SUBOXONE (CIII)
(buprenorphine HCl and naloxone HCl dihydrate sublingual tablets)

SUBUTEX (CIII)
(buprenorphine HCl sublingual tablets)

Rx only

Under the Drug Addiction Treatment Act of 2000 (DATA) codified at 21 U.S.C. 823(g), prescription use of this product in the treatment of opioid dependence is limited to physicians who meet certain qualifying requirements, and have notified the Secretary of Health and Human Services (HHS) of their intent to prescribe this product for the treatment of opioid dependence.

DESCRIPTION
SUBOXONE sublingual tablets contain buprenorphine HCl and naloxone HCl dihydrate at a ratio of 4:1 buprenorphine: naloxone (ratio of free bases).

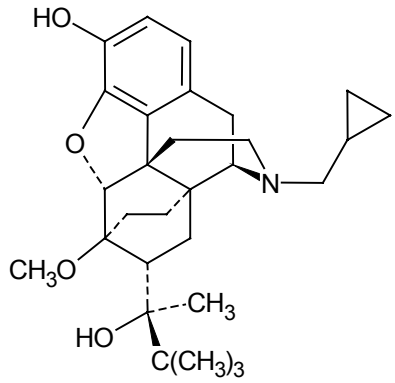
SUBUTEX sublingual tablets contain buprenorphine HCl.

Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Naloxone is an antagonist at the mu-opioid receptor.

Buprenorphine is a Schedule III narcotic under the Controlled Substances Act.

Buprenorphine hydrochloride is a white powder, weakly acidic with limited solubility in water (17mg/mL). Chemically, buprenorphine is 17-(cyclopropylmethyl)-α -(1,1-dimethylethyl)-4, 5-epoxy-18, 19-dihydro-3-hydroxy-6-methoxy- α -methyl-6, 14-ethenomorphinan-7-methanol, hydrochloride [5α, 7α(S)]-. Buprenorphine hydrochloride has the molecular formula $C_{29}H_{41}NO_4HCl$ and the molecular weight is 504.10.

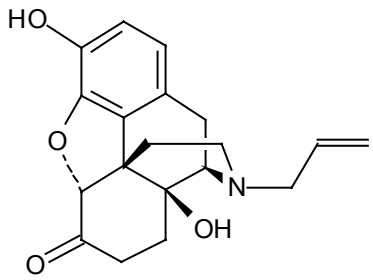
STRUCTURAL FORMULA OF BUPRENORPHINE



.HCl

Naloxone hydrochloride is a white to slightly off-white powder and is soluble in water, in dilute acids and in strong alkali. Chemically, naloxone is 17-Allyl-4,5 α -epoxy-3, 14-dihydroxymorphinan-6-one hydrochloride. Naloxone hydrochloride has the molecular formula $C_{19}H_{21}NO_4$ HCl $.2H_2O$ and the molecular weight is 399.87.

STRUCTURAL FORMULA OF NALOXONE



.HCl

SUBOXONE is an uncoated **hexagonal orange tablet** intended for sublingual administration. It is available in two dosage strengths, 2mg buprenorphine with 0.5mg naloxone, and 8mg buprenorphine with 2mg naloxone free bases. Each tablet also contains lactose, mannitol, cornstarch, povidone K30, citric acid, sodium citrate, FD&C Yellow No.6 color, magnesium stearate, and the tablets also contain Acesulfame K sweetener and a lemon / lime flavor.

SUBUTEX is an uncoated **oval white tablet** intended for sublingual administration. It is available in two dosage strengths, 2mg buprenorphine and 8mg buprenorphine free base. Each tablet also contains lactose, mannitol, cornstarch, povidone K30, citric acid, sodium citrate and magnesium stearate.

CLINICAL PHARMACOLOGY

***Subjective Effects**:*

Comparisons of buprenorphine with full agonists such as methadone and hydromorphone suggest that sublingual buprenorphine produces typical opioid agonist effects which are limited by a ceiling effect.

In non-dependent subjects, acute sublingual doses of SUBOXONE tablets produced opioid agonist effects, which reached a maximum between doses of 8 mg and 16mg of SUBUTEX. The effects of 16mg SUBOXONE were similar to those produced by 16mg SUBUTEX (buprenorphine alone).

Opioid agonist ceiling effects were also observed in a double-blind, parallel group, dose ranging comparison of single doses of buprenorphine sublingual solution (1, 2, 4, 8, 16, or 32 mg), placebo, and a full agonist control at various doses. The treatments were given in ascending dose order at intervals of at least one week to 16 opioid-experienced, non-dependent subjects. Both drugs produced typical opioid agonist effects. For all the measures for which the drugs produced an effect, buprenorphine produced a dose-related response but, in each case, there was a dose that produced no further effect. In contrast, the highest dose of the full agonist control always produced the greatest effects. Agonist objective rating scores remained elevated for the higher doses of buprenorphine (8-32 mg) longer than for the lower doses and did not return to baseline until 48 hours after drug administrations. The onset of effects appeared more rapidly with buprenorphine than with the full agonist control, with most doses nearing peak effect after 100 minutes for buprenorphine compared to 150 minutes for the full agonist control.

Physiologic Effects:

Buprenorphine in intravenous (2mg, 4mg, 8mg, 12mg and 16 mg) and sublingual (12mg) doses has been administered to non-dependent subjects to examine cardiovascular, respiratory and subjective effects at doses comparable to those used for treatment of opioid dependence. Compared with placebo, there were no statistically significant differences among any of the treatment conditions for blood pressure, heart rate, respiratory rate, O_2 saturation or skin temperature across time. Systolic BP was higher in the 8 mg group than placebo (3 hour AUC values). Minimum and maximum effects were similar across all treatments. Subjects remained responsive to low voice and responded to computer prompts. Some subjects showed irritability, but no other changes were observed.

The respiratory effects of sublingual buprenorphine were compared with the effects of methadone in a double-blind, parallel group, dose ranging comparison of single doses of buprenorphine sublingual solution (1, 2, 4, 8, 16, or 32 mg) and oral methadone (15, 30, 45, or 60 mg) in non-dependent, opioid-experienced volunteers. In this study, hypoventilation not requiring medical intervention was reported more frequently after buprenorphine doses of 4 mg and higher than after methadone. Both drugs decreased O_2 saturation to the same degree.

Effect of Naloxone:

Physiologic and subjective effects following acute sublingual administration of SUBOXONE and SUBUTEX tablets were similar at equivalent dose levels of buprenorphine. Naloxone, in

the SUBOXONE formulation, had no clinically significant effect when administered by the sublingual route, although blood levels of the drug were measurable. SUBOXONE, when administered sublingually even to an opioid-dependent population, was recognized as an opioid agonist, whereas when administered intramuscularly, combinations of buprenorphine with naloxone produced opioid antagonist actions similar to naloxone. In methadone-maintained patients and heroin-dependent subjects, intravenous administration of buprenorphine/naloxone combinations precipitated opioid withdrawal and was perceived as unpleasant and dysphoric. In morphine-stabilized subjects, intravenously administered combinations of buprenorphine with naloxone produced opioid antagonist and withdrawal effects that were ratio-dependent; the most intense withdrawal effects were produced by 2:1 and 4:1 ratios, less intense by an 8:1 ratio. SUBOXONE tablets contain buprenorphine with naloxone at a ratio of 4:1.

Pharmacokinetics:

Absorption:

Plasma levels of buprenorphine increased with the sublingual dose of SUBUTEX and SUBOXONE, and plasma levels of naloxone increased with the sublingual dose of SUBOXONE (Table 1). There was a wide inter-patient variability in the sublingual absorption of buprenorphine and naloxone, but within subjects the variability was low. Both C_{max} and AUC of buprenorphine increased in a linear fashion with the increase in dose (in the range of 4 to 16 mg), although the increase was not directly dose-proportional.

Naloxone did not affect the pharmacokinetics of buprenorphine and both SUBUTEX and SUBOXONE deliver similar plasma concentrations of buprenorphine. The levels of naloxone were too low to assess dose-proportionality. At the three naloxone doses of 1 mg, 2 mg, and 4 mg, levels above the limit of quantitation (0.05 ng/mL) were not detected beyond 2 hours in seven of eight subjects. In one individual, at the 4mg dose, the last measurable concentration was at 8 hours. Within each subject (for most of the subjects), across the doses there was a trend toward an increase in naloxone concentrations with increase in dose. Mean peak naloxone levels ranged from 0.11 to 0.28ng/ml in the dose range of 1-4 mg.

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

Pharmacokinetic Parameter	**Suboxone® 4 mg**	**Suboxone® 8 mg**	**Suboxone® 16 mg**	**Subutex® 16 mg**
C_{max}, ng/mL	1.84 (39)	3.0 (51)	5.95 (38)	5.47 (23)
AUC_{0-48}, hour*ng/mL	12.52 (35)	20.22 (43)	34.89 (33)	32.63 (25)

Distribution:

Buprenorphine is approximately 96% protein bound, primarily to alpha and beta globulin.

Naloxone is approximately 45% protein bound, primarily to albumin.

Metabolism:
Buprenorphine undergoes both N-dealkylation to norbuprenorphine and glucuronidation. The N-dealkylation pathway is mediated by cytochrome P-450 3A4 isozyme. Norbuprenorphine, an active metabolite, can further undergo glucuronidation.

Naloxone undergoes direct glucuronidation to naloxone 3-glucuronide as well as N-dealkylation, and reduction of the 6-oxo group.

Elimination:
A mass balance study of buprenorphine showed complete recovery of radiolabel in urine (30%) and feces (69%) collected up to 11 days after dosing. Almost all of the dose was accounted for in terms of buprenorphine, norbuprenorphine, and two unidentified buprenorphine metabolites. In urine, most of buprenorphine and norbuprenorphine was conjugated (buprenorphine, 1% free and 9.4% conjugated; norbuprenorphine, 2.7% free and 11% conjugated). In feces, almost all of the buprenorphine and norbuprenorphine were free (buprenorphine, 33% free and 5% conjugated; norbuprenorphine, 21% free and 2% conjugated).

Buprenorphine has a mean elimination half-life from plasma of 37 h.

Naloxone has a mean elimination half-life from plasma of 1.1 h.

Special Populations:
Hepatic Disease:
The effect of hepatic impairment on the pharmacokinetics of buprenorphine and naloxone is unknown. Since both drugs are extensively metabolized, the plasma levels will be expected to be higher in patients with moderate and severe hepatic impairment. However, it is not known whether both drugs are affected to the same degree. Therefore, in patients with hepatic impairment dosage should be adjusted and patients should be observed for symptoms of precipitated opioid withdrawal.

Renal Disease:
No differences in buprenorphine pharmacokinetics were observed between 9 dialysis-dependent and 6 normal patients following intravenous administration of 0.3mg buprenorphine.

The effects of renal failure on naloxone pharmacokinetics are unknown.

