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IV. RECOMMENDATIONS

A. OPDRA has no objections to the use of the proprietary name, Suboxone.

B. OPDRA recommends the above labeling revisions which might lead to safer use of the product.

OPDRA would appreciate feedback of the final outcome of this consult (e.g. copy of the revised label/labeling/packaging). We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Lauren Lee, Pharm.D. at (301)827-3243.

[/S/] 11/1/99

Lauren Lee, Pharm.D.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

[/S/] 11/1/99

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

APPEARS THIS WAY
ON ORIGINAL

ABUSE LIABILITY REVIEW

NDA #: 20-733

TRADE NAME: SUBOXONE®

DRUG: Buprenorphine Hydrochloride /Naloxone Hydrochloride Sublingual Tablets

SPONSOR: Reckitt & Colman Pharmaceuticals, Inc.
(The National Institute on Drug abuse (NIDA) and Reckitt & Colman have entered a Cooperative Research & Development Agreement (CRADA) to develop the product for the indication. Through NIDA-funded studies, buprenorphine has been studied for the indication under 47 different INDs)

PROPOSED INDICATION: Treatment of Opiate Dependence

DOSAGE FORMS: Sublingual tablets of 2 mg buprenorphine + 0.5 mg naloxone and 8 mg buprenorphine + 2.0 mg naloxone

DATE OF NDA SUBMISSION: June 7, 1999

DATE OF REVIEW: October 7, 1999

REVIEWER: Michael Klein, Ph.D. [/S/]

The Sponsor submitted for Agency review the following data and information in NDA # 20-733, as the abuse liability section of the NDA:

1. Summary and description of drug abuse and dependence studies on buprenorphine dosage forms.

   This includes some preclinical studies described in the original buprenorphine product (Buprenex; NDA # 18-401) which are applicable to the abuse liability assessment of the NDA # 20-733 and # 20-732.

2. Actual experience reports of abuse of sublingual preparations of buprenorphine marketed worldwide:

   a. France
   b. New Zealand
   c. United Kingdom
   d. Ireland

e. Scotland
f. Spain
g. India
h. Australia
i. Others (Belgium, Sri Lanka, Germany)

3. Description of issues related to abuse in NDA clinical, pharmacokinetics and chemistry sections.

4. Recommendation in the form of an eight factor analysis to place the combination product and the single entity buprenorphine (Subutex®) product (NDA # 20-732) into Schedule V. Although buprenorphine was recommended for Schedule III in the pharmacology/toxicology review (March 12, 1981), final placement of the product and substance was in Schedule V (1985).

In addition, subsequent to filing the original submission, the National Institute on Drug Abuse (NIH/NIDA/MDD) provided additional data:

1. Information on overdoses of buprenorphine reported in France.

2. Results of a NIH-funded study (U.S. Public Health Service Research Scientist Award K05 DA00050, Scientist Development Award K02 DA 00332, and R01 DA08045 from the National Institute on Drug Abuse) entitled "Effects of buprenorphine versus buprenorphine/naloxone tablets in non-dependent opioid abusers" that has been sent to the journal Psychopharmacology for publication.

BACKGROUND:

Jasinski *et al.* (1978) were the first to look at the pharmacology and abuse potential of buprenorphine. Incarcerated male volunteers with histories of narcotic addiction were given single or repeated doses of buprenorphine. The single dose study showed buprenorphine to have typical morphine-like effects. However, unlike morphine which produces effects for approximately 4 to 5 hours, buprenorphine was found to produce effects through a 72-hour observation period following administration. Initially in the repeated dose study, 5 subjects were administered daily doses of buprenorphine. Three of the 5 subjects completed the experiment and received buprenorphine for 57 consecutive days. After the 57th day, buprenorphine was abruptly discontinued. Several days after the cessation of buprenorphine was abruptly discontinued. Several days after the cessation of buprenorphine, subjects began experiencing severe withdrawal symptoms which were alleviated by gradual, decreasing doses of morphine and diazepam.

Jasinski *et al.* felt that any substance that has the ability to produce subjective morphine-like feelings of euphoria, and which can lead to physical dependence has the potential for abuse. Buprenorphine was shown to have both of these properties. However, because of its long-lasting effects and the low doses needed to induce morphine-like euphoria, the

potential for abuse was judged to be less than that of heroin and addicts might be successfully maintained on doses administered less frequently than once daily. However, with increasing numbers of reports of abuse of buprenorphine, that conclusion has been increasingly questioned. (Jasinski D. R., Pevnick J. S., Griffith J. D. Human pharmacology and abuse potential of the analgesic buprenorphine. Arch. Gen. Psych., 35:501-516, 1978).

ABUSE POTENTIAL STUDY OF SUBLINGUAL BUPRENORPHINE PRODUCTS

Study: Effects of Buprenorphine Versus buprenorphine/Naloxone Tablets in Non-dependent Opioid Abusers

Investigators: [redacted]

Rationale: The characteristics and abuse potential of intact buprenorphine and buprenorphine/ naloxone tablets in non-dependent opioid abusers has not been determined. Non-parenteral abuse of opioids such as buprenorphine may be more likely in people who have less severe substance abuse disorders (that is, are not physically dependent upon opioids). While non-dependent opioid abusers may dissolve and inject tablets, such populations with less severe levels of opioid abuse will have lower rates of injecting drug use. These non-dependent abusers may experiment and abuse buprenorphine tablets via the sublingual route, if sufficient opioid agonist effects are produced. The purpose of this study was to examine the pharmacologic characteristics of sublingual buprenorphine/ naloxone tablets in non-dependent abusers, determining if buprenorphine effects are modulated by the addition of naloxone, and assessing the relative abuse potential of sublingual buprenorphine/naloxone tablets in this population.

Objectives: To assess the abuse potential of sublingual buprenorphine and buprenorphine/ naloxone tablets in non-dependent opioid abusers.

Subjects: 7 Adult volunteers with active opioid abuse, but not physically dependent (6 males/ 1 female); average age 38.4 years (range 33-47 years). The number of illicit opioid uses per week was between 1 and 4.

Study Setting: In-patient. Urine samples collected at admission and intermittently throughout participation and tested for the presence of illicit drugs using an EMIT system.

Study Procedure: Participants were monitored drug-free for a minimum of 48 hours after admission to study site to ensure they had no evidence of physical dependence on opioids. Each subject participated in a minimum of 13 experimental sessions and resided on the ward for 7 weeks.

Laboratory Sessions: Subjects were informed they may receive combinations of buprenorphine and naloxone, and other opioid agonist medications or placebo. Subject and observer questionnaires were presented and responses entered. Examples of opioid agonists and antagonists and the types of effects produced by each were described to participants. Sessions lasted 3½ hours. 15 minutes after the start of each session, 15 minutes of baseline physiological data were obtained, all subject and observer questionnaires were completed. 30 Minutes after the start of the session, participants received an intramuscular injection followed by the administration of sublingual tablets. The session then continued for 3 hours, with collection of data.

Drugs & Doses: Sublingual buprenorphine (4, 8, 16 mg) sublingual buprenorphine/naloxone (1/.25, 2/.5, 4/1. 8/2. 16/4 mg), as well as intramuscular hydromorphone (2, 4 mg) [serving as positive opiate agonist control] and placebo in laboratory sessions conducted twice per week. All medications were administered using double-blind and double-dummy procedures.

Measures:

1. Physiological measures: heart rate, blood pressure, skin temperature, respiratory rate, pupil diameter, and oxygen saturation.
2. Subject and Observer measures: Subjective effect reports and observer rating questionnaires were completed 15 minutes before and at 15 minute intervals up to 180 minutes following drug administration. Subjects completed visual analog scales (High, Drug Effects, Good Effects, Bad Effects, Liking, and Sick), a pharmacological class questionnaire, and an adjective rating questionnaire. Each scale was a horizontal line on the computer screen, and the subject positioned an intersecting vertical line along the horizontal line. Ends of the horizontal line were labelled "None" and "Extremely" and responses were scored proportionately on a 100-point scale. The pharmacological class questionnaire asked the subject to select one of 10 drug classes to which the administered drug was most similar. The adjective rating questionnaire consisted of 37 items which the participant rated on a 5-point sclae from 0 (not at all) to 4 (extremely); the items constituted 2 scales: a 16-item opioid agonist scale (morphine-like effects), and a 21-item Withdrawal scale (adjectives associated with opioid withdrawal-like effects). Ratings for individual item were summed for a total score for each scale. Observer ratings included the same adjective rating scale, as well as an assessment of 7 signs of opioid withdrawal (lacrimation, rhinorrhea, perspiration, piloerection, bowel sounds, yawing and restlessness). Each opioid withdrawal item was scored either 0, 1, or 2 (with higher scores corresponding to greater severity), and scores for all items were summed to prodcue a total observer Withdrawal Signs Score. These ratings were done at the same times as the subject ratings. Item ratings were summed to produce total scores for the Agonist and Withdrawal scale.
3. Psychomotor/Cognitive Performance measures: 3 Tasks were completed during the session: a computerized form of the Digit Symbol Substitution Task, a Circular Lights Task, and a computerized form of the Trail-Making Test. Results were summarized for sequence errors and length of work product. Each of the 3 tasks were

completed during the baseline period (15 minutes before drug administration and at the same times as the subject ratings.

Data Analysis: Peak values for each session were determined for each measure. Since some measures decrease in response to acute opioid agonist effects, absolute nadir effect for these measures was examined.Tukey's honestly significant difference (HSD) was used to compare peak saline values to the peak value of each active drug condition. The mean square error term needed to perform these tests was calculated using a repeated measures, 2-factor analysis of variance; main effects were the 11 drug conditions and time (baseline vs. peak effect). Time course effects were analyzed with a repeated measures analysis of variance. Main effects were the 11 drug conditions and 13 time points.

Results: Higher doses of buprenorphine and buprenorphine/naloxone produced similar opioid agonist-like effects. There was no evidence to suggest that the addition of naloxone attenuated opiate agonist effects of buprenorphine in this population when buprenorphine was delivered by the sublingual route. All drugs produced significant effects relative to placebo. There were dose-related increases in ratings of Drug Effects, High, Good Effects, and Liking for hydromorphone, buprenorphine and buprenorphine/naloxone. Predominant effects were seen with the highest doses tested. There were no increases in ratings of Bad Effects or Sick. The lowest doses tested produced ratings that were of modest magnitude, for hydromorphone as well as the buprenorphines. Results from the subject adjective rating questionnaire showed only the highest doses of buprenorphine and buprenorphine/naloxone producing significantly increased ratings relative to placebo. There were no significant results for the subject-rated adjective score for opioid withdrawal. (See TABLE 1 below).

Skin temperature was increased for all hydromorphone doses, all buprenorphine doses and the highest dose of the combination product. Pupil diameter showed significant constriction for all of the doses tested except the lowest dose of the combination product. Oxygen saturation was decreased for the 8 and 16 mg buprenorphine doses and the 16/4 mg buprenorphine naloxone dose.

Results from the psychomotor tasks showed significantly higher changes for the highest doses of buprenorphine and buprenorphine/naloxone.

Results from time course effects showed that none of the variables effected buprenorphine/naloxone significantly different from buprenorphine alone, although pairwise comparisons against placebo showed that each alone had similar patterns of differing from placebo. Neither sublingual buprenorphine nor buprenorphine/naloxone showed onset of effects until 30 minutes after the start of the session. Peak effects did not differ from each other or hydromorphone for VAS ratings. The hydromorphone time to peak response for physiological measures was significantly shorter, however.

TABLE 1. Summary of Peak Drug Effects[a]

Measure	Placebo	Hydromorphone i.m.		Buprenorphine sublingual			Buprenorphine/Naloxone sublingual				
		2	4	4	8	16	1/.25	2/.5	4/1	8/2	16/4
Subjective measures (VAS)											
High	1.6	10.1	23.1*	10.4	22.0*	29.4 **	6.9	9.3	16.0	13.6	26.7**
Drug effects	2.4	9.4	23.3	11.9	26.6*	31.7 **	12.0	9.9	17.1	16.1	25.0
Good effects	2.6	9.6	22.6	15.1	29.1*	33.4 **	14.1	8.4	17.6	16.1	28.3
Liking	1.3	11.0	27.3	11.4	29.3*	32.0 **	9.0	10.4	20.7	18.6	28.9*
Adjective agonist rating scale	11.9	11.3	13.7	12.0	13.3	16.0 **	12.0	11.4	12.1	13.7	15.6*
Observer-rated measures											
Adjective agonist rating scale	11.7	13.1	16.3*	12.9	15.4	16.7 **	14.0	12.4	14.3	19.7**	17.9**
Physiologic measures											
Skin temperature	81.4	91.0 **	89.7*	90.0*	91.8 **	91.8 **	84.9	87.0	88.7	88.5	91.4**
Pupil diameter	4.3	3.0**	2.5**	2.9*	2.6 **	2.4**	3.7	3.4**	3.1**	2.6**	2.4**
Oxygen saturation	97.9	97.6	97.3	97.5	97.1	96.7 **	97.4	97.7	97.7	97.4	97.0**
Psychomotor tasks											
Circular lights	76.1	71.0	64.0	70.6	66.0	60.6 **	70.7	71.9	67.0	54.7**	60.6**
Trails (total line length, cm)	542.0	601.1	609.8	598.4	685.5	677.9	596.3	558.6	581.3	665.7	836.4**

[a]Values shown are the mean peak response (N=7). All doses are in milligrams. Results shown are for items with a significant effect for at least one dose condition; comparisons are to peak placebo effect. For subjective measures, observer-rated measures, skin temperature, and the Trails outcome the maximum positive increase was examined. For all other physiological measures and Circular lights the maximum decrease was examined. *$p<0.05$, **$p<0.01$.

