PROBUPHINE® (buprenorphine) implants

BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use Probuphine safely and effectively. See package insert for Full Prescribing Information

INDICATIONS AND USAGE

PROBUPHINE contains buprenorphine, a partial opioid agonist. 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 trans mucosal buprenorphine-containing product (i.e., doses of no more than 8 mg per day of Subutex or Suboxone sublingual tablet or generic equivalent).

PROBUPHINE should be used as part of a complete treatment program to include counseling and psychosocial support.

PROBUPHINE is not appropriate for new entrants to treatment and patients who have not achieved and sustained prolonged clinical stability.

WARNING: IMPLANT MIGRATION, PROTRUSION, EXPULSION, and NERVE DAMAGE ASSOCIATED WITH INSERTION and REMOVAL

Risk Associated with Insertion and Removal.

Insertion and removal of PROBUPHINE are associated with the risk of implant migration, protrusion, and expulsion resulting from the procedure. Rare but serious complications including nerve damage and migration resulting in embolism and death may result from improper insertion of drug implants inserted in the upper arm. Additional complications may include local migration, protrusion and expulsion. Incomplete insertions or infections may lead to protrusion or expulsion.

Because 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. Patients must be monitored to ensure that PROBUPHINE is removed by a healthcare provider certified to perform insertions.

CONTRAINDICATIONS

Hypersensitivity to buprenorphine or any other ingredients in PROBUPHINE (e.g., ethylene vinyl acetate - EVA).

WARNINGS AND PRECAUTIONS

Serious Complications from Insertion and Removal of PROBUPHINE

Rare but serious complications including nerve damage and migration resulting in embolism and death may result from improper insertion of drug implants inserted in the upper arm. Additional complications may include local migration, protrusion, and expulsion.

PROBUPHINE REMS Program

PROBUPHINE is available only through a restricted program under a REMS, called the PROBUPHINE REMS Program, because of the risk of complications of migration, protrusion and expulsion, and nerve damage associated with the insertion and removal of PROBUPHINE. Further information is available at www.PROBUPHINEREMS.com or 1-844-859-6341.

Addiction, Abuse, and Misuse
PROBUPHINE contains buprenorphine, a Schedule III controlled substance that can be abused in a manner similar to other opioids. Buprenorphine is sought by people with opioid use disorders and is subject to criminal diversion.

Respiratory Depression
Life-threatening respiratory depression and death have occurred in association with buprenorphine use. Warn patients of the potential danger of self-administration of benzodiazepines or other CNS depressants while under treatment with PROBUPHINE.

Neonatal Opioid Withdrawal Syndrome
Neonatal opioid withdrawal syndrome (NOWS) is an expected and treatable outcome of prolonged use of opioids during pregnancy.

Adrenal Insufficiency
If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid.

Unintentional Pediatric Exposure
Buprenorphine can cause severe, possibly fatal, respiratory depression in children who are accidentally exposed to it. Instruct patients to keep the expelled implant(s) away from others, especially children.

Risk of Opioid Withdrawal with Abrupt Discontinuation of PROBUPHINE Treatment
Patients who elect to discontinue PROBUPHINE treatment should be monitored for withdrawal with consideration given to use of a tapering dose of transmucosal buprenorphine.

Risk of Hepatitis, Hepatic Events
Monitor liver function tests prior to initiation and during treatment and evaluate suspected hepatic events.

Hypersensitivity Reactions
Allergic reactions to buprenorphine and/or EVA are possible. Cases of hypersensitivity to sublingual buprenorphine have been reported both in clinical trials and in the post-marketing experience. A history of hypersensitivity to buprenorphine or EVA is a contraindication to PROBUPHINE use.

Precipitation of Opioid Withdrawal in Patients Dependent on Full Agonist Opioids
Because of the partial opioid agonist properties of buprenorphine, buprenorphine may precipitate opioid withdrawal signs and symptoms in persons who are currently physically dependent on full opioid agonists such as heroin, morphine, or methadone before the effects of the full opioid agonist have subsided. Verify that patients are clinically stable on transmucosal buprenorphine and not dependent on full agonists before inserting PROBUPHINE.

Risks Associated with Treatment of Emergent Acute Pain
While on PROBUPHINE, situations may arise where patients need acute pain management, or may require anesthesia. Treat patients receiving PROBUPHINE with a non-opioid analgesic whenever possible. If opioid therapy is required, monitor patients closely because higher doses may be required for analgesic effect.

Use in Patients with Impaired Hepatic Function
Patients with pre-existing moderate to severe hepatic impairment are not candidates for treatment with PROBUPHINE.

Impairment of Ability to Drive and Operate Machinery
PROBUPHINE may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery.

