

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**20-732**

**20-733**

**MEDICAL REVIEW(S)**



**FDA CENTER FOR DRUG EVALUATION AND RESEARCH**  
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS  
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857 (301) 827-7410

**REVIEW AND EVALUATION OF CLINICAL DATA**

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<b>NDA #</b>	20-732 (Subutex) 20-733 (Suboxone)
<b>Sponsor</b>	Reckitt Benckiser Pharmaceuticals
<b>Generic Name</b>	Buprenorphine (Subutex) Buprenorphine with naloxone (Suboxone)
<b>Proprietary Name</b>	Subutex Suboxone
<b>Pharmacologic Class</b>	Partial opioid agonist (buprenorphine) Opioid antagonist (naloxone)
<b>Proposed Indication</b>	Treatment of narcotic addiction
<b>Submission Date</b>	December 31, 2001
<b>Dosage forms</b>	Tablets
<b>Strengths</b>	Subutex: 2 mg buprenorphine; 8 mg buprenorphine Suboxone: 2 mg buprenorphine/0.5 mg naloxone; 8 mg buprenorphine/2.0 mg naloxone
<b>Route</b>	Sublingual
<b>Medical Reviewer</b>	Gerald J. Dal Pan, MD, MHS
<b>Supervisory Medical Reviewer</b>	Celia Winchell, MD
<b>Completion Date</b>	May 17, 2002

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## **Executive Summary**

### **1 SAFETY CONCLUSIONS AND RECOMMENDATIONS**

The safety profile of Subutex and Suboxone in opiate addicts is generally consistent with the known spectrum of comorbidities in a population of opiate addicts, as well as with the known safety profile of an opioid agent. Special safety issues include the development of abnormal liver function tests (LFTs), allergic reactions to buprenorphine, use in pregnancy, and the potential for abuse, misuse, and accidental exposure. The hepatic data are notable for a high frequency (12.3%) of clinically abnormal LFTs in the clinical trials, and for a broad spectrum of hepatic adverse events in the post-marketing safety database, including severe cases of hepatic disease.

Interpretation of hepatic adverse events and LFT data from each of these data sources is limited by the presence of confounding factors, such as abnormal LFTs at baseline, ongoing intravenous drug abuse, chronic hepatitis B or C infection, concurrent alcohol use, use of potentially hepatotoxic concomitant medications, and other factors. Nonetheless, there are cases in both the clinical trials database and in the post-marketing database suggesting that buprenorphine may have a causative or contributory role in the development of hepatic abnormalities. No firm conclusion, however, can be made about these cases, mainly because of insufficient detail. Appropriate warnings in the label, as well as a post-marketing study to define the role of buprenorphine in the development of hepatic abnormalities in opiate addicts, are recommended. The available safety data provide reasonably convincing evidence that buprenorphine is the causative agent of a variety of allergic reactions, including angioneurotic edema, bronchospasm, and anaphylaxis. These findings will be addressed in the label. The post-marketing experience is notable for misuse and abuse of the product, mainly through intravenous injection of the crushed Subutex tablets. The full spectrum of clinical consequences of opiate overdose has been reported. Accidental exposure of Subutex in children has also been reported in the post-marketing database, resulting in a clinical picture consistent with opioid overdose. These issues will need to be addressed through labeling and a risk management plan.

### **2 SUMMARY OF CLINICAL FINDINGS**

#### **2.1 Overview of Clinical Program**

Buprenorphine HCl is a narcotic analgesic, marketed in the United States as an injectable formulation (Buprenex) for the treatment of moderate to severe pain. For nearly two decades, use of this agent as a treatment for opiate addiction has been explored.

Subutex (NDA 20-732) is a sublingual tablet formulation of buprenorphine. Suboxone (NDA 20-733) is a sublingual tablet formulation of buprenorphine and naloxone. The manufacturer and commercial Sponsor of these New Drug Applications, Reckitt Benckiser Pharmaceuticals (formerly Reckitt & Colman Pharmaceuticals) has prepared the marketing application based largely on research conducted by the National Institute of Drug Abuse (NIDA) under a cooperative research and development agreement (CRADA), as well as on about 40 individual-investigator INDs, sponsored mainly by NIDA grantees. Orphan drug status has been granted for these products.

Subutex has been marketed in Europe and elsewhere since 1995, and post-marketing safety data from these countries has supplemented the safety data from clinical trials. Suboxone is not approved in any country.

Dr. Celia Winchell has outlined the clinical research and regulatory history of these products in her memoranda of December 8, 1998 and December 22, 2000.

This review focuses on the Sponsor's answer to Item 8 in the Approvable letter of January 26, 2001, which addresses safety issues.

## **2.2 Efficacy**

Efficacy data have been previously reviewed. These reviews have concluded that the product is effective. Efficacy data are not further considered in this review.

## **2.3 Safety**

This review summarizes and analyzes the Sponsor's response to specific safety issues raised in a prior Approvable letter.

The data addressing the potential hepatotoxicity of the product include clinical trial data, published observations in the medical literature, and post-marketing data from outside of the United States. The clinical trial data show a high frequency (12.3%) of patients who have a "clinically abnormal" liver function test (LFT) at some point during the study. "Clinically abnormal" LFTs were defined as aspartate transaminase (AST), alanine transaminase (ALT), gamma glutamyl transaminase (GGT), and total bilirubin levels of three times the upper limit of normal or higher. Review of the narratives for these cases is notable for a high prevalence of factors that confound the interpretation of the abnormal LFT data. These factors include abnormal LFTs at baseline, ongoing intravenous drug abuse, chronic hepatitis B or C infection, concurrent alcohol use, use of potentially hepatotoxic concomitant medications, and other factors. There are some cases, however, of the development of clinically abnormal LFTs in subjects with normal baseline LFTs who are known to be serologically negative for both hepatitis B and hepatitis C. While a determination of the etiology is limited by an overall lack of clinical information, a causative or contributory role of buprenorphine can not be excluded. A notable feature of the LFT values in the clinical trials is their fluctuation. Thus, LFT value increases were frequently followed by LFT value decreases, even when study drug was continued. Though some cases of clinically symptomatic hepatitis were reported, many of these cases had a reasonable alternative explanation that did not involve buprenorphine. In the majority of cases of clinically abnormal LFTs, clinically symptomatic hepatitis was not reported. Cases of abnormal LFTs and the hepatic adverse events from the post-marketing adverse event database were qualitatively different from those in the clinical trials database in several respects. First, many of these post-marketing cases were associated with the intravenous injection of crushed Subutex tablets, rather than with the intended sublingual use. Second, many of these cases involved cholestasis, rather than transaminase elevation, which was the primary abnormality in the clinical trials. Third, many of the cases in the post-marketing database were more severe than those in the clinical trials database. For example, some of the post-marketing cases reported hepatic failure, hepatic necrosis, and hepatic encephalopathy. Fourth, some of the cases in the post-marketing database involved concomitant renal failure. As with the data from the clinical trials, the interpretation of the post-marketing data is limited by the presence of multiple confounding factors. Nonetheless, there are cases in both the

clinical trials database and in the post-marketing database suggesting that buprenorphine may have a causative or contributory role in the development of hepatic abnormalities. No firm conclusion, however, can be made about these cases, mainly because of insufficient detail. Appropriate warnings in the label, as well as a post-marketing study to define the role of buprenorphine in the development of hepatic abnormalities in opiate addicts, are recommended.

Signs and symptoms of allergic reactions have been reported in the clinical trials data and in post-marketing safety reports. The spectrum of allergic reactions ranges from rashes and pruritus to angioneurotic edema, bronchospasm, and anaphylaxis. The available data are reasonably convincing that buprenorphine is the causative agent. These findings will be addressed in the label.

Evidence for abuse and misuse of the product comes largely from the post-marketing safety database. In fact, many of the adverse events in the post-marketing safety database are related to intravenous injection of crushed Subutex tablets, rather than to the intended sublingual use. The intravenous use of the product can result in the full spectrum of clinical consequences of opiate overdose. In many cases, other substances, such as alcohol, cocaine, or benzodiazepines, were also involved. These findings point to the need for an appropriate risk management plan, which is beyond the scope of this review. It is important to note that the post-marketing data pertain only to Subutex, and not to Suboxone, which is not marketed anywhere in the world at this time. The impact of the addition of the opiate antagonist naloxone to the formulation will have to be determined by post-marketing surveillance.

Accidental exposure to Subutex in children has been reported. The clinical consequences are those of an opioid overdose, including respiratory depression. Appropriate warnings in the label and a risk management plan must address this issue.

Review of the deaths in the clinical trials and in the post-marketing database indicates that many of the deaths are related to the known co-morbidities that accompany opiate addiction. In many of the post-marketing deaths, use of multiple substances affecting the central nervous system was common. In many cases, there was too little information to make a conclusion about the cause of death.

Review of the serious adverse event (SAE) profile in the clinical studies suggests that the SAE profile is largely consistent with the known comorbidities present in a population of opiate addicts. An exception to this general statement is the case of allergic reaction, in which a direct causative role of the buprenorphine-containing products is likely. While the SAE profile does not strongly implicate the buprenorphine-containing products in any other serious adverse events, ongoing post-marketing surveillance will be required to examine trends in cardiovascular and hepatic morbidity, as well as cases of overdose.

Adverse events that led to study drug discontinuation or dose reduction were recorded in the clinical trials. Adverse events in this category were varied in nature, but were generally consistent with those expected in a population of opiate addicts or with opiate treatment, such as nausea and vomiting. Two cases of allergic reaction appear to be a direct result of Subutex treatment.

Data on use of the products in pregnancy come largely from post-marketing safety reports (mainly from 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. Labeling will address the use of the product in pregnancy.

## 2.4 Special Populations

The products have not been studied in pediatric or elderly populations.

# Clinical Review

## 1 INTRODUCTION AND BACKGROUND

### 1.1 Proposed Indications

The Sponsor's proposed indication is "SUBOXONE and SUBUTEX are indicated for the treatment of opioid dependence."