Participants' responses to the drug class identification questionnaire are presented in TABLE 2 below. Placebo was identified as placebo 79% of the time. The largest number of opiate agonist identifications was for the higher doses of hydromorphone, buprenorphine and buprenorphine/naloxone, although the latter drug group was identified as other drug classes between 2% and 19% of the time.

TABLE 2. DRUG IDENTIFICATION RESPONSES[a]

Drug Administered (mg)	Opioid Agonist	Placebo	Other Classes[b]
Saline	14 (17%)	66 (79%)	4 (5%)
Hydromorphone 2	44 (52%)	40 (48%)	0
Hydromorphone 4	65 (77%)	19 (23%)	0
Buprenorphine 4	43 (51%)	41 (49%)	0
Buprenorphine 8	62 (74%)	19 (23%)	3 (3%)
Buprenorphine 16	63 (75%)	21 (25%)	0
Buprenorphine/Naloxone 1/0.25	29 (35%)	50 (60%)	5 (5%)
Buprenorphine/Naloxone 2/0.5	38 (46%)	46 (54%)	0
Buprenorphine/Naloxone 4/1	36 (43%)	33 (39%)	15 (19%)
Buprenorphine/Naloxone 8/2	53 (63%)	26 (31%)	5 (5%)
Buprenorphine/Naloxone 16/4	70 (83%)	12 (14%)	2 (2%)

[a] Numbers shown are total number of drug identifications made for each dose condition administered. Total identifications for each dose condition = 84 (7 subjects x 12 times each).
[b] A total of 34 identifications for Other Classes (<4%), which are combined numbers of identified as Others (28), Opioid Antagonists (2), Benzodiazepines (2), and Stimulants (2). There were no identifications as Antidepressants, Hallucinoges, Phenothiazines, and Barbiturates.

Conclusions: This study tested the effects of buprenorphine and buprenorphine/ naloxone only by the sublingual route and in non-dependent volunteers. Results suggest sublingual buprenorphine and buprenorphine/ naloxone both may be abused by opioid users who are not physically dependent upon opioids, and therefore may be a recreational drug of abuse. The authors concluded that buprenorphine and buprenorphine/naloxone tablets in the dose range tested have moderate potential for abuse comparable in magnitude to 4 mg of parenteral hydromorphone. This study did not test the relative abuse potential of parenteral or intranasal administration of the substances, but of the intact dosage form.

The purpose of adding naloxone to buprenorphine is to decrease abuse potential in opioid dependent individuals who might inject buprenorphine. In abusers who are not physically dependent on opioids, addition of naloxone will not exert a similar precipitated withdrawal. There were only small non-significant differences observed between buprenorphine and buprenorphine/naloxone.

REPORTS OF ABUSE OF BUPRENORPHINE SUBLINGUAL TABLETS IN NDA #20-733 AND FROM NIDA.

1. Experience in France.

Through the National Institute on Drug Abuse (NIDA/MDD), the following communication was received from [redacted], France, personal communication, 1999, unpublished): "*The impact on mortality of buprenorphine availability to drug*

using subjects in comparison to methadone. *Work in progress. 1999.*

Over a three-year period (1996-98), during which a little over subjects have been receiving buprenorphine at any given time, 20 so called "buprenorphine-related deaths" have been reported and documented. Of these, only one had no associated substances (benzodiazepines and/or alcohol). All occurred among out-of-treatment subjects (black market buprenorphine). During the same time period, for 5,000 methadone subjects, 20 so called 'methadone-related deaths' have been reported. During the same time period, overdose deaths registered by the Police, have gone from over 500/y to 200/y. The decrease is due to a decrease of heroin related deaths, medication related deaths are unchanged. Of course, there are many approximations in these numbers and caution is warranted, but, if anything, what is going on in France seems to support highly the safety of buprenorphine considering the overall lack of control and the importance of black market access and intravenous diversion."

Most of the adverse events reported by subjects receiving buprenorphine in clinical trials and by patients receiving Subutex for treatment of opiate addiction in France appear to be that of opiate withdrawal. Most commonly reported withdrawal-related symptoms include asthenia, hypertonia, headache, lacrimation disorder, nausea, abdominal pain, bone pain and rhinitis.

Post-marketing data from France indicate the use of buprenorphine (Subutex) among pregnant opiate-dependent women that has resulted in a number of neonates experiencing some degree of withdrawal symptoms. The level of withdrawal is generally reported to be of a low level and short duration. Small open studies of buprenorphine in 29 pregnant opioid dependent women have shown normal deliveries and only mild neonatal withdrawal. Seven fetal deaths among mothers receiving Subutex were reported in the French post-marketing experience. These fetal deaths occurred among a population at extremely high risk for adverse fatal outcomes and there is no clear association between the drug and fetal demise for any of these cases. The following publications were provided by the author for review.

1. Auriacombe M. Buprenorphine use in France: background and current use. In: Ritter A, Kutin J, Lintzeris N, Bammer G ed. Expanding treatment options for heroin dependence in Victoria: buprenorphine, LAAM, naltrexone and slow-release oral morphine. New pharmacotherapies project - feasibility phase. Fitzroy, Victoria: Turning Point Alcohol and Drug Center Inc.; 1997:73-80.

> In February 1996, buprenorphine in 0.4, 2 and 8 mg sublingual tablets was made officially available for treatment of opiate dependent subjects. In 15 months, it was estimated that as many as 40,000 patients were receiving buprenorphine prescriptions for treatment of opiate addiction (approximately 25% of total addict population). Average prescribed dose is 8 mg daily. Supervision of drug delivery to the addicts is conducted by pharmacists. In a survey of 2,646 pharmacies, it was estimated that 80% of the Subutex was used in the prescribed way and that

70% of prescriptions were not resold. From these data intravenous injection of Subutex was estimated at minimum between 10 to 15% of subjects. Patient compliance was considered good in 71% of cases (up to 74% in October 1996). As of June 1997, there were some reports of adverse effects with buprenorphine use by addicts. One report of 6 deaths involved combined use of buprenorphine i.v. with benzodiazepines and alcohol. All 6 subjects used illegally obtained buprenorphine and were not included in a comprehensive treatment program. The author points out on balance there was a 20% reduction in opiate overdose deaths during this time (that is, 100 fewer deaths from the usual 450-500 annual deaths). Another series of adverse effects concerns reports of increases in liver enzymes among addicts treated with buprenorphine, leading to the recommendation that addict patients on buprenorphine be closely monitored , as over 75% of opiate drug users in treatment in France are positive for hepatitis C virus.

2 Auriacombe M, Franques P, Bertoprelle V., Tignol J. Use of buprenorphine for substitution treatment: a French experience in Bordeaux and Bayonne. Research and Clinical Forums 1997; 19: 47-50.

The article largely advocates the use of buprenorphine in treatment of opiate addiction and discusses the successes which include reduction in alcohol and drug use after 12 months and improvement in quality of life. The author discusses some reports where buprenorphine use was not successful and attributes these to insufficient dosing or inadequate counseling programs. This raises the issue of determining whether tolerance develops to use of buprenorphine and how dosing adjustments that may be needed are handled to maintain effectiveness of the drug.

3. Auriacombe M. Overview on substitution treatment for heroin users in France. In: Farrell M, Howes S, Verster A, Davoli M ed. Reviewing current practice in drug substitution treatment in Europe (CT. 98 DR.10). Lisbon: EMCDDA; 1999:61-68.

This article contained the same material as in the 2 previous articles.

Other articles submitted in the NDA:

Arditti, J., Bourdon, J.H., Jean, P., Landi, H., Nasset, D., Jouglard, J., Thirion, X., "Buprenorphine abuse in a group of 50 drug-use abusers admitted to Marseilles Hospital.

Buprenorphine was placed on the market in 1987. Its indication is for the rapid treatment of intense pain, particularly in postoperative situations. However, abuse of its therapeutic use as outlined in the Marketing Authorization was quickly suspected. Buprenorphine is prescribed to addicts by certain doctors for opiate withdrawal but is also used illicitly, and although its physical dependence potential is less than other morphine products, it does give rise to addiction and drug dependence. Through the toxicology activities at Marseilles Hospital, urine samples of addicted patients are provided as part of the analytic activity at the Drug Dependence Evaluation and Information center. Samples of

urines of 50 addicted patients upon admittance to the hospital between June and October 1992 were sent to the laboratory. Search for the main substances used in drug dependence (amphetamines, benzodiazepines, cannabis, cocaine, opiates) was carried out. Buprenorphine and norbuprenorphine were not detected during the search for opiates due to the presence of a modified morphinane nucleus and the absence of morphine-like metabolism. Although a small sample, the frequency of occurrence of each substance was calculated (C.I. at 95% of the percentage). The 50 patients included 39 males and 11 females. Average age was 28.6 ±5.6 years. A urine sample was analyzed for each of these individuals. See TABLE 3.

TABLE 3. SUBSTANCES IDENTIFIED AMONG THE 50 DRUG ADDICTS.

SUBSTANCE	Positive samples		Conf. Interval (95% of %)
	No.	%	
Heroin	40/50	80	69 to 91
Benzodiazepines	36/50	72	61 to 83
Cannabis	10/50	20	9 to 31
Buprenorphine	9/50	18	8 to 28
Cocaine	3/50	6	0 to 12
Amphetamines	0/50	0	

Nine of the 50 samples analyzed are positive for buprenorphine and/or norbuprenorphine (18%), with a C.I. of between 8 and 28%. The sampled group includes essentially the use of buprenorphine within the context of heroin addiction (8 cases). In only one case, buprenorphine was substituted for heroin in the course of therapeutic withdrawal. These 9 patients were monitored within the framework of an addiction consultation (3 cases), or admission to hospital (6 cases). In September 1992, the Health Minister published special conditions for issuing and rpescribing buprenorphine orally for patients not admitted to hospital. Prescriptions must be made on a voucher taken from the counterfoil book and retained by the pharmacist for a period of 3 years.

Baumevieille M., Haramburu, F., Begaud, B., "Abuse of prescription medicines in southwestern France, Ann. Pharmacother., 31: 847-850, 1997.

In France, prescription drugs with addiction potential are subject to the recommendations of the U. N. and the WHO. Duration of treatment and renewal of prescription medicines are strictly limited. Addicts are thus frequently forced to attempt to procure these drugs by falsifying a prescription. Theft of prescription forms and blank forms and falsification original forms are methods that are used. Pharmacies are thus in the front line for detection and quantification of this phenomenon. To estimate its magnitude, a survey of falsified prescription forms was conducted within a network of pharmacies. A secondary objective was that alerting pharmacists to the amount of abuse of prescription medicines would help to decrease the problem through more careful screening of prescriptions. Falsified prescriptions were used as an indicator of abuse. Community pharmacists in a representative network were asked to report any falsified prescription form presented over a 1-year period. Sales data were used to express results as abuse rate and abuse rate ratio. Two-thirds of the 130 pharmacies in the network reported at least 1 falsified

prescription. The reported incidence of falsified prescriptions was 2.3 per 10,000 inhabitants. A total of 392 falsified prescription forms was collected. The abuse rate ratios were 171 (95% CI 140 to 210) for dextroamphetmaine-phenobarbital in combination, 168 (95% CI 131 to 216) for fenozolone, 67 (95% CI 53 to 84) for buprenorphine and 40.5 (95% CI 33 to 50) for clobenzorex.

Falsified or forged medical prescriptions as an indicator of pharmacodependence: A pilot study. M Lapeyre-Mestre, C. Damase-Michel, P; Adams, P. Michaud, J. L. Montastruc, Eur J Clin Pharmacol (1997) 52: 37-39.

Survey of prescription forgeries in community pharmacies in the Midi-Pyrenees area (southwest France). Main criteria used to identify forgeries were inadequate dosage, multiple use of the prescription form, drafting not in accordance with the rules of prescription or false prescription forms (stolen prescription forms, photocopies). Results: A total of 165 falsified prescriptions were collected. The 305 drugs involved in these forged prescriptions were opiate analgesics, benzodiazepines, amphetamines and minor opiate analgesics. Medications were essentially buprenorphine, flunitrazepam (2mg dosage), phenobarbitone+amphetamine, and clorazepate. See TABLE 4.

TABLE 4. Top 10 drugs reported in the 165 forged prescription forms

Drugs	No.	%
Buprenorphine	62	37.6
Flunitrazepam	28	17.0
Amphetamine+Phenobarbitone	21	12.7
Clorazepate	17	10.3
Acetaminophen	13	7.9
Bromazepam	7	4.2
Amfepramone	6	3.6
Fenozolone	5	3.0
Lorazepam	4	2.4
Clobenzorex	4	2.4

The most frequently requested drugs, buprenorphine and flunitrazepam, could be used as substitute drugs when local availability of heroin decreased. Subjects who presented forged prescriptions of buprenorphine primarily (85%) men younger than 30 years. The pattern of use of buprenorphine declined from September 1991 to April 1993, because of a 1992 law regulating prescription of buprenorphine.

