

period (ranges: BUN -0.2 to 0.5 mg/dL; creatinine -0.01 to 0.02 mg/dL). Only two subjects had elevation in BUN or creatinine that were “possibly clinically significant” during the 52-week study period in Study 96/014.

### Section 8.5.1.2 Hematology

There were no treatment emergent, clinically significant changes in hematology parameters. For example, mean red blood cell indices values were within the normal range at baseline (hemoglobin 14.12 g/dL; hematocrit 42.1%). All mean change values for both parameters showed a small decrease (ranges: hemoglobin -0.02 to -0.24 g/dL; hematocrit -0.1 to -0.9 %), but there was no upward or downward trend over the 52-week study period.

Similarly, the proportion of subjects who had WBC or platelet count values outside the normal range did not change substantially from baseline throughout the study period (WBC: baseline 14.6%; range 12.2% to 18.6%; platelets: baseline 9.2%; range 8.0% to 14.0%). A clinically insignificant but noticeable decrease in platelet count over time was evident. A large number of subjects experienced possibly clinically abnormal ( $\geq 10\%$ ) eosinophil percentages.

### Section 8.5.1.3 Urinalysis

There were no treatment emergent, clinically significant changes in urinalysis tests. In the subjects who received at least 6 months of combination therapy, the proportion of subjects who had values outside the normal range did not change substantially from baseline throughout the study period (specific gravity: baseline 11.6%; range 7.0% to 12.9%; pH: baseline 2.1%; range 0% to 3.5%).

## SECTION 8.5.2 VITAL SIGNS

The criteria for identifying vital sign and laboratory values are provided below. Changes in vital signs of a magnitude that could be considered “possibly clinically significant” are listed in table below

**Table 82. Definitions of “Possibly Clinically Significant” Vital Sign Abnormalities**

Variable	Change Relative to Baseline
Systolic blood pressure	Change of $\geq 20$ mm Hg provided the resultant value was $\geq 180$ mm Hg or $\leq 90$ mm Hg
Diastolic blood pressure	Change of $\geq 15$ mm Hg provided the resultant value was $\geq 105$ mm Hg or $\leq 50$ mm Hg
Pulse	Change of $\geq 15$ bpm provided the resultant pulse was $\geq 120$ bpm or $\leq 50$ bpm
Temperature	Change of $\geq 2^\circ\text{F}$ provided the resultant temperature was $\geq 101^\circ\text{F}$
Body Weight	Change of $\geq 7\%$ of body weight

Data Source: Based on Sponsor's Table 31 Vol 93, page 31

Vital signs (blood pressure, pulse, body weight, and temperature) were measured at baseline and monthly during the study (CR96/013). For systolic and diastolic blood pressures, pulse, and body temperature there were no remarkable trends in change over the course of the study (systolic blood pressure: mean baseline 121.3 mm Hg, range of mean change -1.7 to 3.7 mm Hg; diastolic blood pressure: mean baseline 76.2 mm Hg, range of mean change -1.8 to 2.3 mm Hg; pulse: mean baseline 73.9 beats/min, range of mean change -0.8 to 1.7 beats/min; and body temperature: mean baseline 98.12°F, range of mean change -0.16 to 0.09°F). Only three subjects had elevation in diastolic blood pressure that were “possibly clinically significant” during the 52-week study period in Study 96/014. Similarly, There were no apparent effects of dose or of chronicity of dosing on mean or median systolic or diastolic blood pressure in the pooled Studies CR88/130, CR92/099, CR92/100, and CR92/102.

***Respiratory Rate.*** No significant differences in respiratory rate were seen in the study.

### SECTION 8.5.3 BODY WEIGHT

There was a steady increase in mean body weight from baseline (164.5 pounds) through the study with mean increases of about 5 pounds during the latter weeks of the study (Table 84). Number of subjects with possible clinically significant changes in body weight ( $\geq 7\%$  of baseline body weight pre-specified) in the safety study (1008B) are provided in table below. The incidence of “possibly clinically significant” body weight values was more common, and ‘increased’ body weight values were greater at later time points. Similar changes were also observed in the solution studies. In the dosing groups that received more than 1 mg/day, there was an increase in the proportion of subjects who had shifts from the normal to the high range, the largest of which was in the subjects who were receiving the middle dose levels (4 and 8 mg/day).

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Table 83. Number of subjects with possible clinically significant changes in body weight ( $\geq 7\%$  of baseline body weight) in the safety study (1008B)

Week	Weight		
	N Assessed	N (%)	
	(N)	Low (7% or more below baseline weight)	High (7% or more above baseline weight)
4	393	8 (2.0)	16 (4.1)
8	345	11 (3.2)	26 (7.5)
12	318	16 (5.0)	26 (8.2)
16	299	14 (4.7)	38 (12.7)
20	264	18 (6.8)	41 (15.5)
24	257	17 (6.6)	49 (19.1)
28	241	15 (6.2)	48 (19.9)
32	227	22 (9.7)	48 (21.1)
36	210	16 (7.6)	48 (22.9)
40	199	16 (8.0)	47 (23.6)
44	176	14 (8.0)	49 (27.8)
48	171	17 (9.9)	48 (28.1)
52	91	12 (13.2)	22 (24.2)

Data Source: Based on Sponsor's Table 106 Vol 153,page 176

There were 63 subjects who had possible clinically significant changes in body weight in Week 28. The reviewer did additional analyses on their weight changes. Twenty-eight subjects (out of 63) had their height recorded in baseline, and thus body mass index (BMI) could be calculated. All 28 subjects met overweight definition (a BMI  $\geq 27.8$  for men and  $\geq 27.3$  for women). Nine out of 28 (32%) subjects lost weight ( $15.5 \pm 3.4$  pound, mean  $\pm$  SD) while 19 subjects gained weight ( $19.7 \pm 10.8$  pound, mean  $\pm$  SD). Suboxone effects on body weight cannot be determined definitely from data submitted. Weight changes in solution studies were similar.

#### SECTION 8.5.4 ELECTROCARDIOGRAM

In Study CR96/013 and CR96/014, ECGs were to be obtained at baseline, Week 4, Week 12, Week 24, Week 36 and Week 52, relative to the subject's original study (1008) entry date. Of the 257 subjects with both baseline and on-treatment ECG data available, 24.7% of the combination therapy group, 18.5% of the monotherapy group, and 13.8% of the placebo group had abnormal ECGs at baseline. At Week 4, 22.5% of the combination therapy group, 19.8% of the monotherapy group, and 6.9% of the placebo group had abnormal ECGs. Examination of the number of subjects who shifted from overall normal ECGs to overall abnormal ECGs between baseline and Week 4 showed that there were some differences between treatment groups. Of the more serious individual ECG abnormalities observed, "other rhythm abnormalities", "first degree A-V block" and "RBB block" were identified in 16 subjects, of whom 4 received combination therapy, 8

received monotherapy, and 4 received placebo. Eleven subjects has at least one QTc interval of > 450 msec. Nine subjects had these abnormally high values at baseline. Two subjects had the increase found only in the treatment phase. One subject was in Subutex group and another was in placebo.

The proportion of subjects with abnormal ECGs was high at baseline (24.3%) and was fairly constant during the 52-week study period (range 24.2% to 32.9%), showing no clear upward or downward trend.

## SECTION 8.6 DOSE-RESPONSE ADVERSE EXPERIENCE INFORMATION

Dose-response adverse events have been presented in Section 8.4.1., 8.5.1.1 and 8.8 in this review. Dose ranges evaluated for Suboxone are from 4/1 mg to 24/6 mg, and from 1 mg to 32 mg for the solution studies. Many frequently reported AEs in body as a whole, digestive system and nervous system are higher in higher doses than lower doses. There were ten adverse events, for which the differences in incidence > 10% when the dose of 24/6 mg compared the dose of 4/1 mg (Suboxone). These adverse events were: flu syndrome, headache, infection, pain, back pain, withdrawal syndrome, constipation, tooth disorder, insomnia, and rhinitis. By comparison, there were six adverse events in the solution studies, for which the differences in incidence > 10% when similar doses were compared (2 mg vs 16 mg). Those adverse events were: headache, pain, withdrawal syndrome, infection, constipation, and insomnia.

Table 84. Dose-response adverse events: Difference > 10% between Low and High Doses

<i>Adverse Event</i>	<i>Bup/Nal 4/1 mg (N=131)</i>	<i>Bup/Nal 20/5 mg (N=48)</i>	<i>Bup 2 mg (N=117)</i>	<i>Bup 16 mg (N=84)</i>
$\Delta > 10\%$ :				
Pain	16.0%	43.8%	20.5%	30.7%
Withdrawal Syn	17.6%	33.3%	12.3%	26.4%
Infection	1.5%	31.3%	16.2%	29.1%
Headache	13.0%	27.1%	13.7%	34.7%
Insomnia	8.4%	20.8%	19.7%	32.3%
Constipation	1.5%	14.6%	1.7%	12.6%
$\Delta > 10\%$ in Bup/Nal only:				
Back Pain	11.5%	27.1%	10.3%	18.1%
Flu Syndrome	1.5%	20.8%	8.6%	7.9%
Vomiting	1.5%	16.7%	1.0%	8.7%
Rhinitis	2.3%	12.5%	11.1%	14.6%

Data Source: Table 64 and 65 in this review

The differences in dose-response AEs between Suboxone and the solution formulation might be due to naloxone in Suboxone. Naloxone might be responsible for increasing

differences of flu syndrome, back pain, rhinitis and vomiting (between the low and high doses).

## **SECTION 8.7 DRUG-DRUG INTERACTIONS**

Potential drug interactions with benzodiazepines, opiates, analgesics, tricyclic antidepressants, monoamine oxidase inhibitors and antibiotics will be discussed in the biopharm review for this NDA.

## **SECTION 8.8 ADVERSE EFFECTS IN LONG TERM USE**

Adverse events of Suboxone in long term use (up to 52 weeks, including 261 patients for more than 28 weeks) were assessed in Study 1008B. Among all subjects receiving the buprenorphine/naloxone tablet, the most frequently reported events were headache, pain, withdrawal syndrome, infection, insomnia, back pain, and constipation, each reported by more than 20% of subjects. Flu syndrome, abdominal pain, nausea, rhinitis, sweating, accidental injury, depression, anxiety, pharyngitis, vomiting, diarrhea, and asthenia were each reported by more than 10% of subjects. Frequency of common adverse events was higher in the long-term study than the short-term study (table below).

