

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

NPROBUPHINE®

Buprenorphine hydrochloride implant

Subdermal implant, 80 mg

Partial Opioid Agonist

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATION

PROBUPHINE® (buprenorphine hydrochloride subdermal implant) is indicated in the management of opioid dependence in patients clinically stabilized on no more than 8 mg of sublingual buprenorphine in combination with counseling and psychosocial support.

PROBUPHINE (buprenorphine hydrochloride subdermal implant) must be inserted and removed only by Healthcare Professionals who have successfully completed a live training program, the PROBUPHINE Education Program (see **DOSAGE AND ADMINISTRATION**).

1.1 Paediatrics

Paediatrics (<18 years of age): No data is available for paediatrics. PROBUPHINE is not indicated in paediatrics.

1.2 Geriatrics

Geriatrics (>65 years of age): No data is available for geriatrics. PROBUPHINE is not indicated in geriatrics. In general, drug use for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, respiratory or cardiac function, concomitant disease or other drug therapy.

2 CONTRAINDICATIONS

PROBUPHINE (buprenorphine hydrochloride subdermal implant) is contraindicated in:

- patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see **DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**
- patients who have severe respiratory insufficiency, acute respiratory depression, elevated carbon dioxide levels in the blood and cor pulmonale
- patients with severe hepatic insufficiency
- patients with severe CNS depression, increased cerebrospinal or intracranial pressure and head injury
- patients with acute alcoholism or delirium tremens
- opioid naïve patients
- patients with convulsive or seizure disorders
- patients with known or suspected mechanical gastrointestinal obstruction (e.g., bowel obstruction or strictures) or any diseases/conditions that affect bowel transit (e.g., ileus of any type).
- congenital Long QT Syndrome or QTc prolongation at baseline
- uncorrected hypokalemia, hypomagnesemia, or hypocalcemia

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Insertion and removal of PROBUPHINE (buprenorphine hydrochloride subdermal implant) are associated with the risk of implant migration, protrusion, expulsion, and nerve damage resulting from the procedure (see WARNINGS AND PRECAUTIONS).
- 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 (see WARNINGS AND PRECAUTIONS).
- Prolonged maternal use of opioids during pregnancy can result in neonatal opioid withdrawal syndrome (NOWS), which may be life-threatening (see WARNINGS AND PRECAUTIONS, Pregnant Women, Labor or Delivery, Breast-feeding).
- Prolonged maternal use of opioids during pregnancy can result in neonatal respiratory depression (see WARNINGS AND PRECAUTIONS, Pregnant Women, Labor or Delivery, Breast-feeding).
- QTc prolongation (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, DRUG INTERACTIONS, ACTION AND CLINICAL PHARMACOLOGY).

4 DOSAGE AND ADMINISTRATION

4.1 Healthcare Professional Information

All Healthcare Professionals performing insertions and/or removals of PROBUPHINE must successfully complete a live training program, and demonstrate procedural competency prior to inserting or removing the implants.

As a prerequisite for participating in the live training program leading to certification, the Healthcare Professionals must have performed at least one qualifying surgical procedure in the last 3 months.

Qualifying procedures are those performed under local anesthesia using aseptic technique, and include, at a minimum, making skin incisions, or placing sutures. PROBUPHINE is available only through a controlled distribution process.

Information concerning the insertion and removal procedures can be obtained by calling 1-844-483-5636.

4.2 Dosing Considerations

- PROBUPHINE (buprenorphine hydrochloride subdermal implant) must be inserted and removed only by Healthcare Professionals who have successfully completed a live training program, the PROBUPHINE Education Program.
- The use of PROBUPHINE in pregnant women or in women of childbearing potential requires that the benefits of its use be weighed against the risk to the foetus. The risks associated with using PROBUPHINE should be discussed with the patient. The use of a formulation allowing for dosage adjustment may be considered during pregnancy (see **WARNINGS AND PRECAUTIONS, Pregnant Women**).
- Physicians may obtain more information about the PROBUPHINE Education Program by calling the following toll-free phone number: 1-844-483-5636.
- PROBUPHINE implants should be used only in patients who are opioid dependent and clinically stabilised on no more than 8 mg of sublingual buprenorphine per day. Patients prescribed PROBUPHINE should be carefully monitored within a framework of medical, social and psychological support as part of a comprehensive opioid dependence treatment program.
- One dose of PROBUPHINE involves that four PROBUPHINE implants are inserted subdermally in the inner side of the upper arm for up to 6 months of treatment and are removed by the end of the sixth month.