Drug-drug interactions:
CYP 3A4 Inhibitors and Inducers: A pharmacokinetic interaction study of ketoconazole (400 mg/day), a potent inhibitor of CYP 3A4, in 12 patients stabilized on SUBOXONE [8mg (n=1) or 12mg (n=5) or 16mg (n=6)] resulted in increases in buprenorphine mean Cmax values (from 4.3 to 9.8, 6.3 to 14.4 and 9.0 to 17.1) and mean AUC values (from 30.9 to 46.9, 41.9 to 83.2 and 52.3 to 120) respectively. Subjects receiving SUBUTEX or SUBOXONE should be

closely monitored and may require dose-reduction if inhibitors of CYP 3A4 such as azole antifungal agents (e.g. ketoconazole), macrolide antibiotics (e.g., erythromycin) and HIV protease inhibitors (e.g. ritonavir, indinavir and saquinavir) are co-administered. The interaction of buprenorphine with CYP 3A4 inducers has not been investigated; therefore it is recommended that patients receiving SUBUTEX or SUBOXONE should be closely monitored if inducers of CYP 3A4 (e.g. phenobarbital, carbamazepine, phenytoin, rifampicin) are co-administered (SEE WARNINGS).

CLINICAL STUDIES

Clinical data on the safety and efficacy of SUBOXONE and SUBUTEX are derived from studies of buprenorphine sublingual tablet formulations, with and without naloxone, and from studies of sublingual administration of a more bioavailable ethanolic solution of buprenorphine.

SUBOXONE tablets have been studied in 575 patients, SUBUTEX tablets in 1834 patients and buprenorphine sublingual solutions in 2470 patients. A total of 1270 females have received buprenorphine in clinical trials. Dosing recommendations are based on data from one trial of both tablet formulations and two trials of the ethanolic solution. All trials used buprenorphine in conjunction with psychosocial counseling as part of a comprehensive addiction treatment program. There have been no clinical studies conducted to assess the efficacy of buprenorphine as the only component of treatment.

In a double blind placebo- and active controlled study, 326 heroin-addicted subjects were randomly assigned to either SUBOXONE 16 mg per day, 16 mg SUBUTEX per day or placebo tablets. For subjects randomized to either active treatment, dosing began with one 8 mg tablet of SUBUTEX on Day 1, followed by 16 mg (two 8 mg tablets) of SUBUTEX on Day 2. On Day 3, those randomized to receive SUBOXONE were switched to the combination tablet. Subjects randomized to placebo received one placebo tablet on Day 1 and two placebo tablets per day thereafter for four weeks. Subjects were seen daily in the clinic (Monday through Friday) for dosing and efficacy assessments. Take-home doses were provided for weekends. Subjects were instructed to hold the medication under the tongue for approximately 5 to 10 minutes until completely dissolved. Subjects received one hour of individual counseling per week and a single session of HIV education. The primary study comparison was to assess the efficacy of SUBUTEX and SUBOXONE individually against placebo. The percentage of thrice-weekly urine samples that were negative for non-study opioids was statistically higher for both SUBUTEX and SUBOXONE, than for placebo.

In a double-blind, double-dummy, parallel-group study comparing buprenorphine ethanolic solution to a full agonist active control, 162 subjects were randomized to receive the ethanolic sublingual solution of buprenorphine at 8 mg/day (a dose which is roughly comparable to a dose of 12 mg/day of SUBUTEX or SUBOXONE), or two relatively low doses of active control, one of which was low enough to serve as an alternative to placebo, during a 3-10 day induction phase, a 16-week maintenance phase and a 7-week detoxification phase. Buprenorphine was titrated to maintenance dose by Day 3; active control doses were titrated more gradually.

Maintenance dosing continued through Week 17, and then medications were tapered by approximately 20-30% per week over Weeks 18-24, with placebo dosing for the last two weeks. Subjects received individual and/or group counseling weekly.

Based on retention in treatment and the percentage of thrice-weekly urine samples negative for non-study opioids, buprenorphine was more effective than the low dose of the control, in keeping heroin addicts in treatment and in reducing their use of opioids while in treatment. The effectiveness of buprenorphine, 8 mg per day was similar to that of the moderate active control dose, but equivalence was not demonstrated.

In a dose-controlled, double-blind, parallel-group, 16-week study, 731 subjects were randomized to receive one of four doses of buprenorphine ethanolic solution. Buprenorphine was titrated to maintenance doses over 1-4 days (Table 2) and continued for 16 weeks. Subjects received at least one session of AIDS education and additional counseling ranging from one hour per month to one hour per week, depending on site.

Table 2. Doses of Sublingual Buprenorphine Solution used for Induction in a Double-Blind Dose Ranging Study

Target Dose of Buprenorphine *	Induction Dose			Maintenance dose
	Day 1	Day 2	Day 3	
1 mg	1 mg	1 mg	1 mg	1 mg
4 mg	2 mg	4 mg	4 mg	4 mg
8 mg	2 mg	4 mg	8 mg	8 mg
16 mg	2 mg	4 mg	8mg	16 mg

*Sublingual solution. Doses in this table cannot necessarily be delivered in tablet form, but for comparison purposes:
2 mg solution would be roughly equivalent to 3 mg tablet
4 mg solution would be roughly equivalent to 6 mg tablet
8 mg solution would be roughly equivalent to 12 mg tablet
16 mg solution would be roughly equivalent to 24 mg tablet

Based on retention in treatment and the percentage of thrice-weekly urine samples negative for non-study opioids, the three highest tested doses were superior to the 1mg dose. Therefore, this study showed that a range of buprenorphine doses may be effective. The 1mg dose of buprenorphine sublingual solution can be considered to be somewhat lower than a 2 mg tablet dose. The other doses used in the study encompass a range of tablet doses from approximately 6 mg to approximately 24 mg.

INDICATIONS AND USAGE
SUBOXONE and SUBUTEX are indicated for the treatment of opioid dependence.

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

WARNINGS

Respiratory Depression*:*

Significant respiratory depression has been associated with buprenorphine, particularly by the intravenous route. A number of deaths have occurred when addicts have intravenously misused buprenorphine, usually with benzodiazepines concomitantly. Deaths have also been reported in association with concomitant administration of buprenorphine with other depressants such as alcohol or other opioids. Patients should be warned of the potential danger of the self-administration of benzodiazepines or other depressants while under treatment with SUBUTEX or SUBOXONE.

IN THE CASE OF OVERDOSE, THE PRIMARY MANAGEMENT SHOULD BE THE RE-ESTABLISHMENT OF ADEQUATE VENTILATION WITH MECHANICAL ASSISTANCE OF RESPIRATION, IF REQUIRED. NALOXONE MAY NOT BE EFFECTIVE IN REVERSING ANY RESPIRATORY DEPRESSION PRODUCED BY BUPRENORPHINE.

SUBOXONE and SUBUTEX should be used with caution in patients with compromised respiratory function (e.g., chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression).

CNS Depression:

Patients receiving buprenorphine in the presence of other narcotic analgesics, general anesthetics, benzodiazepines, phenothiazines, other tranquilizers, sedative/hypnotics or other CNS depressants (including alcohol) may exhibit increased CNS depression. When such combined therapy is contemplated, reduction of the dose of one or both agents should be considered.

Dependence:

Buprenorphine is a partial agonist at the mu-opiate receptor and chronic administration produces dependence of the opioid type, characterized by withdrawal upon abrupt discontinuation or rapid taper. The withdrawal syndrome is milder than seen with full agonists, and may be delayed in onset

Hepatitis, hepatic events:

Cases of cytolytic hepatitis and hepatitis with jaundice have been observed in the addict population receiving buprenorphine both in clinical trials and in post-marketing adverse event reports. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of hepatic failure, hepatic necrosis, hepatorenal syndrome, and hepatic encephalopathy. In many cases, the presence of pre-existing liver enzyme abnormalities, infection with hepatitis B or hepatitis C virus, concomitant usage of other potentially hepatotoxic drugs, and ongoing injecting drug use may have played a causative or contributory role. In other cases, insufficient data were available to determine the etiology of the abnormality. The possibility exists that buprenorphine had a causative or contributory role in the development of the hepatic abnormality in some cases. Measurements of liver function tests prior to initiation of treatment is recommended to establish a baseline. Periodic monitoring of liver function tests during treatment is also recommended. A

biological and etiological evaluation is recommended when a hepatic event is suspected. Depending on the case, the drug should be carefully discontinued to prevent withdrawal symptoms and a return to illicit drug use, and strict monitoring of the patient should be initiated.

Allergic Reactions:
Cases of acute and chronic hypersensitivity to buprenorphine have been reported both in clinical trials and in the post-marketing experience. The most common signs and symptoms include rashes, hives, and pruritus. Cases of bronchospasm, angioneurotic edema, and anaphylactic shock have been reported. A history of hypersensitivity to buprenorphine is a contraindication to Subutex or Suboxone use. A history of hypersensitivity to naloxone is a contraindication to Suboxone use.

Use in Ambulatory Patients*:*
SUBOXONE and SUBUTEX may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery, especially during drug induction and dose adjustment. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that buprenorphine therapy does not adversely affect their ability to engage in such activities. Like other opioids, SUBOXONE and SUBUTEX may produce orthostatic hypotension in ambulatory patients.

Head Injury and Increased Intracranial Pressure*:*
SUBOXONE and SUBUTEX, like other potent opioids, may elevate cerebrospinal fluid pressure and should be used with caution in patients with head injury, intracranial lesions and other circumstances where cerebrospinal pressure may be increased. SUBOXONE and SUBUTEX can produce miosis and changes in the level of consciousness that may interfere with patient evaluation.

Opioid withdrawal effects*:*
Because it contains naloxone, SUBOXONE is highly likely to produce marked and intense withdrawal symptoms if misused parenterally by individuals dependent on opioid agonists such as heroin, morphine, or methadone. Sublingually, SUBOXONE may cause opioid withdrawal symptoms in such persons if administered before the agonist effects of the opioid have subsided.

PRECAUTIONS
General:
SUBOXONE and SUBUTEX should be administered with caution in elderly or debilitated patients and those with severe impairment of hepatic, pulmonary, or renal function; myxedema or hypothyroidism, adrenal cortical insufficiency (e.g., Addison's disease); CNS depression or coma; toxic psychoses; prostatic hypertrophy or urethral stricture; acute alcoholism; delirium tremens; or kyphoscoliosis.

The effect of hepatic impairment on the pharmacokinetics of buprenorphine and naloxone is unknown. Since both drugs are extensively metabolized, the plasma levels will be expected to be higher in patients with moderate and severe hepatic impairment. However, it is not known whether both drugs are affected to the same degree. Therefore, dosage should be adjusted and patients should be watched for symptoms of precipitated opioid withdrawal.

Buprenorphine has been shown to increase intracholedochal pressure, as do other opioids, and thus should be administered with caution to patients with dysfunction of the biliary tract.

As with other mu-opioid receptor agonists, the administration of SUBOXONE or SUBUTEX may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

Drug Interactions:
Buprenorphine is metabolized to norbuprenorphine by cytochrome CYP 3A4. Because CYP 3A4 inhibitors may increase plasma concentrations of buprenorphine, patients already on CYP 3A4 inhibitors such as azole antifungals (e.g. ketoconazole), macrolide antibiotics (e.g. erythromycin), and HIV protease inhibitors (e.g. ritonavir, indinavir and saquinavir) should have their dose of SUBUTEX or SUBOXONE adjusted.