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**Table 85. Comparisons of Adverse Events Reported by at Least 5% of Subjects: Short-term Use vs Long-term Use**

Adverse Event (COSTART Coded Term)	All Subjects (N = 472) long-term Study (1008B)	All Subjects (N = 107) 4-Week Study (1008A)
<b>Body as a Whole</b>		
Asthenia	48 (10.2%)	7 (6.5%)
Chills	44 (9.3%)	8 (7.5%)
Fever	36 (7.6%)	< 5%
Flu Syndrome	89 (18.9%)	< 5%
Headache	202 (42.8%)	39 (36.4%)
Infection	149 (31.6%)	6 (5.6%)
Accidental Injury	72 (15.3%)	< 5%
Pain	197 (41.7%)	24 (22.4%)
Pain Abdomen	77 (16.3%)	12 (11.2%)
Pain, Back	132 (28.0%)	4 (3.7%)
Withdrawal Syndrome	194 (41.1%)	27 (25.2%)
<b>Cardiovascular System</b>		
Vasodilation	29 (6.1%)	10 (9.3%)
<b>Digestive System</b>		
Constipation	115 (24.4%)	13 (12.1%)
Diarrhea	50 (10.6%)	4 (3.7%)
Dyspepsia	45 (9.5%)	< 5%
Nausea	76 (16.1%)	16 (15.0%)
Tooth Disorder	37 (7.8%)	< 5%
Vomiting	61 (12.9%)	8 (7.5%)
<b>Metabolic and Nutritional</b>		
Peripheral Edema	24 (5.1%)	< 5%
<b>Musculoskeletal System</b>		
Myalgia	31 (6.6%)	< 5%
<b>Nervous System</b>		
Anxiety	65 (13.8%)	< 5%
Depression	70 (14.8%)	< 5%
Dizziness	33 (7.0%)	< 5%
Insomnia	138 (29.2%)	15 (14.0%)
Nervousness	42 (8.9%)	< 5%
Paresthesia	28 (5.9%)	< 5%
Somnolence	40 (8.5%)	< 5%
<b>Respiratory System</b>		
Cough Increased	36 (7.6%)	< 5%
Pharyngitis	64 (13.6%)	< 5%
Rhinitis	75 (15.9%)	5 (4.7%)
<b>Skin and Appendages</b>		
Sweating	74 (15.7%)	15 (14.0%)

Data Source: Based on Sponsor's Table 66 Vol 93; page 115

Adverse events reported by at least 5% of subjects by dose level in the long-term study are summarized below

**Table 86. Adverse Events (≥ 10%) in Subjects Exposed to Combination Therapy ≥ 6 months (1008B)**

Adverse Event (COSTART Coded Term)	Buprenorphine/Naloxone Dose (mg)							All Subjects (N=)
	Other Doses (N=31)	4/1 (N=118)	8/2 (N=152)	12/3 (N=199)	16/4 (N=230)	20/5 (N=138)	24/6 (N=34)	
Subjects Reporting NO Adverse Events	9 (29.0%)	37 (31.4%)	39 (25.7%)	28 (14.1%)	29 (12.6%)	11 (8.0%)	2 (5.9%)	3 (1)
<b>Body as a Whole</b>	<b>18 (58.1%)</b>	<b>54 (45.8%)</b>	<b>84 (55.3%)</b>	<b>147 (73.9%)</b>	<b>187 (81.3%)</b>	<b>107 (77.5%)</b>	<b>30 (88.2%)</b>	<b>245 (58.1%)</b>
Asthenia	1 (3.2%)	3 (2.5%)	3 (2.0%)	9 (4.5%)	18 (7.8%)	17 (12.3%)	3 (8.8%)	39 (17.3%)
Fever	0	0	3 (2.0%)	2 (1.0%)	10 (4.3%)	8 (5.8%)	4 (11.8%)	26 (11.4%)
Flu Syndrome	1 (3.2%)	2 (1.7%)	6 (3.9%)	12 (6.0%)	30 (13.0%)	28 (20.3%)	9 (26.5%)	78 (33.4%)
Headache	5 (16.1%)	17 (14.4%)	22 (14.5%)	36 (18.1%)	66 (28.7%)	37 (26.8%)	11 (32.4%)	129 (56.5%)
Infection	4 (12.9%)	1 (0.8%)	19 (12.5%)	29 (14.6%)	52 (22.6%)	42 (30.4%)	13 (38.2%)	124 (54.3%)
Accidental Injury	0	3 (2.5%)	7 (4.6%)	14 (7.0%)	26 (11.3%)	24 (17.4%)	5 (14.7%)	58 (25.4%)
Pain	3 (9.7%)	21 (17.8%)	32 (21.1%)	50 (25.1%)	94 (40.9%)	56 (40.6%)	19 (55.9%)	151 (65.7%)
Pain, Abdomen	0	1 (0.8%)	4 (2.6%)	17 (8.5%)	19 (8.3%)	17 (12.3%)	3 (8.8%)	48 (20.8%)
Pain, Back	3 (9.7%)	15 (12.7%)	27 (17.8%)	40 (20.1%)	62 (27.0%)	37 (26.8%)	9 (26.5%)	103 (45.3%)
Withdrawal Syndrome	12 (38.7%)	22 (18.6%)	20 (13.2%)	66 (33.2%)	73 (31.7%)	38 (27.5%)	11 (32.4%)	121 (53.0%)
<b>Cardiovascular System</b>	<b>1 (3.2%)</b>	<b>3 (2.5%)</b>	<b>10 (6.6%)</b>	<b>17 (8.5%)</b>	<b>22 (9.6%)</b>	<b>11 (8.0%)</b>	<b>2 (5.9%)</b>	<b>43 (18.7%)</b>
<b>Digestive System</b>	<b>7 (22.6%)</b>	<b>14 (11.9%)</b>	<b>30 (19.7%)</b>	<b>63 (31.7%)</b>	<b>101 (43.9%)</b>	<b>56 (40.6%)</b>	<b>14 (41.2%)</b>	<b>172 (75.0%)</b>
Constipation	0	2 (1.7%)	7 (4.6%)	26 (13.1%)	47 (20.4%)	34 (24.6%)	4 (11.8%)	80 (35.3%)
Nausea	1 (3.2%)	2 (1.7%)	4 (2.6%)	12 (6.0%)	21 (9.1%)	7 (5.1%)	4 (11.8%)	43 (18.7%)
Tooth Disorder	1 (3.2%)	1 (0.8%)	6 (3.9%)	5 (2.5%)	12 (5.2%)	4 (2.9%)	4 (11.8%)	29 (12.6%)
Vomiting	0	1 (0.8%)	2 (1.3%)	8 (4.0%)	19 (8.3%)	7 (5.1%)	8 (23.5%)	42 (18.5%)
<b>Endocrine System</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>1 (0.7%)</b>	<b>0</b>	<b>1 (0.4%)</b>
<b>Hemic and Lymphatic System</b>	<b>1 (3.2%)</b>	<b>0</b>	<b>3 (2.0%)</b>	<b>6 (3.0%)</b>	<b>10 (4.3%)</b>	<b>7 (5.1%)</b>	<b>1 (2.9%)</b>	<b>19 (8.3%)</b>
<b>Metabolic/Nutritional Disorders</b>	<b>0</b>	<b>5 (4.2%)</b>	<b>11 (7.2%)</b>	<b>17 (8.5%)</b>	<b>19 (8.3%)</b>	<b>17 (12.3%)</b>	<b>4 (11.8%)</b>	<b>44 (19.1%)</b>
<b>Musculoskeletal System</b>	<b>1 (3.2%)</b>	<b>8 (6.8%)</b>	<b>6 (3.9%)</b>	<b>17 (8.5%)</b>	<b>24 (10.4%)</b>	<b>21 (15.2%)</b>	<b>9 (26.5%)</b>	<b>58 (25.4%)</b>
Myalgia	0	2 (1.7%)	1 (0.7%)	4 (2.0%)	7 (3.0%)	9 (6.5%)	4 (11.8%)	25 (10.9%)
<b>Musculoskeletal System (cont.)</b>								
<b>Nervous System</b>	<b>4 (12.9%)</b>	<b>34 (28.8%)</b>	<b>57 (37.5%)</b>	<b>93 (46.7%)</b>	<b>107 (46.5%)</b>	<b>65 (47.1%)</b>	<b>18 (52.9%)</b>	<b>170 (74.1%)</b>
Anxiety	0	9 (7.6%)	18 (11.8%)	20 (10.1%)	24 (10.4%)	17 (12.3%)	2 (5.9%)	49 (21.3%)
Depression	1 (3.2%)	18 (15.3%)	28 (18.4%)	31 (15.6%)	24 (10.4%)	20 (14.5%)	10 (29.4%)	59 (25.8%)
Insomnia	1 (3.2%)	11 (9.3%)	25 (16.4%)	39 (19.6%)	55 (23.9%)	34 (24.6%)	8 (23.5%)	96 (42.1%)

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Adverse Event (COSTART Coded Term)	Buprenorphine/Naloxone Dose (mg)							All Subjects (N=261)
	Other Doses (N=31)	4/1 (N=118)	8/2 (N=152)	12/3 (N=199)	16/4 (N=230)	20/5 (N=138)	24/6 (N=34)	
Nervousness	0	4 (3.4%)	3 (2.0%)	9 (4.5%)	14 (6.1%)	3 (2.2%)	4 (11.8%)	25 (9.6%)
<b>Respiratory System</b>	<b>2 (6.5%)</b>	<b>12 (10.2%)</b>	<b>18 (11.8%)</b>	<b>44 (22.1%)</b>	<b>68 (29.6%)</b>	<b>44 (31.9%)</b>	<b>10 (29.4%)</b>	<b>133 (51.0%)</b>
Pharyngitis	0	3 (2.5%)	4 (2.6%)	9 (4.5%)	25 (10.9%)	20 (14.5%)	3 (8.8%)	53 (20.3%)
Rhinitis	0	3 (2.5%)	5 (3.3%)	20 (10.1%)	28 (12.2%)	14 (10.1%)	5 (14.7%)	57 (21.8%)
<b>Skin and Appendages</b>	<b>4 (12.9%)</b>	<b>7 (5.9%)</b>	<b>11 (7.2%)</b>	<b>35 (17.6%)</b>	<b>43 (18.7%)</b>	<b>28 (20.3%)</b>	<b>4 (11.8%)</b>	<b>86 (33.0%)</b>
Sweating	0	0	3 (2.0%)	13 (6.5%)	23 (10.0%)	11 (8.0%)	3 (8.8%)	37 (14.2%)
<b>Special Senses</b>	<b>0</b>	<b>1 (0.8%)</b>	<b>5 (3.3%)</b>	<b>9 (4.5%)</b>	<b>29 (12.6%)</b>	<b>9 (6.5%)</b>	<b>1 (2.9%)</b>	<b>46 (17.6%)</b>
<b>Urogenital System</b>	<b>0</b>	<b>11 (9.3%)</b>	<b>14 (9.2%)</b>	<b>27 (13.6%)</b>	<b>29 (12.6%)</b>	<b>26 (18.8%)</b>	<b>6 (17.6%)</b>	<b>74 (28.4%)</b>