4.3 Recommended Dose and Dosage Adjustment

Each PROBUPHINE is a sterile, single, off-white, soft, flexible, rod-shaped ethylene vinyl acetate (EVA) implant, 26 mm in length and 2.5 mm in diameter, containing 74.2 mg of buprenorphine (equivalent to 80 mg of buprenorphine hydrochloride).

Each dose consists of four PROBUPHINE implants inserted subdermally in the inner side of the upper arm.

PROBUPHINE subdermal implants are intended to be in place for 6 months of treatment. Remove PROBUPHINE implants at the end of the sixth month period.

If continued treatment is desired at the end of the six-month treatment with PROBUPHINE, the implants should be replaced by new implants (implanted in the opposite arm) at the time of removal. If new implants are not inserted on the same day as the removal, patients should be switched back to their previous dose of transmucosal buprenorphine (i.e., the dose from which they were transferred to PROBUPHINE treatment) prior to additional PROBUPHINE treatment.

After one insertion in each arm, most patients should be transitioned back to their previous sublingual buprenorphine dose (i.e., the dose from which they were transferred to PROBUPHINE treatment) for continued treatment. At this time, there is no experience with inserting additional implants into other sites of the arm, sites other than the upper arm or re-insertion into previously-used sites. Should a decision be taken to continue treatments beyond two 6-month periods, follow the instructions under section 4.4.3.

Although some patients may require occasional supplemental dosing with buprenorphine, patients should not be provided with prescriptions for transmucosal buprenorphine-containing products for as-needed (PRN) use. Instead, patients who feel the need for supplemental dosing should be seen and evaluated promptly. Ongoing use of supplemental dosing with transmucosal buprenorphine indicates that the amount of buprenorphine delivered by PROBUPHINE is not adequate for stable maintenance. Consider use of alternate buprenorphine products for maintenance of treatment.

Hepatic Impairment

PROBUPHINE is contraindicated in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment. The effect of hepatic impairment on the pharmacokinetics of implanted buprenorphine, such as PROBUPHINE, has not been studied but, since buprenorphine is extensively metabolized, the plasma levels can be expected to be higher in patients with moderate and severe hepatic impairment.

Renal Impairment

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

4.4 Administration

4.4.1 Insertion of PROBUPHINE

Preparation

Prior to inserting PROBUPHINE, carefully read the full insertion instructions as well as the full prescribing information. Confirm that:

- The patient does not have any contraindications for the use of PROBUPHINE (see **CONTRAINDICATIONS**).
- The patient has had a medical history and physical examination.
- The patient understands the benefits and risks of PROBUPHINE.
- The patient has received a copy of the Patient Medication Information Leaflet included in the packaging.
- The patient does not have allergies to the antiseptic and anesthetic to be used during insertion.

Insert PROBUPHINE under aseptic conditions.

The following equipment is recommended for implant insertion:

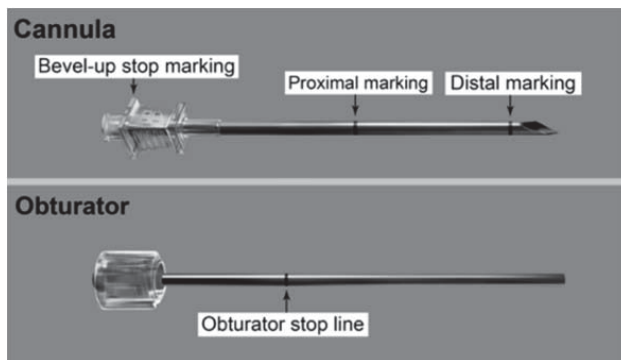
- An examination table for the patient to lie on
- Instrument stand, sterile tray
- Adequate lighting (e.g., headlamp)
- Sterile fenestrated drape
- Latex and talc-free sterile gloves
- Disinfectant pads

- Surgical marker
- Antiseptic solution (e.g., chlorhexidine)
- Local anesthetic (e.g., 1% lidocaine with epinephrine 1:100,000)
- 5 mL syringe with 1.5-inch 25G needle
- Adson single tooth tissue forceps
- #15 blade scalpel
- ¼ inch thin adhesive strip (butterfly strip) (e.g., Steri-strip skin closures)
- 4x4 sterile gauze
- Adhesive bandages
- 3-inch pressure bandages
- Liquid adhesive (e.g., Mastisol)
- 1 fan-shaped stencil (optional)
- 4 PROBUPHINE implants
- 1 PROBUPHINE disposable applicator (Figure 1)

The applicator and its parts are shown in Figure 1.