### 1.2 Milestones in Product Development

An "Approvable" letter was sent to the Sponsor on January 26, 2001. Item 8 of this letter addressed clinical safety issues. This item from that letter is reproduced below:

8. Provide a safety update, including a complete review of all existing safety data, including data from ongoing and completed studies sponsored by Reckitt & Coleman's CRADA partner, NIDA, and its grantees. This update should specifically examine the potential for buprenorphine-induced hepatotoxicity, the role of viral hepatitis in increasing vulnerability to hepatotoxicity, and the proper approach to prevention and management of hepatic adverse events. Analyses should focus on outliers and extreme values rather than measures of central tendency, and should provide comparison groups wherever available. Data sets with unique patient identifiers should be submitted together with the reports of the analyses. The analyses of uncontrolled studies of buprenorphine should compare the course seen in treated patients to the natural history of hepatic enzyme fluctuation in viral hepatitis. In addition, the safety data should be examined for any cases of acute allergic reaction to buprenorphine.

In addition, under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

- a. Describe in detail any significant changes or findings in the safety profile.
- b. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
  - (1) Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

- (2) Present tabulations of the new safety data combined with the original NDA data.
- (3) Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
- (4) For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
- (5) Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
- (6) Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
- (7) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
- (8) Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
- (9) Provide English translations of current approved foreign labeling not previously submitted.

### 1.3 Foreign Marketing

The Sponsor reports that Subutex is approved in 13 European Union countries, as well as in 14 other countries. Subutex is also under review in

Suboxone is not approved in any country. The Sponsor notes that the

## 2 FINDINGS FROM OTHER REVIEW DIVISIONS OR CONSULTS

This review considers only the specific clinical safety issues addressed in the current resubmission. Dr. Winchell will address any issues from other review division in her supervisory memorandum. The findings and recommendations of a consultation performed by the Office of Drug Safety regarding the potential hepatotoxicity of buprenorphine are discussed in the section of this review dealing with hepatic adverse events.

### 3 REVIEW METHODS

#### 3.1 Conduct of Review

The data on hepatic safety included summaries of LFT abnormalities by study, narratives of cases where at least one LFT was “clinically abnormal”, and a dataset containing SAS transport files of all LFT data. Other safety data, such as prior and concomitant illnesses, medication data, and adverse event data were not contained in the SAS transport files or in any other format (eg, printed data listings, narratives, summary tables, etc.). The review of the hepatic data consisted primarily of reviewing the narratives of the patients who had “clinically abnormal” LFT values. The review did not focus on group measures of central tendency of LFT values, as these were not provided by the Sponsor.

Review of adverse events focused on deaths, serious adverse events, and adverse events leading to study drug discontinuation, dose reduction, and temporary study drug interruption. This review focused on review of narratives, and, like the review of the hepatic data, did not focus on group means or other rates. The review also considered the post-marketing deaths and adverse events, which were provided in line-listing format.

Review of data related to allergic reactions consisted of review of adverse event reports from both clinical trials and of the post-marketing adverse event experience.

Review of data related to pregnancy consisted of review of post-marketing adverse event reports and summaries of the published literature that the Sponsor has provided.

#### 3.2 Overview of the Submission

The Sponsor has submitted a Periodic Safety Update Report (PSUR). The Sponsor notes that PSUR contains safety data from clinical studies and publications during the period February 1, 2000 to July 31, 2001. The following information pertains to the summary of the safety of the products:

- In this review period, buprenorphine was administered to 1,455 subjects in 19 sponsored clinical studies. Of these, only one study was a prospective study with case report forms (CRFs) (Study CR96/015, “Suboxone versus methadone plus lofexidine detoxification”).
- An additional 48 publications describe the clinical use of buprenorphine in 1,610 subjects. Some of these reports include safety information. Some of these reports contain information on the use of the product in opioid-dependent pregnant women, while others contain post-marketing safety information.
- The Sponsor has also included information on the post-marketing exposure to Subutex in foreign countries. The product is currently marketed in 21 countries. During the 18-month review period, the Sponsor reports that — Subutex tablets were distributed for the treatment of opioid-dependent patients. A total of 507 adverse events were reported during this period .
- An analysis of potential hepatotoxicity. The analysis uses data from clinical trials, 6 publications describing 12 “hepatic cases”, and 103 cases of hepatic adverse events reported following the marketing of Subutex.
- An analysis of acute allergic reactions to buprenorphine.

- Information from ongoing clinical trials and from published reports has been included in the PSUR. This included a new PK study examining buprenorphine levels following administration of Subutex and ketoconazole, a potent inhibitor of CYP 3A4.
- Final reports of nonclinical studies (a report on fertility and early embryonic development in the rat, and a report to qualify buprenorphine and naloxone impurities) and a status report on an ongoing rat carcinogenicity study).
- A review of the worldwide post-marketing experience, with a focus on the experience in France.
- Two studies on the use of Subutex in medically assisted withdrawal (NEPOD #26/27 and NEPOD #06). Protocol for NIDA-sponsored trials for medically assisted withdrawal (CTN-001, CTN-002 and CTN-003).
- Proposed labeling (unannotated) is presented.

Study reports included in the resubmission include:

Study Number and Title	Product	Volume 1 Location	Attachment Location	Reviewer's Comments
Study SCH 2844: Effects of ketoconazole on the pharmacokinetics of buprenorphine	Subutex	Section 7.1.1.1, pages 63-67	Attachment 1, Part 2 (Volume 1)	The data listings, referred to in the report's Table of Contents and in the text of the report, are not included. CRFs for one subject with an SAE are included.
Study 0600501: A pilot study to assess the pharmacokinetic profile of buprenorphine from a rapidly-disintegrating sublingual tablet in healthy non-patient volunteers	Subutex and 	Section 7.1.1.3, pages 75-77	Attachment 6 (Volume 7)	Report appears to include all applicable tables and listings
Study 0600503: "A four-way crossover study to assess the bioequivalence of buprenorphine administered sublingually as a conventional tablet (Subutex) and a fast-dissolving tablet  at 2mg and 8 mg in healthy volunteers under a naltrexone blockade"	Subutex and 	Section 7.1.1.4, pages 78-82	Attachment 7, (Volumes 8 and 9)	All required tables and listings appear to be present
Study 0600506: "A study of sequential two-way crossover design, to assess the bioequivalence of buprenorphine administered as conventional tablets (Subutex) and a fast dissolving tablet  , at 12mg and 16mg in healthy volunteers under naltrexone blockade"			Attachment 8, Part 1 (Volume 10)	Protocol only submitted. Study is listed as "Ongoing" on page 59, Volume 1.
Study BPRU #9925: Transitioning Individuals from Buprenorphine to Naltrexone	Subutex Sublingual solution	Section 7.1.2.1, pages 83-84	Attachment 8, Part 2 (Volume 10)	Minimal AE update, lots of IRB correspondence, and study outline presented. Study is listed as "Completed" on page 59, Volume 1. No final report.
NEPOD #18: "The effects of substitution pharmacotherapies on simulated driving: implications for road safety"	Subutex	Section 7.1.2.2, pages 85-86	Attachment 8, Part 3 (Volume 10)	Study report, but not a standard clinical study report. No discussion of general safety. No data listings. Study listed as "Completed" in Table 20 on page 59, Volume 1.
NEPOD #19: "Neuropsychological effects study: LAAM, buprenorphine and methadone"	Not clear what buprenorphine formulation was used	Section 7.1.2.3, page 87	Attachment 8, Part 4 (Volume 10)	Study report, but not a standard clinical study report. No discussion of general safety. No data listings. Study listed as "Completed" in Table 20 on page 59, Volume 1.
NIDA # 1018: "Multicenter safety trial of buprenorphine/naloxone for the treatment of opiate dependence"	Suboxone	Section 7.2.1.3, pages 102-104	Attachment 8, Part 5 (Volume 10)	Interim study report, lots of information about enrollment and baseline characteristics, but no really meaningful information about adverse events. Study listed as "Ongoing" in Table 21 on page 60, Volume 1.
BPRU #9605: Medication Comparison Study	Not clear what formulation used	Section 7.3.2.1, pages 147-151	Attachment 8, Part 6 (Volume 10)	Numbers of AE presented, but full study information not available. Study has been published in NEJM.
BPRU #9817: Medication Comparison of Abrupt	Subutex	Section	Attachment	Numbers of AE presented, but full study

Study Number and Title	Product	Volume 1 Location	Attachment Location	Reviewer's Comments
Withdrawal		7.2.2.5, pages 134-135	8, Part 6 (Volume 10)	information not available. Study is listed as "Ongoing" in Table 21 on page 60, Volume 1.
BPRU #9820: Medication Compliance of Outpatient Detoxification	Subutex	Section 7.2.2.6, pages 137-138	Attachment 8, Part 6 (Volume 10)	Numbers of AE presented, but full study information not available. Study is listed as "Ongoing" in Table 21 on page 60, Volume 1.
BPRU #9938: Methadone and Buprenorphine Ante- and Post-Partum	Subutex	Section 7.2.2.7, pages 140-141	Attachment 8, Part 6 (Volume 10)	Numbers of AE presented, but full study information not available. Study is listed as "Ongoing" in Table 21 on page 60, Volume 1.
NIDA #1009: "Buprenorphine formulation comparison protocol: Sublingual tablet versus liquid"	Sublingual tablet and liquid	Section 7.1.1.2, pages 68-75	Attachment 9 (Volume 11)	No safety data in study report
06000201: "A Phase III, double-blind, double dummy, randomized, single-center, parallel group study to compare the efficacy of buprenorphine/naloxone stabilization and withdrawal with methadone stabilization plus lofexidine-assisted withdrawal in opiate-dependent addicts"	Suboxone	Section 7.2.1.1, pages 93-101	Attachment 10 (Volumes 12-17)	Full study report, apparently with all required tables and listings
NIDA-CTN-0001: "Buprenorphine/naloxone versus clonidine for inpatient opiate detoxification"	Suboxone	Section 7.2.1.4, pages 105-109	Attachment 11 (Volume 18)	Protocol only – not listed in Table 20 or 21 (Pages 59 and 60, Volume 1)
NIDA-CTN-0002: "Buprenorphine/naloxone versus clonidine for inpatient opiate detoxification"	Suboxone	Section 7.2.1.4, pages 105-109	Attachment 11 (Volume 18)	Protocol only – listed as "Ongoing" in 21 (Page 60, Volume 1)
NIDA-CTN-0003: "Comparison of three taper schedules for opiate detoxification"	Suboxone	Section 7.2.1.5, page 111	Attachment 11 (Volume 18)	Protocol only – not listed in Table 20 or 21 (Pages 59 and 60, Volume 1)
NEPOD #26/27: "Inpatient dose titration study"	Subutex	Section 7.2.2.2, pages 117-121	Attachment 12 (Volume 19)	In-text safety data tables (see Table 2.14 – Adverse Events, page 92, Volume 19). No AE listings
NEPOD #06: "A randomized controlled trial of buprenorphine in the management of outpatient heroin withdrawal"	Subutex	Section 7.2.2.3, pages 122-131	Attachment 12 (Volume 19)	In-text safety data tables (see Table 4.29 – Adverse Events, page 159, Volume 19) No AE listings
NEPOD #10: "Buprenorphine Implementation Trial"	Subutex	Section 7.2.2.4, pages 131-133	Attachment 13 (Volume 20)	In-text safety data information (see Serious Adverse Events, page 88, Volume 20)
CR97/008: "Suboxone versus methadone maintenance"	Suboxone	Section 7.2.1.2, page 102	None	No safety data
CR96/005: comparative study of subutex and methadone in treatment of opioid dependence (update only)	Subutex	Section 7.2.2.1, pages 114-117	Attachment 5, part 2, Volume 6	Only update is SAEs

### 3.3 Materials Consulted

The material consulted included the initial IND submission as well as the additional submissions provided by the Sponsor, summarized in the table below.

