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# FOR YOUR INPHARMATION



## PHARMACY NEWSLETTER



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### **Buprenorphine-(Subutex®)-A New Opioid Dependence Treatment**

#### **Introduction**

Buprenorphine Hydrochloride (BUP) is a synthetic partial mu ( $\mu$ ) opiate agonist as well as a weak kappa ( $\kappa$ ) opiate antagonist. (1, 2) BUP is now approved by Health Canada to treat adult opiate addiction. With anticipated market launch in 2006, BUP represents the latest therapeutic alternative for opiate dependence treatment since methadone.

#### **Indication**

BUP is indicated for substitution treatment in adult patients with opioid drug dependence. At this time, this federally scheduled narcotic is not approved for pain management. BUP should only be prescribed when the daily intake can be supervised by a healthcare professional. As well the prescribing physician should have experience with substitution treatment of opioid drug dependence and have completed the Subutex® National Education Program. (3)

#### **Pharmacology**

BUP has both agonist ( $\mu$  receptors) and weak antagonist ( $\kappa$  receptors) effects. The agonist effects increase linearly with increasing dose of BUP to a plateau or ceiling effect at about 24-32 mg. (1, 4) At higher doses, BUP can precipitate withdrawal symptoms due to its antagonist effects. BUP exhibits a slow rate of

dissociation from its receptor *in vitro* which results in its long duration of action. (5) BUP also shows a corresponding insensitivity to displacement by naloxone. (5)

#### **Clinical Studies**

The Australian Treatment Outcome Study for heroin dependence involved more than 700 heroin dependent patients and 80 heroin users not seeking treatment. The results of the study showed substantial reduction in heroin and other drug use across three modalities: methadone or BUP maintenance therapy (65%), detoxification (52%), residential rehabilitation (63%) compared to the non-treatment sample (25%) as well a substantial reduction in risk taking, crime, and injection related health problems. (6)

Another study suggests BUP, in contrast to methadone, improves decision-making and therefore may be more effective in rehabilitation programs of opiate-dependent subjects. (7) As well, patients using BUP had less cognitive impairment as detected by psychomotor testing battery. This difference is especially pertinent in driving ability and social functioning. (8)

A Cochrane Review found BUP effective in treating patients withdrawing from opioids. This review was based on 14 studies (11 randomized controlled trials) including 784 subjects. Seven studies compared BUP with clonidine, three compared BUP with methadone, and one with oxazepam. Three compared different rates of BUP dose reduction, and one compared three different

starting doses of BUP. BUP was shown to be more effective than clonidine for management of opioid withdrawal. There was no significant difference between BUP and methadone in regard to the completion of treatment, but the withdrawal symptoms resolved more quickly with BUP. (9) One study that reviewed 13 trials, found BUP reduced heroin use effectively; however, it was not more effective than methadone. (10)

Some suggested advantages of BUP compared with methadone (11) include a decreased risk of problems associated with accidental overdose (12, 13), less abuse in opioid dependent individuals (13, 14, 15), less than daily maintenance dosing (16, 17, 18, 19) and a greater ease of withdrawal (18, 20, 21)

### **Pharmacokinetics**

BUP undergoes first pass hepatic metabolism with N-dealkylation and glucuroconjugation in the small intestine, therefore, it should not be used orally. It is given sublingually to avoid first pass effects. (5, 22) The peak serum concentration of BUP is reached 90 minutes after sublingual administration. The drug is metabolized in the liver primarily by CYP3A4, suggesting the potential for drug interactions, to an inactive metabolite, norbuprenorphine (a mu agonist with weak intrinsic activity) and other metabolites. (1, 5)  $C_{max}$  and AUC increase in a linear fashion with dose increases. (1) BUP is highly bound to plasma protein (96%), primarily to  $\alpha$  and  $\beta$  globulin and does not appear to bind substantially to albumin. (2, 5) BUP is excreted mostly in feces by biliary excretion of the glucuroconjugated metabolites (about 70%) and the rest eliminated in urine. (5) The mean elimination half-life is 37 hours. (4)

