Indication & Important Safety Information

INDICATIONS AND USAGE

PROBUPHINE ® (buprenorphine) 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 equivalent 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, while being maintained on buprenorphine 8 mg per day or less of a Subutex or Suboxone sublingual tablet or generic equivalent.

IMPORTANT SAFETY INFORMATION

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

<u>Risk Associated with Insertion and Removal</u>
Insertion and removal of PROBUPHINE are associated with the risk of implant migration, protrusion, 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.

PROBUPHINE is contraindicated in patients with a history of hypersensitivity to buprenorphine or any other ingredients in PROBUPHINE (e.g., EVA).

SUMMARY OF WARNINGS AND PRECAUTIONS

- Serious Complications from Insertion and Removal: 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. All Healthcare Providers must successfully complete a live training program on the insertion and removal procedures and become certified in the PROBUPHINE REMS program prior to performing insertions or prescribing PROBUPHINE implants.
- Addiction, Abuse, and Misuse: Buprenorphine can be abused in a manner similar to other opioids. Monitor patients for conditions indicative of diversion or progression of opioid dependence and addictive behaviors.

- Respiratory and CNS Depression: Life-threatening respiratory depression and death have occurred in association with buprenorphine use.
- Concomitant Use of Benzodiazepines or other CNS Depressants: concomitant use increases the risk of adverse reactions including overdose and death. Ensure that other healthcare providers prescribing benzodiazepines or other CNS depressants are aware of the patient's buprenorphine treatment and coordinate care to minimize this risk.
- 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: In the event an implant protrudes or comes out, keep the implant away from children. Buprenorphine can cause severe, possibly fatal, respiratory depression in children.
- Risk of Opioid Withdrawal with Abrupt Discontinuation: If treatment with PROBUPHINE is temporarily interrupted or discontinued, monitor patients for withdrawal and treat appropriately.
- Risk of Hepatitis, Hepatic Events: Monitor liver function tests prior to initiation and during treatment and evaluate suspected hepatic events.
- Risk of Withdrawal in Patients Dependent on Full Agonist Opioids: Verify that patient is clinically stable on transmucosal buprenorphine and not dependent on full agonists before inserting PROBUPHINE.
- Treatment of Emergent Acute Pain: Treat pain with a non-opioid analgesic whenever possible. If opioid therapy is required, monitor patients closely because higher doses may be required for analgesic effect.
- Impairment of Ability to Drive and Operate Machinery: PROBUPHINE may impair the abilities required for potentially dangerous tasks such as driving a car or operating machinery, especially for the first 24-48 hours following initial insertion.

Adverse events commonly associated with PROBUPHINE administration (>10% of subjects) were implant-site pain, pruritus, and erythema, as well as non-implant-site related events (≥5%) of headache, depression, constipation, nausea, vomiting, back pain, toothache, and oropharyngeal pain.

To report SUSPECTED ADVERSE REACTIONS, contact Braeburn at 1-844- 859-6341 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

Please see FULL PRESCRIBING INFORMATION, including BOXED WARNING and MEDICATION GUIDE.