SUBOXONE (buprenorphine + naloxone)

2mg/0.5mg and 8mg/2mg Sublingual Tablets

NAME OF THE DRUG

SUBOXONE sublingual tablets contain buprenorphine hydrochloride and naloxone hydrochloride at a ratio of 4:1 buprenorphine : naloxone.

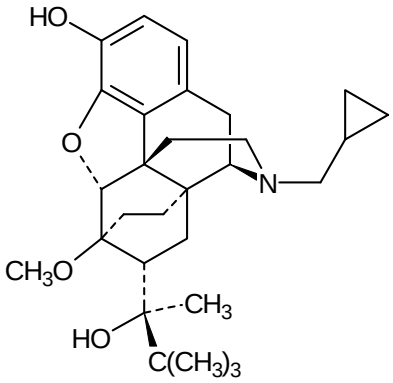
DESCRIPTION

SUBOXONE is an uncoated tablet intended for sublingual administration. It is available in two dosage strengths, 2mg buprenorphine + 0.5mg naloxone and 8mg buprenorphine + 2mg naloxone. Each tablet also contains lactose, mannitol, maize-starch, povidone, citric acid anhydrous, sodium citrate, magnesium stearate, acesulfame potassium and Lemon & Lime flavour

Buprenorphine hydrochloride is a white powder, weakly acidic with limited solubility in water (19.5 mg /mL at 37°, pH 4.1). Chemically, it is 21-Cyclopropyl-7α-[(S) -1- hydroxy-1,2,2 -trimethylpropyl]-6,14-*endo* –ethano-6,7,8,14-tetrahydrooripavine hydrochloride.. Buprenorphine hydrochloride has the molecular formula $C_{29}H_{41}NO_4$ HCl and the molecular weight is 504.09. The CAS number is 53152-21-9.

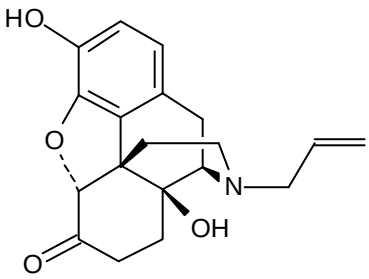
Naloxone hydrochloride is a white to slightly off-white powder that exists as the dihydrate and is soluble in water, in dilute acids and in strong alkali. Chemically, it is (-)-17-Allyl-4,5α-epoxy-3, 14-dihydroxymorphinan-6-one hydrochloride dihydrate. Naloxone hydrochloride has the molecular formula $C_{19}H_{21}NO_4$ HCl .$2H_2O$ and the molecular weight is 399.87. The CAS number of naloxone hydrochloride dihydrate is 51481-60-8.

The chemical structures of buprenorphine hydrochloride and naloxone hydrochloride dihydrate are:



.HCl

buprenorphine hydrochloride



.HCl. $2H_20$

naloxone hydrochloride dihydrate

PHARMACOLOGY

Pharmacodynamic properties

Buprenorphine is a μ (mu) opioid receptor partial agonist, κ (kappa) opioid receptor antagonist. Its activity in opioid maintenance treatment is attributed to its slow dissociation from the μ receptors in the brain which reduces craving for opioids and opiate withdrawal symptoms. This minimises the need of the addicted patient for illicit opiate drugs.

During clinical pharmacology studies in opiate-dependent subjects, buprenorphine demonstrated a ceiling effect on a number of parameters, including positive mood, “good effect”, and respiratory depression.

Naloxone is an antagonist at μ (mu) opioid receptors**.** Because of its almost complete first pass metabolism, naloxone administered orally or sublingually has no detectable pharmacological activity. However, when administered intravenously to opiate dependent persons, the presence of

naloxone in SUBOXONE produces marked opiate antagonist effects and opiate withdrawal, thereby deterring intravenous abuse.

Pharmacokinetic properties:

Absorption
When taken orally, buprenorphine undergoes first-pass metabolism with N-dealkylation and glucuroconjugation in the small intestine and the liver. The use of SUBOXONE by the oral route is therefore inappropriate. SUBOXONE tablets are for sublingual administration.

Plasma levels of buprenorphine and naloxone increased with the sublingual dose of SUBOXONE although the increases were not directly dose-proportional (Table 1). The levels of naloxone were too low to determine area under the curve values. There was a wide inter-patient variability in the sublingual absorption of buprenorphine and naloxone from SUBOXONE tablets, but within subjects the variability was low. Naloxone did not appear to affect the pharmacokinetics of buprenorphine. SUBOXONE tablets are expected to deliver similar plasma concentrations of buprenorphine as tablets containing buprenorphine alone, with sublingual dosing.