Correctly performed subdermal insertion of the implants will facilitate their removal. Implants should be placed just under the skin to avoid the large blood vessels that lie in the subcutaneous deep tissue. If the implants are placed improperly, resulting in deep tissue placement, the implants will be more difficult to remove.

Figure 1



Insertion Procedure

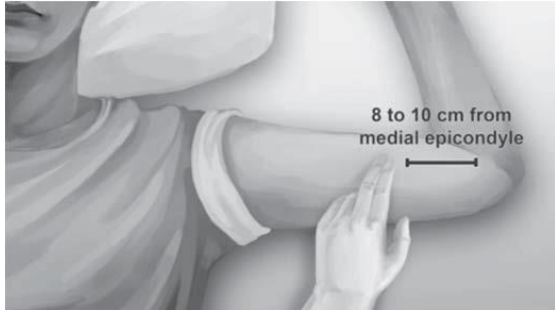
Step 1. Have the patient lie on his/her back, with the intended arm flexed at the elbow and externally rotated, so that the hand is positioned next to the head (Figure 2).

Figure 2



Step 2. Identify the insertion site, which is at the inner side of the upper arm about 8-10 cm (3-4 inches) above the medial epicondyle of the humerus in the sulcus between the biceps and triceps muscle. Having the patient flex the biceps muscle may facilitate identification of the site (Figure 3).

Figure 3



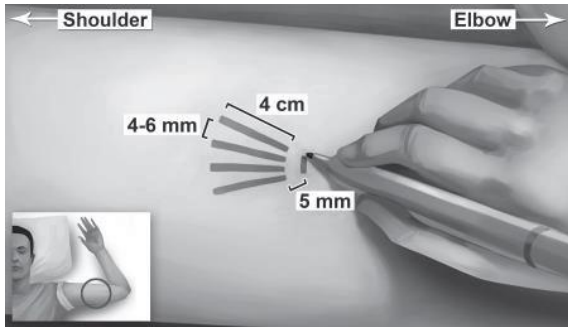
Step 3. Clean the insertion site with a disinfectant pad prior to marking the skin.

Note: Steps 4 and 5 can be performed using the fan-shaped stencil that was provided separately with the drug product package.

Step 4. Mark the insertion site with the surgical marker. The implants will be inserted through a small 2.5 mm-3 mm subdermal incision.

Step 5. Using the surgical marker, mark the channel tracks where each implant will be inserted by drawing 4 lines with each line 4 cm in length. The implants will be positioned in a close fan-shaped distribution 4-6 mm apart with the fan opening towards the shoulder (Figure 4). The closer the implants lie to each other at time of insertion, the more easily they can be removed. There should be at least 5 mm between the incision and the implant when the implant is properly positioned.

Figure 4



Step 6. Put on sterile gloves.

Step 7. Using aseptic technique, place the sterile equipment, PROBUPHINE implants and the applicator on the sterile field of the instrument stand. One applicator is used to insert all 4 implants.

Step 8. Check applicator function by removing the obturator from the cannula and relocking it.

Step 9. Clean the insertion site with an antiseptic solution (e.g., chlorhexidine) using gentle repeated back-and-forth strokes for 30 seconds. If using triple swab stick applicators, use each swab stick sequentially within the 30 seconds. Allow the area to air dry for approximately 30 seconds and do not blot or wipe skin.

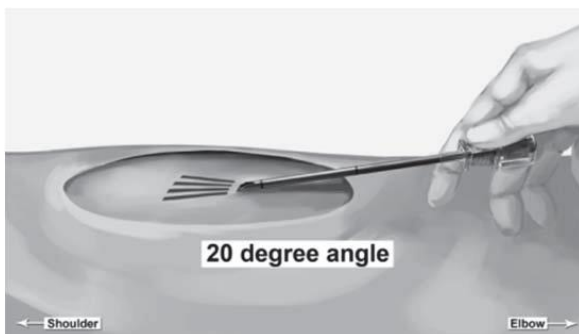
Step 10. Apply the sterile drape to the arm of the patient.

Step 11. Anesthetize the insertion area at the incision site and just under the skin along the planned insertion channels using local anesthetic (for example, by injecting 5 mL lidocaine 1% with epinephrine 1:100,000).

Step 12. After determining that anesthesia is adequate and effective, make a shallow incision that is 2.5-3 mm in length.

