oxycodone/Ibuprofen 10 mg/400 mg (Forest)
Study	604-003-01 604-004-01	OXY-MD3-96-02-000 OXY-PK1-97-02-000	OXY-MD3-96-01-000 OXY-PK1-96-01-000 OXY-PK1-97-02-000	OXY-MD-05 OXY-MD-06 OXY-MD-08 OXY-PK-04	OXY-MD-06 OXY-MD-08	OXY-PK-04 OXY-PK-03	OXY-PK-03
Manufacturing Process							
Lot Numbers	901440	97047C	97002A	99229K	99230K	00069C	00084D
Ibuprofen							
Oxycodone HCl, USP	5.00					5.0	10.0
Povidone USP							
Sodium Starch Glycolate, NF							
Microcrystalline Cellulose, NF							
Colloidal Silicon Dioxide, NF							
Stearic Acid, NF							
Calcium Stearate, NF							
Core Tablet Weight (mg)							
Opadry II White (Y-22-7719)							
Coated Tablet Weight (mg)							

Note: Applicant is not seeking approval of the 10 mg/ 400 mg strength at this time.

4.2 General Clinical Pharmacology

Is there any exposure-response relationship information for combination tablet?

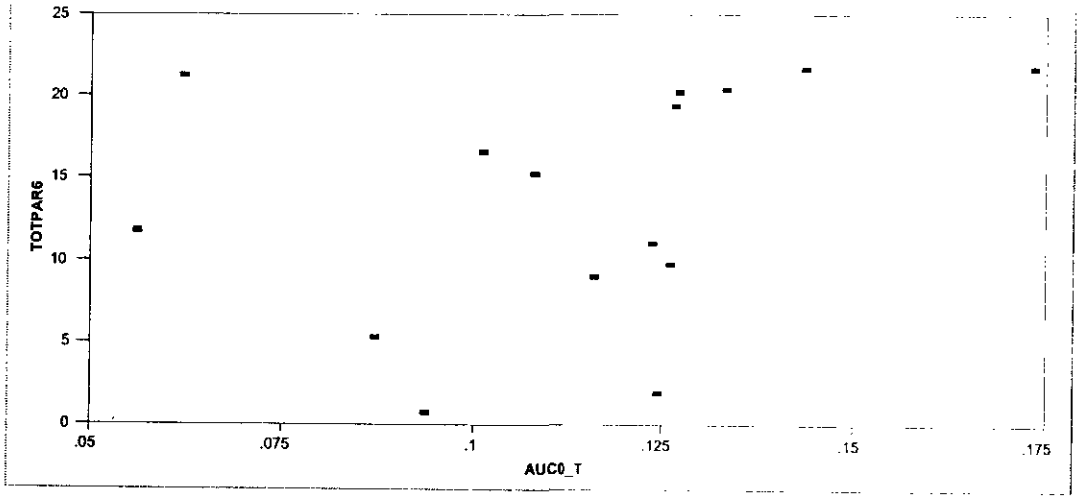
Studies Oxy-MD-05, a pivotal clinical trial, and Oxy-MD3-96-01, a supportive trial, obtained PK (Cmax and AUC) and PD (TOTPAR6, TOTPAR8, SPID6, SPID8, etc) parameters. The Applicant stated in the study reports that there were no apparent relationships between ibuprofen/oxycodone plasma concentrations (exposure) and the primary efficacy results (PD response) for this combination tablet. The following additional analysis (from MD-05 Study) was conducted to substantiate the Applicant's claim.

MD-05 Study

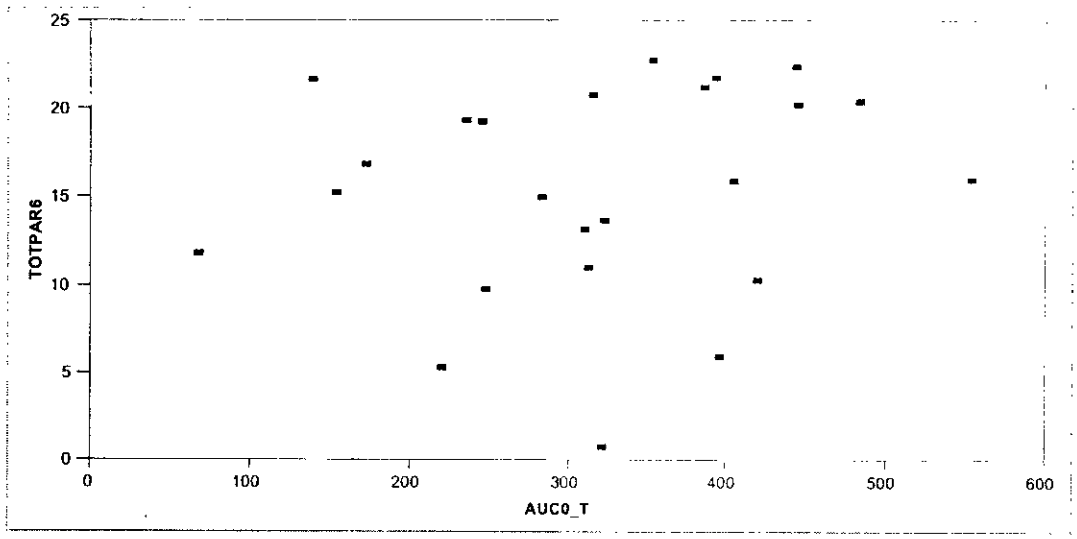
This study measured Total Pain Relief Scores over 6 Hours (TOTPAR6) and Sum of Pain Intensity Difference Scores over 6 and 8 Hours (SPID6 and SPID8) as primary endpoints. The following figures are generated to assess any relationships between efficacy endpoints (TOTPAR6 and SPID6) and pharmacokinetic parameters (Cmax and AUC). The figures suggested that there is no exposure-response relationship for this combination tablet.

By AUC 0-t parameter:

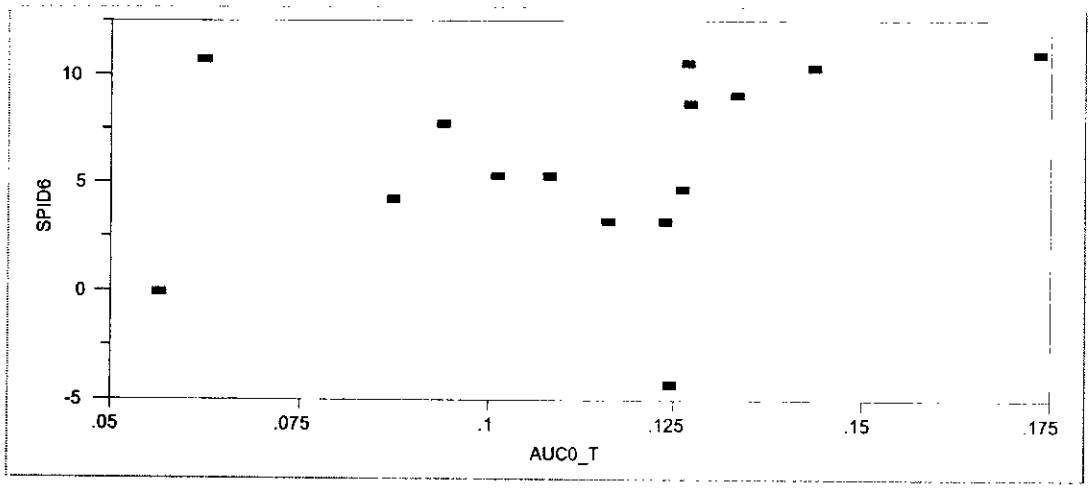
Oxycodone Treatment: TOTPAR6 By AUC0_T



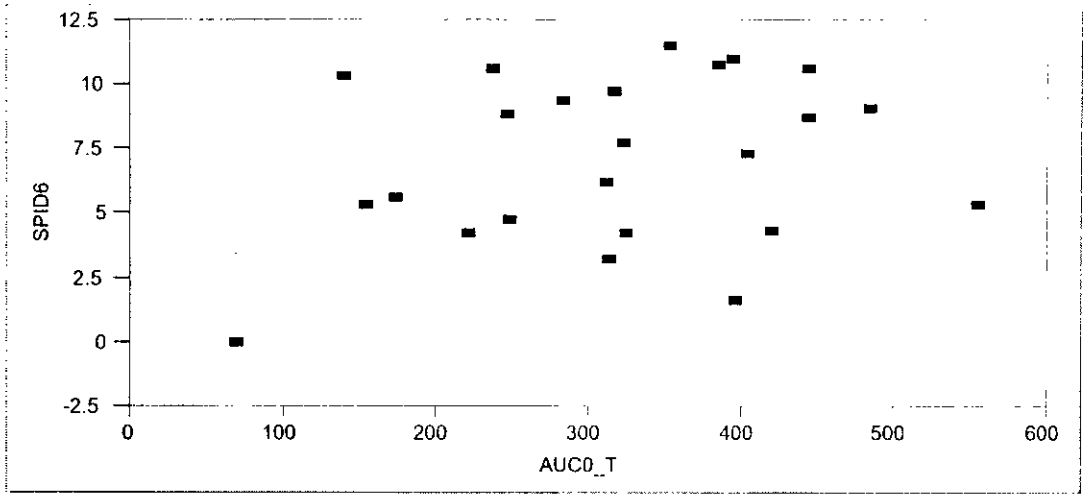
Total Ibuprofen treatment: TOTPAR6 By AUC0_T



Oxycodone Treatment: SPID6 By AUC0_T

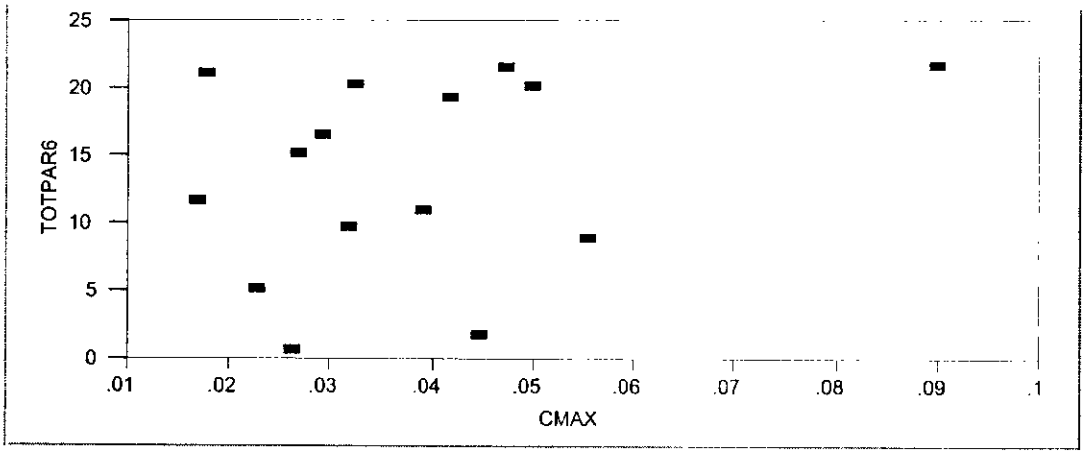


Total Ibuprofen treatment: SPID6 By AUC0_T

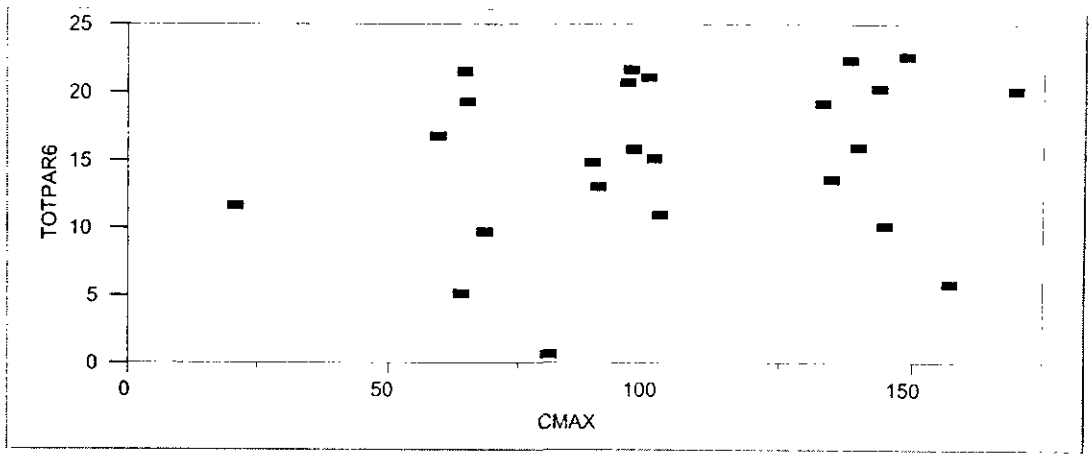


By Cmax parameter:

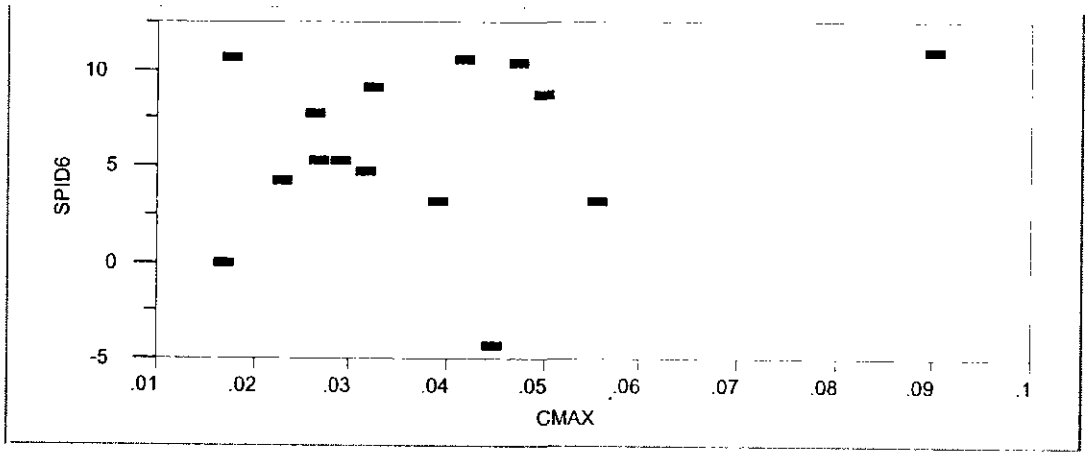
Oxycodone Treatment: TOTPAR6 By CMAX



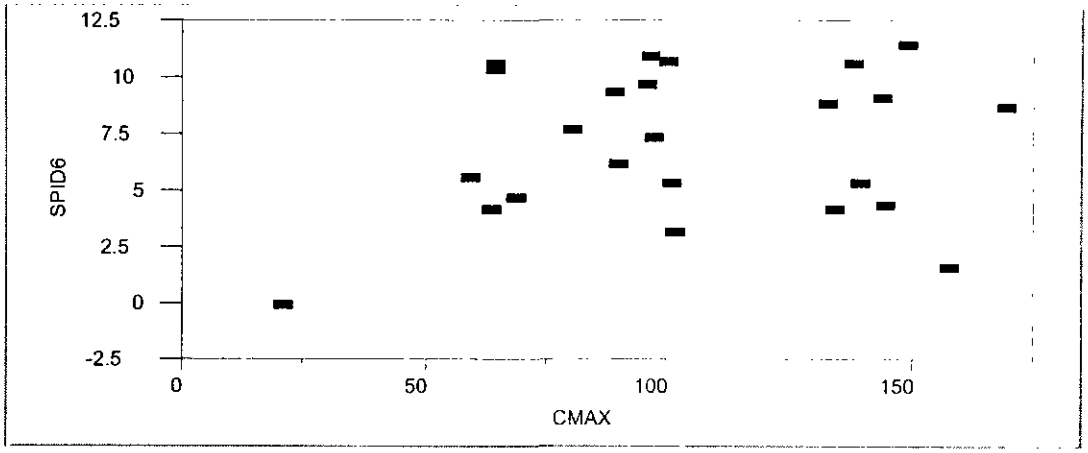
Tot Ibuprofen Treatment: TOTPAR6 By CMAX



Oxycodone Treatment: SPID6 By CMAX



Tot Ibuprofen treatment: SPID6 By CMAX



MD3-96-01 Study

For MD3-96-01 study, the comparison of the efficacy endpoints (TOTPAR8 and SPID8) and pharmacokinetic parameters (Cmax or AUC) were not feasible; the compiled database for this study did not permit the analysis. However, the Applicant submitted the pharmacokinetic parameters from this study. The results indicated that pharmacokinetic parameters are similar to that of other studies.

Mean (± SD) Pharmacokinetic Parameters of Ibuprofen After Administration of Both Treatments

PK Parameter	*Treatment A: Oxy/Ibu 5/400 mg (n=12)*	*Treatment B: Ibu 400 mg (n=12)*	*p-value*
C_{max} (µg/mL)	24.5 ± 6.6	28.5 ± 11.4	0.4813
AUC_{0-t} (µg·hr/mL)	77.8 ± 27.6	87.6 ± 26.9	0.3398
$AUC_{0-\infty}$ (µg·hr/mL)	86.5 ± 34.8	98.6 ± 26.9*	0.2221
T_{max} (hr)	1.6 ± 1.0	2.3 ± 1.4	0.1975
$T_{1/2}$ (hr)	1.9 ± 0.4	2.0 ± 1.6*	0.4039

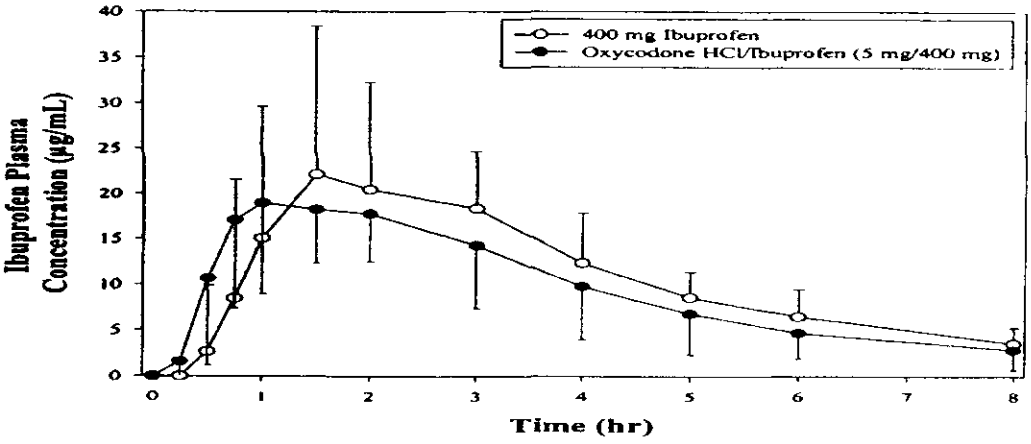
* n = 11

Mean (± SD) Pharmacokinetic Parameters of Oxycodone After Administration of Both Treatments

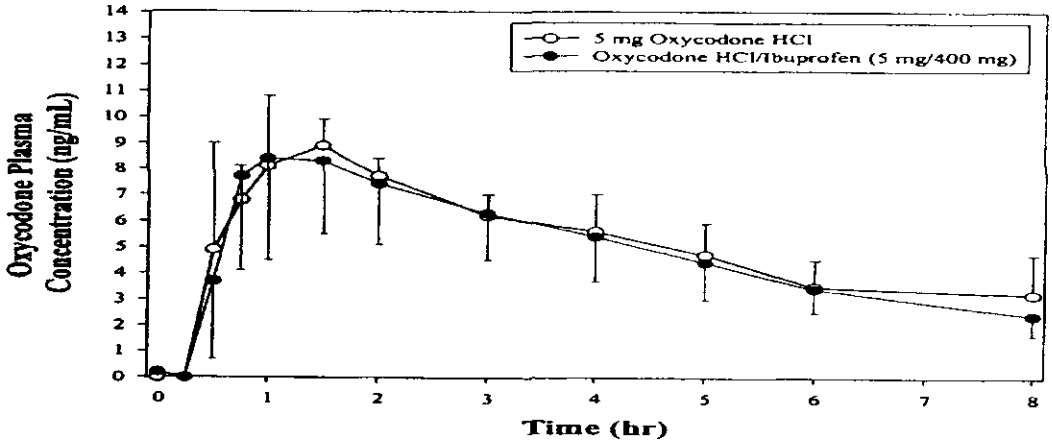
PK Parameter	*Treatment A: Oxy/Ibu 5/400 mg (n=12)*	*Treatment C: Oxy 5 mg (n=4)*	*Ratio Treatment A over C*
C_{max} (ng/mL)	9.8 ± 2.7	9.6 ± 0.7	1.02
AUC_{0-t} (ng·hr/mL)	39.4 ± 10.0	41.0 ± 3.9	0.96
$AUC_{0-\infty}$ (ng·hr/mL)	51.4 ± 13.9	56.3 ± 9.0	0.91
T_{max} (hr)	1.4 ± 1.2	1.1 ± 0.5	n/c
$T_{1/2}$ (hr)	3.4 ± 0.6	3.4 ± 0.8	n/c

n/c = not calculated.

Mean (± SD) Ibuprofen Plasma Concentrations (µg/mL) after Single Dose Oral Administration of the Two Treatments



Mean (± SD) Oxycodone Plasma Concentrations (ng/mL) after Single Dose Oral Administration of the Two Treatments



Does the to-be-marketed combination tablet show accumulation after multiple dosing?

From Oxy-PK-03 Study, there was, as expected based on the elimination half-life of total ibuprofen (T1/2 = 2 hr and the dosing interval τ = 6 hr), no accumulation of total ibuprofen (and S-ibuprofen) after multiple doses of oxycodone/ibuprofen (5 mg/400 mg) every 6 hours (study days 9-11).

There was moderate accumulation of oxycodone after multiple doses of oxycodone/ibuprofen (5 mg/400 mg) every six hours for 3 1/2 days, as expected, based on the elimination half life of oxycodone (T1/2 = 3.5 hours) and a dosing interval of 6 hours.

However, the trough concentrations obtained for both ibuprofen and oxycodone indicated that there were no accumulations of total ibuprofen and oxycodone.

Ibuprofen

	Single Dose				Multiple Dose
PK Parameter	5/400 fasted	5/400 fed	10/400 fasted	10/400 fed	5/400 t.i.d. for 3.5 days
C_{max} (µg/mL)	34.3 ± 4.3	28.8 ± 6.0	33.6 ± 10.5	24.3 ± 6.5	34.3 ± 7.6
AUC_{0-t} (µg•hr/mL)	120.4 ± 20.3	113.8 ± 18.3	117.7 ± 26.6	109.5 ± 32.8	105.1 ± 22.7*
$AUC_{0-\infty}$ (µg•hr/mL)	123.1 ± 19.3	116.7 ± 18.0	120.0 ± 26.0	113.2 ± 33.2	n/c
T_{max} (hr)	1.8 ± 0.9	2.1 ± 0.8	2.2 ± 1.3	2.0 ± 1.0	2.2 ± 1.9
$T_{1/2}$ (hr)	2.1 ± 0.3	2.1 ± 0.3	2.0 ± 0.2	2.7 ± 0.9	2.0 ± 0.3

n/c = not calculated *$AUC_{0-\tau}$ (τ = 6 hr)

Note that the Applicant is not seeking approval of the 10 mg/400 mg strength at this time.

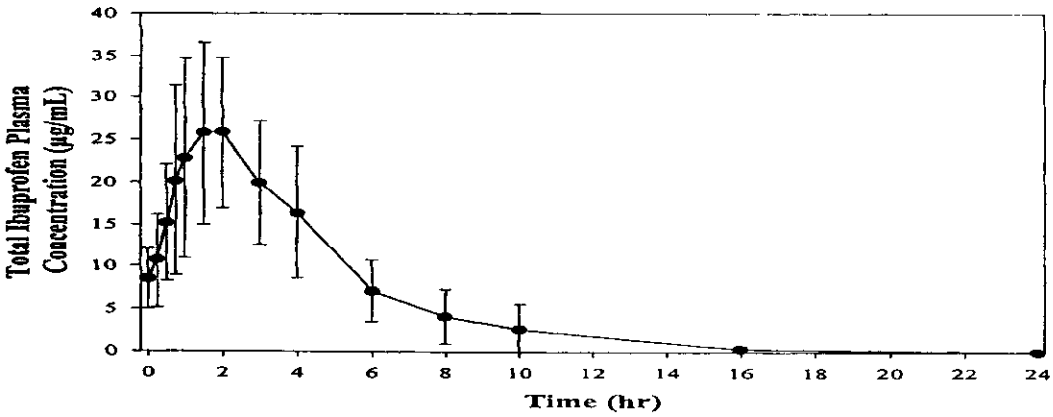
Oxycodone

	Single Dose				Multiple Dose
PK Parameter	5/400 fasted	5/400 fed	10/400 fasted	10/400 fed	5/400 t.i.d. for 3.5 days
C_{max} (µg/mL) observed dose-adjusted*	11.7 ± 2.5	13.6 ± 3.1	20.3 ± 5.9 10.2 ± 3.0	21.5 ± 4.7 10.7 ± 2.3	17.8 ± 4.1
AUC_{0-t} (µg•hr/mL) observed dose-adjusted	58.2 ± 15.0	70.3 ± 13.3	96.3 ± 27.7 48.2 ± 13.8	121.9 ± 28.0 60.9 ± 14.0	70.7 ± 1.4**
$AUC_{0-\infty}$ (µg•hr/mL) observed dose-adjusted	62.8 ± 14.9	75.2 ± 14.2	101.3 ± 28.4 50.6 ± 14.2	127.0 ± 29.3 63.5 ± 14.6	n/c
T_{max} (hr)	1.5 ± 0.6	2.0 ± 0.6	1.4 ± 0.4	2.1 ± 1.0	1.4 ± 0.5
$T_{1/2}$ (hr)	3.5 ± 0.4	3.5 ± 0.5	3.1 ± 0.4	3.4 ± 0.5	4.0 ± 0.7

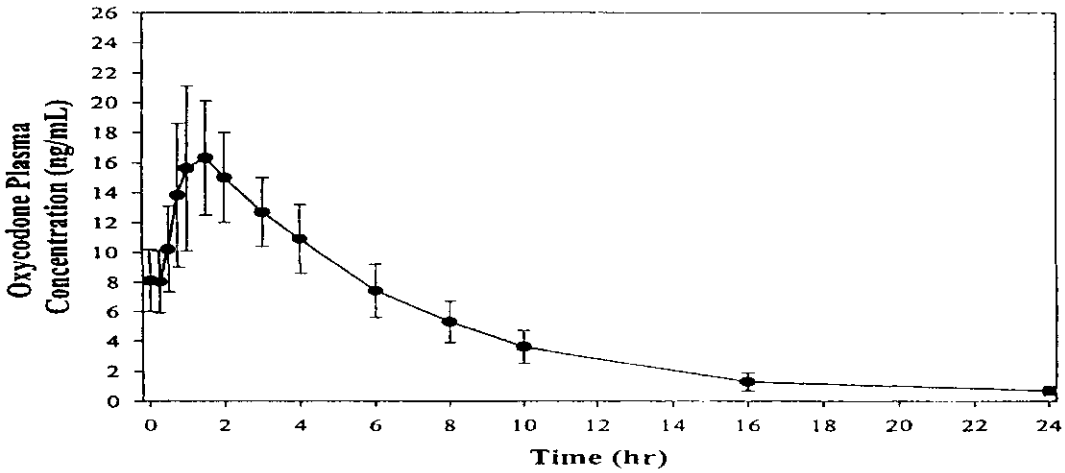
n/c = not calculated *dose-adjusted to the 5-mg dose **$AUC_{0-\tau}$ (τ = 6 hr)

Mean plasma profiles after multiple dosing:

Mean Total Ibuprofen Plasma Concentrations (µg/mL) after Multiple Dose Administration of One Oxycodone/Ibuprofen (5 mg/400 mg) Combination Tablet Every 6 Hours for 3 ½ Days.