Table 1. Mean Cmax and AUC of buprenorphine and naloxone following single sublingual doses of SUBOXONE tablets.

	4 mg SUBOXONE (4 mg buprenorphine + 1 mg naloxone)	**8 mg SUBOXONE (8 mg buprenorphine + 2 mg naloxone)**	**16 mg SUBOXONE (16 mg buprenorphine + 4 mg naloxone)**	**24 mg SUBOXONE (24 mg buprenorphine + 6 mg naloxone)**
Buprenorphine				
Subjects	22	22	21	12
C_{max} ng/mL	2.16 (0.68-4.33)	3.33 (1.10-6.36)	5.87 (2.48-10.0)	6.44 (3.43-10.5)
AUC_{0-tn} h. ng/mL	12.88 (5.18-23.24)	22.14 (8.62-44.11)	37.67 (18.71-74.13)	47.55 (24.23-96.43)
Naloxone				
Subjects	20	21	20	12
C_{max} ng/mL	0.12 (0.06-0.25)	0.23 (0.09-0.42)	0.39 (0.07-1.15)	0.47 (0.08-1.02)

Naloxone did not affect the pharmacokinetics of buprenorphine and both SUBOXONE and buprenorphine deliver similar plasma concentrations of buprenorphine. Compared with intravenous administration, the mean absolute bioavailability of buprenorphine from sublingual SUBOXONE 8mg tablets was 13.6% (range 5.1-24.9%) and that of naloxone was approximately 3%.

Distribution
The absorption of buprenorphine is followed by a rapid distribution phase (distribution half-life of 2 to 5 hours). Following intravenous administration, naloxone is rapidly distributed (distribution half-life of around 4 minutes).

Buprenorphine is highly lipophilic which leads to rapid penetration of the blood-brain barrier. The drug is around 96% protein bound primarily to alpha and beta globulin. Naloxone is approximately 45% protein bound, primarily to alpha and beta globulin.

Metabolism and elimination
In animals and man buprenorphine is metabolised by Phase 1 (oxidative) and Phase 2 (conjugation) reactions. It is oxidatively metabolised by N-dealkylation to norbuprenorphine by CYP 3A4. In in vitro metabolic studies addition of specific inhibitors of CYP 3A4 (e.g. ketoconazole, gestodene, nifedipine, norfluoxetine, ritonavir) inhibited formation of norbuprenorphine. (see also PRECAUTIONS and Interactions with Other Drugs)There was no indication of the involvement of CYP 1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 and 2E1 in the N-dealkylation of buprenorphine. Buprenorphine was a weak competitive inhibitor of CYP 2D6 and CYP 3A4. Norbuprenorphine is a μ (mu) agonist with weak intrinsic activity and is considered to be an inactive metabolite.

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

Elimination of buprenorphine is bi- or tri-exponential, with a long terminal elimination phase (mean half-life of 34.6 hours, range 20.4-72.9 hours), due in part to re-absorption of buprenorphine after intestinal hydrolysis of the conjugated metabolite, and in part to the highly lipophilic nature of the molecule. Naloxone has a short elimination half-life (mean 1.1 hours, range 0.63-1.94 hours).

Buprenorphine is essentially eliminated in the faeces by biliary excretion of the glucuroconjugated metabolites (70%), the rest being eliminated in the urine. Naloxone is excreted in the urine.

***Elderly*:** No pharmacokinetic data in elderly patients are available

CLINICAL TRIALS
All trials used buprenorphine in conjunction with psychosocial counselling 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.

Efficacy and safety data for SUBOXONE are primarily derived from a one-year clinical trial, comprising a 4 week randomised double blind comparison of SUBOXONE, buprenorphine and placebo tablets followed by a 48 week safety study of SUBOXONE (Study CR96/013 + CR96/014).

In the double blind placebo- and active controlled study, 326 heroin-addicted subjects were randomly assigned to either SUBOXONE 16 mg per day, 16 mg buprenorphine per day or placebo tablets. For subjects randomised to either active treatment, dosing began with one 8 mg tablet of buprenorphine on Day 1, followed by 16 mg (two 8 mg tablets) of buprenorphine on Day 2. On Day 3, those randomised to receive SUBOXONE were switched to the combination tablet. Subjects were seen daily in the clinic (Monday through Friday) for dosing and efficacy assessments. Take-home doses were provided for weekends. The primary study comparison was to assess the efficacy of buprenorphine and SUBOXONE individually against placebo. The percentage of thrice-weekly urine samples that were negative for non-study opioids was statistically higher for both SUBOXONE versus placebo ($p < 0.0001$) and buprenorphine versus placebo ($p < 0.0001$).

