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APPLICATION NUMBER:

20-732

20-733

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 20-733/N-000 BB

SUBMISSION DATE: 9/10/02

NAME: Suboxone[®] (Buprenorphine HCl/Naloxone HCl) 2mg/0.5mg, 8mg/2mg Sublingual Tablets

SPONSOR: Reckitt Benckiser Pharmaceuticals, Inc., 1909 Huguenot Road, Richmond, VA

SUBMISSION TYPE: Original Amendment

REVIEWER: Suresh Doddapaneni, Ph.D.

I. Executive Summary

Currently, the Agency is evaluating the sponsor's response to the deficiencies outlined in the approvable letter (dated 1/26/01) for NDA 20-733. During this review cycle, the sponsor proposed changing the shape of the sublingual tablet from the previously tested (clinical and pharmacokinetic studies)  shape to the new hexagonal shape to  of the tablet. Since, only two strengths are available (2 mg and 8 mg) and multiples of these two strengths will be used to achieve a range of doses (4 mg to 24 mg), there was a concern that the new shape may affect the *in vivo* bioavailability as the hexagon shaped tablet may fit poorly under the tongue when multiple tablets are used (for a 20 mg dose, two each of 8 mg and 2 mg tablets will be used). In order to address this concern, the sponsor conducted a study in healthy volunteers tracking the *in vivo* dissolution of the hexagon shaped tablets relative to the  shaped tablet (Study 02-3). In this submission, the sponsor submitted the results of this study. This issue also pertains to NDA 20-732 (Subutex[®]) which contains buprenorphine only and which is also currently undergoing evaluation of the data submitted in response to the approvable letter to this NDA. No significant differences were evident between the new hexagon shaped tablets and the previously tested  shaped tablets with respect to *in vivo* dissolution times.

II. Recommendation

From the viewpoint of Division II of the Office of Clinical Pharmacology and Biopharmaceutics, this submission is acceptable.

Suresh Doddapaneni
Team Leader
DPEII/OCPB

Concurrence: John Hunt 
Deputy Director
DPEII/OCPB

CC: NDA 20-733, Celia Winchell, Cynthia McCormick, Dale Koble, Ali Al-Hakim, Pat Maturu, Albert Chen, Suresh Doddapaneni, John Hunt, Henry Malinowski.

Study Summary

This was an open-label, randomized, three-treatment, three-way crossover study with at least a three day washout period between each treatment. The three treatments were;

Reference:

A. Simultaneous dosing of — shaped tablets: 20 mg dose (4 tablets, 2 x 2 mg+ 2 x 8 mg tablets) simultaneously underneath the tongue.

Test:

B. Simultaneous dosing of hexagon shaped tablets: 20 mg dose (4 tablets, 2 x 2 mg+ 2 x 8 mg tablets) simultaneously underneath the tongue.

C. Sequential dosing of hexagon shaped tablets: 20 mg dose administered sequentially as two 8 mg tablets initially followed by two 2 mg tablets.

The lot numbers of the tablets used in this study were; — Suboxone 2 mg tablets -batch # 20720090, — Suboxone 8 mg tablets- batch # 20590090, hexagon Suboxone 2 mg tablets - batch # 26497, and hexagon Suboxone 8 mg tablets -batch # 24088.

Subjects received 100 mg naltrexone orally 24 hours and 1 hour before and 24 hours after Suboxone administration to counteract buprenorphine's opioid agonist effects.

A total of 9 subjects were enrolled in the study. These eight subjects ranged in age from 23 to 41 years of age and weighed in the range of 57 to 102 kg.

Subjects were advised to place study medications under the tongue and to avoid swallowing until the tablets were dissolved. The sublingual space was briefly examined at 5-minute intervals after dosing and the state of the tablets in the mouth recorded. Subjects signaled by hand when subjectively they believed that the tablets were dissolved. The time required for all the tablets to completely dissolve was recorded.

For Simultaneous dosing, mean of 15.9 minutes was observed for — tablets to dissolve *in vivo* compared to 13.6 minutes for the hexagon tablets (Table 1). For sequential dosing, mean of 18.6 minutes was observed. These differences are minor and overall, it can be concluded that significant differences were not evident between the new hexagon shaped tablets and the previously tested — shaped tablets with respect to *in vivo* dissolution times. In vitro dissolution test data submitted previously showed that both — and hexagon tablets met the specification of —

Table 1. In vivo dissolution times of hexagon and oval shaped tablets.

IN VIVO TESTING OF BUPRENORPHINE AND NALOXONE (SUBOXONE®) SUBLINGUAL TABLETS Study 02-3				
Comparison of Mean In Vivo Tablet Dissolution Times (min) between Dosing Regimens using Repeated Measures ANOVA				
	Simultaneous Dosing: — Tablets (Treatment A)	Simultaneous Dosing: Hexagon Tablets (Treatment B)	Sequential Dosing: Hexagon Tablets (Treatment C) 1st Dosing	Sequential Dosing: Hexagon Tablets (Treatment C) 2nd Dosing
Subject 02031 02032 02039 02040 02041 02042 02047 02055 02057	<u>Sublingual Tablet Dissolution Time (min)</u>			
Mean	15.9	13.6	11.3	18.6
SD	15.3	6.7		14.3
SE	5.1	2.2		4.8
Variance	234.6	45.5		205.3
CV	96.4	49.8		77.2
Minimum	[]	[]		[]
Maximum	[]	[]		[]
Range	[]	[]		[]
P value	<i>p</i> = 0.22, n.s.			

SD = Standard Deviation; SE = Standard Error; CV = Coefficient of Variation. Statistical significance was measured at $p \leq 0.05$.

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John P. Hunt
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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 20-733

SUBMISSION DATE: 2/4/02

NAME: Suboxone[®] (Buprenorphine HCl/Naloxone HCl) 2mg/0.5mg, 8mg/2mg Sublingual Tablets

SPONSOR: Reckitt Benckiser Pharmaceuticals, Inc., 1909 Huguenot Road, Richmond, VA

SUBMISSION TYPE: General Correspondence REVIEWER: Suresh Doddapaneni, Ph.D.

I. Background

An approvable letter for NDA 20-733 was sent on January 26, 2001. In it, a pharmacokinetic study was requested to be conducted as outlined below;

Conduct a pharmacokinetic study to establish the proper method of administering doses requiring more than two tablets of buprenorphine, comparing simultaneous dosing at various intervals, in order to provide specific dosing instructions to patients and physicians that will permit the accurate delivery of the desired dose.

This issue also pertains to NDA 20-732 (Subutex[®]) which contains buprenorphine only. Previous Clinical Pharmacology and Biopharmaceutics reviews of NDA's 20-732 (dated 2/10/98) & 20-733 (dated 9/11/99) contain discussions of this issue. To address this deficiency, the sponsor developed a protocol entitled "A Pharmacokinetic Study of Simultaneous and Sequential Dosing of Buprenorphine and Naloxone (Suboxone) Sublingual Tablets in Healthy Volunteers Pretreated with Naltrexone (Study 01-1)". On July 8 of 2001 the sponsor was provided feedback in a teleconference on the design aspects of this study. In this submission, the sponsor submitted the report for this study.

II. Comments

Based on the results of this study, the following should be stated in the D & A section of the package insert for Subutex[®] and Suboxone[®];

For doses requiring the use of more than two tablets, depending upon their comfort, patients are advised to either place all the tablets at once or alternatively (if they cannot fit more than two tablets comfortably) place two tablets at a time underneath the tongue. Either way, the patients should continue to hold the tablets until they are fully dissolved swallowing the tablets reduces the bioavailability of the drug. should follow the same manner of dosing with continued use of the product.

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III. Recommendation

From the viewpoint of Division II of the Office of Clinical Pharmacology and Biopharmaceutics, the sponsor adequately addressed the deficiency stated in the approvable letter dated January 26, 2001 for NDA 20-733. The results of this study should be incorporated into the package insert as stated in the Comments section.

/S/

Suresh Doddapaneni
Team Leader
DPEII/OCPB

Concurrence: John Hunt _____
Deputy Director
DPEII/OCPB

CC: NDA 20-733, Celia Winchell, Cynthia McCormick, Dale Koble, Ali Al-Hakim, Pat Maturu, Albert Chen, Suresh Doddapaneni, John Hunt, Henry Malinowski.

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Study Summary

This was an open-label, randomized, two-treatment, two-way crossover study with a two-week washout period between each treatment. The two treatments were;

Simultaneous dosing: 20 mg dose (4 tablets, 2 x 2 mg+ 2 x 8 mg tablets) simultaneously underneath the tongue.

Sequential dosing: 20 mg dose administered sequentially as two 8 mg tablets initially followed by two 2 mg tablets.

The lot numbers of the tablets used in this study were; Suboxone 2 mg tablets -lot # 00620052 & Suboxone 8 mg tablets- lot # 00620053.

Subjects received 100 mg naltrexone orally 24 hours and 1 hour before and 24 hours after Suboxone administration to counteract buprenorphine's opioid agonist effects.

A total of 14 subjects were enrolled in the study. The first six swallowed the tablets at 10 minutes instead of holding until dissolution. Additional eight subjects were then enrolled into the study and provide the database for the objective of the study. These eight subjects ranged in age from 25 to 43 years of age and weighed in the range of 53 to 85 kg.

Blood samples were obtained at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, and 72 hours post dose.

Subjects were advised to place study medications under the tongue and to avoid swallowing until the tablets were dissolved. The sublingual space was briefly examined at 5-minute intervals after dosing and the state of the tablets in the mouth recorded. Subjects signaled by hand when subjectively they believed that the tablets were dissolved. Sequential doses were held sublingually for up to 25 minutes and simultaneous doses were held for up to 37 minutes before swallowing was permitted.

An LC/MS/MS method with _____ LOD for buprenorphine and naloxone was used for analysis. The LLOQ was _____ ng/mL for both buprenorphine and naloxone. The standard curve ranged from _____ ng/mL for both. The inter-day precision ranged from 5.2% to 6.5% for buprenorphine and from 6.6% to 8.4% for naloxone. The accuracy ranged from -2.7% to 9.13% for buprenorphine and from -2.7% to 7.9% for naloxone.

No significant differences were found between simultaneous and sequential dosing with respect to the *in vivo* dissolution times and pharmacokinetic parameters of buprenorphine and naloxone (Table 1 and Table 2). However, in both cases the tablet dissolution times were quite long for a sublingual dosage form. It took an average of 22 minutes for the simultaneous dosing and 18 minutes for sequential dosing. It has to be pointed out that potentially five tablets can also be used (for a 22 mg dose-2 x 8 mg + 3 x 2 mg tablets). In the previous pharmacokinetic studies

subjects were instructed to swallow the tablets after 10 minutes. This study points out that the subjects can use either method depending upon their comfortability but that they should hold the tablets until they are dissolved and not swallow them prematurely.

Table 1. Pharmacokinetic parameters for buprenorphine after the administration of 20 mg dose of Suboxone simultaneously and sequentially.