Orthostatic Hypotension
PROBUPHINE may produce orthostatic hypotension in ambulatory patients.

Elevation of Cerebrospinal Fluid Pressure
Buprenorphine 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.

Elevation of Intracholedochal Pressure
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.

Effects in Acute Abdominal Conditions
Buprenorphine may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

Infection at Implant Site
Infection may occur at the site of the insertion or removal.

ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Serious Complications from Insertion and Removal of PROBUPHINE
- Addiction, Abuse, and Misuse
- Respiratory and CNS Depression
- Neonatal Opioid Withdrawal Syndrome
- Adrenal Insufficiency
- Opioid Withdrawal
- Hepatitis, Hepatic Events
- Hypersensitivity Reactions
- Orthostatic Hypotension
- Elevation of Cerebrospinal Fluid Pressure
- Elevation of Intracholedochal Pressure
- Infection

USE IN SPECIFIC POPULATIONS

Pregnancy

- The data on use of buprenorphine, the active ingredient in PROBUPHINE implant, in pregnancy, are limited; however, these data do not indicate an increased risk of major malformations specifically due to buprenorphine exposure.
- Dose adjustments of buprenorphine may be required during pregnancy, even if the patient was maintained on a stable dose prior to pregnancy.
- Opioid-dependent women on buprenorphine maintenance therapy may require additional analgesia during labor.

Lactation
Buprenorphine passes into the mother’s milk.

Females and Males of Reproductive Potential
Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible.

Pediatric Use
The safety and effectiveness of PROBUPHINE have not been established in children or adolescents younger than 16 years of age.

Geriatric Use
Due to possible decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy in geriatric patients, the decision to prescribe PROBUPHINE should be made cautiously in individuals 65 years of age or older and these patients should be monitored for signs and symptoms of toxicity or overdose.

Hepatic Impairment
Patients with pre-existing moderate to severe hepatic impairment are not candidates for treatment with PROBUPHINE. Monitor patients who develop moderate or severe hepatic impairment while being treated with PROBUPHINE for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine.

Renal Impairment
Clinical studies of PROBUPHINE did not include subjects with renal impairment.

DRUG ABUSE AND DEPENDENCE

Controlled Substance
PROBUPHINE contains buprenorphine, a Schedule III controlled substance under the Controlled Substances Act. Under the Drug Addiction Treatment Act (DATA) codified at 21 United States Code (U.S.C.) 823(g), use of this product in the treatment of opioid dependence is limited to healthcare providers who meet certain qualifying requirements, and who have notified the Secretary of Health and Human Services (HHS) of their intent to prescribe or dispense this product for the treatment of opioid dependence and have been assigned a unique identification number that must be included on every prescription.

Abuse
Buprenorphine, like morphine and other opioids, has the potential for being abused and is subject to criminal diversion. Abuse of buprenorphine poses a risk of overdose and death. This risk is increased with the concomitant abuse of buprenorphine and alcohol and other substances, especially benzodiazepines.

Dependence
Buprenorphine is a partial agonist at the mu-opioid receptor and chronic administration produces physical dependence of the opioid type, characterized by moderate withdrawal signs and symptoms upon abrupt discontinuation or rapid taper. The withdrawal syndrome is typically milder than seen with full agonists and may be delayed in onset.

DRUG INTERACTIONS

Benzodiazepines: Use caution in prescribing PROBUPHINE for patients receiving benzodiazepines or other CNS depressants and warn patients against concomitant self-administration/misuse.

CYP3A4 Inhibitors and Inducers: Monitor patients starting or ending CYP3A4 inhibitors or inducers for potential over- or under-dosing.

Antiretrovirals: Patients who are on chronic buprenorphine treatment should have their dose monitored if NNRTIs are added to their treatment regimen. Monitor patients taking buprenorphine and atazanavir with and without ritonavir. Dose reduction of buprenorphine may be warranted.

Serotonergic Drugs: Concomitant use may result in serotonin syndrome. Discontinue PROBUPHINE if serotonin syndrome is suspected.

Monoamine Oxidase Inhibitors (MAOIs): The use of PROBUPHINE is not recommended for patients taking MAOI or within 14 days of stopping such treatment. MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma).

Muscle Relaxants: PROBUPHINE may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

Diuretics: Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Anticholinergic Drugs: The concomitant use of anticholinergic drugs may increase the risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.

OVERDOSAGE

The manifestations of acute buprenorphine overdose include pinpoint pupils, sedation, hypotension, respiratory depression, and death.
In case of overdose, priorities are the re-establishment of a patent and protected airway and institution of assisted ventilation, if needed. The opioid antagonist naloxone is a specific antidote to respiratory depression resulting from opioid overdose. Naloxone may be of value for the management of buprenorphine overdose.