2. Experience in New Zealand.

Dore, G. M., Hargreaves, G., Niven, B. E., Cape, G. S., "Dependent opioid users assessed for methadone treatment in Otago: patterns of drug use," New Zealand Med. J., 162-165, 1997.

A retrospective case note review was carried out for 126 consecutive clients who were assessed for methadone treatment in the Otago province over a 2-year period. Patterns of drug use were assessed. Over 60% of those presenting were using 3 or more opioid

drugs, with most common being what is referred to as "homebake" (63%) which is largely comprised of the extractives from codeine-containing combination products, as well as sustained release morphine sulfate tablets (62%), buprenorphine (52%), opium poppies (50%) and methadone (41%). As access to heroin in the 1990's has been limited, heroin use was reported primarily from individuals returning from overseas travel.. The majority of injected drugs are pharmaceuticals, "homebake" and opium poppies. Most injecting drug users attending methadone clinics in the early 190's were dependent on buprenorphine, morphine, opium poppy, extract, methadone, "homebake", meperidine. Codeine based tablets and cough syrups were also abused. See TABLE 5.

TABLE 5. Percentage of Individuals Reporting Use of Different Opioids during Prior 3 Months Period.

OPIOID NAME	PERCENT
Homebake	63
Morphine (sustained release tablets)	62
Buprenorphine	52
Opium poppies	50
Methadone	41
Opium tincture	21
Codeine	16
Meperidine	14
Dextropropoxyphene	13
Dextromoramide	9
Heroin	5
Diphenoxylate HCl/atropine sulfate	3
Pentazocine	2

G. M. Robinson, P. D. Dukes, B. J. Robinson, R. r. Cooke, and G. N. Mahoney, "The misuse of buprenorphine and a buprenorphine-naloxone combination in Wellington, New Zealand," Drug and Alcohol Dependence, 33: 81-86, 1993.

Two surveys of 12 months duration were undertaken on opioid users at the Wellington Alcohol and Drug Centre before and after introduction of a combination buprenorphine 0.2 mg – naloxone 0.17 mg tablet (Bu-Nx), which was launched in 1991 in the hope of reducing intravenous misuse. There was considerable iv misuse of buprenorphine 0.2 mg tablets (Bu) in 1990 with self-reports of misuse in 81% of the patients over the 4 weeks prior to presentation, and 65% of the patients had buprenorphine in their urine. In the repeat survey 57% reported misuse of the Bu-Nx combination over the previous 4 weeks, and 43% had buprenorphine and naloxone detected in their urine. There was a reduction in the street price of Bu-Nx. One third of the patients who used Bu-Nx i.v. reported instances of withdrawal symptoms, and subjectively the drug was less attractive to misusers, though it remains a drug of abuse. See TABLE 6.

TABLE 6. Opioid preparations: Wellington self-reports of any use in previous 4 weeks.

DRUG	1990 (N=54) No. (%)	mid-1991-92 (N=44) No. (%)
Buprenorphine (only)	44 (81%)	3 (7%)
Buprenorphine-naloxone (only)	N/A	11 (25%)
Buprenorphine & Buprenorphine-naloxone	N/A	14 (32%)
Pharmaceutical morphine from long-acting tablets	37 (68%)	38 (86%)
'Homebake' (morphine/heroin) made from codeine	27 (50%)	21 (48%)
Heroin (imported)	19 (35%)	5 (11%)
Local poppy	17 (31%)	13 (29%)
Others	14 (26%)	8 (18%)

The addition of naloxone to the Bu sublingual tablet was an attempt to reduce its potential for injection. This study revealed however that with the dose of naloxone employed it remained injectable, even by the polyopioid user population, although it was probably less acceptable than the Bu alone. Street price has fallen. Bu and Bu-Nx tablets have remained less expensive on the street than slow-release morphine tablets which cost about NZ $2/mg and which are another major drug of i.v. misuse in New Zealand. Doses of Bu used per injection are relatively low, less than 0.8 mg, especially compared to doses which have been used (SL) in studies exploring the use of Bu as a possible treatment for heroin dependence. The mean number of tablets of Bu-Nx used per injection was 2 compared with 3 Bu tablets in the first survey. More patients reported that Bu-Nx was 'easy to obtain' on the street than the number reporting this for Bu n 1990, and that Bu-Nx had a lower street price. Possibly opioid dependent users have found that 2 Bu-Nx tablets are an optimal injectable dose, above which withdrawal effects may predominate. This is in contrast to studies in volunteer opioid dependents, on methadone 30 mg daily, where sc doses of buprenrophine 0.2 mg /naloxone 0.2 mg and buprenrophine 0.3 mg/naloxone 0.2 gm produced withdrawal signs and symptoms. Because of the high receptor affinity of Bu, it was never predicted that injecting Bu-Nx would be aversive in those dependent solely on Bu (or Bu-Nx). It was anticipated that users might largely confine their use to Bu or Bu-Nx, which was not the case. One-third of the users of Bu-Nx at some time reported withdrawal symptoms after injecting, consistent with the hypothesis that i.v. misuse of Bu-Nx may be unattractive to polyopioid dependents.

H. B. Rainey, "Abuse of buprenorphine," New Zealand Med. Journal, 72, 1986.

New Zealand was one of the first countries in the world to use the sublingual form of buprenorphine. Considerable experience in medical use with the properties of the drug and its use in treatment has been gained. Buprenorphine is a drug abused by hard core users in New Zealand, and cases of physical dependence to buprenorphine have been reported. At times of shortage of supply of heroin, buprenorphine is frequently used as the drug of choice. Case records from treatment centers of the National Society on Alcoholism and Drug Dependency (NSAD) show that a minimum of 20% of all patients report using buprenorphine in the month prior to admission. The author contests the assertion that the potential for abuse is very low.

3. Experience in Australia.

T. Lebedevs. "Buprenorphine abuse." Pharmaceutical Jour. 541, 1985.

For more than 18 months, buprenorphine was available on prescription in W. Australia for use as an analgesic. However, the product was also used in treating opioid dependence. Injectable form was prescribed almost exclusively. In one 6-month period, over 800 people obtained prescriptions for the drug, and at least 700 were recognized as abusers of buprenorphine. People were going to different doctors and pharmacies to obtain their supply as well as buying the drug on the black market, and were using up to 10 ampules of 0.6 mg buprenorphine daily. Doctors prescribed the drug believing that addicts could detoxify themselves. Eventually, it was placed on a Controlled Drugs List. Almost overnight, harassment of doctors and pharmacists by drug users was halted as they realized they could no longer obtain the drug easily.

Quigley, A. J., Bredemeyer, D. E. and Seow, S. S., "A case of buprenorphine abuse," Med. J. Of Australia, 425-6, 1984.

The drug abuse treatment clinic of the Western Australian Alcohol and Drug Authority, in conjunction with the Pharmaceutical Branch of the Public Health Department, monitored the prescription trends of buprenorphine in Western Australia since the injectable product was marketed in November 1982. Up until February 1984, 125 notified drug addicts had obtained buprenorphine prescriptions from general practitioners. The case of the first of these addicts to seek treatment was reported. The addict, a 24-year old heroin user, used buprenorphine to satisfy his craving for opiates for 6 months. Buprenorphine use was perpetuated due to the discomfort on withdrawal. Administration of naloxone (10 mg) precipitated a pronounced withdrawal syndrome.

4. Experience in Scotland.

T. L. Lavelle, R. Hammersley, A. Forsyth, and D. Bain, "The use of buprenorphine and temazepam by drug injectors," J. Addictive Diseases, Vol. 10(3):5-14 (1991).

Because of concern over growing misuse of buprenorphine and temazepam in Scotland, interviews with 78 clients of Glasgow drug agencies were conducted during 1989-1990; it was found that buprenorphine and temazepam were more widely and frequently misused than heroin or other opiates. Fifty-eight percent of buprenorphine users administered the drug 6 to 7 days each week. See TABLE 7.

TABLE 7. Misuse of Various Drugs Among 78 Drug Users.

Drug	Ever Used N (%)	Ever Injected N (%)	Average Days Used	Average Daily Use
Heroin	76 (97%)	67 (88%)	93.1	0.5 gram
Buprenorphine	73 (94%)	70 (96%)	243.0	7.4 pills
Other Opiates	73 (94%)	38 (52%)	71.0	14.8 pills
Temazepam	76 (96%)	57 (75%)	160.4	11.2 pills
Amphetamine	69 (88%)	46 (67%)	44.8	1.0 gram
Cocaine	52 (67%)	24 (46%)	13.2	0.25 gram

"Drug injectors in Glasgow: a community at risk? A report from a multidisciplinary group" Health Bulletin 5 (16) November 1993.

In 1987, there was an increase in number of drug injectors with HIV infection in a district in the north of Glasgow. A multidisciplinary group was set up to examine the extent and spread of infection, and its relationship to behavioral and environmental factors. By 1989, a WHO working group developed a standardized methodology, consisting of an interview schedule and voluntary anonymous HIV testing procedures. The study has been operational annually in Glasgow since 1990, with a concurrent project that evaluates prevalence of drug use by injection in the general population. The Glasgow HIV Behavioral and Prevalence Study was designed to give a representative sample of the city's injectors, being comprised of a variety of in-treatment and out-of-treatment sites.

Of the estimated 8,500 injectors in Glasgow (1.35% of the population aged 15-55), 503 and 535 injectors were recruited to the study in 1990 and 1991, respectively. Over 90% of respondents injected daily and reported injecting, an average of 4 different types of drugs in the 6 months prior to interview; the 3 most commonly injected drugs, in order, are buprenorphine, heroin and temazepam. While HIV prevalence remains low, all-cause mortality among injectors in Glasgow is high. See TABLE 8.

TABLE 8. Proportion of samples reporting injection of selected drugs in the 6 months prior to interview.

Drugs	1990 (N=503) Percentage	1991 (N=535) Percentage
Opiates		
Buprenorphine	82.3	76.8
Heroin	69.8	70.1
Diconal	38.6	29.7
Palfium	35.2	27.5
Methadone	5.0	3.6
Tranquillizers		
Temazepam	47.3	44.7
Triazolam	10.9	7.7
Diazepam	2.0	1.1
Stimulants		
Cocaine	10.3	7.5
Amphetamines	26.4	29.9
Ecstasy	0.6	1.7
Crack-cocaine	0.2	0.2

J. R. Robertson & A. B. V. Bucknall, "Buprenorphine: dangerous drug or overlooked therapy?", Br. Med. J., 292, 1465, 1986.

Because of the decline in purity of heroin in Edinburgh Scotland, buprenorphine, abused intravenously, is currently the drug of choice and is obtained directly or indirectly from the NHS. Doctors have been warned of the dangers of prescribing the drug. Authors' practice has instituted a voluntary ban on its prescription because of its widespread resale and iv abuse. Authors suggest that manufacturers produce a noninjectable form and conduct a clinical trial on the use of buprenorphine in an appropriate unit.

Sakol, M. S., Stark, C., and Sykes, R., "Buprenrophine and temazepam abuse by drug takers in Glasgow – an increase," 439-441, Brit Med J, 1988

There has been a change in the pattern of drug abuse in the West of Scotland with an increase in use of both temazepam and buprenorphine by drug takers, a trend also observed in Edinburgh and Newcastle, suggesting their use is more widespread than previously realized. From the Drug Project In Glasgow, an outpatient help agency, 180 new clients attended between May 1986 and November 1, 1987. Seventy new attendees were seen in the 9-month period from May 1, 1986. Twenty-four percent of this group abuse temazepam: 12% i.v. and 94% p.o. and 6% by both routes. In the same 9-month period, 7% of new clients were taking buprenorphine (20% i.v., the remainder p.o.). New clients (N=110) were seen in the second 9-month period from February 1987. Thirty-eight percent were abusing temazepam. Buprenorphine was taken by 16% of the new attendees in this period. Eighty-two percent administered the drug iv and the remainder orally. There has been an increase in the proportion of new increases of 14% and 9%, respectively, who took temazepam and buprenorphine. Increases in i.v. administration of the drugs took place in the time period (23% with temazepam and 62% with buprenorphine). During this same time, drug takers reported a decrease in quantity and quality of 'street heroin'. Supplies of buprenorphine are diverted to the street. Buprenorphine is easily soluble because of its intended sublingual route. A particle-free solution is easily and quickly prepared.

Forsyth, A. J. M., Farquhar, D., Gemmell, M., Shewan, D., and Davies, J. B., "The dual use of opioids and temazepam by drug injectors in Glasgow (Scotland)," Drug & Alcohol Dependence, 32: 277-280, 1993.

Data on drug use from 100 interviews of prisoners was obtained. Forty of the prisoners interviewed were found to be drug injectors. Comparison with data from earlier studies revealed an apparent decrease in use of buprenorphine relative to the use of heroin, 42.5% and 72.5%, respectively. Temazepam with heroin abuse continues.

Frischer, M. "Estimated prevalence of injecting drug use in Glasgow," Br. J. Addiction, 87: 235-243, 1992. See TABLE 9.

Although drug users continue to inject opiates, buprenorphine rather than heroin appeared to be the most commonly used opiate in Glasgow.

TABLE 9. Estimated prevalence of injecting drug use in Greater Glasgow for 1989.

Age Range	Estimated no. IDUs +95% interval	Population	Prevalence/ Per 1000
15-19	1103 ± 1160	88,424	12.47
20-24	3001 ± 1400	103,543	28.98
25-29	2588 ± 1564	95,814	27.01
30-34	1243 ± 812	80,856	15.37
35-55	1489 ± 1716	258,844	5.72
Total	9424 ± 2460	627,480	15.02

Gray, R. F., Ferry, A., and Jauhar, P., Emergence of buprenorphine dependence, Br. J Addiction, 1989.