Step 13. Lift the edge of the incision opening with toothed forceps. While applying counter-traction to the skin, insert only the tip of the applicator at a slight angle (no greater than 20 degrees), into the subdermal space (depth of 3-4 mm below the skin), with the bevel-up stop marking on the cannula facing upwards and visible with the obturator locked fully into the cannula (Figure 5).

Figure 5



Step 14. Lower the applicator to a horizontal position, lift the skin up with the tip of the applicator but keep the cannula in the subdermal connective tissue (Figure 6). While tenting (lifting), gently advance the applicator subdermally along the channel marking on the skin until the proximal marking on the cannula just disappears into the incision (Figure 7).

Figure 6

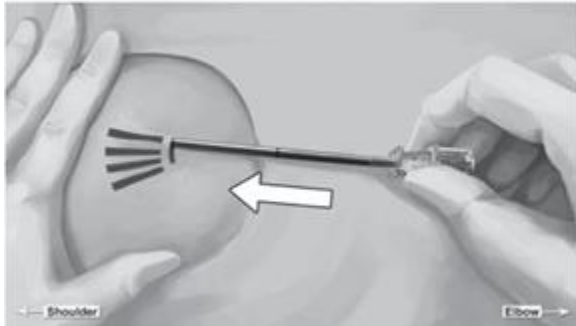
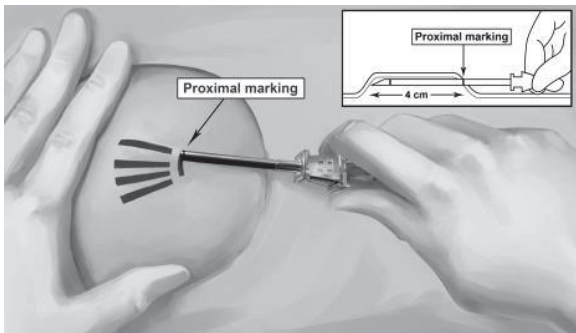


Figure 7



Step 15. While holding the cannula in place, unlock the obturator and remove the obturator.

Step 16. Insert one implant into the cannula (Figure 8), re-insert the obturator, and gently push the obturator forward (mild resistance should be felt) until the obturator stop line is level with the bevel-up stop marking, which indicates the implant is positioned at the tip of the cannula (Figure 9). Do not force the implant beyond the end of the cannula with the obturator. There should be at least 5 mm between the incision and the implant when the implant is properly positioned.

Figure 8

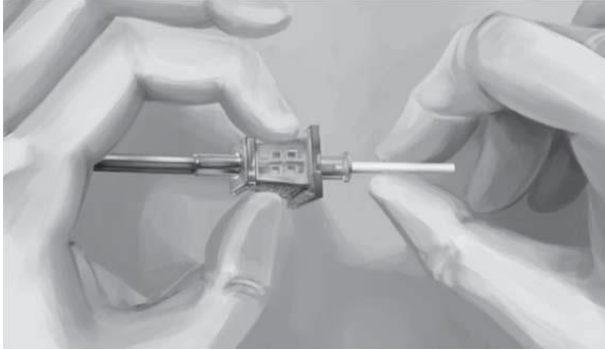
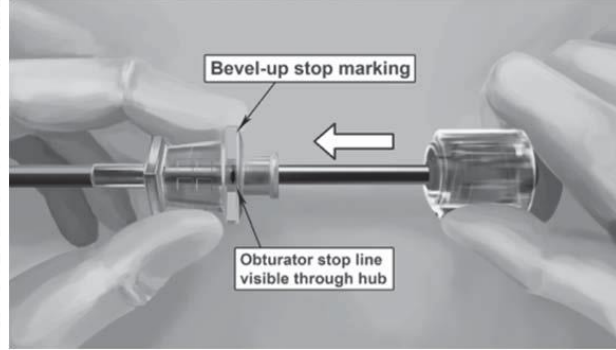
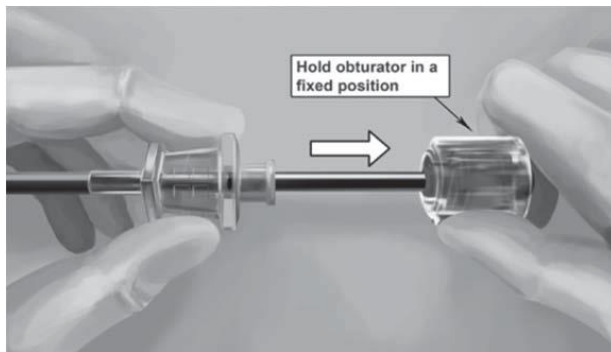


Figure 9



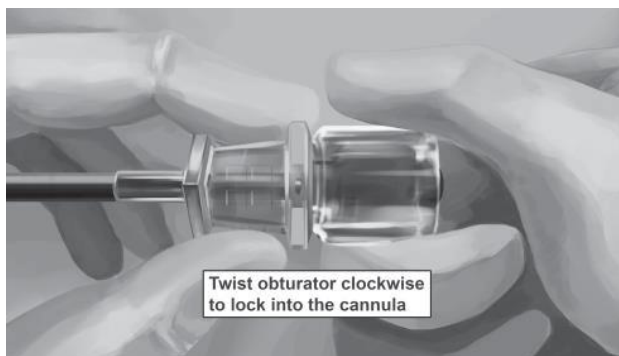
Step 17. While holding the obturator fixed in place on the arm, retract the cannula along the obturator, leaving the implant in place (Figure 10). Note: do not push the obturator. By holding the obturator fixed in place on the arm and by retracting the cannula, the implant will be left in its correct subdermal position.

Figure 10



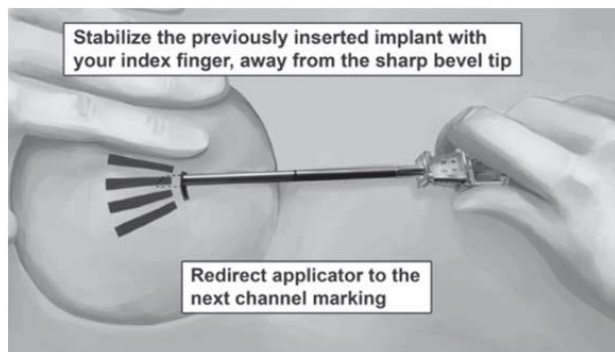
Step 18. Withdraw the cannula until the hub is flush with the obturator, and then twist the obturator clockwise to lock onto the cannula (Figure 11). Retract the applicator, bevel up, until the distal marking of the cannula is visualized at the incision opening (the sharp tip remaining in the subcutaneous space).

Figure 11



Step 19. Redirect the applicator to the next channel marking while stabilizing the previously inserted implant, with your index finger, away from the sharp tip (Figure 12). Follow steps 13 through 18 for the insertion of the three remaining implants through the same incision, placing implants in a close fan-shaped distribution 4-6 mm apart at the top of the implant. The applicator can now be removed.

Figure 12



Step 20. Always verify the presence of each implant by palpation of the patient's arm immediately after the insertion. By palpating both ends of the implant, you should be able to confirm the presence of the 26-mm implant (Figure 13). If you cannot feel each of the 4 implants, or are in doubt of their presence, use other methods to confirm the presence of the implant. Suitable methods to locate are: Ultrasound with a high frequency linear array transducer (10 MHz or greater) or Magnetic Resonance Imaging (MRI). Please note that the PROBUPHINE implants are not radiopaque and cannot be seen by X-ray or CT scan.

If it is determined that any of the implants was inserted below the fascia, i.e. in the biceps muscle, then removal should be performed by a qualified physician as soon as possible. A replacement implant should be inserted in a new location.

Figure 13



Step 21. Apply pressure to the incision site for approximately 5 minutes if necessary.

Step 22. Clean the incision site. Apply liquid adhesive to the skin margins and allow to dry before closing the incision with the ¼ inch thin adhesive strip (butterfly strip).

Step 23. Place a small adhesive bandage over the insertion site.

Step 24. Apply a pressure bandage with sterile gauze to minimize bruising. The pressure bandage can be removed in 24 hours and the adhesive bandage can be removed in 3 to 5 days.

Step 25. Complete the Patient Identification (ID) Card and give it to the patient to keep. Also, complete the Patient Chart Label and affix it to the patient medical record or scan and input into electronic medical record. Provide the patient with the Patient Medication Information Leaflet and explain proper care of the insertion site.

Step 26. The applicator is for single use only. Dispose of the applicator in accordance with guidelines for biohazardous waste.

Step 27. Instruct the patient to apply an ice pack on his/her arm for 40 minutes every 2 hours for the first 24 hours and as needed.

Step 28. Complete the PROBUPHINE Insertion / Removal Log.