Subject	In vivo dissolution time (minutes)			T _{max} (hour)		C _{max} (ng/mL)		AUC _{0-∞} (ng hour/mL)	
	Sim	Seq1*	Seq2#	Sim	Seq	Sim	Seq	Sim	Seq
1044									
1046									
1057									
1063									
1069									
1084									
1085									
1095									
Mean	22.1	17.6	8.13	1.16	1.16	5.62	7.18	44.0	47.8
%CV	37.8	33.2	38.6	41.6	32.6	42.7	57.5	24.0	39.5

* Sequential first dose (2 x 8 mg tablets)

Sequential second dose (2 x 2 mg tablets)

Table 2. Pharmacokinetic parameters for naloxone after the administration of 20 mg dose of Suboxone simultaneously and sequentially.

Subject	In vivo dissolution time (minutes)			T _{max} (hour)		C _{max} (ng/mL)	
	Sim	Seq1*	Seq2#	Sim	Seq	Sim	Seq
1044							
1046							
1057							
1063							
1069							
1084							
1085							
1095							
Mean	22.1	17.6	8.13	0.8	0.9	0.201	0.180
%CV	37.8	33.2	38.6	31	25	45	47.4

* Sequential first dose (2 x 8 mg tablets)

Sequential second dose (2 x 2 mg tablets)

Note: AUC not shown, as the plasma levels were not quantifiable beyond 3 hours post dosing.

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/s/

Suresh Doddapaneni
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John P. Hunt
6/5/02 11:39:57 AM
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**NDA 20-732 (Subutex 2 and 8 mg sublingual tablets)
and NDA 20-733 (Subuxone 2 and 8 mg sublingual
tablets)**

Attachment 1

**Dissolution Data/Profiles (01/11/02, 02/01/02, and
02/04/02 Submissions)**

8 Page(s) Withheld

**C. 02/04/02 Dissolution Data/Profiles for the Subuxone Biobatches
used in the PK Study No. 01-1**

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Suboxone 2mg Batch 00620052

% buprenorphine dissolution (with respect to label claim)

Sample time (Min)	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Mean	StdDev
0							0	0.0
1							23	6.9
3							65	11.9
5							90	6.4
7.5							96	3.0
10							95	3.3
15							92	1.4
20							88	1.8

Suboxone 2mg Batch 00620052

% naloxone dissolution (with respect to label claim)

Sample time (Min)	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Mean	StdDev
0							0	0.0
1							30	7.7
3							74	10.8
5							96	2.3
7.5							97	1.1
10							96	1.2
15							95	0.5
20							93	1.1

Suboxone 8mg Batch 00620053

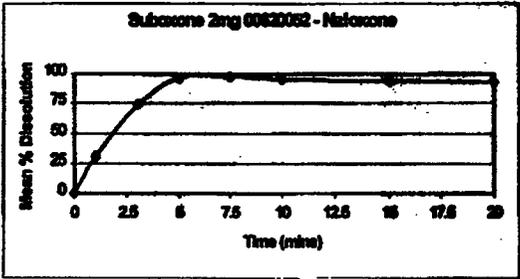
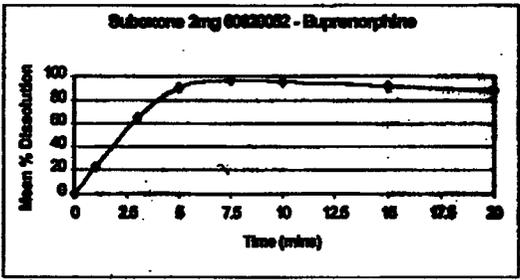
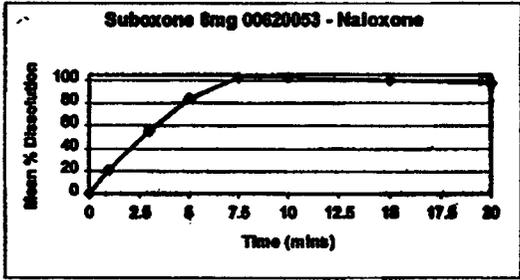
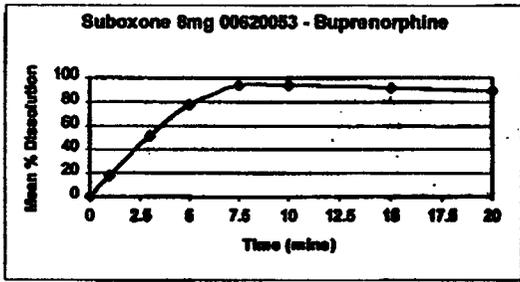
% buprenorphine dissolution (with respect to label claim)

Sample time (Min)	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Mean	StdDev
0							0	0.0
1							18	2.9
3							52	2.4
5							78	1.6
7.5							94	0.9
10							94	0.9
15							92	0.9
20							90	0.6

Suboxone 8mg Batch 00620053

% naloxone dissolution (with respect to label claim)

Sample time (Min)	Vessel 1	Vessel 2	Vessel 3	Vessel 4	Vessel 5	Vessel 6	Mean	StdDev
0							0	0.0
1							20	2.5
3							56	2.8
5							84	2.6
7.5							103	2.1
10							102	2.4
15							100	1.7
20							98	1.6



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/s/

Tien-Mien Chen
3/10/02 02:39:12 PM
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Suresh Doddapaneni
3/12/02 07:51:53 AM
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CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

<u>NDA:</u> 20-732	<u>BRAND NAME:</u>	<u>SUBMISSION DATE:</u>
Buprenorphine	Subutex Sublingual Tablets	07/28/00 (code: AZ)

→ NDA: 20-733
Buprenorphine+Naloxone Suboxone Sublingual Tablets 07/28/00 (code: AZ)

SPONSOR: Reckitt & Colman

REVIEWER: Tien-Mien Chen, Ph.D.

TYPE OF SUBMISSION: Responses To Agency's Approvable Letter and Labeling Update

TITLE: "Review of A New Study Report and the Sponsor's Responses to Agency's Previous Comments"

Both NDAs 20-732 (Subutex; buprenorphine) and 20-733 (Suboxone; buprenorphine + naloxone) were submitted to the Agency for review and were deemed approvable pending resolution of several deficiencies. On 07/28/00, the sponsor submitted their responses to both NDAs. Included in the 07/28/00 submission were 1) a new study report, 2) sponsor's responses to Phase IV commitments and to address the deficiencies, and 3) proposed labeling update. Therefore, the above submissions are reviewed here.

I. Study Report No. 97-1 (Synopsis in Attachment 1)

Title: "Relative Bioavailability of Oral and Sublingual Buprenorphine and Naloxone Tablets"

- **Design:** Open-label, 3x3 Latin square crossover with a 7-day washout period
- **Objectives:** 1) To assess the absolute bioavailability (F_{abs}) and relative bioavailability (F_{rel}) of Suboxone sublingual tablets when given orally and sublingually compared to an intravenous (IV) solution and 2) to assess the physiologic effects of Suboxone tablets
- **Subjects:** Nine patients (6M+3F) aged between 21-45 yrs old
- **Drugs:** Suboxone (8 mg buprenorphine+2 mg naloxone) sublingual tablet manufactured by Reckitt and Colman (Lot No. 0600/086) and an IV solution provided by NIDA (8 mg buprenorphine+2 mg naloxone; Lot No. 971106 manufactured by _____).
- **Procedure:** Suboxone sublingual tablet given as instructed, orally or sublingually, after overnight fast and an IV solution given by 15-min infusion
- **Sampling:** Venous blood (10 ml each) collected at pre-dose and at 0.125, 0.25, 0.33, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 30, 36, and 48 hr post IV dosing and at 0.25,

0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 30, 36, and 48 hr post oral dosing (total 360 ml). Urine samples collected 0-24 and 24-48 hrs postdose.

- **Assay:** Blood samples centrifuged to harvest plasma. Aliquots of plasma and urine samples stored at -20°C until assayed by an LC/MS/MS method. Assay method validated and found acceptable for measuring buprenorphine, its metabolite (norbuprenorphine), and naloxone plasma levels.
- **Data Analysis:** Mean (\pm Standard deviation; SD) PK parameters obtained and ANOVA used for statistical analysis.

Results:

The mean PK parameters obtained for buprenorphine, norbuprenorphine, and naloxone are shown below in Tables 1 and 2:

Table 1. Mean (\pm SD) Plasma PK parameters Obtained from 9 Patients

Pharmacokinetic Parameters	Oral (O) Bup 8 mg, Nal 2 mg	Sublingual (SL) Bup 8 mg, Nal 2 mg	Intravenous (IV) Bup 2mg, Nal 0.5 mg	Statistical P Value for Treatment Effect and Contrasts
BUPRENORPHINE				
AUC unextrapolated (hr ² ng/ml per mg dose)	1.13 \pm 0.76	2.35 \pm 0.79	21.1 \pm 12.3	0.0001 O<SL; O<I.V.; SL<I.V.
AUC extrapolated* (hr ² ng/ml per mg dose)	2.12 \pm 1.52	3.63 \pm 1.44	41.5 \pm 44	0.001 O<I.V.; SL<I.V.
Peak concentration** (ng/ml per mg dose)	0.132 \pm 0.076	0.396 \pm 0.145		0.0014 O<SL
Time to peak conc (hr)**	1.81 \pm 3.11	1.06 \pm 0.43		0.5
NORBUPRENORPHINE				
AUC unextrapolated (hr ² ng/ml per mg dose)	1.98 \pm 0.70	2.01 \pm 0.72	2.90 \pm 1.59	0.081
AUC extrapolated* (hr ² ng/ml per mg dose)	4.74 \pm 2.44	8.63 \pm 8.51	7.87 \pm 2.72	0.069
Peak concentration** (ng/ml per mg dose)	0.110 \pm 0.045	0.115 \pm 0.059		0.93
Time to peak conc (hr)**	2.11 \pm 3.05	4.81 \pm 8.06		0.38
Ratio of AUC unextrapolated norbup/buprenorphine	2.24 \pm 1.41	0.956 \pm 0.576	0.207 \pm 0.200	0.0001 O>SL; O>I.V.; SL>I.V.
NALOXONE				
AUC unextrapolated* (hr ² ng/ml per mg dose)	Too small to estimate	0.0815 \pm 0.0485	4.71 \pm 0.98	0.0003 SL<I.V.
AUC extrapolated* (hr ² ng/ml per mg dose)	Too small to estimate	0.151 \pm 0.088	4.70 \pm 0.71	Not estimable
Peak concentration** (ng/ml per mg dose)	Too small to estimate	0.0799 \pm 0.0497		Not estimable
Time to peak conc (hr)**	Not estimable	0.752 \pm 0.333		Not estimable

* For buprenorphine AUC extrapolated, n=8 for oral and sublingual doses; for norbuprenorphine AUC extrapolated, n=8 for the oral dose, n=7 for the other two doses; for naloxone AUC unextrapolated, n=6 for the SL doses; for naloxone AUC extrapolated, n=5 for the SL dose, n=8 for the IV dose.
 ** Analysis for peak concentrations and times: includes data from oral and sublingual doses only.

Table 2. Mean Urinary PK parameters Obtained from 9 Patients

Pharmacokinetic Parameters	Oral (O) Bup 8 mg, Nal 2 mg	Sublingual (SL) Bup 8 mg, Nal 2 mg	Intravenous (IV) Bup 2 mg, Nal 0.5 mg	Statistical P Value for Treatment Effect and Contrasts
BUPRENORPHINE % excreted as buprenorphine	0.0022 ± 0.0051	0.0068 ± 0.0086	0.0925 ± 0.101	0.0095 O<IV; SL<IV
% excreted as buprenorphine conjugates	0.266 ± 0.153	0.624 ± 0.206	5.06 ± 1.82	0.0001 O<IV; SL<IV
% excreted as buprenorphine or its conjugates	0.268 ± 0.155	0.631 ± 0.210	5.15 ± 1.84	0.0001 O<IV; SL<IV
% excreted as norbuprenorphine	0.493 ± 0.319	0.410 ± 0.250	0.605 ± 0.388	0.13
% excreted as norbuprenorphine conjugates	1.41 ± 0.82	1.56 ± 0.87	2.28 ± 1.95	0.39
% excreted as norbuprenorphine or its conjugates	1.90 ± 1.00	1.97 ± 1.08	2.89 ± 2.07	0.31
% excreted as buprenorphine or norbuprenorphine or their conjugates	2.17 ± 1.05	2.60 ± 1.04	8.04 ± 1.66	
NALOXONE % excreted as naloxone	0.0075 ± 0.0161	0.0806 ± 0.121	0.953 ± 1.718	0.0006 O<IV; SL<IV
% excreted as naloxone conjugates	11.4 ± 6.3	13.1 ± 6.6	29.0 ± 12.6	0.0005 O<IV; SL<IV
% excreted as naloxone or its conjugates	11.4 ± 6.3	13.2 ± 6.5	30.0 ± 12.3	0.0002 O<IV; SL<IV

The PK of buprenorphine in plasma (NOT shown in Table 1):

- The mean terminal half-life ($T_{1/2}$) values were calculated to be 41.9 ± 30.6 hr and 45.2 ± 48.2 hrs for oral and sublingual routes, respectively, however, for IV route, it was estimated to be 83.5 ± 186 hrs,
- Mean clearance (CL) was 61.4 ± 29.2 liter/hr,
- The mean F_{abs} was estimated to be 14 ± 7 % and 6 ± 4 % for sublingual and oral routes, respectively, (the mean F_{rel} for oral vs. sublingual being 43%), and
- According to the ratios of unextrapolated AUCs for norbuprenorphine/buprenorphine, buprenorphine was subject to more metabolism after oral dosing then sublingual, and the least by IV dosing (ratios being 2.24 ± 1.41 , 0.956 ± 0.576 , 0.207 ± 0.200 , respectively)

The PK of buprenorphine in urine (Table 2):

- Buprenorphine was extensively metabolized and the mean A_e values (amount of unchanged drug excreted in urine) were $<0.01\%$ post oral or sublingual administration,
- About 0.3 to 0.7% of dose was excreted as buprenorphine plus its conjugates and that for norbuprenorphine plus its conjugate was $<2.0\%$ post oral or sublingual dosing, and

- Post IV dosing, the Ae was only <0.1% of dose and about 5.2% and 2.9% of dose were excreted as buprenorphine plus its conjugates and norbuprenorphine plus its conjugate, respectively.

The PK of naloxone in plasma (NOT shown here)

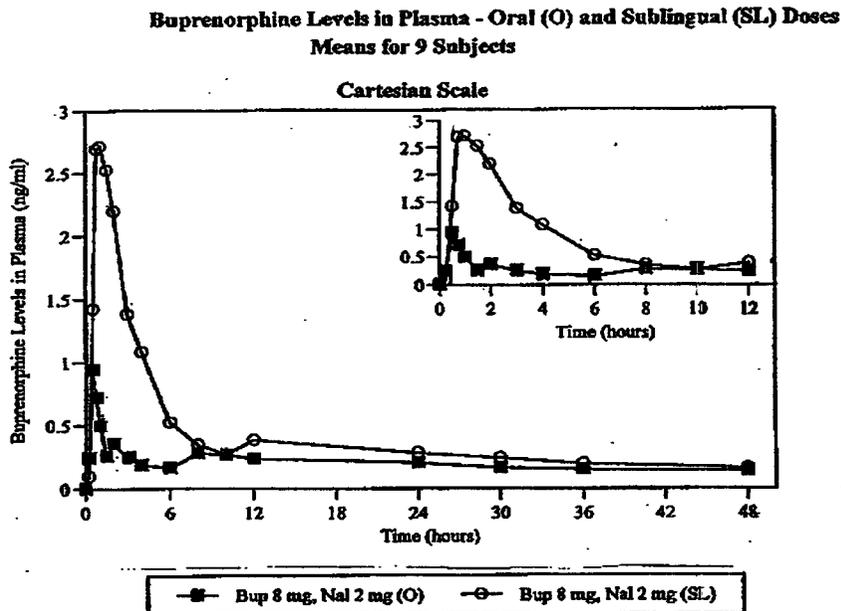
- Most of the plasma levels of naloxone post oral and/or sublingual dosing were not detectable and
- The F_{abs} values for naloxone were expected to be low, 3% for sublingual and practically zero % for oral routes.

The PK of naloxone in urine (NOT shown here)

- Mean Ae was estimated to be <0.1% for oral or sublingual dosing and that for IV dosing was <1% and
- About 11-13% of dose was excreted as naloxone conjugates and that for IV route was around 30%.

The Plasma profiles of buprenorphine, norbuprenorphine, naloxone, are shown below in Figures 1 to 3:

Figure 1. Mean Plasma profiles of Buprenorphine Post Oral and Sublingual Dosing



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Figure 2. Mean Plasma profiles of Norbuprenorphine Post Oral and Sublingual Dosing

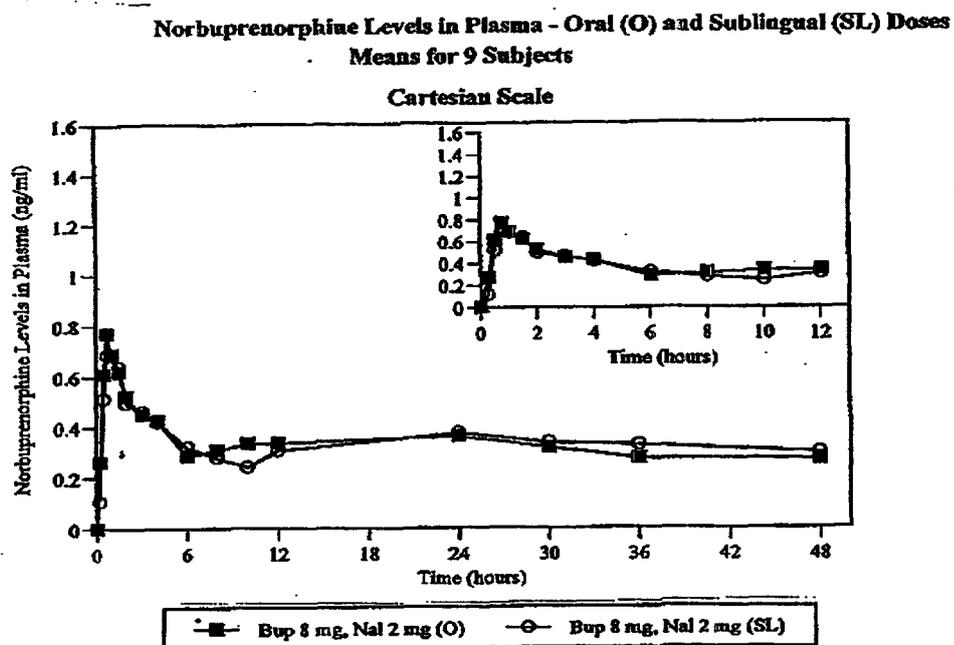
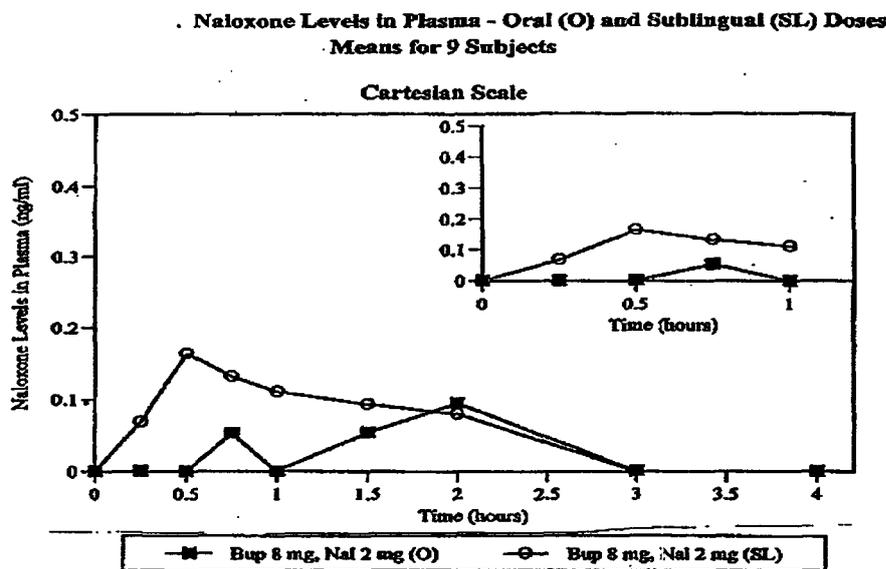


Figure 3. Mean Plasma profiles of Naloxone Post Oral and Sublingual Dosing



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Comments:

When compared to unextrapolated AUC_{0-t} , the extrapolated $AUC_{t-\infty}$ for buprenorphine contributed to 35-49% of mean total $AUC_{0-\infty}$ due to unusually long terminal $T_{1/2}$ obtained. It is, therefore, believed that the $AUC_{0-\infty}$ values were overestimated. As a result, the reported F_{abs} values for buprenorphine post sublingual and oral dosing were underestimated, 14% and 6%, which were lower than those obtained previously. The long $T_{1/2}$ (even after IV dosing; 83.5 ± 186 hr) could be partly due to enterohepatic recirculation of buprenorphine and/or the assay method used. However, the actual reasons for the above discrepancies were not known. No rationales were provided by the sponsor either. Therefore, the study results included in this submission could only be considered as supportive data. No labeling changes based on this study report will be made.

IIa. Phase IV commitments: Included in NDA 20-733 submission dated 07/28/00

7a. *Within one year of approval, evaluate the pharmacokinetics of buprenorphine and naloxone in patients with varying degrees of hepatic impairment, to determine appropriate dosage adjustment strategies.*

The sponsor's response:

We agree to conduct a study in patients with hepatic impairment and will work with the Agency to develop a protocol for the study.

The Agency's comment:

The sponsor's response is acceptable and the Agency is looking forward to working with the sponsor for protocol development and reviewing the study report once it is submitted for review.

7b. *Within one year of approval, conduct pharmacokinetic studies to determine the appropriate method of delivering more than two tablets. Submitted a labeling amendment that provides more precise instructions to clinicians.*

The sponsor's response:

We agree to undertake a study of the best method of delivering the daily dose where this is made up of more than two 8 mg tablets and will work with the Agency to develop a protocol for the study.

The Agency's comment:

The sponsor's response is acceptable and the Agency is looking forward to working with the sponsor for protocol development and reviewing the study report once it is submitted for review.

IIb. Deficiency: stated in the approvable letter

I.



Note: The sponsor included their response in NDA 20-732 submission dated 07/28/00

The Agency's Comment:

At the time when this review is signed off, this issue is still under discussion within the Agency and Dr. Suresh Doddapaneni will write an addendum to this review addressing the issue.

III. Labeling Update: Please see the Labeling Comment section below for details.

Recommendation:

The study report No. 97-1 that was submitted under NDAs 20-732 (Subutex sublingual tablets) and 20-733 (Suboxone sublingual tablets) on 07/28/00 has been reviewed by OCPB/DPEII. OCPB is of the opinion that 1) the above study report is considered supportive and no labeling changes based on the study results is made, 2) the responses to the Phase IV Comments and Deficiencies are acceptable, and 3) the sponsor's proposed labeling update is acceptable provided that the Agency's revision is incorporated into the labeling changes. The Agency's version of labeling update under Labeling Comment below needs to be conveyed to the sponsor.

Labeling Comment:

The revised PK subsection under Clinical Pharmacology section for Subutex and Suboxone sublingual tablets (Attachment 2) should be sent to the sponsor.

11/22/00

Tien-Mien Chen, Ph.D.

Division of Pharmaceutical Evaluation II

RD initialed by S. Doddapaneni, Ph.D. S.D. 11/28/00

FT initialed by S. Doddapaneni, Ph.D. _____

cc: NDAs 20-732 & 20-733, HFD-170 (C. Winchell, S. Shepherd), HFD-870 (H. Malinowski, S. Doddapaneni, T.M. Chen), CDR (Z. Zadeng).

**NDA 20-732 (Subutex Sublingual Tablets, buprenorphine)
NDA 20-733 (Suboxone Sublingual Tablets,
buprenorphine+naloxone)**

Attachment 1

Study Synopsis

REPORT SUMMARY

Title: RELATIVE BIOAVAILABILITY OF ORAL AND SUBLINGUAL BUPRENORPHINE AND NALOXONE TABLETS (Study 97-1)

Funding Source: NIDA Contract #N01DA-4-8306

Contract Officer: Nora Chiang, Ph.D.

Investigators: PI: Reese T. Jones, M.D.
Co-PIs: John Mendelson, M.D., and Robert Upton, Ph.D.

Objective: (1) To assess the relative and absolute bioavailability of a buprenorphine (8 mg) and naloxone (2 mg) tablet when administered orally and sublingually. (2) To evaluate the subjective and physiologic effects of orally and sublingually administered buprenorphine and naloxone tablets.

Design: The study was an open-label, balanced 3x3 Latin square crossover design. Testing sessions were approximately 7 days apart. Treatment conditions: Oral dose tablet containing buprenorphine (8 mg) and naloxone (2 mg); sublingual dose tablet containing buprenorphine (8 mg) and naloxone (2 mg); intravenous dose containing buprenorphine (2 mg) and naloxone (0.5 mg). The main purpose of the intravenous dose was to allow for computation of the buprenorphine and naloxone absolute bioavailability.

Study Setting: Subjects were admitted as inpatients to the General Clinical Research Center (GCRC) the day before the experimental session, and remained at the GCRC for a 48 hour period following drug administration. Treatment sessions were conducted at the Drug Dependence Research Center.

Subjects: Subjects were 6 men and 3 women between the ages of 22 and 43 years. All were experienced in opiate use, but not opiate-dependent by DSM-IV criteria. All were in good mental and physical health.

Physiologic and Subjective Measures: Heart rate, systolic and diastolic blood pressure, rate pressure product, respiration rate, and pupil size were measured prior to dosing and at frequent intervals post-dose. Subjective measures included Visual Analog scales, and Opiate Agonist and Withdrawal scales.

Assay: Plasma samples, obtained predose and at 0.125, 0.25, 0.33, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 30, 36, 48 hours postdose, were analyzed for buprenorphine, norbuprenorphine, and naloxone using the LC/MS/MS analytical procedure.

Statistical Analysis: Physiologic and subjective data were analyzed by repeated measures analysis of variance (ANOVA). Change scores (postdose minus predose values) were used in the analysis. Pharmacokinetic parameters of buprenorphine and naloxone (C_{max} , T_{max} , AUC) were determined from plasma concentration-time profiles. Buprenorphine and naloxone pharmacokinetic parameter estimates were compared using analysis of variance (ANOVA).

Results and Conclusions: The sublingual tablet produced a significantly greater decrease in both respiration rate and pupil size than the oral tablet. The sublingual tablet produced significantly higher rating of "drug liking", "good drug effect", and opiate intoxication than the oral tablet. The absolute buprenorphine bioavailability from the sublingually administered tablet was significantly greater than the bioavailability from the oral tablet ($14 \pm 7\%$ compared to $6 \pm 4\%$). Naloxone was approximately 3% bioavailable from the sublingual tablet, while its bioavailability from the oral tablet was practically zero. The AUC ratio between tablet treatments indicates that the sublingual tablet yields 2.5 times more buprenorphine bioavailability than the oral tablet.

**NDA 20-732 (Subutex Sublingual Tablets, buprenorphine)
NDA 20-733 (Suboxone Sublingual Tablets,
buprenorphine+naloxone)**

Attachment 2

Sponsor's Proposed Labeling and The Agency's Revision

38 Draft Labeling Page(s) Withheld

/s/

Tien-Mien Chen
11/28/00 03:00:18 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
11/30/00 02:00:58 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 20-733

CODE: 4P

NAME: Suboxone[®] (Buprenorphine HCL/Naloxone HCL) 2 mg/0.5 mg, 8 mg/2 mg Sublingual Tablets

SPONSOR: Reckitt & Colman Pharmaceuticals, Inc., 1909 Huguenot Road, Richmond, VA

SUBMISSION TYPE: Original NDA

SUBMISSION DATE: 6/9/99, 7/28/99

REVIEWER: Suresh Doddapaneni, Ph.D.

8/9/99

SYNOPSIS

Reckitt & Colman Pharmaceuticals Inc. and National Institute on Drug Abuse (NIDA) have been engaged in a Cooperative Research and Development Agreement (CRADA) to develop buprenorphine alone (Subutex[®]) and in combination with naloxone (Suboxone[®]) for the treatment of opiate dependence. The NDA (20-732) for Subutex[®] was submitted on 3/28/97 and an approvable action was taken on 6/30/98 pending resolution of several deficiencies. Although the clinically tested sublingual 30% alcoholic solution and the to-be-marketed sublingual tablet (strengths of 2 and 8 mg) dosage forms are not bioequivalent, available data permitted adequate conversion of tablet doses achieved to corresponding efficacious solution doses. Proposed maintenance dosing range of 8 to 24 mg with Suboxone[®] tablets approximates the solution doses of 2.8 mg to 16.8 mg applying a constant relative bioavailability of 0.7 throughout the dose range. Although, 4 mg, 8 mg, 12 mg, and 16 mg doses of Suboxone[®] can be administered reliably using the 2 mg and 8 mg tablet strengths, practical considerations dictate need for administering two tablets at one time (for 24 mg dose, two 8 mg tablets initially followed by a single 8 mg tablet) in a sequential fashion to obtain 20 mg and 24 mg doses. However, the relative bioavailability of such a dosing regimen is unknown at this time. 16 mg dose of Suboxone[®] and Subutex[®] were found to result in similar C_{max} and AUC values indicating that naloxone does not affect the pharmacokinetics of buprenorphine. This combined with the fact that the two formulations are compositionally similar indicates that Suboxone[®] and Subutex[®] will deliver similar buprenorphine concentrations. Further, clinical study 1008A provided evidence for the efficacy of 16 mg dose of Suboxone[®] and Subutex[®] compared to placebo. Naloxone plasma concentrations were in general very low, when Suboxone[®] was administered in the dose range of 4 to 16 mg. However, the plasma concentrations tended to increase with increase in dose.

RECOMMENDATION

From the viewpoint of the Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation II, this product can be approved. However, additional bioavailability data is needed for 20 mg and 24 mg doses which have to be achieved by sequentially administering no more than two tablets at one time to overcome the practical limitations imposed by Suboxone[®] tablet strengths and sublingual route of administration. The comments on page 18 should be sent to the sponsor.

[/S/] 11/12/99

Suresh Doddapaneni, Ph.D.
Clinical Pharmacologist
DPE II/OCPB

[/S/] 11/12/99

F/T initialed by Ramana Uppoor, Ph.D.

CC: NDA 20-733 (Original), HFD-770 (Division Files, Chite), HFD-850 (Lesko), HFD-870 (Doddapaneni, Mei-Ling Chen, Uppoor), CDR (Barbara Murphy).

**APPEARS THIS WAY
ON ORIGINAL**

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1.0. INTRODUCTION

Buprenorphine is a partial μ agonist that has morphine-like subjective effects but with less intensity. Therefore, it produces mild physical dependence with limited withdrawal signs and symptoms. In the U.S., buprenorphine is currently marketed by Reckitt & Colman Pharmaceuticals, Inc., under the trade name Buprenex[®] (NDA 18-401). Buprenex[®] is used as a sterile solution for the treatment of moderate to severe pain in doses of 0.3 to 0.6 mg intramuscularly or intravenously at 6 hour intervals.

Reckitt & Colman Pharmaceuticals Inc. and National Institute on Drug Abuse (NIDA) have been engaged in a Cooperative Research and Development Agreement (CRADA) to develop buprenorphine alone (Subutex[®]) and in combination with naloxone (Suboxone[®]) for the treatment of opiate dependence. Subutex[®]

The NDA (20-732) for Subutex[®] was submitted on 3/28/97 and an approvable action was taken on 6/30/98 pending resolution of several deficiencies. The reader is referred to the Clinical Pharmacology and Biopharmaceutics review dated 2/10/98 for further information on Subutex[®]. Since Subutex[®] and Suboxone[®] are closely related products (from the viewpoint of formulation and proposed indications) and share similar Clinical Pharmacology and Biopharmaceutics issues and concerns, Subutex[®] will be also be discussed along with Suboxone[®] during the course of this review. FDA's Office of Orphan Product Development has determined that buprenorphine qualifies for orphan designation for the treatment of opiate addiction in opiate users based on the projected low commercial potential. FDA also waived the User Fee for Subutex[®] and Suboxone[®].

Suboxone[®] has not been marketed in any country. Subutex[®] is currently marketed in France and United Kingdom. Marketing authorization has been granted in Argentina, Finland, Luxembourg, and Switzerland.