Mean Oxycodone Plasma Concentrations (ng/mL) after Multiple Dose Administration of One Oxycodone/Ibuprofen (5 mg/400 mg) Combination Tablet Every 6 Hours for 3 ½ Days.



Accumulation ratios:

Accumulation of Total Ibuprofen after Multiple Doses (n=12).

Accumulation Index	Ratio of C_{max} on Day 12 and C_{max} on Day 1	Ratio of Trough Concentrations 6 hr Post-Dose on Day 12 and Day 1
1.16 ± 0.06	1.03 ± 0.20	1.04 ± 0.36

Accumulation of Oxycodone after Multiple Doses (n=12).

Accumulation Index	Ratio of C_{max} on Day 12 and C_{max} on Day 1	Ratio of Trough Concentrations 6 hr Post-Dose on Day 12 and Day 1
1.43 ± 0.09	1.63 ± 0.24	1.83 ± 0.32

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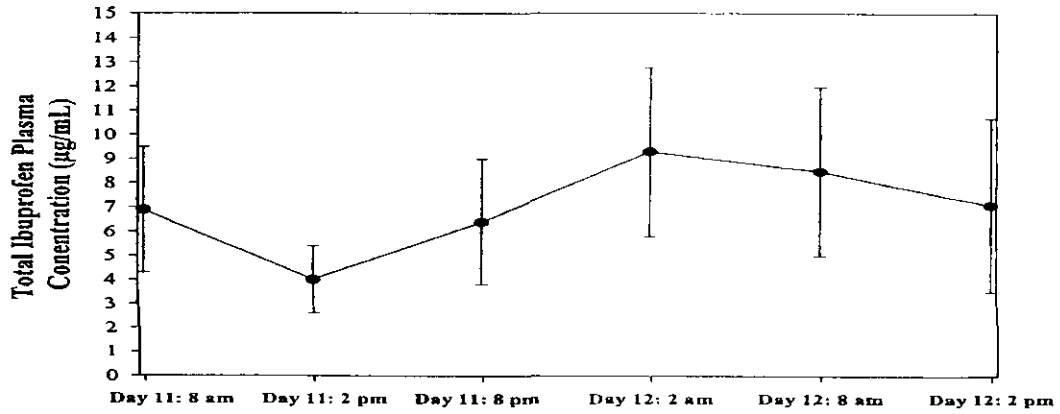
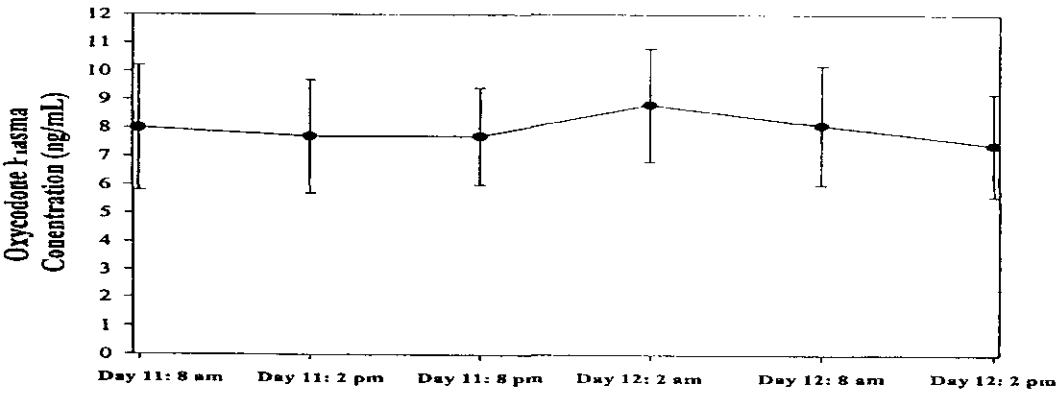
Trough Plasma concentrations:

Mean Trough Ibuprofen Plasma Concentrations (µg/mL) on Day 11 and Day 12 after Multiple Dose Administration of One Oxycodone/Ibuprofen (5 mg/400 mg) Combination Tablet Every 6 Hours.



Mean Trough Oxycodone Plasma Concentrations (ng/mL) on Day 11 and Day 12 after Multiple Dose Administration of One Oxycodone/Ibuprofen (5 mg/400 mg) Combination Tablet Every 6 Hours.



Does the to-be-marketed combination tablet show oxycodone dose proportionality?

Oxy-PK-03 Study

Under fasted conditions, peak plasma concentrations and systemic exposure of oxycodone show dose proportionality. Under fed conditions, a slight deviation from dose proportionality was observed, which may be due to the higher degree of variability in pharmacokinetic parameters in the presence of food. Note that the Applicant is not seeking approval of the 10 mg/ 400 mg strength at this time.

Ibuprofen

	Single Dose				Multiple Dose
PK Parameter	5/400 fasted	5/400 fed	10/400 fasted	10/400 fed	5/400 t.i.d. for 3.5 days
C_{max} (µg/mL)	34.3 ± 4.3	28.8 ± 6.0	33.6 ± 10.5	24.3 ± 6.5	34.3 ± 7.6
AUC_{0-t} (µg•hr/mL)	120.4 ± 20.3	113.8 ± 18.3	117.7 ± 26.6	109.5 ± 32.8	105.1 ± 22.7*
$AUC_{0-\infty}$ (µg•hr/mL)	123.1 ± 19.3	116.7 ± 18.0	120.0 ± 26.0	113.2 ± 33.2	n/c
T_{max} (hr)	1.8 ± 0.9	2.1 ± 0.8	2.2 ± 1.2	2.0 ± 1.0	2.2 ± 1.9
$T_{1/2}$ (hr)	2.1 ± 0.3	2.1 ± 0.3	2.0 ± 0.2	2.7 ± 0.9	2.0 ± 0.3

n/c = not calculated

*$AUC_{0-\tau}$ (τ = 6 hr)

Oxycodone

	Single Dose				Multiple Dose
PK Parameter	5/400 fasted	5/400 fed	10/400 fasted	10/400 fed	5/400 t.i.d. for 3.5 days
C_{max} (µg/mL) observed dose-adjusted*	11.7 ± 2.5	13.6 ± 3.1	20.3 ± 5.9 10.2 ± 3.0	21.5 ± 4.7 10.7 ± 2.3	17.8 ± 4.1
AUC_{0-t} (µg•hr/mL) observed dose-adjusted	58.2 ± 15.0	70.3 ± 13.3	96.3 ± 27.7 48.2 ± 13.8	121.9 ± 28.0 60.9 ± 14.0	70.7 ± 1.4**
$AUC_{0-\infty}$ (µg•hr/mL) observed dose-adjusted	62.8 ± 14.9	75.2 ± 14.2	101.3 ± 28.4 50.6 ± 14.2	127.0 ± 29.3 63.5 ± 14.6	n/c
T_{max} (hr)	1.5 ± 0.6	2.0 ± 0.6	1.4 ± 0.4	2.1 ± 1.0	1.4 ± 0.5
$T_{1/2}$ (hr)	3.5 ± 0.4	3.5 ± 0.5	3.1 ± 0.4	3.4 ± 0.5	4.0 ± 0.7

n/c = not calculated

*dose-adjusted to the 5-mg dose

**$AUC_{0-\tau}$ (τ = 6 hr)

Dose Proportionality of Oxycodone at the Dose Levels 5 and 10 mg.

Parameter	10 mg/400 mg (dose-normalized) vs. 5 mg/400 mg		
	Fasted (n=24)	Fed (n=24)	Fasted and Fed Combined (n=24)
C_{max} Ratio (%) p-value	 87 0.1373	 79 0.0180	 83 0.0416
AUC_{0-t} Ratio (%) p-value	 83 0.1090	 87 0.1123	 83 0.1204
$AUC_{0-\infty}$ Ratio (%) p-value	 81 0.0528	 84 0.0693	 83 0.0637

Oxy-PK1-97-02 Study

This study compared one oxycodone/ibuprofen 5 mg/400 mg tablet vs. two oxycodone/ibuprofen 5 mg/200 mg tablet. The objective of the study was to evaluate the dose proportionality of oxycodone at 5 and 10 mg when administered in the presence of the same amount of ibuprofen.

The study results showed that 90% C.I. of Cmax for total ibuprofen was 78-99. Otherwise dose proportionality was demonstrated at the dose levels of 5 and 10 mg oxycodone.

Pharmacokinetic parameter of total ibuprofen

Total Ibuprofen			
PK Parameter	**2 x 5 mg/200 mg Oxycodone/ Ibuprofen Test**	**5 mg/400 mg Oxycodone/ Ibuprofen Reference**	**90% CI**
C_{max} (µg/mL) Observed	28.2 ± 7.5	32.4 ± 9.7	78 - 99
AUC_{0-t} (µg•hr/mL) Observed	124.3 ± 30.0	124.0 ± 29.0	96 - 103
$AUC_{0-\infty}$ (µg•hr/mL) Observed	127.2 ± 29.4	126.5 ± 29.6	97 - 103

Pharmacokinetic Parameters (Mean ± SD) of S-Ibuprofen after Both Treatments (n=23).

PK Parameter	Two Oxycodone/Ibuprofen (5 mg/200 mg) Tablets Test	One Oxycodone/Ibuprofen (5 mg/400 mg) Tablet Reference	90% CI or p-value
C_{max} (µg/mL)	13.1 ± 3.3	15.2 ± 4.7	78 – 99
AUC_{0-t} (µg•hr/mL)	64.9 ± 18.4	66.5 ± 17.0	93 - 101
$AUC_{0-\infty}$ (µg•hr/mL)	67.9 ± 18.0	69.0 ± 17.6	94 - 102
T_{max} (hr)	2.2 ± 1.7	2.3 ± 1.6	p-value: 0.8388
$T_{1/2}$ (hr)	2.6 ± 0.8	2.5 ± 0.9	p-value: 0.6572

Pharmacokinetic parameters of oxycodone

Oxycodone			
PK Parameter	**2 x 5 mg/200 mg Oxycodone/ Ibuprofen Test**	**5 mg/400 mg Oxycodone/ Ibuprofen Reference**	**90% CI**
C_{max} (ng/mL)			
Observed	19.4 ± 5.6	10.2 ± 2.3	
Dose-adjusted	9.7 ± 2.8		87 - 103
AUC_{0-t} (ng•hr/mL)			
Observed	105.4 ± 32.1	47.4 ± 12.7	
Dose-adjusted	52.7 ± 16.0		104 - 117
$AUC_{0-\infty}$ (ng•hr/mL)			
Observed	111.2 ± 33.1	52.3 ± 13.4	
Dose-adjusted	55.9 ± 13.3		101 - 111

4.3 Intrinsic Factors

Are there any gender differences observed for combination tablet?

No significant differences between men and women were observed for the combination tablet (Study PK 04). Below text was scanned from the Applicant's submission.

9.3 Gender Analysis

A gender analysis was carried out for the pharmacokinetic parameters of total ibuprofen, S-ibuprofen, R-ibuprofen and oxycodone. C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ values were normalized by dose per body weight prior to the gender analysis. Table 9-4 displays the p-values for the gender comparisons for all analytes. No gender differences were detected for any of the pharmacokinetic parameters of total ibuprofen, S-ibuprofen,R-ibuprofen and oxycodone. Results of the statistical analysis are included in Appendix C: Statistical Output.

Results of the Gender Analysis for Total Ibuprofen, S-Ibuprofen, R-Ibuprofen and Oxycodone (p-values).

PK Parameter	Total Ibuprofen	S-Ibuprofen	R-Ibuprofen	Oxycodone
C_{max}	0.48	0.09	0.95	0.51
AUC_{0-t}	0.59	0.54	0.08	0.86
$AUC_{0-\infty}$	0.71	0.48	0.10	0.98

Are there any age differences observed for combination tablet?

The effect of age on the pharmacokinetics of acamprosate was not systematically evaluated.

4.4 Extrinsic Factors

Does food affect the bioavailability of to-be-marketed combination tablet ?

Oxy-PK-03 Study

The presence of food did alter the rate and extent of absorption of **ibuprofen** slightly (**decrease in 16%** and **5.2%** for Cmax and AUC0-inf, respectively) after single dose administration of oxycodone/ibuprofen (5 mg/400 mg). For the higher dose (10 mg/400 mg), the rate and extent of ibuprofen absorption **decreased by 27.7%** and **5.7%**, respectively.

The presence of food did alter the rate and extent of absorption of **oxycodone** slightly (**increase in 16.2%** and **19.7%** for Cmax and AUC0-inf, respectively) after single dose administration of oxycodone/ibuprofen (5 mg/400 mg). For the higher dose (10 mg/400 mg), the rate and extent of oxycodone absorption **increased by 5.9%** and **25.4%**, respectively.

Ibuprofen

	Single Dose				Multiple Dose
PK Parameter	5/400 fasted	5/400 fed	10/400 fasted	10/400 fed	5/400 t.i.d. for 3.5 days
C_{max} (µg/mL)	34.3 ± 4.3	28.8 ± 6.0	33.6 ± 10.5	24.3 ± 6.5	34.3 ± 7.6
AUC_{0-t} (µg•hr/mL)	120.4 ± 20.3	113.8 ± 18.3	117.7 ± 26.6	109.5 ± 32.8	105.1 ± 22.7*
$AUC_{0-\infty}$ (µg•hr/mL)	123.1 ± 19.3	116.7 ± 18.0	120.0 ± 26.0	113.2 ± 33.2	n/c
T_{max} (hr)	1.8 ± 0.9	2.1 ± 0.8	2.2 ± 1.2	2.0 ± 1.0	2.2 ± 1.9
$T_{1/2}$ (hr)	2.1 ± 0.3	2.1 ± 0.3	2.0 ± 0.2	2.7 ± 0.9	2.0 ± 0.3

n/c = not calculated *$AUC_{0,\tau}$ (τ = 6 hr)

Oxycodone

	Single Dose				Multiple Dose
PK Parameter	5/400 fasted	5/400 fed	10/400 fasted	10/400 fed	5/400 t.i.d. for 3.5 days
C_{max} (µg/mL) observed dose-adjusted*	11.7 ± 2.5	13.6 ± 3.1	20.3 ± 5.9 10.2 ± 3.0	21.5 ± 4.7 10.7 ± 2.3	17.8 ± 4.1
AUC_{0-t} (µg•hr/mL) observed dose-adjusted	58.2 ± 15.0	70.3 ± 13.3	96.3 ± 27.7 48.2 ± 13.8	121.9 ± 28.0 60.9 ± 14.0	70.7 ± 1.4**
$AUC_{0-\infty}$ (µg•hr/mL) observed dose-adjusted	62.8 ± 14.9	75.2 ± 14.2	101.3 ± 28.4 50.6 ± 14.2	127.0 ± 29.3 63.5 ± 14.6	n/c
T_{max} (hr)	1.5 ± 0.6	2.0 ± 0.6	1.4 ± 0.4	2.1 ± 1.0	1.4 ± 0.5
$T_{1/2}$ (hr)	3.5 ± 0.4	3.5 ± 0.5	3.1 ± 0.4	3.4 ± 0.5	4.0 ± 0.7

n/c = not calculated *dose-adjusted to the 5-mg dose **$AUC_{0,\tau}$ (τ = 6 hr)

4.5 General Biopharmaceutics

Are the clinical (Forest Lot #99229K ~) and to-be-marketed (Forest Lot# 00069C ~) formulations bioequivalent?

Yes, the data from Study PK-04 showed that two formulations were bioequivalent.

Total Ibuprofen

Total Ibuprofen			
PK Parameter	Commercial Formulation Test	Clinical Formulation Reference	90% CI
C_{max} (µg/mL)	34.3 ± 7.5	31.4 ± 7.5	98 - 124
AUC_{0-t} (µg•hr/mL)	131.4 ± 37.8	128.0 ± 38.7	97 - 109
$AUC_{0-\infty}$ (µg•hr/mL)	134.3 ± 38.6	129.5 ± 39.6	98 – 111

S-ibuprofen (active)

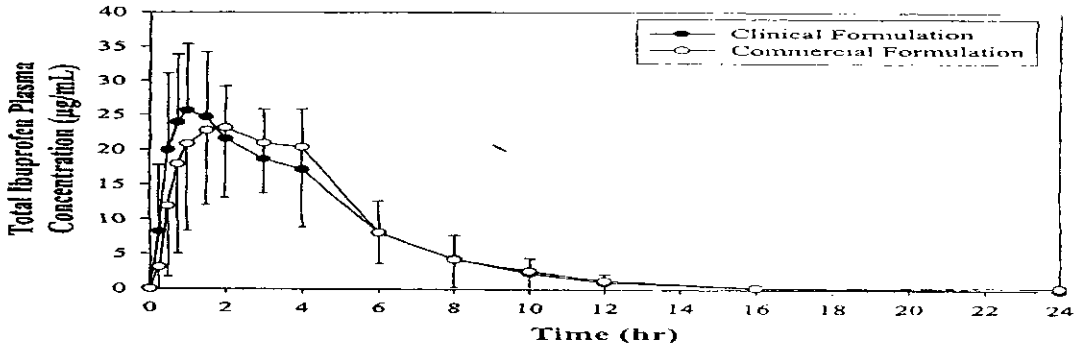
Pharmacokinetic Parameters (Mean ± SD) of S-Ibuprofen after Both Treatments (n=23).

PK Parameter	Commercial Formulation Test	Clinical Formulation Reference	90% CI or p-value
C_{max} (µg/mL)	16.3 ± 3.0	15.0 ± 3.0	98 – 121
AUC_{0-t} (µg•hr/mL)	68.1 ± 19.8	65.4 ± 18.6	99 - 109.
$AUC_{0-\infty}$ (µg•hr/mL)	70.5 ± 21.0	67.1 ± 19.3	99 – 111

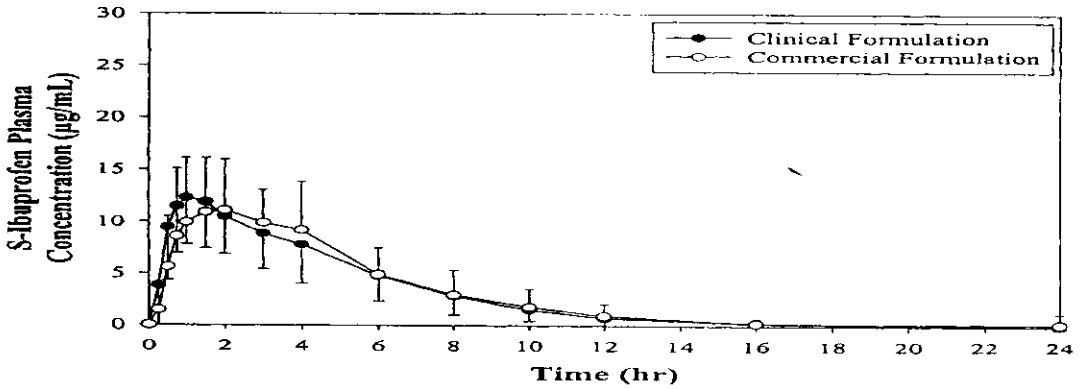
Oxycodone

Oxycodone			
PK Parameter	Commercial Formulation Test	Clinical Formulation Reference	90% CI
C_{max} (ng/mL)	10.2 ± 3.1	11.4 ± 3.7	80 - 100
AUC_{0-t} (ng•hr/mL)	52.5 ± 13.0	57.5 ± 17.4	87 – 97
$AUC_{0-\infty}$ (ng•hr/mL)	55.2 ± 13.2	60.6 ± 17.8	87 – 97

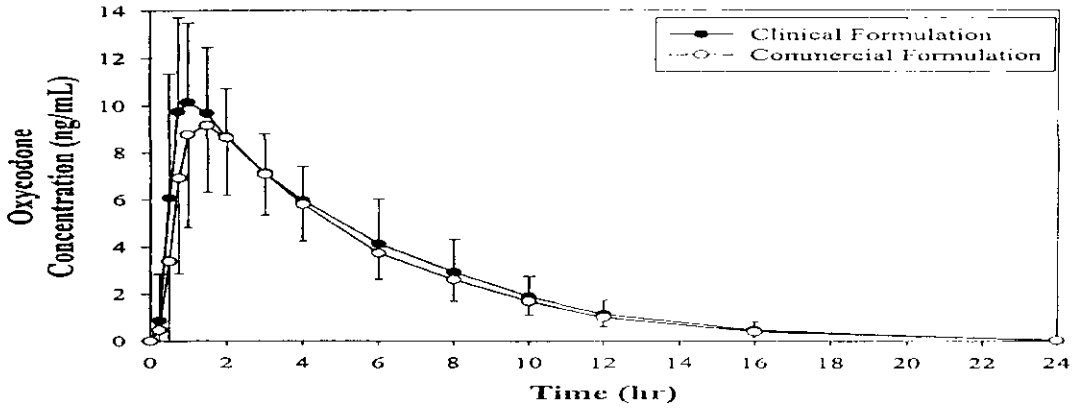
Total ibuprofen mean plasma vs. time profile



S-ibuprofen mean plasma vs. time profile



Oxycodone mean plasma vs. time profile



Is the proposed in vitro dissolution testing acceptable?

The Applicant's proposal is acceptable, however the submitted dissolution data displayed that C ⁻ at 30 minutes is also achievable. Therefore it is recommended that C ⁻ at 30 minutes for the combination drug product. The Applicant's original proposal for oxycodone/ibuprofen tablet:

> USP basket method at 100 RPM in 500 mL of pH 7.2 phosphate buffer at 37°C. The release is C ⁻ at ⁻

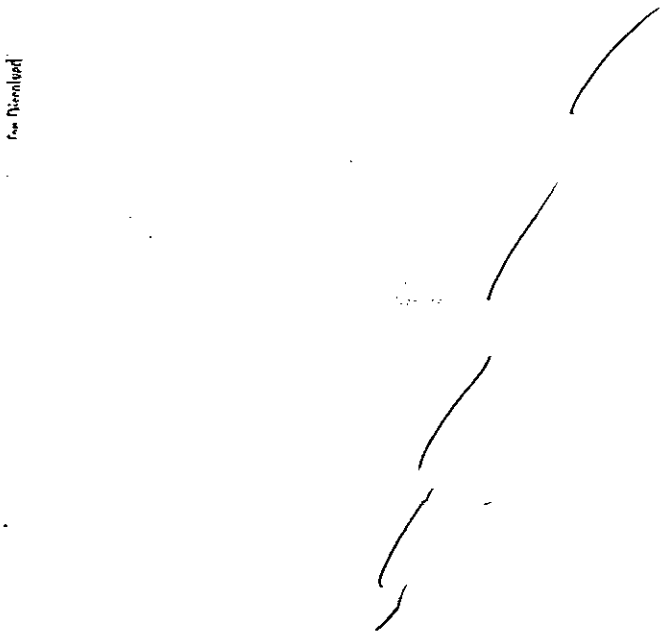
Additionally the Applicant submitted the dissolution profiles of two formulations utilized in bioequivalence study. Dissolution information was obtained by using 500 mL of phosphate buffer at 37 C, basket method at 150 RPM. The dissolution was performed with 12 tablets each. The dissolution of oxy and ibu was complete for both formulations after 30 min.

The profiles are different for two formulations, but the % dissolved at 30 min. appears to be the same. Since the two formulations are bioequivalent, it seems that there is no in-vitro and in-vivo correlation for this combination product.

Dissolution of Both Forest Formulations

	Forest Oxycodone/Ibuprofen Clinical Formulation		Forest Oxycodone/Ibuprofen Commercial Formulation	
Lot Number	99229K		00069C	
Date of Manufacture	10/12/1999		03/31/2000	
Active ingredient	Oxycodone: 5 mg Ibuprofen: 400 mg		Oxycodone: 5 mg Ibuprofen: 400 mg	
Time (min)	% Dissolved			
	Ibuprofen	Oxycodone	Ibuprofen	Oxycodone
5				
10				
15				
20				
25				
30				

Dissolution experiments were carried out in 500 mL of phosphate buffer at 37°C using the basket method at 150 RPM.



Time (hr)

Is the bioavailability of clinical combination tablet (Forest Lot #97002A wet granulation) similar with that of individual components given concomitantly?

In Oxy-PK1-96-01-000 study, the combination tablet was compared with Roxicodone® (oxycodone) 5 mg, which is not an approved drug product, given alone and Nuprin® (ibuprofen) 2 x 200 mg given alone in a three-way crossover study. The results showed that the rate and extent of absorption of oxycodone was similar (See table below).

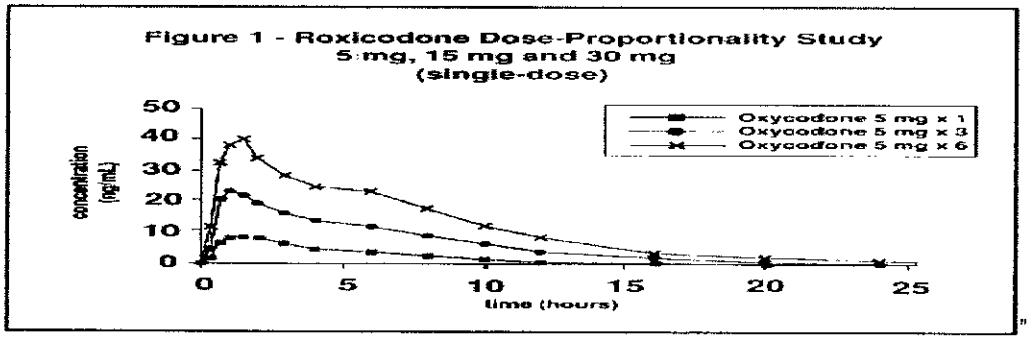
However, Cmax of total ibuprofen (and S-ibuprofen) from the combination tablet was lower than from Nuprin®. The Cmax differences observed may not be clinically significant.

