- Patient L9502_7019 had a baseline ALT that was mildly elevated (65U/L, ULN=45U/L). On Day 49, AST and ALT were both clinically abnormal (AST=138 U/L, ULN=45 U/L and ALT=222U/L, ULN=45U/L). GGT was also mildly elevated (62 U/L, ULN=52 U/L). On Day 72, these LFTs were high, but not clinically abnormal. On Day 93, the ALT rose to a clinically abnormal level (137U/L), and AST and GGT remained high but not clinically abnormal. The narrative notes that the patient was using cocaine illicitly, and mentions the cocaine use as a possibly explanation for the increased LFTs. No data on serological status for hepatitis are provided.

6.10.2.6 Study CR96/013 and CR96/014

Study CR96/013 was a 4-week, randomized, placebo-controlled, double-blind study in which patients were randomized to 16 mg Suboxone per day, 16 mg Subutex per day, or placebo. CR96/014 was an open label study, which enrolled subject who had finished the 4-week double-blind phase or who were enrolled directly into this study. The Sponsor reports that 326 subjects were randomized into Study CR96/013 (110 Suboxone, 106 Subutex, and 110 Placebo). The Sponsor further notes that 323 subjects received study treatment (109 Suboxone, 105 Subutex, and 109 Placebo) and were thus evaluable for efficacy. Four-hundred-seventy-two subjects enrolled into Study CR96/014, 279 of whom had participated in the double-blind study (CR96/013) and 193 of whom enrolled directly into the open-label phase. Laboratory measurements were taken at baseline, and the end of the 4-week double-blind phase, and then monthly throughout the open-label phase.

The Sponsor summarizes its previous analysis of hepatic adverse events and hepatic function as follows:

- 314/323 subjects who received treatment in Study CR96/013 were tested for Hepatitis B and Hepatitis C.
- In the open-label study CR96/014, 464/472 subjects were tested for Hepatitis B and Hepatitis C.
- Hepatitis status was classified as negative for both B and C, positive for B only, positive for C only, and positive for both B and C.
- In general, subjects with Hepatitis C, regardless of hepatitis B status, were older and had a longer duration of heroin use, compared to subjects who were negative for hepatitis C.
- The subjects with Hepatitis C also tended to have higher AST, ALT, and GGT levels at baseline, compared to subjects without hepatitis C. The higher mean baseline levels were near the upper end of the normal range.
- In subjects with Hepatitis C (regardless of Hepatitis B status), treatment with either active medication (Suboxone or Subutex) or placebo was associated with a rise in AST and ALT levels. Such a rise was not observed in patients without Hepatitis C, regardless of Hepatitis B status.
- In the long-term open-label study, the increase in AST and ALT was sustained in patients with Hepatitis C only, and appeared not to increase. In patients with both Hepatitis B and C, the initial increase seemed to return to near baseline after about four months.
- In subjects with Hepatitis B only or in those who tested negative for Hepatitis B and Hepatitis C, there was little change over time in AST and ALT values.

- The increase noted in Hepatitis C patients were judged by the Sponsor to be "small in magnitude, and probably are not clinically significant in this type of subject."

In the current submission, the Sponsor notes that 62 (13.1%) of the 472 subjects had clinically abnormal liver function tests as some point during the study. Fifty-five (88.7%) of these 62 subjects with clinically abnormal liver enzymes tested positive for Hepatitis C. Thirty-nine of these subjects also tested positive for Hepatitis B. Seven subjects with clinically abnormal LFTs tested negative for Hepatitis B and C, while no serological data were available for 16 subjects.

Some notable individual cases from these two studies are as follows:

- Subject M1008_5781090 was serologically negative for both Hepatitis B and C. During the initial four-week double-blind study, she was treated with placebo. Elevations of GGT at during this phase (values of 322 U/L and 240 U/L on Days – 2 and 26, respectively) were noted. Other LFTs were normal during this period. During the open-label phase, she was treated with Suboxone at an average daily dose of 16mg/4mg buprenorphine/naloxone for four weeks, reducing to 4mg/1mg for 4 weeks, and then increasing to 8mg/2mg for 4 weeks, and finally increasing to 16mg/4mg for 28 weeks. Apart from the elevation in GGT noted in the double-blind phase, LFT values remained relative stable during the open-label phase until Study Day 198, when AST was 144 U/L (ULN=45 U/L), ALT was 270 U/L (ULN=65 U/L), GGT was 632 U/L (ULN=85U/L), AlkPhos was 231 U/L (ULN=136 U/L), and total bilirubin was 3.0 mg/dL (ULN=1.2 mg/dL). LFTs were re-tested on Day 218, when a persistent elevation of GGT (199U/L) was noted, but all other were within the normal range. From Day 218 through the day of the last LFT measurement (day 331), the GGT remained high (range 191-394 U/L), with mild elevations in ALT (<2XULN) and a minimal elevation of Alk Phos on Day 309. Apart from these abnormalities, the LFTs remained normal throughout the remainder of the study. The narrative notes that although the clinically abnormal elevation of the LFTs was classified as an adverse event, there were no comments noted to explain further the nature of this event.

- Subject M1008_6891018 was enrolled in the open-label study CR96/014, and was found to be seropositive for Hepatitis C at baseline. Apart from a minimally elevated ALT at baseline, (48U/L), all other baseline LFTs were normal. The subject was treated with buprenorphine tablets, and follow-up LFTs at Day 30 were normal The subject was the switched to buprenorphine/naloxone tables. On Day 71, AST and ALT were both markedly abnormal (422 U/L and 691 U/L, respectively). These transaminases increased to 816 U/L and 1457 U/L on Day 95. Total bilirubin was normal on both Day 71 but increased to 2.9 mg/dL on Day 95. At about this time, conversions of Hepatitis B antigen and core antibody were documented. At the final visit on Day 128, the AST was 285 U/L, the ALT was 536 U/L, the total bilirubin was 1.1 mg/dL. No further details are available, and the elevation in LFTs was attributed to acute hepatitis B infection, from which the subject was asymptomatic.

- Subject M1008_6892066 was enrolled in both Study CR96/013 and in the open-label extension CR96/014. In both studies he was treated with buprenorphine/naloxone tablets. LFT values are as follows:

LFT Data for Subject M1008_6892066 in Studies CR96/013 and CR96/014						
Dose (mg/day)	Day	AST (ULN=41)	ALT (ULN=41)	GGT (ULN=51)	AlkPhos (ULN=140)	Total Bili (ULN=1.6)
None	-5	100	66	128	140	1.2
12	35	111	69	108	136	1.8
12	56	100	65	110	152	1.7
12	95	136	93	146	175	1.5
9.71	136	109	53	119	156	1.6
11.6	170	156	104	144	166	2.2

As can be seen in the table above, this subject's LFTs, with the exception of the total bilirubin, were generally elevated throughout the study. The reason for the increase at Day 170, including the reason for the notable increase in total bilirubin at that time, is not known. No information is available to shed light on this case.