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Date of Submission	Description
December 31, 2001	Period Safety Update Report
March 12, 2002	Answer to Item 1 about Studies CR96/013 and CR96/014 of Agency's March 6, 2002 letter
March 19, 2002	Submission on pages 137-197 of Appendix 3 in Attachment 4, that were missing in the original PSUR submission
March 30, 2001	Answer to Item 2 of Agency's March 6, 2002 letter
April 4, 2002	Answer to Items 1-6 of Agency's March 12, 2002 letter
April 5, 2002	Answer to Item 7 of Agency's March 12, 2002 letter, with updated Hepatic Report
April 24, 2002	Answer to Agency questions regarding completeness of response
April 25, 2002	Submission of missing pages 138-139 of Volume 3.
May 1, 2002	Submission of revised integrated list of adverse events from studies CR96/013 and CR96/005 (revised from April 24, 2002 submission)

### 3.4 Evaluation of Data Quality and Integrity

During the course of the clinical review, it was found that the when using the patient numbering system for studies CR96/013 and its extension study CR96/014, the numbers of patients listed in the summary of the study could not be confirmed. In a letter to the Sponsor on March 6, 2002, the Agency asked the Sponsor to explain the numbering system and to provide a list of all patients in those studies in order to demonstrate that the number of patients reported in the text could be confirmed. The Sponsor answered this request in a submission dated March 12, 2002.

During review of the hepatic report, it was noted that whenever the Sponsor reported the number of patients with a "high" LFT value, the reported number actually corresponded to the number of patients with a "clinically abnormal" LFT value, not simply a "high" LFT value. The Sponsor acknowledged this error, but also noted that the numbers presented accurately reflected the number of patients with a "clinically abnormal" LFT value. In response to a question by the Agency, the Sponsor further noted that the numbers of patients with a "clinically abnormal" LFT value did not include patients whose post-baseline "clinically abnormal" value was recorded at a time when no study medication was being taken. The Sponsor notes that 12 patients in 3 studies had a post-baseline "clinically abnormal" LFT value at a time when no study medication was being taken.

The Sponsor did not present integrated information regarding deaths, serious adverse events, or adverse events leading to study drug discontinuation, dose reduction, or temporary study drug interruption. The Agency requested line listings of this information on March 12. The Sponsor provided this information on April 4, 2002.

## 4 DESCRIPTION OF DATA SOURCES

### 4.1 Primary Source Data

The primary source of data for this review was the information submitted in the Period Safety Update Report on December 31, 2001, and in the subsequent information amendments.

## **4.2 Postmarketing Experience**

The Sponsor has also included information on the post-marketing exposure to Subutex in foreign countries. The product is currently marketed in 21 countries. During the 18-month review period, the Sponsor reports that                     . Subutex tablets were distributed for the treatment of opioid-dependent patients. A total of 507 adverse events were reported during this period.

## **4.3 Literature Search**

The Sponsor has conducted an extensive review of the literature and has supplied copies of numerous articles. The Sponsor added serious adverse events and deaths noted in the published literature to the post-marketing safety database (see Sponsor letter of April 24, 2002).

## **5 REVIEW OF EFFICACY**

Efficacy data have been previously reviewed. These reviews have concluded that the product is effective. Efficacy data are not further considered in this review.

## **6 REVIEW OF SAFETY ISSUES**

### **6.1 Extent of Exposure**

The Sponsor has divided exposure to buprenorphine into three groups:

- Exposure to Suboxone, Subutex, and buprenorphine sublingual solution in clinical trials, including ongoing and completed clinical trials and published reports of clinical trials with buprenorphine.
- Exposure to Subutex marketed for the treatment of opioid dependence, based on data from the manufacturer, Reckitt Benckiser Healthcare (UK) Ltd, for this indication.
- Exposure to marketed low-dose analgesic products (Buprenex, Temgesic, Buprex, each containing 0.3 mg buprenorphine in 1 mL) marketed for the treatment of pain. Other low-dose buprenorphine-containing products include buprenorphine sublingual tablets (0.2 or 0.4 mg per tablet), and buprenorphine suppositories (marketed only in Japan).

Exposure to buprenorphine in clinical trials during the review period of February 1, 2000 to July 31, 2001 came from 8 clinical pharmacology studies, 11 clinical trials, and 48 publications. A total of 1,455 subjects in 19 sponsored clinical trials were exposed to buprenorphine. Additionally 1,610 patients were exposed to buprenorphine, as described in 48 publications. The number of buprenorphine-treated patients from each of these sources is summarized in the table below:

Source of Exposure Data in Review Period February 1, 2000- July 31, 2001				
Source of Data	Number of Studies	Buprenorphine-treated patients		
		Total	Male*	Female*
PK/PD Studies	8	309	191	70
Clinical Trials	11	1146	542	301
Clinical Publications	48	1610	614	530
Source: Adapted from Sponsor Table 5, Volume 1, Page 27				
*In many cases, gender was not specified				

In the review period February 1, 2000 through July 31, 2001, \_\_\_\_\_ Subutex tablets were distributed for the treatment of opioid dependence. The table below summarizes post-marketing exposure to Subutex, both from launch of the product through January 2000 and from February 1, 2000 through July 31, 2001.

Post-marketing exposure to Subutex			
	1995 – Jan 2000	Feb 2000 – July 2001	Total
Subutex Dosage Form	_____ of tablets		
0.4 mg	_____	_____	_____
2 mg	_____	_____	_____
8 mg	_____	_____	_____
Total	_____	_____	_____
	_____ of daily doses of Subutex*		
Dose units of 8mg	_____	_____	_____
*Assumes an average daily dose of 8mg/day			
Source: Sponsor Table 6, Volume 1, page 28.			

The Sponsor reports that \_\_\_\_\_ units of low-dose buprenorphine products marketed for the treatment of pain were distributed. These products include sterile injection of buprenorphine (0.3 mg in 1 mL), buprenorphine sublingual tablets (0.2 or 0.4 mg per tablet), and buprenorphine suppositories (0.3 mg).

## 6.2 Methods for Review of Safety

The data on hepatic safety included summaries of LFT abnormalities by study, narratives of cases where at least one LFT was “clinically abnormal”, and a dataset containing SAS transport files of all LFT data. Other safety data, such as prior and concomitant illnesses, medication data, and adverse event data were not contained in the SAS transport files or in any other format (eg, printed data listings, narratives, summary tables, etc.). The review of the hepatic data consisted primarily of reviewing the narratives of the patients who had “clinically abnormal” LFT values. The review did not focus on group measures of central tendency of LFT values, as these were not provided by the Sponsor.

Review of adverse events focused on deaths, serious adverse events, and adverse events leading to study drug discontinuation, dose reduction, and temporary study drug interruption. This review focused on review of narrative, and, like the review of the hepatic data, did not focus on group means or other rates. The review also considered the post-marketing deaths and adverse events, which were provided in line-listing format.

Review of data related to allergic reactions focused on reports of adverse events in clinical trials and in post-marketing reports.

Review of data related to pregnancy focused on the Sponsor's review of the published literature and on the post-marketing adverse events.

### 6.3 Review of Individual Study Summaries

In Section 7.1 and 7.2 of the Periodic Safety Update Report (Volume 1), the Sponsor presents summaries of several clinical studies completed or ongoing during the reporting period. Since the relevant safety data (deaths, serious adverse events, adverse events leading to discontinuation or dose reduction, and hepatic data) have been presented in an integrated fashion, these summaries, as well as the individual study reports presented as attachments to the PSUR, are not reviewed individually.

### 6.4 Deaths

#### 6.4.1 Deaths in Clinical Trials

The Sponsor reports that six deaths in clinical trials were previously reported. An additional three previously unreported are presented in the current safety update. The table below summarizes the information on these three newly reported deaths.

Newly Reported Deaths in Clinical Trials					
Case No.	Study No.	Age/ Gender	Treatment	Medical History	Cause of Death
600-DA-0035	NIDA # 1018	23/ Female	Suboxone 6 mg	No details	Found dead by husband. No details.
PR/010522/467	NEPOD # 10	28/ Male	Subutex 32 mg QOD	Bipolar disorder	Suicide by carbon monoxide poisoning, attributed to mood disorder
L063	CR69/005	Unknown/ Female	Methadone 35 mg	Amphetamine use	Fell while climbing from one floor to another via a balcony, apparently while using amphetamines

Source: Section 6.1.1 of Safety Update, Volume 1, pages 29-30

None of the above deaths was considered related to the study medication. No information in any of the reports clearly implicates the drug as having contributed to the death, though the first report of the woman found dead contains insufficient information to make any meaningful assessment about a potentially causal role of the drug.

The six previously reported deaths occurred in three patients taking buprenorphine solution (one case each of drug overdose [temazepam], coronary thrombosis, and dehydration and sepsis), two taking methadone (one case each of multiple injuries and, multiple stab wounds), and one person whose treatment assignment was unknown (who died of cancer).

Each of the nine deaths was judged by the investigator to be unrelated to the study drug. The narratives of the deaths in the buprenorphine-treated subjects do not point to any obvious contribution of buprenorphine to the death, though many of these narratives do not contain many details.