INDICATIONS
Treatment of opiate dependence, within a framework of medical, social and psychological treatment. Naloxone is included in SUBOXONE to deter intravenous misuse of the product.

CONTRAINDICATIONS
Hypersensitivity to buprenorphine or naloxone or any other component of the tablet.
Children less than 16 years of age.
Severe respiratory or hepatic insufficiency. (Child-Pugh B or C)
Acute intoxication with alcohol or other CNS depressant.
Pregnant Women
Breast-feeding.

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

Buprenorphine increases intracholedochal pressure as do other opiates. Therefore, caution should be exercised when SUBOXONE is to be administered to patients with dysfunction of the biliary tract.

As with other opioids, caution is advised in patients using buprenorphine and having:
- Hypotension,
- Prostatic hypertrophy and urethral stenosis.

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

Respiratory Depression: SUBOXONE is intended for sublingual use only. Significant respiratory depression has been associated with buprenorphine, particularly by the intravenous route. A number of deaths have occurred when addicts have intravenously misused tablets containing buprenorphine as the only active, 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 CNS depressants at the same time as receiving SUBOXONE.

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. High doses of naloxone hydrochloride 10-35 mg/70 kg may be of limited value in the management of buprenorphine overdose.

SUBOXONE 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 SUBOXONE in the presence of other narcotic analgesics, general anaesthetics, benzodiazepines, phenothiazines, other tranquillisers, 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. SUBOXONE should be used cautiously with MAOIs, based on experience with morphine.

Hepatitis, Hepatic Events*:* Hepatic necrosis and hepatitis with jaundice have been reported with buprenorphine use. 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. Serious cases of acute hepatic injury have also been reported in a context of misuse, especially by the intravenous route. These hepatic injuries were dose-related, and could be due to mitochondrial toxicity. Pre-existing or acquired mitochondrial impairment (genetic diseases, viral infections particularly chronic hepatitis C, alcohol abuse, anorexia, associated mitochondrial toxins, e.g. aspirin, isoniazid, valproate, amiodarone, antiviral nucleoside analogues) could promote the occurrence of such hepatic injuries. These co-factors must be taken into account before prescribing SUBOXONE and during treatment monitoring. 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 upon the findings, the medicinal product may be discontinued cautiously so as to prevent withdrawal syndrome and to prevent a return to drug addiction. If the drug treatment is continued, hepatic function should be monitored closely.

Hepatic Disease: Because buprenorphine is metabolised by the liver, its activity may be increased and/or extended in those individuals with impaired hepatic function. Naloxone metabolism may also be impaired in hepatic failure patients. Because hepatic elimination plays a relatively large role (~70%) in the overall clearance of SUBOXONE, lower initial doses and cautious titration of dosage may be required in patients with hepatic dysfunction.

CYP3A4 Inhibitors: Because CYP3A4 inhibitors may increase concentrations of buprenorphine, patients already treated with CYP3A4 inhibitors should have their dose of SUBOXONE titrated carefully since a reduced dose may be required in these patients (see **Interactions with Other Drugs**).

Renal Disease: Renal elimination plays a relatively small role (~30%) in the overall clearance of buprenorphine. Therefore no dose modification based on renal function is required. Metabolites of buprenorphine accumulate in patients with renal failure. Caution is recommended when dosing patients with severe renal impairment (CL_{cr} <30 ml/min).

Use in Ambulatory Patients: SUBOXONE 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 accordingly. Like other opiates, SUBOXONE may produce orthostatic hypotension in ambulatory patients.

Head Injury and Increased Intracranial Pressure*:* SUBOXONE, like other potent opiates may itself 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 can produce miosis and changes in the level of consciousness that may interfere with patient evaluation.

Opiate Withdrawal Effects: Because SUBOXONE contains naloxone, it is highly likely to produce marked and intense opiate withdrawal symptoms if injected.

SUBOXONE may produce withdrawal symptoms in opiate dependent subjects if it is administered too soon after another opiate. Discontinuation of treatment may result in a withdrawal syndrome that may be delayed. Studies in animals, as well as clinical experience, have showed that buprenorphine may produce dependence but at a lower level than morphine. Consequently, it is important to follow the **DOSAGE AND ADMINISTRATION** recommendations.

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