IF SPONTANEOUS EXPULSION OF THE IMPLANT OCCURS AFTER INSERTION, THE FOLLOWING STEPS SHOULD BE TAKEN:

- Schedule an appointment for the patient to return to the office of the inserting healthcare professional as soon as possible and to the office of the prescribing healthcare professional, if different.
- Instruct the patient to place the implant in a plastic bag, store it safely out of reach of children, and to bring it to the healthcare professional's office to determine whether the full implant has been expelled.
- If the patient returns the expelled implant, measure it to ensure that the entire implant was expelled (26 mm).
- Dispose of the removed implant in keeping with the recommendations governing the disposal of pharmaceutical biohazardous waste.
- Examine incision site for infection. If infected, treat appropriately and determine if the remaining implants need to be removed.
- If the expelled implant is not intact, palpate the insertion location to identify the location of any remaining partial implant.
- Remove the remaining partial implant using the removal techniques described below.
- Call 1-844-483-5636 to obtain a new kit that will include 4 implants and return instructions for any unused implants.
- The prescribing healthcare professional must carefully monitor patient until the implant is replaced to evaluate for withdrawal or other clinical indicators that supplemental transmucosal buprenorphine may be needed.
- Schedule an appointment to insert replacement implant(s).
- Insert the replacement implant(s) in same arm either medially or laterally to in situ implants. Alternatively, replacement implant(s) may be inserted in the contralateral arm.
- Complete a new Patient ID Card and Patient Chart Label and record the new lot number in the PROBUPHINE Insertion / Removal Log.

4.4.2 PROBUPHINE Removal Procedure

Before initiating the removal procedure, read the instructions for removal.

Identify the location of the implants by consulting the Patient Chart Label. The exact location of all implants in the arm (patients will have four implants) should be verified by palpation.

If any of the implants are not palpable, use other methods to confirm the presence of the implant(s). **Non-palpable implants should always be located prior to attempted removal.** Suitable methods to locate implants are: Ultrasound with a high frequency linear array transducer (10 MHz or greater) or Magnetic Resonance Imaging (MRI). Note that PROBUPHINE implants are not radiopaque and cannot be seen by X-ray or CT scan.

After localization of a non-palpable implant, removal should be performed under ultrasound guidance. Exploratory surgery without knowledge of the exact location of all implants is strongly discouraged.

There is a greater risk of injury to neural and vascular structures during removal of implants located deeper than the subdermal space. As the anatomical location of these structures must be taken into consideration during the removal of deeply inserted implants, the procedure should only be attempted by healthcare professionals familiar with this anatomy.

Preparation

Before removal of PROBUPHINE, confirm that:

- The patient does not have allergies to the antiseptic or the anesthetic to be used. Implants should be removed under aseptic conditions.

The following equipment is recommended for implant removal:

- An examination table for the patient to lie on
- Instrument stand
- Sterile tray
- Adequate lighting (e.g., headlamp)
- Sterile fenestrated drapes
- Latex and talc-free sterile gloves
- Disinfectant pads
- Antiseptic solution (e.g., chlorhexidine)
- Surgical marker
- Local anesthetic (e.g., 1% lidocaine with epinephrine 1:100,000)
- 5 mL syringe with 1.5-inch 25G needle
- Adson single tooth tissue forceps
- Mosquito forceps
- Two X-plant clamps (vasectomy fixation clamps with 2.5 mm ring diameter)
- Iris scissors
- Needle driver
- #15 blade scalpel
- Sterile ruler
- 4x4 sterile gauze
- Adhesive bandage
- 3-inch pressure bandage
- Sutures (e.g., 4-0 Prolene™ with an FS-2 cutting needle) (may be absorbable)

Removal Procedure

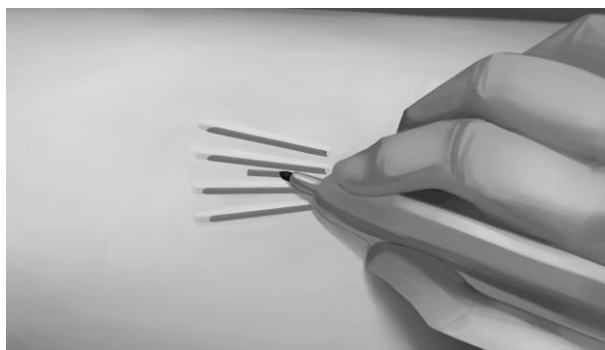
Step 1. Have the patient lie on his/her back, with the implant arm flexed at the elbow and externally rotated, so that the hand is positioned next to the head.

Step 2. Reconfirm the location of the implants by palpation.

Step 3. Clean removal site with disinfectant pad prior to marking the skin.

Step 4. Mark the location of the implants with a surgical marker. In addition, mark the location of the incision, parallel to the axis of the arm, between the second and third implants (Figure 14).

Figure 14



Step 5. Put on sterile gloves.