Based on anecdotal reports, there may be an interaction between buprenorphine and benzodiazepines. There have been a number of reports in the post-marketing experience of coma and death associated with the concomitant intravenous misuse of buprenorphine and benzodiazepines by addicts. In many of these cases, buprenorphine was misused by self-injection of crushed SUBUTEX tablets. SUBUTEX and SUBOXONE should be prescribed with caution to patients on benzodiazepines or other drugs that act on the central nervous system, regardless of whether these drugs are taken on the advice of a physician or are taken as drugs of abuse. Patients should be warned of the potential danger of the intravenous self-administration of benzodiazepines while under treatment with SUBOXONE or SUBUTEX.

Information for Patients:
Patients should inform their family members that, in the event of emergency, the treating physician or emergency room staff should be informed that the patient is physically dependent on narcotics and that the patient is being treated with SUBOXONE or SUBUTEX.

Patients should be cautioned that a serious overdose and death may occur if benzodiazepines, sedatives, tranquilizers, antidepressants, or alcohol are taken at the same time as SUBOXONE or SUBUTEX.

SUBOXONE and SUBUTEX may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery, especially during drug induction and dose adjustment. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that buprenorphine therapy does not adversely affect their ability to engage in such activities. Like other opioids, SUBOXONE and SUBUTEX may produce orthostatic hypotension in ambulatory patients.

Patients should consult their physician if other prescription medications are currently being used or are prescribed for future use.

Carcinogenesis, Mutagenesis and Impairment of Fertility:

Carcinogenicity: Carcinogenicity data on SUBOXONE are not available. Carcinogenicity studies of buprenorphine were conducted in Sprague-Dawley rats and CD-1 mice. Buprenorphine was administered in the diet to rats at doses of 0.6, 5.5, and 56 mg/kg/day (estimated exposure was approximately 0.4, 3 and 35 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis) for 27 months. Statistically significant dose-related increases in testicular interstitial (Leydig's) cell tumors occurred, according to the trend test adjusted for survival. Pair-wise comparison of the high dose against control failed to show statistical significance. In an 86-week study in CD-1 mice, buprenorphine was not carcinogenic at dietary doses up to 100 mg/kg/day (estimated exposure was approximately 30 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis).

Mutagenicity:

SUBOXONE: The 4:1 combination of buprenorphine and naloxone was not mutagenic in a bacterial mutation assay (Ames test) using four strains of *S. typhimurium* and two strains of *E. coli.* The combination was not clastogenic in an *in vitro* cytogenetic assay in human lymphocytes, or in an intravenous micronucleus test in the rat.

SUBUTEX: Buprenorphine was studied in a series of tests utilizing gene, chromosome, and DNA interactions in both prokaryotic and eukaryotic systems. Results were negative in yeast (*Saccharomyces cerevisiae)* for recombinant, gene convertant, or forward mutations; negative in *Bacillus subtilis* "rec" assay, negative for clastogenicity in CHO cells, Chinese hamster bone marrow and spermatogonia cells, and negative in the mouse lymphoma L5178Y assay. Results were equivocal in the Ames test: negative in studies in two laboratories, but positive for frame shift mutation at a high dose (5mg/plate) in a third study. Results were positive in the Green-Tweets (*E. coli*) survival test, positive in a DNA synthesis inhibition (DSI) test with testicular tissue from mice, for both in vivo and in vitro incorporation of [^{3}H]thymidine, and positive in unscheduled DNA synthesis (UDS) test using testicular cells from mice.

Impairment of Fertility:

SUBOXONE: Dietary administration of SUBOXONE in the rat at dose levels of 500 ppm or greater (equivalent to approximately 47 mg/kg/day or greater; estimated exposure was approximately 28 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis) produced a reduction in fertility demonstrated by reduced female conception rates. A dietary dose of 100 ppm (equivalent to approximately 10 mg/kg/day; estimated exposure was approximately 6 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis) had no adverse effect on fertility.

SUBUTEX: Reproduction studies of buprenorphine in rats demonstrated no evidence of impaired fertility at daily oral doses up to 80mg/kg/day (estimated exposure was approximately 50 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis) or up to 5mg/kg/day *im* or *sc* (estimated exposure was approximately 3 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis).

Pregnancy:
Pregnancy Category C:
Teratogenic effects:
SUBOXONE: Effects on embryo-fetal development were studied in Sprague-Dawley rats and Russian white rabbits following oral (1:1) and intramuscular (3:2) administration of mixtures of buprenorphine and naloxone. Following oral administration to rats and rabbits, no teratogenic effects were observed at doses up to 250 mg/kg/day and 40 mg/kg/day, respectively (estimated exposure was approximately 150 times and 50 times, respectively, the recommended human daily sublingual dose of 16 mg on a mg/m² basis). No definitive drug-related teratogenic effects were observed in rats and rabbits at intramuscular doses up to 30 mg/kg/day (estimated exposure was approximately 20 times and 35 times, respectively, the recommended human daily dose of 16 mg on a mg/m² basis). Acephalus was observed in one rabbit fetus from the low-dose group and omphacele was observed in two rabbit fetuses from the same litter in the mid-dose group; no findings were observed in fetuses from the high-dose group. Following oral administration to the rat, dose-related post-implantation losses, evidenced by increases in the numbers of early resorptions with consequent reductions in the numbers of fetuses, were observed at doses of 10 mg/kg/day or greater (estimated exposure was approximately 6 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis). In the rabbit, increased post-implantation losses occurred at an oral dose of 40 mg/kg/day. Following intramuscular administration in the rat and the rabbit, post-implantation losses, as evidenced by decreases in live fetuses and increases in resorptions, occurred at 30 mg/kg/day.

SUBUTEX: Buprenorphine was not teratogenic in rats or rabbits after *im* or *sc* doses up to 5 mg/kg/day (estimated exposure was approximately 3 and 6 times, respectively, the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis), after *iv* doses up to 0.8 mg/kg/day (estimated exposure was approximately 0.5 times and equal to, respectively, the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis), or after oral doses up to 160 mg/kg/day in rats (estimated exposure was approximately 95 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis) and 25 mg/kg/day in rabbits (estimated exposure was approximately 30 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis). Significant increases in skeletal abnormalities (e.g., extra thoracic vertebra or thoraco-lumbar ribs) were noted in rats after *sc* administration of 1 mg/kg/day and up (estimated exposure was approximately 0.6 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis), but were not observed at oral doses up to 160 mg/kg/day. Increases in skeletal abnormalities in rabbits after *im* administration of 5 mg/kg/day (estimated exposure was approximately 6 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis) or oral administration of 1 mg/kg/day or greater (estimated exposure was approximately equal to the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis) were not statistically significant.

In rabbits, buprenorphine produced statistically significant pre-implantation losses at oral doses of 1 mg/kg/day or greater and post-implantation losses that were statistically significant at *iv* doses of 0.2 mg/kg/day or greater (estimated exposure was approximately 0.3 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis).

There are no adequate and well-controlled studies of SUBOXONE or SUBUTEX in pregnant women. SUBOXONE or SUBUTEX should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus.

Non-teratogenic effects.
Dystocia was noted in pregnant rats treated *im* with buprenorphine 5 mg/kg/day (approximately 3 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis). Both fertility and peri- and postnatal development studies with buprenorphine in rats indicated increases in neonatal mortality after oral doses of 0.8 mg/kg/day and up (approximately 0.5 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis), after *im* doses of 0.5 mg/kg/day and up (approximately 0.3 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis), and after *sc* doses of 0.1 mg/kg/day and up (approximately 0.06 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis). Delays in the occurrence of righting reflex and startle response were noted in rat pups at an oral dose of 80 mg/kg/day (approximately 50 times the recommended human daily sublingual dose of 16 mg on a mg/m² basis).

Neonatal Withdrawal:
Neonatal withdrawal has been reported in the infants of women treated with SUBUTEX during pregnancy. From post-marketing reports, the time to onset of neonatal withdrawal symptoms ranged from Day 1 to Day 8 of life with most occurring on Day 1. Adverse events associated with neonatal withdrawal syndrome included hypertonia, neonatal tremor, neonatal agitation, and myoclonus. There have been rare reports of convulsions and in one case, apnea and bradycardia were also reported.

Nursing Mothers:
An apparent lack of milk production during general reproduction studies with buprenorphine in rats caused decreased viability and lactation indices. Use of high doses of sublingual buprenorphine in pregnant women showed that buprenorphine passes into the mother's milk. Breast-feeding is therefore not advised in mothers treated with SUBUTEX or SUBOXONE.

Pediatric Use:
SUBOXONE and SUBUTEX are not recommended for use in pediatric patients. The safety and effectiveness of SUBOXONE and SUBUTEX in patients below the age of 16 have not been established.

ADVERSE REACTIONS
The safety of SUBOXONE has been evaluated in 497 opioid-dependent subjects. The prospective evaluation of SUBOXONE was supported by clinical trials using SUBUTEX (buprenorphine tablets without naloxone) and other trials using buprenorphine sublingual solutions. In total, safety data are available from 3214 opioid-dependent subjects exposed to buprenorphine at doses in the range used in treatment of opioid addiction..

Few differences in adverse event profile were noted between SUBOXONE and SUBUTEX or buprenorphine administered as a sublingual solution.

In a comparative study, adverse event profiles were similar for subjects treated with 16 mg SUBOXONE or 16mg SUBUTEX. The following adverse events were reported to occur by at least 5% of patients in a 4-week study (Table 3).

Table 3. Adverse Events (≥ 5%) by Body System and Treatment Group in a 4-week Study

	N (%)	N (%)	N (%)
Body System /Adverse Event (COSTART Terminology)	**SUBOXONE 16 mg/day N = 107**	**SUBUTEX 16 mg/day N = 103**	**Placebo N = 107**
Body As A Whole			
Asthenia	7 (6.5%)	5 (4.9%)	7 (6.5%)
Chills	8 (7.5%)	8 (7.8%)	8 (7.5%)
Headache	39 (36.4%)	30 (29.1%)	24 (22.4%)
Infection	6 (5.6%)	12 (11.7%)	7 (6.5%)
Pain	24 (22.4%)	19 (18.4%)	20 (18.7%)
Pain Abdomen	12 (11.2%)	12 (11.7%)	7 (6.5%)
Pain Back	4 (3.7%)	8 (7.8%)	12 (11.2%)
Withdrawal Syndrome	27 (25.2%)	19 (18.4%)	40 (37.4%)
Cardiovascular System			
Vasodilation	10 (9.3%)	4 (3.9%)	7 (6.5%)
Digestive System			
Constipation	13 (12.1%)	8 (7.8%)	3 (2.8%)
Diarrhea	4 (3.7%)	5 (4.9%)	16 (15.0%)
Nausea	16 (15.0%)	14 (13.6%)	12 (11.2%)
Vomiting	8 (7.5%)	8 (7.8%)	5 (4.7%)
Nervous System			
Insomnia	15 (14.0%)	22 (21.4%)	17 (15.9%)
Respiratory System			
Rhinitis	5 (4.7%)	10 (9.7%)	14 (13.1%)
Skin And Appendages			
Sweating	15 (14.0%)	13 (12.6%)	11 (10.3%)

The adverse event profile of buprenorphine was also characterized in the dose-controlled study of buprenorphine solution, over a range of doses in four months of treatment. Table 4 shows adverse events reported by at least 5% of subjects in any dose group in the dose-controlled study.