With respect to utilizing the non-approved Roxicodone™ 5 mg tablet, there is no clinical pharmacology issue, since the currently approved Roxicodone™ 15 mg and 30 mg package insert provided the needed bioequivalence linkage between 5 mg and 15 mg.

The currently approved package insert, for ROXICODONE™ 15 mg and 30 mg tablets, stated that:

"ROXICODONE™ 15 mg tablets and 30 mg tablets are bioequivalent to the 5 mg ROXICODONE™ tablet (see Table 1 for pharmacokinetic parameters). Dose proportionality of oxycodone has been established using the ROXICODONE™ 5mg tablets at doses of 5 mg, 15 mg (three 5 mg tablets) and 30 mg (six 5 mg tablets) based on extent of absorption (AUC) (see Figure 1).

Table 1 Pharmacokinetic Parameters (Mean±SD)						
Dose/Parameters	AUC (ngxhr/mL)	Cmax (ng/mL)	Tmax (hr)	Cmin (ng/mL)	Cavg (ng/mL)	Half-Life (hr)
Single Dose Pharmacokinetics						
ROXICODONE 5 mg tabs × 3	133.2±33	22.3±8 2	1.8±1 8	n/a	n/a	3 73±0 9
ROXICODONE 15 mg tab	128.2±35.1	22.2±7.6	1 4±0 7	n/a	n/a	3.55±1 0
ROXICODONE Intensol 15 mg oral solution	130.6±34.7	21.1±6.1	1 9±1 5	n/a	n/a	3.71±0.8
ROXICODONE 30 mg tab	268.2±60.7	39.3±14.0	2 6±3.0	n/a	n/a	3.85±1.3
Food-Effect, Single Dose						
ROXICODONE 10 mg/10 mL oral sol'n (fasted)	105±6.2	19.0±3.7	1.25±0 5	n/a	n/a	2.9±0 4
ROXICODONE 10 mg/10 mL oral sol'n (fed)	133±25 2	17.7±3.0	2.54±1.2	n/a	n/a	3 3±0.5
Multiple-Dose Studies	AUC(72-84)					
ROXICODONE 5 mg tabs q6h × 14 doses	113.3±24.0	15.7±3.2	1.3±0.3	7 4±1.8	9.4±2 0	n/a
ROXICODONE 3.33 mg (3.33 mL) oral sol'n. q4h × 21 doses	99.0±24.8	12.9±3.1	1.0±0.3	7.2±2 3	9.7±2 6	n/a



PK parameters of total ibuprofen and oxycodone:

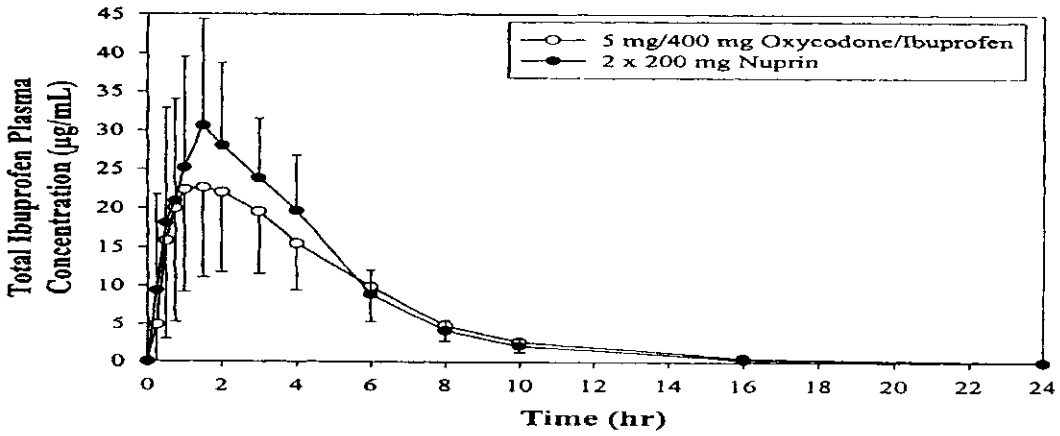
Total Ibuprofen				Oxycodone			
PK Parameter	Forest Oxycodone/ Ibuprofen (5 mg/400 mg) Test	Nuprin 2 x 200 mg Reference	90% CI	PK Parameter	Forest Oxycodone/ Ibuprofen (5 mg/400 mg) Test	Nuprin 2 x 200 mg Reference	90% CI
C_{max} (µg/mL)	30.4 ± 11.3	37.7 ± 9.4	67 - 91	C_{max} (ng/mL)	9.9 ± 2.2	9.4 ± 2.1	100 - 110
AUC_{0-t} (µg•hr/mL)	129.5 ± 35.6	144.6 ± 33.2	84 - 93	AUC_{0-t} (ng•hr/mL)	51.0 ± 12.7	47.4 ± 10.6	102 - 112
$AUC_{0-\infty}$ (µg•hr/mL)	132.4 ± 34.9	147.0 ± 32.6	85 - 94	$AUC_{0-\infty}$ (ng•hr/mL)	55.9 ± 13.3	52.3 ± 10.8	102 - 110

Note: For oxycodone, the reference product is with Roxicodone™ (oxycodone) 5 mg, not Nuprin®.

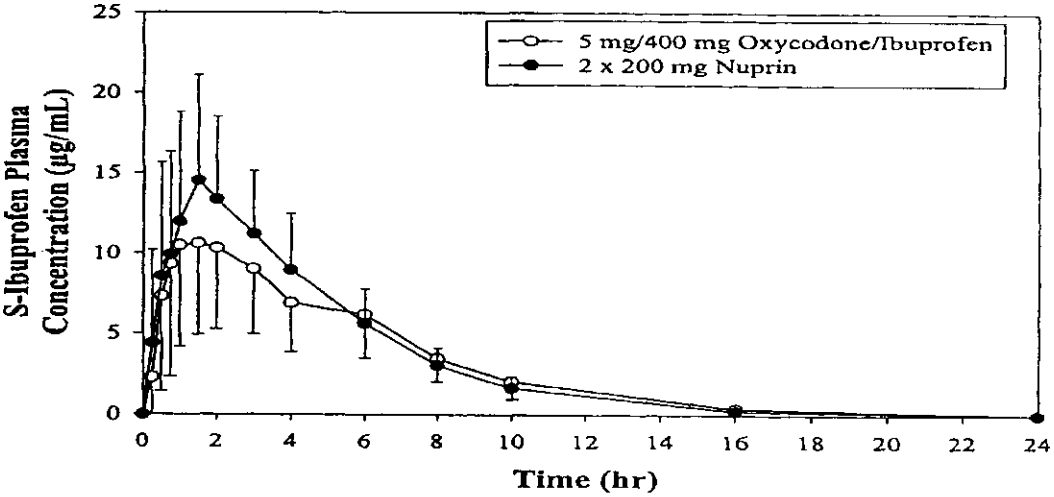
Pharmacokinetic Parameters (Mean ± SD) of S-Ibuprofen after Ibuprofen Treatments (n=24).

PK Parameter	Forest Oxycodone/Ibuprofen (5 mg/400 mg) Test	2 Nuprin® Tablets (400 mg ibuprofen) Reference	90% CI or p-value
C_{max} (µg/mL)	14.7 ± 5.0	17.8 ± 4.3	70 - 93
AUC_{0-t} (µg·hr/mL)	68.8 ± 20.3	75.2 ± 20.5	85 - 96
$AUC_{0-\infty}$ (µg·hr/mL)	71.5 ± 19.9	77.6 ± 20.1	86 - 97

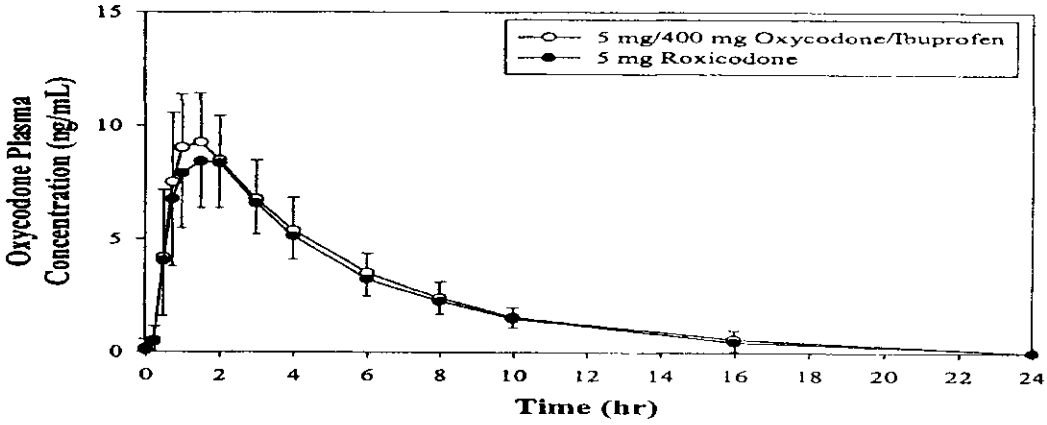
Mean Total Ibuprofen Plasma Concentrations (µg/mL) after Single Dose Oral Administration of One Tablet of Oxycodone/Ibuprofen (5 mg/400 mg) and Two Tablets of Nuprin® (2 x 200 mg of Ibuprofen).



Mean S-Ibuprofen Plasma Concentrations (µg/mL) after Single Dose Oral Administration of the Two Treatments



Mean Oxycodone Plasma Concentrations (ng/mL) after Single Dose Oral Administration of One Tablet of Oxycodone/Ibuprofen (5 mg/400 mg) and One Tablet of Roxicodone® (5 mg of Oxycodone).



4.6 Analytical

Overall, the Applicant submitted adequate assay information (e.g., standard curves, QCs, validation results, etc.) There are no issues identified within the NDA submission regarding analytical procedures. Below texts are scanned from the submission.

Oxycodone Assays:

5.1.3 Results

Note: Scanned text.

Ibuprofen Assays:

5.2.3 Results

Note: Scanned text.

5 Labeling

The Applicant's proposed labeling contain the clinical pharmacology information from the Applicant's oxycodone and ibuprofen combination drug product and literature information (e.g., individual oxycodone and ibuprofen distribution, metabolism and special population clinical pharmacology information). With respect to the Applicant generated oxycodone and ibuprofen information, it appears to be adequate. With respect to literature information, the values "transcribed" from the literature articles appear to be adequate. However, a thorough review of the proposed labeling will be conducted under a separate review for this combination drug product.

6 Appendix

6.1 Proposed labeling

The Applicant's proposed labeling attached.

17 Page(s) Withheld

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

____ § 552(b)(5) Deliberative Process

____ § 552(b)(5) Draft Labeling

6.2. Individual Study Reviews

NDA 21-378 oxycodone/ibuprofen individual study reports

Forest Study OXY-PK-04

Title of Report		
A Single-Center, Single-Dose, Two-Way Crossover, Open Label, Bioequivalence Study Comparing Oxycodone HCl/Ibuprofen Tablets (5 mg/400 mg) Used in Clinical Studies With Oxycodone HCl/Ibuprofen Tablets (5 mg/400 mg) Intended for Marketing in Healthy Volunteers		
Purpose of Study		
To demonstrate bioequivalence between the clinical and commercial formulations of oxycodone/ibuprofen (5 mg/400 mg)		
Date of Report	**Studies were carried out**	
February 26, 2001	**From**	**To**
	April 28, 2000	May 24, 2000
Statistical Methodology	**Phase of Development**	**Number of Subjects**
An analysis of variance (ANOVA) was performed on the pharmacokinetic parameters using the GLM procedures of SAS. The ANOVA model included the variables Sequence, Sex, Subject (nested in Sequence and Sex), Period, and Treatment.	Phase 1	24 (23 completed)
Design of Study	**Analytical Site**	**Mode of Administration**
Two-way crossover, open label, single dose, dose proportionality study	Forest Laboratories, Inc.	Oral – fasted
Clinical Site	**Formulations**	
	1. Oxycodone/Ibuprofen 5mg/400 mg tablet (Forest Laboratories, Inc., clinical formulation, Lot #: 99229K; Manufacture Date: 10/12/99) 2. Oxycodone/Ibuprofen 5mg/400 mg tablet (Forest Laboratories, Inc., commercial formulation, Lot #: 00069C; Manufacture Date: 3/31/2000)	

Test Formulations Administered	
Treatment A	**Treatment B**
One oxycodone/ibuprofen (5 mg/400 mg) tablet (clinical formulation), administered with 240 mL of water following a 10-hour overnight fast.	One oxycodone/ibuprofen (5 mg/400 mg) tablets (commercial formulation), administered with 240 mL of water following a 10-hour overnight fast.

Summary and Conclusions

The volunteers received the following treatments:

1. One oxycodone/ibuprofen (5 mg/400 mg) Tablet (Forest Laboratories, Inc.), **clinical formulation,** administered with 240 mL of water following a 10-hr overnight fast.

2. One oxycodone/ibuprofen (5 mg/400 mg) Tablet (Forest Laboratories, Inc.), **commercial formulation,** administered with 240 mL of water following a 10-hr overnight fast.

Blood samples were obtained at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 and 24 hours. Plasma samples were analyzed for oxycodone by and R-ibuprofen and S-ibuprofen by n with validated assays that displayed appropriate accuracy, linearity, reproducibility, and precision. Total ibuprofen concentrations were calculated by adding corresponding R-ibuprofen and S-ibuprofen concentrations.

Results:

Single dose administration of oxycodone/ibuprofen (5 mg/400 mg) was well tolerated and safe.

Total Ibuprofen				Oxycodone			
PK Parameter	Commercial Formulation Test	Clinical Formulation Reference	90% CI	PK Parameter	Commercial Formulation Test	Clinical Formulation Reference	90% CI
C_{max} (µg/mL)	34.3 ± 7.5	31.4 ± 7.5	98 - 124	C_{max} (ng/mL)	10.2 ± 3.1	11.4 ± 3.7	80 - 100
AUC_{0-t} (µg•hr/mL)	131.4 ± 37.8	128.0 ± 38.7	97 - 109	AUC_{0-t} (ng•hr/mL)	52.5 ± 13.0	57.5 ± 17.4	87 – 97
$AUC_{0-\infty}$ (µg•hr/mL)	134.3 ± 38.6	129.5 ± 39.6	98 – 111	$AUC_{0-\infty}$ (ng•hr/mL)	55.2 ± 13.2	60.6 ± 17.8	87 – 97

The bioequivalence between the clinical and commercial formulations of oxycodone/ibuprofen (5 mg/400 mg) was demonstrated, based on the two one-sided test procedure (90% confidence interval) using log-transformed data with the clinical formulation as the reference.

Statistical analysis

7.2 Statistical Testing

An analysis of variance (ANOVA) was performed on the pharmacokinetic parameters using the GLM procedures of SAS. The ANOVA model included the following factors: Sequence, Sex, Subject (nested within sequence and Sex), Sex, Period, and Treatment. Because subjects are nested within a sequence and sex, the sequence effect (thus, the carryover effect) and gender effects were tested against the mean square for Subject (Sequence and Sex) from the ANOVA model. The residual error term was used to test all other main effects. In the GLM procedure, the statements of LSMEANS and ESTIMATE were used to calculate least square means for treatment effects. The plasma concentration data and the derived parameters tend to be skewed to the lower side of the distribution; therefore, the PK parameters of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were log-transformed before they were analyzed by the GLM procedure. The clinical formulation was used as the reference. The 90% confidence intervals for the ratio between the test and reference means were constructed for the pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. For the comparison of T_{max} and $T_{1/2}$ values, p-values from the ANOVA were provided. The statistical output for all analytes is included in Appendix C.

7.1.14 Demographics

Demographic Variable	All Completed Subjects (n =23)	All Completed Male Subjects (n=12)	All Completed Female Subjects (n=11)
Mean Age (years)	27.8	27.1	28.5
Min – Max	18 – 35	20 – 35	18 – 35
Standard Deviation	5.4	4.5	6.3
Mean Weight (kg)	67.7	74.2	60.7
Min – Max	44.1 – 82.7	59.1 – 82.7	44.1 – 82.7
Standard Deviation	18.1	7.0	13.1
Mean Height (cm)	166.9	173.6	159.6
Min – Max	149.9 – 190.5	165.1 – 190.5	149.9 – 172.7
Standard Deviation	10.2	7.5	7.4

Results:

1. Total Ibuprofen

Total Ibuprofen			
PK Parameter	Commercial Formulation Test	Clinical Formulation Reference	90% CI
C_{max} (µg/mL)	34.3 ± 7.5	31.4 ± 7.5	98 - 124
AUC_{0-t} (µg•hr/mL)	131.4 ± 37.8	128.0 ± 38.7	97 - 109
$AUC_{0-\infty}$ (µg•hr/mL)	134.3 ± 38.6	129.5 ± 39.6	98 – 111

2. S-ibuprofen (active)

Pharmacokinetic Parameters (Mean ± SD) of S-Ibuprofen after Both Treatments (n=23).

PK Parameter	Commercial Formulation Test	Clinical Formulation Reference	90% CI or p-value
C_{max} (µg/mL)	16.3 ± 3.0	15.0 ± 3.0	98 – 121
AUC_{0-t} (µg•hr/mL)	68.1 ± 19.8	65.4 ± 18.6	99 - 109
$AUC_{0-\infty}$ (µg•hr/mL)	70.5 ± 21.0	67.1 ± 19.3	99 – 111

3. Oxycodone

Oxycodone			
PK Parameter	Commercial Formulation Test	Clinical Formulation Reference	90% CI
C_{max} (ng/mL)	10.2 ± 3.1	11.4 ± 3.7	80 - 100
AUC_{0-t} (ng•hr/mL)	52.5 ± 13.0	57.5 ± 17.4	87 – 97
$AUC_{0-\infty}$ (ng•hr/mL)	55.2 ± 13.2	60.6 ± 17.8	87 – 97

4. Gender analysis

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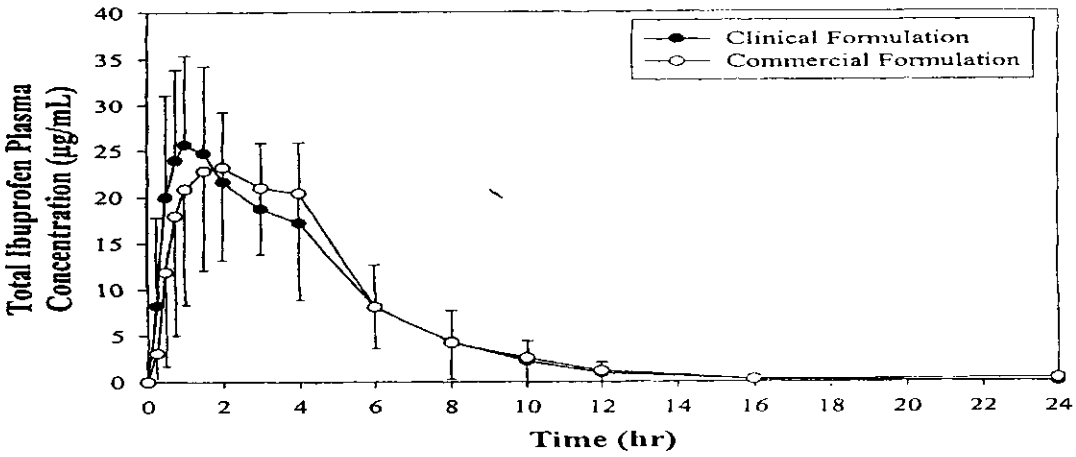
9.3 Gender Analysis

A gender analysis was carried out for the pharmacokinetic parameters of total ibuprofen, S-ibuprofen, R-ibuprofen and oxycodone. C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ values were normalized by dose per body weight prior to the gender analysis. Table 9-4 displays the p-values for the gender comparisons for all analytes. No gender differences were detected for any of the pharmacokinetic parameters of total ibuprofen, S-ibuprofen,R-ibuprofen and oxycodone. Results of the statistical analysis are included in Appendix C: Statistical Output.

Results of the Gender Analysis for Total Ibuprofen, S-Ibuprofen, R-Ibuprofen and Oxycodone (p-values).

PK Parameter	Total Ibuprofen	S-Ibuprofen	R-Ibuprofen	Oxycodone
C_{max}	0.48	0.09	0.95	0.51
AUC_{0-t}	0.59	0.54	0.08	0.86
$AUC_{0-\infty}$	0.71	0.48	0.10	0.98

5. Total ibuprofen mean plasma vs. time profile



6. S-ibuprofen mean plasma vs. time profile

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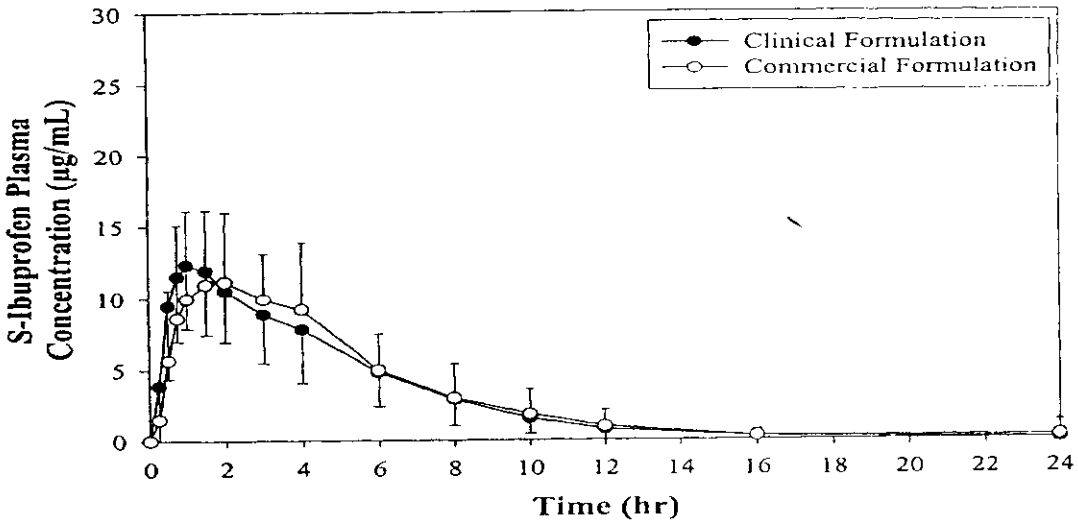
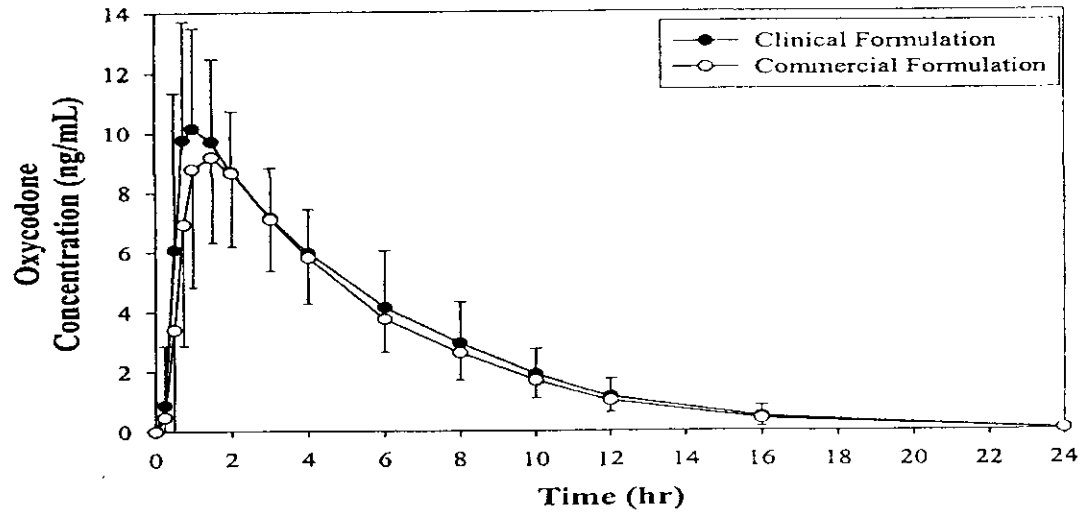


7. Oxycodone mean plasma vs. time profile



7.2 8. Dissolution of two formulations

Dissolution information was obtained by using 500 mL of phosphate buffer at 37 C, basket method at 150 RPM. The dissolution was performed with 12 tablets each. The dissolution of oxy and ibu was complete for both formulations after 30 min.

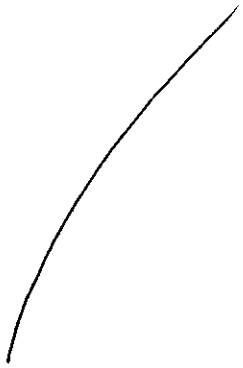
The profiles are different for two formulations, but the % dissolved at 30 min. appears to be the same. Since the two formulations are bioequivalent, it seems that there is no in-vitro and in-vivo correlation for this combination product.

Dissolution of Both Forest Formulations

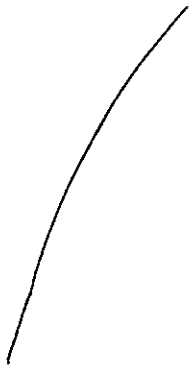
	Forest Oxycodone/Ibuprofen Clinical Formulation		Forest Oxycodone/Ibuprofen Commercial Formulation	
Lot Number	99229K		00069C	
Date of Manufacture	10/12/1999		03/31/2000	
Active ingredient	Oxycodone: 5 mg Ibuprofen: 400 mg		Oxycodone: 5 mg Ibuprofen: 400 mg	
Time (min)	**% Dissolved**			
	Ibuprofen	Oxycodone	Ibuprofen	Oxycodone
5				
10				
15				
20				
25				
30				

Dissolution experiments were carried out in 500 mL of phosphate buffer at 37°C using the basket method at 150 RPM.

a. Percent ibuprofen dissolved vs. time



b. Percent oxycodone dissolved vs. time



Time (hr)

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Forest Study OXY-PK1-96-01-000

Title of Report		
A Three-Way Crossover, Single Dose, Comparative Bioavailability Study of Oxycodone and Ibuprofen from a Combination Oxycodone HCL/Ibuprofen Tablet or Ibuprofen Tablets or Oxycodone HCl Tablet Administered Separately to Human Volunteers		
Purpose of Study		
To compare the rate and extent of absorption of oxycodone and ibuprofen when administered in combination or separately.		
Date of Report	**Studies were carried out**	
March 29, 2001	**From**	**To**
	March 18, 1997	April 3, 1997
Statistical Methodology	**Phase of Development**	**Number of Subjects**
An analysis of variance (ANOVA) was performed on the pharmacokinetic parameters using the GLM procedures of SAS. The ANOVA model included the variables Sequence, Subject (nested in Sequence and Gender), Gender, Period and Treatment.	Phase 1	24 (24 completed)
Design of Study	**Analytical Site**	**Mode of Administration**
Open Label, Three-Way Crossover Study	Forest Laboratories, Inc.	Oral
Clinical Site	**Formulations**	
	1. Oxycodone/Ibuprofen combination 5 mg/400 mg tablet (Forest Laboratories, Inc., Lot #: 97002A; Manufacture Date: 1/13/1997) 2. Roxicodone® 5 mg tablet (Roxane Laboratories, Lot #: 962439, Expiration Date: 11/1/1998) 3. Nuprin® 200 mg tablet (Bristol Myer Squibbs Company, Lot # 603151, Date of Expiration: 10/2000)	

Test Formulations Administered	
Treatment A	**Treatment B**
One oxycodone HCl/ibuprofen (5 mg/400 mg) tablet (Forest Laboratories, Inc.), administered with 240 mL of water following a 10-hour overnight fast.	One Roxicodone® 5 mg tablet (Roxane Laboratories, Inc.), administered with 240 mL of water following a 10-hour overnight fast.
Treatment C	
Two Nuprin® 200 mg tablets (Bristol Myers Squibb Co.), administered with 240 mL of water following a 10-hour overnight fast.	