## 6.4.2 Deaths Associated with the Marketing of Subutex

The original NDA and its later amendments contained information on 68 deaths reported to Schering Plough from the launch of Subutex in France in February 1996 through January 31, 2000. The Sponsor reports in the current safety update that there were additional deaths during this period that were not reported to either Schering Plough or to the French Ministry. These deaths have been added to the database and are now being reported, along with deaths that occurred in the new reporting period, February 1, 2000 through July 31, 2001. The table below summarizes, by year of occurrence, the number of previously reported and the number of newly reported deaths.

Number of reports of deaths associated with the Marketing of Subutex, February 1996 through July 2001						
	Year of Death					
	1996	1997	1998	1999	2000	2001
Deaths reported previously in the NDAs and amendments	25	17	21	5		
New reports of deaths	2	7	21	13	35	36
Total	27	24	42	18	35	36
Overall Total	183					

Source: Table 7 in Safety Update, Volume 1, page 30.

The Sponsor notes that in 140 of the 183 deaths, concomitant alcohol or drug use was reported. One-hundred-twenty-eight of these 140 deaths were classified as "overdoses". Benzodiazepine use was reportedly very common in many of these cases, as was concomitant alcohol use. The Sponsor further notes that in the remaining 43 cases where no concomitant alcohol or drug use was reported, the overall level of reporting in 28 cases was very poor, and concomitant alcohol or drug use may have simply been omitted from these reports.

Further review of the line listings of the post-marketing deaths (See Attachment 3, Part 2, Volume 4) reveals that in many cases, there is no specific underlying cause of death listed. In many cases, the "Reaction Description" is simply listed as "Death", "Death, Drug Interaction", "Asphyxia", or "Death (suicide)". In many cases in which the "Reaction Description" term is "Death, Drug Interaction" or "Asphyxia", there are usually several concomitant medications listed.

In the 43 cases where no concomitant medication usage was reported, the "Reaction Description" terms are still very vague (eg, "Death" "Injury Accidental"). The Sponsor notes (Volume 1, page 32) that the level of reporting for these cases is very poor. Of note, there are four deaths in which a hepatic cause of death is noted, as summarized in the table below:

Post-Marketing Hepatic-Associated Deaths in Cases With No Concomitant Medications				
Sponsor Reference No.	Country	Subutex Dose	Gender/ Age	Reaction Description
96-08-0142	France	4-8 mg	M/ 33	Hepatocellular damage, asthenia, jaundice, hepatitis aggravated
97-02-0671	France	4 mg	M/ 32	Hepatic cirrhosis
97-12-0716	France	10 mg	M/ 31	Hepatic cirrhosis aggravated
2000-10-1479	France	Unknown	UNK/ UNK	Jaundice (in neonate with kernicterus)

Source: Table 2, Appendix 3, Part 2, Volume 4, pages 48-49.

Review of the line listings of deaths is notable for some "Reaction Description" that are both specific, and not necessarily part of the spectrum of illnesses that might be seen in a population of opiate addicts.

Sponsor Reference No.	Country	Subutex Dose	Gender/ Age	Reaction Description	Other Drugs
2001-04-0056	France	12 mg qd	M/ 36	Cryoglobulinemia, edema generalized, renal insufficiency, glomerulonephritis, pulmonary edema	Rebetol, Enalapril, Stavudine, Lamivudine
2000-07-0712	France	16 mg	F/ 40	Embolism pulmonary	None listed

Source: Table 2, Appendix 3, Part 2, Volume 4

While these two cases are not totally unexpected in a population of drug addicts, they are notable for the fact that the underlying cause of the events is not clear.

### 6.4.3 Deaths Reported in the Published Literature

The Sponsor notes that in the review period there were four reports of deaths associated with buprenorphine usage in the treatment of opioid dependence. These reports (see page 33 of Volume 1) are summarized as follows:

- A case report of a 25 year-old man who apparently committed suicide and was found to have buprenorphine, norbuprenorphine, and benzodiazepines in his blood and other body fluids (reference: "Fatal intoxication following self administration of a massive dose of buprenorphine" J Forensic Sci, Vol 45, 226-228)
- A report in JAMA estimating that the rate of deaths in France attributable to methadone is at least 3 times higher than the rate attributable to buprenorphine (reference: "Deaths attributable to methadone versus buprenorphine in France" JAMA, Volume 285, 45)
- A retrospective review of deaths due to morphine-like compounds (heroin, codeine, dextropropoxyphene and buprenorphine) in 302 subjects. Buprenorphine was implicated in 13 of 271 cases in which a single agent was involved. The Sponsor has added these cases to the post-marketing adverse event line listings. (reference: "Fatal overdoses with opiates and opioids examined at the Forensic Medical Institute in Strasbourg: 302 cases(1991-1997): J Med Legale Droit Medecale, Vol 42, 3-10)
- A publication describing 117 deaths associated with the use of Subutex that occurred in France from launch in February 1996. The Sponsor has added these cases to the post-marketing adverse event line listings. (reference: "Deaths involving buprenorphine: a compendium of French cases", Forensic Science International, Vol 121, 65-69)

As noted, the Sponsor had added these deaths to the post-marketing deaths, and these have been reviewed in the section above.

### 6.5 Non-Fatal Serious Adverse Events

Other serious adverse events were defined as serious adverse events other than death, including those temporally associated with or preceding death

### 6.5.1 Non-Fatal Serious Adverse Events in the Clinical Studies

In an amendment to the PSUR (amendment dated April 4, 2002), the Sponsor has provided a line listing of all serious adverse events in the clinical trials. Rates based on treatment assignment have not been provided, though for each serious adverse event, the treatment assignment is known. For the purpose of this review, the serious adverse events will be summarized and analyzed qualitatively by body system.

Three cases of an Application Site Reaction were reported in methadone-treated patients. One patient developed an infection at the site of temazepam injection. These other two cases were reported in a single patient who developed an infection at the site of dermatitis on the hand, possibly related to food allergies. It is not clear why these two cases were classified as application site reactions. Each case involved infection of the affected skin area, and each was judged to be unrelated to the study drug.

Three patients (one in each of the Suboxone, Subutex, and placebo groups) had an adverse event in the Benign and Malignant Neoplasms system. Among the two buprenorphine-treated patients were one case of anal cancer (reported after 128 days of treatment) and one case of cervical “pre-cancer” (reported after 4 days of treatment). The placebo-treated patient had kidney cancer (reported after 4 days of treatment). Each of these neoplasms was judged by the investigator to be unrelated to the study drug.

Serious adverse events in the Body As A Whole system included one case of alcoholism, seven cases of chest pain, and one case of pedal edema. Each of these events was judged by the investigator to be unrelated to the study drug. The seven cases of chest pain occurred in five buprenorphine-treated patients, one methadone-treated patient, and in one patients whose treatment at the time of the event was not known but who had taken methadone during an earlier phase of the study. Review of the narratives of chest pain indicate that most events were thought to be chest pain of non-cardiac origin, after an evaluation for cardiac disease in many cases.

Serious adverse events in the Cardiovascular system occurred in 15 patients. With the exception of one patient who apparently was never dosed with study medication, all cardiovascular events occurred in buprenorphine-treated patients. Five cases of chest pain were reported. The narratives for these cases do not indicate clear-cut cardiac diagnoses, though some patients were treated with cardiac medications. An additional case of angina was reported, though the basis for that diagnosis is not evident in the narrative. One patient had two related cardiac serious adverse events, congestive heart failure and endocarditis. The former was thought to be due to endocarditis-related valve disease, for which the patient underwent valve replacement. Two cases of hypertension were reported, including one in a patient with known hypertension and cocaine use, and one in a patient for whom few details were available. Two cases of myocardial infarction were reported, each in patients known cardiovascular risk factors. Each case was characterized as a mild myocardial infarction, and each was judged by the investigator to be possibly related to the study drug. One case of palpitations with shortness of breath was reported, though an evaluation was “negative”. One case of a deep venous thrombosis was also reported. Review of the individual serious adverse events in the Cardiovascular system does not point to any specified cardiac event or syndrome being related to a buprenorphine-containing product. In fact, only the two cases of myocardial infarction and the single case of palpitations were judged by the investigator to be “possibly” related to study drug. It is noteworthy, however, that all serious cardiovascular adverse events were reported in buprenorphine-treated patients – none was reported in methadone or placebo

treated patients. The significance of this finding is not clear, given the lack of specificity of the serious cardiovascular adverse events reported in the buprenorphine-treated patients.

Serious adverse events in the Central and Peripheral Nervous system were reported in seven patients. In five buprenorphine-treated patients, these events included one case of confusion (no other details), one case of dizziness (diagnosed as syncope), one case of migraine (in a patient with a history of headaches), and two cases of seizures (one in a patient with a history of seizures and one attributed to benzodiazepine withdrawal). Seizures were also reported in two methadone-treated patients. All seven patients continued in the study.

Serious adverse events in the Gastrointestinal system were reported in nine patients. These included one case each of epigastric pain, gastric ulcer, gastroenteritis, gastrointestinal bleeding, and strangulated intestine. Each of these events was judged by the investigator to be unrelated to study medication. Review of the narratives does not suggest a causative role for buprenorphine in those cases where sufficient information was presented. Three serious cases of vomiting were reported – two in buprenorphine-treated patients and one in a methadone-treated patient. In one of these cases, the investigator judged the vomiting as “possibly” related to buprenorphine because of that agent’s known effect on gastrointestinal motility.

Serious adverse events in the Immune System included one case of AIDS in a methadone-treated patient, and three cases of allergic reactions in buprenorphine-treated patients. In two of the buprenorphine-treated patients, an allergic reaction developed shortly after the first dose of study medication – three-and-one-half hours in one case and 20 minutes in the other case. The first case consisted of a generalized, pruritic body rash with respiratory distress and wheezing, which responded to anti-inflammatory treatment. The second case consisted of headache, ‘scrambled thoughts’, diarrhea, petechial rash, hives, watery eyes, and puffy eyelids. The event was judged to be definitely related to study medication. The third case of an allergic reaction was attributed to Bactrim.