Table 4. Adverse Events (≥ 5%) by Body System and Treatment Group in a 16-week Study

Body System /Adverse Event (COSTART Terminology)	**Buprenorphine Dose***				
	Very Low* (N=184)	**Low* (N=180)**	**Moderate* (N=186)**	**High* (N=181)**	**Total* (N=731)**
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Body as a Whole					
Abscess	9 (5%)	2 (1%)	3 (2%)	2 (1%)	16 (2%)
Asthenia	26 (14%)	28 (16%)	26 (14%)	24 (13%)	104 (14%)
Chills	11 (6%)	12 (7%)	9 (5%)	10 (6%)	42 (6%)
Fever	7 (4%)	2 (1%)	2 (1%)	10 (6%)	21 (3%)
Flu Syndrome	4 (2%)	13 (7%)	19 (10%)	8 (4%)	44 (6%)

Headache	51 (28%)	62 (34%)	54 (29%)	53 (29%)	220 (30%)
Infection	32 (17%)	39 (22%)	38 (20%)	40 (22%)	149 (20%)
Injury Accidental	5 (3%)	10 (6%)	5 (3%)	5 (3%)	25 (3%)
Pain	47 (26%)	37 (21%)	49 (26%)	44 (24%)	177 (24%)
Pain Back	18 (10%)	29 (16%)	28 (15%)	27 (15%)	102 (14%)
Withdrawal Syndrome	45 (24%)	40 (22%)	41 (22%)	36 (20%)	162 (22%)
Digestive System					
Constipation	10 (5%)	23 (13%)	23 (12%)	26 (14%)	82 (11%)
Diarrhea	19 (10%)	8 (4%)	9 (5%)	4 (2%)	40 (5%)
Dyspepsia	6 (3%)	10 (6%)	4 (2%)	4 (2%)	24 (3%)
Nausea	12 (7%)	22 (12%)	23 (12%)	18 (10%)	75 (10%)
Vomiting	8 (4%)	6 (3%)	10 (5%)	14 (8%)	38 (5%)
Nervous System					
Anxiety	22 (12%)	24 (13%)	20 (11%)	25 (14%)	91 (12%)
Depression	24 (13%)	16 (9%)	25 (13%)	18 (10%)	83 (11%)
Dizziness	4 (2%)	9 (5%)	7 (4%)	11 (6%)	31 (4%)
Insomnia	42 (23%)	50 (28%)	43 (23%)	51 (28%)	186 (25%)
Nervousness	12 (7%)	11 (6%)	10 (5%)	13 (7%)	46 (6%)
Somnolence	5 (3%)	13 (7%)	9 (5%)	11 (6%)	38 (5%)
Respiratory System					
Cough Increase	5 (3%)	11 (6%)	6 (3%)	4 (2%)	26 (4%)
Pharyngitis	6 (3%)	7 (4%)	6 (3%)	9 (5%)	28 (4%)
Rhinitis	27 (15%)	16 (9%)	15 (8%)	21 (12%)	79 (11%)
Skin and Appendages					
Sweat	23 (13%)	21 (12%)	20 (11%)	23 (13%)	87 (12%)
Special Senses					
Runny Eyes	13 (7%)	9 (5%)	6 (3%)	6 (3%)	34 (5%)

*Sublingual solution. Doses in this table cannot necessarily be delivered in tablet form, but for comparison purposes:
"Very low" dose (1mg solution) would be less than a tablet dose of 2 mg
"Low" dose (4mg solution) approximates a 6 mg tablet dose
"Moderate" dose (8mg solution) approximates a 12 mg tablet dose
"High" dose (16mg solution) approximates a 24 mg tablet dose

DRUG ABUSE AND DEPENDENCE

SUBOXONE and SUBUTEX are controlled as Schedule III narcotics under the Controlled Substances Act.

Buprenorphine is a partial agonist at the mu-opioid receptor and chronic administration produces dependence of the opioid type, characterized by moderate withdrawal upon abrupt discontinuation or rapid taper. The withdrawal syndrome is milder than seen with full agonists, and may be delayed in onset (SEE WARNINGS)

Neonatal withdrawal has been reported in the infants of women treated with SUBUTEX during pregnancy (See PRECAUTIONS)

SUBOXONE contains naloxone and if misused parenterally, is highly likely to produce marked and intense withdrawal symptoms in subjects dependent on other opioid agonists.

OVERDOSAGE

Manifestations*:*

Manifestations of acute overdose include pinpoint pupils, sedation, hypotension, respiratory depression and death.

Treatment:
The respiratory and cardiac status of the patient should be monitored carefully. In the event of depression of respiratory or cardiac function, primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated.

IN THE CASE OF OVERDOSE, THE PRIMARY MANAGEMENT SHOULD BE THE RE-ESTABLISHMENT OF ADEQUATE VENTILATION WITH MECHANICAL ASSISTANCE OF RESPIRATION, IF REQUIRED NALOXONE MAY NOT BE EFFECTIVE IN REVERSING ANY RESPIRATORY DEPRESSION PRODUCED BY BUPRENORPHINE.

High doses of naloxone hydrochloride, 10-35 mg/70 kg may be of limited value in the management of buprenorphine overdose. Doxapram (a respiratory stimulant) also has been used.

DOSAGE AND ADMINISTRATION
SUBUTEX or SUBOXONE is administered sublingually as a single daily dose in the range of 12 to 16 mg/day. When taken sublingually, SUBOXONE and SUBUTEX have similar clinical effects and are interchangeable. There are no adequate and well-controlled studies using SUBOXONE as initial medication. SUBUTEX contains no naloxone and is preferred for use during induction. Following induction, SUBOXONE, due to the presence of naloxone, is preferred when clinical use includes unsupervised administration. The use of SUBUTEX for unsupervised administration should be limited to those patients who cannot tolerate SUBOXONE, for example those patients who have been shown to be hypersensitive to naloxone.

Method of administration:
SUBOXONE and SUBUTEX tablets should be placed under the tongue until they are dissolved. For doses requiring the use of more than two tablets, patients are advised to either place all the tablets at once or alternatively (if they cannot fit in more than two tablets comfortably) place two tablets at a time under the tongue. Either way, the patients should continue to hold the tablets under the tongue until they dissolve; swallowing the tablets reduces the bioavailability of the drug. To ensure consistency in bioavailability, patients should follow the same manner of dosing with continued use of the product.

Induction:
Prior to induction, consideration should be given to the type of opioid dependence (i.e. long- or short-acting opioid), the time since last opioid use, and the degree or level of opioid dependence. To avoid precipitating withdrawal, induction with SUBUTEX should be undertaken when objective and clear signs of withdrawal are evident.

In a one-month study of SUBOXONE tablets induction was conducted with SUBUTEX tablets. Patients received 8mg of SUBUTEX on day 1 and 16mg SUBUTEX on day 2. From day 3 onward, patients received SUBOXONE tablets at the same buprenorphine dose as day 2. Induction in the studies of buprenorphine solution was accomplished over 3-4 days, depending on the target dose. In some studies, gradual induction over several days led to a high rate of drop-out of buprenorphine patients during the induction period. Therefore it is recommended that an adequate maintenance dose, titrated to clinical effectiveness, should be achieved as rapidly as possible to prevent undue opioid withdrawal symptoms.

Patients taking heroin or other short-acting opioids:
At treatment initiation, the dose of SUBUTEX should be administered at least 4 hours after the patient last used opioids or preferably when early signs of opioid withdrawal appear.

Patients on methadone or other long-acting opioids:
There is little controlled experience with the transfer of methadone-maintained patients to buprenorphine. Available evidence suggests that withdrawal symptoms are possible during induction to buprenorphine treatment. Withdrawal appears more likely in patients maintained on higher doses of methadone (>30mg) and when the first buprenorphine dose is administered shortly after the last methadone dose.

Maintenance:
SUBOXONE is the preferred medication for maintenance treatment due to the presence of naloxone in the formulation.

Adjusting the dose until the maintenance dose is achieved:
The recommended target dose of SUBOXONE is 16 mg/day. Clinical studies have shown that 16mg of SUBUTEX or SUBOXONE is a clinically effective dose compared with placebo and indicate that doses as low as 12 mg may be effective in some patients. The dosage of SUBOXONE should be progressively adjusted in increments / decrements of 2mg or 4mg to a level that holds the patient in treatment and suppresses opioid withdrawal effects. This is likely to be in the range of 4mg to 24mg per day depending on the individual.

Reducing dosage and stopping treatment:
The decision to discontinue therapy with SUBOXONE or SUBUTEX after a period of maintenance or brief stabilization should be made as part of a comprehensive treatment plan. Both gradual and abrupt discontinuation have been used, but no controlled trials have been undertaken to determine the best method of dose taper at the end of treatment.

HOW SUPPLIED
SUBOXONE is supplied as sublingual tablets in white HDPE bottles:

Hexagonal orange tablets containing 2mg buprenorphine with 0.5mg naloxone
NDC 12496-1283-2 30 tablets per bottle

Hexagonal orange tablets containing 8mg buprenorphine with 2mg naloxone

NDC 12496-1306-2 30 tablets per bottle

Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]

SUBUTEX is supplied as sublingual tablets in white HDPE bottles:

Oval white tablets containing 2mg buprenorphine
NDC 12496-1278-2 30 tablets per bottle

Oval white tablets containing 8mg buprenorphine
NDC 12496-1310-2 30 tablets per bottle

Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]

Manufactured by:
Reckitt Benckiser Healthcare (UK) Ltd
Hull, UK, HU8 7DS

Distributed by:
Reckitt Benckiser Pharmaceuticals, Inc.
Richmond, VA 23235

Patient Information Leaflet

PATIENT INFORMATION

SUBOXONE® (sub-OX-own)
(buprenorphine HCl/naloxone HCl dihydrate, sublingual tablet) (C*)

SUBUTEX® (SUB-u-tex)
(buprenorphine HCl, sublingual tablet) (C*)

Read this information carefully before you take SUBOXONE or SUBUTEX and each time you get more SUBOXONE or SUBUTEX. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment. Only you and your doctor can decide if SUBOXONE or SUBUTEX is right for you. Share the important information in this leaflet with members of your household.

What is the most important information I should know about SUBOXONE and SUBUTEX?

- **SUBOXONE and SUBUTEX can cause death from overdose,** especially if you inject them with tranquilizers. Use SUBOXONE or SUBUTEX exactly the way your doctor tells you to with medicines used to treat depression or anxiety.
- **Use SUBOXONE and SUBUTEX only for the condition for which it was prescribed**.

- **SUBOXONE and SUBUTEX can cause** drug dependence. This means that you can get withdrawal symptoms if you stop using the medicine too quickly. SUBOXONE and SUBUTEX are not for occasional ("as needed") use.
- **Prevent theft and misuse.** SUBOXONE and SUBUTEX contain a narcotic painkiller that can be a target for people who abuse prescription medicines or street drugs. Therefore, keep your tablets in a safe place, to protect them from theft. Never give them to anyone else. Selling or giving away this medicine is against the law.
- **In an emergency**, have family members tell emergency room staff that you are dependent on opioids (narcotic painkillers) and are being treated with SUBOXONE or SUBUTEX.