Data Source: Based on Sponsor's Section 13.4.2.2 Vol 93;page 278-285-

A subset of 261 subjects in the safety study was exposed to combination therapy for at least 6 months. The frequencies of adverse events in this sample were similar to the adverse events discussed in 1008A and solution studies. Frequently reported adverse events (at least 20%) had a somewhat higher incidence in subjects exposed for at least 6 months and included pain, headache, infection, withdrawal symptoms, back pain, insomnia, constipation, flu syndrome, depression, accidental injury, rhinitis, and pharyngitis. Anxiety, abdominal pain, nausea, vomiting, asthenia, sweating, diarrhea, dyspepsia, tooth disorder, chills, fever, and paresthesia were each reported by 10% or more of the subjects. Many of those adverse events had a dose-response pattern. Of note is the presence of abnormal liver function tests in 16 subjects (6.1%) who completed at least 6 months of combination therapy (not listed in the table). There were 10 reports of increases in individual liver function parameter values including increased LDH (3 reports) and increased alkaline phosphatase (2 reports), increased SGOT (2 reports) and increased SGPT (3 reports).

The incidence of adverse events appeared to increase with dose level; 89 of the 131 subjects (67.9%) taking the lowest dose (4 mg buprenorphine/1 mg naloxone) reported adverse events whereas 46 of the 48 subjects (95.8%) taking the highest dose (24 mg buprenorphine/6 mg naloxone) reported adverse events. At the most commonly prescribed dose level (16 mg buprenorphine/4 mg naloxone), 339 of the 394 subjects (86.0%) reported adverse events. There were some events that appeared to occur with higher incidence as the dose increased. Since the design of the study was titration with low doses and progressively increasing doses, there was also an increase in duration of exposure as the dose increased. Therefore, the apparently increasing incidences of fever, flu

syndrome, and infection could be attributed either to dose or to “more opportunity” for occurrence given the longer treatment duration. Constipation and vomiting, which also apparently increased with dose, may be more likely dose-related.

Adverse events first reported after at least 6 months of study treatment were examined and are summarized in table below. There were no apparent trends in these late onset adverse events and the majority of events with a first occurrence after 6 months of treatment were reported only once.

**Table 87. Adverse Events First Reported after at Least 6 Months of Combination Therapy in the Safety Study – 1008B (N=261 Subjects)**

Body System and Event	N (%)
<b>Body as a Whole</b>	
Hostility	2 (0.8%)
Pelvic Pain	1 (0.4%)
Rib Pain	1 (0.4%)
<b>Cardiovascular System</b>	
Angina Pectoris	2 (0.8%)
Hypotension	1 (0.4%)
Myocardial Infarction	1 (0.4%)
Thrombosis	1 (0.4%)
Deep Thrombophlebitis	1 (0.4%)
Varicose Vein	1 (0.4%)
<b>Digestive System</b>	
Tongue Discoloration	2 (0.8%)
Rectal Hemorrhage	1 (0.4%)
Hepatitis C	1 (0.4%)
<b>Metabolic and Nutritional Disorders</b>	
BUN Increased	1 (0.4%)
Creatinine Increased	1 (0.4%)
Electrolyte Abnormality	1 (0.4%)
Hypokalemia	1 (0.4%)
<b>Respiratory System</b>	
Emphysema	1 (0.4%)
Voice Alteration	1 (0.4%)
<b>Skin and Appendages</b>	
Fungal Dermatitis	1 (0.4%)
Maculopapular rash	1 (0.4%)
<b>Urogenital System</b>	
Mastitis	1 (0.4%)
Metrorrhagia	1 (0.4%)
Testis Disorder	1 (0.4%)

Data Source: Based on Sponsor's Table 67 Vol 93;page 117

## SECTION 8.9 FOREIGN MARKETING EXPERIENCES

### Section 8.9.1 Post-marketing Data for Buprenorphine Sublingual Tablets (Subutex)

Buprenorphine is available in France for any doctor to prescribe to a narcotic addict. The prescription is filled by a pharmacist who may or may not supervise daily dosing, but take-homes are allowed. Pharmacies are surveyed quarterly, and 886 pharmacists who were dispensing Subutex to addicts reported (1998) that the most frequent prescriptions were for doses between 2mg and 6mg (54%) with 27% for the 8mg tablet (Table 88). The same pharmacists reported that 38% of the patients were receiving Subutex on a daily basis.

**Table 88. Distribution of Doses of Subutex Tablets in France**

Daily Dose	% of Patients
Less than 2mg	5.40
2 to 6mg	54.10
8mg	27.70
10 to 14 mg	3.50
16mg or greater	1.90
Not specified	7.40

Data Source: Based on Dr. Scheinbaum's Review Table 11; page 36

As noted earlier, approximately — subjects have received Subutex since it was first marketed in France in February 1996 until May 1998. A summary of the adverse events that have been spontaneously reported, including those in the Safety Update (through July 31, 1999) is provided in this section. Important adverse events, including severe hepatic events, neonatal withdrawal syndrome and other neonatal events, overdose, and all events with a fatal outcome, have been discussed in related sections in this review.

Eight hundred and six adverse events were reported in 402 subjects during this time period (Table 89). The most frequently reported adverse events involved the central and peripheral nervous system (94 reports), neonatal and infancy disorders (66 reports), the body as a whole (62 reports), respiratory system disorders (42 reports), psychiatric (40 reports), liver and biliary (34 reports), and disorders of the eye (25 reports). The individual events reported most frequently were neonatal withdrawal (66); coma (31), miosis (25), and asphyxia (22). Those events reported by 5 or more subjects are summarized in the table below.

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**Table 89. French Post-marketing Adverse Events by 5 or More Subjects: Subutex February 1996 through July 31 1999**

<b>Categorization</b>	<b>N of Common Reports</b>	<b>Most Frequent Events (N)</b>
Application (Injection) Site Disorders	19	Injection site abscess (6) Injection site reactions (13)
Body as a Whole	62	Death (15) Edema (5) Fever (9) Headache (9) Malaise (8) Withdrawal (16)
Cardiovascular Disorders	5	Hypotension (5)
Central and Peripheral Nervous System Disorders	94	Coma (31) Somnolence (15) Convulsions + Grand Mal (13) Confusion (10) Tremor neonatal (8) Delirium (6) Hypertonia (6) Paresthesia (5)
Disorders of Blood	5	Lymphadenopathy (5)
Disorders of the Eye	25	Miosis (25)
Gastrointestinal	24	Abdominal pain (8) Vomiting (6) Nausea (5) Diarrhea (5)
Liver and Biliary System Disorders	34	Hepatic enzymes increased (14) Hepatitis (10) Jaundice (10)
Metabolic and Nutritional	10	Weight decrease (10)
Neonatal and Infancy Disorders	66	Withdrawal syndrome (66)
Psychiatric Disorders	40	Agitation (15) Hallucination (11) Suicide attempt (7) Aggressive Reaction (7)
Respiratory System Disorders	42	Asphyxia (22) Hypoventilation (12) Dyspnea (8)
Skin and Subcutaneous Tissue	19	Erythema (8) Pruritis (6) Sweating Increased (5)
<b>Total Number of Events</b>		806
<b>Total number of Subjects</b>		402

Data Source: Based on Sponsor's Safety Update Table 18, Vol 1; page 30

### Section 9.8.2 Low Dose Buprenorphine Analgesic Products: Postmarketing Experience (1978-1998)

There is widespread marketing experience with low dose buprenorphine for analgesia. This includes Buprenex marketed in the USA and abroad as a 0.3 mg/ml sterile solution for injection. Sublingual tablets of 0.2 mg and 0.4 mg are marketed for analgesia abroad as Temgesic. There is also a suppository marketed as Lepetan in Japan.

The Reckitt & Colman database contains a total of 2631 reports of adverse events following the marketing of the low-dose buprenorphine analgesic products between 1978 and 1998. These adverse events derive from the marketing of approximately 100 million dose units over the 20 year period. Although precise data as to the overall dose units represented within each of the formulation subcategories (*i.e.*, injection, sublingual and suppository) are not available, an estimate of these data, based upon the total amount of drug manufactured over the 20 year period (100 million) the average dose per unit (0.3 mg) and the approximate proportions of each of the formulations manufactured (injection; 1/3 tablet; 1/3 or less suppository, manufactured only in Japan) results in the following approximations: 33 million units of injection; 33 million units of tablets; and 33 million of suppositories. The total number of adverse events by body system is summarized below in table below. In addition, 55 events of the hemic and lymphatic system, 45 of the metabolic system, 30 of the musculoskeletal system, 18 of the reproductive system and 3 neoplasms were reported.