Serious adverse events in the Infection and Infestation category included 11 cases of abscess, 9 cases of “infection” (various infections), one case of meningitis, and 10 cases of pneumonia. Each case in this category was judged to be unrelated to study medication. In all cases, the patient was hospitalized for treatment. Study medication was continued in all but three cases. Review of the narratives reveals no pattern of infection that would imply a causative role for a buprenorphine product.

Serious adverse events in the Injury and Poisoning category include 23 accidents and/or fractures. These events were diverse in nature. Though review of the narratives reveals no pattern of injury that would imply a causative role for a buprenorphine product, there is the possibility that buprenorphine could have impaired mental acuity to an extent sufficient to result in an accident. However, the narratives provide no evidence for such an effect.

Serious adverse events in the Liver and Biliary System include 48 reports of “elevated LFTs” and two cases of “hepatitis”. Hepatic issues are discussed more thoroughly in the section of this review that addresses LFT data.

Serious adverse events in the Metabolic and Nutritional system included one case each of dehydration and hypoglycemic collapse, both of which resulted in hospitalization and both of which were considered unrelated to study drug.

Serious adverse events in the Musculoskeletal system included five cases of back pain or herniated disc, as well as three other cases of joint disease. All cases were judged to be unrelated to study drug.

Serious adverse events in the Psychiatric system included six cases of anxiety, 26 cases of depression, 12 cases of detoxification, one case of dissociation, one case of drug abuse, one manic episode, 20 cases of overdose, two cases of "psychiatric episode" not further specified, eight suicide attempts, and five cases of suicidal ideation. Review of the narratives of the cases of anxiety and depression is notable for an underlying history of these disorders in some cases and alternative reasons for anxiety (eg, cocaine use) in other cases. Though many narratives lack sufficient information to make an assessment of the causality of the drug in the development of depression or anxiety, the narratives do not suggest a causal role for buprenorphine. All but one case of "overdose" involved substances other than the study drug, usually heroin, cocaine, alcohol, benzodiazepines, or some combination of these or other drugs of abuse. Most of these cases were judged to be unrelated to study drug. In one case (Subject 055/034 in Studies CR92/099 and CR92/100), the subject was given the wrong dosage of study medication (32 mg instead of 2 mg). She experienced some vomiting, but this resolved. No further problems were reported. Review of the cases of suicide attempt is notable for the fact that many of the subjects had a prior history of depression and/or polysubstance abuse. Most suicide attempts were with heroin or other substances (but not the study drug). All but one case of suicide attempt or suicidal ideation were judged to be unrelated to study drug.

Serious adverse events in the Renal and Urinary System include one case each of cholecystitis (not clear why this SAE was coded into this body system), nephrolithiasis, renal colic, and urinary tract infection. Each of these SAEs was judged to be unrelated to study medication. Review of the narratives provides no evidence to implicate the study drug in these events.

Serious adverse events in the Reproductive system included only one case of a termination of pregnancy in a methadone-treated woman.

Serious adverse events in the respiratory system included seven cases of asthma, one case of bronchospasm, one case of hemoptysis, three cases of obstructive pulmonary disease, and one case of respiratory arrest. Five of the seven cases of asthma were in patients with a prior reported history of asthma, and two of these required ventilatory support. In one of these cases (Subject 689/1037), the event was judged by the investigator to be "possibly" related to the study drug (Suboxone 16 mg), though the subject continued in the study. In all three cases of obstructive pulmonary disease, the patients had a prior history of COPD. In two of these three cases, the investigator judged the event to be "possibly" related to study drug (Suboxone 20 mg in both cases). The reason for the attribution is not clear, and the patients continued in the study. The case of respiratory arrest occurred in a patient who had been taking paroxetine and Subutex. He developed respiratory arrest (no details of the actual event are provided) and he was taken to a hospital, where he was found to have a "racing heart, high blood pressure and hypoxia on admission" (again, no details are available). No details of his hospital course are noted, except that he was in the hospital for 40 hours and received heparin and had "3 X-rays and an angiogram of the lungs" (results not provided). Though he was continued in the study, the investigator judged the event to be "possibly" related to the study drug.

Serious adverse events in the Skin and Subcutaneous system included four cases of cellulitis. Though one of these cases was judged to be "possibly" related to the study drug, all patients continued in the study.

Review of all the serious adverse event profile in the clinical studies suggests that the SAE profile is largely consistent with the known comorbidities present in a population of opiate addicts. An exception to this general statement is the case of allergic reaction, in which a direct causative role of the buprenorphine-containing products is likely. While the SAE profile does not strongly implicate the buprenorphine-containing products in any other serious adverse events, ongoing post-marketing surveillance will be required to examine trends in cardiovascular and hepatic morbidity, as well as cases of overdose.

## 6.5.2 Non-Fatal Serious Adverse Events in the Post-marketing Experience

The Sponsor has provided in the Periodic Safety Update Report an update of the post-marketing adverse event (see Attachment 3 contained in Volume 4 of the PSUR). The Sponsor has provided a tabulation of the most frequently-reported post-marketing adverse events (see Section 6.6, Volume 1, pages 55-56), both during the review period (February 1, 2000 through July 31, 2001) as well as a total (from 1995 through July 31, 2000). During the review period, there were a total of 507 adverse event reports, describing 985 adverse event terms. Review of this list is notable for the following:

- A total of 99 deaths were reported during the review period, bring the total to 114. The Sponsor attributes this large increase to delayed reported of earlier deaths. Deaths associated with the marketing of Subutex have been reviewed above.
- A substantial number of post-marketing adverse events were reported in the setting of pregnancy. The common adverse events, and the total number of reports from 1995 through July 31, 2001, are as follows: maternal drug exposure (n=91), withdrawal syndrome neonatal (n=142), weight decrease neonatal (n=16), feeding disorder neonatal (n=14), tremor neonatal (n=18), and growth retarded (n=9). The experience of buprenorphine use in pregnancy is summarized later in this review.
- A total of 51 reports of “drug interaction” were reported, with 50 of these being newly reported during the reporting period. Review of the individual cases indicates that at least 40 cases resulting in death involved use of Subutex with one or more other agents that act on the central nervous system (most commonly benzodiazepines, opiates, alcohol). In most cases the death was judged to be possibly related to Subutex. It is not known if overdoses of Subutex were involved. It appears that because the possibility of a drug interaction was noted in the adverse event report, the term “drug interaction” was reported in the listing. Review of the other deaths in the post-marketing adverse event listing is notable for other deaths in which multiple substances were reported, but the possibility of a drug interaction was not noted, and thus not recorded.
- The total number of hepatic-related adverse events includes hepatitis (n=39), SGPT increased (n=21), SGOT increased (n=20), jaundice (n=26), and cholestasis (n=5). These events are discussed elsewhere in the review of hepatic-related adverse events.
- A total of 12 cases of eye infection have been reported, all during the reporting period. The Sponsor notes it “can offer no explanation” for these reports. Review of the line listings reveals that 10 of these cases were reported by a pharmacist

who reported that patients were misusing Subutex by injecting it intravenously and who then later developed candidal ocular infections. At least one other case of eye infection was also associated with intravenous injection of Subutex. Additionally, 5 cases of “retinal disorder” appear to be related to fungal eye infection related to injecting drug use.

- There is a report that in “2 or 3” patients treated with sublingual buprenorphine “fasciitis to eosinophil appeared...one with abdominal localization.” The nature of this finding, as well as its outcome, is not reported.
- One case of thrombocytopenia (platelet count = 31,000), in a patient with HCV infection and on another medication (doliprane for bad dentition) was reported. The patient had been taking Subutex 8 mg for nearly four years. A “central origin” of the thrombocytopenia was apparently excluded, and its cause remained unknown.
- Some cases of overdose, both with buprenorphine and/or other substances, leading to death (either intentional or unintentional) are reported. In some cases, injection of Subutex was involved.
- One patient treated with Subutex (duration unknown) developed bronchospasm, for which the Subutex was stopped. Upon re-initiation of the Subutex the bronchospasm recurred. Subutex was stopped, and she was switched to methadone. No allergy was reported, though this case may be related to an allergic-reaction.
- Overall review of the post-marketing adverse events is notable for the substantial number of reports associated with intravenous injection of Subutex. Complications of such misuse of the drug include skin (injection site) reactions, infections (both systemic and local), hepatitis, and overdoses, which in some cases were fatal. These cases point not only to the complications of intravenous injection of Subutex, but also to the potential for such misuse of Subutex.

The post-marketing adverse events differ most substantively from the adverse events in the clinical trials due the number of reports related to intravenous misuse of the product, overdoses, and use of the product in pregnancy. The significance of one case of thrombocytopenia of unknown etiology, one case of possible allergic bronchospasm, and two or three cases of possible eosinophilic fasciitis is not clear. Additional post-marketing surveillance will have to define further the nature and significance of these events.

## **6.6 Overdoses**

In Section 7.3.3 of the PSUR (Volume 1, pages 156-163), the Sponsor summarizes the published literature regarding overdoses of buprenorphine, with a focus on overdose-related deaths.

The Sponsor cites two studies (one by Auriacombe and Tignol [JAMA 2001;285:45] and the other by Touzeau and Bouchez [presented at the 2001 CPPD]), which conclude that the death rate attributable to methadone overdoses is higher than that attributable to buprenorphine overdoses. The methodologies of these studies and the actual data would require detailed review to

substantiate this conclusion. As the raw data are not available, the validity of this claim can not be assessed.

The Sponsor also presents the results of a retrospective study by Tracqui et al (Journal de Medecine Legale Droit Medicale 1999;42;3-10) which notes that opioid-related deaths are often complicated by at least one non-opioid substance, such as benzodiazepines, cannabis, or alcohol.

The Sponsor present the result of a study by Kintz (Forensic Science International 2001;121:65-69), in which 117 deaths due to buprenorphine were reviewed. Risk factor for overdose fatalities included injection of crushed tablets and concomitant usage of other agents acting on the central nervous system (such as benzodiazepines, neurolopetics, cannabis, cocaine, or alcohol).

The above data are consistent with the known overdose potential of opioid agents. The Sponsor notes that in France, the overall death rates attributed to heroin overdose declined dramatically, a reflection of the success of opioid-substitution therapy and the easing of restrictions that allow any physician to prescribe Subutex. Review of such an assessment is beyond the scope of this review.