### **Contraindications**

Known hypersensitivity to BUP and to any constituents of the product is a contraindication for its use. BUP should not be administered to patients who have severe respiratory insufficiency, hepatic

insufficiency, acute alcoholism or delirium tremens as well as women who are breast-feeding. (5)

### **Precautions (not inclusive)**

BUP should be prescribed cautiously to polydrug using patients, especially sedatives such as alcohol, benzodiazepines and antidepressants. Deaths have been reported when BUP is used with benzodiazepines and other sedatives. (3, 23). Higher doses of BUP can precipitate withdrawal in opioid-dependent individuals due to its antagonist effect. Chronic administration of BUP (as a partial agonist) can elicit opiate-type dependence, characterized by withdrawal upon discontinuation or rapid tapering. (1, 3) Even though BUP is shown to be less of a target for diversion than methadone. (3) BUP can be abused and diversion of the drug has been reported. BUP with fixed doses of naloxone have been used to address this concern.

Use BUP with caution in compromised respiratory function, severe liver disorder, recent head injury, increased intracranial pressure, hypotension, acute abdominal conditions, severe renal disease, adrenal cortical insufficiency, CNS depression or coma, toxic psychosis, kyphoscoliosis, acute alcoholism, delirium tremens, prostatic hypertrophy, urethral stricture, diabetes mellitus, elderly/debilitated patients, compromised mental and physical ability (activities that require alertness). (1, 5, 23)

BUP may not be effective for patients that require higher dose of methadone (60 mg or more). (3) The manufacturer of BUP does not recommend that patients on methadone doses greater than 30mg/day and stabilized on methadone treatment be converted until adequate clinical trials have determined an optimal regimen. (5)

The safety and efficacy of BUP has not been established in adults over 65 years of age and in children under 18 years of age, therefore BUP is not recommended in these patients. (5)

### **Use in Pregnancy (5, 23)**

The safety of BUP in human pregnancy is not established. In rat and rabbit studies, fetotoxicity including post implantation loss and decreased post-natal survival were observed. Withdrawal syndrome in neonates has been observed with chronic use of BUP during the last 3 months of pregnancy. Respiratory depression in neonates has been observed with high doses of BUP, even for short durations in the third trimester. Therefore, the use of BUP is not recommended during the second and third trimester of pregnancy.

BUP passes into the mother's milk, therefore, breastfeeding is not recommended. (1, 5)

### **Adverse Effects (1, 5, 22, 24)**

Adverse effects occur most commonly in the first 2 to 3 days of therapy. The most common adverse effects include headache (30%), insomnia (21-25%), anxiety (12%), nausea (10-14%), abdominal pain (12%), constipation (8-11%), sweating (13%), drowsiness, increase in liver enzymes, cases of cytolytic hepatitis, hepatitis with jaundice, hepatic necrosis and failure have been reported. Clinicians should monitor liver function tests periodically.

### **Drug Interactions (not inclusive)**

Some of the clinically significant drug interactions include interactions with the potent CYP 3A4 inhibitors such as azole antimycotics (e.g. ketoconazole), calcium channel blockers, macrolide antibiotics (e.g. erythromycin) and HIV protease inhibitors (e.g. ritonavir, indinavir, saquinavir) which can cause increase levels of BUP. Conversely, CYP3A4 inducers such as carbamazepine, phenytoin, rifampin and phenobarbital can decrease the levels of BUP. Deaths have been reported when IV or high doses of BUP have been used in combination with benzodiazepines. CNS depression and deaths have been reported in combination with CNS depressants (e.g. alcohol). (1, 2, 5) Increased risk of CNS and

respiratory depression has been observed with high doses of BUP with narcotics (e.g. morphine, meperidine, and fentanyl) (1)