1.0 APPLICATION OVERVIEW

Although Suboxone[®] is a combination product of buprenorphine and naloxone (in the ratio of 4:1), the primary purpose of naloxone is to prevent the intravenous misuse of buprenorphine (concept originally used in currently marketed pentazocine product, Talwin[®] NX). This could be done because naloxone has poor oral bioavailability. Therefore, the sponsor claims that for practical purposes naloxone can be deemed to be an inactive ingredient in this product. Studies 92/111 (solution), 95/001 (tablet), and 97/007 (tablet) provide bioavailability data on naloxone to be able to assess this claim. To satisfy the 505 b (2) requirement, the relative bioavailability linkage of this product to the approved intravenous buprenorphine product can be found as follows; Study CR92/111 links iv and solution formulations of buprenorphine/naloxone combination product. Studies CR94/001 and CR96/009 assess the relative bioavailability of solution and Subutex[®] tablets. Study CR95/001 assessed the relative bioavailability of 16 mg doses of Subutex[®] and Suboxone[®] tablets. Much of the data presented in this NDA was also submitted to and reviewed in NDA 20-732. Therefore, only new studies conducted since then and relevant data from NDA 20-732 as applicable to Suboxone[®] will be discussed in this review.

2.0 PHYSICOCHEMICAL PROPERTIES

Buprenorphine is a weak base with a pKa of 8.4. As such, pH of the saliva will play a role in the amount of buprenorphine absorbed from the oral mucosa. The solubility of buprenorphine is \sim at pH 6 but only \sim at pH 7, a 10-fold decrease. It is highly lipid soluble (log partition coefficient of octanol/pH 6.6 is 3.37).

3.0 METABOLISM

In humans, buprenorphine undergoes both N-dealkylation to norbuprenorphine as well as direct glucuronidation to buprenorphine 3-glucuronide. The N-dealkylation pathway is mediated by cytochrome P-450 3A4 isozyme. Norbuprenorphine can further undergo glucuronidation to norbuprenorphine glucuronide. Norbuprenorphine is considered to be an inactive metabolite. Mass balance study showed complete recovery of radiolabel in urine (30%) and feces (69%) collected up to 11 days after dosing (study CR94/006). Almost all of the dose was accounted for in terms of buprenorphine, norbuprenorphine, and two unidentified (less than 2% together) buprenorphine metabolites. Most of the drug in urine was excreted as buprenorphine (1% free and 9.4% conjugated) and norbuprenorphine (2.7% free and 11% conjugated). In feces, almost all of the buprenorphine (33% free and 5% conjugated) and norbuprenorphine (21% free and 2% conjugated) were free. It is likely that the free buprenorphine and norbuprenorphine observed in feces was eliminated as glucuronide conjugates only to be hydrolyzed in the GIT to generate the aglycones. The absolute bioavailability after sublingual administration of 30% alcoholic solution of buprenorphine is 40% (study CR92/111). Since the relative bioavailability of Suboxone is 70% compared to the alcoholic solution, the absolute bioavailability of Suboxone is approximately 30%. Buprenorphine is primarily bound to plasma α - and β - globulin fractions to the extent of 96%.

After oral administration, naloxone undergoes extensive first pass metabolism and consequently has poor oral bioavailability. Direct glucuronidation to naloxone 3-glucuronide seems to be the major metabolic pathway. N-dealkylation and reduction of the 6-oxo group appears to be a minor pathway. Naloxone 3-glucuronide is excreted in the urine. The absolute bioavailability of sublingual naloxone given as a 30% alcoholic solution is less than 10% (study CR92/111). The terminal half-life of naloxone is very short (about 1-1.5 hours). Naloxone is primarily bound to albumin in plasma to the extent of 45%.

4.0 ANALYTICAL METHODOLOGY

Several different analytical methodologies were used for the determination of plasma buprenorphine throughout the product development. Studies CR91/080, CR92/108, CR94/001 used an HPLC method. Studies CR87/027 and CR90/061 used radioimmunoassay procedures that were cross-reactive to norbuprenorphine and in the case of study CR90/061 the assay methodology reported cross-reactivity to norbuprenorphine glucuronide as well. In light of this, data from studies CR87/027 and CR90/061 should be viewed with caution. Studies CR92/111, CR95/001, CR96/009, CR96/012, CR96/013, and CR96/014 used an LC/MS/MS method. Naloxone was quantified using LC/MS/MS method. The studies were accompanied by

separate information relating to assay performance during that study. All in all, the sponsor presented acceptable analytical documentation on the performance of the assay for these studies.

5.0 FORMULATION

Parenteral administration for this indication was not chosen primarily to move addicts away from injecting drugs. The sublingual route was chosen as oral administration results in a marked first-pass metabolism with associated low oral bioavailability. The pivotal clinical studies were carried out using sublingual solutions of buprenorphine dissolved in 30% ethanol/water (— ethanol/water in one study). However, sublingual tablets developed by Reckitt & Colman (in strengths of 2 and 8 mg) are proposed to be marketed —

The formulations for the two strengths of Subutex[®] and Suboxone[®] tablets are shown in Table 1. Both the 2 and 8mg strengths of Subutex[®] and Suboxone[®] are very similar in composition of the major ingredients and have identical tablet weights with the only difference being that Suboxone[®] has naloxone, lime and lemon flavor, acesulfame sweetener, and — yellow color (together these account for — of Suboxone[®] tablet weight). As can be seen from table 1, both 2 mg and 8 mg tablets are approximately proportional with respect to the active and inactive ingredients.

Table 1. Composition of the 2.0, and 8.0 mg Subutex[™] and Suboxone[™] SL tablets.

Ingredient	Subutex [™]		Suboxone [™]	
	2.0 mg Tablet	8.0 mg Tablet	2.0 mg Tablet	8.0 mg Tablet
Buprenorphine HCL				
Naloxone HCL				
Lactose				
Mannitol				
— Starch				
Povidone K30				
Citric Acid —				
Sodium Citrate				
Magnesium Stearate				
Lemon & Lime Flavor				
Acesulfame K				
— Yellow				
Tablet Weight	2	8	2	8
Size				

For a sublingual tablet which is meant to be held under the tongue, the sequence of steps in the drug absorption process would be; (i) disintegration of the tablet (ii) dissolution of the drug in the saliva and (iii) absorption of the dissolved drug through the mucosa. In the case of the 30% alcoholic solution (— alcoholic solution in study CR90/061), the drug is already dissolved

in a cosolvent and is in a form ready to be absorbed from the moment it is introduced at the absorption site (dose of any size is dissolved in 1 mL (1.5 mL in study CR90/061) of the solution). The physicochemical properties (solubility, pH and therefore ionization) of buprenorphine may be substantially different for the sublingual tablet (influenced by the inactive components of the tablet). Therefore, increasing the tablet size (or number of administered tablets per dose) may result in decreased absorption of the drug as the surface area underneath the tongue and the saliva available for the disintegration/dissolution of the sublingual tablet are limited. This is especially true for this product where the limited number of available strengths means using multiples of tablets to achieve a particular dose. Since, 2.0 and 8.0 mg are the only strengths of the tablet available and the recommended dose range is up to 24 mg, certain doses would involve use of multiple tablets (for example, 24 mg = 3 x 8mg tablets, 20 mg = 2 x 8mg tablets + 2 x 2mg tablets, 16 mg = 2 x 8mg tablets, 12 mg = 1 x 8mg tablet + 2 x 2mg tablets).

6.0 RELATIVE BIOAVAILABILITY & DOSE PROPORTIONALITY

Safety information for buprenorphine is available in the dose range of 1 to 32 mg of buprenorphine using the sublingual solution (study CR90/061). With Subutex[®] and Suboxone[®] tablets, the highest dose proposed is 24 mg. Since the tablets have a lower bioavailability relative to the solution and the highest tablet dose proposed is 24 mg, there is a considerable safety margin with the tablet in the proposed dosage regimen.

Efficacy data obtained with solution showed that buprenorphine 8 mg/day and 4mg/day doses were superior to 1 mg/day with an enhanced effect at 16 mg/day dose (study CR92/099). With respect to the efficacy of tablet, 16 mg doses of Subutex[®] and Suboxone[®] tablets were shown to be superior to placebo (study 1008A).

Since the solution and tablet dosage forms were not bioequivalent and a reliable relative bioavailability estimate was not previously available, it was difficult to determine what doses of the Subutex[®] and Suboxone[®] tablets correspond to the efficacious solution doses of 4, 8, and 16 mg. However, analysis of data from study CR95/001 (Suboxone[®] dose-proportionality) and study CR96/016 (solution dose-proportionality) provided a relative bioavailability factor that is applicable in the range of 4 to 16 mg tablet doses.

7.1. DOSE-PROPORTIONALITY OF SUBOXONE[®] TABLETS

This was a single dose, four-way crossover study in eight (8) subjects (study CR95/001). This study evaluated 4mg (2x 2 mg tablets), 8mg (1x 8 mg tablet), and 16mg (2x 8 mg tablets) doses of Suboxone[®] and 16 mg (2x8mg tablets) dose of the Subutex[®] tablet.

Table 2 presents the main pharmacokinetic parameter values from this study. Both C_{max} and AUC of buprenorphine increased in a linear fashion in the range of 4 to 16 mg with the increase in dose of Suboxone[®], although the increase was not directly dose-proportional. Bioequivalence analysis (on log transformed parameters) was conducted to see if 16 mg doses of Subutex[®] and Suboxone[®] were bioequivalent (note: study was not powered for bioequivalence analysis). C_{max} failed narrowly on the high side (upper limit of 129) while AUC₀₋₄₈ was within the limits.

Lack of the effect of naloxone on buprenorphine pharmacokinetics can also be seen from study CR92/111. This study provides an estimate of the absolute bioavailability of an 8 mg dose of a 30% alcoholic solution of buprenorphine dosed daily to steady state alone or in conjunction with 4 mg or 8 mg naloxone. The steady state absolute bioavailability of buprenorphine with 0, 4, and 8 mg naloxone was $42 \pm 9\%$, $42 \pm 2\%$, and $40 \pm 7\%$ respectively.

Overall, from these data, it can be seen that naloxone did not affect the pharmacokinetics of buprenorphine in Suboxone[®] tablets. This combined with the fact the Subutex[®] and Suboxone[®] formulations are similar indicates that similar buprenorphine concentrations will be delivered by same dose of Subutex[®] and Suboxone[®]. Clinical evidence for the above is available from efficacy study 1008A where 16 mg dose of Subutex[®] and Suboxone[®] were shown to be efficacious compared to placebo.

The levels of naloxone were very low to assess dose-proportionality (Table 3). At the three naloxone doses of 1 mg, 2 mg, and 4 mg, levels above the quantitation (--- ng/mL) were not detected beyond 2 hours in all eight subjects (with one exception at the 4mg dose in one subject where the last measurable concentration was at 8 hours). Within each subject (for most of the subjects), across the doses there seems to be a trend in the increase of the naloxone concentrations with dose increase.

Table 2. Pharmacokinetic parameters of buprenorphine after the administration of 4 mg, 8mg, and 16 mg Suboxone[®] doses and 16mg Subutex[®] dose (mean (%CV)).