Summary and Conclusions

A total of 24 healthy young male or female subjects received the following treatments:

1. Single oral dose of one oxycodone HCl/ibuprofen (5mg/400mg) Tablet (Forest Laboratories, Inc.), administered with 240 mL of water following a 10-hour overnight fast.

2. Single oral dose of one Roxicodone® 5 mg Tablet (Roxane Laboratories, Inc.), administered with 240 mL of water following a 10-hour overnight fast.

3. Single oral dose of two Nuprin® 200 mg Tablets (Bristol Myers Squibb Co.), administered with 240 mL of water following a 10-hour overnight fast.

This study was not designed to be a bioequivalence study but rather as a comparative bioavailability study.

Plasma and urine samples were analyzed for oxycodone, R-ibuprofen and S-ibuprofen with validated assays that displayed appropriate accuracy, linearity, reproducibility and precision. Total ibuprofen concentrations were calculated by adding the corresponding R-ibuprofen and S-ibuprofen plasma concentrations.

Results:

The combined administration of oxycodone and ibuprofen from the Forest formulation was well tolerated and safe.

Total Ibuprofen				Oxycodone			
PK Parameter	Forest Oxycodone/ Ibuprofen (5 mg/400 mg) Test	Nuprin 2 x 200 mg Reference	90% CI	PK Parameter	Forest Oxycodone/ Ibuprofen (5 mg/400 mg) Test	Nuprin 2 x 200 mg Reference	90% CI
C_{max} (µg/mL)	30.4 ± 11.3	37.7 ± 9.4	67 - 91	C_{max} (ng/mL)	9.9 ± 2.2	9.4 ± 2.1	100 - 110
AUC_{0-t} (µg·hr/mL)	129.5 ± 35.6	144.6 ± 33.2	84 - 93	AUC_{0-t} (ng·hr/mL)	51.0 ± 12.7	47.4 ± 10.6	102 - 112
$AUC_{0-\infty}$ (µg·hr/mL)	132.4 ± 34.9	147.0 ± 32.6	85 - 94	$AUC_{0-\infty}$ (ng·hr/mL)	55.9 ± 13.3	52.3 ± 10.8	102 - 110

Similar pharmacokinetic profiles were obtained for oxycodone and total (racemic) ibuprofen after combined administration of oxycodone and ibuprofen (5 mg/400 mg) from the Forest formulation, compared to the administration of oxycodone (5 mg) and ibuprofen (400 mg) separately. Renal excretion of unchanged total ibuprofen was low (less than 0.2% of the administered dose). For oxycodone, less than 4% of the administered dose was excreted unchanged in urine. No gender effects were observed for the major pharmacokinetic parameters of oxycodone and total ibuprofen.

Pharmacokinetic Parameters (Mean ± SD) of S-Ibuprofen after Ibuprofen Treatments (n=24).

PK Parameter	Forest Oxycodone/Ibuprofen (5 mg/400 mg) Test	2 Nuprin® Tablets (400 mg ibuprofen) Reference	90% CI or p-value
C_{max} (µg/mL)	14.7 ± 5.0	17.8 ± 4.3	70 - 93
AUC_{0-t} (µg·hr/mL)	68.8 ± 20.3	75.2 ± 20.5	85 - 96
$AUC_{0-\infty}$ (µg·hr/mL)	71.5 ± 19.9	77.6 ± 20.1	86 - 97

There were no period or sequence (carry-over) effects for total ibuprofen, S-ibuprofen and R-ibuprofen. While the rate of release of total ibuprofen and S-ibuprofen from the Forest combination formulation was lower than from Nuprin®, the extent of release of total ibuprofen and S-ibuprofen was similar between formulations. Values for T_{max} were not different between formuations for total ibuprofen. $T_{1/2}$ was shorter after administration of ibuprofen alone, compared to the Forest combination formulation. For S-ibuprofen, T_{max} and $T_{1/2}$ values were similar after administration of both ibuprofen treatments.

The rate and extent of absorption of oxycodone from the Forest formulation and from Roxicodone® was similar. Values for T_{max} and $T_{1/2}$ were similar after the administration of both oxycodone treatments.

There were no sequence (carry-over) effects for oxycodone.

1. Treatment A

Name:	Oxycodone HCl/Ibuprofen
Route:	Oral
Dose per tablet:	5 mg oxycodone/400 mg ibuprofen
Manufacturer:	Forest Laboratories, Inc.
Lot Number:	97002A
Date of Manufacture:	1/13/1997

2. Treatment B

Name	Roxicodone®
Route:	Oral
Dose per tablet:	5 mg
Manufacturer:	Roxane Laboratories, Inc.
Lot Number:	962439
Expiration Date:	11/1/1998

3. Treatment C

Name:	Nuprin®
Route:	Oral
Dose per tablet:	200 mg
Manufacturer:	Bristol Meyers Squibb Co.
Lot Number:	603151
Expiration Date:	10/2000

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4.4.3 Diet and Fluid Control

No xanthine-containing food or beverage was consumed for forty-eight hours prior to dosing and until the last blood sample was collected in each study period. Subjects also refrained from the use of alcohol for forty-eight hours prior to and throughout the course of this study.

Water was allowed *ad libitum* except for the period from one hour prior to drug administration to one hour after dosing.

Standardized bland low-fat meals were provided to all subjects at 1200 hours and 1700 hours each day the subject was institutionalized during the study. A snack was provided at 2100 hours on each day of institutionalization. On Day 2, breakfast was provided at approximately 0900 hours. The meals were free of xanthine-containing compounds (including caffeine) with less than 20 grams of fat each and were identical during each study period.

Subjects were required to consume the entire contents of each meal and snack. When meal times coincided with the vital signs and blood sampling schedule, vital signs were measured first, then blood samples were drawn prior to meals.

A copy of the menu with the total nutritional content (fat, protein, carbohydrates and calories) of each component of each meal and snack is included in the final clinical report (see Appendix H – Clinical Summary).

No concurrent medication was permitted during the study. Subjects were instructed not to take any drugs for at least 14 days prior to and during the course of the study. They were specifically reminded that this included aspirin, ibuprofen, acetaminophen, naproxen, other over-the-counter analgesics, prescription medications, vitamin preparations, cough syrup, etc. Concomitant medication use was assessed at the start of each study period.

Fourteen blood samples were collected during each period of the study according to the following schedule:

> 0 (pre-dose), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 16 and 24 hours after dose administration

Urine samples from each subject were collected for the determination of unchanged oxycodone and unchanged R-ibuprofen and S-ibuprofen concentrations on each day of dosing at the following intervals:

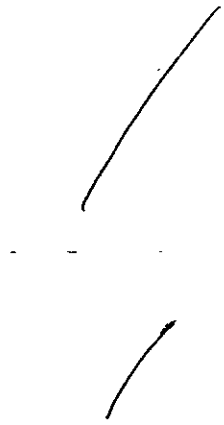
> 0 - 2, 2 - 4, 4 - 6, 6 - 8, 8 - 10, 10 - 12 and 12 - 24 hours after the 0800 hours dose administration.

The subjects were instructed to void urine completely prior to dosing at the beginning of each period. The clock times of all urine collections were recorded and reported for each subject along with the total volume and pH of the voided urine for each time interval. All urine containers were labeled at the site with the subject number, period number, urine collection time and a code number that was provided by the Sponsor.

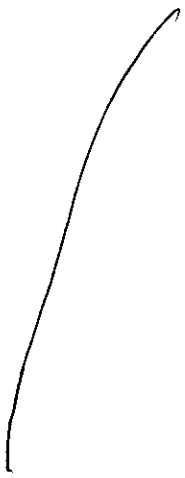
The bioanalytical procedures used to measure plasma and urine drug concentrations were HPLC or GC/MS methods, which were validated to demonstrate the accuracy, linearity, reproducibility, and precision of the analytical procedure, together with a standard calibration curve and data exhibiting stability under freeze-thaw conditions are included in the method validation reports (Appendix I). Bioanalytical reports are included in Appendix J. Chromatograms for the various analytes are included in Appendix K.

5.1 Determination of Oxycodone in Plasma

This method (Forest Method) utilized a
, to quantitate oxycodone in plasma.



5.2 Determination of R-Ibuprofen and S-Ibuprofen in Plasma



5.3 Determination of Oxycodone in Urine

5.4 Determination of R-Ibuprofen and S-Ibuprofen in Urine

7.2 Statistical Testing

An analysis of variance (ANOVA) was performed on the pharmacokinetic parameters using the GLM procedures of SAS. The ANOVA model included the following factors: Sequence, Sex, Subject (nested within Sequence and Gender), Gender, Period, and Treatment. Because subjects are nested within a sequence and gender, the sequence effect (thus, the carryover effect) and gender effects were tested against the mean square for Subject (Sequence and Gender) from the ANOVA model. The residual error term was used to test all other main effects. In the GLM procedure, the statements of LSMEANS and ESTIMATE were used to calculate least square means for treatment effects. The plasma concentration data and the derived parameters tend to be skewed to the lower side of the distribution; therefore, the PK parameters of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were log-transformed before they were analyzed by the GLM procedure. Roxicodone® and Nuprin® were used as the reference formulations. The 90% confidence intervals for the ratio between the test and reference means were constructed for the pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. For the comparison of T_{max} and $T_{1/2}$ values, p-values from the ANOVA were provided. The statistical output for all analytes is included in Appendix C.

8 Results

1. Demographics

Summary of Demographic Characteristics of Subjects who Completed the Study

Demographic Variable	All Subjects (n=24)	Male Subjects (n=12)	Female Subjects (n=12)
Mean Age (years)	28.3	25.7	30.3
Min - Max	18 – 35	18 – 32	24 – 35
Standard Deviation	4.8	5.1	3.7
Mean Weight (kg)	68.9	72.4	64.5
Min - Max	53.1 – 105.2	60.3 – 105.0	53.1 – 80.7
Standard Deviation	11.7	12.5	9.2
Mean Height (cm)	165.9	173.1	158.9
Min – Max	145.0 – 191.0	163.0 – 191.0	145.0 – 173.0
Standard Deviation	10.1	7.2	7.4

2. Urinary output:

Mean Urinary Parameters for Total Ibuprofen after Administration of Ibuprofen Treatments (n=24).

PK Parameter	Forest Oxycodone/Ibuprofen (5 mg/400 mg)) Test	2 Nuprin® Tablets (2 x 200 mg ibuprofen) Reference	p-value
$A_{ex(0\text{-}24hr)}$ (µg)	538.0 ± 433.4	588.2 ± 590.9	0.6115
% Dose Excreted	0.13 ± 0.11	0.15 ± 0.15	0.6038

No differences between formulations were found in the excretion of total ibuprofen or S-ibuprofen.

Mean Urinary Parameters for S-Ibuprofen after Administration of Ibuprofen Treatments (n=24).

PK Parameter	Forest Oxycodone/Total Ibuprofen (5 mg/400 mg) Test	2 x 200 mg Nuprin Tablets Reference	p-value
$A_{ex(0\text{-}24hr)}$ (µg)	517.5 ± 423.1	556.7 ± 546.7	0.6581
% Dose Excreted	0.10 ± 0.09	0.11 ± 0.11	0.6887

Mean Urinary Parameters for Oxycodone after Administration of Both Oxycodone Treatments (n=24).

PK Parameter	Forest Oxycodone/Ibuprofen (5 mg/400 mg) Test	Roxicodone (5 mg) Reference	p-value
$A_{ex(0\text{-}24hr)}$ (µg)	179.8 ± 72.8	195.9 ± 76.4	0.3047
% Dose Excreted	3.6 ± 1.5	3.9 ± 1.5	0.3096

Urinary clearance was not significantly different between the two formulations.

3. Gender analysis: It should be noted that in the report that there is no statement indicating whether gender analysis was conducted with parameters normalized by dose per body weight.

Results of the Gender Analysis for Pharmacokinetic Parameters of Total Ibuprofen.

PK Parameter	Male (n=12)	Female (n=12)	p-value
C_{max} (ng/mL)	33.9 ± 10.7	34.3 ± 11.3	0.7344
AUC_{0-t} (ng·hr/mL)	139.4 ± 37.4	134.8 ± 32.8	0.8308
$AUC_{0-\infty}$ (ng·hr/mL)	142.0 ± 37.0	137.5 ± 31.9	0.8331
T_{max} (hr)	1.8 ± 1.5	2.3 ± 1.7	0.6588
$T_{1/2}$ (hr)	2.2 ± 0.61	2.0 ± 0.5	0.3274
$A_{ex(0\text{-}24hr)}$ (µg)	526.9 ± 363.7	599.4 ± 635.0	0.6996
% Dose Excreted in Urine	0.13 ± 0.09	0.15 ± 0.16	0.7069

No gender differences were found for any of the pharmacokinetic parameters of total ibuprofen. Similarly, no gender differences were detected for the individual ibuprofen enantiomers (Appendix E).

Results of the Gender Analysis for Pharmacokinetic Parameters of S-Ibuprofen.

PK Parameter	Male (n=12)	Female (n=12)	p-value
C_{max} (ng/mL)	16.4 ± 5.0	16.1 ± 4.8	0.9775
AUC_{0-t} (ng·hr/mL)	75.3 ± 24.7	68.7 ± 14.9	0.4577
$AUC_{0-\infty}$ (ng·hr/mL)	77.9 ± 24.2	71.2 ± 14.4	0.4344
T_{max} (hr)	1.8 ± 1.5	2.6 ± 1.8	0.5171
$T_{1/2}$ (hr)	2.6 ± 0.7	2.3 ± 0.5	0.0791
$A_{ex(0\text{-}24hr)}$ (µg)	499.1 ± 327.4	575.1 ± 607.1	0.7101
% Dose Excreted in Urine	0.10 ± 0.07	0.12 ± 0.12	0.6983

Results of the Gender Analysis for Pharmacokinetic Parameters of R-Ibuprofen.

PK Parameter	Male (n=12)	Female (n=12)	p-value
C_{max} (ng/mL)	17.6 ± 5.9	18.2 ± 6.9	0.6275
AUC_{0-t} (ng·hr/mL)	63.1 ± 15.5	65.2 ± 19.8	0.7789
$AUC_{0-\infty}$ (ng·hr/mL)	64.3 ± 15.7	66.4 ± 20.1	0.7875
T_{max} (hr)	1.9 ± 1.5	2.1 ± 1.5	0.8699
$T_{1/2}$ (hr)	1.7 ± 0.5	1.5 ± 0.6	0.3230

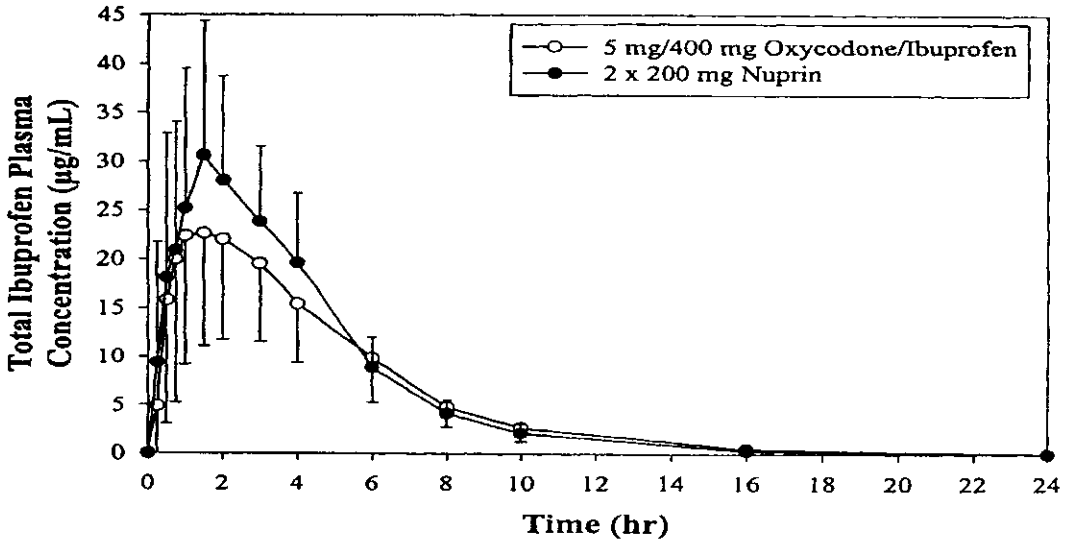
Results of the Gender Analysis for Pharmacokinetic Parameters of Oxycodone.

PK Parameter	Male (n=12)	Female (n=12)	p-value
C_{max} (ng/mL)	9.2 ± 1.8	10.2 ± 2.4	0.1350
AUC_{0-t} (ng·hr/mL)	45.2 ± 10.9	53.2 ± 11.3	0.0583
$AUC_{0-\infty}$ (ng·hr/mL)	50.5 ± 11.7	57.7 ± 11.7	0.0792
T_{max} (hr)	1.2 ± 0.4	1.5 ± 0.5	0.1860
$T_{1/2}$ (hr)	3.7 ± 0.6	3.7 ± 0.8	0.8199
$A_{ex(0-24hr)}$ (µg)	174.5 ± 80.7	201.2 ± 66.2	0.0178
% Dose Excreted in Urine	3.5 ± 1.6	4.0 ± 1.3	0.0194

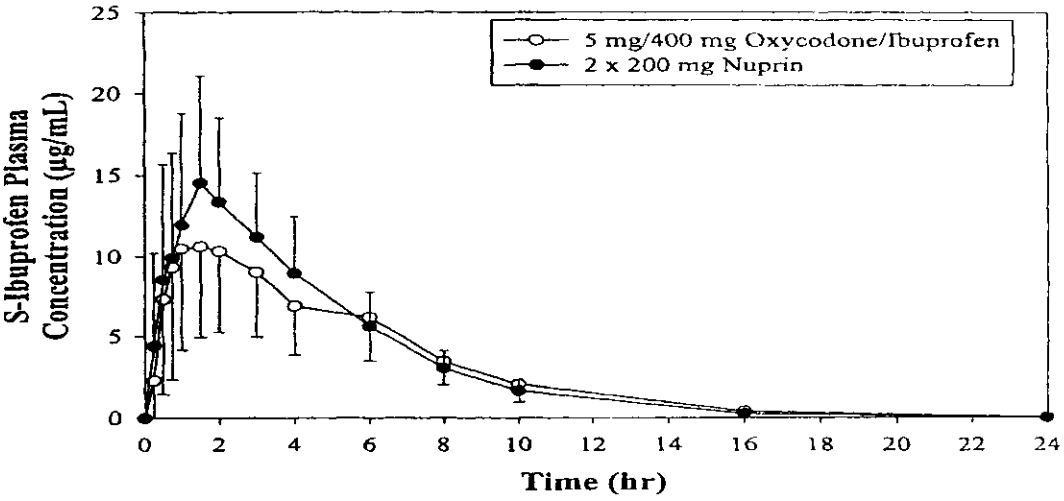
No gender differences were found for the major pharmacokinetic parameters of oxycodone.

4. Figures

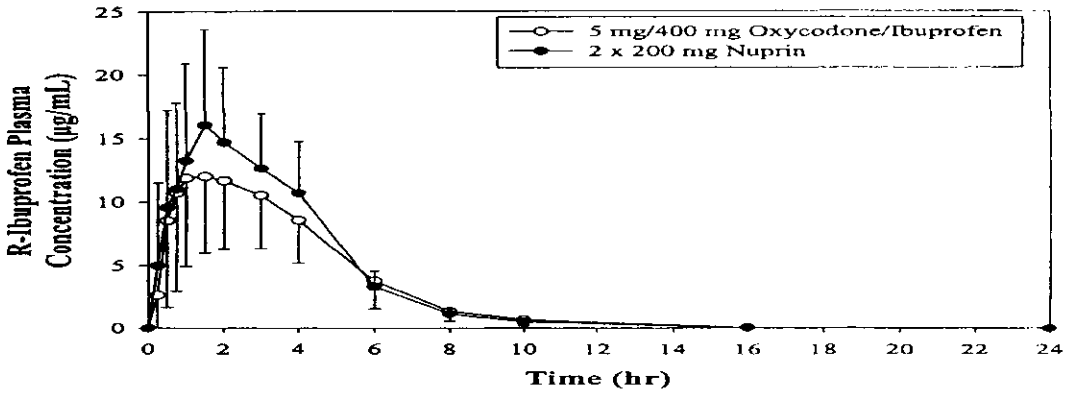
Mean Total Ibuprofen Plasma Concentrations (µg/mL) after Single Dose Oral Administration of One Tablet of Oxycodone/Ibuprofen (5 mg/400 mg) and Two Tablets of Nuprin® (2 x 200 mg of Ibuprofen).



Mean S-Ibuprofen Plasma Concentrations (µg/mL) after Single Dose Oral Administration of the Two Treatments



Mean R-Ibuprofen Plasma Concentrations (µg/mL) after Single Dose Oral Administration of the Two Treatments



Mean Oxycodone Plasma Concentrations (ng/mL) after Single Dose Oral Administration of One Tablet of Oxycodone/Ibuprofen (5 mg/400 mg) and One Tablet of Roxicodone® (5 mg of Oxycodone).

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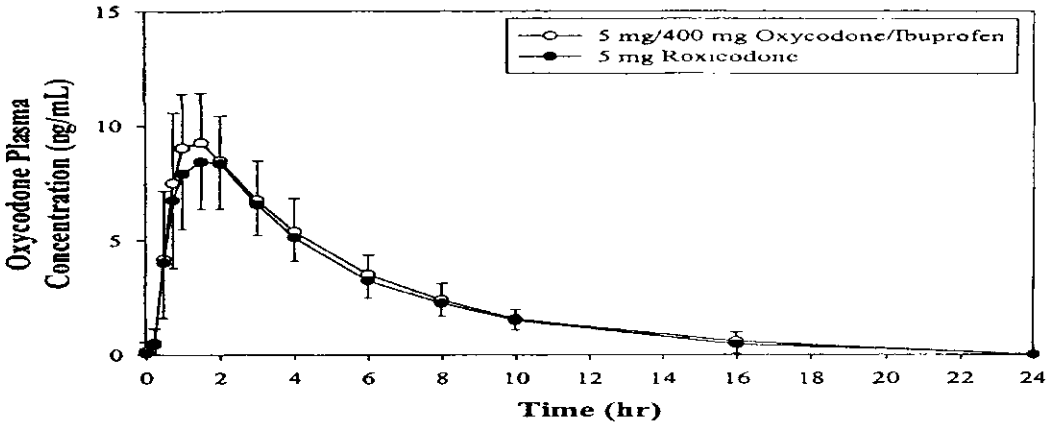
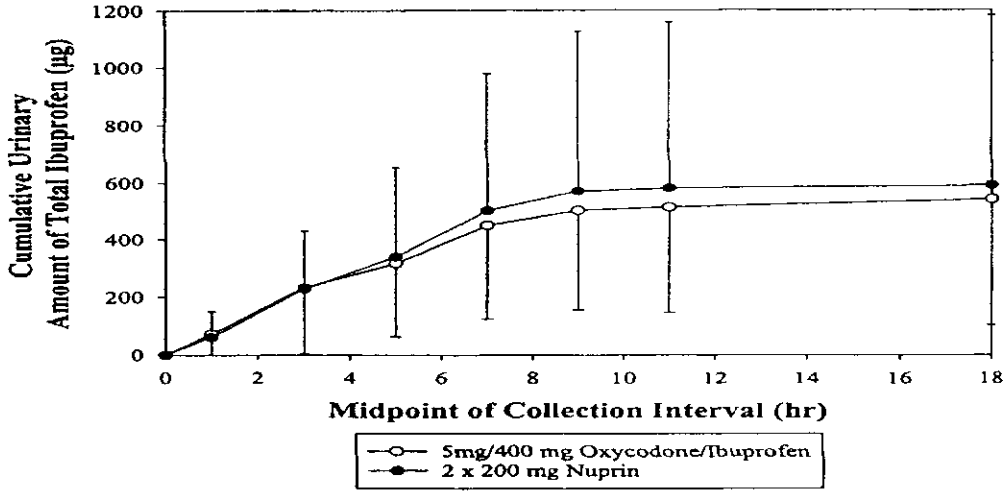


Mean Cumulative Amounts of Total Ibuprofen in Urine after Single Dose Oral Administration One Tablet of Oxycodone/Ibuprofen (5 mg/400 mg) and Two Tablets of Nuprin® (2 x 200 mg of Ibuprofen).



Mean Cumulative Amounts of Oxycodone in Urine after Single Dose Oral Administration One Tablet of Oxycodone/Ibuprofen (5 mg/400 mg) and One Tablet of Roxicodone® (5 mg of Oxycodone).

