RATIONALE FOR INCLUSION IN PA PROGRAM

Background

Suboxone, Zubsolv, Bunavail, Probuphine and buprenorphine sublingual tablets are Schedule III narcotics with a single indication, the maintenance treatment of opioid dependence. Buprenorphine is a partial pain receptor agonist at mu-opioid receptors unlike typical opioids of dependence, which are full agonists. Naloxone is an opioid receptor antagonist. Treatment using buprenorphine with or without naloxone should occur only under the care of a physician who meets qualifying requirements per Health and Human Services (HHS). The use of buprenorphine with or without naloxone should also be part of a comprehensive plan which includes counseling and psychosocial support. They should not be used for analgesia or in opioid naïve patients (1-5).

Regulatory Status

FDA-approved indication: Buprenorphine and buprenorphine with naloxone is indicated for maintenance treatment of opioid dependence. Prescription use of this product is limited under the Drug Addiction Treatment Act (1-5).

The recommended target dose of buprenorphine is 16 mg per day. Doses may range from 16 mg to 24 mg per day (3). The difference in bioavailability between Bunavail and Zubsovl compared to Suboxone sublingual tablet requires a different dosage strength to be administered to the patient. A Bunavail 4.2/0.7 mg buccal film or a Zubsolv 5.4/1.4 mg sublingual tablet provides equivalent buprenorphine exposure to a Suboxone 8/2 mg sublingual tablet. The recommended target dosage of Bunavail buccal film is 8.4/1.4 mg per day as a single daily dose. The maintenance dose of Bunavail buccal film is generally in the range of 2.1/0.3 mg buprenorphine/naloxone to 12.6/2.1 mg buprenorphine/naloxone per day depending on the individual patient. The maintenance dose of Zubsolv sublingual tablet is generally in the range of 2.8 mg/0.72 mg buprenorphine/naloxone to 17.2 mg/4.2 mg buprenorphine/naloxone per day depending on the individual patient. Dosages higher than this have not been demonstrated to provide any clinical advantage (1-4).

Probuphine is indicated for the maintenance treatment of opioid dependence in patients who have achieved and sustained prolonged clinical stability on low-to-moderate doses of a transmucosal buprenorphine containing product (i.e., doses of no more than 8 mg per day of Subutex or Suboxone sublingual tablet or generic equivalent). Probuphine is not appropriate for new entrants to treatment and patients who have not achieved and sustained prolonged clinical stability, while being
Suboxone / Zubsolv / Bunavail / Buprenorphine / Probuphine
(buprenorphine with naloxone / buprenorphine SL)

maintained on buprenorphine 8 mg per day or less of a Subutex or Suboxone sublingual tablet or
generic equivalent. Probuphine implants should be used only in patients who are opioid tolerant (5).

Probuphine carries a boxed warning of the risks associated with insertion and removal, Probuphine
is available only through a restricted program called the Probuphine REMS Program. All Healthcare
Providers must successfully complete a live training program on the insertion and removal
procedures and become certified, prior to performing insertions or prescribing Probuphine implants
(5).

Buprenorphine has boxed warnings for the following (1-4):

- Respiratory depression is the chief hazard of opioid agonists, including morphine sulfate,
which if not immediately recognized and treated, may lead to respiratory arrest and death.
Risk is increased in patients receiving concurrent CNS depressants (including alcohol),
patients with chronic obstructive pulmonary disease, orthostatic hypotension, increased
intracranial pressure, biliary tract diseases, seizure disorders. To reduce the risk of
respiratory depression, proper dosing, titration, and monitoring are essential.

- All patients treated with opioids require careful monitoring for signs of abuse and addiction,
since use of opioid analgesic products carries the risk of addiction even under appropriate
medical use.

- Prolonged use of opioid agonists during pregnancy can result in neonatal opioid withdrawal
syndrome, which may be life-threatening.

- Patients should not consume alcohol or any products containing alcohol while taking.

Probuphine dosing consists of four implants inserted subdermally in the inner side of the upper arm.
The implants are intended to be in place for 6 months of treatment. New implants may be inserted in
the other arm that has not been previously used at the time of removal, if continued treatment is
desired. If new implants are not inserted on the same day as the removal of implants, maintain
patients on their previous dosage of transmucosal buprenorphine (i.e., the dose from which they
were transferred to Probuphine treatment) prior to additional Probuphine treatment. After one
insertion of Probuphine in each arm, most patients should be transitioned back to a transmucosal

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buprenorphine-containing product for continued treatment. There is no experience with inserting additional implants into other sites in the arm to recommend an approach to a second insertion into a previously-used arm. Neither re-insertion into previously-used administration sites, nor into sites other than the upper arm, has been studied (5).

Suboxone, Zubsolv and Bunavail have the potential for misuse, abuse, and diversion. Patient use should be monitored as part of counseling and psychosocial support during treatment and precautions taken against potential abuse. As with other opioids, physical dependence, respiratory depression, and overdose may also occur; hence monitoring and frequent patient evaluation should be used as part of an overall treatment plan (1,2).

Safety and effectiveness in patients under the age 18 has not been established (1,2).

Summary
Suboxone, Zubsolv, Bunavail, Probuphine and buprenorphine sublingual tablets are Schedule III narcotics with a single indication, the maintenance treatment of opioid dependence. Prescription use of this product is limited under the Drug Addiction Treatment Act (DATA) to limited to physicians who meet certain qualifying requirements, have notified the Secretary of Health and Human Services (HHS), and have a unique identification number on each prescription. They have the potential for misuse, abuse, and diversion. Patient use should be monitored as part of counseling and psychosocial support during treatment and precautions taken against potential abuse. As with other opioids, physical dependence, respiratory depression, and overdose may also occur; hence monitoring and frequent patient evaluation should be used as part of an overall treatment plan. Safety and effectiveness in pediatric patients under the age of 18 has not been established (1-5).

Prior approval is required to ensure the safe, clinically appropriate and cost effective use of Suboxone, Zubsolv, Bunavail, Probuphine and buprenorphine sublingual tablets while maintaining optimal therapeutic outcomes.

References