Pharmacokinetic Parameter	Suboxone [®] 4 mg	Suboxone [®] 8 mg	Suboxone [®] 16 mg	Subutex [®] 16 mg	90% Confidence Intervals for Suboxone [®] /Subutex [®]
C _{max} , ng/mL	1.84 (39)	3.0 (51)	5.95 (38)	5.47 (23)	84-129
AUC ₀₋₄₈ [*] , hour*ng/mL	12.52 (35)	20.22 (43)	34.89 (33)	32.63 (25)	88-123

* AUC₀₋₃₆ in two out of 24 doses.

Table 3. Pharmacokinetic parameters of naloxone after the administration of 4 mg, 8mg, and 16 mg doses of Suboxone[®] (mean (%CV)).

Pharmacokinetic Parameter	Suboxone [®] 4 mg (Naloxone 1 mg)	Suboxone [®] 8 mg (Naloxone 2 mg)	Suboxone [®] 16 mg (Naloxone 4 mg)
C _{max} , ng/mL	0.107 (25)	0.178 (57)	0.279 (68)
AUC ₀₋₄₈ , hour*ng/mL	0.103 [#]	0.148 (33)	0.259 (45)

[#] one subject

7.2. DOSE-PROPORTIONALITY OF BUPRENORPHINE SOLUTION

This study evaluated the dose-proportionality of 4, 8, 16, and 32 mg doses of buprenorphine given as 30% ethanolic solution held in the mouth for 5 minutes in 12 subjects (study CR96/016). Table 4 presents the main pharmacokinetic parameters of buprenorphine. Mean values of AUC and C_{max} increased linearly with dose, although the increase was not directly dose-proportional. Mean AUC's ranged from 17 ng*hour/mL to 70 ng*hour/mL over the dose range of 4 to 32mg.

It should be noted that in NDA 20-732, dose-proportionality data from study CR90/061 was submitted evaluating 1, 2, 4, 8, 16, and 32 mg doses of buprenorphine given as ethanolic solution in four subjects. C_{max} was found to increase non-linearly with increasing doses. AUC was however linear. The actual buprenorphine levels were very high and the sponsor attributed this to cross-reactivity to norbuprenorphine of the RIA assay used in this study. Mean buprenorphine AUC's ranged from 45 ng*hour/mL to 476 ng*hour/mL over the dose range of 2 to 32mg.

Table 4. Pharmacokinetic parameters of buprenorphine after the administration of 4mg, 8mg, 16mg, and 32mg solution doses (mean(%CV)).

Pharmacokinetic Parameter	Bup 4mg	Bup 8mg	Bup 16mg	Bup 32mg
C_{max} , ng/mL	3.56 (42)	5.83 (47)	8.37 (34)	13.7 (23)
AUC ₀₋₇₂ , hour*ng/mL	17.36 (31)	22.42 (30)	48.3 (28)	70.3 (23)

7.3. RELATIVE BIOAVAILABILITY OF SOLUTION AND TABLETS

Relative bioavailability of the tablets and solution were determined in studies CR94/001 and CR96/009 at tablet doses of 8 mg and 16 mg, respectively. These studies indicate the relative bioavailability of the tablets to be about 50% at 8 mg dose and about 70% at the 16 mg dose. The relative bioavailability at different doses has not been evaluated through one controlled study. However, dose-proportionality data described below provides some information. As can be seen from figure 1, the dose versus AUC plots for Suboxone[®] and solution formulations (from studies CR95/001 and CR96/016) are reasonably parallel indicating that the relative bioavailability of Suboxone[®] compared to solution formulation is relatively constant across the dose range of 4 to 16 mg for Suboxone[®]. Linear regression of the solution data and Suboxone[®] data separately yielded slopes of 1.82 and 1.86 confirming that these profiles are reasonably parallel. The relative bioavailability values for Suboxone[®] at doses of 4 mg, 8mg, and 16 mg were 0.72, 0.66, and 0.72 respectively. Assuming a mean relative bioavailability of 0.70, table 5 relates the efficacious solution doses to equivalent tablet doses.

Dose versus AUC

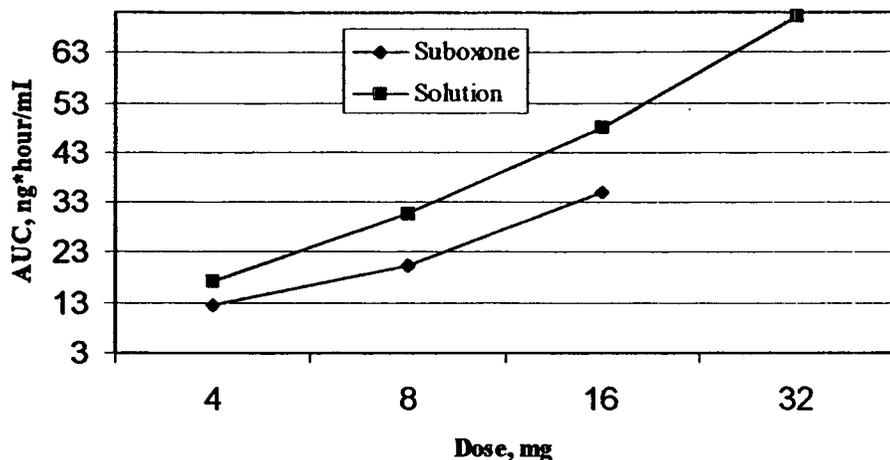


Figure 1. AUC versus dose plots for Suboxone[®] and solution formulations.

Table 5. Equivalent Suboxone[®] and solution doses.

Tablet doses	Solution doses
4 mg (2 x 2 mg tablets)	2.8 mg
6 mg (3 x 2 mg tablets)	4.2 mg
8 mg (1 x 8 mg tablet)	5.6 mg
12 mg (1 x 8 mg tablet + 2 x 2 mg tablets)	8.4 mg
16 mg (2 x 8 mg tablets)	11.2 mg
20 mg (2 x 8 mg tablets + 2 x 2 mg tablets)	14 mg
24 mg (3 x 8 mg tablets)	16.8 mg

*Proposed dosing recommends a target of 16 mg with up and down titration in 4 mg increments.

However, in the Suboxone[®] dose-proportionality study CR97/007, the absorption at 24 mg dose administered as 3 x 8 mg tablets was very variable and impractical to administer. The sponsor proposed an alternate dosing regimen of sequential dosing of 2 tablets at one time. Table 6 presents the physical characteristics of the different combinations of 2 mg and 8 mg tablets. As can be seen from the table, the surface area of 20 mg is close to that of 24 mg. Therefore, even 20 mg dose has to be achieved using sequential dosing. However, the bioavailability of such a sequential dosing of 2 tablets at one time to achieve 20 mg and 24 mg doses is unknown and remains to be determined.

Table 6. Physical characteristics of buprenorphine tablets.

Buprenorphine Dose	Tablet Weight (Mg)	Tablet Volume (Cu mm)	Surface Area (Sq mm)	Number of 2 mg Tablets	Number of 8 mg Tablets
2				1	0
4				2	0
6				3	0
8				0	1
10				1	1
12				2	1
14				3	1
16				0	2
18				1	2
20				2	2
22				3	2
24				0	3

7.4. PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSIS

This report contains the analysis of plasma concentrations from three hundred and four (304) subjects receiving:

- (1) Single doses of either 8 mg buprenorphine solution or 8 mg Subutex[®] tablet (study CR94/01- relative bioavailability of solution and Subutex[®]).
- (2) Single doses of 4 mg, 8 mg, 16 mg Suboxone[®] tablets and 16 mg Subutex[®] tablets (study CR95/01-Suboxone[®] dose-proportionality study).
- (3) Single doses of 4 mg, 8 mg, 16 mg, and 24 mg Suboxone[®] tablets (study PK/0496-Suboxone[®] dose-proportionality).
- (4) Daily doses of 16 mg Subutex or 16 mg Suboxone or placebo (Study 1008A-randomized, double-blind placebo controlled trial).
- (5) Daily doses of up to 24 mg Suboxone (Study 1008B- open label safety follow up study of 1008A).

Studies CR94/01, CR95/01, and PK/0496 are intensive sampling, single dose, cross-over, traditional pharmacokinetic studies in opiate experienced subjects while blood samples were obtained sparsely from clinical studies 1008A and 1008B in patients.

Buprenorphine pharmacokinetics was describable by either 1 or 2 compartment model with 1st order absorption and a lag time. Concentrations in the terminal phase of the two compartment model were close to the lower limit of quantitation. Covariates that predicted at least a 20% decrease in clearance (one compartment model) were increasing age (range of 18 to 59 years) and AST or ALT. Clearance appeared to decrease with increased bilirubin, increased ALT, and female gender (two compartment model).

The sparse data available for naloxone provided only a limited description of its pharmacokinetics.

Buprenorphine concentrations predicted a decrease in craving score. A simultaneous fit of concentrations and effects estimated an E_{max} (% of E_0) of -32.3% with an EC_{50} of 0.184 ng/mL and an equilibration half-time of 93 hours. Craving score is not considered to be a meaningful endpoint for treatment of opiate dependence.

Buprenorphine concentrations were associated with increasing the probability of a negative test for urinary opioids (<300 ng/mL). Buprenorphine (16 mg/day) is predicted to increase the probability of reduction of opioid presence in urine by 15.0% from a baseline of 0.3%. The equilibration half-time of 428 hours (18 days) means that the effect is slow to reach its peak. Because, the data in 1008B were not placebo controlled, meaningful results could not be obtained both through separate analysis of 1008B data and combining 1008A and 1008B data. Therefore, the probability of a negative urine test could not be established at doses other than 16 mg.

8.0. SPECIAL POPULATIONS

8.1. EFFECT OF AGE AND GENDER

The individual pharmacokinetic studies conducted had small subject numbers and therefore did not have the proper mix of subjects to permit the determination of a gender effect or age effect (studies had very few subjects >65 years of age) on the pharmacokinetics of buprenorphine. The sponsor attempted to pool data from the different pharmacokinetic studies to see if there is a gender or age effect (up to 35 years of age and >35 years). There were no dramatic differences that were seen in the C_{max} and AUC values that would suggest a gender or age effect. NONMEM analysis did reveal increasing age and gender as factors contributing to a lower clearance of about 20%. However, since Suboxone[®] is a titratable drug product and the predicted decrease in clearance is only 20%, no dosage adjustments are warranted.

8.2. HEPATIC FAILURE

No special pharmacokinetic studies were conducted in hepatic failure patients investigating the pharmacokinetics of buprenorphine and naloxone. However, a general statement is provided in the package insert to the effect that buprenorphine's pharmacokinetics may be changed in hepatic failure patients because of its predominant hepatic metabolism. Since naloxone metabolism may also be impaired in hepatic failure patients and the increased bioavailability may precipitate withdrawal symptoms even after dosage adjustment for

buprenorphine, Suboxone[®] should not be used in hepatic failure patients. Subutex[®] should be used after dosage adjustment. Population pharmacokinetic analysis also indicated decreased clearance of buprenorphine with elevated bilirubin and ALT levels. Therefore, a systematic evaluation of pharmacokinetics of Suboxone[®] in patients with hepatic impairment should be conducted as a phase IV commitment.

