Controlled Medicine

Desud Plus 8 mg/ 2 mg Sublingual Tablets

Composition

Each Desud Plus 8 mg/2 mg sublingual tablet contains:

Buprenorphine · HCl…… 8.624mg and Naloxone · HCl · $2H_2O$…….2.443mg

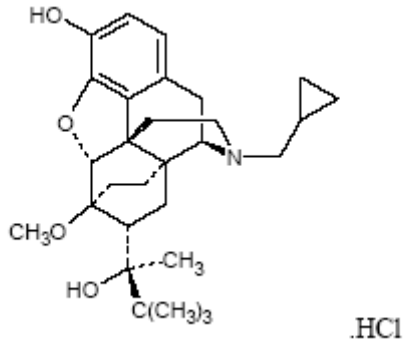
(Eq. to Buprenorphine……8.0mg and Naloxone……..2.0mg)

Product Description

Desud Plus 8 mg/2 mg sublingual tablets contain buprenorphine HCl and naloxone HCl dihydrate with a 4:1 buprenorphine to naloxone ratio (free bases).

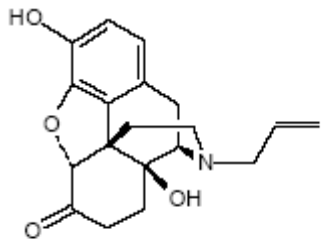
The tablets are orange, hexagon, biconvex tablets, debossed with “LP” on one side and “24” on the other side for identification purpose.

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 $C_{19}H_{21}NO_4HCl.2H_2O$ and the molecular weight is 399.87

Structural Formula of Naloxone HCl



.HCl .$2H_2O$

Desud Plus 8 mg/2 mg sublingual tablets are uncoated hexagonal orange tablets intended for sublingual administration at a dose of 8mg buprenorphine free base plus 2mg naloxone free base.

Clinical Pharmacology

Main Effects:

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

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

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 or 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 administration. The onset of effects appeared more rapidly with buprenorphine than with the full agonist control, with most doses nearing the peak effect after 100 minutes for buprenorphine compared to 150 minutes for the full agonist control.

Physiological Effects:

ACTIONS Buprenorphine is an opioid partial agonist/antagonist, which attaches itself to the μ - (mu) and k (kappa) receptors of the brain. Its activity in opioid maintenance treatment is attributed to its slowly reversible link with the receptors which, over a prolonged period,

minimizes the need of the addicted patient for drugs. Opiate agonist ceiling effects were observed during clinical pharmacology studies in opiate-dependent persons. Naloxone is an antagonist at μ (mu)- opiate 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 produces marked opiate antagonist effects and opiate withdrawal, thereby deterring intravenous abuse.

Effect of Naloxone:

Physiological and subjective effects following acute sublingual administration of buprenorphine ＋naloxone tablets and buprenorphine tablets were similar at equivalent dose levels of buprenorphine.

Naloxone, in the buprenorphine＋naloxone formulation, had no clinically significant effect when administered by the sublingual route, although blood levels of the drug were measurable. Buprenorphine＋naloxone, when administered sublingually even to an opioid-dependent population, was recognized as an opioid agonist, whereas when administered intramuscularly, combination 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, intravenous 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. Desud Plus 8 mg/2 mg sublingual tablets contain buprenorphine and naloxone at a ratio of 4:1

Pharmacokinetics:

Buprenorphine:

Absorption:

When taken orally, Buprenorphine undergoes first-pass hepatic metabolism with N dealkylation and glucuroconjugation in the small intestine and the liver. The use of this medication by the oral route is therefore inappropriate.

Peak plasma concentrations are achieved 90 minutes after sublingual administration and the maximal dose concentration relationship is linear, between 4 mg and 16 mg.

Distribution:

The absorption of buprenorphine is followed by a rapid distribution phase and a half-life of 2 to 5 hours.

Metabolism and elimination:

Buprenorphine is metabolized by 14-N-dealkylation and glucuroconjugation of the parent molecule and the dealkylated metabolite. Clinical data confirm that CYP3A4 is responsible for the N-dealkylation of buprenorphine. N dealkybuprenorphine is a μ (mu) agonist with weak intrinsic activity.