In situations wherein the supply of illicit opiates (specifically heroin) has declined dramatically, often times anything with similar activity that is easily obtainable may likely be substituted and be the preferred drug of abuse. Buprenorphine is sold in 0.2 mg tablets either individually (price between 3.00 and 3.50 pounds each) or in groups of 10. The sublingual tablets are usually broken or crushed, placed into a syringe along with warm or clod water, and shaken vigorously before being injected intravenously. The immediate and prolonged euphoric effect as seen with heroin use then occurs. There are no reports of the tablets being taken orally. More than half use buprenorphine as their preferred drug. Sixty-nine percent use buprenorphine in combination. See TABLE 10.

TABLE 10. Preferred Drugs of 62 Glasgow Drug Users.

Drugs	Users	
	N	% of Total
Heroin	9	14.5
Heroin & others (4 heroin & buprenorphine) (1 heroin & LSD)	5	8.1
Amphetamines	2	3.2
Amphetamines & others	1	1.6
Dihydrocodeine	1	1.6
Buprenorphine	36	58.1
Buprenorphine & others (4 buprenorphine & temazepam) (1 buprenorphine & alcohol) (2 buprenorphine & heroin)	7	11.3
Multidrug	1	1.6
Total	62	

APPEARS THIS WAY ON ORIGINAL

5. Experience in United Kingdom.

Harris, A. J., "Buprenorphine abuse," Pharmaceut. Journal, May 1987.

Author provides warning on abuse of buprenorphine and predicts that it will eventually be a controlled substance. (Greater Yarmouth, U.K.)

Haydock, G., "Buprenorphine abuse," Pharmaceut. Journal, April 1987.

Buprenorphine abuse is widespread in the Lancashire area. Forged stolen prescriptions are used for obtaining drug. (U.K.)

WHO Drug Information, Buprenorphine abuse. Advisory Notices, Vol 2., No. 2, 1988.

From U. K., buprenorphine (Temgesic) in the Northern Regional Health Authority recently received several reports of buprenorphine abuse and has requested doctors and pharmacists to remain alert to such cases. Reconsideration of the legal status of buprenorphine was suggested. At present, it is available on prescription only and is not subject to control as a narcotic. Such controls have already been applied in Austria, Germany and New Zealand.

Strang, J., "Abuse of buprenorphine," Lancet, 725, 1985.

Over the past few weeks, widespread intravenous abuse of buprenorphine has been observed in Greater Manchester. Much of this appears to have resulted from over 100 stolen prescription forms which were fraudulently used to obtain supplies of buprenorphine tablets (0.2 mg) sometimes with supplementary supplies of cyclizine hydrochloride 50 mg. These tablets of buprenorphine are reportedly being sold on the black-market for between 50 pence and one pound each. Frequently, they are then crushed and injected. Five such tablets are regarded as approx. equivalent to a 10 pound wrap of black market heroin (approx. 1/8 gram of heroin). Buprenorphine injected in combination with cyclizine is said to prolong the opioid effect. Cyclizine is available in combination with dipipanone which is now controlled under a 1984 amendment to the Misuse of Drugs Act, following widespread abuse.

Strang, J., "Abuse of buprenorphine (Temgesic) by snorting," BMJ. 302: 969, 1991.

A new form of abuse of buprenorphine (Temgesic) tablets has been encountered. Sublingual tablets are crushed and then snorted like snuff. The tablets are crushed into a fine powder and then snorted in the same manner as black market amphetamines, cocaine, and heroin. This reportedly results in a more rapid psychoactive effect than the sublingual route and seems to be associated with strong hedonic tone. Two patients reported that their drug and route of preference was Temgesic by snorting, for which they would occasionally substitute black market heroin by snorting when Temgesic was not available. Snorting of buprenorphine is now moderately well established as a pattern of

abuse in parts of London and Glasgow. The sublingual tablets are sold on the black market for 2.50 pounds each and are diverted from prescription supplies. (Kent, UK)

Wood, P. J., "Opiate dependence in West Yorkshire." In Opioids – Use and Abuse, Eds. J. Levy and K. Budd, Royal Society of Medicine Services International Congress and Symposium Series No. 107. Published by Royal Society of Medicine Services Limited, 1986.

Heroin in powder form bought on the street is the most common opioid taken by addicts as seen at the drug dependence clinic in Waddiloves Hospital, Bradford, U.K. There has been a dramatic increase in the referral of opiate addicts from West Yorkshire to the drug dependency clinic in recent years, approximately a 3-fold increase in 3 years. There are varied estimates of the number of opiate addicts in Bradford, ranging widely from 20 to 350. The numbers of addicts notified to the Home Office have also been increased very rapidly in the preceding 3 to 4 years. Over the past 2 to 3 years, individuals addicted to buprenorphine (Temgesic) have begun to be encountered. Other opioids (methadone, codeine, dihydrocodeine, pethidine, morphine, dextromoramide) are abused as well.

6. Experience in Ireland.

J. J. O'Connor, E. Moloney, R. Travers, A. Campbell, "Buprenorphine abuse among opiate addicts," Brit. J Addiction (1988) 83, 1085-1087.

Sporadic reports in the world literature appear to contradict the view that the drug has a low abuse potential. Buprenorphine was introduced in Ireland in 1980. It seemed to satisfy the criteria for a potent, nonaddictive analgesic, being 25-40 times as potent as morphine on a dose-for-dose basis, having a milder euphorigenic effect and minimal withdrawal symptoms. The following analysis of opiate addicts attending the National Drug Advisory & Treatment Centre (NDATC) challenged this view, however, per issues raised in the world literature, that buprenorphine is a drug of abuse. A retrospective survey was carried out of all opiate addicts first presented at the NDATC (9-1-86 to 8-31-87). Buprenorphine is now established as a major drug of abuse among Dublin's opiate addicts and its abuse is becoming increasingly common. The object of the study is to establish the extent of buprenorphine abuse among opiate addicts. The study relies on self-reporting of drugs abused by addicts. Buprenorphine is abused mainly intravenously. Tablets are sold on the illicit drug market for between 3 and 5 Irish pounds each. They are crushed and either taken sublingually, snorted or more frequently dissolved and injected intravenously. It is not considered the preferred drug of abuse, but is used to prevent withdrawal symptoms when heroin is unavailable. Decreased street availability of heroin is a likely reason for dramatic increase in abuse of buprenorphine. Until 7-1-87, buprenorphine could be obtained without a prescription in Ireland. This was one reason for increased prescribing and use of the drug. On the black market, a heroin habit of 0.5 g per day (10-15% purity) is satisfied by 8-10 buprenorphine 0.2 mg tablets. The former costs 80 IR pounds and the latter 24-50 IR pounds per day. This is one reason for increased popularity among younger, unemployed addicts. Cheaper price and easier availability explain its widespread abuse. Supposedly, addicts have reported a

less intense euphoria as compared with heroin. Buprenorphine has become a prescription-only medication in Ireland (Misuse of Drugs Regulations – Schedule 2).

7. Experience in India.

Chowdhury, A. N., Chowdhury, S., "Buprenorphine abuse: report from India," Brit. J. Addiction, 85: 1349-1350, 1990.

An analysis of 2½ years experience of opiate addiction cases at a clinic in Calcutta revealed an increasing rate of abuse of buprenorphine, especially as a substitute for heroin. In 1987, no buprenorphine abuse was reported. In 1988, out of 498 outpatient opiate addict cases, 24 were for buprenorphine addiction, 20 (4%) attributed to IM injection and 4 (0.8%) to sublingual tablets. Individuals had a mean duration of heroin addiction history of 3.5 and 3.8 years, respectively. Of the 20 cases of buprenorphine injection abuse and 4 cases of tablet addiction, 6 patients and 1 patient, respectively, were on buprenorphine alone, the remainder abused both heroin and buprenorphine. Sixty percent procured buprenorphine by physicians' prescriptions. In 1989, increased numbers of buprenorphine addicts were reported. Of 285 opiate addicts, 21 (7.4%) were using buprenorphine injection and 9 (3.2%) were of abusing the tablet. Addicts had a mean duration of heroin abuse of 3.6 and 2.9 years, respectively. Mean duration of buprenorphine abuse was 5.4 and 5.1 months, respectively.

8. Experience in Spain.

Buprenorphine (0.3 mg ampules) and sublingual tablets (0.2 mg) were marketed for analgesia in Spain in 1985 and 1986, respectively.

Segui, J., Cascio, A., Aragon, C., Llovet, J. M., Soler, J. M. & Salvador, L., Prevalencia del consumo de buprenorfina en una muestra de pacientes toxicomanos ambulatorios, Prevalence of buprenorphine use in a sample of outpatient drug-addicts, Rev. Clin. Esp., 189: 14-17, 1991.

A group of 184 patients who met the DSM III-R diagnostic criteria for opiate dependence, at the CAS (Outpatients' Department) of Sta. Eulalia over a period of 18 months, in order to determine the prevalence of buprenorphine use. Data was collected from the patients' reports and no specific checks were carried out to detect their actual consumption of buprenorphine. The period prevalence was 79% (43.5% of them were occasional users and 35.5% habitual), whereas the point prevalence was 16.8% (6.5% occasional users and 10.3% habitual). The average length of time during which buprenorphine was used was 6.1 ± 9.9 months. The characteristic method of consumption was to use burpenorphine tablets, which were crushed and injected iv after dilution. Buprenorphine is usually obtained through dealers, while a third of the sample admits having dealt in this drug at some time.

Luis, S., Torrens, M., Castillo, C., Porta, M, and de la Torre, R., "Consumption of buprenorphine and other drugs among heroin addicts under ambulatory treatment: results from cross-sectional studies in 1988 and 1990," Addiction, 88:1341-1349, 1993.

The prevalence of consumption of buprenorphine and other drugs among heroin addicts under ambulatory treatment in 2 cross-sectional studies conducted in 1988 (188 subjects) and in 1990 (1,197 subjects). Patients were enrolled in one of three different programs: methadone maintenance program, antagonist maintenance program and drug-free program. Urine samples were tested for detection of heroin, cocaine, dextropropoxyphene, cannabis and benzodiazepines, and buprenorphine. Sixty-two percent of patients in 1988 and 71% of patients in 1990 reported having consumed buprenorphine at some time during their history of drug dependence and 5.9% and 6.1%, respectively, tested positive for the drug in urine screens. In over 70% of these patients, consumption was by the i.v. route. Consumption of cannabis, cocaine and benzodiazepines was also very high in the study population. Overall, patients in the DFP group consumed the largest number of the drugs tested, while those in the AMP group consumed the smallest number. Abuse of buprenorphine could be more widespread than previously reported.

From the time buprenorphine was first marketed as an analgesic in Spain, sales figures for both ampules and tablets rose steadily. This had been difficult to explain since Spain is the European country in which fewest opioid analgesics are prescribed. Heroin addicts are the market for the drug. In this study, 70% of patients reported consuming buprenorphine at some point in time. A total of 4.2% of patients in 1988 and 7.6% in 1990 said they were regularly consuming buprenorphine at the time of study. As might be expected in patients who regularly abuse heroin i.v., consumption of buprenorphine (mostly crushed tablets) was predominantly by the intravenous route as opposed to the oral or sublingual routes.

9. Experience in Other Countries.

The NDA included brief mention of possible indicators of abuse of buprenorphine in Belgium, Germany and Sri Lanka.

CHEMISTRY ISSUES:

Suboxone tablets are composed of buprenorphine hydrochloride and naloxone hydrochloride in two tablet strengths: 8 mg/2 mg and 2.0 mg/0.5 mg.

The rationale for the drug combination is that naloxone purportedly has poor sublingual bioavailability, and buprenorphine is bioavailable by the sublingual route of administration. Therefore, the tablets by the sublingual route are intended to produce predominantly the buprenorphine opiate agonist effect. However, most of the documented abuse, carried out by opioid-dependent persons, of sublingual buprenorphine tablets has involved crushing of tablets, dissolving active ingredients, and injection of the water soluble extraction. Buprenorphine combined with naloxone and parenterally

administered to opioid-dependent individuals has been shown to precipitate a withdrawal syndrome. While dissolving and injecting such tablets may be aversive for the opioid-dependent individual, the effects produced by the combination in opioid abusers who are not physically dependent, but recreational abusers nonetheless, has not been previously studied. See review of Strain *et al.* study and review above.