8.3. RENAL FAILURE

No special pharmacokinetic studies were conducted in renal failure patients by the sponsor. However, data from a published article was used in support of a statement provided in the package insert. Essentially, this article concludes that the pharmacokinetics of intravenous buprenorphine were unchanged in patients with impaired renal function. This is consistent with the mass balance study where only 30% of the dose was excreted in the urine with a negligible amount as unchanged buprenorphine. Effect of renal failure on naloxone pharmacokinetics is unknown.

8.4. LABOR AND DELIVERY

No special pharmacokinetic studies were conducted in pregnant women. As such it is unknown if the pharmacokinetics of buprenorphine and naloxone are changed in pregnant women. Similarly, it is unknown if buprenorphine and naloxone are excreted in the breast milk from nursing mothers.

8.5. DRUG-DRUG INTERACTIONS

No special pharmacokinetic drug-drug interaction studies were conducted. A search of the scientific literature relative to the cytochrome P450 enzyme(s) relationship to buprenorphine metabolism and drugs which are likely to be coadministered with buprenorphine was performed. Since buprenorphine is metabolized by CYP 3A4 isozyme, it is conceivable that coadministration of inhibitors of CYP3A4 isozyme will result in elevated buprenorphine plasma levels. *In vitro* studies examining the inhibitory potential of ritonavir, indinavir, and saquinavir showed that ritonavir was the most potent with a K_i value of 0.02 μM followed by indinavir and saquinavir (0.8 and 7 μM). Thus there is a potential for significant drug-drug interactions upon concurrent administration of buprenorphine and protease inhibitors. Other inhibitors of CYP3A4 isozyme may also have a significant drug-drug interaction potential ((i.e., some drugs in the drug classes of azole antimycotics, calcium channel antagonists, and macrolide antibiotics).

9.0. DISSOLUTION METHODOLOGY

The proposed dissolution method and specifications are as follows; 500 mL water with a (USP Apparatus I) basket speed of --- at a temperature of 37°C and a sampling time of 5 minutes. The set specifications are $Q = \text{---}$ released after 5 minutes for buprenorphine (for Subutex[®]) and $Q = \text{---}$ and $Q = \text{---}$ released after 5 minutes for buprenorphine and naloxone (for Suboxone[®]), respectively.

The dissolution of Suboxone® tablets was examined as a function of basket rotation speeds of _____ rpm. The results showed that the time to maximum dissolution increased as the rotation speed was reduced. At both _____ rpm, greater than _____ of buprenorphine and naloxone were released within 5 minutes. At _____ rpm, the rate of dissolution was markedly reduced and the variability was greater owing to the poor mixing of the actives.

The dissolution of Suboxone tablets was also examined as a function of pH in the range of _____ (salivary pH range reported in literature and observed in pharmacokinetic studies is 5.8 to 7.5) at a basket rotation speed of _____ rpm. At pH values higher than _____ the *in vitro* dissolution of buprenorphine is compromised, attributed to the limited aqueous solubility arising from the basic nature of the drug and its known solubility profile. Further, dissolution in pH range of _____ is very similar. The opposite effect occurs with the dissolution of naloxone decreasing at pH values below _____ under the conditions of the test method. From this data, it appears that consumption of acidic beverages may not significantly increase the absorption of buprenorphine or naloxone.

10.0. CONCLUSIONS

1. 16 mg dose of Suboxone® and Subutex® were found to deliver similar C_{max} and AUC values indicating that naloxone does not affect the pharmacokinetics of buprenorphine. This combined with the fact that the two formulations are compositionally proportional indicates that Suboxone® and Subutex® will deliver similar buprenorphine concentrations. Clinical study 1008A provided evidence for the efficacy of 16 mg dose of Suboxone® and Subutex® compared to placebo.
2. Proposed maintenance dosing range of _____ to 24 mg with Suboxone® tablets approximates the solution doses of _____ to 16.8 mg assuming a constant relative bioavailability of 0.7 throughout the dose range. Although, 4 mg, 8 mg, 12 mg, and 16 mg doses of Suboxone® can be achieved reliably, practical considerations dictate achieving 20 mg and 24 mg doses administering two tablets at one time in a sequential fashion. However, the bioavailability of such a dosing regimen is unknown.
3. Naloxone plasma concentrations were in general very low. However, the plasma concentrations tended to increase with increase in dose.

11.0. PROPOSED PACKAGE INSERT

Strikethrough and underlined text are Agency suggested deletions and additions to the sponsor proposed text.

Pharmacokinetics:
Absorption:

[. . .]

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11.0. COMMENTS

The following two studies should be conducted as phase IV commitments;

1. It may not be practical to achieve (a) 20 mg dose administering 2x8mg tablets and 2x2mg tablets all at once and (b) 24 mg dose administering 3x8mg tablets all at once. Alternate dosing regimen such as sequential dosing of two tablets at one time is suggested by the sponsor. However, the bioavailability of such a sequential dosing of two tablets at one time to achieve 20 mg and 24 mg doses is unknown and needs to be determined.
2. Systematic evaluation of pharmacokinetics of Suboxone® in patients with hepatic impairment should be conducted.

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APPENDIX

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SUBOXONE DOSE-PROPORTIONALITY

Study Type: Dose-proportionality

Study Title: Dose-proportionality of Sublingual Buprenorphine and Naloxone.

NDA: 20-733 **Submission Date:** 6/9/99 **Volume:** 54 **Study:** CR 95/001

Study Design:

Clinical

Analytical

Investigator: []

Investigator: []

Single Dose: Yes **Cross-Over:** Four-way

Other Design: Open, randomized

Fasted: One hour before and after dosing

Wash-Out Period: One week

Subject Breakdown

Normal Yes **Young Yes** **Number=8** **Male=7** **Female=1**

Weight; Mean 76 Range 67-96 kg

Age; Mean 29 Range 22-40 yrs

Formulation

Treatment Groups	Dose	Dosage Form	Strength	Lot	Lot Size
Bup/Nal	4/1 mg	Tablet	2/0.5 mg	06001/040	-
Bup/Nal	8/2 mg	Tablet	8/2 mg	06001/037	-
Bup/Nal	16/4 mg	Tablet	8/2 mg	06001/037	-
Bup	16 mg	Tablet	8 mg	950201B	-

Analytical Methodology

Plasma Sampling Times: Prior to dosing, and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 30, 36, and 48 hours post dose.

Assay Method: LC/MS/MS

Assay Sensitivity: The limit of quantitation was --- ng/mL for buprenorphine and naloxone.

Assay was linear in the range of --- ng/mL for both.

Assay Accuracy: The inter-day precision and accuracy parameters were within acceptable limits. The precision ranged from 5.2% to 6.5% for buprenorphine and from 6.6% to 8.4% for naloxone. The accuracy ranged from -2.7% to 9.1% for buprenorphine and -2.7% to 7.9% for naloxone.

Labeling Claims: none

Objectives

- 1) To determine whether naloxone affects the pharmacokinetics of buprenorphine.
- 2) To evaluate whether plasma concentrations of buprenorphine increase proportionally to buprenorphine dose.
- 3) To determine plasma concentrations of naloxone.

Study Features

The study consisted of the following four treatments;

- A. 2 x 8 mg Suboxone[®] tablets (total dose of buprenorphine/naloxone, 16 mg/4 mg).
- B. 2 x 2 mg Suboxone[®] tablets (total dose of buprenorphine/naloxone, 4 mg/1 mg).
- C. 2 x 8 mg Subutex[®] tablets (total dose of buprenorphine, 16 mg).
- D. 1 x 8 mg Suboxone[®] tablet (total dose of buprenorphine/naloxone, 8 mg/2 mg).

Note 1: Comparison of treatments A and C should give information on the pharmacokinetic interaction of buprenorphine and naloxone. Comparison of groups A, B, and D should give information on the dose-proportionality of buprenorphine between 4-16 mg and that of naloxone between 1-4 mg.

Note 2: Since buprenorphine is a partial opiate agonist, to minimize the abuse potential naloxone—a short acting narcotic antagonist is incorporated. Because of the large differences in the duration of action (1 day versus 1 hour) and in sublingual potency (30-40% versus 10%), it is expected that buprenorphine efficacy would not be significantly attenuated when the combination product is administered sublingually and make the product less attractive for parenteral abuse (similar to Talwin[®] NX-pentazocine 50 mg/naloxone 0.5 mg).

Results And Discussion

Table 1 presents the main pharmacokinetic parameter values from this study. Both C_{max} and AUC_{0-48} of buprenorphine increased in a linear fashion in the range of 4 to 16 mg with the increase in dose of Suboxone[®], although the increase was not directly proportional. $AUC_{0-\infty}$ showed a similar trend to that of AUC_{0-48} although the extrapolated $AUC_{0-\infty}$'s comprised unacceptable high percentages of $AUC_{48-\infty}$'s. The C_{max} and AUC_{0-48} values were similar between Subutex[®] 16mg and Suboxone[®] 16mg. The mean C_{max} and AUC_{0-48} ratios for Suboxone compared to Subutex[®] were 1.08 and 1.07. Statistical analysis (on log transformed parameters) was conducted to see if 16 mg doses of Subutex[®] and Suboxone[®] were bioequivalent (note: study was not powered for bioequivalence analysis). C_{max} failed narrowly on the high side (upper limit of 129) while AUC_{0-48} was within the limits.

Lack of the effect of naloxone on buprenorphine pharmacokinetics can also be seen from study CR92/111. This study provides an estimate of the absolute bioavailability of an 8 mg dose of a ~~sublingual~~ alcoholic solution of buprenorphine dosed daily to steady state in conjunction with 0, 4, and 8 mg naloxone. The steady state absolute bioavailability of 8 mg dose of buprenorphine with 0, 4, and 8 mg naloxone was $42 \pm 9\%$, $42 \pm 2\%$, and $40 \pm 7\%$ respectively.

Overall, from these data, it can be seen that naloxone did not affect the pharmacokinetics of buprenorphine in Suboxone[®] tablets. This combined with the fact the Subutex[®] and Suboxone[®] formulations are similar indicates that similar buprenorphine concentrations will be delivered by same dose of Subutex[®] and Suboxone[®]. Clinical evidence for

the above is available from efficacy study 1008A where 16 mg dose of Subutex® and Suboxone® were shown to be efficacious compared to placebo.

The levels of naloxone were very low to assess dose-proportionality. At the three naloxone doses of 1, 2, and 4 mg, levels above the quantitation were not detected beyond 2 hours in all eight subjects (with one exception at the 4 mg dose in one subject where the last measurable concentration was at 8 hours). Within each subject (for most of the subjects), across the doses there seems to be a trend in increase of the naloxone concentrations with dose increase.

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Table 1. Pharmacokinetic parameters of buprenorphine after the administration of 4 mg, 8mg, and 16 mg Suboxone[®] doses and 16mg Subutex[®] dose (mean (%CV)).