- Subject M1008_7501027 was enrolled in both Study CR96/013 and in the open-label extension CR96/014. In both studies he was treated with buprenorphine tables in CR96/013 and with buprenorphine/naloxone tablets CR96/014. LFT values are as follows:

LFT Data for Subject M1008_7501027 in Studies CR96/013 and CR96/014							
Study Treatment	Dose	Day	AST (ULN=37)	ALT (ULN=39)	GGT (ULN=32)	Alk Phos (ULN=143)	Total Bili (ULN=1.1)
BUP_TAB	None	-2	64	118	24	88	1.0
BUP_TAB	10.3	30	51	84	17	72	1.2
BNX_TAB	0.71	137	80	157	20	78	2.3
BNX_TAB	17.9	178	75	144	20	81	1.3

The reason for the increase in ALT and total bilirubin on day 137 in the above table is not known. The narrative notes that at the time of the visit on Day 137, the subject had not taken any study medication for 11 weeks.

The data from these cases illustrate that clinically significant elevations of liver function tests can occur, without apparent reason, in patients taking buprenorphine who are seronegative for Hepatitis B and Hepatitis C, and that these elevations can return toward normal even while patients remain on buprenorphine. Aysmptomatic seroconversion of Hepatitis B can occur, and unless a clinician tests for this event, LFTs can rise and fall without explanation.

6.10.2.7 Study CR90/066

Study CR90/066 was a double-blind, double-dummy, multiple-dose, parallel-group comparison of sublingual buprenorphine and oral methadone, One-hundred-sixty-four subjects were enrolled – 84 in the buprenorphine group and 80 in the methadone group. Subjects were titrated over the first few days of the study to a stable dose, and were maintained on that dose through Week 16, though some dose adjustments were allowed. From Week 17 through Week 26, the daily dose was tapered each week at a rate of 10% of the subject's Week 16 dose.

The Sponsor reports that of the 64 patients in the study, 20 in the buprenorphine group and 20 in the methadone group had AST and/or ALT levels that were above the upper limit of normal at

baseline. Further review of the data indicate 20 subjects in each of the treatment groups had at least one LFT that was clinically abnormal either at baseline (and alsc had follow-up data) or post-baseline (at a time when study medication was being administered [for example, subject B9019_0004, who had clinically abnormal LFTs on Day 145, was not included in this tally because no study medication – methadone in this case – was recorded on this day]).

As with the LFT data from other studies, there is much fluctuation in the subjects' LFTs, especially in AST and ALT. The following cases illustrate some of the patterns of LFT changes as well as the reasons, when known, for these changes:

- Subject B9019_0017, who received buprenorphine liquid and whose LFTs were all normal for three separate on-treatment measures, developed 'clinically abnormal' AST (302 U/L), ALT (777 U/L) and Alkaline Phosphatase (318 U/L) ten days after treatment was stopped. He was found to have contracted acute Hepatitis B, and was referred for further therapy. No other details are available.

- Subject B9019_0020, who was treated with buprenorphine liquid, had 'High' (but not 'Clinically Abnormal') AST and ALT at baseline and at 33 days after the initiation of therapy. Both AST and ALT became clinically abnormal on three further on-treatment visits (Days 61, 94, and 128), and each had their peak on Day 61 (AST 189 U/L and ALT 313 U/L). Hepatitis serostatus is not known, and no other clinical comments are available. There is no further follow-up available.

- Subject B9019_0080, who was treated with buprenorphine liquid and had positive serology for both Hepatitis B and Hepatitis C, had normal LFTs at baseline, though other pre-treatment LFT measurements were notable for clinically abnormal AST (139 U/L) and ALT 153 U/L on Day-5. AST and ALT on treatment days 29 and 56 were high, but not clinically abnormal. AST and ALT became clinically abnormal on day 103 (AST 305 U/L and ALT 541 U/L), with alkaline phosphatase 210 U/L. At the time of the final available measurement, AST and ALT were 160 U/L and 195 U/L, respectively. No clinical comments or other information are available.

- Subject B9019_0087, who was treated with buprenorphine liquid and was seronegative for both Hepatitis B and Hepatitis C, had normal LFTs at baseline. On Days 29, 62, and 87 AST and ALT were either "High" (but not clinically abnormal) or normal. On Day 120 AST, ALT and alkaline phosphatase were all 'clinically abnormal' (269 U/L, 368 U/L, and 196 U/L, respectively). On Day 131, a marked increase was noted (AST 1080 U/L, ALT 1850 U/L , and alkaline phosphatase 516 U/L). The narrative notes that his final on-treatment visit was on Day 86, though the database notes that he was on 12 mg buprenorphine liquid on Day 120. LFTs began to resolve on Day 140, though they were still clinically abnormal at that time. They were normal by Day 161. The narrative notes that this patient was being treated with isoniazid for tuberculosis prophylaxis, and that this treatment may have been the reason for the marked increase in LFT measurements. No other details are available.

6.10.2.8 Study CR92/012

Study CR92/012 was a 2-week placebo-controlled study of buprenorphine sublingual solutions Part I), followed by a 11-week double-blind, multiple-dose parallel-group comparison of two different dose regimens of sublingual buprenorphine (8 mg/day versus 8 mg every other day) (Part II). After the 11-week double-blind phase of Part II, subjects' doses were tapered over a 10-day period. One-hundred-fifty patients entered Part I (60 in the buprenorphine 2mg solution group, 30 in the buprenorphine 8 mg solution group, and 60 in the placebo group). One-hundred-eight patients entered Part II (60 in the 8 mg/day group and 48 in the 8 mg every other day group). A total of seven subjects had AST and/or ALT levels that were clinically abnormal. Many of these subjects had normal LFTs at baseline. The following case history illustrates a clinically significant rise in AST and ALT after initiation of buprenorphine therapy, but a lack of clinical details preclude a comprehensive assessment regarding the cause of these abnormal LFTs.

- Subject B9212_1726 had high, but not clinically abnormal, levels of AST and ALT at baseline (both approximately twice the upper limit of normal). He was treated with buprenorphine liquid 2mg/day, and then switched to 8mg every other day. AST and ALT were again high at Day 22 (between 2 and 3 times the upper limit of normal). Clinically abnormal AST (237 U/L, ULN=46 U/L) and ALT (242 U/L, ULN=50 U/L) were noted on Day 81. Six weeks post-treatment, on Day 139, AST and ALT were high, but not clinically abnormal. No clinical comments were recorded, and hepatitis serology data were not obtained for this subject.

6.10.2.9 Study CR96/005

Study CR96/005 was a 13-week, double-blind study in which subjects were randomized to receive Subutex tablets or methadone syrup. A total of 405 subjects at three centers were randomized to buprenorphine or methadone. A total of 394 subjects received study medication. Eleven subjects were not dosed with any study medication.

The Sponsor notes that three subject had elevations has AST and/or ALT that were "clinically abnormal." The Sponsor notes that these three subjects all had Hepatitis C, and that two had no baseline LFTs. Narratives for these three subjects shed no additional light on the role of buprenorphine in the development of drug-induced hepatic abnormalities.

6.10.2.10 Study CR96/008

Study CR96/008 was designed to compare the bioavailability, clinical effects and patient preference of buprenorphine sublingual solution and Subutex tablets in patients treated with chronic dosing. The study used a double-blind, double-dummy design. A total of 184 opiate-dependent subjects were enrolled and randomly assigned to one of the two treatments. The Sponsor notes that 10 subjects had at least one LFT measure that was greater than three times the upper limit of normal at baseline or during the study. The cases of subjects L9608_6130 and L9608_6131 underscore the fact that subjects with normal pre-treatment baseline LFTs can develop abnormal post-treatment LFTs with no clearly documented explanation. LFTs for these two subjects are presented in the table below.