Elimination of buprenorphine is bi- or tri-exponential, with a long terminal elimination phase of 34.4 hours, due in part to reabsorption of buprenorphine after intestinal hydrolysis of the conjugated derivative, and in part to the highly lipophilic nature of the molecule.
Buprenorphine is essentially eliminated in the feces by biliary excretion of the glucuroconjugated metabolites (70%), the rest being eliminated in the urine.

Naloxone:
Absorption and Distribution:
Following oral administration, naloxone is barely detectable in plasma; following sublingual administration, plasma naloxone concentrations are low and decline rapidly.

Metabolism and elimination:
The drug is metabolized in the liver, primarily by glucuronide conjugation, and excreted in the urine. Naloxone has a mean elimination half-life from plasma of 1.3 hours.

SPECIAL POPULATIONS:
Elderly: no pharmacokinetic data in elderly patients are available.
Renal impairment: No dose modification based on renal function is required but caution is recommended when dosing subjects with severe renal impairment.
Hepatic impairment: hepatic elimination plays a relatively large role (~70%) in the overall clearance and the action of buprenorphine may be prolonged in subjects with impaired hepatic clearance. Lower initial doses and cautious titration of dosage may be required in patients with mild to moderate hepatic dysfunction. Contraindicated in patients with severe hepatic dysfunction.

Drug-drug interactions:

DRUG INTERACTIONS:
This product should not be taken together with alcoholic drinks or medications containing alcohol. Alcohol increases the sedative effect of buprenorphine, which can make driving vehicles and operating machinery hazardous. This product should be used cautiously together with:
Benzodiazepines: This combination may potentiate respiratory depression of central origin, with risk of death; therefore, this combination must be avoided in case of risk of misuse.
Other central nervous system depressants; other opioid derivatives (analgesics and antitussives); certain antidepressants, sedative H1-receptor antagonists, barbiturates, benzodiazepines, anxiolytics other than benzodiazepines, neuroleptics, clonidine and related substances. This combination increases central nervous system depression and can make driving vehicles and operating machinery hazardous. Monoamine oxidase inhibitors (MAOI): Possible exaggeration of the effects of opioids, based on experience with morphine.
CYP3A4 Inhibitors: An interaction study of buprenorphine with ketoconazole (a potent inhibitor of CYP3A4) resulted in increased Cmax and AUC of Buprenorphine (approximately 70% and 50% respectively) and, to a lesser extent, of norbuprenorphine. Patients receiving this product should be closely monitored, and may require dosereduction if combined with potent CYP3A4 inhibitors (e.g. protease inhibitors like ritonavir, nelfinavir or indinavir or azole antifungals such

as ketoconazole or itraconazole).
CYP3A4 Inducers: The interaction of buprenorphine with CYP3A4 inducers has not been investigated, therefore it is recommended that patients receiving Desud Plus 8 mg/2 mg Sublingual Tablets should be closely monitored if enzyme inducers (e.g. phenobarbital, carbamazepine, phenytoin, rifampicin) are co-administered.
To date, no notable interaction has been observed with cocaine, the agent most frequently used by multi-drug abusers in association with opioids.

Indications

Substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment. Naloxone is included to deter intravenous misuse of this product.

Contraindications

Hypersensitivity to buprenorphine, naloxone, or to any component of the product; severe respiratory insufficiency; severe hepatic insufficiency; acute alcoholism or delirium tremens, pregnancy, and breastfeeding.

Warnings and Precautions

Due to the lack of data in adolescents (age 15≤18), Desud Plus 8 mg/2 mg Sublingual Tablets should be used only with caution in this age group.

Patients should be closely monitored during the switching period from buprenorphine or methadone to Desud Plus 8 mg/2 mg Sublingual Tablets since withdrawal symptoms have been reported.

Diversion:
Diversion refers to the introduction of buprenorphine into the illicit market either by patients or by individuals who obtain the medicinal product through theft from patients or pharmacies. This diversion may lead to new addicts using buprenorphine as the primary drug of abuse, with the risks of overdose, spread of blood borne viral infections, respiratory depression and hepatic injury. Because the naloxone in the combination tablet precipitated withdrawal in individuals dependent on heroin, methadone, or other full agonists, Desud Plus 8 mg/2 mg Sublingual Tablets is expected to be less likely to be diverted for intravenous use.

Precipitated withdrawal:
When initiating treatment with buprenorphine, the physician must be aware of the partial agonist profile of buprenorphine and that it can precipitate withdrawal in opioid-dependent patients particularly if administered less than 6 hours after the last use of heroin or other short acting opioid, or if administered less than 24 hours after the last dose of methadone. Conversely, withdrawal symptoms may also be associated with suboptimal dosing.

The risk of serious undesirable effects such as overdose or treatment dropout is greater if a

patient is under dosed with Desud Plus 8 mg/2 mg Sublingual Tablets and continues to self medicate withdrawal symptoms with opioids, alcohol or other sedative-hypnotics in particular benzodiazepines.

Dependence:
Buprenorphine is a partial agonist at the mu-opiate receptor and chronic administration produces dependence of the opioid type.

Discontinuation of treatment may result in a withdrawal syndrome that may be delayed.

Desud Plus 8 mg/2 mg Sublingual Tablets may cause drowsiness, particularly when taken together with alcohol or central nervous system depressants (such as tranquilisers, sedatives or hypnotics).

Studies in animals, as well as clinical experience, have demonstrated that buprenorphine may produce dependence but at a lower level than morphine.

Respiratory depression:
A number of cases of death due to respiratory depression have been reported, particularly when buprenorphine was used in combination with benzodiazepines, or when buprenorphine was not used according to prescribing information.

Deaths have been reported in association with concomitant administration of buprenorphine and other depressants such as alcohol or other opioids.

Hepatitis and hepatic events:
Cases of acute hepatic injury have been reported in opioid-dependent addicts 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, hepato-renal syndrome and hepatic encephalopathy. In many cases the presence of pre-existing liver enzyme abnormalities, infection with hepatitis B or hepatitis C virus, concomitant use of other potentially hepatotoxic medicines, and ongoing injecting drug use may have a causative or contributory role. These underlying factors must be taken into consideration before prescribing Desud Plus 8 mg/2 mg Sublingual Tablets and during treatment. When a hepatic event is suspected, further biological and etiological evaluation is required. Depending upon the findings, the medicinal product may be discontinued cautiously so as to prevent withdrawal symptoms and to prevent a return to illicit drug use. If the treatment is continued, hepatic function should be monitored closely.

As buprenorphine is an opioid, pain as a symptom of a disease may be attenuated.

Athletes must be aware that this medicine may cause a positive reaction to 'anti-doping' tests.

As with other opioids, caution is requested in patients using buprenorphine and having head injury, increased intracranial pressure, hypotension, prostatic hypertrophy or urethral stenosis.

This product should be used with care in patients with: asthma or respiratory insufficiency (cases of respiratory depression have been reported with buprenorphine); renal insufficiency (30 % of the administered dose is eliminated by the renal route; thus, renal elimination may be prolonged); hepatic insufficiency (hepatic metabolism of buprenorphine may be altered).

Medicines that inhibit the enzyme CYP3A4 may give rise to increased concentrations of buprenorphine. A reduction of the Desud Plus 8 mg/2 mg Sublingual Tablets dose may be needed. Patients already treated with CYP3A4 inhibitors should have their dose of Desud Plus 8 mg/2 mg Sublingual Tablets titrated carefully since a reduced dose may be sufficient in these patients.

The concomitant use of monoamine oxidase inhibitors (MAOI) might produce exaggeration of the effects of opioids, based on experience with morphine.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Drug Abuse and Dependence

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 sublingual tablets during pregnancy (See Precautions).

Desud Plus 8 mg/2 mg sublingual tablets contain naloxone and if misused parenterally, is highly likely to produce marked and intense withdrawal symptoms in subjects dependent on other opioid agonists.

Side-Effects

Buprenorphine used alone for treatment of opioid dependency has been associated with the following symptoms: constipation, headache, insomnia, asthenia, drowsiness, nausea and vomiting, fainting and dizziness, orthostatic hypotension, and sweating. Other undesirable effects have been reported in association with buprenorphine alone. These are:

- respiratory depression,
- hepatic necrosis and hepatitis,
- hallucinations,
- cases of bronchospasm, angioneurotic oedema and anaphylactic shock.

In cases of intravenous misuse, local reactions, sometimes septic, and potentially serious acute hepatitis have been reported.

In patients presenting with marked drug dependence, initial administration of buprenorphine can produce a withdrawal effect similar to that associated with naloxone.

Spontaneous abortion has been reported with both buprenorphine and buprenorphine-naloxone. It is not possible to establish a causal relationship since cases typically involve other drug use or risk factors for spontaneous abortion.

A neonatal abstinence syndrome has been reported among newborns of women who have received buprenorphine during pregnancy. The syndrome may be milder and more protracted than that from short acting full μ-opioid agonists. The nature of the syndrome may vary depending upon the mother's drug use history.

Symptoms And Treatment of Overdose

In the event of overdose, general supportive measures should be instituted, including close monitoring of respiratory and cardiac status of the patient. The major symptom requiring intervention is respiratory depression, which could lead to respiratory arrest and death. If the patient vomits, care must be taken to prevent aspiration of the vomitus.

Treatment: Symptomatic treatment of respiratory depression, and standard intensive care measures, should be implemented. A patent airway and assisted or controlled ventilation must be assured. The patient should be transferred to an environment within which full resuscitation facilities are available.

Use of an opioid antagonist (i.e., naloxone) is recommended, despite the modest effect it may have in reversing the respiratory symptoms of buprenorphine compared with its effects on full agonist opioid agents.

The long duration of action of Desud Plus 8 mg/2 mg Sublingual Tablets should be taken into consideration when determining the length of treatment and medical surveillance needed to reverse the effects of an overdose.

Dosage and Administration

The recommended starting dose is one to two tablets of Buprenorphine Plus Naloxone 2 mg/0.5 mg sublingual tablets. An additional one to two tablets of the Buprenorphine Plus Naloxone 2 mg/0.5 mg may be administered on day one depending on the individual patient's requirement.

Opioid-dependent drug addicts who have not undergone withdrawal: When treatment starts, the first dose of Buprenorphine Plus Naloxone Sublingual Tablets should be taken when signs of withdrawal appear, but not less than 6 hours after the patient last used opioids (eg. heroin; short acting opioids).

Patients receiving methadone: Before beginning Buprenorphine Plus Naloxone Sublingual Tablets therapy, the dose of methadone must be reduced to a maximum of 30 mg/day. The first

dose of Buprenorphine Plus Naloxone Sublingual Tablets should be taken when signs of withdrawal appear, but not less than 24 hours after the patient last used methadone. Buprenorphine may precipitate symptoms of withdrawal in patients dependent upon methadone.

Dosage adjustment and maintenance: The dose of Buprenorphine Plus Naloxone Sublingual Tablets should be increased progressively according to the clinical effect of the individual patient and should not exceed a maximum single daily dose of 24 mg. The dosage is titrated according to reassessment of the clinical and psychological status of the patient and should be made in steps of 2-8 mg.

During the initiation of treatment, daily dispensing of buprenorphine is recommended. After stabilisation, a reliable patient may be given a supply of Buprenorphine Plus Naloxone Sublingual Tablets sufficient for several days of treatment. It is recommended that the amount of Buprenorphine Plus Naloxone Sublingual Tablets be limited to 7 days or according to local requirements.

Less than daily dosing: After a satisfactory stabilisation has been achieved the frequency of Buprenorphine Plus Naloxone Sublingual Tablets dosing may be decreased to dosing every other day at twice the individually titrated daily dose. For example, a patient stabilised to receive a daily dose of 8 mg may be given 16 mg on alternate days, with no dose on the intervening days. However, the dose given on any one day should not exceed 24 mg. In some patients, after a satisfactory stabilisation has been achieved, the frequency of Buprenorphine Plus Naloxone Sublingual Tablets dosing may be decreased to 3 times a week (for example on Monday, Wednesday and Friday). The dose on Monday and Wednesday should be twice the individually titrated daily dose, and the dose on Friday should be three times the individually titrated daily dose, with no dose on the intervening days. However, the dose given on any one day should not exceed 24 mg. Patients requiring a titrated daily dose> 8 mg/day may not find this regimen adequate.

Dosage reduction and termination of treatment: After a satisfactory stabilisation has been achieved, if the patient agrees, the dosage may be reduced gradually to a lower maintenance dose; in some favourable cases, treatment may be discontinued. The availability of the sublingual tablet in doses of 2 mg and 8 mg allows for a downward titration of dosage. For patients who may require a lower buprenorphine dose, buprenorphine 0.4 mg sublingual tablets may be used. Patients should be monitored following termination of treatment because of the potential for relapse.

Elderly:
No data is available on elderly patients.

Paediatrics:
Desud Plus 8 mg/2 mg Sublingual Tablets is not recommended for use in children below age 15 years due to lack of data on safety and efficacy.

Patients with impaired hepatic function:
The effect of hepatic impairment on the pharmacokinetics of buprenorphine and naloxone is unknown. Since both active substances are extensively metabolized, the plasma levels will be expected to be higher in patients with moderate and severe hepatic impairment. It is not known whether both active substances are affected to the same extent.

As Desud Plus 8 mg/2 mg Sublingual Tablets pharmacokinetics may be altered in patients with hepatic insufficiency, lower initial doses and careful dose titration in patients with mild to moderate hepatic impairment are recommended.

Patients with impaired renal function:
Modification of the Desud Plus 8 mg/2 mg Sublingual Tablets dose is not required in patients with renal insufficiency. Caution is recommended when dosing patients with severe renal impairment (CLcr < 30 ml/min)

Route of Administration:

Desud Plus 8 mg/2 mg sublingual tablets should be placed under the tongue until they are dissolved. For doses requiring more than two tablets, patients are advised to either place all the tablets at once or alternatively (if patients feel uncomfortable when more than two tablets are placed at once) 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 opioids), the time since last opioid use, and the degree or level of opioid dependence. To avoid precipitating withdrawal, induction with Buprenorphine 8 mg sublingual tablets should be undertaken when objective and clear signs of withdrawal are evident. It is recommended that an adequate maintenance dose, titrated to clinical effectiveness, should be achieved as rapidly as possible to prevent undue opioid-like withdrawal symptoms.

In a one-month study of buprenorphine/naloxone sublingual tablets, induction was conducted with buprenorphine sublingual tablets. Patients received 8mg buprenorphine sublingual tablets on Day 1 and 16mg buprenorphine/naloxone sublingual tablets on Day 2. From Day 3 onward, patients received buprenorphine/naloxone sublingual tablets (at the same buprenorphine dose as that in 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 drop-out rate among patients on buprenorphine.

Patients on heroine or other short-acting opioids:

At treatment initiation, the dose of Buprenorphine 8 mg 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 experiences with the transfer of methadone-maintained patients to buprenorphine. Withdrawal symptoms are possible during induction to buprenorphine. Withdrawal symptoms appear 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:

Desud Plus 8 mg/2 mg sublingual tablets are the preferred medication for maintenance treatment due to the presence of naloxone in the formulation.

Titration to the maintenance dose:

The recommended target dose of Desud Plus 8 mg/2 mg sublingual tablets is 4-16 mg/day, administered once a day or separately in a week. Clinical studies have shown that 16mg of buprenorphine sublingual tablets (with or without naloxone at a 4:1 ratio) 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 Desud Plus 8 mg/2 mg sublingual tablets 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. The dosage varies with each patient.

Reduction of dosage and discontinuation of treatment:

The decision to discontinue therapy with Desud Plus 8 mg/2 mg sublingual tablets after a period of maintenance or brief stabilization should be made as part of a comprehensive treatment plan. Both gradual and abrupt discontinuations have been used, but no controlled trials have been undertaken to determine the best method of dose taper at the end of treatment.

Because the product does not have doses lower than 8mg, the administration, use dosage, and suggestions mentioned above may require combined use of products with a lower unit content from other manufacturers.

Regimens:

A regimen for alternative therapies consists of three to six months. At the end of each regimen, reassessments must be performed. During the treatment period, psychological treatment or counseling and related health education on acquired immunodeficiency syndrome should be arranged periodically for patients. The counseling progress and cooperation from patients shall be the reference for next regimen assessments. This drug should be taken under supervision of healthcare professionals.

Package:

28-tablets aluminum foil box.

Storage condition:
Store below 30°C, away from direct sunlight and children.

Duration
Please be aware of and comply with the expiry date indicated on the package.

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