**Table 90. Most Frequently Reported Adverse Events (N ≥ 20) from Marketed Low-dose Buprenorphine Analgesic Products**

Preferred Terms	Injection	Sublingual	Suppository	Unspecified	Total
<b>Body As A Whole</b>	<b>140</b>	<b>169</b>	<b>8</b>	<b>7</b>	<b>324</b>
Malaise	3	55	2	0	60
Death	42	10	0	1	53
Drug interaction	28	11	0	3	42
Fever	20	11	2	0	33
Edema	2	18	1	1	22
<b>Cardiovascular</b>	<b>122</b>	<b>139</b>	<b>5</b>	<b>11</b>	<b>277</b>
Hypotension	51	43	1	2	97
Bradycardia	9	19	1	1	30
<b>Gastrointestinal</b>	<b>265</b>	<b>748</b>	<b>26</b>	<b>36</b>	<b>1075</b>
Vomiting	116	352	8	17	493
Nausea	117	231	10	15	373
Diarrhea	3	18	0	2	23
<b>Genitourinary</b>	<b>26</b>	<b>49</b>	<b>3</b>	<b>0</b>	<b>78</b>
Urine retention	20	29	0	0	49

<b>Preferred Terms</b>	<b>Injection</b>	<b>Sublingual</b>	<b>Suppository</b>	<b>Unspecified</b>	<b>Total</b>
<b>Nervous</b>	<b>454</b>	<b>933</b>	<b>50</b>	<b>29</b>	<b>1466</b>
Dizziness	23	215	2	6	246
Hallucinations	43	93	0	2	138
Dependence	81	18	18	3	120
Headache	18	64	1	3	86
Vertigo	11	61	0	1	73
Confusion	33	35	1	1	70
Sedation	13	39	0	0	52
Syncope	3	41	0	1	45
Lethargy	1	35	2	0	38
Drug dependence	20	13	3	0	36
Withdrawal syndrome	7	23	1	5	36
Stupor	14	13	6	0	33
Paresthesia	7	21	0	0	28
Ataxia	2	25	0	0	27
Tremor	3	22	0	0	25
Convulsions	7	15	1	1	24
<b>Respiratory</b>	<b>198</b>	<b>62</b>	<b>11</b>	<b>8</b>	<b>279</b>
Respiratory depression	129	23	8	5	165
Respiratory arrest	20	8	1	2	31
<b>Skin</b>	<b>87</b>	<b>245</b>	<b>6</b>	<b>15</b>	<b>353</b>
Sweating increased	14	55	1	3	73
Rash unspecified	24	32	1	0	57
Pruritus	21	24	2	2	49
Itching	12	23	0	0	35
Urticaria	3	21	0	2	26
<b>Special Senses</b>	<b>7</b>	<b>69</b>	<b>1</b>	<b>1</b>	<b>78</b>
Vision abnormal	1	19	1	0	21

Data Source: Based on Sponsor's Table 65 Vol 153;page 112-113

## **SECTION 8.10 EFFECTS OF SUBLINGUAL NALOXONE IN OPIOID DEPENDENT SUBJECTS**

A combination product of buprenorphine plus naloxone may have lower abuse potential than buprenorphine alone. However, differences in adverse event profiles (reviewed in Section 8.4.1) calls into question the clinical equivalence of the two tablets (Suboxone and Subutex), and the assertion that naloxone is an inactive ingredient when it is administered in combination with buprenorphine as Suboxone.

The sponsor has provided two supplements (three documents) on September 30, 1999 to respond to the questions above. The three documents are:

- “Naloxone in Suboxone tablets - A review of the data that show that naloxone is an inactive ingredient when administered in combination with buprenorphine as Suboxone”
- “Supplementary clinical study report: comparative assessment of opiate withdrawal symptoms” and
- A letter responds to question raised by the Division regarding the apparent dose relatedness of the incidence of some adverse events in the study of Suboxone (buprenorphine + naloxone) sublingual tablets (CR96/013 and CR96/014).

The purpose of this review section is to evaluate those new supplements by focusing on two review questions:

- To assess whether the dose of naloxone in Suboxone may have contributed to some adverse events (withdrawal effects), and
- To address whether these adverse events do or do *not* have efficacy implications, i.e., to exert any attenuation of the effects of buprenorphine during Suboxone treatment.

### **8.10.1 Evaluation of effects of sublingual naloxone in Suboxone**

#### **8.10.1.1 Low sublingual doses of naloxone and precipitate withdrawal in methadone-dependent subjects**

There is clear evidence that low sublingual doses of naloxone are able to precipitate withdrawal in methadone-dependent subjects. Preston KL et al published a study titled “Effect of sublingual given naloxone in opioid-dependent human volunteers” in *Drug and Alcohol Dependence*, 1990.

This was an open label rising dose, inpatient study. The purpose of the study is to determine whether sublingual naloxone could precipitate withdrawal in opioid dependent subjects. Naloxone was administered in increasing doses (0 – 8 mg) to six heroin abusers and three methadone (30 mg/day p.o.) maintenance patients. Naloxone hydrochloride powder was dissolved in sterile water. The subject was instructed to hold the liquid under his tongue for 10 mins. The study consisted of three parts. Part 1 and 2 were conducted in 6 subjects who received an initial dose of 20mg methadone on the day of admission and every day thereafter. Part 3 was conducted in 3 subjects who were being maintained on 30mg methadone daily. In part 1: three subjects received Naloxone 0, 0.4 and 0.8mg on day 1, and 1, 2 and 4mg on day 2 (2h intervals). In part 2: three subjects received 0 and 0.2mg on day 1, and 4 and 8mg on day 2 (2.5h intervals). In part 3: three subjects received 0, 0.25 and 0.5mg on day 1, and 1, 2 and 4mg on day 2 (2.5h intervals).

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**TABLE 91. SUBLINGUAL EFFECTS OF NALOXONE IN OPIOID DEPENDENT SUBJECTS**

Subject	Age	Weight (lb)	Race	Meth. Dose (mg)	Year of opioid use	Current drug use (drug; tomes/day; approx. amount/day)	Highest dose of naloxone Tested (mg)	Signs of withdrawal
<b>Part I</b>								
1	40	126	B	20	16	Heroin; 3 times	4	No
2	40	176	B	20	15	Heroin; 2-3 times; \$150	4	No
3	27	152	B	20	7	Heroin; 2-3 times; \$100-200	4	No
<b>Part II</b>								
4	30	145	B	20	15	Heroin; 2-3 times; \$50-100	8	No
5	30	162	B	20	14	Heroin; 2-5 times; \$200-300	4	Yes
6	29	134	W	20	9	Heroin & Non-Rx Meth 45 mg; one or both daily; \$100	4	Yes
<b>Part III</b>								
7	45	265	W	30	12	Meth Maintenance 30 mg	4	Yes
8	34	150	W	30	12	Meth Maintenance 30 mg	1	Yes
9	30	203	B	30	8	Meth Maintenance 30 mg	4	Yes

Source: Sponsor's No.: Bupp 3238; Publication: Vol 86, Page 245

Naloxone precipitated withdrawal in two of six heroin abusers and in all three methadone subjects. It is concluded from this study that Sublingual naloxone dose 1 mg may be enough to precipitate withdrawal in some opioid abusers/addicts.

**8.10.1.2 Effects of sublingual naloxone in buprenorphine maintained subjects**

To assess whether dose of naloxone in Suboxone is sufficient enough to precipitate withdrawal in buprenorphine maintained subjects, this analysis includes three parts: overview of literature, sublingual absorption of naloxone from Suboxone tablets and clinical data on withdrawal effects of sublingual naloxone.

**8.10.1.2.1 . Overview of Literature**

This literature overview is based on the sponsor's NDA submission, including Vol. 86, 91 and 146. Three volumes contain more than 50 published papers or reports, including three reports cited in the sponsor's supplements. The three studies were conducted by Jasinski et al, Kosten et al, and Eissenberg et al, who tried to reverse the effects of sublingual buprenorphine using naloxone.

The appearance of a distinctive pattern of signs and symptoms (a withdrawal syndrome) is characteristic of physical dependence. The physical dependence produced by an opioid is commonly assessed by abrupt discontinuation of opioid treatment (spontaneous withdrawal) or by antagonist challenge (precipitated withdrawal). Several studies (Jasinski et al., 1978; Fudala et al., 1988; Kosten et al., 1990; Nigam et al., 1994, Eissenberg et al., 1995) have used naloxone to investigate buprenorphine's physical dependence. In the study by Jasinski, subcutaneous doses of 4mg naloxone failed to precipitate withdrawal effects in subjects (N=4) maintained on 8 mg/day s.c. of

buprenorphine (on Days 45 to 52). However, Kosten et al., (1990) were able precipitate withdrawal in humans maintained on a lower dose of buprenorphine (2-3 mg/day sublingually) using a much higher naloxone dose (35 mg/70 kg i.v.). Nigam et al (1994) also observed precipitated withdrawal when i.v. buprenorphine abusers using 1.33 mg/day on average were challenged with 1.2 mg i.v. of naloxone. In the study by Eissenberg et al., (1995), eight opioid-dependent volunteers maintained on 8 mg/day sublingual buprenorphine were challenged on independent occasions with placebo, i.m. naloxone (0.3, 1.0, 3.0 and 10.0 mg/70 kg) and p.o. naltrexone (0.3, 1.0, and 3.0 mg/70 kg) 14 hr after their daily buprenorphine dose using a repeated measures, cross-over design. Both naloxone and naltrexone precipitated reliable, time- and dose-dependent withdrawal (see figure in the following page). Significant precipitated withdrawal occurred at 3.0 and 10 mg/70 kg i.m. of naloxone and 3.0,g/70kg p.o. of naltrexone. The study suggested that the antagonist dose necessary to precipitate withdrawal in buprenorphine-maintained patients was approximately 10 times greater than doses which precipitated withdrawal in subjects maintained on 30 mg of p.o. methadone (e.g., Preston et al., 1988; Strain et al., 1992, 1995).

The intensity of withdrawal precipitated by a given antagonist dose is related to the physical dependence level present. The antagonist doses (3.0 and 10.0 mg/70 kg i.m. of naloxone; ) used in Eissenberg's study were lower than those that were effective in other studies (e.g., the 35 mg/70 kg i.v. naloxone challenge described by Kosten et al., (1990) or the 25 mg p.o. naltrexone challenge used by van Dyck et al., 1994). However, the daily buprenorphine dose was higher in Eissenberg's study (8 mg/day s.l. compared with 2-3 mg/day s.l. in Kosten's study and 2 mg/day s.l. in van Dyck's study. Therefore, higher doses are needed to precipitate withdrawal during maintenance with low agonist dose as compared to maintenance with high agonist doses.

Other features of buprenorphine's complex pharmacology also affect the antagonist dose necessary to precipitate withdrawal in buprenorphine-maintained subjects. Buprenorphine has a low intrinsic activity which implies that buprenorphine has to occupy a greater number of receptors, relative to an opioid agonist with higher intrinsic activity, to produce a given effect (Martin et al, 1976). This suggests that an antagonist may have to replace a larger number of buprenorphine than morphine molecules, at doses producing equivalent agonist effects, to produce a withdrawal effect of a given intensity.