LFT Data for Subjects L9608_6130 and L9608_6131 in Studies CR96/008							
Subject ID	Dose (mg/day)	Day	AST (ULN=35)	ALT (ULN=35)	GGT (ULN=50)	AlkPhos (ULN=125)	Total Bili (ULN=1.4)
L9608_6130	None	-10	13	6	15	83	0.5
	9	43	16	12	19	95	0.3
	15.4	88	32	119	155	183	1.6
L9608_6131	None	-5	17	32	11	49	0.7
	29.3	115	87	147	29	74	0.5

The narratives note that subject L9608_6130 had a diagnosis of alcohol and sedative hypnotic dependence, but no other clinical comments were recorded. The narrative for subject L9608_6131 notes that no clinical comments were recorded.

6.10.2.11 Study 97/003

Study CR97/003 was an 11-week study in opioid dependent subjects to determine whether 8 mg Suboxone tablets could be administered safely and effectively every other day, and whether multiples of the daily dose were essential for maintaining an efficacious alternate-day treatment. Based on the Sponsor's presentation of the study data, it is not clear how many subjects were treated with a buprenorphine-containing product. The Sponsor notes that seven subjects had abnormal LFTs at baseline, and that only two of these had post-baseline measurements. It appears that no LFT data from this study is in the dataset provided by the Sponsor. The narratives for the two patients who had abnormal post-baseline measures (Patients #53 and #98) note that each was HCV positive and had histories of alcohol dependence. No other information was provided that could shed light on these cases.

6.10.2.12 Study CR97/004

Study CR97/004 was generally similar in design to Study 97/003. The Sponsor reports that three patients had abnormal LFTs at baseline, but none had on-treatment measurements. No hepatic data or narratives are presented for these or any other patients in this study.

6.10.2.13 Study CR97/008

Study CR97/008 was a double-blind, double-dummy, parallel-group study in 272 opioid-dependent patients comparing Suboxone to methadone for opioid maintenance treatment. The Sponsor reports that 24 of the 272 patients had LFTs that were above normal at entry, but that only three had on-treatment measurements. Narratives for these patients shed no light on the nature or possible causes of the LFT abnormalities, though one subject was noted to be HCV positive. Actual LFT data are not presented for any subjects in this study.

6.10.2.14 Study BPRU #9605

Study BPRU #9605 was a study comparing the efficacy of fixed low dose methadone and variable doses of buprenorphine, LAAM, and high-dose methadone over a 17-week period in 220 patients. There were 55 patients in each treatment group. The Sponsor notes that four subjects had AST and/or ALT levels that were clinically abnormal either at baseline or on treatment. Each of these subjects received either LAAM or methadone. Actual LFT data are not provided for this study.

6.10.3 Review of Hepatic Data in Selected Subpopulations

6.10.3.1 Review of Hepatic Data in Subject Serologically Negative for Hepatitis B and Hepatitis C

Several subjects were documented to be seronegative for B and C at the time of enrollment in studies CR96/005, CR96/013 and CR96/014, CR90/066, and BUPP5074. Review of the LFT data from patients in these studies who had both baseline and post-baseline LFT data indicate that normal LFTs (defined as AST, ALT, GGT, alkaline phosphatase, and total bilirubin all in the normal range) were common in this group. A shift table of 144 serologically negative subjects with both baseline and post-baseline LFT measures is shown below. This table includes all subjects who were documented to be seronegative for Hepatitis B and Hepatitis C at baseline, and who had baseline LFTs and at least one set of post baseline LFTs. Subjects were included in this table without regard to the treatment groups they were in. For subjects who participated in both Study CR96/013 and Study 96/014, the baseline value was the value prior to receiving study drug in Study CR96/013. The post-baseline value was the most abnormal value during the combined periods of Studies CR96/013 and 96/014. In this table, a baseline value of "Normal" indicates that all LFTs were normal at baseline, a value of "High" indicates that the most abnormal LFT at baseline was "High", and a value of "Clinically Abnormal" indicates that the most abnormal LFT at baseline was "Clinically Abnormal". For the post-baseline period, the same logic holds, and the assigned value pertains to the most abnormal value at any post-baseline visit.

		Post-Baseline		
		Clinically Abnormal	High	Normal
Baseline	Clinically Abnormal	0	0	0
	High	4	25	0
	Normal	6	17	92

CA=Clinicallly Abnormal (ie, at least one LFT at any baseline or post-baseline visit is clinically abnormal)
H=High (ie, at least one LFT at any baseline or post-baseline visit is high, but none is clinically abnormal)
N=Normal (ie, all LFTs at all baseline or post-baseline visits is normal)

Review of the above table is notable for the fact that no patient who was serologically negative for hepatitis B and C at baseline had a clinically abnormal LFT at baseline. However, several patients developed clinically abnormal LFTs during the course of the study. These cases presumably avoid the confounding influence of chronic hepatitis B and/or C infection. A summary of these cases in patients serologically negative for both Hepatitis B and C at baseline who had at least one clinically abnormal LFT value post-baseline is presented below:

STUDY	SUBJECT	TREAT	LFT Values			Comments
			Baseline	Abnormal	Final	
CR90/066	B9019_0002	METH		CA	CA	No baseline LFTs. Also negative for Hep A. No other clinical comments recorded.
CR90/066	B9019_0087	BUP_LIQ	N	CA	N	Attributed to isoniazid treatment
CR90/066	B9019_0093	METH	H	CA	N	No clinical comments noted.
CR96/013	M1008_5122065	BNX_TAB	H	CA	N	No clinical comments recorded.
CR96/013	M1008_5781025	PLACEBO	N	CA	CA	Received only placebo. Alcohol noted as possible reason for increased LFTs. No other clinical comments noted.
CR96/013	M1008_5781054	BUP_TAB	H	CA	H	No clinical comments recorded.
CR96/013	M1008_5781090	PLACEBO BNX_TAB	H	CA	H	LFTs rose on active treatment (buprenorphine). No other clinical

STUDY	SUBJECT	TREAT	LFT Values			Comments
			Baseline	Abnormal	Final	
						comments recorded.
CR96/013	M1008_6301031	PLACEBO BNX_TAB	N	CA	N	LFTs were normal while on placebo, and rose while on buprenorphine. Increase attributed to illicit drug use.
CR96/013	M1008_6302051	BNX_TAB	N	CA	CA	No clinical comments reported.
CR96/013	M1008_6622039	BNX_TAB	N	CA	H	Attributed to acute Hepatitis C infection
BUPP5074	V5074_0035	BUP_LIQ	N	CA	H	No clinical comments recorded.