Step 6. Using aseptic technique, place the sterile equipment on the sterile field of the instrument stand.

Step 7. Clean the removal site with an antiseptic solution (e.g. chlorhexidine) using gentle repeated back and forth strokes for 30 seconds. If using triple swab stick applicators, use each swab stick sequentially within the 30 seconds. Allow the area to air dry for approximately 30 seconds and do not blot or wipe skin.

Step 8. Apply the sterile drape to the arm of the patient.

Step 9. Anesthetize the incision site and the subcutaneous space containing the implants (for example, by injecting 5-7 mL lidocaine 1% with epinephrine 1:100,000). Separate needles may be used for the incision site and the subcutaneous injections. NOTE: Be sure to inject the local anesthetic just beneath the implants; this will effectively lift the implants toward the skin, facilitating removal of the implants.

Step 10. After determining that anesthesia is adequate and effective, make a 7-10 mm incision with a scalpel, parallel to the axis of the arm, between the second and third implants.

Step 11. Pick up the skin edge with Adson single-toothed tissue forceps and separate the tissues above and below the first visualized implant using an iris scissors or curved mosquito forceps (Figure 15). Grasp the center of the implant with the X-plant clamp and apply gentle traction. Use the technique of spreading and closing with either the iris scissors or mosquito forceps to separate the fibrous tissue (Figure 16). If the implant is encapsulated use the scalpel to shave the tissue sheath and carefully dissect the tissue around the implant. The implant can then be removed.

Figure 15

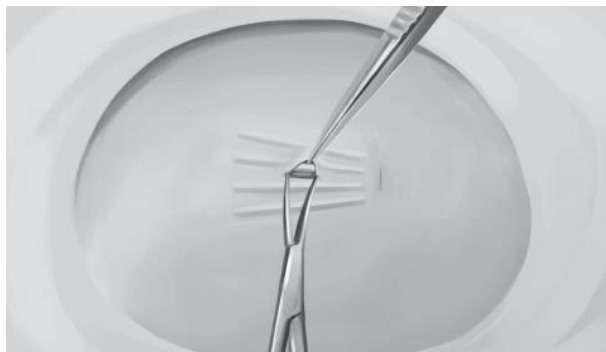
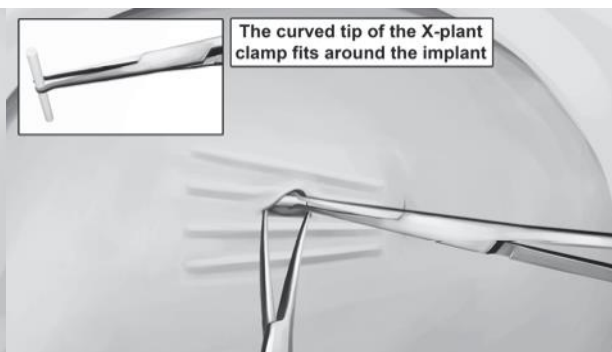


Figure 16



Step 12. Retract the next visible implant toward the incisional opening. You may see tenting of the skin at this point if the surrounding tissue is still adhering to the implant. Maintain gentle traction on the implant while you continue to dissect proximally and distally until the implant is free of all adhering tissue. At this point, you may require the use of your second X-plant clamp to remove the implant. If the implant is encapsulated use the scalpel to shave the tissue sheath and carefully dissect the tissue around the implant. The implant can then be removed.

Step 13. After removal of an implant, measure its length (which should be 26 mm long) to confirm that it has been totally removed. If a partial implant (less than 26 mm) is removed, the remaining piece(s) should be removed by following the same removal instructions. Follow steps 11 through 13 for the removal of the remaining implants through the same incision. Visual identification of whether an entire implant has been removed is unreliable. Therefore, it is important to measure the implant to ensure the entire implant has been removed.

Step 14. After removal of all 4 implants, clean the incision site.

Step 15. Close the incision with sutures.

Step 16. Place an adhesive bandage over the incision.

Step 17. Use the sterile gauze and apply gentle pressure for 5 minutes to the incision site to ensure hemostasis.

Step 18. Apply a pressure bandage with sterile gauze to minimize bruising. The pressure bandage can be removed in 24 hours and the adhesive bandage in 3 to 5 days.

Step 19. Counsel the patient on proper aseptic wound care. Instruct the patient to apply an ice pack to his/her arm for 40 minutes every 2 hours for the first 24 hours and as needed.

Step 20. Schedule an appointment for the sutures to be removed.