## **6.7 Misuse and Abuse of Oral Buprenorphine**

The Sponsor presents the results of a variety of surveys and other studies in France that note that intravenous use of Subutex tablets is a common form of misuse and abuse. The data presented are largely from surveys in France. One report noted that some patients went from one physician to another in search of multiple prescriptions for Subutex. The overall conclusion is that misuse and abuse is most common by means of the intravenous route of administration. The potential for abuse or misuse via the oral or sublingual routes was not addressed. A population estimate of the frequency of misuse and/or abuse is not provided.

## **6.8 Other Significant Adverse Events**

### **6.8.1 Adverse Events Resulting in Study Drug Discontinuation, Dose Reduction, or Temporary Study Drug Interruption**

The Sponsor reports that 93 subjects had adverse events that led to study drug discontinuation or to dose changes. Based on a listing of these AEs (see Section 3.5 of April 4, 2002 submission) it appears that all but four of these events were previously reported. Most of these events were listed as "non-serious". The most common adverse event required study drug discontinuation was "withdrawal" (n=13.) Nausea, vomiting, and a combination of these two events also accounted for a total of 14 discontinuations. The remainder of AEs in this category were varied in nature. Two cases of allergic reaction appear to be a direct result of Subutex treatment. Other events, such as dizziness, nausea, and vomiting are commonly associated with opioids. The remaining adverse events in this category are generally consistent with those expected in a population of opiate addicts.

## **6.9 Overall Evaluation of Adverse Events**

### **6.9.1 Common Adverse Events in Clinical Trials**

Review of common adverse events was not a focus of the safety update or of this review, though the Sponsor was asked in the Approvable letter of January 26, 2001 to include “tabulation of common adverse events associated with the use of Suboxone, Subutex, and buprenorphine sublingual solution.” In response to a request by the Agency asking the Sponsor to identify the location of a tabulation of common adverse events, the Sponsor responded (see April 24, 2002 submission) that “there are no new relevant AE data to integrate for Suboxone and buprenorphine solution” and noted that these data are contained in the original NDA (ISS Volumes 1 and 2, NDA Volumes 153 and 154). The Sponsor further notes that additional data for Subutex comes from Study CR96/005, which was submitted after the ISS was prepared and contains adverse events following 13 weeks of treatment with Subutex or methadone.

In the April 24, 2002 submission, the Sponsor has presented an integrated listing of Subutex adverse events. In the original NDA, Subutex was administered to 103 subjects. In the new study CR96/005, Subutex was administered to an additional 192 subjects. Thus, revised adverse event frequency data are based on 295 subjects. The most common adverse events in this new group (n=295) are as follows:

Common Adverse Events (>5%) in Pooled Subutex Studies			
Body System	Adverse Event	Frequency (n=295) (%)	Change from Prior Frequency (n=103) (%)
Body as a Whole	Headache	18.64	-10.48
Nervous System	Insomnia	15.93	-5.43
Body as a Whole	Withdrawal Syndrome	13.56	-4.89
Body as a Whole	Pain	15.59	-2.85
Digestive System	Nausea	16.95	3.36
Skin and Appendages	Sweating	13.90	1.28
Body as a Whole	Infection	7.12	-4.53
Body as a Whole	Pain, Abdomen	8.81	-2.84
Respiratory	Rhinitis	6.44	-3.27
Body as a Whole	Pain, Back	6.78	-0.99
Body as a Whole	Chills	7.12	-0.65
Digestive System	Vomiting	8.47	0.71
Digestive System	Constipation	9.49	1.72
Body as a Whole	Flu Syndrome	5.08	4.11

Source: Table 2 in April 24, 2002 Submission

Review of the above table indicates that the common adverse events recorded in subjects taking Subutex are consistent with those expected in a population of opiate addicts being treated with an opioid for opiate addiction.

## 6.9.2 Adverse Events in the Published Literature

The Sponsor notes in the April 24, 2002 submission that “published reports of adverse events associated with buprenorphine use are routinely recorded on the Reckitt Benckiser and Schering Plough adverse event databases.” Because adverse events from the published literature are incorporated into the post-marketing safety database, which was reviewed above, these adverse events will not again be reviewed here.

## 6.10 Analysis of Hepatic-Related Adverse Events

The potential for buprenorphine to cause hepatic injury and other hepatic-related adverse events and laboratory abnormalities has been noted throughout the development of the two products. While hepatic abnormalities have been noted in subjects taking buprenorphine, the causative role of buprenorphine, if any, has been difficult to determine. The challenges to determining the role of buprenorphine in the development of hepatic abnormalities have been discussed and summarized by Dr. Winchell in her reviews of November 16, 1999 and December 22, 2000. In brief, some of the issues that confound and complicate the interpretation of the hepatic data include:

- Baseline LFT abnormalities are common in the population studied.
- Co-morbid illnesses, such as Hepatitis B or C infection, are frequent in this population
- Some subjects acquire Hepatitis B or C infection during the course of the clinical trials
- Concomitant alcohol abuse, when present, can lead to hepatic abnormalities
- In some studies, lack of a placebo group has made interpretation of the data difficult
- Literature reports of buprenorphine-associated hepatic abnormalities have lacked appropriate controls

Dr. Winchell's review of December 22, 2000 noted that data from Bickel et al, provided by Dr. Bickel to the Sponsor and included in the July 28, 2000 submission, indicated that subjects with a history of hepatitis were more likely to have significant increases in LFTs. Using data from placebo-controlled trial CR96/013 and its follow-on study CR096/014, Dr. Winchell determined that majority of patents who had significant increases in LFT measures (AST, ALT, GGT, and total bilirubin) were those who had a history of hepatitis. She also noted that both buprenorphine-treated patients and placebo-treated patients with a history of Hepatitis C had fluctuations in LFTs. In patients treated with buprenorphine during an uncontrolled, open-label extension, patients with a prior history of hepatitis were more likely to have significant abnormalities in LFTs compared to buprenorphine-treated patients with no such history. However, as Dr. Winchell noted in her review, the lack of a placebo control makes interpretation of these data difficult.

In the approvable letter of January 26, 2001, the Division asked for a period safety update, with the following request pertaining to hepatic function data:

*This update should specifically examine the potential for buprenorphine-induced hepatotoxicity, the role of viral hepatitis in increasing vulnerability to hepatotoxicity, and the proper approach to prevention and management of hepatic adverse events. Analyses should focus on outliers and extreme values, rather than measure of central tendency, and should provide comparison groups wherever available. Data sets with unique patient identifiers should be submitted together with reports of the analyses. The analyses of uncontrolled studies of buprenorphine should compare the course seen in treated patients to the natural history of enzyme fluctuation in viral hepatitis.*

To address this request, the Sponsor has submitted the following information:

- Data from 5 clinical trials, comprising 1615 patients, in which hepatic parameters were measured at baseline and at regular intervals during treatment.
- Data from 8 clinical trials, comprising 1597 patients, in which hepatic parameters were measured at baseline and occasionally during treatment, including data from a publication by Petry et al. (ie, the same data provided by Dr. Bickel).
- Information from an additional 6 publications describing 12 hepatic cases
- Information on 103 cases of hepatic adverse events reported following the marketing on Subutex, from launch through the end of July 2001.

## 6.10.1 Review of Published Literature

### 6.10.1.1 Review of Pre-Clinical Data in the Literature

The Sponsor cites a paper by Berson et al (Mechanisms for experimental buprenorphine hepatotoxicity: major role for mitochondrial dysfunction versus metabolic activation), in which the authors suggest that while both buprenorphine and norbuprenorphine undergo metabolic activation, only buprenorphine impairs mitochondrial respiration and ATP formation, an effect that may lead to hepatic dysfunction. The authors note, however, that the concentrations needed to observe this effect were about 250 time the maximum expected therapeutic concentration of buprenorphine.

The Sponsor also cites data by Hayase et al (Relationship between cocaine-induced hepatotoxic neurobehavioral and biochemical changes in mice. The antidotal effects of buprenorphine). This paper noted that cocaine resulted in an elevation in ALT and a reduction in liver ATP, effects that were significantly reduced by low doses of buprenorphine. At higher doses, cocaine appeared to exacerbate the biochemical changes, though buprenorphine itself produced no biochemical changes.

### 6.10.1.2 Review of Clinical Data from the Literature

The Sponsor has presented cases from the published literature, which are summarized in the table below:

Authors/Citation	Summary
Hirschauer et al. Is buprenorphine hepatotoxic?	Patient taking buprenorphine for chronic pain developed cytolytic hepatitis 3 months after starting buprenorphine treatment. LFTs resolved after withdrawal of buprenorphine, but rose again after its re-introduction. LFTs again resolved after withdrawal. Authors postulated an immunoallergic reaction, but could not exclude a direct hepatotoxic effect.
Dol et al. Edema in the legs in an HIV-seropositive patient: a secondary effect of ritonavir?	Patient taking ritonavir, buprenorphine, and multiple other medication developed leg edema, which resolved after ritonavir was discontinued. Relevance of this to buprenorphine-related hepatotoxicity is not clear.
Houdret et al. Hepatonephritis and massive ingestion of buprenorphine	Patient with history of chronic paracetamol/codeine use also receiving Subutex for codeine dependence. No evidence of viral hepatitis or alcoholism. Severe hepatitis, with elevated total bilirubin, AST, ALT, alkaline phosphatase GGT, and ammonia, was noted. Prothrombin time was 20%, and Factor V was 16%. Buprenorphine levels of 224 ng/mL (far above the therapeutic range) was noted. Paracetamol levels were within the normal ranges. Measurements for alcohol, codeine and morphine were negative. LFTs returned toward

Authors/Citation	Summary
	normal after buprenorphine was discontinued. Renal failure required 5 dialysis sessions, but renal function also returned to normal. The subject reportedly made a complete recovery.
Zylberberg et al. Dilated bile duct in patients receiving narcotic substitution.	The authors report 3 cases dilated bile ducts (without obstruction) in 36 patients receiving narcotic substitution (buprenorphine or methadone). Among 298 injecting drug users not receiving substitution, there was only one case of a dilated bile duct without obstruction. The narcotic substitution treatments that the patients were receiving is not known.
Petry et al. Elevated liver enzyme levels in opioid-dependent patients treated with buprenorphine.	Authors report that AST and ALT levels increase with buprenorphine, in a manner that appears to be dose related. LFT data from this study are reviewed below.
Wisniewski et al. Acute hepatitis related to intravenous injection of buprenorphine in a drug addict on maintenance treatment	A case of hepatitis developed in a patient with a history of chronic viral hepatitis C and heroin addiction on buprenorphine maintenance who also regularly injected buprenorphine intravenously after dissolving a 0.4 mg tablet in water. The hepatitis resolved after the injections of buprenorphine stopped.
Berson et al. Hepatitis after intravenous buprenorphine misuse in heroin addicts.	Five patients who misused buprenorphine by injecting it developed hepatitis. Four of the five had hepatitis C, and all five had HIV infection. The condition resolved promptly in four of the five patients after intravenous use of buprenorphine stopped.
Source: Volume 5, Section 2.3, pages 4-10.	