### **Dosage (1, 4, 5, 25)**

BUP is administered sublingually. Chewing or swallowing the sublingual tablets will decrease its bioavailability. (4) Patients should be instructed to use BUP under the tongue and allow the tablet(s) to dissolve which may take 2 to 10 minutes. 4 mg doses will dissolve in two minutes while 32 mg doses may take five to 10 minutes. (3) BUP should not be started until at least 4 hours after the last use of short acting opioid or at least 24 hours after a long acting one such as methadone, preferably after the patient experiences early withdrawal symptoms. (4, 5)

#### *Induction Phase*

The titration needs to achieve adequate maintenance dose as rapidly as possible to prevent drop out from the treatment (2). The titration dosing for induction starts with 2 or 4 mg on day 1 and can be repeated every 2 to 4 hours if withdrawal symptoms subside and then reappear. The maximum dose on day 1 is 8 mg. The dose can then be titrated up 2 to 4 mg increments to 12 to 16 mg on day 2. Higher doses during induction can cause opioid withdrawal symptoms. (4) Continue with the day 2 dose from day 3 onward. Most patients can be stabilized on 8 to 32 mg per day. Due to its long half-life, alternate day and three times a week regimen have been used effectively. (1, 4)

#### *Stabilization Phase*

When the patient has discontinued or greatly reduced using the drug of abuse, and presented with no more cravings and few side effects, the dose of BUP can be titrated down in increments/decrements of 2 to 4 mg that can suppress both cravings and withdrawal symptoms. The usual dose range is 4 to 24 mg per day depending on individual patients. (1)

### *Maintenance Phase*

In this phase, the patient has achieved a stable dose of BUP. (1) Clinical studies have shown that the usual effective dose is in the range of 8 to 16 mg/day. There is limited safety information for doses greater than 20 mg/day, thus the maximum recommended dose is 16 mg/day. Some patients in clinical trials have been maintained on lower or higher doses (maximum 32 mg/day). (5) The patient may require indefinite maintenance therapy or the drug may be gradually withdrawn. (1)

### **Dosage Supplied**

Subutex<sup>®</sup> (buprenorphine hydrochloride) is available in 0.4mg, 2mg, and 8mg sublingual tablets. The non-medicinal ingredients include citric acid, lactose monohydrate, magnesium stearate, corn starch, mannitol, povidone K30 and sodium citrate. The tablet comes in blister packages of 7 or 28 tablets. The manufacturer is Schering Canada Inc. (5)

### **Cost**

The cost is not known, because BUP is not yet available in Canada.

### **Regulatory**

BUP is federally scheduled as a narcotic. In B.C., it falls under the controlled prescription program, formally the Triplicate Prescription Program. The College of Physicians and Surgeons of B.C. has restricted the prescribing of BUP to physicians who have an exemption to prescribe methadone. (3)

Training in Subutex<sup>®</sup> National Education Program administered by CSAM (The Canadian Society of Addiction Medicine) is required. Health Care

Professionals may request more information on the Subutex<sup>®</sup> National Education Program with the following toll-free phone number: 800-463-5442. (5)

### **Summary**

BUP appears to be as effective as moderate doses of methadone for both detoxification and maintenance treatment of opioid dependence. (4, 6) BUP (partial agonist) is associated with a safer profile in high doses than a full opioid agonist (3, 23) and with a lower risk of diversion (3), but may not be effective for patients on high methadone doses. (3) Methadone is the treatment of choice in patients with high levels of opioid dependence. (1). Adequate training (Subutex<sup>®</sup> National Education Program and substitution Treatment) of Health Care professionals is required, in conjunction with behavioral and psychosocial therapies (careful monitoring within a framework of medical, social and psychological support), to ensure the success of the treatment. (1, 4, 23)

The manufacturer of Subutex<sup>®</sup> does not recommend that patients on methadone doses greater than 30mg/day and stabilized on methadone treatment be converted until adequate clinical trials have determined an optimal regimen. Present available evidence suggests that withdrawal symptoms are more prominent in this population. (5)

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