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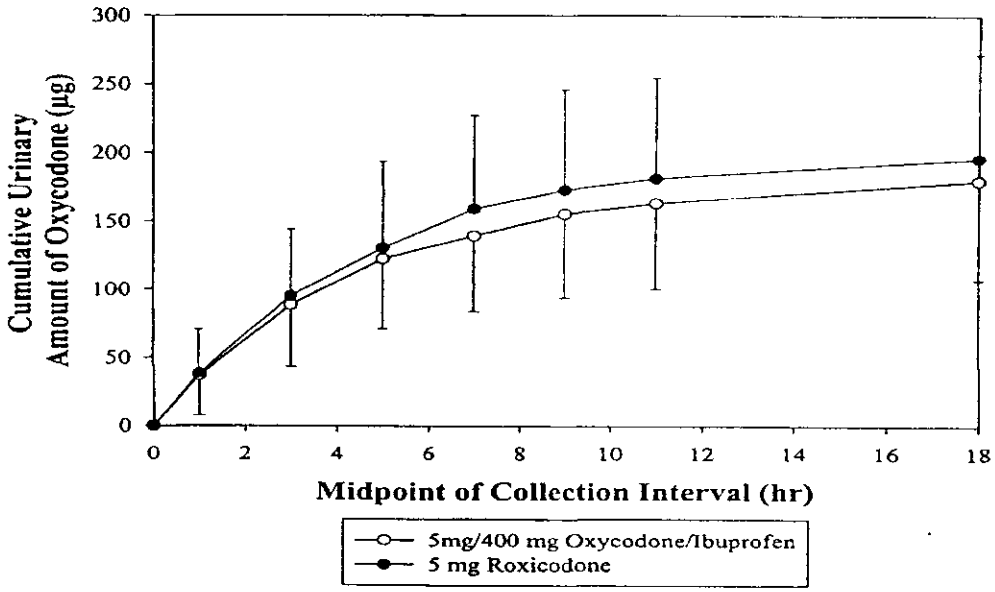

Discussion:

The objective of this study was to compare the rate and extent of absorption and excretion of a single oral dose of oxycodone HCl/ibuprofen (5 mg/400 mg) from Forest's combination product with a marketed oxycodone HCl (Roxicodone®) or ibuprofen (Nuprin®) formulation. This study was not a bioequivalence study; it was designed instead as a comparative bioavailability study.

The Applicant stated that the difference seen in the rate of ibuprofen absorption was not of significant magnitude to be of clinical relevance in the use of the product for the acute treatment of moderate severe to severe pain.

SYNOPSIS

A SINGLE-DOSE CROSSOVER STUDY IN HEALTHY VOLUNTEERS TO COMPARE THE RELATIVE BIOAVAILABILITY OF DuP 604 TABLETS AND SINGLE DOSES OF 400 mg IBUPROFEN AND 5 mg OXYCODONE ADMINISTERED TOGETHER

Investigator and Affiliation:

Study Objectives and Design: The purpose of this study was to compare the rate and extent of absorption of DuP 604 tablets given as a single oral dose, with the rate and extent of absorption of 2x200-mg ibuprofen caplets and 1x5-mg oxycodone HCl tablets given together as a single dose.

This study was an open-label, randomized, two-way, two-period single-dose crossover design study conducted at a single clinical site. Twenty-four subjects received, in random order, sequential single doses of one DuP 604 (5-mg oxycodone HCl/400-mg ibuprofen) tablet, and one oxycodone HCl 5-mg tablet plus 2x200-mg — (ibuprofen) caplets on each of two dosing periods. Doses were separated by a 6- or 7-day washout period. Blood samples were collected pre-dose and for 10 hours after drug administration for each phase to evaluate the pharmacokinetics of each of the drug substances. Serial urine samples collected predose and through 24-hours post drug administration were obtained in the event that an alternative means of assessing drug absorption was needed.

Study Population: Twenty-four healthy adult males participated in and completed the study.

Pharmacokinetic Results: The pharmacokinetic parameters for ibuprofen were not significantly different between the two treatments, DuP 604 versus ibuprofen plus oxycodone, except for Tmax.

August 12, 1991

The difference in Tmax was largely attributable to three subjects who had two peaks, the second had a higher ibuprofen peak plasma concentration, when administered the ibuprofen caplets. Analysis of the 90% confidence intervals for the parameters AUCT and AUC indicated equivalence for ibuprofen between DuP 604 and ibuprofen plus oxycodone. The parameter Cmax had an upper limit of 121%, which is above the usual limit of 120% used to declare bioequivalence. However, even though the confidence interval was 1% higher, the Cmax values were comparable and essentially indicated equivalence for ibuprofen from DuP 604 and ibuprofen plus oxycodone.

The pharmacokinetic parameters for oxycodone were not significantly different between the two treatments, DuP 604 versus ibuprofen plus oxycodone. Analysis of the 90% confidence intervals for the parameters Cmax, AUC_{0-4} and AUC indicated equivalence for oxycodone between DuP 604 and ibuprofen plus oxycodone.

Parameter	Treatment			90% Confidence Interval[a] or ANOVA[b]
	DuP 604 (Test)	Ibuprofen + Oxycodone (Reference)		
Ibuprofen (n=24)				
Cmax (μg/mL)	30.8	28.1	-	96.7-121.0
Tmax (hr)	1.4	2.2	-	SIG
AUCT (μg·hr/mL)	112.4	109.6	-	97.8-108.2
AUC (μg·hr/mL)	122.4	115.8	-	97.4-114.1
λ_z (hr^{-1})	0.336	0.361	-	N.S.
$t_{1/2}$ (hr)[c]	2.09	1.91	-	N.D.
Oxycodone (n=24)				
Cmax (ng/mL)	7.52	-	6.81	84.7-103.1
Tmax (min)	86.3	-	82.5	N.S.
AUC_{0-4} (ng·min/mL)	1161.2	-	1152.4	91.2-110.3
AUC (ng·min/mL)	2191.4	-	2164.7	89.8-111.0
λ_z (min^{-1})	0.0041	-	0.0041	N.S.
$t_{1/2}$ (min)[c]	168.9	-	169.2	N.D.

[a] Confidence interval calculated from two one-sided t-test
[b] SIG = significantly different ($p \leq 0.05$); N.S. = Not significant; N.D. = not determined
[c] $t_{1/2}$ reported as harmonic mean

Parameter	Treatment			90% Confidence Interval[a] or ANOVA[b]
	DuP 604 (Test)	Ibuprofen + Oxycodone (Reference)		

Ibuprofen (n=24)

Cmax (μg/mL)	36.6	26.1	-	98.7-121.6
Tmax (hr)	1.4	2.2	-	SIG
AUCT (μg·hr/mL)	112.4	109.5	-	97.6-108.2
AUC (μg·hr/mL)	122.4	115.6	-	97.4-114.1
λ_n (hr^{-1})	0.335	0.361	-	N.S.
$t_{1/2}$ (hr)[c]	2.09	1.91	-	N.D.

Parameter	Treatment			90% Confidence Interval[a] or ANOVA[b]
	DuP 684 (Test)	Ibuprofen + Oxycodone (Reference)		
Oxycodone (n=24)				
Cmax (ng/mL)	7.52	-	8.01	84.7-103.1
Tmax (min)	86.3	-	82.5	N.S.
AUC_{0-t} (ng·min/mL)	1161.2	-	1152.4	91.2-110.3
AUC (ng·min/mL)	2191.4	-	2184.7	89.6-111.6
λ_n (min^{-1})	0.0041	-	0.0041	N.S.
$t_{1/2}$ (min)[c]	168.9	-	169.2	N.D.

[a] Confidence interval calculated from two one-sided t-test
[b] SIG = significantly different ($p \leq 0.05$); N.S. = Not significant; N.D. = not determined
[c] $t_{1/2}$ reported as harmonic mean

DuP 684-663 Ibuprofen 400 mg
APPENDIX E.4.1 RELATIVE BIOAVAILABILITY ANALYSIS
METHOD #1: 90% CONFIDENCE INTERVAL BASED ON TWO ONE-SIDED T-TESTS

VARIABLE	TEST FORMULATION DUP 684	STANDARD FORMULATION I+O	RATIO TEST/STANDARD	PERCENT DIFFERENCE	DF	MSE	90% CONFIDENCE INTERVAL LOWER LIMIT	90% CONFIDENCE INTERVAL UPPER LIMIT
AUC	122.443	115.793	1.05743	5.74299	22	383.818	97.385	114.121
AUCT	112.385	109.535	1.02602	2.60238	22	151.551	97.831	108.173
CMAX	38.575	33.892	1.08840	8.84011	22	47.333	86.700	120.986
LN(AUC)	4.784	4.738	1.00984	0.98572	22	0.023	97.134	113.008
LN(AUCT)	4.704	4.685	1.00405	0.40780	22	0.012	98.416	107.760
LN(CMAX)	3.573	3.500	1.02108	2.10818	22	0.061	95.122	121.308

DuP 684-663 Oxycodone 5 mg
APPENDIX E.8.1 RELATIVE BIOAVAILABILITY ANALYSIS
METHOD #1: 90% CONFIDENCE INTERVAL BASED ON TWO ONE-SIDED T-TESTS

VARIABLE	TEST FORMULATION DUP 684	STANDARD FORMULATION I+O	RATIO TEST/STANDARD	PERCENT DIFFERENCE	DF	MSE	90% CONFIDENCE INTERVAL LOWER LIMIT	90% CONFIDENCE INTERVAL UPPER LIMIT
AUC 0-t	1161.16	1152.35	1.00764	0.76379	22	49528.187	91.191	110.337
AUC	2191.41	2184.66	1.00309	0.30889	22	221091.959	89.621	110.997
CMAX	7.52	8.01	0.93879	-6.12076	22	2.296	84.682	103.078
LN(AUC 0-t)	7.05	7.05	0.99903	-0.09714	22	0.030	90.446	109.864
LN(AUC)	7.05	7.08	0.99647	-0.35290	22	0.041	88.868	107.648
LN(CMAX)	1.99	2.08	0.96442	-3.55705	22	0.030	85.267	101.266

Urine samples were not analyzed based on the equivalent plasma AUC results.

Safety: Study medications were well tolerated by the volunteers. Overall, 30 clinical and laboratory adverse events were recorded for 11 volunteers. One subject had muscle damage secondary to excessive weight lifting with resultant elevations in SGOT, SGPT, LDH, creatine kinase, and urinary occult blood all occurring predose (CPK was not tested however, until Day 3). These abnormalities diminished over time. Post dosing, other events included dizziness (15), fatigue (2), nausea (1), abdominal cramping (1), vomiting (1), headache (1), nervousness (1), thinking abnormality (decreased concentration) (1), and epistaxis (1). All other clinical laboratory, vital signs measurements, and electrocardiograms were within normal limits for healthy young male adults.

Conclusions: DuP 604 provided pharmacokinetic profiles of ibuprofen and oxycodone which were equivalent (not strictly true for ibuprofen Cmax, since it was 1% above the 120% upper bound) to those obtained when the compounds were administered together. These results indicated that ibuprofen given in the combination, DuP 604, was equivalent to ibuprofen 2x200-mg caplets. Additionally, oxycodone HCl given in the combination, DuP 604, was equivalent to an oxycodone HCl 5-mg tablet.

MEDICATION DISPOSITION SUMMARY

Product	Lot #	Strength	Quantity Received	Quantity Dispensed	Quantity Remaining
DuP 604	981446	5 mg/400 mg	36 tablets	24 tablets	6 tablets
Oxycodone HCl plus Ibuprofen	981447	5 mg	30 tablets	24 tablets	6 tablets
	98PH-826	200 mg	60 caplets	48 caplets	12 caplets

The 'quantity remaining' column reflects those medications retained by the principal investigator as retention samples (Federal Register, Thursday, November 6, 1998, 21 CFR Parts 312, 314, and 320; Retention of Bioavailability and Bioequivalence Testing Samples; Final Rule). Clinical manufacturing and packaging of the test medications occurred several months prior to the issuance of the FDA November 6, 1998 interim ruling. Thus, the quantities retained by the investigator as retention samples do not equal 5 times the release testing amount stated in this rule.

Drug Administration

Subjects reported to the study clinic the evening prior to each dose and were discharged approximately 24 hours post drug administration. Subjects checked into the clinic facility the evenings of Days 0 and 7. Urine specimens were provided upon checkin, and all results of tests for substances of abuse were confirmed as negative before any subject was administered test medication.

Following an overnight fast, each subject received his assigned dose of test medication with 240 mL of water. The medication doses were administered at 2-minute intervals to consecutively numbered subjects beginning at 0800h on Study Days 1 and 8. Subjects remained fasted and seated or ambulatory for 4 hours after dosing. All doses were administered by the principal investigator or a sub-investigator who remained at the study site for at least 4 hours following dosing.

Food was not permitted until 4 hours after each dose, although water was consumed *ad lib* during the confinement periods. Meals served to the subjects while confined were

low fat, caffeine- and alcohol-free. A standard lunch was provided 4 hours following dose administration, and a standard dinner was served 9 hours following dose administration.

Plasma Samples

Venous blood samples (20 mL) were obtained immediately before dosing and 30 minutes, 1, 1.5, 2, 3, 4, 6, 7 and 10 hours following dosing on Days 1 and 8 for determination of plasma oxycodone and ibuprofen concentrations. Blood samples were collected in two (2) 10 mL blood collection tubes containing EDTA, and centrifuged in a refrigerated centrifuge at 2800 rpm for 15 minutes. Plasma samples were then transferred into three polypropylene Cryotubes® and flash frozen in an alcohol and dry ice bath. The plasma samples were divided into 6 mL (2 x 3 mL) and 2 mL aliquots. The 2 mL samples were retained by — for ibuprofen analysis. The 6 mL sample aliquots were shipped to The Du Pont Merck Pharmaceutical Company for oxycodone analysis. All samples remained frozen (-20°C) until assayed.

Urine Samples

Urine was collected at 0-2, 2-4, 4-6, 6-8, 8-10, and 10-24 hour intervals post-drug administration. During each collection interval, the time, volume, and pH of each void was recorded. Urine for each collection interval was pooled and was kept refrigerated in a container identified by the subject's initials and number. At the end of each pooled collection interval, the total volume of urine was recorded. The start and end times of each urine collection interval were recorded. A 10 mL aliquot of the pooled volume was collected in a plastic vial, and stored frozen (-20°C) in an

Analytical Methodology

Ibuprofen

Ibuprofen was quantified in human plasma extracts by

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. A full report for this assay method and validation results is in Appendix C.1. Tabulated in Appendix C.2 are the accuracy and precision results of the extracted controls and standards analyzed during the actual analysis of subject samples.

Oxycodone

Oxycodone was quantified in human plasma extracts by

. The assay was specific for oxycodone. A full report for this assay method and validation results is in Appendix C.3. Tabulated in Appendix C.4 are the accuracy and precision results of the extracted controls and standards analyzed during the actual analysis of subject samples.

Pharmacokinetic Parameters

The primary objective of this study was to assess the bioavailability of oxycodone HCl 5 mg and ibuprofen 400 mg given as the combination tablet DuP 604 relative to oral doses of oxycodone HCl 5-mg tablets and ibuprofen 2x200-mg caplets given together. Bioavailability of oxycodone and ibuprofen were assessed separately. For each, the single-component drug was considered to be the reference, and the drug given as Dup 604 was the test formulation. Data from 24 subjects was used in all assessments.

Pharmacokinetic parameters used to assess the relative bioavailability of oxycodone and of ibuprofen from different sources (DuP 604 or single component drug) were AUC_{0-4}, AUCT, AUC and Cmax. λ_n and Tmax were tested for sequence and treatment effects using analysis of variance, but were not used to assess bioavailability. Parameters were listed for individual subjects, and summary statistics were tabulated by sequence and by source. Possible transformations from the Box-Cox family of transformations were explored. Analyses were performed on transformed (natural logarithm) data, as well as on the untransformed data. All parameters were tested for carryover effect using crossover analysis techniques in SAS Procedure GLM. In the event that unequal carryover effect was exhibited, a first period analysis was performed.

The primary method used to evaluate relative bioavailability was 90% confidence intervals computed from the two one-sided t-test method introduced by Schuirmann[2], with overall alpha = 0.10.

Results:

1. Demographics

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STUDY STATISTICS OF DEMOGRAPHIC VARIABLES

		Sequence		
		1	2	ALL
Age (years)	N	12	12	24
	MEAN	22.9	26.8	24.8
	STD	2.5	6.4	5.0
	MIN	20.0	20.0	20.0
	MAX	30.0	38.0	38.0
Height (in)	N	12	12	24
	MEAN	72.2	71.6	71.9
	STD	1.9	2.4	2.2
	MIN	68.5	68.0	68.0
	MAX	76.0	76.0	76.0
Weight (lbs)	N	12	12	24
	MEAN	171.1	176.8	174.0
	STD	17.6	19.8	18.5
	MIN	138.0	142.5	138.0
	MAX	202.0	205.0	205.0

TABLE OF RACE BY SEQ

RACE(Race)	SEQ(Sequence)		
Frequency Percent Row Pct Col Pct	1	2	Total
WHITE	12 50.00 52.17 100.00	11 45.83 47.83 91.67	23 95.83
BLACK	0 0.00 0.00 0.00	1 4.17 100.00 8.33	1 4.17
Total	12 50.00	12 50.00	24 100.00

2. Plasma concentrations

IBUPROFEN MEAN PLASMA CONCENTRATIONS AFTER ADMINISTRATION OF DuP 604, AND IBUPROFEN 2x200-mg CAPLETS AND OXYCODONE HCl 5-mg TABLETS TO HEALTHY VOLUNTEERS

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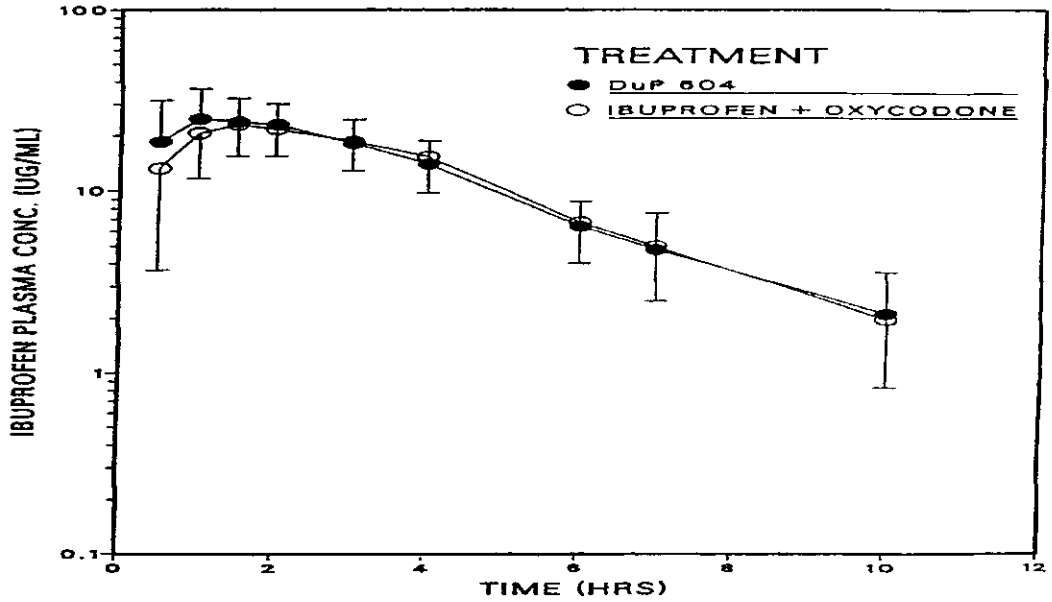
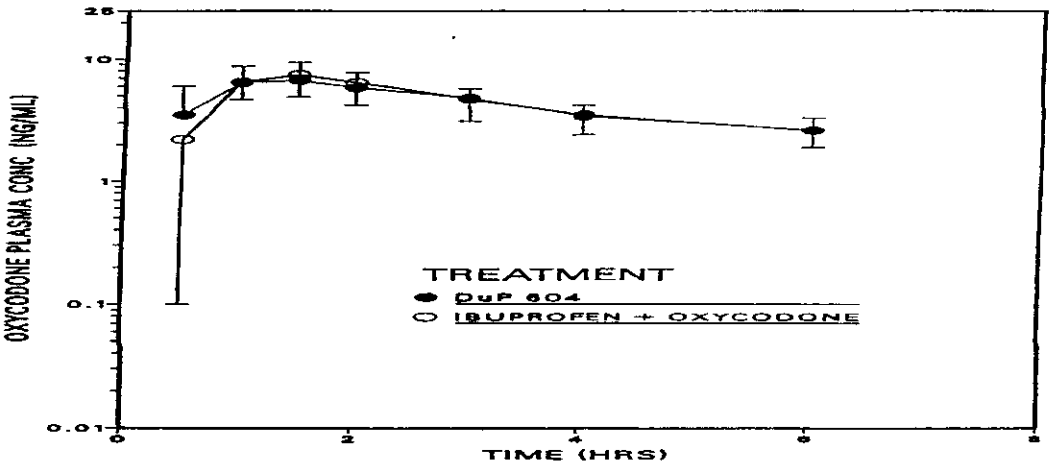


OXYCODONE MEAN PLASMA CONCENTRATIONS AFTER ADMINISTRATION OF DuP 604, AND IBUPROFEN 2x200-mg CAPLETS AND OXYCODONE HCl 5-mg TABLETS TO HEALTHY VOLUNTEERS



3. Assay

9 Ibuprofen

Linearity

The calibration curve parameters are in Table 2. The calibration curves for ibuprofen in human plasma had good linearity in the concentration range from with correlation coefficients greater than 0.9991.

Precision

The within-day precision of the method was determined from the relative standard deviation (RSD) of six replicate analyses of each of three pooled quality control samples (controls). The overall precision of the method was determined from the . The control data are in Tables 3 through 5. The overall RSD for all three controls was within

Accuracy

The accuracy of the method was determined by comparing the means of the measured concentrations of the controls described above with their theoretical concentrations. All overall mean values were within of their theoretical concentrations (Tables 3 through 5).

Limit of Quantitation

The limit of quantitation was set at of ibuprofen in plasma. At that concentration, the RSD of the peak height ratios was that of the measured concentrations was (Table 1). The deviation of the mean of the measured concentrations from the theoretical value was

Absolute Recoveries

The absolute recoveries were determined by comparing the peak heights of the extracted calibration standards with the peak heights of pure unextracted standards at the same concentrations (Table 6). The mean recoveries were for the ibuprofen concentrations at respectively.

Stability

The spiked control samples remained stable from preparation to extraction (. Stability will be monitored and reported in an upcoming sample report.

10

11 Oxycodone

The lower limit of quantification for oxycodone was set at . This limit is 80% of the concentration of the lowest standard in the validated assay. This approach is permitted under the Drug Metabolism and Pharmacokinetics Standard Operating Procedure (SOP VII). All oxycodone concentrations in this report were reported as bql if the concentration was below

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DuPont Perck Study 604-004-01

SYNOPSIS

A SINGLE-DOSE CROSSOVER STUDY IN HEALTHY VOLUNTEERS TO COMPARE THE PHARMACOKINETIC PROFILES OF OXYCODONE AND IBUPROFEN WITH THAT OF THE COMBINATION PRODUCT DuP 604

Investigator and Affiliation: —

—

Study Objectives and Design: The purpose of this study was to compare the pharmacokinetic profiles of single oral doses of oxycodone HCl 5-mg tablets and ibuprofen 2x200-mg caplets given individually, with the pharmacokinetic profiles of oxycodone and ibuprofen given as the oral combination product DuP 604 (oxycodone HCl 5 mg/ibuprofen 400-mg tablet).

The study was an open-label, randomized, three-way, three-period single-dose crossover study conducted at a single clinical site. In random order, 24 subjects received sequential single doses of one DuP 604 tablet (5-mg oxycodone HCl/400-mg ibuprofen), one oxycodone HCl 5-mg tablet, and 2x200-mg (ibuprofen) caplets on each of three dosing days. Doses were separated by a seven-day washout period. Blood samples were collected pre-dose and for 10 hours after drug administration for each phase to evaluate the pharmacokinetics of ibuprofen and oxycodone. Serial urine samples collected predose and through 24-hours post drug administration were obtained in the event that an alternative means of assessing drug absorption was needed.

Study Population: Twenty-four healthy adult males participated in the study. Twenty-three subjects completed the study, with one subject discontinuing his participation following the first study period due to nausea.

Pharmacokinetic Results: The pharmacokinetic parameters for ibuprofen were not significantly different between the two treatments, DuP 604 versus ibuprofen. One subject's plasma

concentrations were extremely low after the ibuprofen caplet treatment. This subject was not included in the statistical analysis. Analysis of the 90% confidence intervals for the parameters Cmax, AUCT, and AUC indicated equivalence for ibuprofen between DuP 604 and ibuprofen alone.

The pharmacokinetic parameters for oxycodone were not statistically different between the two treatments, DuP 604 versus oxycodone. Five subjects' AUC_{0-4} and six subjects' AUC and λ_n values were not included in the statistical analysis because paired data was not obtainable. Analysis of the 90% confidence intervals for the parameter Cmax and AUC_{0-4} indicated equivalence for oxycodone between DuP 604 and oxycodone alone. The parameter AUC had an upper limit of 121.7%, which is above the usual limit of 120% used to declare bioequivalence. However, even though the confidence interval was 1.7% higher, the AUC values were comparable and essentially indicated equivalence for oxycodone from DuP 604 and oxycodone alone.

Parameter	Treatment			90% Confidence Interval[a] or ANOVA[b]
	DuP 604	Ibuprofen	Oxycodone	
Ibuprofen (n=22)				
Cmax (μg/mL)	32.1	32.2	-	90.2-108.9
Tmax (hr)	1.5	1.3	-	N.S.
AUCT (μg•hr/mL)	116.5	116.0	-	93.6-107.2
AUC (μg•hr/mL)	122.0	121.8	-	93.6-107.2
λ_z (hr^{-1})	0.368	0.362	-	N.S.
$t_{1/2}$ (hr)[c]	1.93	1.91	-	N.D.
Oxycodone (n=23)				
Cmax (ng/mL)	7.45	-	7.57	85.8-111.8
Tmax (min)	60.9	-	83.5	N.S.
AUC_{0-4} (ng/mL)[d]	1832.8	-	1838.1	84.7-115.8
AUC (ng•min/mL)[e]	2191.8	-	2157.7	81.6-121.7
λ_z (min^{-1})[e]	0.0043	-	0.0044	N.S.
$t_{1/2}$ (min)[c,e]	160.7	-	156.5	N.D.

[a] Confidence interval calculated from two one-sided t-test
[b] N.S. = not significant, N.D. = not determined
[c] $t_{1/2}$ reported as harmonic mean
[d] n = 18
[e] n = 17

Parameter	Treatment			90% Confidence Interval[a] or ANOVA[b]
	DuP 604	Ibuprofen	Oxycodone	

Ibuprofen (n=22)

Cmax (μg/mL)	32.1	32.2	-	98.2-108.9
Tmax (hr)	1.5	1.3	-	N.S.
AUCT (μg*hr/mL)	116.5	118.0	-	93.6-107.2
AUC (μg*hr/mL)	122.6	121.8	-	93.8-107.2
λ_n (hr^{-1})	0.366	0.362	-	N.S.
$t_{1/2}$ (hr)[c]	1.93	1.91	-	N.D.

Oxycodone (n=23)

Cmax (ng/mL)	7.46	-	7.67	85.8-111.8
Tmax (min)	88.9	-	83.5	N.S.
AUC_{0-4} (ng/mL)[d]	1832.8	-	1838.1	84.7-116.8
AUC (ng*min/mL)[e]	2191.8	-	2167.7	81.5-121.7
λ_n (min^{-1})[e]	0.0043	-	0.0044	N.S.
$t_{1/2}$ (min)[c,e]	168.7	-	158.5	N.D.

[a] Confidence interval calculated from two one-sided t-test
[b] N.S. = not significant, N.D. = not determined
[c] $t_{1/2}$ reported as harmonic mean
[d] n = 18
[e] n = 17

Urine samples were not analyzed based on the equivalent plasma AUC results.

Safety: Study medications were well tolerated by the volunteers. Overall, twelve clinical adverse events were reported by 5 volunteers that included nausea (4), dizziness (4), somnolence (1), abdominal pain (1), dyspepsia (1), and back strain (1). One subject withdrew prior to Period II of study due to experiencing nausea in Period I. The subject was not replaced. Clinical laboratory, vital sign measurements, and electrocardiograms were within normal limits for healthy young male adults.

Conclusions: DuP 604 provided pharmacokinetic profiles of ibuprofen and oxycodone which were equivalent (not strictly true for oxycodone AUC, since it was 1.7% above the 120% upper bound) to those obtained when either compound was administered separately. These results indicate that there was no pharmacokinetic drug interaction between either ibuprofen or oxycodone when administered as the combination tablet DuP 604.

Study Medications:

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MEDICATION DISPOSITION SUMMARY

Product	Lot #	Strength	Quantity Received	Quantity Dispensed	Quantity Remaining
DuP 604	981448	5 mg/400 mg	30 tablets	23 tablets	7 tablets
Oxycodone HCl	981447	5 mg	30 tablets	24 tablets	6 tablets
Ibuprofen	98PH-528	200 mg	60 caplets	46 caplets	14 caplets

The "quantity remaining" column reflects those medications retained by the principal investigator as retention samples (Federal Register, Thursday, November 8, 1998, 21 CFR Parts 312, 314, and 320; Retention of Bioavailability and Bioequivalence Testing Samples; Final Rule). Clinical manufacturing and packaging of the test medications occurred several months prior to the issuance of the FDA November 8, 1998 interim ruling. Thus the quantities retained by the investigator as retention samples do not equal 6 times the release testing amount stated in this rule.

Dissolution Data

The *in vitro* dissolution tests for the tablets and caplets were conducted as follows. For DuP 604 the method used was a USP basket at 150 RPM in 900 mL of pH 7.2 phosphate buffer at 37°C using manual sampling. On average for DuP 604, oxycodone dissolved at — , and ibuprofen dissolved at — at 30 minutes. For oxycodone tablets, the method used was a USP paddle at 50 RPM in 500 mL of purified, deaerated water at 37°C using manual sampling. On average, oxycodone tablets dissolved at — at 45 minutes. For — caplets, the method used was a USP basket at 150 RPM in 900 mL of pH 7.2 phosphate buffer at 37°C using manual sampling. On average, ibuprofen dissolved at — at 30 minutes. All individual tablet and caplet data are presented in Appendix B.

Sampling Information

Plasma Samples

Venous blood samples (20 mL) were obtained immediately before dosing and 30 minutes, 1, 1.5, 2, 3, 4, 6, 7 and 10 hours following dosing on Days 1, 8 and 15 for determination of plasma oxycodone and ibuprofen concentrations. Blood samples were collected in two (2) 10 mL blood collection tubes containing EDTA, and centrifuged in a refrigerated centrifuge at 2800 rpm for 15 minutes. Plasma samples were then transferred into three polypropylene Cryotubes® and flash frozen in an alcohol and dry ice bath. The plasma samples were divided into 6 mL (2 x 3 mL) and 2 mL aliquots. The 2 mL samples were retained by — for ibuprofen analysis. The 6 mL sample aliquots were shipped to The Du Pont Merck Pharmaceutical Company for oxycodone analysis. The plasma samples from the periods in which subjects received oxycodone alone or ibuprofen alone were only assayed for the compound administered. All samples remained frozen (-20°C) until assayed.

Urine Samples

Urine was collected at predose and 0-2, 2-4, 4-6, 6-8, 8-10, and 10-24 hour intervals post-drug administration. During each collection interval, the time, volume, and pH of each void was recorded. Urine for each collection interval was pooled and was kept refrigerated in a container identified by the subject's initials and number. At the end of each pooled collection interval, the total volume of urine was recorded. The start and end times of each urine collection

interval were recorded. A 10 mL aliquot of the pooled volume was collected in a plastic vial, and stored frozen (−20°C) in an upright position. All urine samples were shipped to y.

Analytical Methodology

Ibuprofen

for
The
assay was specific for ibuprofen. A full report for this assay method and validation results is in Appendix C.1. Tabulated in Appendix C.2 are the accuracy and precision results of the extracted controls and standards analyzed during the actual analysis of subject samples.

Oxycodone

The
assay was specific for oxycodone. A full report for this assay method and validation results is in Appendix C.3. Tabulated in Appendix C.4 are the accuracy and precision results of the extracted controls and standards analyzed during the actual analysis of subject samples.

Analysis

Pharmacokinetic parameters used to assess the relative bioavailability of oxycodone and of ibuprofen from different sources (DuP 604 or single component drug) included AUCT, AUC, Cmax. λ_n and Tmax were tested for sequence and treatment effects using analysis of variance, but were not used to assess relative bioavailability. Parameters were listed for individual subjects, and summary statistics were tabulated by sequence and by source. Possible transformations from the Box-Cox family of transformations were explored. Analyses were performed on transformed (natural logarithm) data, as well as on the untransformed data. All parameters were tested for carryover effect using crossover analysis techniques in SAS Procedure GLM.

The primary method used to evaluate relative bioavailability was 90% confidence intervals computed from the two one-sided t-tests method introduced by Schuirmann[2], with overall alpha = 0.10.

Three other methods were used to verify the results of the two one-sided t-test method. These were calculation of Bayesian posterior probabilities[3], Westlake's 90% symmetric confidence limits[4], and Anderson and Hauck's hypothesis tests[5].

Results:

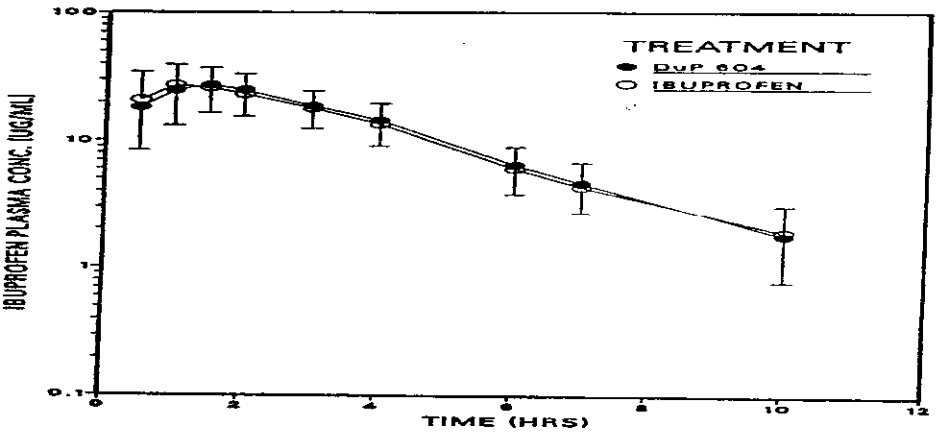
Demographics

		Sequence*						ALL
		A	B	C	D	E	F	
Age (years)	N	4	4	4	4	4	4	24
	MEAN	27.5	26.8	24.8	26.5	23.8	23.8	26.8
	STD	3.4	5.5	8.9	8.7	3.9	3.8	5.4
	MIN	23.8	20.8	19.8	22.8	21.8	20.8	19.8
	MAX	31.8	36.8	36.8	39.8	29.8	28.8	39.8
Height (in)	N	4	4	4	4	4	4	24
	MEAN	70.8	70.8	72.4	69.8	71.8	72.9	71.3
	STD	2.1	1.7	2.3	2.8	0.9	2.2	2.1
	MIN	69.8	70.8	69.5	67.5	71.8	71.8	67.5
	MAX	73.8	73.5	74.5	72.8	73.8	76.8	76.8
Weight (lbs)	N	4	4	4	4	4	4	24
	MEAN	159.5	181.5	185.5	158.5	162.5	173.8	170.1
	STD	22.5	9.3	8.4	15.3	12.8	17.8	17.3
	MIN	133.5	172.8	176.5	142.8	148.8	162.8	133.5
	MAX	187.5	194.8	195.8	188.8	178.8	198.8	198.8

* Sequence: A = D->I->DUP604 B = D->DUP604->I C = I->D->DUP604
D = I->DUP604->D E = DUP604->I->D F = DUP604->D->I

Mean plasma concentrations vs. time profiles

IBUPROFEN MEAN PLASMA CONCENTRATIONS AFTER ADMINISTRATION OF DuP 604 AND IBUPROFEN 2x200-mg CAPLETS TO HEALTHY VOLUNTEERS



OXYCODONE MEAN PLASMA CONCENTRATIONS AFTER ADMINISTRATION OF DuP 604 AND OXYCODONE HCl 5-mg TABLETS TO HEALTHY VOLUNTEERS

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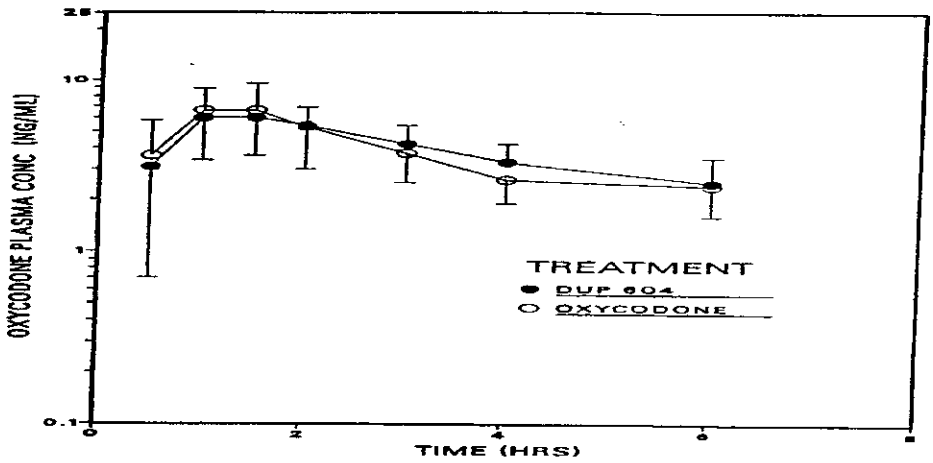

DuP 604-604 Ibuprofen 400 mg
APPENDIX E.4.1 RELATIVE BIOAVAILABILITY ANALYSIS
METHOD #1: 90% CONFIDENCE INTERVAL BASED ON TWO ONE-SIDED T-TESTS

VARIABLE	TEST FORMULATION DUP 604	STANDARD FORMULATION IBU	RATIO TEST/STANDARD	PERCENT DIFFERENCE	DF	MSE	90% CONFIDENCE INTERVAL LOWER LIMIT	90% CONFIDENCE INTERVAL UPPER LIMIT
AUC	121.980	121.686	1.00143	0.14265	20	270.287	83.648	107.230
AUCT	116.523	116.018	1.00435	0.43620	20	229.981	83.038	107.233
CMAX	32.000	32.227	0.99563	-0.43724	20	33.706	80.182	108.843
LN(AUC)	4.772	4.769	1.00060	0.00060	20	0.014	94.388	106.563
LN(AUCT)	4.728	4.724	1.00086	0.00010	20	0.014	94.478	106.713
LN(CMAX)	3.437	3.442	0.99856	-0.14439	20	0.039	89.849	110.197

DuP 604-604 Oxycodone 5 mg
APPENDIX E.4.1 RELATIVE BIOAVAILABILITY ANALYSIS
METHOD #1: 90% CONFIDENCE INTERVAL BASED ON TWO ONE-SIDED T-TESTS

VARIABLE	TEST FORMULATION DUP 604	STANDARD FORMULATION OXYCODONE	RATIO TEST/STANDARD	PERCENT DIFFERENCE	DF	MSE	90% CONFIDENCE INTERVAL LOWER LIMIT	90% CONFIDENCE INTERVAL UPPER LIMIT
AUC 0-4	1032.70	1030.10	1.00261	0.26081	16	75469.712	84.742	116.779
AUC	2101.84	2107.75	1.01630	1.58813	16	619462.361	81.486	121.084
CMAX	7.45	7.57	0.98423	-1.57855	21	3.542	86.016	111.032
LN(AUC 0-4)	6.91	6.90	1.00092	0.09270	16	0.078	85.701	110.166
LN(AUC)	7.84	7.82	1.00216	0.21547	16	0.071	80.597	110.334
LN(CMAX)	1.96	1.97	0.98998	-1.00154	21	0.076	88.248	112.778

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Dose Proportionality/Food Effect/Multiple Dose studies:

Forest Study OXY-PK-03

<table>
<tr><td colspan="3">Title of Report</td></tr>
<tr><td colspan="3">A Study to Investigate the Effects of Food on the Rate and Extent of Absorption of Oxycodone and Ibuprofen from Combination Oxycodone HCl/Ibuprofen Products after Single Dose and to Investigate the Degree of Accumulation of Oxycodone and Ibuprofen after Multiple Doses</td></tr>
<tr><td colspan="3">Purpose of Study</td></tr>
<tr><td colspan="3">1. To investigate the rate and extent of absorption of oxycodone and ibuprofen after administration of oxycodone HCl/ibuprofen either as a 5 mg/400 mg or a 10 mg/400 mg combination tablet under fasted and fed conditions.

2. To determine the degree of accumulation of oxycodone and ibuprofen after multiple dose administration of a 5 mg/400 mg combination tablet.</td></tr>
<tr><td rowspan="2">Date of Report</td><td colspan="2">Studies were carried out</td></tr>
<tr><td>From</td><td>To</td></tr>
<tr><td rowspan="2">June 5, 2001</td><td>October 14, 2000</td><td>November 10, 2000</td></tr>
<tr><td>Statistical Methodology</td><td>Phase of Development</td><td>Number of Subjects</td></tr>
<tr><td>An analysis of variance (ANOVA) was performed on the pharmacokinetic parameters using the GLM procedures of SAS to assess the effects of food. The ANOVA model included the variables Sequence, Subject (nested in Sequence), Period, and Treatment.</td><td>Phase 1</td><td>24 (24 completed)</td></tr>
<tr><td>Design of Study</td><td>Analytical Site</td><td>Mode of Administration</td></tr>
<tr><td>Single center, open label, randomized study consisting of a single dose cross-over phase (study part I), followed by a multiple dose phase (study part II) in 24 healthy young subjects</td><td>Forest Laboratories, Inc.</td><td>Oral – fasted

Oral – fed</td></tr>
<tr><td>Clinical Site</td><td colspan="2">Formulations</td></tr>
<tr><td></td><td colspan="2">1. Oxycodone/Ibuprofen 5 mg/400 mg tablet (Forest Laboratories, Inc., Lot #: 00069C; Manufacture Date: 3/2000)

2. Oxycodone/Ibuprofen 10 mg/400 mg tablet (Forest Laboratories, Inc., Lot #: 00084D; Manufacture Date: 4/2000)</td></tr>
</table>

Name of Company	**Individual study Table Referring to Part of the Dossier**
Forest Laboratories, Inc.	
Name of Finished Product	
	Volume:
Name of Active Ingredient	
Oxycodone/Ibuprofen	**Page:**
Test Formulations Administered	
Study Part I (Single Dose)	
Treatment A	**Treatment B**
(n=12)	
One oxycodone/ibuprofen (5 mg/400 mg) tablet, administered with 240 mL of water following a 10-hour overnight fast.	One oxycodone/ibuprofen (5 mg/400 mg) tablet administered with 240 mL of water following a standardized, high-fat breakfast.
Treatment C	**Treatment D**
(n=12)	
One oxycodone/ibuprofen (10 mg/400 mg) tablet, administered with 240 mL of water following a 10-hour overnight fast.	One oxycodone/ibuprofen (10 mg/400 mg) tablet administered with 240 mL of water following a standardized, high-fat breakfast.
Study Part II (Multiple Doses)	
Treatment E (n=24)	
One oxycodone/ibuprofen (5 mg/400 mg) tablet every 6 hours for 3 ½ days	

Summary and Conclusions

Twelve subjects received the following two treatments in study part I in random order:

A. One oxycodone/ibuprofen (5 mg/400 mg) tablet, administered with 240 mL of water following a 10-hr overnight fast.

B. One oxycodone/ibuprofen (5 mg/400 mg) tablet, administered with 240 mL of water following a standardized, high-fat breakfast.

Twelve subjects received the following two treatments in study part I in random order:

C. One oxycodone/ibuprofen (10 mg/400 mg) tablet, administered with 240 mL of water following a 10-hr overnight fast.

D. One oxycodone/ibuprofen (10 mg/400 mg) tablet, administered with 240 mL of water following a standardized, high-fat breakfast.

After completion of study part I, all 24 subjects received the following treatment in study part II:

E. One oxycodone/ibuprofen (5 mg/400 mg) tablet every six hours for 3 ½ days.

Blood samples were obtained at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 16 and 24 hours. Plasma samples were analyzed for oxycodone by assays that demonstrated appropriate accuracy, linearity, reproducibility, and precision. Total ibuprofen plasma concentrations were calculated by adding corresponding R-ibuprofen and S-ibuprofen plasma concentrations.

Results:

Ibuprofen

	Single Dose				Multiple Dose
PK Parameter	5/400 fasted	5/400 fed	10/400 fasted	10/400 fed	5/400 t.i.d. for 3.5 days
C_{max} (µg/mL)	34.3 ± 4.3	28.8 ± 6.0	33.6 ± 10.5	24.3 ± 6.5	34.3 ± 7.6
AUC_{0-t} (µg•hr/mL)	120.4 ± 20.3	113.8 ± 18.3	117.7 ± 26.6	109.5 ± 32.8	105.1 ± 22.7*
$AUC_{0-\infty}$ (µg•hr/mL)	123.1 ± 19.3	116.7 ± 18.0	120.0 ± 26.0	113.2 ± 33.2	n/c
T_{max} (hr)	1.8 ± 0.9	2.1 ± 0.8	2.2 ± 1.2	2.0 ± 1.0	2.2 ± 1.9
$T_{1/2}$ (hr)	2.1 ± 0.3	2.1 ± 0.3	2.0 ± 0.2	2.7 ± 0.9	2.0 ± 0.3

n/c = not calculated

*$AUC_{0-\tau}$ (τ = 6 hr)

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Summary and Conclusions

Results (continued):

Oxycodone

PK Parameter	Single Dose				Multiple Dose
	5/400 fasted	5/400 fed	10/400 fasted	10/400 fed	5/400 t.i.d. for 3.5 days
C_{max} (µg/mL) observed dose-adjusted*	11.7 ± 2.5	13.6 ± 3.1	20.3 ± 5.9 10.2 ± 3.0	21.5 ± 4.7 10.7 ± 2.3	17.8 ± 4.1
AUC_{0-t} (µg•hr/mL) observed dose-adjusted	58.2 ± 15.0	70.3 ± 13.3	96.3 ± 27.7 48.2 ± 13.8	121.9 ± 28.0 60.9 ± 14.0	70.7 ± 1.4**
$AUC_{0-\infty}$ (µg•hr/mL) observed dose-adjusted	62.8 ± 14.9	75.2 ± 14.2	101.3 ± 28.4 50.6 ± 14.2	127.0 ± 29.3 63.5 ± 14.6	n/c
T_{max} (hr)	1.5 ± 0.6	2.0 ± 0.6	1.4 ± 0.4	2.1 ± 1.0	1.4 ± 0.5
$T_{1/2}$ (hr)	3.5 ± 0.4	3.5 ± 0.5	3.1 ± 0.4	3.4 ± 0.5	4.0 ± 0.7

n/c = not calculated *dose-adjusted to the 5-mg dose **$AUC_{0-\tau}$ (τ = 6 hr)

Based on 90% confidence interval calculations, the presence of food did not have an effect on the rate and extent of ibuprofen absorption, as measured by C_{max} and AUC values. The rate of oxycodone absorption, as measured by C_{max} values, was unaltered in the presence of food, whereas the extent of absorption was slightly increased when oxycodone was administered with food, independent of oxycodone dose.

Dose proportionality was demonstrated for oxycodone at 5 and 10 mg, when administered under fasting conditions in the presence of 400 mg ibuprofen. Under fed conditions, a slight deviation from dose proportionality was observed. Similar pharmacokinetic profiles were obtained for ibuprofen when coadministered with either 5 or 10 mg oxycodone.

There was no accumulation of ibuprofen after multiple dose administration of oxycodone/ibuprofen every 6 hours for 3 ½ days (accumulation index R = 1.16). For oxycodone, moderate accumulation was observed (accumulation index R = 1.43). This was in good agreement with theoretical considerations, based on the elimination half-life of ibuprofen ($T_{1/2}$ = 2 hr) and oxycodone ($T_{1/2}$ = 3.5 hr), indicating linear pharmacokinetics.

Note that the Applicant obtained the confidence interval using 80-125% and 70-143% for AUC and Cmax, respectively.

Ibuprofen

PK Parameter	Single Dose				Multiple Dose
	5/400 fasted	5/400 fed	10/400 fasted	10/400 fed	5/400 t.i.d. for 3.5 days
C_{max} (µg/mL)	34.3 ± 4.3	28.8 ± 6.0	33.6 ± 10.5	24.3 ± 6.5	34.3 ± 7.6
AUC_{0-t} (µg•hr/mL)	120.4 ± 20.3	113.8 ± 18.3	117.7 ± 26.6	109.5 ± 32.8	105.1 ± 22.7*
$AUC_{0-\infty}$ (µg•hr/mL)	123.1 ± 19.3	116.7 ± 18.0	120.0 ± 26.0	113.2 ± 33.2	n/c
T_{max} (hr)	1.8 ± 0.9	2.1 ± 0.8	2.2 ± 1.3	2.0 ± 1.0	2.2 ± 1.9
$T_{1/2}$ (hr)	2.1 ± 0.3	2.1 ± 0.3	2.0 ± 0.2	2.7 ± 0.9	2.0 ± 0.3

n/c = not calculated *$AUC_{0-\tau}$ (τ = 6 hr)

Oxycodone

	Single Dose				Multiple Dose
PK Parameter	5/400 fasted	5/400 fed	10/400 fasted	10/400 fed	5/400 t.i.d. for 3.5 days
C_{max} (µg/mL) observed dose-adjusted*	11.7 ± 2.5	13.6 ± 3.1	20.3 ± 5.9 10.2 ± 3.0	21.5 ± 4.7 10.7 ± 2.3	17.8 ± 4.1
AUC_{0-t} (µg•hr/mL) observed dose-adjusted	58.2 ± 15.0	70.3 ± 13.3	96.3 ± 27.7 48.2 ± 13.8	121.9 ± 28.0 60.9 ± 14.0	70.7 ± 1.4**
$AUC_{0-\infty}$ (µg•hr/mL) observed dose-adjusted	62.8 ± 14.9	75.2 ± 14.2	101.3 ± 28.4 50.6 ± 14.2	127.0 ± 29.3 63.5 ± 14.6	n/c
T_{max} (hr)	1.5 ± 0.6	2.0 ± 0.6	1.4 ± 0.4	2.1 ± 1.0	1.4 ± 0.5
$T_{1/2}$ (hr)	3.5 ± 0.4	3.5 ± 0.5	3.1 ± 0.4	3.4 ± 0.5	4.0 ± 0.7

n/c = not calculated *dose-adjusted to the 5-mg dose **AUC_{0-t} (τ = 6 hr)

The FDA recommended high fat (50% of total caloric content of the meal) and high calorie (approximately 1000 calories) breakfast consisted of 2 eggs fried in butter, 2 bacon strips, 2 slices of toast with butter, 4 ounces of hash brown potatoes and 8 ounces of whole milk (i.e., approximately 150 protein calories, 250 carbohydrate calories, 500-600 fat calories).

Fourteen blood samples were collected during each period of the study according to the following schedule:

Days 1 and 8 for study part I and day 12 after the 0800 hour dose for study part II:

Pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 16 and 24 hours

Results of the Statistical Analysis (90% CI and p-values) for Total Ibuprofen

PK Parameter	oxycodone/ ibuprofen 5 mg/400 mg fed vs. fasted	oxycodone/ ibuprofen 10 mg/400 mg fed vs. fasted	10 mg/400 mg fasted vs. 5 mg/400 mg fasted	10 mg/400 mg fed vs. 5 mg/400 mg fed
C_{max} (µg/mL)	72 – 95	64 – 86	p = 0.5435	p = 0.1010
AUC_{0-t} (µg•hr/mL)	87 – 103	84 – 100	p = 0.6879	p = 0.5059
$AUC_{0-\infty}$ (µg•hr/mL)	88 – 102	85 – 101	p = 0.6503	p = 0.5546
T_{max} (hr)	p = 0.4398	p = 0.7513	p = 0.3865	p = 0.9560
$T_{1/2}$ (hr)	p = 0.7125	p = 0.0129	p = 0.4135	p = 0.0537

The presence of food did not alter the rate and extent of absorption of ibuprofen after single dose administration of oxycodone/ibuprofen (5 mg/400 mg), since the 90% confidence intervals were within the acceptance criterion (C.I.: 70 - 143%). For the higher dose (10 mg/400 rog), a decrease in the rate of ibuprofen absorption, as measured by Cm, x values, was noted, whereas the extent of ibuprofen absorption remained similar in the presence of food. The presence of 5 or 10 mg of oxycodone did not change the pharmacokinetics of ibuprofen, as

can be seen by the p-values for the comparison of fasted or fed data for ibuprofen. Similarly, the presence of food did not alter the rate and extent of absorption of S-ibuprofen.

Results of the Statistical Analysis (90% CI or p-values) for Oxycodone

PK Parameter	oxycodone/ ibuprofen 5 mg/400 mg fed vs. fasted	oxycodone/ ibuprofen 10 mg/400 mg fed vs. fasted
C_{max} (µg/mL)	103 – 130	101 – 114
AUC_{0-t} (µg•hr/mL)	116 – 130	120 – 137
$AUC_{0-\infty}$ (µg•hr/mL)	115 – 127	119 – 135
T_{max} (hr)	p = 0.1156	p = 0.0294
$T_{1/2}$ (hr)	p = 0.7342	p = 0.1248

The rate of oxycodone absorption was unchanged in the presence of food, as indicated by the 90% confidence intervals when calculated either within the 5-mg or 10-mg dose ~oup (acceptance limit: C.I., 70 - 143 %). The extent of absorption, as measured by the AUC values, was slightly increased (by approximately 25%) in the presence of food (acceptance limit: C.I., 80 - 125%).

Dose Proportionality of Oxycodone at the Dose Levels 5 and 10 mg.

Parameter	10 mg/400 mg (dose-normalized) vs. 5 mg/400 mg		
	Fasted (n=24)	Fed (n=24)	Fasted and Fed Combined (n=24)
C_{max} Ratio (%)	87	79	83
p-value	0.1373	0.0180	0.0416
AUC_{0-t} Ratio (%)	83	87	83
p-value	0.1090	0.1123	0.1204
$AUC_{0-\infty}$ Ratio (%)	81	84	83
p-value	0.0528	0.0693	0.0637

Under fasted conditions, peak plasma concentrations and systemic exposure of oxycodone increased in a predictable, dose-related manner at the dose levels of 5 and 10 mg under fasting conditions. Under fed conditions, a slight deviation firom dose proportionality was observed, which may be due to the higher degree of variability in pharmacokinetic parameters in the presence of food.

Accumulation of Total Ibuprofen after Multiple Doses (n=12).

Accumulation Index	Ratio of C_{max} on Day 12 and C_{max} on Day 1	Ratio of Trough Concentrations 6 hr Post-Dose on Day 12 and Day 1
1.16 ± 0.06	1.03 ± 0.20	1.04 ± 0.36

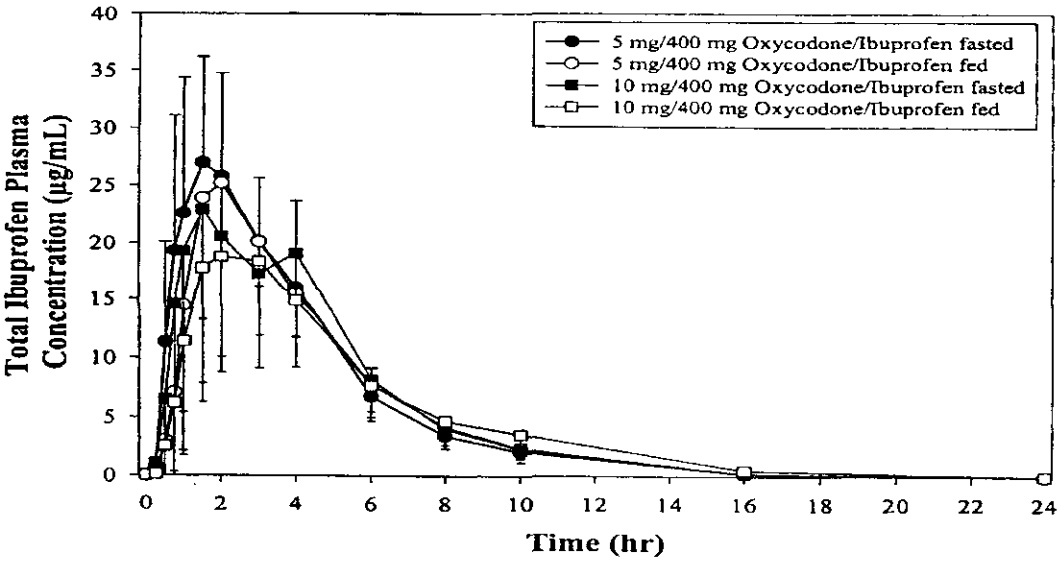
There was, as expected based on the elimination half life of total ibuprofen (T~n = 2 hr) and the dosing interval 0: = 6 hr), no accumulation of total ibuprofen after multiple doses of oxycodone/ibuprofen (5 mg/400 mg) every 6 hours. Similar results were obtained for R-ibuprofen (see Appendix E, Table E-27) and S-ibuprofen (see Appendix E, Table E28).

Accumulation of Oxycodone after Multiple Doses (n=12).

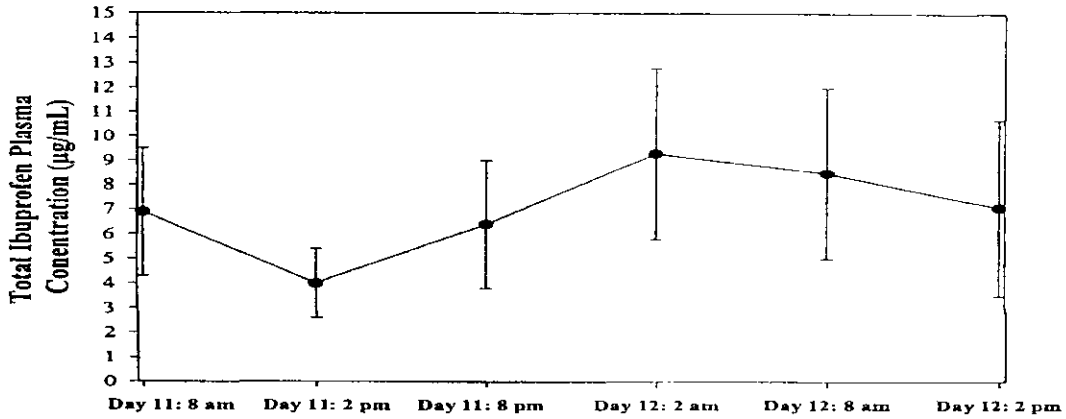
Accumulation Index	Ratio of C_{max} on Day 12 and C_{max} on Day 1	Ratio of Trough Concentrations 6 hr Post-Dose on Day 12 and Day 1
1.43 ± 0.09	1.63 ± 0.24	1.83 ± 0.32

There was moderate accumulation of oxycodone after multiple doses of oxycodone/ibuprofen (5 mg/400 mg) every six hours for 3 V2 days, as expected, based on the elimination half life of oxycodone (T~/2 = 3.5 hours) and a dosing interval of 6 hours.

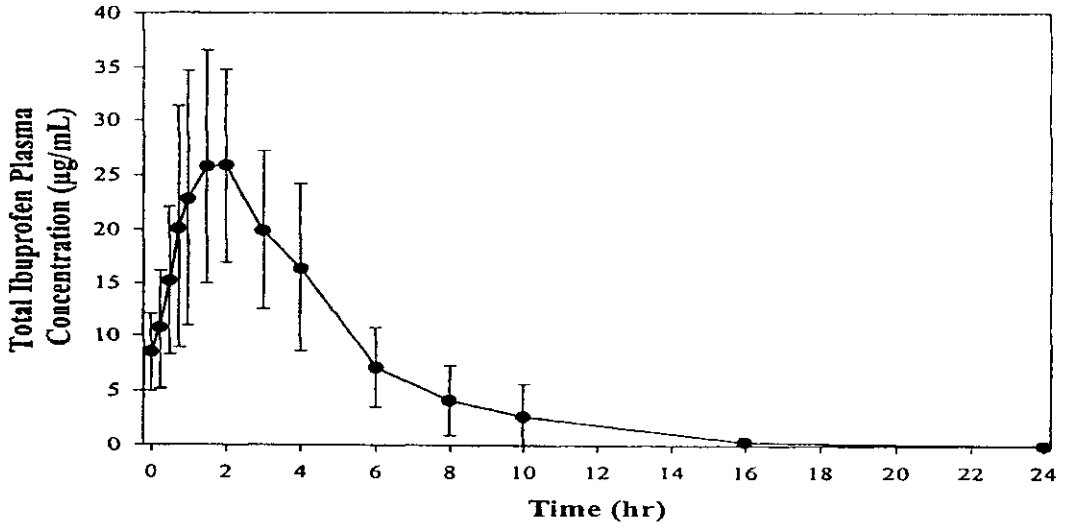
Mean Total Ibuprofen Plasma Concentrations (µg/mL) after Single Dose Oral Administration of Oxycodone/Ibuprofen (5 mg/400 mg) and (10 mg/400 mg) under Fasted and Fed Conditions.



Mean Trough Ibuprofen Plasma Concentrations (µg/mL) on Day 11 and Day 12 after Multiple Dose Administration of One Oxycodone/Ibuprofen (5 mg/400 mg) Combination Tablet Every 6 Hours.



Mean Total Ibuprofen Plasma Concentrations (µg/mL) after Multiple Dose Administration of One Oxycodone/Ibuprofen (5 mg/400 mg) Combination Tablet Every 6 Hours for 3 ½ Days.



Mean Oxycodone Plasma Concentrations (ng/mL) after Single Dose Oral Administration of Oxycodone/Ibuprofen (5 mg/400 mg) and (10 mg/400 mg) under Fasted and Fed Conditions.

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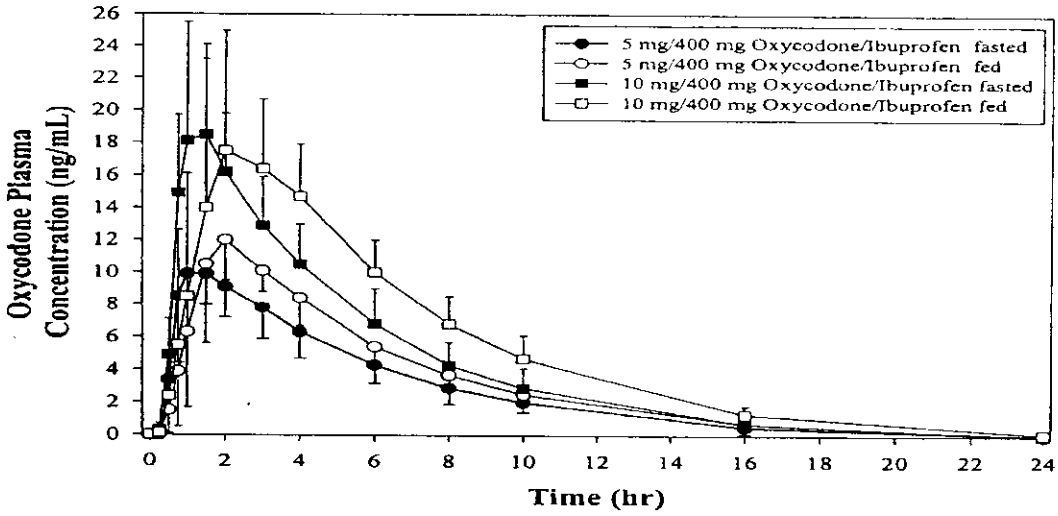
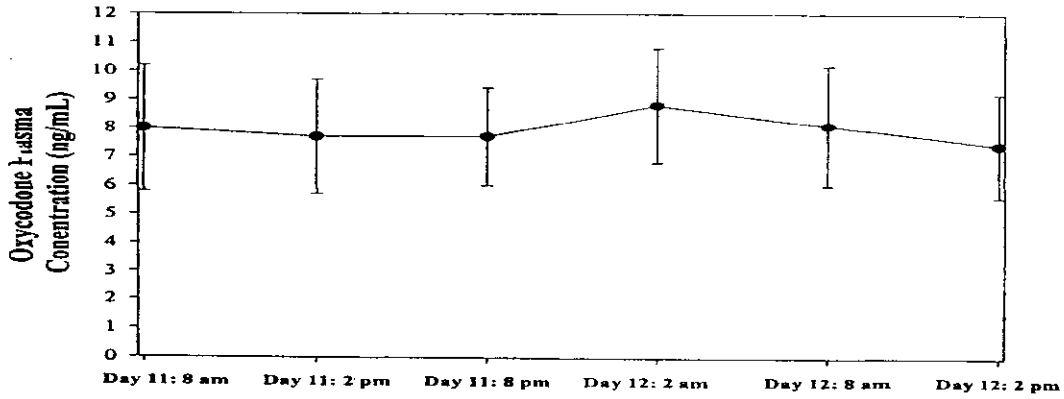


Mean Trough Oxycodone Plasma Concentrations (ng/mL) on Day 11 and Day 12 after Multiple Dose Administration of One Oxycodone/Ibuprofen (5 mg/400 mg) Combination Tablet Every 6 Hours.



Mean Oxycodone Plasma Concentrations (ng/mL) after Multiple Dose Administration of One Oxycodone/Ibuprofen (5 mg/400 mg) Combination Tablet Every 6 Hours for 3 ½ Days.

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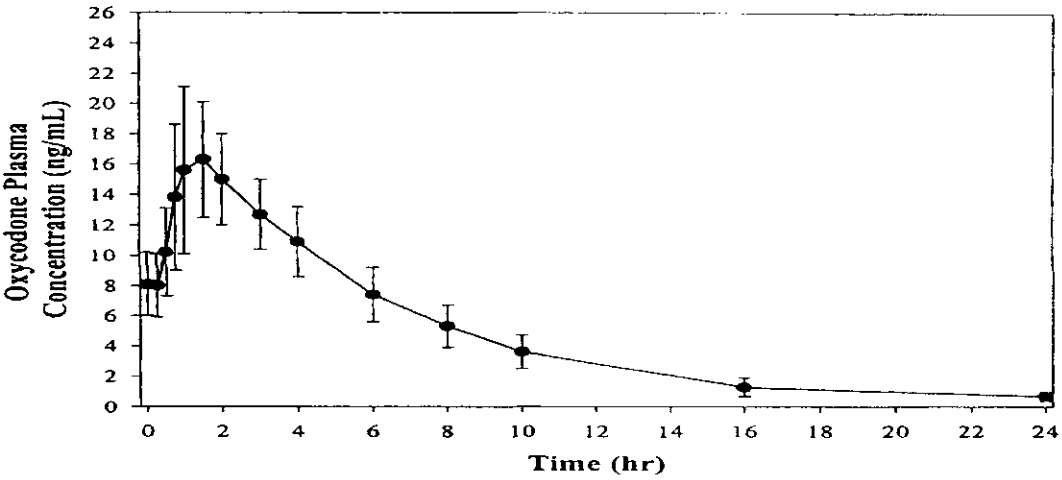

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Forest Study OXY-PK1-97-02-000

Title of Report		
A Pivotal Two-Way Crossover, Single Dose, Dose-Proportionality Study of Oxycodone and Ibuprofen From Two Strengths of a Combination Oxycodone HCl/Ibuprofen Product in Normal Healthy Volunteers		
Purpose of Study		
The objective of this study was to evaluate the dose proportionality of oxycodone at 5 and 10 mg, when administered in the presence of the same amount of ibuprofen.		
Date of Report	**Studies were carried out**	
April 18, 2001	**From**	**To**
	May 13, 1997	May 22, 1997
Statistical Methodology	**Phase of Development**	**Number of Subjects**
An analysis of variance (ANOVA) was performed on the pharmacokinetic parameters using the GLM procedures of SAS. The ANOVA model included the variables Sequence, Gender, Subject (nested in Sequence and Gender), Period and Treatment.	Phase 1	25 (24 completed)
Design of Study	**Analytical Site**	**Mode of Administration**
Single dose, randomized, open-label, two-way crossover study in healthy volunteers	Forest Laboratories, Inc.	Oral
Clinical Site	**Formulations**	
	1. Oxycodone/Ibuprofen 5 mg/400 mg tablet (Forest Laboratories, Inc., Lot #: 97002A; Manufacture Date: 1/13/1997) 2. Oxycodone/Ibuprofen 5 mg/200 mg tablet (Forest Laboratories, Inc., Lot #: 97047C; Manufacture Date: 1/21/1997)	

Test Formulations Administered	
Treatment A	**Treatment B**
One oxycodone HCl/ibuprofen (5 mg/400 mg) tablet (Forest Laboratories, Inc.), administered with 240 mL of water following a 10-hour overnight fast.	Two oxycodone HCl/ibuprofen (5 mg/200 mg) tablets (Forest Laboratories, Inc.), administered with 240 mL of water following a 10-hour overnight fast.

Summary and Conclusions

Subjects received the following treatments:

1. One oxycodone·HCl/ibuprofen (5 mg/400 mg) tablet (Forest Laboratories, Inc.) administered with 240 mL of water following a 10-hr overnight fast.

2. Two oxycodone·HCl/ibuprofen (5 mg/200 mg) tablets (Forest Laboratories, Inc.) administered with 240 mL of water following a 10-hr overnight fast.

The objective of this study was to evaluate the dose proportionality of oxycodone at 5 and 10 mg, when administered in the presence of the same amount of ibuprofen. This study was not designed as a bioequivalence study for ibuprofen.

Plasma and urine samples were analyzed for oxycodone, R-ibuprofen and S-ibuprofen with validated assays that displayed appropriate accuracy, linearity, reproducibility and precision. Total ibuprofen concentrations were calculated by adding the corresponding R-ibuprofen and S-ibuprofen concentrations.

Results:

The combined administration of oxycodone and ibuprofen from both Forest formulations was well tolerated and safe.

Total Ibuprofen				Oxycodone			
PK Parameter	2 x 5 mg/200 mg Oxycodone/ Ibuprofen Test	5 mg/400 mg Oxycodone/ Ibuprofen Reference	90% CI	PK Parameter	2 x 5 mg/200 mg Oxycodone/ Ibuprofen Test	5 mg/400 mg Oxycodone/ Ibuprofen Reference	90% CI
C_{max} (µg/mL) Observed	28.2 ± 7.5	32.4 ± 9.7	78 - 99	C_{max} (ng/mL) Observed	19.4 ± 5.6	10.2 ± 2.3	
				Dose-adjusted	9.7 ± 2.8		87 - 103
AUC_{0-t} (µg·hr/mL) Observed	124.3 ± 30.0	124.0 ± 29.0	96 - 103	AUC_{0-t} (ng·hr/mL) Observed	105.4 ± 32.1	47.4 ± 12.7	
				Dose-adjusted	52.7 ± 16.0		104 - 117
$AUC_{0-\infty}$ (µg·hr/mL) Observed	127.2 ± 29.4	126.5 ± 29.6	97 - 103	$AUC_{0-\infty}$ (ng·hr/mL) Observed	111.2 ± 33.1	52.3 ± 13.4	
				Dose-adjusted	55.9 ± 13.3		101 - 111

Dose proportionality was demonstrated for oxycodone at the dose levels of 5 and 10 mg oxycodone. Similar pharmacokinetic profiles were observed for total (racemic) ibuprofen after both treatments. Renal excretion of unchanged total ibuprofen was low (less than 0.2% of the administered ibuprofen dose). For oxycodone, less than 4% of the oxycodone dose was excreted unchanged in urine.

Total Ibuprofen			
PK Parameter	2 x 5 mg/200 mg Oxycodone/ Ibuprofen Test	5 mg/400 mg Oxycodone/ Ibuprofen Reference	90% CI
C_{max} (µg/mL) Observed	28.2 ± 7.5	32.4 ± 9.7	78 - 99
AUC_{0-t} (µg·hr/mL) Observed	124.3 ± 30.0	124.0 ± 29.0	96 - 103
$AUC_{0-\infty}$ (µg·hr/mL) Observed	127.2 ± 29.4	126.5 ± 29.6	97 - 103

Pharmacokinetic Parameters (Mean ± SD) of S-Ibuprofen after Both Treatments (n=23).

PK Parameter	Two Oxycodone/Ibuprofen (5 mg/200 mg) Tablets Test	One Oxycodone/Ibuprofen (5 mg/400 mg) Tablet Reference	90% CI or p-value
C_{max} (µg/mL)	13.1 ± 3.3	15.2 ± 4.7	78 – 99
AUC_{0-t} (µg•hr/mL)	64.9 ± 18.4	66.5 ± 17.0	93 - 101
$AUC_{0-\infty}$ (µg•hr/mL)	67.9 ± 18.0	69.0 ± 17.6	94 - 102
T_{max} (hr)	2.2 ± 1.7	2.3 ± 1.6	p-value: 0.8388
$T_{1/2}$ (hr)	2.6 ± 0.8	2.5 ± 0.9	p-value: 0.6572

	Oxycodone		
PK Parameter	**2 x 5 mg/200 mg Oxycodone/ Ibuprofen** **Test**	**5 mg/400 mg Oxycodone/ Ibuprofen** **Reference**	**90% CI**
C_{max} (ng/mL)			
Observed	19.4 ± 5.6	10.2 ± 2.3	
Dose-adjusted	9.7 ± 2.8		87 - 103
AUC_{0-t} (ng•hr/mL)			
Observed	105.4 ± 32.1	47.4 ± 12.7	
Dose-adjusted	52.7 ± 16.0		104 - 117
$AUC_{0-\infty}$ (ng•hr/mL)			
Observed	111.2 ± 33.1	52.3 ± 13.4	
Dose-adjusted	55.9 ± 13.3		101 - 111

SCHEDULE OF EVENTS FOR PHARMACOKINETIC SAMPLING AND VITAL SIGNS MONITORING

Day	Period	Dose	Pharmacokinetic Blood Sampling	Pharmacokinetic Urine Sampling	Meals	Vital Signs Monitoring
1	I	A: 1 X Oxycodone HCl 5 mg /Ibuprofen 400 mg tablet OR B:2 X Oxycodone HCl 5 mg /Ibuprofen 200 mg tablet	0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 16 and 24 hours post 0800 hour dose	-2-0, 0-2, 2-4, 4-6, 6-8, 8-10, 10-12 and 12-24 hour intervals post 0800 hour dose	L, D, S	0800 hour (Pre-Dose), 4 hrs and 24 hrs post-dose
8	II	A: 1 X Oxycodone HCl 5 mg /Ibuprofen 400 mg tablet OR B:2 X Oxycodone HCl 5 mg /Ibuprofen 400 mg tablet	0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 16 and 24 hours post 0800 hour dose	-2-0, 0-2, 2-4, 4-6, 6-8, 8-10, 10-12 and 12-24 hour intervals post 0800 hour dose	L, D, S	0800 hour (Pre-Dose), 4 hrs and 24 hrs post-dose

L = Lunch; D = Dinner; S = Snack

LSMEANS and ESTIMATE were used to calculate least square means for treatment effects. The plasma concentration data and the derived parameters tend to be skewed to the lower side of the distribution; therefore, the PK parameters of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were log-transformed before they were analyzed by the GLM procedure. Dose proportionality for oxycodone was evaluated by adjusting the parameters C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ and A_{ex} to the lower dose (5 mg oxycodone). The 90% confidence intervals for the ratio between the test and reference means were constructed for the pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ with the oxycodone/ibuprofen (5 mg/400 mg) as the reference formulation. The statistical output for all analytes is included in Appendix C.

Demographic Variable	All Completed Subjects (n=24)	All Completed Male Subjects (n=9)	All Completed Female Subjects (n=15)
Mean Age (years)	29.2	30.4	28.4
Min - Max	19 – 35	27 – 34	19 – 35
Standard Deviation	4.4	2.8	3.7
Mean Weight (kg)	66.2	72.5	62.1
Min - Max	46.4 – 83.6	61.8 – 83.6	46.4 – 69.1
Standard Deviation	8.2	6.6	6.4
Mean Height (cm)	163.2	173.8	156.9
Min – Max	147.0 – 180.0	163.0 – 180.0	147.0 – 165.0
Standard Deviation	10.3	6.9	5.5

Results:

Mean Urinary Parameters for Total Ibuprofen after Administration of Both Treatments (n=23).

PK Parameter	Oxycodone/Ibuprofen 2 x 5 mg/200 mg Tablets (total dose: 10 mg/400 mg) Test	Oxycodone/Ibuprofen 5 mg/400 mg Tablet (total dose: 5 mg/400 mg) Reference
$A_{ex(0-24hr)}$ (µg)	572.4 ± 337.3	445.5 ± 234.8
% Dose Excreted	0.14 ± 0.08	0.11 ± 0.06

Mean Urinary Parameters for S-Ibuprofen after Administration of Both Treatments (n=23).

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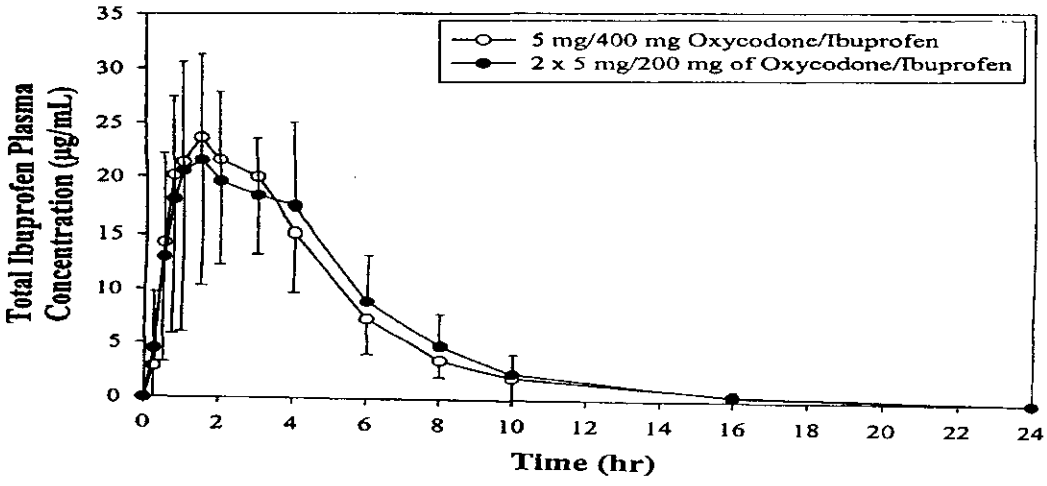
PK Parameter	Two Oxycodone/Ibuprofen (5 mg/200 mg) Tablets Test	One Oxycodone/Ibuprofen (5 mg/400 mg) Tablet Reference	p-value
$A_{ex(0\text{-}24hr)}$ (µg)	520.0 ± 309.5	416.8 ± 215.5	0.0533
% Dose Excreted	0.13 ± 0.08	0.10 ± 0.05	0.0487
CL_r/F (mL/hr)	8.0 ± 5.2	6.3 ± 3.3	0.0403

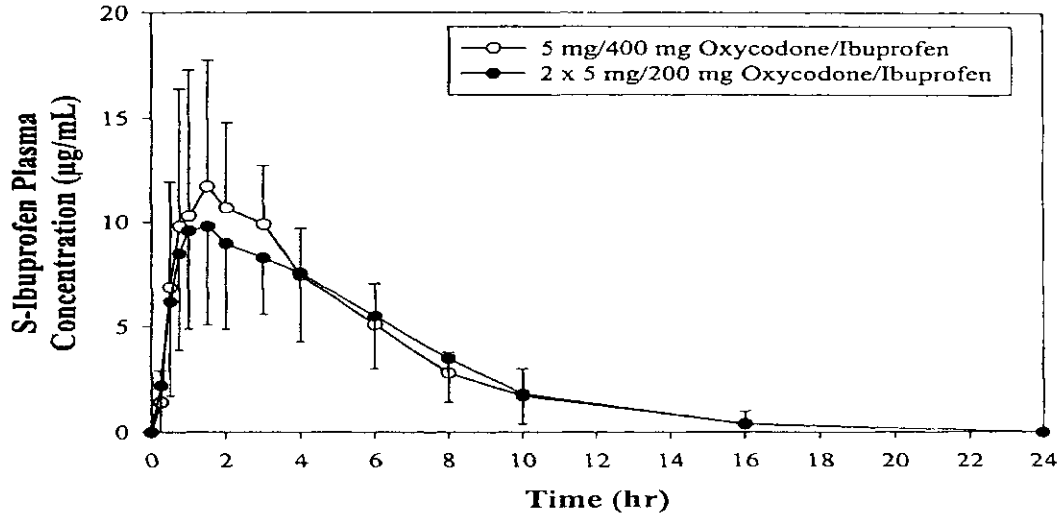
Mean Urinary Parameters for Oxycodone after Administration of Both Treatments (n=23).

PK Parameter	Oxycodone/Ibuprofen 2 x 5 mg/200 mg Tablets (total dose: 10 mg/400 mg) Test	Oxycodone/Ibuprofen 5 mg/400 mg Tablet (total dose: 5 mg/400 mg) Reference
$A_{ex(0\text{-}24hr)}$ (µg) Observed Dose-adjusted	 418 ± 160.4 209.0 ± 80.2	 213.2 ± 79.8
% Dose Excreted	4.2 ± 1.6	4.3 ± 1.6

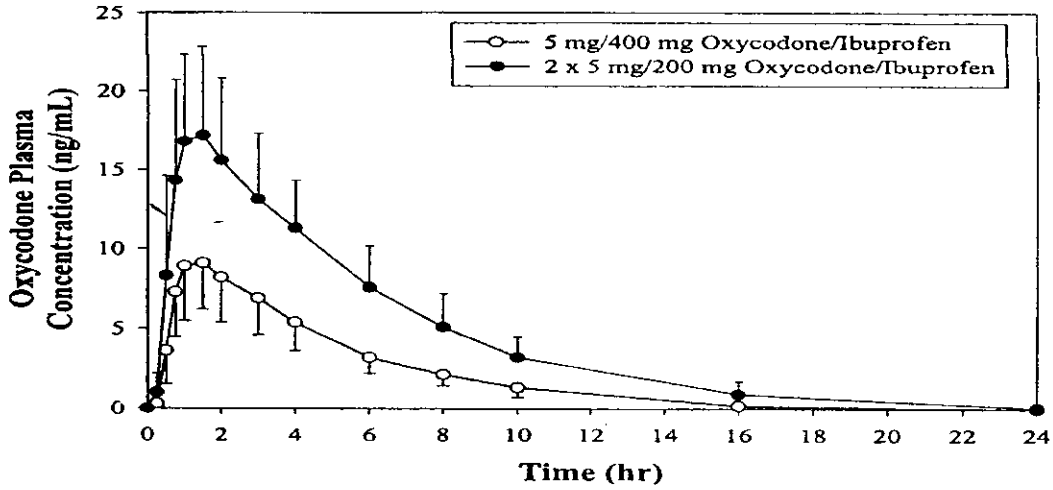
Mean Total Ibuprofen Plasma Concentrations (µg/mL) after Administration of One Oxycodone/Ibuprofen (5 mg/400 mg) Tablet and Two Oxycodone/Ibuprofen (5 mg/200 mg) Tablets.



Average S-Ibuprofen Plasma Concentration Plots after Administration of Both Treatments



Mean Oxycodone Plasma Concentrations (µg/mL) after Administration of One Oxycodone/Ibuprofen (5 mg/400 mg) Tablet and Two Oxycodone/Ibuprofen (5 mg/200 mg) Tablets.



Mean Cumulative Amounts of Total Ibuprofen in Urine after Administration One Tablet of Oxycodone/Ibuprofen (5 mg/400 mg) and Two Tablets of Oxycodone/Ibuprofen (5 mg/200 mg).

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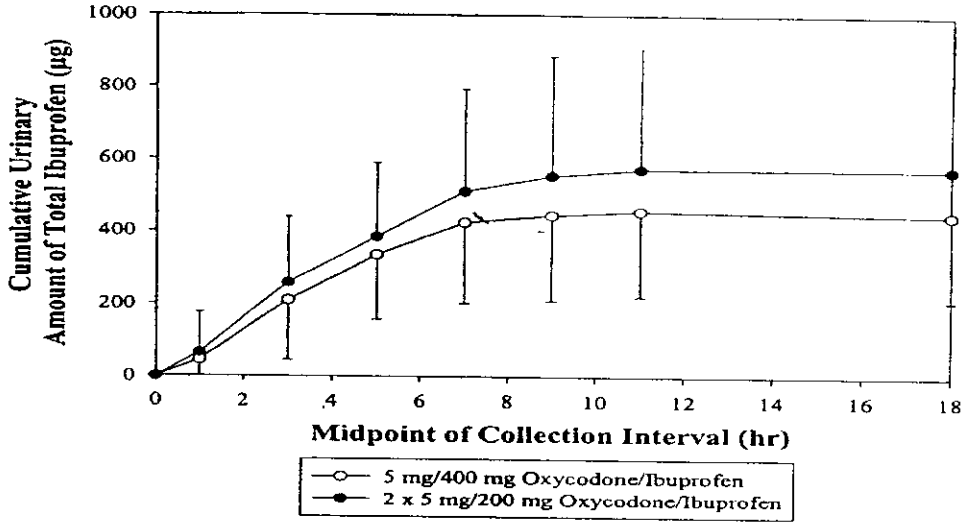
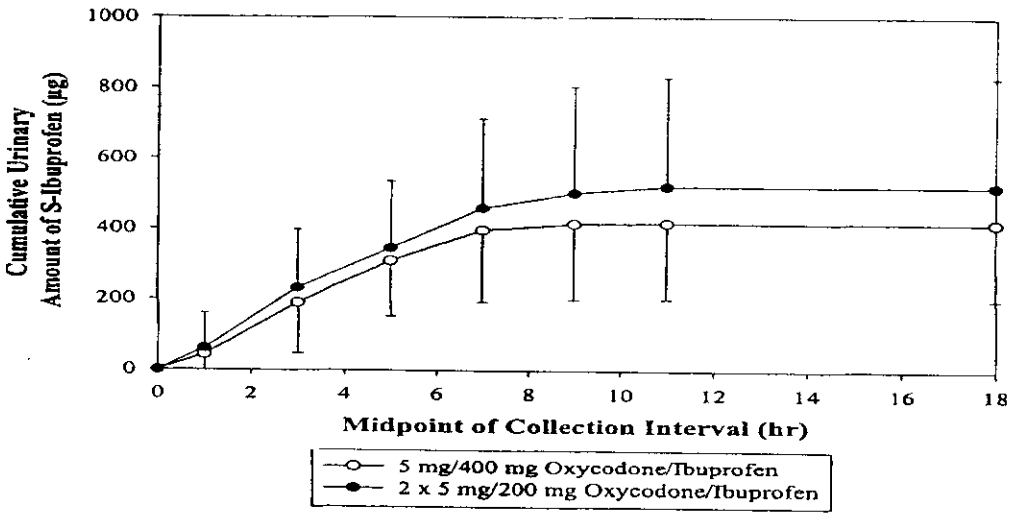


Mean Cumulative Amounts of S-Ibuprofen in Urine after Administration One Tablet of Oxycodone/Ibuprofen (5 mg/400 mg) and Two Tablets of Oxycodone/Ibuprofen (5 mg/200 mg).



Mean Cumulative Amounts of Oxycodone in Urine after Administration One (1) Tablet of Oxycodone/Ibuprofen (5 mg/400 mg) and Two Tablets of Oxycodone/Ibuprofen (5 mg/200 mg).

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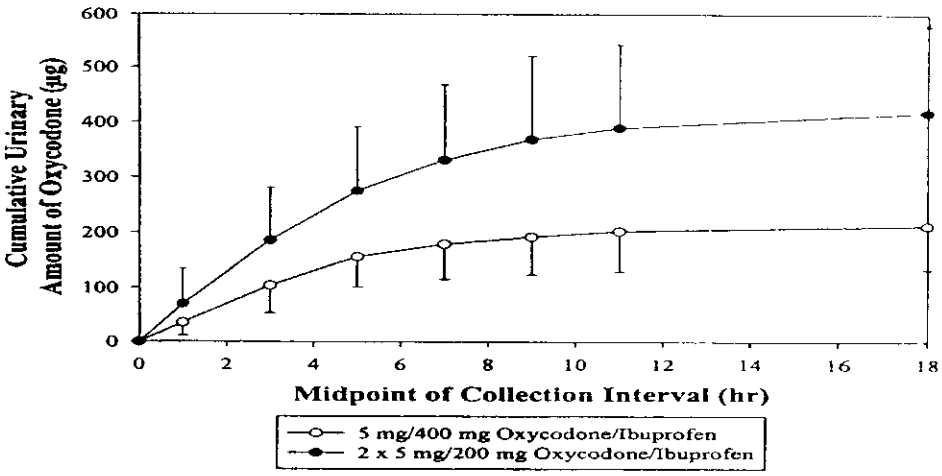

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Other Studies:

Forest Study OXY-MD-05

NAME OF SPONSOR/COMPANY: Forest Laboratories, Inc.	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
NAME OF FINISHED PRODUCT: oxycodone HCl/ibuprofen	Volume:	
NAME OF ACTIVE INGREDIENTS: oxycodone HCl, 5 mg ibuprofen, 400 mg	Page:	

TITLE OF STUDY: A double-blind, placebo-controlled, single-dose parallel study of the analgesic efficacy and safety of oxycodone HCl/ibuprofen 5/400 mg compared to ibuprofen 400 mg alone and oxycodone HCl 5 mg alone in patients with moderate to severe pain following dental surgery

INVESTIGATORS:

STUDY CENTERS:

PUBLICATION (REFERENCE): NA

STUDY PERIOD: April 4, 2000 through November 10, 2000	**DEVELOPMENT PHASE:** III

OBJECTIVES:
Primary: To determine the analgesic efficacy of a single dose of a combination tablet of oxycodone HCl/ibuprofen 5/400 mg relative to oxycodone HCl 5 mg alone, ibuprofen 400 mg alone, and placebo using the third-molar-extraction pain model
Secondary: To characterize the pharmacokinetic profile of the combination drug relative to its active ingredients

METHODOLOGY: Under supervision of Study Coordinator, patients recorded in diary card their assessments over time of pain relief, pain intensity, and overall evaluation of the study drug, based upon mutually agreed upon definition of terms.

STUDY DESIGN: Multisite, double-blind, double-dummy, randomized, parallel-group, single-dose, placebo- and active-controlled study. Patients were randomized to treatment groups in a 3:3:1:1 ratio (Combination 5/400:Ibuprofen 400: Oxycodone HCl 5:Placebo)

NUMBER OF PATIENTS (PLANNED, RANDOMIZED, AND ANALYZED):
448 planned; 498 randomized, 498 analyzed for safety, 497 analyzed for efficacy. A subgroup of 32 patients planned; 36 enrolled; 31 analyzed for pharmacokinetics.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Male and female patients in good health, age 12 years or older who were scheduled for extraction of at least two ipsilateral, bony impacted (partial or complete) third molars.

STUDY DRUG, DOSE AND MODE OF ADMINISTRATION, LOT NUMBER:

Study Medication*	Tablet/Capsule Strength	Lot Number
Oxycodone HCl/Ibuprofen	5 mg/400 mg tablet	99229K
Oxycodone HCl	5 mg oral capsule	119960
Ibuprofen†	200 mg capsule	119959
Placebo X	0 mg tablet	99247L
Placebo Y	0 mg capsule	119958

* The oxycodone HCl/ibuprofen combination and placebo X tablets are identical. Oxycodone HCl, ibuprofen, and placebo Y capsules are identical.
† The ibuprofen 400 mg dose consists of two 200 mg dose capsules.

DURATION OF TREATMENT: Single dose with a subsequent 6-hour observation and evaluation period

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER: Ibuprofen 200 mg capsules (Lot No. 119959), oxycodone HCl 5 mg capsules (Lot No. 119960), placebo tablet (Lot No. 99247L) or placebo capsules (Lot No. 119958) given orally.

CRITERIA FOR EVALUATION:

EFFICACY

Primary: 6-hour total pain relief ($TOTPAR_6$) and 6-hour sum of pain intensity differences ($SPID_6$)

Secondary: 3-hour TOTPAR and SPID, pain relief (PR) at each time point, pain intensity difference (PID) at each time point, combined PR and PID at each time point, peak PR, peak PID, PRID, peak PRID, time to remedication, time to onset of pain relief, proportion of patients reporting pain half gone, and patient global rating.

PHARMACOKINETIC

Area under the ibuprofen and oxycodone plasma concentration time curves (AUC_{0-t}), maximum plasma concentrations (C_{max}) and time to maximum concentration (t_{max}).

SAFETY

Volunteered and observed adverse events and vital sign measurements.

STATISTICAL METHODS:

The efficacy analysis was based on the intent-to-treat (ITT) population, which included all randomized patients who received study medication and had a post-baseline efficacy evaluation. For each patient, missing PR and PI data during the treatment period was imputed using the last observation carried forward (LOCF) procedure. All statistical tests were two-sided with 5% significance level for main effects, and 10% significance level for interaction terms.

Each of the continuous parameters was analyzed using an analysis of variance (ANOVA) model. Categorical parameters were analyzed using the Cochran-Mantel-Haenszel (CMH) test. Time-to-event parameters were analyzed using Kaplan-Meier survival estimates and the log-rank test.

SUMMARY – CONCLUSIONS

Efficacy Results:

In the treatment of postoperative dental pain, a single dose of the combination treatment, oxycodone HCl/ibuprofen 5/400 mg (1) Was more effective in overall analgesia, over the entire 6-hour evaluation period ($TOTPAR_6$ and $SPID_6$), than ibuprofen 400 mg ($p<0.05$ for normalized data); or oxycodone HCl 5 mg ($p<0.001$); (2) Exhibited, through 3 hours postdose, superior ($p<0.001$) overall analgesia ($TOTPAR_3$ and $SPID_3$) and statistically significantly higher PR, PID, and PRID scores at individual time points compared with ibuprofen 400 mg or oxycodone HCl 5 mg taken alone; (3) Demonstrated time to onset and peak of analgesia characteristics that were superior compared with ibuprofen 400 mg ($p<0.05$) or oxycodone HCl 5 mg ($p<0.05$ and $p<0.001$, respectively); (4) At individual time points, was statistically significantly superior in the proportion of patients reporting pain half gone compared with ibuprofen or oxycodone taken alone; (5) Resulted in Patient's Global Evaluation Scores that were statistically significantly superior to ibuprofen 400 mg ($p<0.05$) or oxycodone HCl 5 mg ($p<0.001$) taken alone; (6) and along with the ibuprofen 400 mg alone group demonstrated statistically significant improvements in all primary and secondary endpoints compared with the placebo treatment group.

There was a 14% increase in the AUC for the least mean $TOTPAR_6$ value for the oxycodone HCl/ibuprofen 5/400 mg group compared with ibuprofen alone. Similarly, there was a 22.2% increase in the AUC for the least square mean $SPID_6$.

Total Pain Relief Scores over 6 Hours ($TOTPAR_6$)

Pairwise Comparison	LS Mean	SE	95% CI	p-value
Combination* vs. Ibuprofen 400 mg	1.17	0.65	-0.10, 2.44	0.012+
Combination vs. Oxycodone HCl 5 mg	9.05	0.91	7.27, 10.84	<0.001

Sum of Pain Intensity Difference Scores over 6 Hours ($SPID_6$)

Pairwise Comparison	LS Mean	SE	95% CI	p-value
Combination vs. Ibuprofen 400 mg	1.13	0.41	0.31, 1.94	0.002+
Combination vs. Oxycodone HCl 5 mg	6.40	0.58	5.26, 7.54	<0.001

*Combination=oxycodone HCl/ibuprofen 5/400 mg combination tablet

+Based on analysis of normalized data; p=0.070 ($TOTPAR_6$) and p=0.007 ($SPID_6$) for analysis of new dataset.

Pharmacokinetic Results (N=32): The pharmacokinetics of ibuprofen and oxycodone were similar following administration of the combination treatment or either of the active components alone. There was no apparent relationships between the primary efficacy results and the plasma concentrations of either ibuprofen or oxycodone.

Safety Results: The percent of patients with at least one TEAE was comparable for oxycodone HCl/ibuprofen 5/400 mg (15.5%) ibuprofen alone (10.8%), and placebo (11.3%). Patients receiving oxycodone 5 mg had the highest incidence of TEAEs (27.0%). Overall, the most common TEAEs were nausea and vomiting, occurring in 6.6% and 5.0% respectively of patients overall. Mild to moderate TEAEs were the most frequently reported (98.6%) in all treatment groups. There were no serious adverse events or deaths reported. Two patients in the combination group (1.1%) experienced at least one TEAE (nausea and/or vomiting) that led to discontinuation. Across treatment groups, mean values for vital signs measurements were within the normal range.

CONCLUSION

This single-dose, double-blind, parallel study of the combination analgesic, oxycodone HCl/ibuprofen 5/400 mg, demonstrated clinically important improvements in postoperative dental pain. Compared with oxycodone or ibuprofen alone, the combination treatment provided statistically significant improvements in the primary endpoints, $TOTPAR_6$ and $SPID_6$, and all of the secondary endpoints. Compared with placebo, there were statistically significant improvements in all primary and secondary endpoints for the oxycodone HCl/ibuprofen 5/400 mg and ibuprofen 400 mg dose groups. The combination of oxycodone/ibuprofen was safe and well tolerated.

DATE OF THE REPORT: November 12, 2001

Forest Study OXY-MD3-96-01-000

Name of Sponsor/Company: Forest Laboratories, Inc. **Name of Finished Product:** Oxycodone HCl 5 mg/Ibuprofen 400 mg (combination) **Name of Active Ingredient(s):** 14-hydroxydihydrocodeinone HCl, (±)-2-(*p*-isobutylphenyl) propionic acid	**Individual Study Table Referring to Part IV of Dossier:** **Volume:** **Page:**	*(For National Authority Use Only)*

Title: A Double-Blind, Single Dose Clinical Evaluation of the Analgesic Efficacy, Safety and Pharmacokinetics of Oxycodone HCl 5 mg/Ibuprofen 400 mg versus Ibuprofen 400 mg Alone, Oxycodone HCl 5 mg Alone and Placebo in Patients with Moderate to Severe Pain Following Dental Surgery

Investigators:

Study center(s): 7

Publication (reference): None

Study period: 02 April 1997 (date of first enrollment) 29 September 1997 (date of last patient completion)	**Development phase:** II (Originally planned as Phase III)

Objectives: This study was designed to evaluate the analgesic efficacy and safety of the combination drug oxycodone HCl 5 mg/ibuprofen 400 mg compared to oxycodone HCl 5 mg alone, ibuprofen 400 mg alone, and placebo; and to characterize the pharmacokinetic profile of the combination drug relative to its active ingredients.

Study Design: This was a two-center, double-blind, randomized, placebo- and active-controlled, parallel-group, single-dose study.

Number of patients:
Planned – 448 patients; 168 patients each in the oxycodone HCl/ibuprofen 5/400 mg and ibuprofen 400 mg groups and 56 patients each in the oxycodone HCl 5 mg and placebo groups.
Analyzed (Efficacy, Center 01 only) – 179 randomized patients; 69 patients in the oxycodone HCl 5 mg/ ibuprofen 400 mg group, 65 patients in the ibuprofen group, 22 patients in the oxycodone HCl 5 mg group, and 23 patients in the placebo group. All patients were included in the intent-to-treat patient population.
Analyzed (Pharmacokinetics) – 32 patients total: 12 patients received in the oxycodone/ibuprofen 5/400 mg group; 12 patients in the 400 mg ibuprofen group; 4 patients in the oxycodone 5 mg group and 4 patients in the placebo group.
Analyzed (Safety) – 453 randomized patients; 171 patients in the oxycodone HCl/ibuprofen 5/400 mg group, 168 patients in the ibuprofen group, 56 patients in the oxycodone HCl 5 mg group, and 58 patients in the placebo group.

Diagnosis and main criteria for inclusion: Male and female subjects in good health, at least 16 years of age, who were scheduled for extraction of at least two ipsilateral, bony impacted (partial or complete) third molars.

Study drug treatment group, dose and mode of administration, batch number: Single tablet of oxycodone HCl 5 mg and ibuprofen 400 mg (Lot No. 28470) and two placebo capsules (Lot No. C-9704) administered orally as a single dose.

Duration of treatment: Single oral dose followed by an 8-hour assessment period.

Reference therapy, dose and mode of administration, batch number: All patients received a single dose consisting of one tablet and two capsules of identical appearance across all treatment groups as follows: two capsules of ibuprofen 200 mg (Lot No. C-9703) plus one placebo tablet (Lot No. 28487); one capsule of oxycodone HCl 5 mg (Lot No. C-9706) plus one placebo capsule (Lot No. C-9704) and one placebo tablet (Lot No. 28487); or one placebo tablet (Lot No. 28487) and two placebo capsules (Lot No. C-9704)

Criteria for Evaluation

Efficacy evaluations:

Primary – 8-hour total pain relief ($TOTPAR_8$) and sum of pain intensity differences ($SPID_8$).

Secondary – 3-hour TOTPAR, 3-hour $SPID_3$, at each timepoint, pain relief (PR) pain intensity difference (PID), the combined end point PR + PID = PRID, peak PR, peak PID, and peak PRID; time to remedication, time to onset of relief, and patient global rating.

Pharmacokinetic:

Area under the ibuprofen and oxycodone plasma concentration time curves (AUC_{0-t}), maximum plasma concentrations (C_{max}) and time to maximum concentration (t_{max}).

Safety evaluations: Adverse events and vital sign measurements.

Statistical Methods

Efficacy:

All efficacy analyses were based on the ITT patient population enrolled at study center 1. The primary efficacy parameters ($SPID_8$ and $TOTPAR_8$) were analyzed using ANOVA models with terms for treatment group, investigator site, and investigator by treatment interaction. Each factor was tested using the mean square error (MSE) from the overall model. If the treatment group factor was significant at the 0.05 level, then pairwise comparisons using Fisher's multiple comparison procedure, with each comparison done at the 0.05 level of significance, were performed.

For the secondary efficacy parameters, each of the continuous parameters was analyzed using an ANOVA model. Categorical parameters were analyzed using Cochran-Mantel-Haenszel test. Time-to-event parameters were analyzed using Kaplan-Meier survival estimates and the logrank test.

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Summary:

Efficacy Results: In the treatment of postoperative dental pain, the combination treatment, oxycodone/ibuprofen, as a single dose of 5/400 mg: 1) was superior, over the entire 8-hour evaluation period ($TOTPAR_8$ and $SPID_8$), to either ibuprofen 400 mg ($p = 0.044$ for $TOTPAR_8$ and $p = 0.041$ for $SPID_8$) or oxycodone 5 mg ($p < 0.001$ for both parameters) taken alone. 2) exhibited superior analgesic effects through 3 hours as measured by $TOTPAR_3$ and $SPID_3$ ($p < 0.05$) and significantly higher ($p < 0.05$) PR, PID, and PRID scores during the first hours post-dose compared with ibuprofen 400 mg and oxycodone 5 mg taken alone. 3) demonstrated shorter onset of pain relief times compared with ibuprofen 400 mg ($p = 0.014$) or oxycodone 5 mg ($p < 0.001$) and longer times to remedication compared with oxycodone 5 mg ($p < 0.001$) taken alone. 4) resulted in Patient's Global Evaluation Scores that were superior to ibuprofen 400 mg alone ($p=0.048$) or oxycodone 5 mg alone ($p< 0.001$), 5) yielded greater proportions of patients with pain half gone ($p < 0.05$) during the first hour post-dose compared with either ibuprofen 400 mg alone or oxycodone HCl 5 mg alone. Both the 5/400 mg combination regimen and ibuprofen given alone demonstrated statistically significant improvements in all primary and secondary endpoints compared with placebo treatment.

Because only the data from Study Center 1 were used in the efficacy analyses , the sample size used in these analyses was approximately 40% of the size that was originally planned. The fact that statistically significant differences were achieved between the oxycodone HCl/ibuprofen 5/400 mg group and the individual active components reflects the robust nature of the treatment differences.

Pharmacokinetic Results (N=32): The pharmacokinetics of ibuprofen and oxycodone were similar following administration of the combination treatment or either of the active components alone. There was no apparent relationships between the primary efficacy results and the plasma concentrations of either ibuprofen or oxycodone.

Safety Results: Adverse events were reported in 19% of the patients in this study; 14% of patients in the placebo group, 29% of the patients in the oxycodone HCl 5 mg group, 8% of patients in the ibuprofen 400 mg group, and 28% of the patients in the oxycodone HCl/ibuprofen 5/400 mg combination group. The most frequently reported adverse events (at least 5% of patients in any treatment group) included somnolence, dizziness, nausea, vomiting, and headache. Comparing these TEAEs across groups, somnolence (15.2%) was reported more frequently in the oxycodone HCl/ibuprofen 5/400 mg groups than in the ibuprofen 400 mg (3.6%) or oxycodone HCl 5 mg (5.4%) groups; dizziness (12.3%) and nausea (6.4%) were reported more frequently in the oxycodone/ibuprofen 5/400 mg group than in the ibuprofen 400 mg group (2.4% and 0%, respectively) and vomiting (12.5%), nausea (16.1%) and headache (5.4%) were reported more frequently in the oxycodone HCl 5 mg group than in the oxycodone HCl/ibuprofen 5/400 mg group (4.1, 6.4 and 2.3%, respectively). The vast majority of the AEs reported in this study were mild or moderate in intensity. A total of four patients discontinued the study due to adverse events (one patient in the placebo group, one patient in the ibuprofen group, and two patients in the oxycodone HCl/ibuprofen group). One patient (ibuprofen group) experienced two serious adverse events (cholecystitis and cholelithiasis) considered to be unlikely to be related to the study medication. No deaths occurred in the study. No clinically relevant changes in vital signs were observed.

Conclusions:

This single-dose, double-blind, parallel study of the combination analgesic, oxycodone HCl/ibuprofen 5/400 mg, demonstrated clinically important improvements in postoperative dental pain. Compared with oxycodone or ibuprofen alone, the combination treatment provided statistically significant improvements in the primary endpoints, $TOTPAR_8$ and $SPID_8$, and all of the secondary endpoints. Compared with placebo, there were statistically significant improvements in all primary and secondary endpoints for the oxycodone HCl/ibuprofen 5/400 mg and ibuprofen 400 mg dose groups. The combination of oxycodone/ibuprofen was safe and well tolerated.

Date of the Report: November 20, 2001

6.3 Assay information

5 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

___ § 552(b)(5) Draft Labeling

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