

Buprenorphine Hydrochloride Sublingual Tablets, 2 mg and 8 mg (Base) (CIII)

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

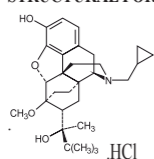
Buprenorphine hydrochloride sublingual tablets contains buprenorphine HCl.

Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-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 (17 mg/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 [5 α , 7 α (S)-]. Buprenorphine hydrochloride has the molecular formula C₂₉H₄₁NO₄Cl and the molecular weight is 504.10.

STRUCTURAL FORMULA OF BUPRENORPHINE



Buprenorphine HCl sublingual tablet is an uncoated **round white tablet** intended for sublingual administration. It is available in two dosage strengths, 2 mg buprenorphine and 8 mg buprenorphine free base. Each tablet also contains citric acid, cornstarch, lactose monohydrate, mannitol, povidone K30, sodium citrate anhydrous and sodium stearyl fumarate. The strengths are clearly marked on the tablets.

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 buprenorphine and naloxone sublingual tablets produced opioid agonist effects, which reached a maximum between doses of 8 mg and 16 mg of buprenorphine. The effects of 16 mg buprenorphine and naloxone sublingual tablets were similar to those produced by 16 mg buprenorphine HCl sublingual tablets (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 to 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 (2 mg, 4 mg, 8 mg, 12 mg and 16 mg) and sublingual (12 mg) 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, O₂ 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 O₂ saturation to the same degree.

Effect of Naloxone:

Physiologic and subjective effects following acute sublingual administration of buprenorphine and naloxone sublingual tablets and buprenorphine HCl sublingual tablets were similar at equivalent dose levels of buprenorphine. Naloxone, in the buprenorphine and naloxone sublingual tablets formulation, had no clinically significant effect when administered by the sublingual route, although blood levels of the drug were measurable.

Pharmacokinetics:

Absorption:

Plasma levels of buprenorphine increased with the sublingual dose of buprenorphine HCl sublingual tablets and buprenorphine and naloxone sublingual tablets, and plasma levels of naloxone increased with the sublingual dose of buprenorphine and naloxone sublingual tablets (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 buprenorphine HCl sublingual tablets and buprenorphine and naloxone sublingual tablets 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 4 mg 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 0.28 ng/mL in the dose range of 1 to 4 mg.

Table 1. Pharmacokinetic parameters of buprenorphine after the administration of 4 mg, 8 mg, and 16 mg buprenorphine and naloxone sublingual tablet doses and 16 mg buprenorphine HCl sublingual tablets dose (mean [%CV])

Pharmacokinetic Parameter	Buprenorphine and Naloxone sublingual tablets 4 mg	Buprenorphine and Naloxone sublingual tablets 8 mg	Buprenorphine and Naloxone sublingual tablets 16 mg	Buprenorphine HCl sublingual tablets 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.

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.

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.

Special Populations:

Hepatic Disease:

The effect of hepatic impairment on the pharmacokinetics of buprenorphine is unknown. Since this drug is extensively metabolized, the plasma levels will be expected to be higher in patients with moderate and severe hepatic impairment. 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 0.3 mg 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 buprenorphine and naloxone sublingual tablets (8 mg (n=1) or 12 mg (n=5) or 16 mg (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 buprenorphine HCl sublingual tablets 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 buprenorphine HCl sublingual tablets 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 buprenorphine HCl sublingual tablets 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.

Buprenorphine and naloxone sublingual tablets have been studied in 575 patients, buprenorphine HCl 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 16 mg buprenorphine and naloxone sublingual tablets per day, 16 mg buprenorphine HCl sublingual tablets per day or placebo tablets. For subjects randomized to either active treatment, dosing began with one 8 mg tablet of buprenorphine HCl sublingual tablet on Day 1, followed by 16 mg (two 8 mg tablets) of buprenorphine HCl sublingual tablets on Day 2. On Day 3, those randomized to receive buprenorphine and naloxone sublingual tablets 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 buprenorphine HCl sublingual tablets and buprenorphine and naloxone sublingual tablets individually against placebo. The percentage of thrice-weekly urine samples that were negative for non-study opioids was statistically higher for both buprenorphine HCl sublingual tablets and buprenorphine and naloxone sublingual tablets, 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 buprenorphine HCl sublingual tablets or buprenorphine and naloxone sublingual tablets), or two relatively low doses of active control, one of which was low enough to serve as an alternative to placebo, during a 3 to 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 to 30% per week over Weeks 18 to 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 to 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 1 mg dose. Therefore, this study showed that a range of buprenorphine doses may be effective. The 1 mg 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

Buprenorphine HCl sublingual tablets is indicated for the treatment of opioid dependence.

CONTRAINDICATIONS

Buprenorphine HCl sublingual tablets should not be administered to patients who have been shown to be hypersensitive to buprenorphine.

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 buprenorphine HCl sublingual tablets.

IN THE CASE OF OVERDOSE, THE PRIMARY MANAGEMENT SHOULD BE THE RE-ESTABLISHMENT OF ADEQUATE VENTILATION WITH MECHANICAL ASSISTANCE OF RESPIRATION, IF REQUIRED.

Buprenorphine HCl sublingual tablets 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 buprenorphine HCl sublingual tablet use.

Use in Ambulatory Patients:

Buprenorphine HCl sublingual tablets 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, buprenorphine HCl sublingual tablets may produce orthostatic hypotension in ambulatory patients.

Head Injury and Increased Intracranial Pressure:

Buprenorphine HCl sublingual tablets, 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. Buprenorphine HCl sublingual tablets can produce miosis and changes in the level of consciousness that may interfere with patient evaluation.