What are SUBOXONE and SUBUTEX?

SUBOXONE and SUBUTEX are prescription medicines used to treat adults addicted to opioid (narcotic painkillers) medicines and drugs, such as morphine and heroin. SUBOXONE and SUBUTEX take the place of these medicines and drugs and may help you stop using and abusing them. SUBOXONE and SUBUTEX are part of a complete addiction treatment program that also includes counseling or behavioral therapy.
SUBOXONE and SUBUTEX have not been studied in children.

SUBOXONE is a tablet that contains 2 medicines.

1. The first medicine is called buprenorphine (BYOO-pruh-NOR-feen). It is like painkiller medicines such as morphine, street drugs like heroin, and addiction treatment medicines like methadone. Buprenorphine may give you less of a "high" than these other prescription medicines and street drugs. Withdrawal or stopping buprenorphine may be easier than stopping other prescription medicines and street drugs.
2. SUBOXONE also contains naloxone (nal-OX-own). When naloxone is injected, it blocks the effects of medicines and drugs like methadone, heroin, and morphine. Naloxone is added to SUBOXONE to stop people from injecting ("shooting-up") SUBOXONE tablets. When you use SUBOXONE under your tongue (sublingually), as prescribed, the naloxone in SUBOXONE should not stop the medicine's effects. However, if you inject SUBOXONE, the naloxone can give you bad withdrawal symptoms.

SUBUTEX is a tablet and it contains only the medicine buprenorphine (see "What is SUBOXONE?" for a description of buprenorphine). SUBUTEX is different from SUBOXONE because it does not contain naloxone. It is usually used under a doctor's direct supervision.

Who Should Not Take SUBOXONE or SUBUTEX?

Do not take SUBOXONE or SUBUTEX if

- your doctor did not prescribe SUBUTEX or SUBOXONE for you.
- you are allergic to buprenorphine, or any of the inactive ingredients in the medicines. See the end of this leaflet for a complete list of ingredients.

Do not take SUBOXONE if

- you are allergic to naloxone or buprenorphine.

Your doctor should know about all your medical conditions before deciding if SUBOXONE or SUBUTEX is right for you or what dose is best. Tell your doctor about all of your medical problems, especially the ones listed below:

- trouble breathing or lung problems
- head injury or brain problem
- liver or kidney problems
- gallbladder problems
- adrenal gland problems, such as Addison's disease
- low thyroid (hypothyroidism)
- enlarged prostate gland (men)
- problems urinating
- a curve in your spine that affects your breathing
- severe mental problems or hallucinations (seeing or hearing things that are not really there)
- alcoholism

If any of these conditions apply to you, make sure you tell your doctor about them before taking SUBOXONE or SUBUTEX**.**

Tell your doctor:

- **if you are pregnant or plan to become pregnant**. SUBOXONE **or** SUBUTEX may not be right for you. It is not known whether SUBOXONE or SUBUTEX could harm your baby.
- **if you are breast feeding**. SUBOXONE **or** SUBUTEX will pass through your milk and may harm your baby.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. They may cause serious side effects when taken with SUBOXONE or SUBUTEX. Sometimes, the doses of certain medicines and SUBOXONE or SUBUTEX need to be reduced if used together.

Do not take any other medicine, herbal, or over-the-counter medicine while using SUBOXONE or SUBUTEX unless your doctor has told you it is okay.

How should I take SUBOXONE or SUBUTEX?

- **Follow your doctor's directions exactly**. Your doctor may change your dose after seeing how the medicine affects you. Do not change your dose unless your doctor tells you to change it. Do not take SUBOXONE or SUBUTEX more often than prescribed.

- **Put the tablets under your tongue and let them melt**. This will take 2 to 10 minutes. Do not chew or swallow the tablets. The medicine will not work this way and you may get withdrawal symptoms.

- **If your doctor tells you to take more than 1 tablet**, you will be told to:
  - take all tablets at the same time together under your tongue, or
  - take 2 tablets, put them under your tongue. After they melt, put the next tablet or tablets under your tongue right away
  - hold the tablets under your tongue until they melt completely. The medicine will not work if swallowed and you may get withdrawal symptoms.
  - Do not change the way you are told to take your medicine or you may get too little or too much medicine.

- **Do not inject ("shoot-up") SUBOXONE or SUBUTEX.** Shooting-up is dangerous and you may get bad withdrawal symptoms.

- **SUBOXONE and SUBUTEX can cause** withdrawal symptoms if you take them too soon after using drugs like heroin, morphine, or methadone.

- **If you miss a dose** of SUBOXONE or SUBUTEX, take it as soon as possible. If it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not take 2 doses at once unless your doctor tells you to.

- **Before stopping** SUBOXONE or SUBUTEX, ask your doctor how to stop to avoid withdrawal symptoms.

- **If you take too much** SUBOXONE or SUBUTEX or **overdose**, call your local emergency number or poison control center right away.

After you stop taking SUBOXONE or SUBUTEX, **flush the unused tablets down the toilet.**

What Should I Avoid While Taking SUBOXONE or SUBUTEX?

- **Do not drive, operate heavy machinery, or perform any other dangerous activities** until you know if this medicine affects how alert you are.

- **Do not drink alcohol or take tranquilizers or sedatives** (medicines that help you sleep) while using SUBOXONE or SUBUTEX. **You can die when you use these products** with SUBOXONE or SUBUTEX.

- **Do not take other medicines without talking to your doctor.** Other medicines include prescription and non-prescription medicines, vitamins, and herbal supplements. Be especially careful about medicines that may make you sleepy.

What are the Possible Side Effects of SUBOXONE and SUBUTEX?

Call your doctor or get medical help right away if

- You feel faint, dizzy, confused, or have any other unusual symptoms.
- Your breathing gets much slower than is normal for you.

These can be signs of an overdose or serious problem.

SUBOXONE and SUBUTEX may cause liver problems. Call your doctor right away if:

- Your skin or the white part of your eyes turns yellow (jaundice).
- Your urine turns dark.
- Your bowel movements (stools) turn light in color.
- You don't feel like eating much food for several days or longer.
- You feel sick to your stomach (nausea).
- You have lower stomach pain.

Your doctor will do blood tests while you are taking SUBOXONE or SUBUTEX to make sure your liver is okay.

- **SUBOXONE and SUBUTEX can cause your blood pressure to drop**. This can make you feel dizzy if you get up too fast from sitting or lying down.
- **SUBOXONE and SUBUTEX can cause allergic reactions** that can make it hard for you to breathe. Other symptoms of a bad allergic reaction include hives, swelling of your face, asthma (wheezing) or shock (loss of blood pressure and consciousness). Call a doctor or get emergency help right away if you get any of these symptoms.

You may have withdrawal symptoms when you start treatment with SUBOXONE or SUBUTEX.

You can develop dependence from taking SUBOXONE or SUBUTEX, and so you may get withdrawal symptoms when you stop taking SUBOXONE or SUBUTEX. There is also a chance that you may abuse or get addicted to SUBOXONE or SUBUTEX because SUBOXONE and SUBUTEX are treatments for other drug addictions.

Some of the common side effects of SUBOXONE and SUBUTEX are headache, pain, problems sleeping, nausea, sweating, stomach pain, and constipation.

These are not all the possible side effects of SUBOXONE or SUBUTEX. For a complete list, ask your doctor or pharmacist.

GENERAL INFORMATION ABOUT THE SAFE AND EFFECTIVE USE OF SUBOXONE and SUBUTEX.

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use SUBOXONE or SUBUTEX for conditions for which they were not prescribed. Do not give SUBOXONE or SUBUTEX to other people, even if they have the same symptoms you have. Sharing is illegal and may cause severe medical problems. Keep SUBOXONE and SUBUTEX out of the reach of children. Accidental overdose in children is dangerous and can result in death.

This leaflet summarizes the most important information about SUBOXONE and SUBUTEX. If you would like more information, talk with your doctor. Also, you can ask your pharmacist or doctor for information about SUBOXONE and SUBUTEX that is written for health professionals. For more information call 1-877- SUBOXONE (1-877-782-6966), or visit our Web site, www.suboxone.com.

What are the ingredients of SUBOXONE and SUBUTEX?

SUBOXONE

Active Ingredients: buprenorphine hydrochloride and naloxone hydrochloride dihydrate

Inactive Ingredients: lactose, mannitol, cornstarch, povidone K30, citric acid, sodium citrate, FD&C Yellow No.6 color, magnesium stearate, and for flavoring, Acesulfame K sweetener and a lemon-lime flavor

SUBUTEX

Active Ingredients: buprenorphine hydrochloride

Inactive Ingredients: lactose, mannitol, cornstarch, povidone K30, citric acid, sodium citrate and magnesium stearate

RX ONLY

Physician Information

Answers to Frequently Asked Questions

Who is qualified to prescribe SUBOXONE or SUBUTEX?

Physicians who:

- Meet one or more of the following training requirements
  - Hold a subspecialty board certification in addiction psychiatry from the American Board of medical Specialties
  - Hold an addiction certification from the American Society of Addiction Medicine
  - Hold a subspecialty board certification in Addiction Medicine from the American Osteopathic Association
  - Have completed not less than 8 hours of authorized training on the treatment or management of opioid-dependent patients. This training may include classroom situations, seminars at professional society meetings, electronic communications, or other media. The American Society of Addiction Medicine, The American Academy of Addiction Psychiatry, the American Medical Association, the American Osteopathic Association, and the American Psychiatric Association are all authorized to provide this training. Details and website addresses can be found in the section below.
- AND meet both of the following criteria:
  - Have the capacity to provide or to refer patients for necessary ancillary services, such as psychosocial therapy.
  - Agree to treat no more than 30 patients at any one time in their individual or group practice

When and where are training sessions being held?

Each of the above organizations has scheduled training sessions. You may contact them directly at the addresses below, or visit their web sites. Additionally, you can call the toll-free SUBOXONE help line at 1-877-SUBOXONE (1-877-782-6966) or log on to our Web site www.suboxone.com.

The American Academy of Addiction Psychiatry
7301 Mission Road, Suite 252
Prairie Village, KS 66208
Telephone: (913) 262-6161
E-mail: info@aaap.org
Web site: www.aaap.org

The American Society of Addiction Medicine
4601 North Park Ave. Arcade Suite 101
Chevy Chase, MD 20815
Telephone (301) 656-3920
E-mail: email@asam.org
Web site http://asam.org

The American Psychiatric Association
1400 K Street N.W.
Washington, DC 20005
Telephone (888) 357-7924
E-mail: apa@psych.org
Web site: http://www.psych.org

American Osteopathic Association
142 East Ontario Street
Chicago, IL 60611
Telephone (800) 621-1773
E-mail: info@aoa-net.org
Web site: http://www.aoa-net.org/

I am already qualified. What do I do next?