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## Precipitated Withdrawal Effects from the Study by Eissenberg et al., (1995)

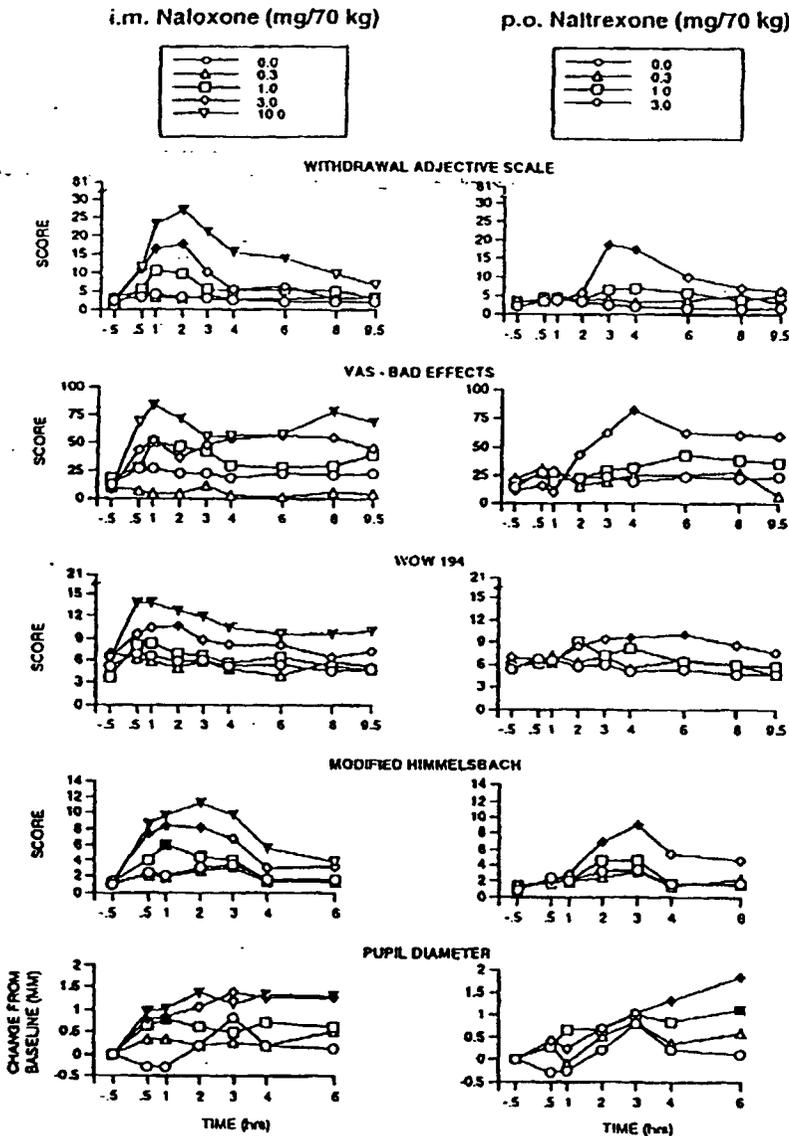


Fig. 1. Time course functions and dose effects for i.m. naloxone (left column) and p.o. naltrexone (right column) on selected measures. Data points show the mean of all eight subjects. Time is expressed relative to double-dummy drug administration (10:00 A.M.). Filled symbols, those values that are significantly different from the corresponding placebo value at the same time point ( $P < .05$ , Tukey's post hoc tests). All data except for pupil data are expressed as raw scores. Pupil data are expressed as peak difference from base line.

Buprenorphine, compared to morphine, also has high affinity for its receptor (Rothman et al., 1995), and thus it can be expected to influence the dose of antagonist necessary to displace it from the receptor to which it is bound. In addition, there may be a ceiling on the dose-effect for the magnitude of withdrawal that can be precipitated in the case of the partial agonist buprenorphine (Walsh et al., 1994, 1995).

Eissenberg's study suggest that the buprenorphine maintenance dose of 8 mg/day s.l. can be challenged with 3-mg parenteral naloxone to precipitate withdrawal, and the study demonstrated the importance of antagonist dose in determining intensity of precipitated withdrawal. It is estimated that a parenteral to sublingual potency ratio of approximately

10- to 20-fold for naloxone or naloxone's sublingual activity is about 5-10% of its parenteral activity (Preston et al 1990). This suggests that it might take 30 mg of naloxone s.l. to produce reliable withdrawal effects among patients who are 8 mg buprenorphine. However, there is no data, but it is likely that some patients who maintain on high doses of buprenorphine such as 16-24 mg/day might experience withdrawal with less naloxone present.

In summary, these results suggest that there are circumstances under which naloxone in the combinations can lead to precipitated withdrawal in buprenorphine-maintained humans. These conditions may involve a relatively high dose of naloxone and patients with high physical dependence (e.g., high buprenorphine dose).

#### **8.10.1.2.2. Sublingual absorption of naloxone from Suboxone tablets**

This section briefly reviews levels of naloxone are absorbed sublingually from Suboxone tablets.

The sublingual absorption of naloxone is low but appears to be linear over the Suboxone dose range of 4mg to 14mg, which is equivalent to 1mg to 6mg sublingual naloxone. Study CR97/007 assessed Suboxone tablet pharmacokinetics. It was an open-label, dose-ascending, 4-way crossover study to evaluate the dose proportionality of buprenorphine and naloxone when administered in Suboxone sublingual tablets. The study was conducted in 14 non-dependent opiate users. Twelve subjects received all four doses of Suboxone tablets of 4mg (2 x 2mg tablets), 8mg, 16mg (2 x 8mg tablets) and 24mg (3 x 8mg tablets). Peak plasma naloxone concentrations and areas under the curve values were low. There was a 4 to 12 fold difference in peak naloxone levels between patients. The highest peak plasma naloxone concentration found in these studies was ~ ng/ml, obtained in a patient treated with 16mg Suboxone. This result may partially explain why the effects of sublingual naloxone in the subjects varied substantially. Another explanation is that differences in levels of opioid dependence discussed in the previous section.

#### **8.10.1.2.3 Clinical data on withdrawal effects of sublingual naloxone**

Some adverse events were identified in this review Section 8.4.1, and 8.6 as being dose-related in CR96/013 and CR96/014. For example, withdrawal syndrome was 24.5%, 17.9% and 38.2% for the Suboxone, Subutex and placebo group in study CR96/013. The differences in dose-response AEs between Suboxone and the solution formulation were noticed in Section 8.6. Naloxone might be responsible for increasing differences of flu syndrome, back pain, rhinitis and vomiting (between the low and high doses, see table below).

Table 92. Dose-response adverse events: Difference &gt; 10% between Low and High Doses

<i>Adverse Event</i>	<i>Bup/Nal 4/1 mg (N=131)</i>	<i>Bup/Nal 20/5 mg (N=48)</i>	<i>Bup 2 mg (N=117)</i>	<i>Bup 16 mg (N=84)</i>
$\Delta > 10\%$ in				
Back Pain	11.5%	27.1%	10.3%	18.1%
Flu Syndrome	1.5%	20.8%	8.6%	7.9%
Vomiting	1.5%	16.7%	1.0%	8.7%
Rhinitis	2.3%	12.5%	11.1%	14.6%

Source: Section 8.6

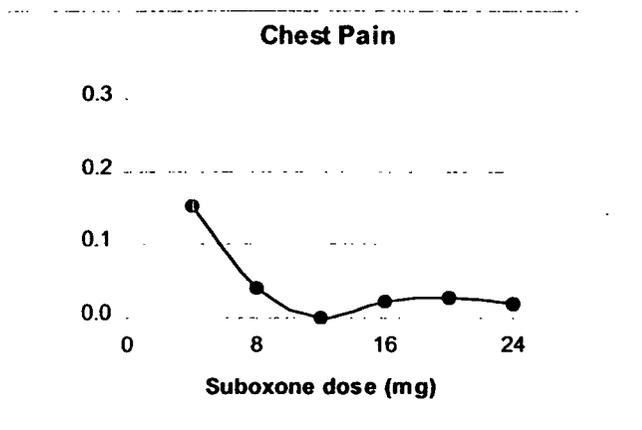
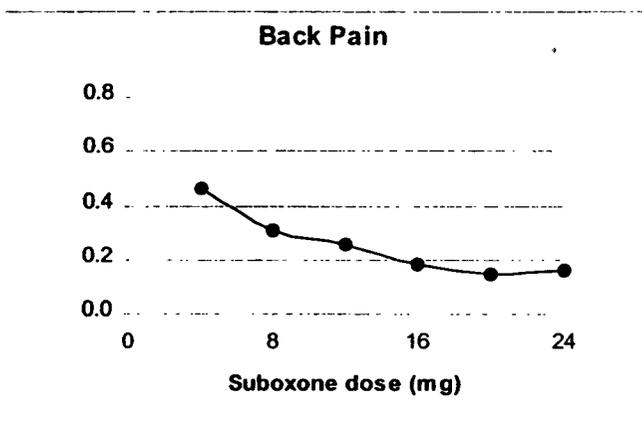
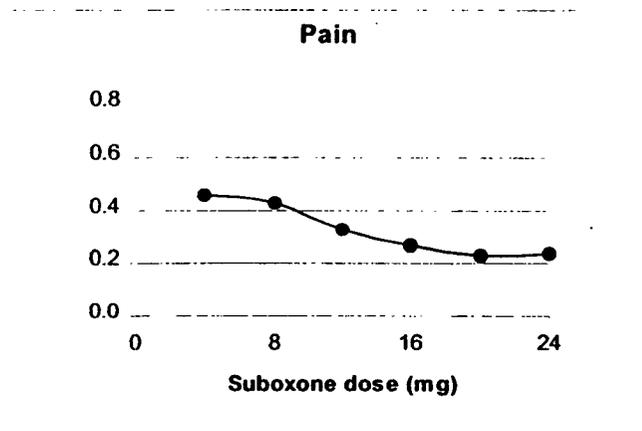
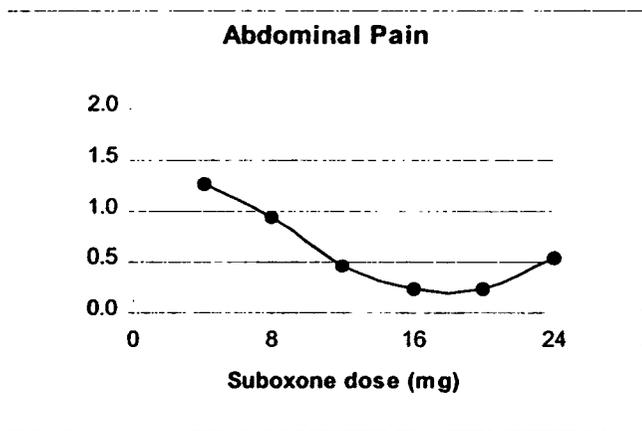
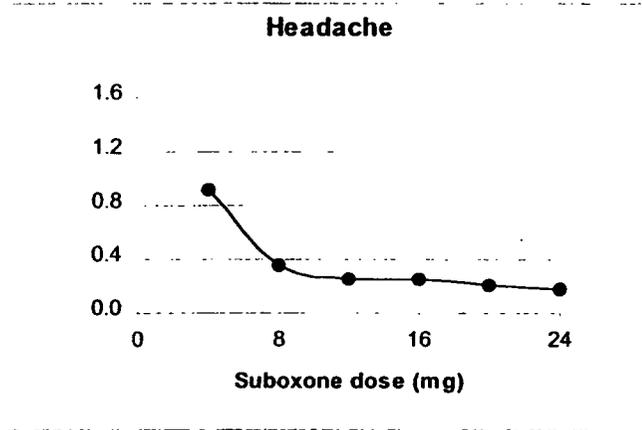
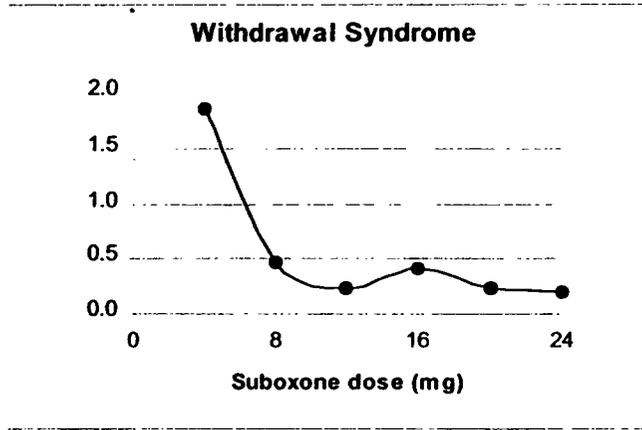
The sponsor was asked during a telephone conference (Sept 9, 1999) whether the increase in incidence by dose could relate to the administration of naloxone in Suboxone.

The sponsor responds that "In the Suboxone study, the overall incidence of adverse events appeared to increase with dose level. However, since the design of the study was titration upwards from an initial low dose, there was also an increase in duration of exposure as the dose increased. This was shown from the average number of person-days at each dose level. Therefore, the apparent increasing incidence of some adverse events could be attributed either to dose or to "more opportunity" for occurrence given the longer treatment duration at some doses. When incidence of adverse event was adjusted for the average person days of exposure, the dose relatedness no longer is present."

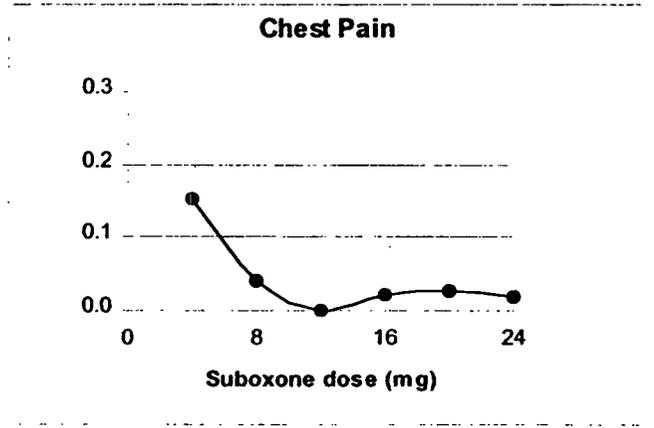
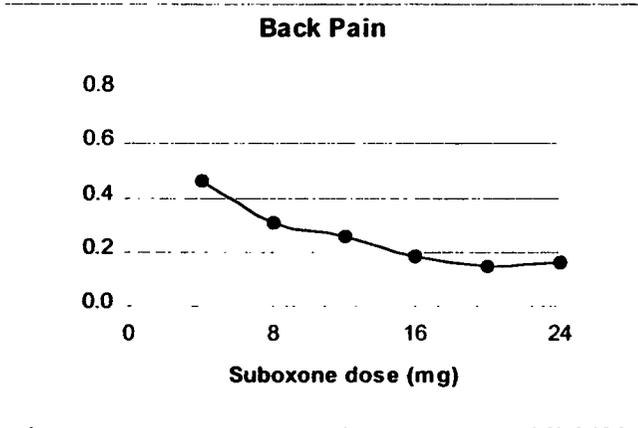
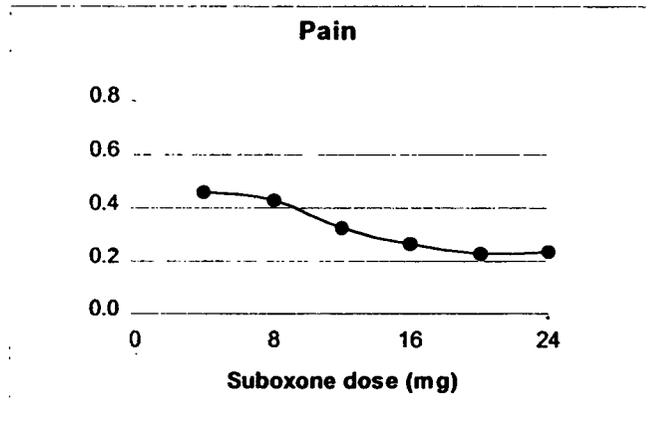
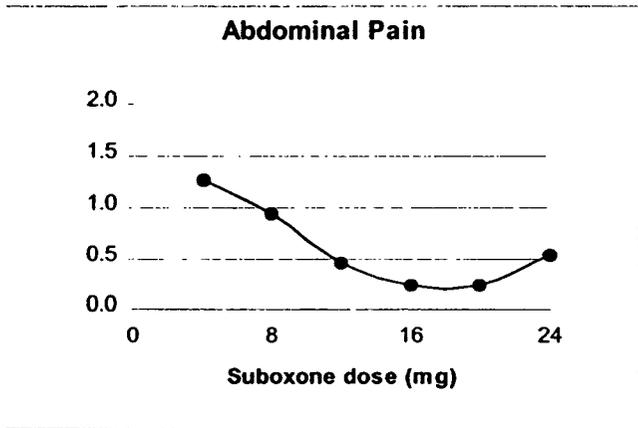
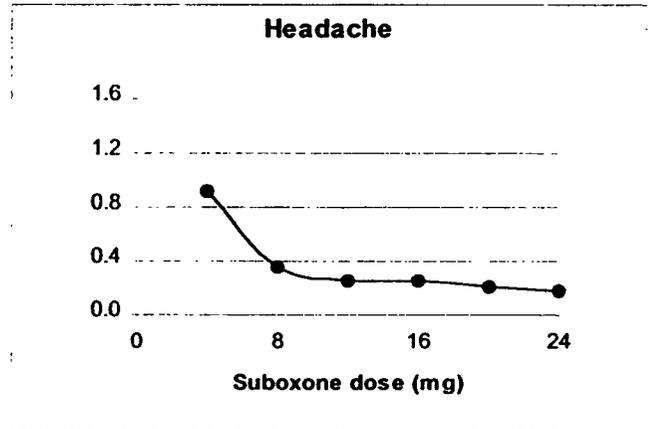
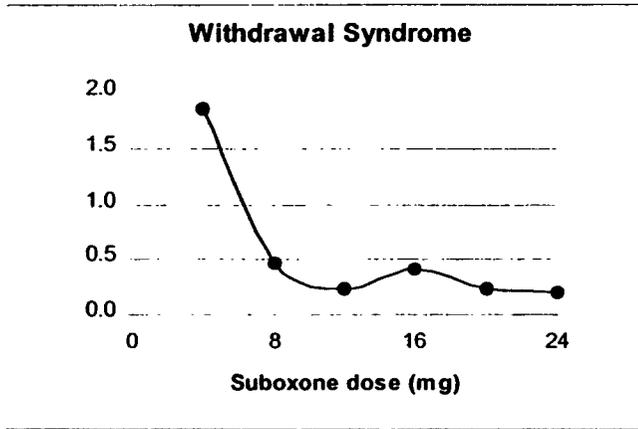
The sponsor's adjusted incidences of adverse events for study CR96/013/CR96/014 are presented below.

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**Figures 15. Study CR96/013 / CR96/014. Percentage incidences of adverse events adjusted for exposure to dose.**

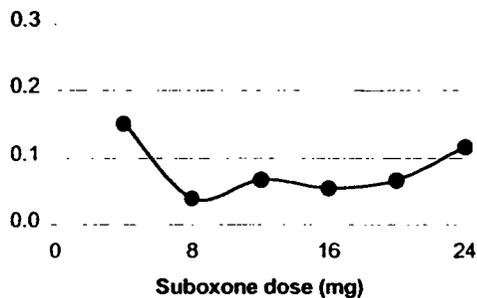


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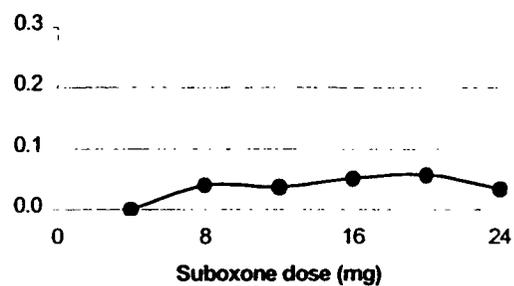


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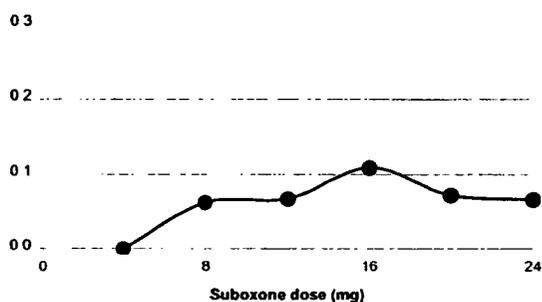
Flu Syndrome



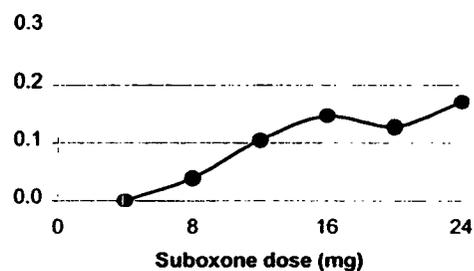
Vomiting



Rhinitis



Constipation



There are several approaches to reanalyze adverse event data. Sponsor's exposure adjusted method is one of them. However, there are indications that incidences of adverse events may be over-adjusted by the sponsor's method. For example, most adjusted incidences of adverse events have highest rate in lowest dose (< 8 mg/day) compared to higher doses, which are very hard explained clinically. The data for the sponsor's analyses come from Study CR96/014. This study used an open-label, dose titration design, and thus any additional retrospective analyses beyond the initial submission may bring some bias to results. Therefore, it is better to focus on withdrawal effects in Study CR96/013 that was a three-arm, randomized, double-blind clinical trial. In consultation with Dr. Tom Permutt, Statistical Reviewer/Team Leader, he agrees with assessments above.

#### 8.10.1.2.3.1 Assessment of Withdrawal Effects in Study CR96/013

A total of 317 subjects were randomized to the active treatment groups received 8mg sublingual buprenorphine on Day 1 and 16mg sublingual buprenorphine on Day 2. Subjects randomized to combination therapy then received 16mg buprenorphine/4mg naloxone sublingually each day for the remainder of the study and subjects randomized to

mono therapy then received 16mg buprenorphine sublingually each day for the remainder of the study. Subjects randomized to placebo received sublingual placebo tablets each day of the study. Therefore, any difference in incidence and severity from Day 2 to Day 3 (the first day on combination dosing) for the combination therapy subjects compared to the monotherapy subjects may be indicative of some effect of the naloxone present in the combination treatment.

Withdrawal symptoms in the study were assessed as part of the overall safety assessment of treatment emergent adverse events. However, for many subjects, withdrawal symptoms (e.g., Chills, Abdominal pain, Diarrhea, Rhinitis) were recorded 'en bloc' as withdrawal side effects and subsequently coded as 'Withdrawal Syndrome', for other subjects only the individual adverse events were recorded such as events associated with opiate treatment (e.g., Nausea, Vomiting). For this analysis, all treatment emergent adverse events, i.e., including 'Withdrawal Syndrome', where 'type of report' was recorded as "Withdrawal" were identified and coded as 'Withdrawal Effects'.

For 'Withdrawal Effects', more subjects who received combination therapy reported an initial onset on Day 3 (the first day on combination dosing) compared to those who received monotherapy (six compared to two subjects). Similar pattern lasted from Day 4 to Day 7 (Table 93). More placebo subjects reported an initial onset than buprenorphine-treated subjects from Day 4 onwards, indicating that the "active" treatments were more effective.

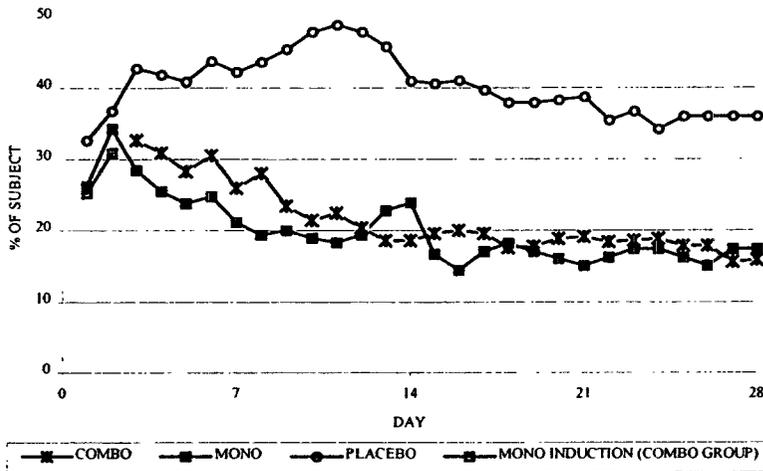
**Table 93. Incidence and Initial Onset of 'Withdrawal Effects' by Treatment Group**

	Combination Therapy (N=107)	Monotherapy (N=103)	Placebo (N=107)	Total (N=317)
<b>INCIDENCE BY SUBJECT</b>				
N (%)	53 (49.5)	48 (46.6)	71 (66.4)	172 (54.3)
<b>Initial Day of Onset</b>				
Day 1	27	27	35	89
Day 2	8	9	6	23
Day 3	6	2	8	16
Day 4 to Day 7	6	4	11	21
Greater than Day 7	6	6	11	23

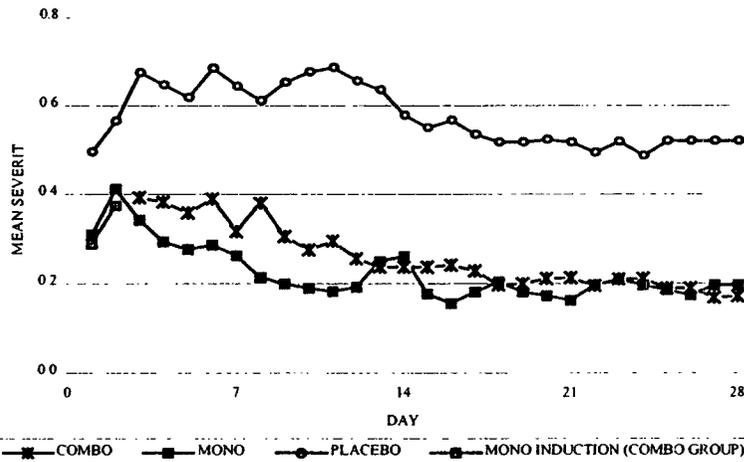
Source: The sponsor's Table 2B in the supplement report.

An additional assessment is the time course of occurrence. The daily incidence and mean severity per day are presented by treatment group for 'Withdrawal Effects' in Figures below (Source: The sponsor's Figure 2A and 2B in the supplement report). The time course curves of both incidence and severity show small, but clear separations between Suboxone and Subutex groups from Day 3 to Day 10, which suggest a possible naloxone effects.

**FIGURE - INCIDENCE OF "WITHDRAWAL EFFECTS"  
FOR ALL SUBJECTS DURING THE DOUBLE BLIND STUDY**



**FIGURE - SEVERITY OF "WITHDRAWAL EFFECTS"  
FOR ALL SUBJECTS DURING THE DOUBLE BLIND STUDY**



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The derived parameters for overall incidence and severity of ‘Withdrawal Effects’ are summarized by treatment group in Table 95. For both parameters, values for the placebo group were statistically significantly higher ( $p < 0.0001$ ) than for either buprenorphine-treated group. There were small, but not statistically significant differences ( $p > 0.1$ ) between the combination therapy group and the monotherapy group.

**Table 94. Overall Incidence and Overall Severity of ‘Withdrawal Effects’ by Treatment Group**

	Combination Therapy (N=107)	Monotherapy (N=103)	Placebo (N=107)	Total (N=317)
<b>OVERALL INCIDENCE (AUCI)</b>				
Mean (SE)	0.24 (0.03)	0.21 (0.03)	0.40 (0.04)	0.28 (0.02)
<b>Overall Severity (AUCS)</b>				
Mean (SE)	0.30 (0.05)	0.23 (0.03)	0.57 (0.06)	0.37 (0.03)

Source: The sponsor’s Table 3B in the supplement report.

**8.10.2 Evaluation of any attenuation of effects of sublingual naloxone during Suboxone treatment.**

The small differences in incidence and severity of ‘Withdrawal Effects’ from Day 3 to Day 10 for the combination therapy subjects compared to the monotherapy subjects is an indicative of some effect of the naloxone present in the combination treatment. These results are consistent with findings in studies using naloxone and naltrexone challenges in patients maintained on buprenorphine. However, the differences were small based on the available data. Critical question is whether the differences are of clinical significance, and have any efficacy implications.

The sponsor presents two small clinical pharmacology studies (CR96/021 and CR95/001) to compare the sublingual pharmacological effects of Subutex and Suboxone tablets. However, the best clinical evidence based on the reviewer’s judgement still come from Study CR96/013, a three-arm, randomized, double-blind clinical trial. In this trial, percentage of urine samples that were negative for opiates were 17.8%, 20.7%, and 5.8% for the combination therapy, monotherapy, and placebo groups, respectively ( $p < 0.0001$  for the difference between each of the buprenorphine treatment groups and the placebo group and  $P > 0.1$  for the difference (2.9%) between the combination therapy and monotherapy groups). It is possible that small naloxone effects causes slight drop of Suboxone efficacy, but, it is not possible to assess whether this is a ‘real’ difference due to naloxone because we only have data from one study.

**In Summary:**

- There are circumstances under which naloxone in the combinations can lead to precipitated withdrawal in buprenorphine-maintained humans. These conditions may involve a relatively high dose of naloxone and patients with high physical dependence (e.g., high buprenorphine dose).
- Dose of naloxone in Suboxone may have contributed to some adverse events (withdrawal effects), but its effects are small both in terms of AE incidences and attenuation of the effects of buprenorphine during Suboxone treatment. Therefore, naloxone can be treated as an inactive ingredient when administered in combination with buprenorphine as Suboxone at present.
- 

**SECTION 8.11 SUMMARY OF EFFICACY AND SAFETY****Efficacy**

This NDA submission contains one "adequate, well-controlled" study (CR96/013 - 1008) for the to-be-marketed buprenorphine sublingual combo tablet (16 mg/day), Suboxone. However, the sponsor submits two more double-blind controlled trials of buprenorphine sublingual solution (CR88/130 and CR92/099) to support the efficacy of Suboxone in the treatment of opioid dependence. PK linkage between Suboxone and buprenorphine sublingual solution has been studied. PK analyses of the dose-proportionality data suggest that the relative bioavailability of Suboxone to the solution is about 70% in the 4-16 mg dose range of Suboxone tablets (see PK review for details). The effective dose range tested in the solution studies, therefore, encloses the Suboxone dose (16 mg/day), and provides a confirmation for its efficacy. An efficacy summary table of the three studies is presented below:

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**Table 95. Mean Percent Urines Negative for Opiates (“Clean”) in the Three Studies**

Study	N	Mean Percent (SE)	P-value vs. Placebo
<b>Std 1008:</b>			
Buprenorphine/naloxone 16/4 mg	109	17.8 (2.3)	<0.0001
Buprenorphine 16 mg	105	20.7 (2.8)	<0.0001
Placebo	109	5.8 (1.7)	-
<b>CR88/130:</b>			
Buprenorphine 8 mg	53	34.5	<0.01
Methadone 20 mg	55	15.3	<0.01
Methadone 60 mg	54	27.4	-
<b>CR92/099</b>			
Buprenorphine 1 mg	84	11.6	-
Buprenorphine 4 mg	180	20.2	<0.001
Buprenorphine 8 mg	186	21.7	<0.001
Buprenorphine 16mg	181	28.8	<0.001

The studies have provided substantial evidence of efficacy of Suboxone for the treatment of opiate dependence.

Efficacy Related to

— Subutex, the mono product, should be used for induction as demonstrated in Study CR96/013 (1008).

### **Efficacy Related to *Maintenance***

Study 1008 provided strong evidence of Suboxone to be used in maintenance. The effective dose is 16 mg/day, given in two 8-mg tablets.

One other study of Suboxone (CR97/004) was submitted as a manuscript without accompanying data. This was an 11 week study (CR97/004) to examine daily versus 3-day/week dosing schedules using Suboxone tablets. All patients were inducted using Subutex. Of the 46 patients who entered the study 22 dropped out during the treatment baseline. A further 11 dropped out during the double blind phase. There were no significant differences across conditions in rates of illicit drug use, and more doses were taken under the 3-day/week schedules. However, this is a small study with 13 patients who completed the study. There is insufficient evidence to support the efficacy of this alternative dosing schedule.

The sponsor provides the study CR96/014 to support a claim in effective dose range. The study is an open label safety rather than efficacy study. It provides information on how much the medication was used, but not necessarily how effective each dose is.

**Efficacy Related to** \_\_\_\_\_



### **Safety**

The primary safety database is the 497 subjects who have received buprenorphine in combination with naloxone as a sublingual tablet in controlled clinical trials. This is supported primarily by 813 subjects in controlled trials of sublingual solution and also by post-marketing reports for Subutex tablets.

The most important adverse event associated with buprenorphine is life-threatening respiratory depression in overdose, occurring especially when the drug is taken concomitantly with other sedative drugs, particularly benzodiazepines. Deaths due to the co-administration of Subutex (probably in inappropriately high doses and always by the

parenteral route) and benzodiazepines were reported in the post-marketing data of Subutex in France.

The most commonly reported serious adverse event in clinical studies of buprenorphine was a large rise in hepatic enzymes ( $\geq$  eight times upper limits of normal) following administration of buprenorphine/naloxone sublingual tablets or buprenorphine solution. This increase usually was detectable after 2 weeks of buprenorphine, and tends to persist over the course of buprenorphine therapy. The increase appears to be dose-related in initial 4 weeks. Up to 4% of patients on Suboxone may experience the elevations in liver function tests, which appeared to be clinically silent; no subjects were withdrawn from the study because of elevations in liver function tests alone. Patients should be informed the risk, and have liver function tests regularly.

**Table 96. Mean SGOT (IU/L) by Visit by Randomized Dose (N=706 Subjects in Pooled Studies)**

Visit	Statistic	Buprenorphine Daily Dose					
		1 mg	4 mg	8 mg	8 mg q.o.d	16 mg	All buprenorphine recipients
Baseline	Mean	<u>40.9</u>	<u>39.7</u>	<u>36.3</u>	<u>35.2</u>	<u>34.0</u>	37.4
2 weeks	Mean	<u>43.0</u>	<u>42.1</u>	<u>44.5</u>	<u>47.6</u>	<u>46.8</u>	44.4
	Mean Difference	2.1	2.4	8.2	12.4	12.8	7.0

On rare occasions, buprenorphine has been associated with clinically severe hepatic adverse events. In marketed use in France, the adverse events were reported as hepatitis, hepatic failure, and hepatic cirrhosis. Three patients died, all of whom were infected with HIV and hepatitis C. No clear association between buprenorphine, hepatic failure and death was made in any of these 3 patients. In one case, however, the patient injected Subutex intravenously at a daily dose of 64 mg/day at unspecified times prior to his death. Subutex is likely to be the cause of death.

Post-marketing adverse event data from France included a number of reports of convulsions, two of grand mal and some reports of hallucinations. In the study of buprenorphine in combination with naloxone, there was 1 report of convulsion (0.2%) and 4 subjects who reported hallucinations (0.8%). Since convulsions are a known side effect of opioid drugs these were not unexpected.

Six fetal deaths among mothers receiving Subutex were reported in the French post-marketing experience. These fetal deaths occurred among a population at extremely high risk for adverse fetal outcomes, and no clear association between the receipt of Subutex and the fetal demise was noted for any of these cases.

Neonates born to mothers receiving buprenorphine commonly exhibit signs of opiate withdrawal. Suboxone tablets are not recommended for use in pregnant women since they present an additional unknown risk factor due to naloxone.

The most frequently reported events during the 4-week double blind portion of the primary study supporting the safety of buprenorphine (reported by at least 10% of subjects) were those often associated with withdrawal (headache, pain, abdominal pain, back pain, withdrawal syndrome, diarrhea, nausea, insomnia, rhinitis, and sweating) or typically associated with opiates (constipation). Of those, headache, pain, abdominal pain, withdrawal syndrome, constipation, nausea, insomnia, and sweating were judged to have been at least possibly related to study treatment.

In the extended open label treatment sample, the most commonly reported adverse events were headache, pain, withdrawal syndrome, insomnia, and constipation. Many adverse events may have followed a dose response pattern. These events included flu syndrome, headache, pain, withdrawal syndrome, constipation, vomiting, myalgia, insomnia, pharyngitis, rhinitis, peripheral edema and sweat as well as infection and accidental injury. Nineteen specific adverse events were reported by 10% or more of these subjects. In order of decreasing frequency, these were headache (43%), pain (42%), withdrawal syndrome (41%), infections (unspecified) (32%), insomnia (29%), back pain (28%), constipation (24%), flu-like syndrome (19%), abdominal pain (16%), nausea (16%), rhinitis (16%), sweating (16%), accidental injury (15%), depression (15%), anxiety (14%), pharyngitis (14%), vomiting (13%), diarrhea (11%), and asthenia (10%).

## **EFFECTS OF SUBLINGUAL NALOXONE IN OPIOID DEPENDENT SUBJECTS**

A combination product of buprenorphine plus naloxone may have lower abuse potential than buprenorphine alone. However, differences in adverse event profiles (reviewed in Section 8.4.1) calls into question the clinical equivalence of the two tablets (Suboxone and Subutex), and the assertion that naloxone is an inactive ingredient when it is administered in combination with buprenorphine as Suboxone. Two review questions are:

- To assess whether the dose of naloxone in Suboxone may have contributed to some adverse events (withdrawal effects), and
- To address whether these adverse events do or do *not* have efficacy implications, i.e., to exert any attenuation of the effects of buprenorphine during Suboxone treatment.

There is clear evidence that low sublingual doses of naloxone are able to precipitate withdrawal in methadone-dependent subjects. To assess whether dose of naloxone in Suboxone is sufficient enough to precipitate withdrawal in buprenorphine maintained subjects, special analyses were conducted, including three parts: overview of literature, sublingual absorption of naloxone from Suboxone tablets and clinical data on withdrawal effects of sublingual naloxone.

Literature suggest that there are circumstances under which naloxone in the combinations can lead to precipitated withdrawal in buprenorphine-maintained humans. These conditions may involve a relatively high dose of naloxone and patients with high physical dependence (e.g., high buprenorphine dose).

PK studies indicated that there was a 4 to 12 fold difference in peak naloxone levels (sublingual route) between patients. The highest peak plasma naloxone concentration found in these studies was ~~—~~ ng/ml, obtained in a patient treated with 16mg Suboxone. This result may partially explain why the effects of sublingual naloxone in the subjects varied substantially.

The small differences in incidence and severity of 'Withdrawal Effects' from Day 3 to Day 10 for the combination therapy subjects compared to the monotherapy subjects is an indicative of some effect of the naloxone present in the combination treatment. These results are consistent with findings in studies using naloxone and naltrexone challenges in patients maintained on buprenorphine. However, the differences were small based on the available data. Critical question is whether the differences are of clinical significance, and have any efficacy implications.

Phase III trial demonstrated that the percentage of urine samples that were negative for opiates were 17.8%, 20.7%, and 5.8% for the combination therapy, monotherapy, and placebo groups, respectively. It is possible that small naloxone effects causes slight drop of Suboxone efficacy, but, it is not possible to assess whether this is a 'real' difference due to naloxone because we have only data from one study.

## SECTION 9.0 CONCLUSIONS

In the opinion of this reviewer, the sponsor has demonstrated the efficacy of Suboxone for the treatment of opiate dependence. There is no adequate data to support the claims of ~~—~~

Induction should be used Subutex.

Based on review of the data submitted, Suboxone appears to be reasonable safe when used as recommended.

Dose of naloxone in Suboxone may have contributed to some adverse events (withdrawal effects), but its effects are small both in terms of AE incidences and attenuation of the effects of buprenorphine during Suboxone treatment. Therefore, naloxone can be treated as an inactive ingredient when administered in combination with buprenorphine as Suboxone at present.

**SECTION 9.1 LABELING REVIEW**

Proposed indication/claims and the reviewer's recommendations are summarized below:

INDICATIONS/CLAIMS	SPONSOR'S PROPOSAL	REVIEWER'S SUGGESTION
Indication	Suboxone is indicated for the treatment of opiate dependence.	No change.
/	/	/
Maintenance	Suboxone tablets have been used to treat opioid dependent subjects for maintenance	No change
/	/	/

**SECTION 10.0 RECOMMENDATIONS**

From a clinical standpoint, approval of NDA 20-733 is recommended pending the approval for Subutex (for induction).

[ /S/ ] 11/12/89  
 Chang Q. Lee, MD, DrPH  
 Medical Review Officer

Celia Winchell, MD  
 Medical Peer Review  
 Team Leader

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