Indication & Important Safety Information

INDICATIONS AND USAGE

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 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

Risk Associated with Insertion and Removal

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

- **Respiratory and CNS Depression**: Significant respiratory depression and death have occurred in association with buprenorphine particularly when taken by the intravenous (IV) route in combination with benzodiazepines or other CNS depressants (including alcohol). Consider dose reduction of CNS depressants when used concomitantly.
- **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 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.
- **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 mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery.
- **Other systemic effects**: PROBUPHINE may cause orthostatic hypotension in ambulatory patients.
- **Effects in Acute Abdominal Conditions***:* As with other opioids, buprenorphine may obscure the diagnosis or clinical course of patients with acute abdomincal conditions.
- **Infection at Implant Site**: Infection may occur at the site of the insertion or removal. Excessive palpation may increase an opportunity for infection. Improper removal carries risk of implant-site infection.
- **General Precautions**: PROBUPHINE should also be administered with caution in patients with a history of keloid formation, connective tissue disease, e.g., scleroderma or history of recurrent MRSA infections.

Adverse events commonly associated with PROBUPHINE administration (>10% of subjects) were implant-site pain, pruritis, 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

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