The Drug Addiction Treatment Act (DATA) requires that before you begin prescribing SUBOXONE or SUBUTEX you must notify the Secretary of Health and Human Services of your intent to treat patients with these products. The agency within the Department of Health and Human Services to be notified is the Substance Abuse and Mental Health Services Administration (SAMHSA). Notification is handled within SAMHSA by the Division of Pharmacologic Therapies (DPT) within the Center for Substance Abuse

Treatment (CSAT). For convenience CSAT has developed a form that may be used for your notification. A copy is enclosed in this package
You may complete the notification form online or download the form by visiting CSAT's web site at www.dpt.samhsa.gov. The form may also be downloaded from www.suboxone.com. If you prefer, you may also notify by letter if you include all of the required information.
All forms (or letters) should be mailed or faxed to:

Substance Abuse and Mental Health Services Administration
Center for Substance Abuse Treatment
Division of Pharmacologic Therapies
Attn. Opioid Treatment Waiver Program
5600 Fishers Lane, Rm. 12-105
Rockville, MD 20857
FAX: (301) 443-3994

Call CSAT/DPT if you have any questions about the notification process or need help completing the form. They can be reached at (301) 443-7745.

What happens after my notification is sent to CSAT?

CSAT will communicate with the Drug Enforcement Administration (DEA), review your notification and then notify DEA that you are qualified as required by the DATA. The DATA allows 45 days for this review process. No later than at the end of that 45-day period, DEA will issue a unique identification number indicating that you are a qualifying physician under the DATA. DEA is developing regulations that will require this number along with your existing DEA registration number to be included on all prescriptions issued for the treatment of opioid dependence under the DATA; therefore it is strongly recommended that you include this number when you write prescriptions for Subutex and Suboxone for the treatment of opioid dependence. CSAT will send you a letter notifying you of the new DEA identification number that will be assigned. You will subsequently receive a revised DEA registration certificate (showing both numbers).

Do I have to wait 45 days before treating patients?

The DATA envisions physicians notifying CSAT as soon as they are qualified, but makes provision for those who find themselves in the position of being qualified and needing to treat a patient, but not having notified CSAT In this case, you must first notify CSAT and DEA of your intent before treating the patient; this can be done electronically on the internet by checking the appropriate box, or by faxing in the form included in this package to CSAT at: (301) 443-3994

During the training sessions, as well as in the product information and CSAT Guidelines, it is recommended that patients be given initial doses under supervision. It is not my normal practice to keep a stock of controlled substances in my office. How do I get SUBOXONE or SUBUTEX for use in the office?

State laws vary regarding stocking of controlled substances. Information on State requirements can be found on our website, If you have a routine supplier of products such as vaccines, or injectable products that you use in your office, that supplier will be able to provide you with SUBOXONE and SUBUTEX. If you do not have a normal supplier of such products we will facilitate the establishment of a relationship with a supplier. Please complete the enclosed pre-addressed request form and mail it to us. Alternately, you may call our toll-free SUBOXONE Help Line at 1 877 SUBOXONE (1-877-782-6966) or log on to our Web site www.suboxone.com. In those States where permitted, we will provide you with an initial supply of SUBOXONE or SUBUTEX for induction use.

What storage and record-keeping requirements are associated with maintenance of a supply of SUBOXONE and SUBUTEX in my office?

For a full listing of requirements for a specific State you may call our toll-free SUBOXONE Help Line at 1 877 SUBOXONE (1-877-782-6966) or log on to our Web site www.suboxone.com. Generally, you will be required to keep the medications in a secure environment. They should be kept in a locked compartment with limited access. You will also be required to maintain a written record of the disposition of all doses. Usually this can be done with the maintenance of a logbook in which you record all incoming doses and account for each dispensed dose as it is used. This record must be kept current at all times. Additional requirements may be in place in your State.

While I appreciate the convenience of maintaining a supply of SUBOXONE and SUBUTEX in my office for induction purposes, the situation at our office precludes such an arrangement. How do I manage supervised induction doses without maintaining such a supply in my office?

For those physicians who do not wish to maintain a supply of SUBOXONE or SUBUTEX in their offices, where State law and regulation allows, we will provide coupons for you to provide to your patient for their initial doses. In this circumstance, you would write a prescription only for the initial dose of SUBOXONE or SUBUTEX. If pharmacy delivery services are available, you may choose to arrange to have the dose delivered to your office; if not give the prescription, and a coupon, to the patient (or, if available, to a trustworthy family member accompanying the patient) with instructions that the prescription is to be taken to the pharmacy, filled, and brought back to your office for dosing. It is recommended that you call or fax ahead to ensure

availability of the medication and to reduce patient waiting time. You should instruct the patient that on his or her return to the office the induction dose will be administered, and that he or she will be monitored in your office. The pharmacist should reiterate this instruction upon filling the prescription. You may wish to limit the prescription to one days' dose, and repeat this method (with or without the coupon) for the first several days of treatment before providing a prescription for several days' supply at one time. Further information regarding this program and a supply of coupons is available by calling our toll-free SUBOXONE Help Line at 1 877 SUBOXONE (1-877-782-6966) or log on to our Web site www.suboxone.com.

Will these coupons and prescriptions be valid at any pharmacy, or will I need to refer patients to a specific store?

The coupons and prescriptions will be valid at any pharmacy. However, prior to prescribing SUBOXONE or SUBUTEX, if you do not maintain a supply of tablets for induction dosing in your office, it is essential that you establish a relationship with one or more specific pharmacies in your area who will be in a position to provide your patients with initial doses as well as instructions for returning to your office for induction and the follow-up prescription. (Such a relationship is also recommended if you intend to maintain initial dosing supplies in your office.) Generally, a pharmacy near your office is recommended for patient convenience. If possible, it is advisable to identify a pharmacy that will deliver initial doses to your office, so that patients do not have to leave and return for induction dosing. Alternatively, it is recommended that you avail yourself of any call-in or fax-in prescription services provided, to reduce patient waiting time. If you do not currently have a commercial or professional relationship with a pharmacy in your area, we will be pleased to assist in facilitating the establishment of such an arrangement, and to help identify pharmacies with delivery service. Please call our toll-free SUBOXONE Help Line at 1 877 SUBOXONE (1-877-782-6966) or log on to our Web site www.suboxone.com.

Are there special confidentiality issues I should consider?

Remember that you may be communicating with the pharmacist to verify prescriptions for a particular patient. As you may know, there are special federal regulations concerning the confidentiality of substance abuse treatment, records (42 CFR Part 2) and the privacy of health records (HIPAA). To ensure that you will be able to communicate with the pharmacist to confirm the validity of a SUBOXONE or SUBUTEX prescription, it is recommended that you have the patient sign a release of information at the time of the office visit. A sample consent form with all the elements required under 42CFR Part 2 is included with this booklet as an attachment. It is particularly important to obtain the patient's consent if you elect to phone or FAX in prescriptions, as this constitutes disclosure of the patient's treatment. When

the prescription is directly transmitted by the physician, there are also prohibitions on the further redisclosure of patient identifying information by the pharmacist. 42CFR Part 2 does not apply when it is the patient who delivers the presciption to the pharmacist, without direct communication from the physician to the pharmacist.

To learn more about these regulations, visit the SAMHSA website www.hipaa.samhsa.gov, or call 1-866-BUP-CSAT

I'm familiar with general principles of addiction treatment, but this is my first experience with office-based prescription of this type of medication. What precautions should I take in my practice to prevent diversion and abuse?

You should consider the following suggestions:

- Initiate treatment with supervised administration, progressing to unsupervised administration as your patient's clinical stability permits.

- Limit the use of Subutex to supervised use, wherever possible. Recall that the Suboxone product contains naloxone, which Subutex does not. The naloxone in Suboxone is likely to precipitate withdrawal symptoms when injected by individuals dependent on heroin, morphine, or other full opiate agonists. Therefore, it is expected that Suboxone will be less attractive to "street addicts" and less likely to be diverted. Therefore, it is strongly recommended that Suboxone be used whenever unsupervised administration is planned.

- As your patients progress, and you consider prescribing Suboxone for take-home use; when determining the size of the prescription you write, you should consider your patient's level of stability, the security of his or her home situation, and other factors likely to affect the ability to manage supplies of take-home medication.

- Have plans in place to deal with patient requests for replacement of prescriptions or supplies of medication that are described as lost or stolen.

- Keep tight control of your prescription pads. Never leave them in the examination room, even inside a desk drawer. Never sign an incomplete prescription blank.

- Write all numbers (quantity and strength) in both numbers and letters – like you write your checks.

- Establish a relationship with the pharmacies you expect to be filling your prescriptions for SUBOXONE or SUBUTEX and discuss potential diversion problems and controls with them.

- Request photo (or other) I.D. and Social Security number and maintain copies in patient's record.

- If you suspect an attempt to divert prescription medications, call your local police department.

Where can I get more information on treating patients with Subutex and Suboxone?

- Refer to the physician package insert for prescribing information. Additional recommendations may be found in treatment guidelines available for free from the Center for Substance Abuse Treatment at the Substance Abuse and Mental Health Services Administration. To obtain a copy please call our toll-free SUBOXONE Help Line at 1 877 SUBOXONE (1-877-782-6966) or log on to our Web site www.suboxone.com. Additional information is also available on the CSAT web site at www.dpt.samhsa.gov

- Refer to the package insert for full information on the adverse events seen during the clinical trials using buprenorphine for opiate addiction treatment. Note the important precautions and warnings to share with patients, such as the risk of fatal respiratory depression when buprenorphine is combined with other depressants. Also note other important safety issues such as the fact that buprenorphine should be administered with caution in the elderly or debilitated patient, and those with severe impairment of hepatic, pulmonary or renal function; and that buprenorphine may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery, especially during drug induction and dose adjustment

- General information on the treatment of addiction is available through;

  The American Academy of Addiction Psychiatry

7301 Mission Road, Suite 252
Prairie Village, KS 66208
Telephone: (913) 262-6161
E-mail: info@aaap.org
Web site: www.aaap.org

The American Society of Addiction Medicine
4601 North Park Ave. Arcade Suite 101
Chevy Chase, MD 20815
Telephone (301) 656-3920
E-mail: email@asam.org
Web site http://asam.org

Substance Abuse and Mental Health
Services Administration
Office of Pharmacologic and Alternative Therapies
CSAT, Rockwall II Building, Suite 740
5600 Fishers Lane
Rockville, MD 20857
Web site: www.dpt.samhsa.gov

Notification of Intent to Use Schedule III, IV, or V Opioid Drugs for the Maintenance and Detoxification Treatment of Opiate Addiction under 21 USC § 823(g)(2)	Form Approved: 0930- 0234 Expiration Date: 10/31/2002 See OMB Statement on Reverse
	DATE OF SUBMISSION

Note: Notification is required by Sec. 303(g)(2), Controlled Substances Act (21 USC § 823(g)(2)). See instructions on reverse.

1a. **NAME OF PRACTITIONER**

b. State Medical License Number **c. DEA Registration Number**

2. ADDRESS OF PRIMARY LOCATION (*Include Zip Code*)	**3. TELEPHONE NUMBER** (*Include Area Code*) **4. FAX NUMBER** (*Include Area Code)* **5. EMAIL ADDRESS (***optional***)**
6. NAME AND ADDRESS OF GROUP PRACTICE **7. GROUP PRACTICE EMPLOYER IDENTIFICATION NUMBER**	**8. PURPOSE OF NOTIFICATION** (Check all that apply) New Immediate

9. GROUP PRACTITIONERS

NAME _____ **DEA Registration Number**

NAME _____ **DEA Registration Number**

(Include additional pages as necessary to identify each group practice member.)

10. CERTIFICATION OF USE OF NARCOTIC DRUGS UNDER THIS NOTIFICATION

I certify that I will only use schedule III, IV, or V drugs or combinations of drugs that have been approved by the FDA for use in maintenance or detoxification treatment and that have not been the subject of an adverse determination.

11. CERTIFICATION OF QUALIFYING CRITERIA (*Check each appropriate source and provide documentation.*) **I certify that I meet at least one of the following criteria and am therefore a qualifying physician (check and provide documentation for all that apply):**

Subspecialty board certification in addiction psychiatry from the American Board of Medical Specialties
Addiction certification from the American Society of Addiction Medicine
Subspecialty board certification in addiction medicine from the American Osteopathic Association
Completion of not less than eight hours of training for the treatment and management of opiate-dependent patients provided by the following organization(s): Date and location of training
American Society of Addiction Medicine
American Academy of Addiction Psychiatry
American Medical Association
American Osteopathic Association
American Psychiatric Association
Other (specify, include date and location)
Participation as an investigator in one or more clinical trials leading to the approval of a schedule III, IV, or V narcotic drug for maintenance or detoxification treatment
State medical licensing board-approved experience or training in the treatment and management of opiate-dependent patients.
OTHER *(Specify)*

12. CERTIFICATION OF CAPACITY

I certify that I have the capacity to refer patients for appropriate counseling and other appropriate ancillary services.

13. CERTIFICATION OF MAXIMUM PATIENT LOAD

I certify that I or my group practice will not exceed 30 patients for maintenance or detoxification treatment at one time. SMA-167

14. CONSENT TO RELEASE IDENTIFYING INFORMATION TO SAMHSA TREATMENT FACILITY LOCATOR

I consent to the release of my name, address, and phone number to the SAMHSA Treatment Facility Locator.

I do not consent to the release of my name, address, and phone number to the SAMHSA Treatment Facility Locator.

15. I certify that the information presented above is true and correct to the best of my knowledge. I certify that I will notify SAMHSA at the address below if any of the information contained on this form changes. Note: Any false, fictitious, or fraudulent statements or information presented above or misrepresentations relative thereto may violate Federal laws and could subject you to prosecution, and/or monetary penalties, and or denial, revocation or suspension of DEA registration (See 18 U.S.C.§1001; 31 U.S.C.§§3801-3812; 21 U.S.C.§824.)

Signature **Date**

Please send the completed form to:
Substance Abuse and Mental Health Services Administration
Office of Pharmacologic and Alternative Therapies
Attention: Opioid Treatment Waiver Program
CSAT, Rockwall II Building, Suite 740
5600 Fishers Lane
Rockville, MD 20857
Fax 301-443-3994
Phone 301-443-7745

This form is intended to facilitate the implementation of the provisions of 21 USC § 823 (g)(2). The Secretary of DHHS will use the information provided to determine whether practitioners meet the qualifications for waivers from the separate registration requirements under the Controlled Substances Act (21 USC § 823 (g)(1)). The Drug Enforcement Administration will assign an identification number to qualifying practitioners and the number will be included in the practitioner's registration under 21 USC § 823 (f).

This form may be completed and submitted electronically (including facsimile) to facilitate processing.

1. The practitioner must identify the DEA registration number issued under 21 USC§ 823(f) to prescribe substances controlled in Schedules III, IV, or V.	**2. The address should be the primary address listed in the practitioner's registration under § 823(f). Only one address should be specified. If the narcotic drugs or combinations to be used under this notification are to be dispensed by the practitioner then the address must reflect the site where the medication will be dispensed.**

6. Group practice is defined under section 1877(h)(4) of the Social Security Act. **14. The SAMHSA Treatment Facility Locator is freely accessible on the World Wide Web (http://findtreatment.samhsa.gov) and is widely used by the members of the treatment seeking public and referring professionals. It lists more than 11,000 facilities that offer specialized drug and alcohol abuse treatment programs and provides links to many other sources of information on substance abuse. The information on physicians will be retrieved by a geographical search of a separate category within the locator. No disclosures to the SAMHSA Treatment Facility Locator will be made in the absence of express consent.**	**8. Purpose of notification:** **New - an initial notification for a waiver submitted for the purpose of obtaining an identification number from DEA for inclusion in the registration under 21 U.S.C. §823(f).** **Immediate - a notification submitted for the purpose of notifying the Secretary and the Attorney General of the intent to immediately facilitate the treatment of an individual (one) patient.** **Note: It is permissible to submit a new and immediate notification simultaneously.**

PRIVACY ACT INFORMATION

Authority: Section 303 of the Controlled Substances Act of 1970 (21 U.S.C §823(g)(2)).
Purpose: To obtain information required to determine whether a practitioner meets the requirements of 21 U.S.C §823(g)(2).
Routine Uses: Disclosures of information from this system are made to the following categories of users for the purposes stated:
A. Medical specialty societies to verify practitioner qualifications.
B. Other federal law enforcement and regulatory agencies for law enforcement and regulatory purposes.
C. State and local law enforcement and regulatory agencies for law enforcement and regulatory purposes.
D. Persons registered under the Controlled Substance Act (PL 91-513) for the purpose of verifying the registration of customers and practitioners.

Effect: This form was created to facilitate the submission and review of waivers under 21 U.S.C. §823(g)(2). This does not preclude other forms of notification.

Paperwork Reduction Act Statement

Public reporting burden for completing this form is estimated to average 5 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the completed form. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. The OMB control number for this project is 0930-0234).

SMA-167

Attachment to Physician's Brochure:

SAMPLE 42 CFR Part 2.31 Consent Form

1. I (name of patient) _____{time}
Authorize:
2. Dr._____
3. To disclose: (kind and amount of information to be disclosed)

Any information needed to confirm the validity of my prescription and for submission for payment for the prescription.

_____
4. To: (name or title of the person or organization to which disclosure is to be made)
The dispensing pharmacy to whom I present my prescription or to whom my prescription is called/sent/faxed, as well as to third party payors.

5. For (purpose of the disclosure)
Assuring the pharmacy of the validity of the prescription, so it can be legally dispensed, and for payment purposes.

_____
6. Date (on which this consent is signed)_____
7. Signature of patient _____
8. Signature of parent or guardian (where required)

_____
9. Signature of person authorized to sign in lieu of the patient (where required)

_____
10. This consent is subject to revocation at any time except to the extent that the program which is to make the disclosure has already taken action in reliance on it. If not previously revoked, this consent will terminate upon: (specific date, event, or condition)

Termination of treatment

(c) Expired, deficient, or false consent. A disclosure may not be made on the basis of a consent which: (1) Has expired; (2) On its face substantially fails to conform to any of the requirements set forth in paragraph (a) of this section; (3) Is known to have been revoked; or (4) Is known, or through a reasonable effort could be known, by the person holding the records to be materially false. (Approved by the Office of Management and Budget under control number 0930-0099)

Notice to accompany disclosure:

Each disclosure made with the patient's written consent must be accompanied by the following written statement: This information has been disclosed to you from records protected by Federal confidentiality rules (42 CFR part 2). The Federal rules prohibit you from making any further disclosure of this information unless further disclosure is expressly permitted by the written consent of the person to whom it pertains or as otherwise permitted

by 42 CFR part 2. A general authorization for the release of medical or other information is NOT sufficient for this purpose.

Information for Pharmacists

SUBOXONE® (buprenorphine HCl/naloxone HCl dihydrate, sublingual tablet)

and SUBUTEX® (buprenorphine HCl, sublingual tablet)

What are SUBOXONE and SUBUTEX?

SUBOXONE and SUBUTEX are sublingual tablets indicated for the treatment of opioid dependence. SUBOXONE contains buprenorphine (a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor) and naloxone (an antagonist at the mu-opioid receptor). SUBUTEX contains buprenorphine only.

Why is it important for all pharmacists to learn about SUBOXONE and SUBUTEX?

For the first time, pharmacists will play a role in the delivery of opiate addiction treatment. SUBOXONE and SUBUTEX are the first medications approved for office-based treatment of opioid dependence under the Drug Addiction Treatment Act of 2000 (DATA). Prior to the passage of this law, it was illegal for a doctor to prescribe narcotic drugs for the treatment of narcotic dependence. Opioid dependence treatment of this type could only be provided at specially registered clinics. Under the new law, only opiate addiction treatment drugs under Schedule II are confined to use in the clinic setting. Less tightly controlled drugs (Schedules III-V) may be *prescribed* for opiate

addiction treatment by specially qualified doctors who treat patients in their private offices.

: **Why are there two formulations?**

SUBOXONE is the preferred medication for maintenance treatment due to the presence of naloxone in the formulation, which is intended to deter intravenous abuse by persons dependent on other opiates. SUBUTEX, which does not contain naloxone, may be better tolerated by patients in the first several days of treatment and is generally preferred for induction. "Induction" refers to the initial period of treatment, during which time the patient should receive medication under the doctor's supervision in the office. Patients or their family members may need to come and pick up induction doses each day for the first several days of treatment (or you may be asked to arrange delivery to the doctor's office, if your pharmacy provides this service). Therefore, while you may see prescriptions for small amounts of SUBUTEX presented for induction doses, you should expect the majority of prescriptions to be for SUBOXONE.

SUBOXONE and SUBUTEX are controlled as Schedule III narcotics under the Controlled Substances Act.

How are they supplied?

SUBOXONE is supplied as hexagonal orange tablets in 2 dosage strengths:

2 mg buprenorphine + 0.5 mg naloxone embossed with a sword logo at the midline and N2 on the reverse side

and 8 mg buprenorphine + 2 mg naloxone embossed with a sword logo at the midline and N8 on the reverse side, ,

SUBUTEX is supplied as oval white tablets in in 2 dosage strengths:

2mg buprenorphine embossed with a sword logo at the midline and B2 on the reverse side

and 8mg buprenorphine embossed with a sword logo at the midline and B8 on the reverse side

I've heard that buprenorphine is safer than methadone. Can these drugs be dangerous?

Significant respiratory depression has been associated with buprenorphine, particularly when administered intravenously. A number of deaths have occurred when addicts have intravenously misused buprenorphine, usually with benzodiazepines concomitantly. Deaths have also been reported in association with concomitant administration of buprenorphine and other depressants such as alcohol or other opioids

Do SUBOXONE and SUBUTEX cause dependence?

Chronic administration of SUBOXONE or SUBUTEX produces dependence of the opiate type, characterized by withdrawal upon abrupt discontinuation or rapid taper. The withdrawal syndrome is milder than seen with full agonists, and may be delayed in onset. Because it contains naloxone, SUBOXONE is highly likely to produce marked and intense withdrawal symptoms if misused parenterally by individuals dependent on opioid agonists such as heroin, morphine, or methadone. Sublingually, SUBOXONE may cause opioid withdrawal symptoms in such persons if administered before the agonist effects of the opioid have subsided.

Be sure to read the full Prescribing Information for complete Warnings & Precautions.

What other information should I relay to patients?

It's important that you make sure patients understand their physicians' instructions, and that you answer any questions they may have.

When counseling patients, be sure to discuss any relevant precautions as listed in the Prescribing Information, including but not limited to the following:

- Patients should inform their family members that, in the event of emergency, the treating physician or emergency room staff should be informed that the patient is physically dependent on opioids and that the patient is being treated with SUBOXONE or SUBUTEX

- Patients should be cautioned that a serious overdose may occur if benzodiazepines, sedatives, tranquilizers, antidepressants, or alcohol are taken at the same time as SUBOXONE or SUBUTEX

- Patients should be cautioned that SUBOXONE or SUBUTEX may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery. Patients should be cautioned not to drive or operate complex machinery until they know how SUBOXONE or SUBUTEX affects their ability to function in these circumstances, such as driving a car.

- Patients should consult their physician if other prescription medications are currently being used or are prescribed for future use

What are the possible side effects of SUBOXONE and SUBUTEX?

The most common adverse events reported in clinical trials with SUBOXONE and SUBUTEX were headache, withdrawal syndrome, pain, nausea, insomnia, sweating, abdominal pain, back pain, constipation, infection, asthenia, rhinitis, anxiety, and depression.

What is the role of the pharmacist in ensuring safe use of SUBOXONE and SUBUTEX?

As a pharmacist, you will play an important role in ensuring that SUBOXONE and SUBUTEX are used safely and appropriately. Each time you fill a prescription for SUBOXONE or SUBUTEX, make sure to:

- Verify that the prescriptions you receive are from physicians who are in compliance with the provisions of the DATA (see below).
- Remind patients who are picking up induction doses to return as directed to the doctor's office so that they can be supervised while taking the medication.
- Be vigilant in detecting fraudulent prescriptions or simultaneous prescriptions for the same patient from multiple suppliers.

Who is qualified to prescribe SUBOXONE and SUBUTEX?

The DATA limits office-based use of SUBOXONE and SUBUTEX to physicians who meet special training criteria and can provide appropriate services. To be qualified, physicians must:

- Meet one or more of the following training requirements

- Hold a subspecialty board certification in addiction psychiatry from the American Board of medical Specialties

- Hold a subspecialty board certification in Addiction Medicine from the American Osteopathic Association

- Hold an addiction certification from the American Society of Addiction Medicine

- Have completed not less than 8 hours of authorized training on the treatment or management of opioid-dependent patients. This training may include classroom situations, seminars at professional society meetings, electronic communications, or other media. The American Society of Addiction Medicine,-The American Academy of Addiction Psychiatry, the American Medical Association, the American Osteopathic Association, and the American Psychiatric Association are all authorized to provide this training.

- AND meet both of the following criteria:
  - Have the capacity to provide or to refer patients for necessary ancillary services, such as psychosocial therapy.

  - Agree to treat no more than 30 patients at any one time in their individual or group practice

How can I be sure a physician is qualified to prescribe SUBOXONE and SUBUTEX?

Physicians who meet the qualification criteria listed in the previous section must also notify the Secretary of Health & Human Services of their intent to prescribe SUBOXONE and SUBUTEX before doing so. Once all relevant criteria are verified, DEA will issue the physician a unique identification number indicating that he or she is a qualifying physician under the DATA.

The Center for Substance Abuse Treatment (CSAT, a component of the Substance Abuse and Mental Health Services Administration) will send a letter informing the physician of the new DEA identification number. The physicians will subsequently receive a revised DEA registration certificate (showing both numbers).

Pharmacists who seek information to verify whether or not physicians have valid waivers may contact 1-866-BUP-CSAT, or by email at info@buprenorphine.samhsa.gov

What if I get a prescription from a doctor who does not have a special DEA identification number?

Call that physician for clarification that the physician has made the appropriate notification to DHHS. DEA is developing regulations that will require this number along with the physician's existing DEA registration number to be included on all prescriptions issued for the treatment of opioid dependence; therefore physicians are being strongly urged to include this number on prescriptions.

Most physicians will make arrangements to obtain the identification number before prescribing SUBOXONE or SUBUTEX, but in rare cases a physician may need to write a prescription before the number has been issued. This is allowed under the DATA provided the physician has notified the Department of Health and Human Services of his/her intention to begin treating a patient right away; the notification form includes a check box for this situation.

Are there confidentiality issues I should be aware of related to substance abuse treatment?

There are special federal regulations concerning the confidentiality of substance abuse treatment records (42 CFR Part 2) and the privacy of health records (HIPAA)which may come into play in your interactions with physicians to verify prescriptions for SUBOXONE and SUBUTEX. To ensure that physicians will be able to communicate

with you to confirm the validity of a SUBOXONE or SUBUTEX prescription, it is recommended that the physician have the patient sign a release of information at the time of the office visit. A sample consent form with all the elements required under 42 CFR Part 2 is included with this booklet as an attachment. It is particularly important to obtain the patient's consent if the physician elects to phone or FAX in prescriptions, as this constitutes disclosure of the patient's treatment. When the prescription is directly transmitted by the physician, there are also prohibitions on the further redisclosure of patient identifying information by the pharmacist. 42CFR Part 2 does not apply when it is the patient who delivers the presciption to the pharmacist, without direct communication from the physician to the pharmacist.

To learn more about these regulations, visit the SAMHSA website www.hipaa.samhsa.gov, or call 1-866-BUP-CSAT for information.

Again, Pharmacists who seek information to verify whether or not physicians have valid waivers may contact 1-866-BUP-CSAT, or by email at info@buprenorphine.samhsa.gov

How will physicians obtain supplies of medication for induction?

Because induction doses of SUBOXONE and SUBUTEX should be given in the physician's office, many physicians will maintain a supply of each medication in their office. Most physicians will get this supply through their normal supplier or the manufacturer. Some physicians, however, will write prescriptions for individual patients' induction doses at the time of the patient appointment. The prescribing physician may call or fax ahead to your pharmacy to request delivery (if you provide this service), or to ensure the medication will be ready in advance of the patient's arrival. (Recall that the patient is likely to be in mild withdrawal while awaiting the prescription.) Some physicians may send a patient's family member to the pharmacy to pick up the induction dose.

What should I do when a patient presents a prescription for an induction dose?

Physicians who choose not to maintain supplies of SUBOXONE or SUBUTEX in their offices may give their patients a prescription for their induction doses with instructions to return to the office for supervision while the dose is administered. Fill the prescription as you normally would, then make sure the patient understands that he or she must return to the doctor's office to take the medication. - It may take several days of supervised administration to complete the induction process, therefore, some patients may be visiting your pharmacy repeatedly at the beginning of treatment.

Where state laws allow, patients may be provided with a coupon that covers the cost of the first day's dose. The coupon presented to you by the patient can be submitted to reimburse the cost of the medication.

Are there any special storage, record-keeping, or other requirements associated with SUBOXONE and SUBUTEX?

As Schedule III controlled substances, SUBOXONE and SUBUTEX are subject to certain federal regulations covering areas such as record-keeping, inventory, proper dispensing and disposal. These are explained in the Drug Enforcement Administration's Pharmacist's Manual, which can be found at **www.deadiversion.usdoj.gov/pubs/manuals/pharm2/index.htm.**

Many states have their own, additional requirements for pharmacists dispensing controlled substances. Be sure to check with the appropriate authority in your state. For more information, visit the website of the National Association of Boards of Pharmacy at www.nabp.org for links to individual state boards of pharmacy.

In addition, since drug addiction is a sensitive topic, you should make sure you have access to a private area in which to counsel patients about SUBOXONE and SUBUTEX therapy. When speaking with these patients, it is important to keep in mind that addicts in withdrawal may be irritable and short on patience.

What else can I do to help safeguard against diversion?

According to federal law, pharmacists and prescribers jointly share legal responsibility for the legitimacy of a prescription. Communication between you and the prescriber is vital to ensure the validity of each prescription you're asked to fill.

However, even if you determine that an individual prescription is legal, you should still be aware of other means by which addicts may attempt to divert their prescriptions. For example, an opioid user may present to 2 or more qualified prescribers, and therefore receive multiple prescriptions for SUBOXONE or SUBUTEX. If a patient brings you more than 1 prescription covering the same therapeutic period, you have a legal duty to recognize that they are probably not for therapeutic use. You should refuse to fill the second prescription, and notify both prescribing physicians.

In addition, you should be aware that the DATA allows each physician to treat no more than 30 patients with buprenorphine at any one time. Obviously, as patients enter and leave treatment, more than 30 patients will be cared for by a particular physician over the course of time. However, if you notice an extraordinary number of new prescriptions from a single physician, you may wish to check with the prescriber to determine whether the prescriptions might be fraudulent.

Where can I get more information on treating opioid addiction with SUBOXONE and SUBUTEX?

- Refer to the package insert for full information on the adverse events seen during the clinical trials using buprenorphine for opiate addiction treatment.

- Clinical guidelines for buprenorphine treatment and general information on the treatment of addiction is available through numerous sources such as the following: Substance Abuse and Mental Health Services (SAMHSA) Center for Substance Abuse Treatment (CSAT) Web site at www.dpt.samhsa.gov American Society of Addiction Medicine Web site at **www.asam.org/** and the American Academy of Addiction Psychiatry website at **www.aaap.org/**

For more information, call our toll-free help line at 1-877-SUBOXONE (1-877-782-6966) or visit our Web site at www.suboxone.com.

Please see enclosed full Prescribing Information

Attachment to Pharmacist Brochure:

SAMPLE 42 CFR Part 2.31 Consent Form

1.I (name of patient) _____{time}
Authorize:
2. Dr._____
3. To disclose: (kind and amount of information to be disclosed)

Any information needed to confirm the validity of my prescription and for submission for payment for the prescription.

_____
4. To: (name or title of the person or organization to which disclosure is to be made)
The dispensing pharmacy to whom I present my prescription or to whom my prescription is called/sent/faxed, as well as to third party payors.

5. For (purpose of the disclosure)
Assuring the pharmacy of the validity of the prescription, so it can be legally dispensed, and for payment purposes.

_____
6. Date (on which this consent is signed)_____
7. Signature of patient _____
8. Signature of parent or guardian (where required)
_____

9. Signature of person authorized to sign in lieu of the patient (where required)

_____

10. This consent is subject to revocation at any time except to the extent that the program which is to make the disclosure has already taken action in reliance on it. If not previously revoked, this consent will terminate upon: (specific date, event, or condition)

Termination of treatment

(c) Expired, deficient, or false consent. A disclosure may not be made on the basis of a consent which: (1) Has expired; (2) On its face substantially fails to conform to any of the requirements set forth in paragraph (a) of this section; (3) Is known to have been revoked; or (4) Is known, or through a reasonable effort could be known, by the person holding the records to be materially false. (Approved by the Office of Management and Budget under control number 0930-0099).

Notice to accompany disclosure:
Each disclosure made with the patient's written consent must be accompanied by the following written statement: This information has been disclosed to you from records protected by Federal confidentiality rules (42 CFR part 2). The Federal rules prohibit you from making any further disclosure of this information unless further disclosure is expressly permitted by the written consent of the person to whom it pertains or as otherwise permitted by 42 CFR part 2. A general authorization for the release of medical or other information is NOT sufficient for this purpose.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Cynthia McCormick

10/8/02 06:03:33 PM