### 6.10.2 Review of Individual Study LFT Values

The Sponsor has submitted data LFT data in two SAS transport files for the following studies:

- CR90/069
- CR92/099 and CR92/100
- CR96/013 and CR96/014
- CR88/130
- CR90/066
- CR92/102
- CR95/002
- CR96/005
- CR96/008
- CR96/024

In addition, the Sponsor has submitted LFT data from a published study by Petry et al in one of the SAS transport files (same data previously provided by Dr. Bickel).

For each of these studies, patients with no LFT data are not included in the dataset.

The Sponsor has presented narratives for all subjects who had a baseline LFT assessment and at least one on-treatment assessment or had only on-treatment assessments, where at least one LFT (AST, ALT, alkaline phosphatase, or total bilirubin) was “possibly clinically abnormal”. The Sponsor has defined “possibly clinically abnormal as follows:

- AST:  $\geq 3$  times upper limit of normal range
- ALT:  $\geq 3$  times upper limit of normal range
- Alkaline Phosphatase:  $\geq 3$  times upper limit of normal range
- Total Bilirubin:  $\geq 3$  times upper limit of normal range

The Sponsor noted that the clinical comments that it has included in the narratives are “based solely on data recorded by the investigator in the individual clinical record for each subject...Any comments do not necessarily represent the views of the Sponsor.”

For some studies, information on the subjects’ history of hepatitis (either reported or documented with serology) is presented. In the majority of studies, however, such information was not collected.

The Sponsor notes, in Section 3.4 of the revised Hepatic Report (April 5, 2002 submission, page 40) that LFT data on 2847 subjects were available. Of these, 350 (12.3%) were “hepatic cases”, defined by the Sponsor as having an elevation in hepatic enzymes, but upon review and subsequent confirmation by the Sponsor, it was determined that these cases are strictly those with at least one “Clinically abnormal” LFT value post-baseline, or at baseline if post-baseline data were available. Of the 350 Sponsor-reported hepatic cases, 249 occurred in patients receiving buprenorphine. Eighty-nine patients had documented HCV infection, and 58 had documented HBV infection, though not all patients underwent routine hepatic serological tests.

#### **6.10.2.1 Data from Petry et al**

Petry et al conducted a retrospective analysis of the relationship between buprenorphine and abnormal LFTs in 120 subjects, who had previously taken part in a number of clinical studies of sublingual buprenorphine solution. This research forms the basis of the publication “Elevated liver enzyme levels in opioid-dependent patients with hepatitis is treated with buprenorphine” (Petry NM, Bickel WK, Piasecki D, Marsch LA Badger GJ. The American Journal on Addictions 2000;9:265-269). Measurements were taken before treatment and following a minimum of 40 days post-treatment with buprenorphine sublingual solution (2, 4, or 8 mg/70 kg per day). The Petry publication observed that among patients with a history of hepatitis, AST and ALT levels increased with buprenorphine treatment. They also concluded that the odds of increase in AST levels increased with buprenorphine dose. Review of the Petry et al publication indicates that the statistical methodologies used are not fully described. Specifically, the paper does not describe which post-baseline value of an LFT was used when multiple post-baseline values were available. Thus, the analysis of Petry et al will not be replicated for this review.

The investigators have provided the Sponsor with the data from their study.

The Sponsor notes that of the 120 patients enrolled in the study, “33 had AST and/or ALT values that were greater than or equal to three times the upper limit or normal either at baseline or during treatment. Review of the data provided by the Sponsor indicates that 33 patients had at least one ‘clinically abnormal’ value of AST and/or ALT at baseline or post-baseline. Furthermore, the Division’s review of the Sponsor’s data indicated that 76 patients had at least one LFT value above the upper limit of normal at baseline and/or post-baseline. Seventy patients had some sort of history of hepatitis noted, though the degree of documentation underlying these reports is not clear.

Of the 33 patients with at least one clinically abnormal LFT, 28 reported or had recorded a history of hepatitis B, hepatitis C, or both. Of the remaining 5 patients, 3 had a hepatitis status noted as “none recorded”, one was “negative”, and one was “recorded”, but was not further specified.

Patients who had at least one clinically abnormal LFT received daily buprenorphine doses ranging from 2 mg/day to 11.4 mg/day. Review of these patients' LFT indicates the following:

- Baseline LFT values were frequently abnormal. In the 33 patients who had at least one clinically abnormal LFT value at any time point, 15 had at least one clinically abnormal LFT value at baseline.
- Clinically abnormal values of AST and ALT were much more common than clinically abnormal values of GGT, alkaline phosphatase, or total bilirubin. Clinically abnormal values of GGT, alkaline phosphatase, and total bilirubin were very uncommon, while nearly each subject with a clinically abnormal LFT value had an abnormality, at some point, of AST and/or ALT.
- Fluctuation in LFT values, especially AST and ALT were common. There is insufficient information to determine if changes in dose, if they occurred, correlate with changes in LFT values in individual subjects

Examples of some interesting cases from this study follow:

- One subject (V5074\_0098) had an AST value (295 U/L) more than three times the upper limit of normal (50 U/L) and a total bilirubin value (2.1 mg/dL) above 2.0 mg/dL. However, this measure was taken at baseline. This subject had a history of hepatitis B and hepatitis C, and was treated with buprenorphine liquid 5.5 mg. On Study Day 48, the AST had decreased to 206 U/L and the total bilirubin had decreased to 1.6 mg/dL.
- One subject (V5074\_0009) had an AST value (183 U/L) more than three times the upper limit of normal (45 U/L) and an ALT value (294 U/L) more than three times the upper limit of normal (41 U/L) at baseline. The subject, who had serologically documented hepatitis B and hepatitis C, received 82 days of buprenorphine treatment, with one dose level recorded as 11.4 mg. The last on-treatment LFT measures, recorded on Day 69, were AST 238 U/L and ALT 405 U/L. Several post-treatment measures were recorded, and by Day 222 AST was 483 U/L and ALT was 737 U/L. Total bilirubin, which was 0.3 mg/dL at baseline, was 0.9 mg/dL on Day 222.
- One subject (V5074\_0035) had negative serologies for Hepatitis A, B, and C. Baseline LFT values normal for all LFTs (AST, ALT, GGT, alkaline phosphatase, and total bilirubin). The first set of post-baseline LFT values, on Day 45, revealed AST 798 U/L, ALT 569 U/L, GGT 761 U/L, Alk Phos 194 U/L and total bilirubin 0.5 mg/dL. By Day 59, these values were AST 1465 U/L, ALT 1265 U/L, GGT 1907 U/L, Alk Phos 440 U/L and total bilirubin 0.6 mg/dL. Serologic assessment at Day 55 confirmed that she was negative for Hepatitis A, B, and C. LFT measurements from Day 66 onward revealed a decrease in the LFT values, though they continued to fluctuate. Values on Day 108 were AST 171 U/L, ALT 124 U/L, GGT 255 U/L, Alk Phos 93 U/L and total bilirubin 0.4 mg/dL. Two weeks after treatment ended, on Day 129, the LFT values were AST 139 U/L, ALT 88 U/L, GGT 280 U/L, Alk Phos 119 U/L and total bilirubin 0.7 mg/dL. No further clinical details are available. This case is notable for the fact that the subject was seronegative for three forms of viral hepatitis, had normal LFTs at baseline, and nonetheless had a dramatic on-treatment increase in LFTs, which partially normalized while still on treatment.

In summary, the data from Petry et al indicate that hepatitis is common in the population they studied and that LFTs, especially AST and ALT, are frequently abnormal prior to buprenorphine treatment. The data also point out the fluctuations in LFTs that patients with hepatitis experience. The case of patient V5075-0035, a patient with clinically abnormal LFTs in the study who was documented to be seronegative for three forms of viral hepatitis, suggests that buprenorphine may result in liver injury. However, the lack of additional medical information, as well as the lack of a placebo comparator, limits any conclusion that can be made from this observation.

#### **6.10.2.2 Study CR88/130**

Study CR88/130 was a randomized, double-blind, double-dummy, parallel-group, multiple-dose study comparing sublingual buprenorphine (8 mg/day) to two fixed doses of oral methadone (20 mg/day and 60 mg/day). One-hundred-sixty-two patients were entered into this study. Laboratory tests were planned for screening, and at days 60, 90, 120 and 180 days. Hepatitis history was not recorded in this study.

The Sponsor notes that 17 patients had LFTs that were clinically abnormal at some point during the study.

Review of the Sponsor's hepatic data from Study CR88/130 reveals the following:

- LFT abnormalities, either "high" or "clinically abnormal" were common both at baseline and post-baseline. LFT elevations, including transient elevations, were common in all treatment groups.
- Two buprenorphine-treated patients, and 15 methadone-treated patients, had at least one clinically abnormal LFT value.
- No buprenorphine-treated subject had an clinical abnormality of either alkaline phosphatase or of total bilirubin.
- Two subjects with at least one transaminase (AST or ALT) above three times the upper limit of normal and a total bilirubin value above 2.0 mg/dL were in the methadone groups.
- Many LFT increases that occurred during the study became less severe by the end of the study. However, it is not clear if there were dose reductions or other study medication-specific factors that contributed to this reduction. For example, patient B0090\_2287 (treatment = buprenorphine liquid) had a baseline AST/ALT of 35/76 (ULN = 37/40). These values increased to 128/237 by Day 59, and then were 23/27 on Day 121 and 15/16 on Day 181. Buprenorphine-treated patient 0090\_2415 had baseline AST/ALT 25/29, which increased to 76/80 (Day 61), then to 77/124 (Day 92), and then to 38/51 (Day120). The Sponsor's report attributes each of these cases to excessive alcohol intake.