Review of this table illustrates that opiate addicts who are seronegative for both Hepatitis B and C can nonetheless have abnormal LFT values prior to buprenorphine treatment, though in most cases no potential cause of for the abnormality is included in the narratives. Review of the above table also indicates that while a possible or probable etiological agent (eg, isoniazid, hepatitis C, or alcohol) is identifiable in some cases, there are other cases where no clear etiologic agent is reported. The cases in which hepatitis seronegative patients received buprenorphine, developed clinically abnormal LFTs, and have no potential explanation for the abnormality noted raise the possibility that buprenorphine may have played a causative role.

6.10.3.2 Review of Hepatic Data in Subjects With Simultaneous Clinically Significant Abnormalities of Transaminases (AST and/or ALT) and Total Bilirubin

To examine severe cases of hepatic involvement, cases in which both a transaminase (ie, AST and/or ALT) was clinically abnormal and total bilirubin was above 2.0 mg/dL were examined. This combination of LFT values point both to significant hepatocellular damage (increased ALTs) and to hepatic dysfunction (increased total bilirubin). The table below summarizes these cases.

						AST		ALT		GGT		Alk Phos		T Bili		
STUDY	SUBJECT	HEP	TREAT	DOSE	DAY	Value	ULN	Value	ULN	Value	ULN	Value	ULN	Value	ULN	Comments
BUPP5074	V5074_0098	HX_BC	BUP_LIQ		1	295	50	150	75		78	95	126	2.1	1.1	None reported
CR88/130	B0090_2774		METH	60.0	89	161	37	96	40			536	390	9.9	1.2	"Major alcohol problem"
CR88/130	B0090_2833		METH	18.6	106	996	37	999	40			163	390	4.0	1.2	Attributed to drug abuse
CR90/066	B9019_0002	NEG	METH	60.0	67	2000	45	2800	50			247	175	2.5	1.5	None reported
CR90/066	B9019_0002	NEG	METH	57.9	74	1860	45	2580	50				175	4.9	1.5	None reported
CR90/066	B9019_0017	B	BUP_LIQ		150	461	45	1385	50			405	175	2.9	1.5	Hep B surface Ag positive
CR90/066	B9019_0057	C	BUP_LIQ	7.3	18	1730	45	2400	50			336	175	7.9	1.5	Acute Hepatitis A infection
CR90/066	B9019_0060	HX_HEP	METH	70.0	89	1380	45	1108	50			210	175	2.8	1.5	Acute Hepatitis B infection
CR90/066	B9019_0087	NEG	BUP_LIQ		131	1080	45	1850	50			516	175	4.7	1.5	Attributed to Isoniazid
CR90/069	L9069_0041		METH	30.0	137	216	45	77	45	395	65	127	125	2.3	1.5	"Alcoholic liver disease"
CR90/069	L9069_0041		METH	30.0	169	284	45	73	45	382	65	136	125	2.9	1.5	"Alcoholic liver disease"
CR90/069	L9069_0041		METH	30.0	194	181	45	55	45	435	65	123	125	5.7	1.5	"Alcoholic liver disease"
CR90/069	L9069_0154		METH	80.0	163	185	45	217	45	62	65	123	125	2.1	1.5	None reported
CR90/069	L9069_0154		METH	80.0	246	187	45	181	45	52	65	144	125	2.1	1.5	None reported
CR90/069	L9069_0154		METH	80.0	273	203	45	186	45	49	65	140	125	2.1	1.5	None reported
CR90/069	L9069_0154		METH	80.0	303	225	45	242	45	64	65	156	125	2.1	1.5	None reported
CR90/069	L9069_0154		METH	80.0	357	186	45	183	45	45	65	156	125	2.0	1.5	None reported
CR92/099	M0999_05715		BUP_LIQ	6.7	15	199	50	125	40	351	33	179	115	5.3	1.2	INH and rifampin treatment
CR92/099	M0999_05715		BUP_LIQ	7.7	31	173	50	108	40	360	33	155	115	2.9	1.2	INH and rifampin treatment
CR92/099	M0999_05908		BUP_LIQ	2.8	113	145	47	86	45	939	52	156	125	2.0	1.2	Hep C and pancreatitis
CR92/099	M0999_05908		BUP_LIQ	3.1	163	331	47	54	45	896	52	179	125	6.2	1.2	Hep C and pancreatitis
CR92/099	M0999_64226		BUP_LIQ	10.7	360	121	40	95	36	576	75	126	125	6.8	1.3	None reported
CR92/099	M0999_64228		BUP_LIQ		0	139	40	49	36	475	75	199	125	2.2	1.3	None reported
CR92/099	M0999_67280		BUP_LIQ	0.8	153	222	40	279	65	211	60	203	136	20.0	1.3	Hepatitis A diagnosed
CR92/099	M0999_67280		BUP_LIQ	0.8	157	287	40	990	65	118	60	169	136	14.0	1.3	Hepatitis A diagnosed
CR92/099	M0999_75041		BUP_LIQ	2.6	127	2770	41	3010	45	126	32	342	110	11.9	1.2	Hepatitis A diagnosed
CR92/099	M0999_75067	HX_HEP	BUP_LIQ	6.2	267	1240	41	2180	45	143	32	194	110	6.4	1.2	"Acute hepatitis" – no details

STUDY	SUBJECT	HEP	TREAT	DOSE	DAY	AST		ALT		GGT		Alk Phos		T Bili		Comments
						Value	ULN	Value	ULN	Value	ULN	Value	ULN	Value	ULN	
CR92/099	M0999_75067	HX_HEP	BUP_LIQ	5.6	271	132	41	665	45		32		110	2.6	1.2	"Acute hepatitis" – no details
CR92/102	B9212_9846		BUP_LIQ	1.4	8	181	46	1210	50		65	342	175	4.3	1.5	"Acute hepatitis" – no details
CR96/005	A9605_W168	C	BUP_TAB		1	123	45	268	55	167	60	121	110	2.0	1.4	None reported
CR96/008	L9608_6169		BUP_TAB	32.0	112	187	35	95	35	382	54	85	125	2.2	1.4	None reported
CR96/014	M1008_5781090	NEG	BNX_TAB	16.0	198	144	45	270	65	632	85	231	136	3.0	1.2	None reported
CR96/014	M1008_6891018	C	BNX_TAB	11.1	95	816	41	1457	41	325	51	158	140	2.9	1.6	Acute Hepatitis B
CR96/014	M1008_6892066	C	BNX_TAB	11.6	170	156	41	104	41	144	51	166	140	2.2	1.6	None reported
CR96/014	M1008_7501027	BC	BNX_TAB	0.7	137	80	37	157	39	20	32	78	143	2.3	1.1	None reported
CR96/024	B9605_0055		LAAM		136	705	40	1225	45	276	85	254	140	5.3	1.2	No narrative
CR96/024	B9605_0055		LAAM		155	105	45	257	45	172	85	121	150	2.0	1.2	No narrative
CR96/024	B9605_0087		LAAM	38.9	43	614	40	479	45	233	85	353	140	2.1	1.2	"Acute hepatitis" – no details
CR96/024	B9605_0087		LAAM	39.6	47	284	40	414	45	323	85	475	140	2.6	1.2	"Acute hepatitis" – no details

Review of the above table is notable for the fact that severe hepatic involvement, as defined above, occurred in buprenorphine-treated patients, methadone-treated patients, and LAAM-treated patients. In each of these three treatment groups, there are some patients for whom a possible etiologic agent is listed (eg, acute hepatitis, alcohol) and others for whom little or no information is available. Though the finding of clinically severe LFT abnormalities with no explanation exists in al three treatment groups, these data do not exclude the possibility that buprenorphine may have played a causative or contributory role in the development of abnormal LFTs.

6.10.4 Review of LFT Values in Subject With Normal LFTs at Baseline

There were several subjects in the clinical studies with normal LFTs at baseline. Review of the LFT data from these subjects potentially affords an opportunity to remove the potential confounding influence of abnormal baseline LFTs on the post-baseline LFT values. Based on the data submitted, it is hard to determine an accurate frequency of shifts form normal (at baseline) to high or clinically abnormal (at post-baseline). Many subjects do not have LFTs recorded both at baseline and post-baseline. In addition, some subjects participated in controlled studies and then participated in open-label follow-on studies. The subject numbering system is not always clear, and it is thus difficult to know if patients are being counted once or more than once. It is also difficult to determine the reason for this shift in some patients. For example, many subjects who do not have a dose recorded at a given visit do not have narratives, even though they have a post-baseline clinically abnormal LFT at that visit.

The table below highlights some of the patients with normal LFTs at baseline who subsequently developed abnormal LFTs during the study participation.

STUDY	SUBJECT	TREAT	FINAL	HEP	COMMENTS
BUPP5074	V5074_0021	BUP_LIQ	H		Returned to normal . "Acute hepatitis" noted but no other details
BUPP5074	V5074_0028	BUP_LIQ	CA	HX_HEP	No clinical comments noted.
BUPP5074	V5074_0035	BUP_LIQ	H	NEG	LFTs fluctuated. No other clinical comments noted.
CR88/130	B0090_2415	BUP_LIQ	H		Attributed to excessive alcohol
CR90/066	B9019_0019	BUP_LIQ	CA		No narrative
CR90/066	B9019_0033	BUP_LIQ	N		LFTs returned to normal. No other clinical comments noted.
CR90/066	B9019_0057	BUP_LIQ	N	C	Attributed to acute hepatitis A
CR90/066	B9019_0087	BUP_LIQ	N	NEG	Attributed to isoniazid treatment
CR90/066	B9019_0104	BUP_LIQ	H	C	No clinical comments noted.
CR90/066	B9019_0162	BUP_LIQ	CA		No narrative
CR90/069	L9069_0155	BUP_LIQ	H		No clinical comments noted.

STUDY	SUBJECT	TREAT	FINAL	HEP	COMMENTS
CR90/069	L9069_0190	BUP_LIQ	H		No clinical comments noted.
CR92/099	M0999_05717	BUP_LIQ	H		LFTs remained high on treatment. Hepatitis B negative
CR92/099	M0999_05761	BUP_LIQ	H		LFTs decreased after peak elevation. No other clinical comments
CR92/099	M0999_05807	BUP_LIQ	N		Terminated from study due to poor compliance. No other clinical comments noted.
CR92/099	M0999_05820	BUP_LIQ	N	HX_HEP	Terminated due to continued drug abuse and poor compliance. No other clinical comments.
CR92/099	M0999_05852	BUP_LIQ	N		No clinical comments noted.
CR92/099	M0999_57839	BUP_LIQ	H		No clinical comments noted.
CR92/099	M0999_63061	BUP_LIQ	H		LFTs remained high. No obvious cause found.
CR92/099	M0999_63074	BUP_LIQ	CA		Alcohol use noted. No other clinical comments.
CR92/099	M0999_67201	BUP_LIQ	H		Elevated CPK also noted, attributed to exercise. No other clinical comments.
CR92/099	M0999_67206	BUP_LIQ	H		No other clinical comments noted.
CR92/099	M0999_67212	BUP_LIQ	CA	HX_HEP	"Heavy alcohol" use noted. No other clinical comments noted.
CR92/099	M0999_67240	BUP_LIQ	H		No clinical comments noted.
CR92/099	M0999_68902	BUP_LIQ	H		No clinical comments noted.
CR92/099	M0999_75011	BUP_LIQ	CA		Referred for further assessment. No other clinical comments noted.
CR92/099	M0999_75027	BUP_LIQ	H		No clinical comments noted.
CR92/099	M0999_75044	BUP_LIQ	H		No clinical signs or symptoms noted.
CR92/099	M0999_75067	BUP_LIQ	N	HX_HEP	Dose reduced due to "hepatitis". LFTs resolved
CR92/102	B9212_9846	BUP_LIQ	N		Negative for Hep A and Hep B. Attributed to "hepatitis" starting at admission to study.
CR92/102	B9212_9885	BUP_LIQ	CA		No clinical comments noted.
CR92/102	B9212_9890	BUP_LIQ	CA		No narrative
CR96/008	L9608_6130	BUP_LIQ	CA		Alcohol and sedative dependence noted. No clinical comments noted.
CR96/008	L9608_6131	BUP_LIQ	CA		No clinical comments noted.
CR96/008	L9608_6176	BUP_LIQ	CA		No clinical comments noted.
CR96/024	B9605_0096	BUP_LIQ	N		No narrative
CR96/024	B9605_0055	LAAM	N		Positive for Hep B and C. No other clinical comments noted.
CR96/024	B9605_0087	LAAM	N		Positive for chronic Hep B and C. Negative for Hep A. Attributed to acute hepatitis of unknown cause.
CR88/130	B0090_2432	METH	N		Cocaine and/or alcohol use noted. No other clinical comments.
CR88/130	B0090_2774	METH	CA		"Major alcohol problem" noted. Subject terminated from study due to liver problems. No other clinical comments.
CR88/130	B0090_3010	METH	CA		No clinical comments noted.
CR88/130	B0090_3027	METH	H		Cocaine use noted. No other clinical comments noted.
CR88/130	B0090_3086	METH	CA		Hospitalized for treatment of "hepatitis" No other clinical comments noted.
CR90/066	B9019_0149	METH	CA		No clinical comments noted.
CR90/069	L9069_0094	METH	H		No clinical comments noted.
CR90/069	L9069_0098	METH	H		No clinical comments noted.
CR96/024	B9605_0124	METH	CA	HX_HEP_C	Attributed to isoniazid use.
CR92/102	B9212_9885	PLACEBO	CA		No clinical comments noted.
CR92/102	B9212_9890	PLACEBO	CA		No narrative
CR96/013	M1008_5781025	PLACEBO	CA	NEG	Required alcohol detoxification program. No other clinical comments noted.

6.10.5 Hepatic Cases From Post-Marketing Surveillance of Subutex

6.10.5.1 Hepatic-Related Deaths

The Sponsor reports four deaths related to liver disease in patients taking Subutex in the period from the launch of the product in France in February 1996 until July 31, 2001. These cases are summarized in the table below.

Sponsor Case Number	Subutex Dose	Details of Subutex Treatment	Cause of Death	Other information
96-08-0142	4-8 mg/day	Narrative notes that patient was treated with Subutex for only six days prior to death, but that he had also injected the drug intravenously at doses of up to 64 mg/day.	Hepatocellular damage and aggravated hepatitis with asthenia and jaundice	No other information
97-02-0671	4 mg/day	Report notes that methadone was substituted for Subutex one month before death.	Hepatic cirrhosis	HIV-, HBV-, and HCV-positive
97-12-0719	10 mg/day	About 15 months	Aggravation of hepatic cirrhosis	HIV-and HCV positive
2000-10-1479	Intravenous route in mother	Not known	Baby had kernicterus and died.	
Source: Volume 5 (Hepatic Report) Section 4.1, page 41.				

As the above table indicates, patients taking Subutex who died had several coexistent medical condition that potentially confound the interpretation of the role of Subutex in their death. These factors include co-existent infection with HIV, HCV, and HBV, intravenous injection of buprenorphine, and maternal use of intravenous buprenorphine. In addition, many other details, such as concomitant medication use, are not available.

6.10.5.2 Severe Hepatic Cases Resulting in Hospitalization

The Sponsor has provided short narratives of 33 "severe hepatic cases" resulting in hospitalization. In many of these cases, several factors limit the ability to assign a causative role to Subutex. These factors include concomitant illnesses (eg. Hepatitis B or C, HIV infection), concomitant medications, concomitant drug abuse, and a general lack of information. Four cases, however, are worth noting.

Case Number	Summary of Narrative
1999-02-0118	A 33 year-old man presented with severe hepatitis and acute renal failure and anuria after ingesting 112 mg of Subutex 48 hours earlier. Subutex was discontinued, hemodialysis was instituted, and hepatic and renal function normalized. This case was also reported by Houdret et al.
2000-04-0924	A 25 year-old male with a history of heroin addiction developed jaundice. He had been taking Subutex 16 mg qd for about 2 months, but had also used it intravenously. Ultrasound revealed slight hepatosplenomegaly. Liver biopsy revealed foci of necrosis. He had clinical improvement after buprenorphine was discontinued.
2000-11-0310	39 year-old woman with a history of hepatitis (unspecified) who had started Subutex treatment five years earlier. A few days after a number of "high" doses of Subutex (doses not specified), she developed a hepatitis (AST 44x the upper limit of normal [ULN], ALT 41X ULN, alkaline phosphatase 6x ULN, and GGT 3.7X ULN). All treatment was stopped. One week later, the AST was 4.5 X ULN and ALT was 25X ULN. The reported consider this a toxic hepatitis possibly related to Subutex.
2001-06-0730	39 year-old woman who had used methadone for six months. She switched to Subutex, and after about

Case Number	Summary of Narrative
	two weeks she developed yellow skin and sclera, nausea, and tiredness. She was hospitalized and diagnoses with cholestatic icterus and renal failure. It was thought the cholestatic icterus may have been due to an allergic reaction to buprenorphine. Subutex was discontinued, and methadone was re-initiated. It was noted that she had a hepatitis vaccine (no details) about the same time the Subutex was started. Drug abuse with diazepam (10 to 20 mg, route unknown) was also noted.
Source: Volume 5 (Hepatic Report) Section 4.2, pages 42-47.	

Review of the above cases is notable for a temporal relationship of the hepatitis to Subutex administration, absence of clearly-defined confounding factors that could explain the hepatitis (except for the intravenous use of Subutex in one subject), the resolution of the hepatitis after the product was discontinued, and the co-occurrence of renal disease in two of the cases.

Some additional cases resulted in "hepatic failure" (reports 97-06-0010, 97-04-0521), "hepatic necrosis" (report 2000-04-0926), "hepatic encephalopathy" (report 1999-03-0360), and "portal hypertension" (report 2000-10-1368). Interpretation of the casual or contributory role of Subutex in each of these cases is complicated by the presence of one or more confounding factors that could result in the observed adverse events.

6.10.5.3 Review of Post-Marketing Hepatic Adverse Events

A number of post-marketing hepatic adverse events have been reported in Europe. Line listings of all events from February 1996 though July 31, 2001 are included in the submission. As with the other hepatic data, lack of details precludes a thorough understanding of each of the reported events.

The most common terms are non-specific indicators of hepatic damage or hepatic dysfunction.

Further review of the post-marketing hepatic adverse events is notable for the following observations:

- Cholestatic hepatitis and jaundice are more obvious in the post-marketing safety data than in the clinical trials. While in most cases there is insufficient information do assess the potential role of buprenorphine, there are some examples that implicate the drug. For example, there is one post-marketing case of a 37-year-old woman (company reference number 2000-08-1200, page 147 of AE Listing submitted on March 19, 2002), who developed elevated ALT and bilirubin 11 days after treatment with Subutex. The drug was stopped, and two days later the liver enzymes gradually decreased. While there is no additional information available, the temporal course of these findings relative to treatment with Subutex suggests a causative role for the drug. Other cases of cholestasis and jaundice either have no information available or are confounded by the presence of viral hepatitis, concomitant medications, or alcohol use.
- Many cases are associated with intravenous injection of Subutex.
- Many cases are reported in patients with multiple potential reasons for hepatitis, such as concomitant Hepatitis B or C infection, concomitant usage of potentially hepatotoxic medications, and injecting drug use.
- Severe hepatic cases, as reviewed in the above section, were more prevalent in the post-marketing cases than in the clinical trials.

6.10.6 FDA Office of Drug Safety Review of Buprenorphine-related Hepatic Events

At the request of the Division of Anesthetics, Critical Care, and Addiction Drug Products, the Office of Drug Safety (ODS) reviewed domestic adverse events associated with buprenorphine. Of note, the only approved buprenorphine product in the United States is Buprenex® (buprenorphine injection) for the relief of pain. The review was completed by Dr. Martin Pollack, in conjunction with Dr. Julie Beitz.

Dr. Pollack identified 24 cases in the Adverse Event Reporting System (AERS) database when the following terms were used for a search: hepatic disorders (excluding neoplasms) (High Level Group Term), hepatobiliary investigations (High Level Group Term), and liver transplant (Preferred Term). He notes that all were based on foreign reports, with 20 of the 24 coming from France. The oral dosage form (especially the sublingual form) was the only dosage from reported in those cases in which any dosage form was reported. Dr. Pollack notes that most patients with a LFT elevation had at least one other hepatic event reported, such as hepatitis. Most, but not all, cases occurred in opioid-dependent patients. Dr. Pollack identified confounding factors in all cases.

With regard to Subutex and Suboxone, Dr. Pollack recommended that the product labeling state that

6.10.7 Sponsor's Conclusions Regarding Hepatic Data

The Sponsor has concluded that the comorbidities that subjects with opiate addiction have play large role in the development of elevated hepatic enzymes. Specifically, the Sponsor states that "the more confounding/contributory factors a patient has, the more likely he or she is to have an exaggerated hepatic enzymes response to treatment with buprenorphine." The quantitative basis for this statement is not provided in the submission. The Sponsor further notes that in view of all these confounders "it cannot be concluded that buprenorphine, *per se*, causes hepatitis, but it still remains a possibility."

6.11 Acute Allergic Reaction to Buprenorphine

In response to a request in the Approvable letter of January 26, 2001, the Sponsor has collected cases of allergic reactions. These are summarized in Section 6.3 (Volume 1, page 40) of the response, and are further detailed in Attachment 5 (Volume 6) of the response.

The case of buprenorphine-treated Subject L012 in Study CR96/005 provides reasonable evidence for a causal role of buprenorphine in the development of an acute allergic reaction. The 22-year-old female subject, with a history of polysubstance abuse, received a singe 4 mg dose of buprenorphine, About three-and-one-half hours later, she developed a rash on her right hand, which progressed to a generalized body rash over the next half hour. She also developed faintness, respiratory distress and wheezing. Other symptoms included nausea, vomiting, profuse diaphoresis, dizziness, blurred vision and aches and pains. She was diagnosed with a type I allergic reaction to buprenorphine with rash and bronchoconstriction. (This case required breaking of the study blind.) She was treated with anti-inflammatory agents, and the condition resolved within 12 hours. The signs and symptoms reported, along with the temporal relation to buprenorphine administration, point to an acute allergic reaction to buprenorphine.

The case of buprenorphine-treated subject L251 in Study CR96/005 also provides reasonably convincing evidence of an acute allergic reaction to buprenorphine. This subject had completed six months of methadone treatment and requested a switch to buprenorphine. About 20 minutes after the first dose of buprenorphine, his physician reported that he developed "allergic reaction, headache, scrambled thoughts, diarrhea, petechial rash/hives, fatigue, watery eyes, puffy eyelids." He was treated with loperamide for diarrhea and Valium for anxiety. He did not require hospitalization. He was also receiving Aropax (paroxetine). He also reported a prior allergic reaction to intravenous Maxolon (metoclopramide) ("his heart stopped").

The above two cases provide reasonable evidence that patients can develop an acute allergic reaction to buprenorphine.

Subutex adverse event report 2001-06-0730 is notable for the development of cholestatic hepatitis and renal failure in a 39-year-old women who had been on buprenorphine for about 12 days. She had previously been treated with methadone. The cholestatic hepatitis was attributed to an allergic reaction to Subutex. She had also received a Hepatitis A vaccine at about the same time Subutex was initiated. She was taking diazepam 10-20 mg/day at this time. The physician attributed the cholestatic hepatitis to Subutex and not to the Hepatitis A vaccine. The reason for this causal attribution is not clear. Specifically, the reason for attributing the reaction to Subutex and not to the Hepatitis A vaccine is not clear.

The Sponsor has also summarized the post-marketing reports of allergic reactions to low-dose buprenorphine products, including Temgesic Injection, Temgesic Sublingual, and Temgesic Suppositories. The Sponsor notes that between 1978 and 1998, the Reckitt Benckiser database contains 2,631 reports of adverse events related to the marketing of low-dose buprenorphine. The Sponsor notes that in this period, approximately [redacted] dose units of the product were marketed.

The Sponsor's review of the post-marketing database revealed 244 event terms relating to "allergy". Of the 244 allergy-related event terms, the most common were "rash unspecified" (n=61), "pruritus" (n=51), "urticaria" (n=33), "rash maculopapular" (n=14), "erythematous rash" (n=12), "anaphylactic shock" (n=12), and "angioneurotic edema" (n=10). For all remaining allergy-related event terms, there were fewer than 10 reports. There were a total of 24 cases that included "allergic reaction" (n=5), "anaphylactic shock" (n=12), "anaphylaxis" (n=5), and "hypersensitivity" (n=2). The Sponsor reports that some were acute reactions, while others were delayed reactions.

Of the 12 cases of anaphylactic shock, the Sponsor has classified two as "acute", five as "delayed reaction", two as "other drug suspected", and three as "unknown". There was also one case of an acute hypersensitivity reaction. One case of an acute anaphylactic reaction occurred in a 71-year-old man with lung cancer who was given buprenorphine by suppository for cancer-related pain. One minute after he was given the drug, his blood pressure began to drop and he began to lose consciousness, with no reported sign of myocardial infarction. He was intubated, received cardiac massage, and medications, but died. The other two cases of acute anaphylactic reaction and the single case of an acute hypersensitivity reaction all resolved. Other cases of acute anaphylactic reactions, in which the role of a buprenorphine product was less clear, also required intervention and, in some cases, hospitalization.

The above data indicate that there is reasonable evidence linking buprenorphine (or buprenorphine-containing products) to acute allergic reactions. These reactions are relatively infrequent, but some are serious and may include bronchospasm and anaphylaxis. Of note, many

opioid products do contain information about allergic reactions in their labels. The issue of allergic reactions will need to be addressed in the product label.

6.12 Cases of Accidental Exposure of Subutex to Children

The Sponsor notes that from 1993 to 1999, 32 cases of accidental exposure of children to buprenorphine products were noted to the Marseille Poison Control Center in France. Subutex 8 mg tablets were involved in 29 cases and Temgesic 0.2 mg tablets were involved in 3 cases.

In 24 cases in which symptoms were reported, the symptoms were consistent with opioid ingestion, and included drowsiness, occasionally alternating with agitation, miosis, ataxia, and gastrointestinal upset with vomiting.

No deaths were reported. Nearly all cases required hospitalization, usually with discharges within 48 hours.

There was one serious cases of respiratory depression reported, in a child in whom an initial dose of naloxone had no effect but in whom a second dose of naloxone resulted in an improved respiratory condition.

6.13 Cases of Pregnancy and Neonatal Withdrawal Associated With Buprenorphine Use

The Sponsor notes three sources of information regarding use of buprenorphine in pregnancy and cases of neonatal withdrawal: published reports of clinical trials in pregnant women associated with buprenorphine use, published case reports, and post marketing adverse event reports.

6.13.1 Published Clinical Trials of Buprenorphine in Pregnant Women

The Sponsor cites 13 published reports in the literature of clinical trials, both controlled and open-label, in which a total of 756 women were treated (525 with a buprenorphine product) for opiate addiction. Six-hundred-sixty-four neonates were born, at least 299 of whom were by mothers treated with Subutex. Three spontaneous and 14 voluntary abortions were reported. The level of safety reporting was variable from study to study. In the studies for which it was reported, the rates of neonatal withdrawal ranged from 47% to 100%.

One study by Aubission et al (Section 6.5.1.5, Volume 1, page 50) reports a comparison of perinatal morbidity and neonatal withdrawal syndrome in neonates of mothers maintained on either methadone or high-dose buprenorphine during pregnancy. Review of the publication (in a translation provided by the Sponsor) does not indicate if the mothers were randomized to their treatment, or if they were enrolled based on already being in a defined treatment. The report notes that there were no differences between the two groups with regard to mean birth weight, mean gestational age, or APGAR score. However, the other measures of perinatal status were less favorable for the methadone group than for the buprenorphine group: prematurity < 37 weeks (18% in the methadone group versus 9% in the buprenorphine group), delayed intrauterine growth (37% in the methadone group versus 30% in the buprenorphine group), size < 10^{th} percentile (45% in the methadone group versus 34% in the buprenorphine group), and head circumference < 10^{th} percentile (16% in the methadone group versus 9% in the buprenorphine group). Neonatal withdrawal syndrome occurred in 65% of neonates in both groups. The authors also examined some measures of the severity of the neonatal withdrawal syndrome and other measure of perinatal

prognosis, and concluded that there were no major differences between the two groups. These data and conclusions are noted but are not being reviewed any further.

[ ]

6.13.2 Published Case Reports of Buprenorphine in Pregnant Women

A variety of case reports describe the development of neonatal withdrawal syndromes in infants born to buprenorphine-treated opiate-dependent mothers. One report describes treatment of these neonates with morphine. No definitive conclusion can be based on these reports, other than the fact that there is a high rate of neonatal withdrawal syndrome infants born to opiate-maintained mothers.

6.13.3 Post-marketing Adverse Events of Maternal Drug Exposure and Neonatal Withdrawal

Since Subutex was launched in 1995 through July 31, 2001, there were 91 reports of maternal drug exposure and 142 reports of neonatal withdrawal syndrome. The Sponsor has provided individual line listings for reports of all post-marketing adverse events in the reporting period, including those related to maternal exposure to buprenorphine and those related to neonatal outcome. Review of the line listings reveals the following:

- Most of the cases that reported "Maternal Drug Exposure" as the sole adverse event were simply reports of maternal exposure to Subutex during pregnancy, and were not necessarily associated with any pre- or post-natal adverse events.
- Some of the cases of neonatal withdrawal syndrome were associated with other drugs in addition to Subutex, including drugs of abuse and drugs acting on the central nervous system with abuse potential. Adverse events associated with neonatal withdrawal syndrome included hypertonia, neonatal tremor, neonatal agitation, and myoclonus. In one case, apnea and bradycardia were also reported.
- Nine cases of fetal death were reported from 1995 through July 31, 2001. In most cases, there was evidence of either use of other drugs or congenital malformations.

6.13.4 Summary of Adverse Events Associated With Maternal Drug Exposure and Neonatal Withdrawal

Based on the data reviewed above, there is insufficient information to recommend the use Subutex or Suboxone in pregnancy. Further study is needed to define the risk/benefit ratio of these products in the treatment of opiate-addicted pregnant women.

6.14 Other Safety Information

6.14.1 Information Letter for Prescribers and Pharmacists in France

The French regulatory authorities (the National Pharmacovigilance Commission and the French Agency for the Safety of Health Products) have reviewed the hepatic and other adverse events related to the marketing of Subutex in France. By agreement with the French Agency for the Safety of Health Products, Schering Plough has written a letter to physicians and pharmacists. The main points of this letter, dated October 2001, are as follows:

- "Subutex may induce cytolytic hepatic crisis (elevated transaminases, hepatitis)"
- Under the recommended conditions of use, the events are rare (1/3150) and, in the majority of cases, uncomplicated.
- Abuse of the product (eg, intravenous usage, and excessive doses) may lead to severe cases of hepatitis.
- Animal studies suggest that the hepatic effects may be the result of mitochondrial toxicity.
- Other confounding factors may "promote the occurrence of these adverse hepatic effects."
- Risk factors for hepatic disease should be taken into account when prescribing or monitoring patients taking Subutex.
- Laboratory tests should be performed to examine the etiology of cases of hepatic dysfunction.
- Respiratory depression, especially with concomitant use of benzodiazepines or with abuse of buprenorphine, is listed as a warning
- A drug interaction with buprenorphine could lead to respiratory depression.

6.14.2 Changes in the Safety Profile of the Drug

The Sponsor notes that there is no change in the severity of listed adverse reactions compared with the previous reporting period, nor were there changes in the outcomes of these reactions.

The Sponsor does note, however, that there was a change in the target population experiencing adverse reactions. Specifically, the Sponsor notes that there has been an increase in the number of children accidentally exposed to Subutex. The clinical picture was consistent with opioid overdose, and most cases required a period of hospitalization. While there were no reported deaths, there was one serious cases of respiratory depression reported, in a child in whom an initial dose of naloxone had no effect but in whom a second dose of naloxone resulted in an improved respiratory condition.

The Sponsor notes that one previously unlisted serious adverse reaction, allergic reaction to buprenorphine, has been identified.

The Sponsor notes that one previously unlisted non-serious adverse reaction, eye infection, had been identified. The Sponsor further notes that these cases, all of which involved fungal eye infections, were not related to buprenorphine.

The Sponsor notes that because of under-reporting in previous years, the number of reports of deaths has increased in the current reporting period. To address the issues of annual death rates, the Sponsor has assigned each death to the year in which it actually occurred, and has then based an annual rate on the number of 8mg Subutex doses distributed in each year. The Sponsor notes that the resulting death rates show reductions 1999 and 2000 compared to previous years.

The Sponsor notes that the number of reported hepatic adverse events has also increased, which the Sponsor attributes to retrospective surveys of cases that occurred in the previous reporting period. The Sponsor further notes that the following listed adverse events have increased infrequency during the reporting period: drug interaction, maternal drug exposure, neonatal feeding disorder, and neonatal weight decrease.

6.14.3 Drug Interaction With Safety Consequences

The Sponsor notes that two drug interaction have been defined in the reporting period. First, in the presence of ketoconazole 400 mg orally per day, circulating levels of buprenorphine increased two-fold. Second, in the presence of psychoactive drugs, a variety of interactions, including some with fatal or life-threatening outcomes, can occur.

6.14.4 Deliberate or Accidental Overdose

The Sponsor characterizes the manifestations of buprenorphine overdose as including respiratory depression, hypotension, sedation, and pinpoint pupils. The treatment should include monitoring or cardiac and respiratory function and supportive care. Naloxone may not be effective in reversing buprenorphine-induced respiratory depression. This issue will need to be addressed in the label.

6.14.5 Drug Misuse and Abuse

The Sponsor notes that that the intravenous route of administration is associated with misuse and abuse of the Subutex product in France. Misuse use of the product, especially in conjunction with benzodiazepines, can have fatal outcomes. The Sponsor, however, also notes that the rate of deaths in methadone-treated patients is higher than in buprenorphine-treated patients. The Sponsor's risk management plan, which is not a topic of this review, will need to address these issues.

7 USE IN SPECIAL POPULATIONS

7.1 Elderly Population

The Sponsor notes that Subutex and Suboxone have not been studied in the elderly population.

7.2 Pediatric Population

The Sponsor notes that Subutex and Suboxone have not been studied in the pediatric population.

7.3 Pregnancy

Data on use of the products in pregnancy come largely from post-marketing safety reports (mainly form France) as well as some published clinical trials, also mainly from France. While there are many adverse fetal outcomes in neonates born to women treated with Subutex, the relationship of these outcomes to the Subutex itself is difficult to separate from a possible relationship to other drugs of abuse or other medical comorbidities that accompany opiate addiction.

8 REVIEW OF LABELLING

Review of labeling in limited to those items addressed in the Periodic Safety Update Report.

8.1 Contraindications

Sponsor's proposed language:

CONTRAINDICATIONS
SUBOXONE and SUBUTEX should not be administered to patients who have been shown to be hypersensitive to buprenorphine, and SUBOXONE should not be administered to patients who have been shown to be hypersensitive to naloxone.

Reviewer's comments:
This contraindication is appropriate, as it is supported by reports of allergic reactions to buprenorphine.

8.2 Warnings

This review addresses only those warning relative to respiratory depression and hepatitis.

Sponsor's proposed language:

WARNINGS
Respiratory Depression: [redacted]

Reviewer's Comments:
The wording should be stronger, as follows:

Respiratory Depression: [redacted]