Pharmacokinetic Parameter	Suboxone [®] 4 mg	Suboxone [®] 8 mg	Suboxone [®] 16 mg	Subutex [®] 16 mg	90% Confidence Intervals for Suboxone [®] /Subutex [®]
C _{max} , ng/mL	1.84 (39)	3.0 (51)	5.95 (38)	5.47 (23)	84-129
T _{max} , hour	1.1 (39)	1.0 (36)	0.8 (34)	1.0 (63)	-
AUC ₀₋₄₈ [*] , hour*ng/mL	12.52 (35)	20.22 (43)	34.89 (33)	32.63 (25)	88-123
AUC _{0-∞} [#] , hour*ng/mL	14.9 (34)	28.7 (57)	51.23 (38)	43.39 (20)	88-129

*AUC₀₋₃₆ in two out of 24 doses.

mean extrapolated AUC_{0-∞}'s comprised unacceptable high percentages of AUC_{48-∞}'s.

Table 2. Pharmacokinetic parameters of naloxone after the administration of 4 mg, 8mg, and 16 mg doses of Suboxone[®] (mean (%CV)).

Pharmacokinetic Parameter	Suboxone [®] 4 mg	Suboxone [®] 8 mg	Suboxone [®] 16 mg
	(Naloxone 1 mg)	(Naloxone 2 mg)	(Naloxone 4 mg)
C _{max} , ng/mL	0.107 (25)	0.178 (57)	0.279 (68)
T _{max} , hour	0.59 (58)	0.65 (58)	0.72 (78)
AUC ₀₋₄₈ , hour*ng/mL	0.103 [#]	0.148 (33)	0.259 (45)
AUC _{0-∞} [*] , hour*ng/mL	0.656 [#]	0.233 (23)	0.558 (76)

[#] one subject

* mean extrapolated AUC_{0-∞}'s comprised unacceptable high percentages of AUC_{48-∞}'s.

SOLUTION DOSE-PROPORTIONALITY

Study Type: Dose-proportionality

Study Title: Dose-proportionality of 4, 8, 16, and 32 mg Sublingual Buprenorphine solutions.

NDA: 20-733 **Submission Date:** 6/9/99

Volume: 65

Study: CR96/016

Study Design:

Clinical

Investigator: []

Analytical

Investigator: []

Single Dose: Yes **Cross-Over:** four-way

Fasted: One hour before and after dosing

Other Design: Open, randomized

Wash-Out Period: One week

Subject Breakdown

Normal Yes

Young Yes

Number=12

Male=10

Female=2

Weight;

Mean 71

Range 58-84 kg

Age;

Mean 27

Range 22-34 yrs

Formulation

Treatment Groups	Dose	Dosage Form	Strength	Lot	Lot Size
Buprenorphine 4mg	4 mg	30%	4 mg/mL	061003-C	-
Buprenorphine 8mg	8 mg	ethanolic	8 mg/mL	061003-D	-
Buprenorphine 16mg	16 mg	solution	16 mg/mL	061003-F	-
Buprenorphine 32mg	32 mg		32 mg/mL	061003-G	-

Analytical Methodology

Plasma Sampling Times: Prior to dosing, and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 18, 24, 30, 36, 48, and 72 hours post dose.

Assay Method: LC/MS/MS

Assay Sensitivity: The limit of quantitation was _____ ng/mL for buprenorphine. Assay was linear in the range of _____ ng/mL.

Assay Accuracy: The inter-day precision (ranged from 5.2% to 6.5%) and accuracy (-2.7% to +9.13%) parameters were within acceptable limits.

Labeling Claims: none

Objectives

To assess the dose-proportionality of buprenorphine administered as a sublingual solution.

Results and Discussion

This study evaluated the dose-proportionality of 4, 8, 16, and 32 mg doses of buprenorphine given as 30% ethanolic solution held in the mouth for 5 minutes in 12 subjects. Figure 1 presents the plasma concentration versus time profiles of buprenorphine. Although buprenorphine could be detected at 72 hours, the levels were very low 10 hours after dosing. Table 1 presents the main pharmacokinetic parameters of buprenorphine. Mean values of AUC and C_{max} increased linearly with dose, although the increase was not directly dose-proportional. Dose-adjusted AUC and C_{max} decreased with each increase in dose size. Mean AUC's ranged from 17 ng*hour/mL to 70 ng*hour/mL over the dose range of 4 to 32mg.

It should be noted that in NDA 20-732, the sponsor submitted dose-proportionality data from study CR90/061 evaluating the dose-proportionality of 1, 2, 4, 8, 16, and 32 mg doses of buprenorphine given as — ethanolic solution held in the mouth for 5 minutes in four subjects. C_{max} was found to increase non-linearly with increasing doses. AUC was however linear. The actual buprenorphine levels were very high and the sponsor attributed this to cross-reactivity to norbuprenorphine of the RIA assay used in this study. Mean buprenorphine AUC's ranged from 45 ng*hour/mL to 476 ng*hour/mL over the dose range of 2 to 32mg.

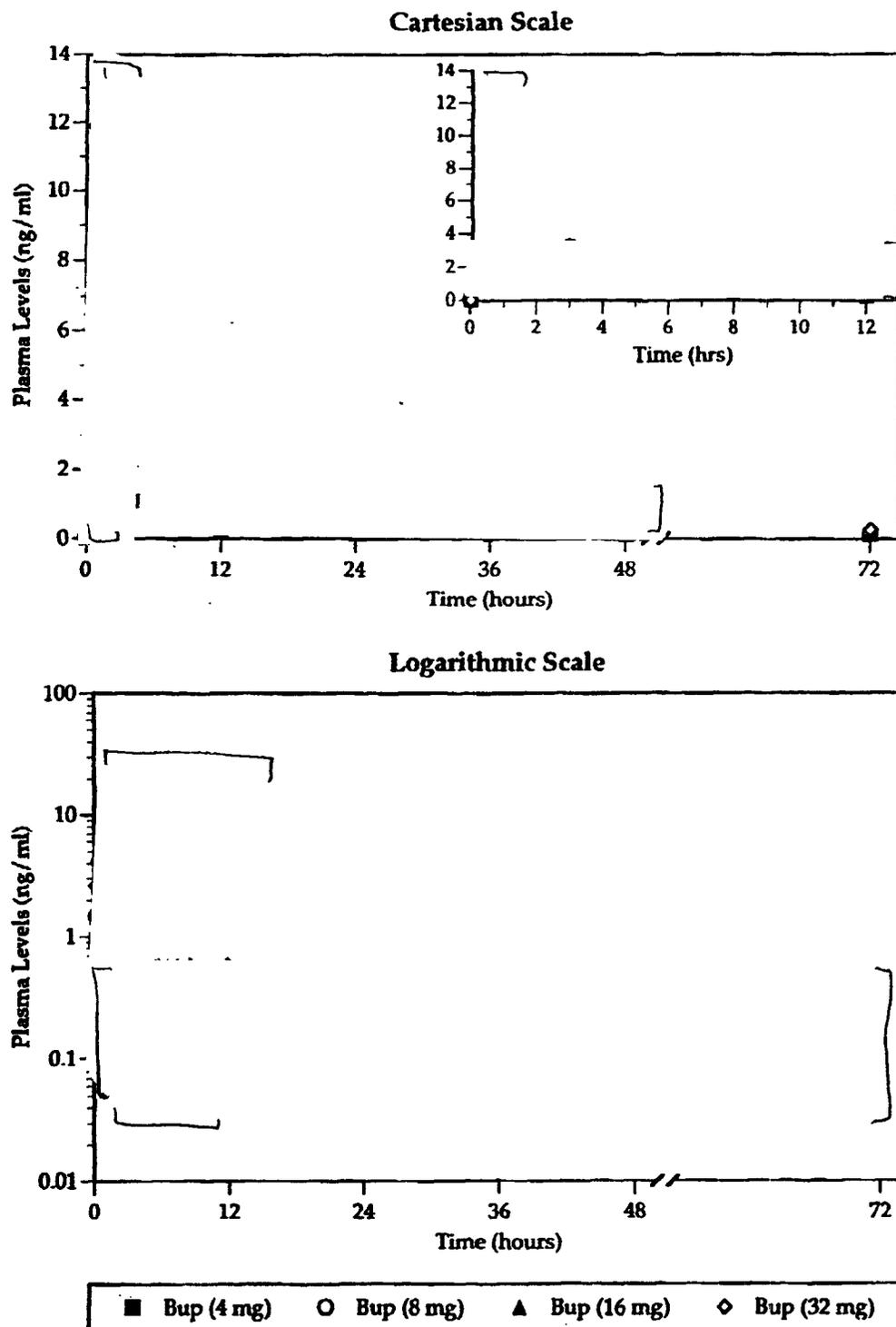
Table 1. Pharmacokinetic parameters of buprenorphine after the administration of 4mg, 8mg, 16mg, and 32mg solution doses (mean (%CV)).

Pharmacokinetic Parameter	Bup 4mg	Bup 8mg	Bup 16mg	Bup 32mg
C_{max} , ng/mL	3.56 (42)	5.83 (47)	8.37 (34)	13.7 (23)
T_{max} , hour	1.1 (37)	1.2 (47)	1.2 (35)	1.0 (63)
AUC ₀₋₇₂ , hour*ng/mL	17.36 (31)	22.42 (30)	48.3 (28)	70.3 (23)
AUC _{0-∞} , hour*ng/mL	30.7 (32)	38.1 (34)	55.8 (24)	107.9 (65)

* mean AUC_{0-∞}'s comprised unacceptable high percentages of extrapolated AUC's.

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Figure 1. Plasma concentration versus time profiles of buprenorphine.



MASS BALANCE

Study Type: Mass-Balance

Study Title: Determination of Buprenorphine Mass Balance.

NDA: 20-733 Submission Date: 6/9/99

Volume: 66

Study: CR94/006

Study Design:

Clinical

Investigator: [

Analytical

Investigator: [

Single Dose: Yes

Fasted: One hour before and after dosing

Other Design: Open, non-randomized

Subject Breakdown

Normal Yes

Young Yes

Number=6

Male=6

Female=0

Weight;

Mean 68

Range 61-73 kg

Age;

Mean 32

Range 23-36 yrs

Formulation

Treatment Groups	Dose	Dosage Form
³ H-Buprenorphine	1 mg as a 60 minute infusion	Sterile solution

Analytical Methodology

Plasma and Urine Sampling Times: Prior to dosing, and at 10, 15, 30, 60 minutes, 2, 4, 8, 18, 24 hours post dose and daily until discharge (10 days).

Feces Sampling Times: Prior to dosing and post dose for 10 days.

Assay Method: _____

Labeling Claims: none

Objectives

To investigate metabolic pathways, urine and fecal profiles.

Results and Discussion

Almost all (99%) of the radiolabel was recovered in urine and feces collected up to 11 days after dosing. Of this, feces comprised 69% while urine comprised 30% of the radiolabel. Almost all of the dose was accounted for in terms of buprenorphine, norbuprenorphine, and two unidentified (less than 2% together) buprenorphine metabolites.

In urine only 1% was recovered as unchanged buprenorphine while 9.4% was conjugated. Similarly, most of norbuprenorphine was conjugated (11%) while 2.7% was free.

In feces, almost all of the buprenorphine (33% free and 5% conjugated) and norbuprenorphine (21% free and 2% conjugated) were free.

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