PRECAUTIONS

General:

Buprenorphine HCl sublingual tablets 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 is unknown. Since buprenorphine is extensively metabolized, the plasma levels will be expected to be higher in patients with moderate and severe hepatic impairment. 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 buprenorphine HCl sublingual tablets 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),

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macrolide antibiotics (e.g., erythromycin), and HIV protease inhibitors (e.g., ritonavir, indinavir and saquinavir) should have their dose of buprenorphine HCl sublingual tablets 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 buprenorphine HCl sublingual tablets. Buprenorphine HCl sublingual tablets 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 buprenorphine HCl sublingual tablets.

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 buprenorphine HCl sublingual tablets.

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 buprenorphine HCl sublingual tablets.

Buprenorphine HCl sublingual tablets 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, buprenorphine HCl sublingual tablets 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 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:

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 (5 mg/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:

Reproduction studies of buprenorphine in rats demonstrated no evidence of impaired fertility at daily oral doses up to 80 mg/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 5 mg/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:

Teratogenic Effects: Pregnancy Category C.

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 0.5 times and equal to, respectively, the recommended human daily sublingual dose of 16 mg on a mg/m² 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/m² 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/m² basis). Significant increases in skeletal abnormalities (e.g., extra thoracic vertebra or thoracolumbar 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/m² 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/m² 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/m² 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/m² basis).

There are no adequate and well-controlled studies of buprenorphine HCl sublingual tablets in pregnant women. Buprenorphine HCl sublingual tablets 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 buprenorphine HCl sublingual tablets 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 buprenorphine HCl sublingual tablets.

Pediatric Use:

Buprenorphine HCl sublingual tablets is not recommended for use in pediatric patients. The safety and effectiveness of buprenorphine HCl sublingual tablets in patients below the age of 16 have not been established.

ADVERSE REACTIONS

The safety of buprenorphine sublingual tablets has been evaluated in clinical trials using buprenorphine HCl sublingual tablets or buprenorphine sublingual solutions, and supported by other trials in 497 opioid-dependent subjects treated by buprenorphine and naloxone sublingual tablets. 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 buprenorphine and naloxone sublingual tablets and buprenorphine HCl sublingual tablets or buprenorphine administered as a sublingual solution.

In a comparative study, adverse event profiles were similar for subjects treated with 16 mg buprenorphine and naloxone sublingual tablets or 16 mg buprenorphine HCl sublingual tablets. 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

Body System / Adverse Event (COSTART Terminology)	N (%)	N (%)	N (%)
	Buprenorphine and Naloxone sublingual tablets 16 mg/day N=107	Buprenorphine HCl sublingual tablets 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%)	28 (15%)	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 (1 mg solution) would be less than a tablet dose of 2 mg.

“Low” dose (4 mg solution) approximates a 6 mg tablet dose.

“Moderate” dose (8 mg solution) approximates a 12 mg tablet dose.

“High” dose (16 mg solution) approximates a 24 mg tablet dose.

DRUG ABUSE AND DEPENDENCE

Buprenorphine HCl sublingual tablets is controlled as a Schedule III narcotic 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 buprenorphine HCl sublingual tablets during pregnancy (SEE PRECAUTIONS).

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.

High doses of naloxone hydrochloride, 10 to 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

Buprenorphine HCl sublingual tablets is administered sublingually as a single daily dose in the range of 12 to 16 mg/day. Buprenorphine HCl sublingual tablets contains no naloxone and is preferred for use during induction. Following induction, buprenorphine and naloxone sublingual tablets, due to the presence of naloxone, is preferred when clinical use includes unsupervised administration. The use of buprenorphine HCl sublingual tablets for unsupervised administration should be limited to those patients who cannot tolerate buprenorphine and naloxone sublingual tablets, for example those patients who have been shown to be hypersensitive to naloxone.

Method of Administration:

Buprenorphine HCl sublingual 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 buprenorphine HCl sublingual tablets should be undertaken when objective and clear signs of withdrawal are evident.

In a one-month study of buprenorphine and naloxone sublingual tablets induction was conducted with buprenorphine HCl sublingual tablets. Patients received 8 mg of buprenorphine HCl sublingual tablets on Day 1 and 16 mg buprenorphine HCl sublingual tablets on Day 2. From Day 3 onward, patients received buprenorphine and naloxone sublingual tablets at the same buprenorphine dose as Day 2. Induction in the studies of buprenorphine solution was accomplished over 3 to 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 buprenorphine HCl sublingual tablets 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 (> 30 mg) and when the first buprenorphine dose is administered shortly after the last methadone dose.

Maintenance:

Buprenorphine and naloxone sublingual tablets 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 buprenorphine HCl sublingual tablets is 16 mg/day. Clinical studies have shown that 16 mg of buprenorphine HCl sublingual tablets 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 buprenorphine HCl sublingual tablets should be progressively adjusted in increments / decrements of 2 mg or 4 mg to a level that holds the patient in treatment and suppresses opioid withdrawal effects. This is likely to be in the range of 4 to 24 mg per day depending on the individual.

Reducing dosage and stopping treatment:

The decision to discontinue therapy with buprenorphine HCl sublingual tablets 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

Buprenorphine HCl sublingual tablets is supplied in white HDPE bottles.

2 mg - White, round, biconvex uncoated tablets with “2” debossed on one side and a dart “→” debossed on the other side
NDC 50383-924-93 30 tablets per bottle

8 mg - White, round, biconvex uncoated tablets with “8” debossed on one side and a dart “→” debossed on the other side
NDC 50383-930-93 30 tablets per bottle

Store at 20° to 25°C (68° to 77°F), excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]

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