Buprenorphine is chemically synthesized from thebaine and therefore was by definition a Schedule II narcotic until it was rescheduled to Schedule V in 1985 which followed its approval as an analgesic. Chemically, the drug is 17-(cyclopropyl-methyl)-α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-3-hydroxy-6-methoxy-α-methyl-6,14-ethenomorphinan-7-methanol hydrochloride. Another chemical name for buprenorphine is [5α,7α(S)]-21-cyclopropyl-7α-[(S)-1-hydroxy-1,2,2-trimethylpropyl]-6,14-endo-ethano-6,7,8,14-tetrahydrooripavine hydrochloride CAS registry numbers are 53152-21-9 (hydrochloride salt) and 52485-79-7 (free base). Its molecular formula is $C_{29}H_{41}NO_4$·HCl, molecular weight is 504.11 (hydrochloride). The salt is a white powder that is sparingly soluble in water,

Naloxone is also chemically synthesized from thebaine and therefore was also a Schedule II narcotic until it was decontrolled in 1974 (hydrochloride in 1971) which followed its approval as an opiate antagonist. Chemically, naloxone is (5α)-4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-morphinan-6-one hydrochloride dihydrate or 17-allyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-one dihydrate. CAS registry number is 51481-60-8. Its molecular formula is $C_{19}H_{21}NO_4$·HCl-$2H_2O$, molecular weight is 399.87 (hydrochloride) and 327.38 (base). Naloxone occurs as a white to slightly off-white powder, soluble in water, dilute acids and strong alkali,

PRECLINICAL INDICATORS OF ABUSE POTENTIAL & DEPENDENCE:

Buprenorphine has been demonstrated in pharmacodynamic and clinical studies to have potency 10-20 times greater than that of morphine as an analgesic. Pharmacologically, buprenorphine behaves as a partial agonist at μ-opiate receptors and an antagonist at κ-opiate receptors. Addition of naloxone to buprenorphine enhances precipitation of abstinence signs by the combination product compared with buprenorphine alone. Human studies have shown that when the combination tablets are taken sublingually, they behave like sublingual buprenorphine, but if taken parenterally combinations of buprenorphine and naloxone precipitate opiate withdrawal in dependent subjects. Direct dependence studies in monkey and rat were negative for both withdrawals induced by simple discontinuation of the treatment and by administration of naloxone. Clinical pharmacology studies have confirmed the observations in animals that Subutex produces physical dependence and will substitute for opioids such as heroin.

Schmidt, W. K., Tam, S. W., Shotzberger, G. S., Smith, D. H., Clark, R., and Vernier, V. G., "Nalbuphine," Drug & Alcohol Depend., 14: 339-362, 1985: Identification of multiple opioid receptors and endogenous opioid peptides is a fundamental

pharmacological concept. Based on studies of their analgesic and side effect profiles, it was proposed that narcotic-related analgesics could be classified as having varying degrees of μ (morphine-like), κ (ketocyclazocine- or nalorphine-like), and σ (SKF 10,047-like) activity in the chronic spinal dog preparation. Also, the existence of a separate δ receptor to explain the action of enkephalin-related peptides. Receptor binding profiles demonstrated that morphine, D-ala-D-leu (DADL)-enkaphalin, (-)-ethylketo-cyclazocine and (+)-SKF 10,047 are potent model ligands for μ, δ, κ and σ receptors, respectively, in guinea pig brain homogenates. Relative selectivity is demonstrated by the generally lower affinities (higher K_i's) each model ligand has for opposing receptor types. Receptor binding studies are equally sensitive to antagonists for each receptor. Naloxone and naltrexone have their highest affinities for the μ receptor, but also have strong affinities for κ and δ receptors at 10-25 times higher concentrations. Nalbuphine binds with moderately high affinity to μ, δ, and κ receptors. In contrast to pentazocine, cyclazocine and butorphanol, nalbuphine is devoid of activity at the sigma receptor. Buprenorphine is the only other analgesic of the partial or mixed agonist class that is inactive at the σ binding site, though it is strongly active at μ, κ, and δ sites (TABLE 11).

TABLE 11. NARCOTIC RECEPTOR BINDING

DRUG	Ki (nM)			
	μ	δ	κ	σ
Morphine (μ)	38	510	1,900	>100,000
DADL-enkephalin (δ)	150	1.8	>10,000	>100.000
(-)-ethylketocyclazocine (κ)	2.3	5.2	2.2	19,000
(+)-ethylketocyclazocine	2,500	>10,000	1,600	55
(-)-SKF 10,047	3.0	15	4.7	1,800
(+)-SKF 10,047 (σ)	1,880	19,000	1,600	48
Nalbuphine	6.3	163	61	>100,000
(±)-pentazocine	39	467	87	18
(±)-cyclazocine	0.45	6.3	5.9	36
(±)-bremazocine	0.90	2.8	0.67	195
Butorphanol	1.7	13	7.4	2,300
Buprenorphine	0.77	2.2	1.1	>100,000
Naloxone	1.2	19	12	>1,000,000
Naltrexone	0.37	9.4	4.8	>100,000

Swain, H. H. and Seevers, M. H., "Examination of new compounds for morphine-like physical dependence in the rhesus monkey." In Problems of Drug Dependence, 1975, 791.: Single-dose studies of buprenorphine in morphine-dependent rhesus monkeys showed that, at a dose of 0.32 mg/kg s.c., buprenorphine precipitated severe, long-lasting (12 hours) abstinence signs. At smaller doses, the abstinence signs were mixed with those of mild, morphine-like depression. The dosage schedule was as follows: Buprenorphine was started at a dose of 0.08 mg/kg, injected s.c. in an aqueous solution at 6-hour intervals. On the 5th day of the study, the dose was raised to 0.16 mg/kg, on the 12th day it became 0.32 mg/kg; on the 19th day it was increased to 0.64 mg/kg; and from the 22nd through the 33rd days of the study, the dose was 1.28 mg/kg. On the 33rd day, drug administration was terminated abruptly.

First administration of the 0.08 mg/kg s.c. dose caused signs of mild CNS depression, such as seen with a small dose of morphine – body sag, slight ataxia, decreased apprehension, pupil dilatation and, in 2 of the animals, lip-smacking. With repeated administration of the 0.08 mg/kg dose, these signs disappeared. When the dosage was raised from 0.08 to 0.16 mg/kg/injection and again when the dose was increased to 0.32 mg/kg, there was the reappearance of these same signs and again their disappearance as the new dose was continued. The increases to doses of 0.64 and 1.28 mg/kg caused no changes in the animal's behavior.

Physical dependence: There was a lack of evidence that buprenorphine resulted in physical dependence upon repeated administration. On the 14th and 28th days of the study, the animals were challenged with nalorphine, in a dose of 2 mg/kg s.c. In neither instance did nalorphine precipitate abstinence signs. Likewise, naloxone was given a dose of 2 mg/kg on the 16th and 29th days and again there were no signs of a withdrawal syndrome. Finally, administration of buprenorphine was terminated abruptly on the 33rd day of the study, without producing signs of abstinence.

Summary: Buprenorphine precipitated severe, long-lasting abstinence signs in morphine-dependent monkeys, had only minimal direct effects, and its administration did not lead to abstinence signs, either when drug administration was discontinued abruptly or when the animals were challenged with either nalorphine or naloxone.

Woods, J. H. and Gmerek, D. E., "Substitution and primary dependence studies in animals", Drug and Alcohol Dependence, 14: 233-247, 1985: Mixed agonist-antagonist and partial agonist analgesics (including buprenorphine) were compared to the prototype μ and κ agonists morphine and Mr2033, respectively, in rhesus monkeys. Tests included: 1. Overt behavioral effects upon acute administration in drug-naive animals; 2. Discriminative stimulus properties in monkeys trained to respond to either etorphine or ethylketazocine; 3. Self-administration of the test agent relative to codeine and single dose suppression; 4. Precipitation in withdrawn and non-withdrawn morphine-dependent monkeys, respectively; and 5. Primary addiction studies in drug-naive animals. Whereas both buprenorphine and nalbuphine precipitated withdrawal in morphine-dependent monkeys, withdrawal following chronic administration of buprenorphine resulted in no observable signs of abstinence.

Buprenorphine was administered every 6 hours at doses increasing from 0.08 to 1.28 mg/kg. Tolerance rapidly developed to the stupor and muscle relaxation produced by buprenorphine. Nalorphine challenge had no effect in buprenorphine-dependent monkeys. Naloxone caused some piloerection, irritability and restlessness, but not enough to justify withdrawal scores above zero. Abrupt withdrawal of buprenorphine resulted in some restlessness, tremor and tongue movements. However, the monkeys did not protect their abdomens while in their cages, nor was there evidence during palpation of abdominal cramping. There were no observable signs indicative of physiological dependence to buprenorphine. Results of primary addiction studies with the test compounds are summarized in the TABLE 12 below.

TABLE 12. RESULTS OF PRIMARY ADDICTION STUDIES.

Drug	Maximum dose (mg/kg/24 hr)	Naloxone-precipitated withdrawal score (2 mg/kg on day 30 of chronic administration	Maximum withdrawal score during natural abstinence	Natural withdrawal type
Buprenorphine	4.8	None	None	None
Butorphanol	24.0	5-6	2-3	κ
Nalbuphine	128.0	2-3	2-3	μ
Pentazocine	48.0	1-2	3	κ
Morphine	12.0	5-6	6-7	μ
UM 1072	12.0	1-2	2	κ

SUMMARY: Buprenorphine has μ-like agonist effects in drug discrimination and self-administration tests, but precipitates withdrawal in morphine-dependent rhesus monkeys. Buprenorphine was unable to produce significant physiological dependence. However, multiple i.v. injections of buprenorphine in chronic spinal dogs resulted in a mild but prolonged abstinence syndrome. Buprenorphine also partially suppresses withdrawal in morphine-dependent chronic spinal dogs and in 8-hour withdrawn morphine dependent rhesus monkeys. These studies indicate that buprenorphine does have the potential to produce dependence. The dependence-producing capacity of buprenorphine can be demonstrated in rats when buprenorphine pretreatment is followed by substitution with morphine. Thus, naloxone-precipitated withdrawal signs are observed following a single dose of morphine in rats pretreated with multiple injections of buprenorphine, but not in saline-pretreated rats. Buprenorphine thus apparently increases the potential of morphine to induce dependence. The few signs of withdrawal that can be observed in direct dependence tests with buprenorphine reflect the slow dissociation of buprenorphine from opiate receptors. See TABLE 13.

TABLE 13. SUMMARY OF THE PROFILE OF EFFECTS OF SELECTED DRUGS IN RHESUS MONKEYS.

DRUG	Shares discriminative effects with		Rate of Self-Administration	Effect or withdrawal in morphine-dependent monkeys		Primary dependence natural-withdrawal type
	Morphine	Ethyl-ketazocine		Suppresses	Precipitates	
Buprenorphine	Yes	No	High	No	Yes	None
Butorphanol	Yes	No	Low	No	No	κ
Nalbuphine	Yes	No	Intermediate	No	Yes	μ
Pentazocine	No	No	Low-high	No	No	κ
Morphine	Yes	No	High	Yes	No	μ
UM 1072	No	Yes	Low	No	No	κ

Yanagita, T., Katoh, S., Wakasa, Y. and Olnuma, N., Dependence potential of buprenorphine studied in rhesus monkeys. In Problems of Drug Dependence 1981, Proceedings of the 43rd Annual Scientific Meeting, The Committee on Problems of

Drug Dependence, Inc., National Institute on Drug Abuse, Research Monograph Series 41, 208215, 1982: Buprenorphine is an opiate partial agonist with a high affinity for opiate receptors and is known to exhibit a strong and relatively long-lasting analgesic effect in animals and man. Analgesic effect in man is approximately 30 times that of morphine, while the effects of buprenorphine continue longer than those of equipotent doses of morphine, meperidine or pentazocine. Also, the drug is a potent opiate antagonist, the effect of which has been reported to be nearly equal to that of naloxone.

Tolerance: Repeated administration of buprenorphine to rhesus monkeys showed that within 2 weeks the depressant effects as seen in the gross behavior of the monkeys became weak. No cross-physical dependence to morphine was observed in suppression test and no withdrawal sign was observed even in the second natural withdrawal test, but some minor atypical withdrawal signs were precipitated in the second test. Thus, from these results it remains unclear whether or not buprenorphine possesses a morphine-like physical dependence potential. In the i.v. cross self-administration experiment with lefetamine, buprenorphine was found to have clear reinforcing effect at the unit doses of 4 μg/kg/inj. or more. In the continuous self-administration experiment also, all 4 monkeys self-administered the drug. The highest daily dose of buprenorphine self-administered by any monkey in any 2-week period during this experiment was 3.3 mg/kg. Doses self-administered by the other monkeys were 2.51, 1.24, and 1.07 mg/kg/day. There is a relatively wide individual variation in the average daily dose level but fell within a non-lethal dose range even if injected i.v. all in one dose.

CLINICAL DEPENDENCE STUDY:

Luis S., Cami, J., Fernandez, T, Olle, J. M., Peri, J. M., and Torrens, M., "Assessment and management of opioid withdrawal symptoms in buprenorphine-dependent subjects," Brit. J. Addiction, 87: 55-62, 1992: The spontaneous physical dependence of buprenorphine was assessed in opioid addicts who switched from heroin to sublingual or intravenous buprenorphine. Twenty-two patients were randomly assigned to double-blind administration of methadone (N=11) or placebo (N=11) for 13 days after abrupt withdrawal of buprenorphine. Methadone was administered according to 4 pre-established dosing schedules depending on the previous amount of daily consumed buprenorphine. No methadone-treated patient required modification of the therapeutic regimen, whereas 8 of 11 placebo-treated patients needed treatment with methadone. Buprenorphine withdrawal syndrome was of the opioid type, beginning somewhat more slowly, and peaking at day 5. Two stages were observed: anxiety, craving, chills, gooseflesh, myalgia, and weakness on days 1-5, and sleep disturbances on days 6-13. Most severe symptoms occurred on days 1-5 after abrupt withdrawal of buprenorphine. All patients switched from intravenous heroin to buprenorphine (mostly i.v. crushed tablets). The mean time on buprenorphine was 8 months with a mean daily dose of 2 mg. Withdrawal effects produced by dose reduction or detoxification are milder compared to heroin or similar narcotics, because of the long action of buprenorphine, and the slow dissociation of buprenorphine from the μ-opioid receptor. The adjustment from "drug exposure" to "drug free" can take place gradually. The persistence of buprenorphine on

the receptor is further shown by the inability of normal low doses of naloxone and naltrexone to displace buprenorphine.

PHARMACOKINETICS ASPECTS:

Pharmacokinetic features of a drug are believed to affect the drug's abuse liability. Buprenorphine has long duration of action due to its slow dissociation from the μ-opioid receptor and its slow elimination rate.

Drug Interactions: Full μ-opiate receptor agonists, are known to produce respiratory depression, coma and death if taken at high doses, especially by the i.v. route, and this is a common cause of fatality in heroin addicts. Most deaths (fatal overdoses) from Subutex have been associated with the drug in combination with other agents. There have been several deaths associated with the drug that have been attributed to misuse of benzodiazepines while receiving Subutex in humans, pointing to a possible interaction.

Inhibition of flunitrazepam metabolism to 3-hydroxyflunitrazepam and desmethylflunitrazepam by buprenorphine and norbuprenorphine was investigated *in vitro* in human liver microsomes and cDNA expressed human CYP 2C19 and CYP 3A4 microsomes. Buprenorphine competitively inhibited 3-hydroxyflunitrazepam formation in human liver and cDNA expressed CYP 3A4 microsomes with mean Ki values of 118 μM and 38 μM respectively. Buprenorphine also competitively inhibited formation of omeprazole sulphone (CYP 3A4 metabolite). However, buprenorphine did not inhibit the formation of desmethylflunitrazepam or 5-hydroxyomeprazole (CYP 2C19 metabolites) in human liver microsomes or cDNA expressed CYP 2C19 microsomes. Concentrations of norbuprenorphine that reached 100 μM did not inhibit either flunitrazepam or omeprazole metabolism. *In vivo* inhibition of CYP 3A4 mediated metabolism of flunitrazepam by *in vivo* concentrations of buprenorphine was estimated at 0.1-2.5%. Inhibition of buprenorphine N-dealkylation *in vivo* by typical plasma concentrations of flunitrazepam (0.03μM) was estimated at 0.08%. Based on these *in vitro* results, concomitant admnistration of buprenorphine and fluntirazepam would have minimal pharmacokinetic interaction and not affect the concentration of either drug when given concurrently in humans. This runs counter to the argument from France that reported deaths involve combinations with benzodiazepines, not the drug alone.

In vitro interactions between methadone or buprenorphine and fluoxetine or fluvoxamine were compared. Fluoxetine inhibited methadone N-demethylation but did not inhibit buprenorphine dealkylation. Norfluoxetine inhibited metabolism of both methadone and buprenorphine metabolism. Fluvoxamine inhibited methadone N-demethylation with a Ki of 7 μM and buprenorphine dealkylation, uncompetitively, with a Ki of 260 μM. Care should be taken when SSRIs are administered in the treatment of drug craving.

The *in vitro* interaction between 3 HIV-1 protease inhibitors, ritonavir, indinavir and saquinavir, and buprenorphine has been investigated. These protease inhibitors are extensively metabolized by liver cytochrome P450 3A4. As this CYP isoform is involved in the metabolism of many medications, co-administration of protease inhibitors

may lead to effects due to enzyme inhibition. Methadone and buprenorphine, both metabolized by CYP 3A4, are potential candidates to drug interactions. The rank order of inhibition potency against metabolism of methadone and buprenorphine was ritonavir>indinavir>saquinavir. Thus, there is potential for clinically significant drug interactions, particularly with ritonavir and caution is needed if HIV-1 protease inhibitors are co-administered with methadone or buprenorphine. Other CYP 3A4 inhibitors which have the potential to increase plasma concentrations of buprenrophine include the cannabinoids.

Bioavailability: Oral administration of Subutex results in very low bioavailability because of extensive metabolism of buprenorphine hydrochloride in the small intestine and liver to N-dealkyl buprenorphine (norbuprenorphine) and gluronides of buprenorphine. These are the major metabolites of buprenorphine hydrochloride in all species including man. The excretion of buprenorphine-related material in all species including man is predominantly (70-90%) via the feces following biliary excretion of buprenorphine and N-dealkyl buprenorphine glucuronides. A marked entero-hepatic recirculation of drug-related material occurs in rats and probably also in other species and in man. This, together with the high lipophilicity of buprenorphine and its distribution to fat tissue, gives rise to a slow total excretion of drug-related material.

Co-administration of naloxone with ^{3}H-buprenorphine (Suboxone) by oral, im and iv routes to the rat and the dog did not alter the disposition, kinetics or metabolism of ^{3}H-buprenorphine. Similarly, co-administration of ^{3}H-naloxone with buprenorphine by these routes had no detectable effect on the disposition, kinetics or metabolism of ^{3}H-naloxone. It should be noted however, that none of the co-administration studies utilized the 4:1 ratio of buprenorphine hydrochloride and naloxone hydrochloride used for Suboxone.

Absorption: Factors affecting the sublingual absorption of buprenorphine are as follows. Steps involved in transport of drugs through the sublingual mucosa are: 1. drug release from the tablet into saliva, 2. dissolution of the drug in the saliva, 3. partitioning into and diffusion of the drug through the epithelial layer, 4. diffusion and partition into the blood vessels, and 5. transport away by the blood flow.

Mean tablet disintegration times were 4.02 min., 6.63 min., and 7.67 min. following the 4 mg, 8 mg and 16 mg doses of Suboxone, and 6.99 min. following the 16 mg Subutex dose. Residual fragments have been observed. Pre-dose salivary pH ranged from pH ~ ~. Post-dose salivary pH ranged from ~ . When Suboxone tablets are dissolved in deionized water the pH equilibrates to around pH ~ Dissolution studies showed that above pH ~ *in vitro* dissolution of buprenorphine from Suboxone tablets is compromised, attributed to limited aqueous solubility arising from the basic nature of the drug and its known solubility profile. The opposite effect occurs with dissolution of naloxone, which decreases below pH For weak bases like buprenorphine, only the non-ionized form of the drug is absorbed across the oral mucosa. Absorption of lipophilic weak bases should increase with salivary pH increases. It appears that the high lipid solubility of buprenorphine allows rapid absorption to the oral tissues. The tissue however serves as a reservoir that delays absorption to the systemic circulation.

Dose proportionality of absorption: A single dose cross-over pharmacology/ blood level study in 8 subjects compared 4 mg, 8 mg and 16 mg Suboxone tablets with 16 mg Subutex tablets. Mean tablet dissolution times *in vivo* were 4.02 min for the 2 mg Suboxone tablets and 6.63 min for the 8 mg Suboxone tablets. Mean tablet dissolution times *in vivo* were 4.02 min for the 2 mg Suboxone tablets and 6.63 min for the 8 mg Suboxone Tablets. The mean *in vivo* dissolution times for 16 mg dose (2 x 8 mg tablets) of Suboxone (7.67 min) and Subutex (6.99 min) were similar. Peak concentrations and AUC values of buprenorphine increased with the dose of Suboxone, although the increase was not proportional and there was a wide inter-patient variability in the levels.

Mean buprenorphine peak concentrations following the 4 mg, 8 mg and 16 mg doses were 1.84, 3.0 and 5.95 ng/mL and mean unextrapolated AUCs were 12.52, 20.22 and 34.89 ng/g.h. Within subjects, there was no difference in the buprenorphine peak concentrations and AUC values following Suboxone and Subutex tablets. Mean peak values were 5.95 and 5.47 ng/mL, respectively, and mean AUC values of 34.89 and 32.63 ng/g.h, respectively. Naloxone was absorbed from Suboxone sublingual tablets; plasma concentrations were [redacted] following the 4 mg (1 mg naloxone), 8 mg (2 mg naloxone) and 16 mg (4 mg naloxone) Suboxone doses, respectively.

Metabolism: Norbuprenorphine, a major metabolite, has a very long half life and may accumulate appreciably, almost equalling the parent drug during multiple dosing. Norbuprenorphine is a full μ-opioid agonist with low intrinsic activity and animal studies have shown that it does not readily enter the brain. The metabolite may be formed primarily in the intestine from swallowed drug. Buprenorphine is extensively metabolized by the hepatic cytochrome P450 in man yielding norbuprenorphine (*in vitro* study). The specific forms of P450 involved in the N-dealkylation is the P450 3A4 isoform. Buprenorphine and norbuprenorphine are also conjugated with glucuronic acid by a number of isoforms of UDP-glucuronosyltransferases. There are at least two unidentified metabolites in urine that account for 0.72% and 0.9% of buprenorphine dose.

Half-life, Distribution and Clearance: Half-life estimates vary from 6 hours to 10-18 hours to a mean of 32 hours (range 16-54 hours). Plasma clearance has been estimated to be 62.5 ± 2.8 L/hr following a 1 mg iv dose. Following an iv dose of 4 mg at steady state, 58.9 ± 11.5 L/hr has been estimated for clearance. Volume of distribution (Vdss) at steady state has been estimated to be 187 L (range 106-274). The value of Vd was estimated to be 2828 ± 1480 L, an order of magnitude greater than the estimate of Vdss. The latter estimate represents the ratio of total drug in the body to the plasma concentration during the terminal δ phase (rather than the second or β phase, when the apparent half life is 35 hours. At this time, significant drug is distributed in the deep compartment relative to the low plasma concentration.

Co-administration of naloxone with ^{3}H-buprenrophine by *po*, *im* and *iv* routes to the rat and the dog did not alter the disposition, kinetics or metabolism of ^{3}H-buprenorphine. Similarly, co-administration of ^{3}H-naloxone with burpenorphine by these routes had no detectable effect on the disposition, kinetics or metabolism of ^{3}H-naloxone.

OVERALL CONCLUSIONS:

1. Numerous reports of abuse and diversion have been submitted in the NDA. The reports come from the countries of Europe, India, New Zealand and Australia where the drug has been marketed. Although the drug is frequently abused by an addict population as an inexpensive substitute for poor quality or expensive heroin, in some areas buprenorphine is preferred to heroin (CSA Schedule I).

2. Actual reports of abuse of buprenorphine include abuse of the intact sublingual tablet itself. Other modes of administration include crushing the tablet followed by either intravenous injection, intranasal administration (snorting), or sublingual administration. Only abuse by intravenous administration in an opiate addicted population was largely considered in the development of the drug product.

3. The Johns Hopkins University study (Strain *et al.*), funded by NIDA, tested the effects of intact tablets of buprenorphine and buprenorphine/naloxone only by the sublingual route and in non-dependent volunteers. Results suggested that sublingual buprenorphine and buprenorphine/naloxone both may be abused by individuals who are not physically dependent upon opioids, and therefore may be recreational drugs of abuse. In addition, the study concluded that buprenorphine and buprenorphine/naloxone tablets in the dose range tested have "moderate potential for abuse" comparable in magnitude to 4 mg of parenteral hydromorphone (which is a Schedule II opiate). The purpose of adding naloxone to buprenorphine is to decrease abuse potential in opioid dependent individuals who might inject buprenorphine. In abusers who are not physically dependent on opioids, addition of naloxone will not exert a similar precipitated withdrawal. There were only small non-significant differences observed between buprenorphine and buprenorphine/naloxone.

4. The Johns Hopkins University study (Strain *et al.*) did not test the relative abuse potential of parenteral or intranasal administration of the substances, but of the intact dosage form. The abuse potential of the drugs by the intranasal route and by sublingual administration of crushed tablets has not been studied, though the drug has been abused by that route.

5. Deaths from France have been attributed to the drug interaction of buprenorphine with benzodiazepines and alcohol. However, no data has been provided to the FDA to verify this assertion. Most of the deaths involved individuals who were not given buprenorphine legally or were part of a comprehensive treatment program.

6. A summary of post-marketing data from France indicates the use of buprenorphine (Subutex) among pregnant opiate-dependent women had resulted in a number of neonates experiencing some degree of withdrawal symptoms. The level of withdrawal was reported to be of a low level and short duration, though

detailed case reports were not provided. Small open studies of buprenorphine in 29 pregnant opioid dependent women have shown normal deliveries and only mild neonatal withdrawal. Seven fetal deaths among mothers receiving Subutex were reported in the French post-marketing experience. These fetal deaths occurred among a population at extremely high risk for adverse fatal outcomes and there is no clear association between the drug and fetal death for any of these cases. However, data was not provided to the FDA to evaluate.

6. Preclinical and clinical pharmacology all are consistent with a level of control under the U. S. Controlled Substances Act (CSA) greater than Schedule V, as has been proposed by the Sponsor. The original pharmacology/toxicology review which included abuse liability assessment (March 12, 1981) for the analgesic product recommended its placement in Schedule III, though final placement of the product and substance was in Schedule V (1985).

7. The standards for abuse potential come from the legislative history of the CSA and are guides in drug scheduling recommendations:

   (a) There is evidence that individuals are taking the drug or drugs containing such a substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or of the community; or
   (b) There is significant diversion of the drug or drugs containing such a substance from legitimate drug channels; or
   (c) Individuals are taking the drug or drugs containing such a substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such drugs in the course of his (her) professional practice; or
   (d) The drug or drugs containing such a substance are new drugs so related in their action to a drug or drugs already listed as having a potential for abuse to make it likely that the drug will have the same potentiality for abuse as such drugs, thus making it reasonable to assume that there may be significant diversions from legitimate channels, significant use contrary to or without medical advice, or that it has a substantial capability of creating hazards to the health of the user or to the community. Evidence of actual abuse of a substance is indicative that a drug has a potential for abuse.

SUBOXONE SAFETY UPDATE

Date: October 1999

Report No.: RC990614

Clinical pharmacology:

1. Buprenorphine/Naloxone Combination Tablet: Effects in non-dependent opioid abusers study (CR96/021)

   A double-blind, double-dummy, crossover study in 7 subjects. Two lab challenge sessions occurred each week, at which patients received both an IM injection and sublingual tablets. The following single dose treatments were administered in a random order: Suboxone sublingual tablet doses of 1, 2, 4, 8 and 16 mg; Subutex sublingual tablet doses of 4, 8, and 16 mg; and hydromorphone IM injection doses of 2 and 4 mg.

   AGONIST EFFECTS: Pharmacological effects following acute sublingual doses of each (Suboxone and Subutex) were similar at similar dose levels of buprenorphine. Effects were dose related and there was the suggestion of a ceiling effect of the adjective agonist score between 8 mg and 16 mg of Suboxone. The 16 mg doses of Suboxone and mono buprenorphine tablets had similar opioid agonist effects to 4 mg IM hydromorphone (equivalent to about 30 mg IM morphine). This indicates that naloxone, in presence of buprenorphine, has no clinically significant effect when administered by sublingual route. Mean subjective and objective adjective agonist scores for Subutex and Suboxone were dose-related and comparable, dose for dose.

   ANTAGONIST EFFECTS: Opiate withdrawal VAS measures (*bad drug* and *sick*) were more greate at the lower (4 mg) dose, than at the other 2 dose levels.

   VITAL SIGNS: No significant changes on measures of blood pressure, heart rate or respiratory rate. Skin temperatures increased for both hydromorphone conditions, all 3 buprenorphine conditions and the highest dose of buprenorphine + naloxone. Also, pupil diameter showed significant constriction for all of the dose conditions tested except the lowest buprenorphine + naloxone condition (1 mg + 0.25 mg). The physiologic measure oxygen saturation was decreased for the 8 mg and 16 mg Subutex and 16 mg Suboxone conditions.

   OVERALL CONCLUSIONS: Suboxone tablets have a clinical pharmacological profile similar to Subutex tablets for all the effects measured in this study.

2. Comparisons of Sublingual, Oral and Intravenous Administration of Buprenorphine + Naloxone Combinations (CR96/023)

A PD/PK study compared 8 mg Suboxone sublingual, 8 mg of Suboxone oral, and 8 mg buprenorphine + 2 mg naloxone intravenous in 9 opioid-experienced non-dependent subjects. Vital signs data after swallowing an 8 mg Suboxone tablet were compared with administration by the SL and IV routes. Confirmation of the low SL absorption of naloxone from Suboxone tablets was demonstrated.

Study was an open label, balanced 3x3 Latin square crossover design. Order of drug administration was randomized. Experimental sessions were approximately 7 days apart. Treatment conditions were as follows: (i) buprenorphine(8 mg) / naloxone (2 mg) (Suboxone), oral; (ii)) buprenorphine(8 mg) / naloxone (2 mg) (Suboxone), sublingual; (iii)) buprenorphine(2 mg) / naloxone (0.5 mg), IV. Drug treatments were separated by at least 7 days.

VITAL SIGNS: Respiration and pupil size decreased following administration of the oral and sublingual tablet. The SL tablet produced a significantly greater decrease in both parameters than the orally administered tablet ($p<0.01$). The greater SL pharmacological effects are consistent with the greater blood levels of buprenorphine obtained SL compared to orally. IV dose produced decreases in respiratory rate and pupil size significantly greater than the orally ($p<0.01$) but not greater than the sublingual route. No significant differences in systolic and diastolic BP, heart rate, and rate pressure product were found between SL and orally administered Suboxone.

OVERALL CONCLUSIONS: No marked acute effects on vital signs. Only low amounts of naloxone are absorbed sublingually from Suboxone tablets. It is expected that there would be no sublingual clinical effect from naloxone and is consistent with the observed similarity between the pharmacological effects of Subutex (no naloxone) and Suboxone (buprenorphine + naloxone). Buprenorphine plasma levels were lower following oral Suboxone. This was the expected result because of the marked metabolism of buprenorphine to norbuprenorphine that occurs in the small intestine and liver.

ADVERSE EVENTS FROM MARKETING OF SUBUTEX

France: Marketed for treatment of opioid dependence in February 1996. Subjects estimated for having received Subutex on the market.

From February 1996 to December 31, 1998, 682 events were reported for 322 subjects. Most frequently reported ADEs involved the central & peripheral nervous system (123 reports), body as a whole (76 reports), respiratory system disorders (66 reports), psychiatric (58 reports), neonatal & infancy disorders (56 reports), and liver & biliary (43 reports). Individual events reported most frequently by subjects were neonatal

withdrawal (50 subjects), coma (29 subjects), miosis (23 subjects), and asphyxia (22 subjects).

Subutex Post-Marketing ADEs reported by 5 or More Subjects (2-96 thru 7-99).

ADVERSE EVENTS	TOTAL
Application Site Disorders	
Injection Site Abscess	6
Injection Site Inflammation	7
Injection Site Reaction + Right Arm	6
Body As A Whole	
Death	15
Edema	5
Fever	9
Headache	9
Malaise	8
Withdrawal Syndrome	16
Cardiovascular Disorders, General	
Hypotension	5
Central & Peripheral Nervous System Disorders	
Coma	31
Confusion	10
Convulsions + Grand Mal	13
Delirium	6
Hypertonia	6
Paresthesia	5
Somnolence	15
Tremor Neonatal	15
Disorders of Blood & Lymphatic System	
Lymphadenopathy	5
Disorders of the Eye	
Miosis	25
Fetal Disorders	
Death Fetal	6
Gastro-Intestinal System disorders	
Abdominal Pain	8
Diarrhea	5
Nausea	5
Vomiting	6
Liver & Biliary System Disorders	
Hepatic Enzymes Increased	14
Hepatitis	10
Jaundice	10
Metabolic & Nutritional Disorders	
Weight Decrease	10

Neonatal & Infancy Disorders	
Withdrawal Syndrome Neonatal	66
Psychiatric Disorders	
Aggressive Reaction	7
Agitation	15
Hallucination	11
Suicide Attempt	7
Respiratory System Disorders	
Asphyxia	22
Dyspnea	8
Hypoventilation	12
Skin & Subcutaneous Tissue Disorders	
Erythema	8
Pruritus	6
Sweating increased	5
TOTAL NUMBER OF EVENTS	**806**
TOTAL NUMBER OF SUBJECTS	**402**

APPEARS THIS WAY
ON ORIGINAL

DEATHS RELATED TO MARKETING OF SUBUTEX.

As of 7-31-99, a total of 66 deaths were reported. Most frequent cause of death was asphyxia (21 subjects), followed by "cause unknown" (20 subjects).

SUMMARY OF PATIENT* DEATHS DURING MARKETING OF SUBUTEX.

Body System	Patients #	Most Frequent Events
Body as a Whole	**22**	**Most reports are "cause unknown"**
Cardiovascular	**1**	**Patient misused Subutex by IV route (cardiac failure, hypertension pulmonary, pleural effusion, tachycardia supraventricular, vasospasm, cyanosis, bradycardia, dyspnea)**
Fetal disorders	**9**	**Congenital anomaly (N=6)**
Infection/Infestation	**1**	**Patient misused Subutex by IV route (septic shock)**
Injury/poisoning	**2**	**Moving vehicle accident (N=2)**
Liver & Biliary	**3**	**One patient misused Subutex by IV route (hepatocellular damage, asthenia, jaundice, and hepatitis aggravated); One patient HIV, Hep B and Hep C positive (hepatic cirrhosis); One patient HIV and Hep C positive (hepatic cirrhosis aggravated).**
Psychiatric	**1**	**Suicide (accomplished)**
Respiratory	**27***	**Asphyxia (N=21) One patient misused Subutex by smoking and sniffing (pulmonary edema, coma)**

***Three of these reports (pulmonary edema) may be repeated information of the same case.**

Neonatal Adverse Events Relating to Use of Subutex During Pregnancy.

There have been 66 reports of neonatal withdrawal syndrome. Other symptoms reported for neonates, whose mothers were treated with Subutex, are listed in the Table below. In some cases, other self-administered drugs could have contributed to the neonatal withdrawal symptoms.

Neonatal Withdrawal Symptoms in Reports Following Marketing of Subutex

ADVERSE EVENT	TOTAL
Body as a Whole – General	
Appetite decreased	1
Crying abnormal	7
Fever	1
CNS disorders	
Coma	1
Convulsions	6
Hyperkinesia	3
Hypertonia	6
Hypokinesia	1
Hypotonia	1
Myoclonus	2
Somnolence	2
Tremor	7
Eye Disorders	
Miosis	1
Heart Rate & Rhythm	
Bradycardia	2
Tachycardia	1
Fetal Disorders	
Fetal Distress	1
GI System	
Diarrhea	2
Vomiting	4
Metabolic & Nutritional	
Acidosis	3
Hypoglycemia	1
Psychiatric	
Agitation	9
Insomnia	1
Nervousness	1
Respiratory	
Respiratory Arrest	1
Respiratory Depression	1
Dyspnea	3
Tachypnea	1
Skin & Subcutaneous	
Sweating	2

Vital Signs & Other Safety Assessments

1. Potential for QT interval prolongation by Suboxone.

554 ECG records for 323 subjects who received at least one dose of drug were available for review. Analysis showed that there was no mean increase in QTc interval from baseline among the 3 treatment groups (16 mg Suboxone, 16 mg Subutex, placebo). Analysis did not show a change in mean QTc from baseline nor individually clinically significant changes in relation to study medication.

2. Significant Adverse Events.

There is only one significant observation, a subject who ingested a massive dose (112 mg) of buprenorphine, leading in 48 hours to serious hepatitis associated with anuric renal failure.

a. Hepatonephritis & Massive Ingestion of Buprenorphine

3. Nonclinical Toxicology.

A series of genotoxicity tests on buprenorphine + naloxone (4:1) was undertaken and submitted. An update was submitted with the safety update. A 2-year carcinogenicity study will be a Phase 4 commitment. A 28-day palatability study in rats has recently been completed. The admixture of buprenorphine + naloxone to rat chow is a satisfactory route of administration of the test substances. This dietary method of administration has been used in an ongoing 90-day toxicity study of buprenorphine + naloxone (4:1). These findings will be used to choose the doses for the 2-year carcinogenicity study.

CONCLUSIONS:

1. It is difficult to distinguish adverse events that are associated with buprenorphine from those that may be caused by opiate withdrawal.
2. With benzodiazepines, 9 more deaths reported. Runs counter to drug interaction PK study.
3. Buprenorphine has been associated with clinically severe hepatic adverse events. Three deaths, all with HIV and hep C.
4. Increasing number of reports of neonatal withdrawal.

ABUSE LIABILITY REVIEW

ABUSE POTENTIAL STUDY OF SUBLINGUAL BUPRENORPHINE PRODUCTS

Study: Pharmacokinetic comparison of the buprenorphine sublingual liquid and tablet

Investigators: Kory J. Schuh and Chris-Ellyn Johanson (Wayne State University School of Medicine, Department of Psychiatry & Behavioral Neurosciences, Research Division on Substance Abuse, 2761 E. Jefferson, Detroit, Michigan 48207, USA).

Source: Drug and Alcohol Dependence 56 : 55-60, 1999.

Rationale: Buprenorphine is a μ-opioid partial agonist that is administered as a sublingual tablet. It has been reported that for abuse the buprenorphine tablet has been crushed, and then taken sublingually. Buprenorphine dispersed in a liquid and administered sublingually which has been studied clinically is analogous, to some extent, to the crushed tablet in facilitating enhanced sublingual absorption by providing more surface area.

Objectives: To compare participants' plasma concentrations after daily maintenance on three buprenorphine liquid doses (2, 4 and 8 mg) and one tablet dose (8 mg). Plasma samples were collected over a 24-hour period after at least 7 days of maintenance on each dose. The present study was done to compare the plasma concentrations produced by 3 doses of the liquid buprenorphine (2, 4 and 8 mg) with the 8-mg tablet when stable plasma concentrations were achieved after a minimum of 7 daily administrations. Mendelson *et al.* (1996) compared an 8-mg sublingual tablet with an 8- mg solution. Results indicated that AUC and peak concentration were less after the tablet than after the solution. The tablet yielded about 50-60 percent of the buprenorphine compared with the 8-mg solution.

Subjects: 14 Adult volunteers (11 males/ 3 female), physically dependent on opioids for 3 to 30 years (average 16 years). Average age 40 years (range 20-50 years).

Study Procedure: Participants were maintained on daily buprenorphine doses of 2, 4, 8 mg liquid, and 8 mg tablet. They participated in 4 test sessions, one at the end of each of these dosing phases. Participants were maintained on each dose for at least 7 days before each of the test sessions. After the last dose, participants were detoxified by receiving 4, 2, 1 and 0 mg buprenorphine for at least one week at each dose. Urine samples were collected 3 times per week and analyzed to determine use of other drugs of abuse.