Review of these data underscores the prevalence of LFT abnormalities in this population. It appears that methadone-treated patients had a higher frequency of clinically abnormal LFTs and two methadone treated patients had both clinically abnormal LFTs and a simultaneously clinically abnormal total bilirubin. The role of buprenorphine, if any, in the development of hepatic abnormalities is confounded by the presence of alcohol intake in the two buprenorphine-treated patients who developed clinically abnormal LFTs.

### 6.10.2.3 Study CR90/069

Study CR90/069 was a 12-month double-blind, double-dummy study in 225 subjects, which compared the 8 mg buprenorphine sublingual solution to 30 mg methadone and to 80 mg methadone. There were 75 patients in each of the three treatment groups. Treatment continued for up to 52 weeks.

Laboratory measures were assessed at screening and planned at every 4 weeks of the study and at termination. Serological analysis for viral hepatitis was not performed.

In all patients, the most common abnormalities were in AST and ALT. No buprenorphine-treated patient had a "clinically abnormal" total bilirubin. Two subjects, both of whom were treated with methadone, developed post-baseline abnormalities of AST/ALT above three times the upper limit of normal with simultaneous elevation of total bilirubin above 2.0 mg/dL. In one case (L9069\_0041) these abnormalities were attributed to alcoholic liver disease. In the other case (L9069\_0154) there were no clinical comments. In most patients, including buprenorphine-treated patients, LFT abnormalities followed a fluctuating course.

Examples of some of the patterns of clinically abnormal LFTs in buprenorphine-treated patients include the following:

- The Sponsor notes that 41 subject had clinically abnormal LFTs at some point during the study. Review of the data suggests that the Sponsor is referring to patients who had at least one "clinically abnormal" LFT at baseline (with follow-up data available). Eleven of the patients were treated with buprenorphine, 12 were treated with methadone 30 mg, and 18 were treated with methadone 80 mg.
- Subject L9069\_0037, treated with buprenorphine liquid, had a more than two-fold increase in AST, ALT and GGT during treatment, although baseline values of each of these enzymes were elevated. This subject was terminated because of alcohol abuse.
- Subject L9069\_0128 had a baseline ALT that was minimally elevated (52 U/L, ULN=45 U/L) with normal AST (41 U/L, ULN=45 U/L) at baseline. At the first post-baseline LFT measurement on Study Day 25, AST had increased to 99 U/L and ALT had increased to 170 U/L. These transaminases remained elevated, though less severely so, at Study Day 53 (AST=66, ALT=141), and were lower, though still above the upper limit of normal, at Study Day 80 (AST=53, ALT=82). No further values of AST and ALT were measured, as the subject was terminated from the study because of continued opiate usage.
- Two buprenorphine-treated subjects with normal LFTs at baseline developed clinically abnormal LFTs during treatment, which improved on continued buprenorphine treatment in each case. Subject L9069\_0155 had an increase in ALT which peaked at 138 U/L (ULN=45 U/L) on Day 82, and returned to normal by Day 166. Subject L9069\_0190 had an increase in AST which peaked at 141 U/L (ULN=45) on Study Day 218, and which decreased to 65 U/L by Day 274. AST remained high for this subject, and the final value on Study Day 359 was 99U/L. It should be noted that this subject had increases in ALT and GGT that were first documented on Study Day 134, which never met criteria for "clinically

abnormal” but which also never returned to the normal range. No clinical comments that could possibly shed light on these cases were recorded for either of these cases.

These data do not further clarify the role of buprenorphine in opiate addicted being treated with buprenorphine. The high numbers of patients with clinically abnormal LFTs in each of the three treatment groups underscores the high prevalence of LFT abnormalities in this patient population.

#### **6.10.2.4 Studies CR92/099 and CR92/100**

Study CR92/099 was a multicenter, double-blind, multiple-dose, parallel-group study comparing four doses of buprenorphine sublingual solutions (1, 4, 8, and 16 mg/day). Subjects attained the target dose by rapid induction over five days, and were maintained on their daily doses of a total period of 16 weeks. The trial enrolled 731 subjects, with approximately one-quarter of the subjects enrolled at each dose level. A total of 375 subjects completed the 16-week study. Most subjects (43% of early terminators) who discontinued prematurely did so because they were classified as “No Shows”. Adverse events accounted for 7% of early terminators and “reasons unrelated to the study” accounted for 24% of early terminators. The Sponsor’s summary of this trial notes that “there were positive dose responses for SGOT, SGPT, and BUN, and negative dose responses for GGT, glucose, WBC, RBC, hemoglobin and hematocrit.” However, data to support these associations are not provided.

Study CR92/100 was a double-blind, multicenter study in patients who completed the 16-week study CR92/099. Subjects in study CR92/100 were maintained on treatment for period of up to one year. A total of 180 patients completed the study. About 50% of patients who did not complete the study were reportedly terminated from the study “for reasons unrelated to the treatment and/or study.” No patients reportedly terminated the study because of adverse events.

Laboratory measurements were undertaken at screening and at 2,4, 8, 12 and 16 weeks in Study CR92/099 and at 28, 40 and 52 weeks in the extension phase (Study CR92/100) or when termination occurred.

The Sponsor reports that a total of 131 of the 731 subjects (17.9%) had clinically abnormal LFTs at some point. Viral hepatitis measures were reported for only a small number of patients. Twenty-one patients had either a history of hepatitis B or C or had serologically confirmed hepatitis B or C. Four patients were documented to be serologically negative for Hepatitis B. An additional twelve patients had a history of unspecified hepatitis, and three others had a history of hepatitis A. Twelve patients had alcohol consumption reported as a potential confounding factor.

Review of the LFTs from the patients with at least one clinically abnormal LFT values reveals the following:

- Baseline abnormalities (either clinically abnormal values or values above the upper limit of normal that did not meet criteria for clinically abnormal) were common.
- Abnormalities of transaminases were more common than abnormalities of alkaline phosphatase or total bilirubin.
- LFT abnormalities fluctuated throughout the course of the study. For example, patient M0999\_75073 had clinically abnormal values of ALT, starting from 188

U/L at baseline, peaking to 191 U/L on Study Day 29, and decreasing to 84 U/L on Study Day 84. No further measures were taken. AST and GGT values were high throughout, but were never clinically abnormal. Alkaline phosphatase and total bilirubin values were normal throughout. The narrative offers no reason for this patient's abnormal LFTs, nor does it offer any reason for the fluctuating course.

- On at least one visit, six subjects had both a clinically abnormal transaminase (ie, AST and/or ALT above three times the upper limit of normal) and a total bilirubin value greater than 2.0 mg/dL. These patients are summarized in the table below:

Patient	Hepatitis History	Study Day of Abnormality	Liver Function Test			Clinical Comments
			AST	ALT	T Bili	
M0999_05715	Unknown	-1	113	51	3.5	Treated with INH and rifampin for TB during the first 8 weeks of treatment. T bili normalized by day 86, and LFTs improved, but remained high though final measure on Day 112.
		15	199	125	5.3	
		31	173	108	2.9	
M0999_05908	Unknown	113	145	86	2.0	LFTs were clinically abnormal at baseline, including markedly elevated GGT (1274 U/L) which remained high throughout the study. At week 24, he was reported to have Hepatitis C (but with no serological confirmation available) and pancreatitis (of which he had a history). LFTs were improved at Day 139, then worsened at Day 163. They began to improve at Day 172, and continued improvement at Days 200 and 208, but began to rise again at Day 250.
		163	331	54	6.2	
		172	131	57	2.3	
M0999_64226	Unknown	360	121	95	6.8	LFTs were basically normal at baseline, except for GGT which was 76 U/L (ULN=75U/L). GGT generally increased throughout therapy, while other LFTs remained generally unremarkable until Day 289, when AST rose to 339, ALT rose to 236, and GGT rose to 623. On The next LFT measurements on Day 360 showed improvement in AST, ALT, and GGT (121, 95, and 576, respectively), though total bilirubin, which had been normal throughout, was now 6.8 mg/dL. No further LFT measurements were made. Isoniazid was started at about week 32, but was stopped over concern that this was the cause of the increased LFTs.

Patient	Hepatitis History	Study Day of Abnormality	Liver Function Test			Clinical Comments
			AST	ALT	T Bili	
M0999_64228	Unknown	0	139	49	2.2	This abnormality was noted at baseline. GGT values were also high and remained high (generally above 3 times the upper limit of normal) throughout the study. AST continued to remain high, as did ALT, though ALT values were generally lower than AST values. No clinical comments were available to shed light on this case.
M0999_67280	Unknown	153	222	279	20	LFTs at baseline and through Day 113 were generally mildly elevated. The dramatic increase in AST, ALT, and total bilirubin was attributed to the diagnosis of hepatitis A.
		157	287	990	14	
M0999_75041	Unknown	127	2770	3010	12	LFT were generally minimally to mildly elevated throughout the study through Day 113. The dramatic increase on Day 127 was attributed to "acute hepatitis" though no further details or follow-up are available.
M0999_75067	History of Hepatitis	267	1240	2180	6.4	LFTs were normal from baseline through Day 197. The abrupt rise in LFTs was associated with icterus. LFTs were improved on Day 281, and were normal at the final measurement on Day 327. No further details are available.
		271	132	665	2.6	

In summary, review of the LFT data from Studies CR92/099 and CR92/100 are notable for a high frequency of baseline LFT abnormalities as well as a high frequency of post-baseline LFT abnormalities, especially in AST and ALT. The LFT abnormalities are generally characterized by a fluctuating course. Review of the cases of simultaneous clinical abnormalities of AST/ALT and total bilirubin are notable for reasonable explanations in some cases (eg, acute hepatitis A in patient M0999\_67280). However, in some cases (M0999\_75067) the lack of any clinical information or follow-up leaves open the possibility that buprenorphine may have a causative role.

#### 6.10.2.5 Study CR95/002

Study CR95/002 was a randomized, double-blind, parallel-group study of three dose levels of Suboxone tablets (4 mg, 8 mg, and 16 mg), with induction doses of either 4 mg or 8 mg. The study enrolled 25 patients, with low to moderate levels of opioid dependence and no prior exposure to methadone. Patients received a single daily dose of study drug for 6 weeks, and could then be enrolled into a "continuation phase" until the last patient completed the pilot study.

One patient had post-baseline clinically abnormal LFTs: