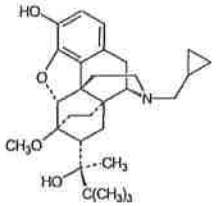
Naloxone is an antagonist at the mu-opioid receptor.

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 $C_{29}H_{41}NO_4$ HCl and the molecular weight is 504.10.

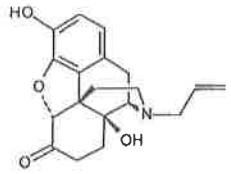
STRUCTURAL FORMULA OF BUPRENORPHINE



.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.

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

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

Effect of Naloxone:
Physiologic and subjective effects following acute sublingual administration of SUBOXONE and tablets were similar at equivalent dose levels of buprenorphine. Naloxone, in the SUBOXONE fo had no clinically significant effect when administered by the sublingual route, although blood lev drug were measurable. SUBOXONE, when administered sublingually even to an opioid-dependent was recognized as an opioid agonist, whereas when administered intramuscularly, combination buprenorphine with naloxone produced opioid antagonist actions similar to naloxone. In metha maintained patients and heroin-dependent subjects, intravenous administration of buprenorphin combinations precipitated opioid withdrawal and was perceived as unpleasant and dysphoric. In stabilized subjects, intravenously administered combinations of buprenorphine with naloxone p opioid antagonist and withdrawal effects that were ratio-dependent; the most intense withdrawa were produced by 2:1 and 4:1 ratios, less intense by an 8:1 ratio. SUBOXONE tablets contain bup with naloxone at a ratio of 4:1.

Pharmacokinetics:
Absorption:
Plasma levels of buprenorphine increased with the sublingual dose of SUBUTEX and SUBOXO plasma levels of naloxone increased with the sublingual dose of SUBOXONE (Table 1). There w inter-patient variability in the sublingual absorption of buprenorphine and naloxone, but within s variability was low. Both C_{max} and AUC of buprenorphine increased in a linear fashion with the i 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 SUBOX similar plasma concentrations of buprenorphine. The levels of naloxone were too low to assess proportionality. At the three naloxone doses of 1 mg, 2 mg, and 4 mg, levels above the limit of (0.05 ng/mL) were not detected beyond 2 hours in seven of eight subjects. In one individual, at dose, the last measurable concentration was at 8 hours. Within each subject (for most of the su across the doses there was a trend toward an increase in naloxone concentrations with increase 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, 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-d pathway is mediated by cytochrome P-450 3A4 isozyme. Norbuprenorphine, an active metaboli further undergo glucuronidation.

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

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

(n=6)] resulted in increases in buprenorphine mean C_{max} 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	8 mg	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

MAY NOT BE EFFECTIVE IN REVERSING ANY RESPIRATORY DEPRESSION PRODUCED BY BUPRENORPHINE.

SUBOXONE and SUBUTEX should be used with caution in patients with compromised respirator (e.g., chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, hypo 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 (alcohol) may exhibit increased CNS depression. When such combined therapy is contemplated, 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 de of the opioid type, characterized by withdrawal upon abrupt discontinuation or rapid taper. The wi 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 buprenorphine both in clinical trials and in post-marketing adverse event reports. The spectrum of abn ranges from transient asymptomatic elevations in hepatic transaminases to case reports of hepat hepatic necrosis, hepatorenal syndrome, and hepatic encephalopathy. In many cases, the presen existing liver enzyme abnormalities, infection with hepatitis B or hepatitis C virus, concomitant usag potentially hepatotoxic drugs, and ongoing injecting drug use may have played a causative or cor role. In other cases, insufficient data were available to determine the etiology of the abnormality. The exists that buprenorphine had a causative or contributory role in the development of the hepatic ab in some cases. Measurements of liver function tests prior to initiation of treatment is recommend establish a baseline. Periodic monitoring of liver function tests during treatment is also recomme biological and etiological evaluation is recommended when a hepatic event is suspected. Dependi case, the drug should be carefully discontinued to prevent withdrawal symptoms and a return to 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 in the post-marketing experience. The most common signs and symptoms include rashes, hives pruritus. Cases of bronchospasm, angioneurotic edema, and anaphylactic shock have been repo history of hypersensitivity to buprenorphine is a contraindication to Subutex or Suboxone use. A 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 performan potentially dangerous tasks such as driving a car or operating machinery, especially during drug and dose adjustment. Patients should be cautioned about operating hazardous machinery, includ automobiles, until they are reasonably certain that buprenorphine therapy does not adversely affe ability to engage in such activities. Like other opioids, SUBOXONE and SUBUTEX may produce o hypotension in ambulatory patients.

Head Injury and Increased Intracranial Pressure:
SUBOXONE and SUBUTEX, like other potent opioids, may elevate cerebrospinal fluid pressure an be used with caution in patients with head injury, intracranial lesions and other circumstances wh cerebrospinal pressure may be increased. SUBOXONE and SUBUTEX can produce miosis and cl 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 withdra symptoms if misused parenterally by individuals dependent on opioid agonists such as heroin, m or methadone. Sublingually, SUBOXONE may cause opioid withdrawal symptoms in such perso 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 with severe impairment of hepatic, pulmonary, or renal function; myxedema or hypothyroidism, cortical insufficiency (e.g., Addison's disease); CNS depression or coma; toxic psychoses; prostatic hy or urethral stricture; acute alcoholism; delirium tremens; or kyphoscoliosis.

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

Buprenorphine has been shown to increase intracholedochal pressure, as do other opioids, and th 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

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/m² 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/m² 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 [³H]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/m² 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/m² 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/m² 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/m² 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/m² basis), after *iv* doses up to 0.8 mg/kg/day (estimated exposure was approximately

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

Neonatal Withdrawal:
Neonatal withdrawal has been reported in the infants of women treated with SUBUTEX during pr
From post-marketing reports, the time to onset of neonatal withdrawal symptoms ranged from D
Day 8 of life with most occurring on Day 1. Adverse events associated with neonatal withdrawal s
included hypertonia, neonatal tremor, neonatal agitation, and myoclonus. There have been rare re
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 ra
decreased viability and lactation indices. Use of high doses of sublingual buprenorphine in pregnan
showed that buprenorphine passes into the mother's milk. Breast-feeding is therefore not advised in
treated with SUBUTEX or SUBOXONE.

Pediatric Use:
SUBOXONE and SUBUTEX are not recommended for use in pediatric patients. The safety and effe
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
of SUBOXONE was supported by clinical trials using SUBUTEX (buprenorphine tablets without n
and other trials using buprenorphine sublingual solutions. In total, safety data are available from
opioid-dependent subjects exposed to buprenorphine at doses in the range used in treatment of
addiction.

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

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

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

Body System / Adverse Event (COSTART Terminology)	N(%) SUBOXONE 16mg/day N=107	N(%) SUBUTEX 16mg/day N=103	N(%) 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%)

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 16mg/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

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

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