Laboratory Sessions: Testing took place over a 3-day period. On the first day, urine and plasma were collected 15 minutes before administering the participant's daily buprenorphine dose (24 hours before the next day's dose). During the 2nd day, a urine

sample and alcohol breath were collected and analyzed. If sober and drug free (except opiates), sesion continued. A plasma sample was collected 15 min before the buprenorphine dose was administered as well as 30, 60, 120, 180, 240 and 360 min. after the dose. On the 3rd day, a plasma sample was collected 15 minutes before the buprenorphine dose (approximately 24 hours after the previous day's dose). Plasma concentrations were determined using liquid chromatography/tandem mass spectrometry.

Drugs & Doses: Buprenorphine hydrochloride as liquid solutions (2, 4 and 8 mg/mL in 1-mL plastic containers) and 8-mg (calculated as base) sublingual tablets. Each does was placed under the tongue and held for at least 5 mintues.

Measures:
Buprenorphine plasma concentration data with dosing and time as factors.

Data Analysis:
Plasma concentration raw data were analyzed using a two-way repeated-measures analysis of variance (ANOVA) with buprenorphine dosing phase and time as factors. Dosing phase within each time point was compared using two-tailed matched-pairs *t*-tests. Raw data were also used to obtain AUCs for each buprenorphine dosing phase. AUCs were calculated based on the plasma concentrations produced by one buprenorphine dose. Therefore, plasma concentrations from the -24-h and -15-min timepoints were not included. Peak concentrations, AUCs, and trough concentrations were analyzed using one-way repeated-measures ANOVAs.

To determine if participants who had high (or low) plasma concentrations during a particular dosing phase also had high (or low) concentrations during the other dosing phases, concentrations produced by the 3 ascending liquid doses and the tablet dose were rank ordered from 1 (participant with the highest concentration at each dosing phase) to 14 (participant with the lowest concentration at each dosing phase). Rank orders were analyzed using a 2-tailed Spearman correlation coefficient.

To determine if plasma concentrations produced by the dosing phases could predict the number of opioid-positive urine samples (e.g., did participants with highest buprenorphine plasma concentrations have fewest opioid-positive urine samples), plasma concentrations averaged over the 4 dosing phases were rank-ordered from 1 (participant with the highest average concentration) to 14 (participant with the lowest average concentration), and were correlated with rank ordered % opioid positive urine samples. Again, a 2-tailed Spearman Correlation Coefficient was used.

Results: The 8-mg liquid produced the highest plasma concentrations. For all doses, average concentrations peaked 120 min. after buprenorphine administration at which time the average plasma concentrations were 1.99, 2.37, 5.22, and 2.87 ng/mL for the 2-, 4-, 8-mg liquid, and the 8-mg tablet doses, respectively. At the 120 min time-point, the plasma concentrations produced the 8-mg tablet were 55% of those produced by the 8-mg liquid.

MEMORANDUM OF TELECON

NDA #: 20-733

DRUG NAME: Suboxone

DATE / TIME OF TELECON: 8/19/99 / 9:30 a.m.

SPONSOR / Phone: Reckitt & Colman / 1-804-379-1090

NOTES TAKEN BY: Tony Chite

INITIATED BY SPONSOR OR FDA: FDA

IN ATTENDANCE/ FDA: Tony Chite; Abi D'Sa; Pat Maturu

IN ATTENDANCE/ SPONSOR: Charles Chapleo; Don Walter; Neil Muir; Charles O'Keefe

DISCUSSION: The purpose of the telecon was to have the agency's chemist present the question on stability of this drug product and to ask what is occuring with failing stability [redacted] This is an early alert that we have a problem with the stability data.

The sponsor stated that [redacted]

The sponsor plans [redacted] they will change the shape to hexagonal.

The agency stated that we will have to see the results and discuss this with the pharmacokineticist before the agency agrees with a change in shape.

The sponsor will amend the file to withdraw [redacted] as an [redacted]

In addition, the sponsor has agreed to send the following data to the agency in 2 weeks :

1) Information on the investigation on [redacted]
2) A Development Pharmaceutics report
3) The uniformity of [redacted]
4) The scale up or process development work
5) All stability data on all lots

Minutes prepared by Tony Chite / Chair Concurrence by Albinus D'Sa, Ph.D. [/S/]

Printed by Anthony Chite

Electronic Mail Message

Date: 19-Aug-1999 02:21pm
From: Mathew Thomas
THOMASM
Dept: HFD-45 MPN1 125
Tel No: 301-594-1032 FAX 301-594-1204

Subject: NDA# 20,733 Suboxone

Dr. Malek has confirmed that three inspections have been assigned for studies submitted in support of NDA# 20,733 (Suboxone). No further action is indicated at this time. DSI will provide a final summary to the Review Division after evaluating the EIRs pertaining to the assigned inspections.

Mathew.

6 Page(s) Withheld

MEMORANDUM OF TELECON

NDA #: 20-733

DRUG NAME: Suboxone

DATE/TIME OF TELECON: 7/9/99; Friday ; 9:20 a.m.

SPONSOR: Reckitt & Colman

NOTES TAKEN BY: Tony Chite

INITIATED BY SPONSOR OR FDA: FDA

IN ATTENDANCE/ FDA: Corinne Moody, Mike Klein, Tony Chite

IN ATTENDANCE/ SPONSOR: Charles O'Keefe

DISCUSSION: The following questions arose from the Filing Meeting on 7/8/99 for the sponsor. These questions were presented to Charles O'Keefe:

1. How are your responses progressing to the Agency's requests in the telecon that we had on June 25, 1999?

Response: The responses to all of the issues in the telecon were sent out to the Agency on 7/8/99 and should be arriving as we speak today (7/9/99)

2. The medical officer needs the SAS data sets for Study 1008A & 1008B.

Response: The sponsor is putting those sets together as we speak and they will be sent.

3. The statistician needs the SAS data sets on the other 2 studies, which are CR92/099 and CR88/130.

Response: The sponsor will be able to send these but wants to know what the statistician is looking for specifically because there are hundreds of files. Mr. O'Keefe stated that all of this data is in Excel and on an IBM laptop computer that was presented to Monte Scheinbaum at the Agency.

4. The pharmacokineticist needs the PK/PD analysis data on diskette.

Response: This will be done.

5. The Abuse Liability team leader needs the individual case reports on neonatal withdrawal that are mentioned in Volumes 147 & 149. Those reports that are referenced in French will be needed in English. Also needed are the complete cases of overdosage.
   Dr. Klein also requested the Eric Strain final study reports.

At the conclusion of the Agency's above requests,Charles O'Keefe stated that he would be sending the response to the mono application in 1-2 weeks (from 7/9/99). He stated that the Case Report Forms are on CD's and for space saving purposes and he would rather not send the paper format of Study 1008 since it involves 60 volumes and all Case Report Forms are already present at the Agency. Ms. Moody stated that she would call Mr. O'Keefe if this was not acceptable.

C/my documents/Telecons/20733Jul9-99

RECKITT & COLMAN
PHARMACEUTICALS
INC.

July 7, 1999

Cynthia McCormick, MD, Director,
Division of Anesthetic, Critical Care and Addiction Research Products
HFD-170
Office of Drug Evaluation III
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

DUPLICATE

NDA 20-733

Dear Dr. McCormick,

This is in response to our telephone meeting of June 25, 1999 and your subsequent letter dated June 28, 1999 relaying minutes of the meeting.

Thank you for the guidelines relating to electronic NDA submissions and the electronic format of Case Report Tabulations. While it is our intention to assist the review by providing electronic information, you should note that it was not our intention to file an electronic submission.

Following are our comments about the discussion items listed in your letter.

1. Unless Reckitt & Colman owns or has right of reference to all data and findings cited in this submission, NDA 20-733 should be filed under 505(b)(2) rather than 505(b)(1). It will also be necessary to identify those parts of the application in which data are relied upon which Reckitt & Colman does not have right of reference. This includes data relied on to support all claims throughout the labeling.

1. Reckitt & Colman owns or has right of reference to all the data in NDA 20-733. Details are provided in **Attachment 1**. Therefore, we believe that the application was correctly filed under 505(b)(1).

2. It will not be possible to waive the requirement for case report tabulations. These are essential to the review and must be submitted in order for the NDA to be filable. There was some discussion how these should be formatted, and the agency agreed to fax Reckitt & Colman the guidance on Electronic Submission that explains how to prepare the tabulations.

1901 HUGUENOT ROAD RICHMOND, VIRGINIA 23235 TELEPHONE (804) 379-1090 FAX (804) 379-1215

2. Reading the guideline on Case Report Tabulations it is clear that these are similar to the data listings that have already been submitted as part of the clinical reports in the Application. **Attachment 2** shows the locations of the data listings for the two Suboxone studies, #1008 (CR96/013 + CR96/014), and the Pilot Study (CR95/002). As requested, we will provide electronic Case Report Tabulations. Unless specifically requested by you we would not also provide paper copies of the CRTs as submitted electronically.

3. The interim study report for Study CR96/005 (Australia) is from August 1997. The agency requires the full study report, including efficacy data and CRFs. Dr Walter explained that the safety data is not ready to submit because the contractor had mixed withdrawal symptoms into the adverse events, and other personnel are presently attempting to sort out the adverse event section. This will take several months. Reckitt & Colman had not anticipated the need to submit this study, as it did not use the Suboxone tablet, but the agency explained that this data is needed to support the Suboxone NDA. The Agency agreed to accept the efficacy data now, for filing, with the understanding that the safety data must be included in the 4 month safety update

3. You have indicated that the Australian study report is needed to support the Suboxone NDA. As we said during the telephone conference, this was unexpected as this is a study of Subutex, not Suboxone. It was never our intention to submit the final report of this study in NDA 20-733. The efficacy data have been finalized but have not been written as a report. It was planned that a complete report would be submitted when all the data were available. To comply with your request we will prepare a brief summary of the efficacy data and submit this for filing with the associated electronic data.

As discussed we are resolving the final queries on the adverse event data from the Australian study. At the time of the Safety Update we expect to have most of the safety data available, and in that document we will provide you with what safety data we have.

4. The requirement for a safety update was discussed. Reckitt & Colman indicated that this would be available in late September 1999. The safety update should be cumulative and should lay out the data in three columns, indicating the data submitted in the NDA, the additional data included in the update, and a cumulative analysis

4. As indicated, we plan to submit a Safety Update in late September 1999.

5. Reckitt and Colman agreed to provide the volume and page number where the following items could be located in the NDA:

- *Analysis of efficacy by demographic subgroups such as sex and race (in ISE)*
- *Table of exposure, dose by duration, for study 1008, especially for 1008b (in ISS)*
- *Protocols for study 1008a and 1008b*

- The analysis of efficacy by sex and race is included in the #1008 study report (CR96/013 + CR96/014: Volumes 93 to 112 of the NDA). This analysis should

also have been included in the ISE, but was omitted in error. A new section for the ISE (Section 8.G.6.2) that reviews these data is presented as **Attachment 3**.

- There are two tables showing exposure to Suboxone by dose and duration: one table describes the exposure for *all* patients, and the other table for patients who remained in treatment with Suboxone for *greater that 6 months*. The table showing exposure for *all* patients was included in the #1008 report text (CR96/013 + CR96/014) as Table 29 in NDA Volume 93, page 65. In error this table was omitted from the ISS. The table showing exposure for *greater that 6 months* was included in both the #1008 report as Table 13.2.4 (NDA Volume 93, page 172), and in the ISS as Appendix 1.3.2 (NDA Volume 154, page 10). These tables are presented here as **Attachment 4**.

- Protocols for Study #1008a and #1008b, plus amendments, are presented in Appendix 14.1.1 of the report (NDA Volume 95, pages 2 to 178).

6. Reckitt & Colman agreed to clarify numerical discrepancies in Table 23, 27 and Tables 24, 25 in ISS, where total patient numbers of the combination tablet vary between 472 in Table 23 and 27 vs N=497 in Table 24 and 25

Full clinical data are available from two studies comprising 497 patients, who have been treated with Suboxone sublingual tablets. A total of 472 patients received at least one dose of Suboxone in study #1008 (CR96/013 + CR96/014, NDA Volumes 93 to 112), and 25 patients received Suboxone in the Pilot study CR95/002 (NDA Volume 145). In Figure 1 of the ISS (page 50), the two numbers (472 and 25) are in separate boxes. In tables 24 and 25 these have been summed (497). In Table 27, the demographics of patients in the two studies are presented separately and together.

7. Reckitt & Colman agreed to clarify the exact method of tablet administration (how many tablets at a time, held for how long) used in study 1008a/b

During the double blind efficacy study, subjects were dosed on a daily basis, except for weekends and public holidays when take home supplies were provided. It was intended that the total dose was taken once daily, sublingually. Each dose was to be given to the subject by a dispensing nurse, from a subject-specific supply, for sublingual self-administration by the subject. The subject was instructed to hold the medication under his/her tongue for approximately 5 to 10 minutes until the tablets were completely dissolved. Take-home medication was provided for weekends and public holidays.

For the safety study, drug was supplied in ————, specially packed depending on target dose level. Supplies were also packaged for take-home use, which was allowable after 2 weeks of daily clinic use. The subject was instructed to hold the medication under his/her tongue for approximately 5 to 10 minutes until the tablets were completely dissolved.

The agency explained that all requested information above must be submitted before July 25, 1999 in order to permit filing of this NDA.