Step 21. The removed implants contain a significant amount of residual buprenorphine. They must be handled with adequate security and accountability. Disposal of PROBUPHINE implants should be in keeping with recommendations governing the disposal of pharmaceutical biohazardous waste.

Step 22. Complete the PROBUPHINE Insertion / Removal Log.

If implant(s) or implant fragment(s) are not removed during a removal attempt, the patient should undergo imaging for localization as soon as is feasible. The subsequent removal attempt should be performed on the same day as localization. If localization and a second removal attempt are not performed on the same day as the initial removal attempt that necessitated imaging for localization, the wound should be closed with sutures in the interim.

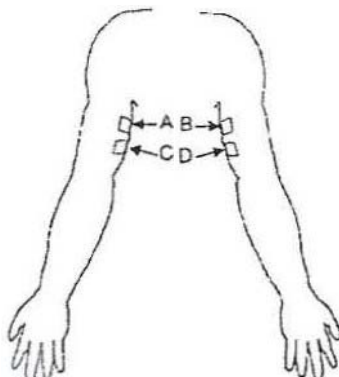
4.4.3 Continuation of Therapy: Subsequent Insertion of PROBUPHINE in the Contralateral Arm

If continued treatment is desired at the end of the first six-month treatment cycle, PROBUPHINE implants may be replaced by new implants in the contralateral arm, following the insertion steps above to locate the appropriate insertion site. If new implants are not inserted on the same day as the removal, patients should undergo re-induction with their previous dose of sublingual buprenorphine (i.e., the dose from which they were transferred to PROBUPHINE treatment) until resuming treatment with new PROBUPHINE implants.

There is no experience with inserting new implants into a previously-used site or using another site of a previously used arm. The following procedures should only be considered if the potential benefits of continuing PROBUPHINE outweigh the potential risks of additional insertion and removal procedures and the clinical need of the patient for ongoing treatment with subdermal medication.

If continued treatment is desired at the completion of two six-month treatment periods, new PROBUPHINE implants may be inserted into a previously **unused** area of the opposite arm (see Figure 17). The first implantation would be at the area A, followed by a second dose six months later at site B, the third dose at site C and fourth dose at site D. Sites A and B should be approximately 8-10 cm above the elbow crease and C and D should be located beneath these sites leaving approximately 1 cm between the previous insertion sites. It is important to avoid previously-implanted sites because the effect of scarring and fibrosis in previously-used insertion sites on either the effectiveness of PROBUPHINE, or the safety of insertion, have not been evaluated. Dosing beyond 24 months (fifth implantation) cannot be recommended at this time.

Figure 17



4.4.4 Clinical Supervision

Examine the insertion site one week following insertion of PROBUPHINE for signs of infection or any problems with wound healing, including evidence of implant extrusion from the skin.

The recommended visit schedule for most patients is a frequency of no less than once a month for continued counseling and psychosocial support.

5 OVERDOSAGE

Clinical Presentation

The manifestations of acute buprenorphine overdose may include miosis, blue or purple lips, sedation, slow heartbeat, hypotension, respiratory depression and may lead to death. Nausea and vomiting may be observed.

Treatment of Overdose

In case of overdose, priorities are the re-establishment of an adequate respiration through a patent and protected airway and institution of assisted ventilation, if needed. Employ other supportive measures (including oxygen, vasopressors) in the management of circulatory shock and pulmonary edema as indicated. ECG monitoring is recommended. Cardiac arrest or arrhythmias will require advanced life support techniques.

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. Buprenorphine has a high affinity for opioid mu-receptors, therefore reducing the binding ability of naloxone on these receptors. Higher than normal doses of naloxone may be necessary to overcome an overdose.

Because PROBUPHINE is an implant and will unremittingly release buprenorphine in the bloodstream, repeated administration of naloxone may be needed until the cause of the overdose is identified. Clinicians should consider the potential role and contribution of buprenorphine, other CNS depressant drugs, and other opioids in a patient's clinical presentation, in determining whether the implants should be removed. In an emergency situation, the removal procedure can be performed by a healthcare professional who is not certified by the PROBUPHINE Education Program.

For an individual physically dependent on opioids, administration of naloxone may precipitate an acute opioid withdrawal syndrome. The severity of the withdrawal will depend on the degree of physical dependence and the dose of the naloxone administered. If a serious respiratory depression in the physically dependent patient is treated, the administration of naloxone should be done with caution.

Acute neonatal opioid withdrawal syndrome (acute NOWS), unlike acute opioid withdrawal syndrome in adults, may be life-threatening in the neonate. Naloxone dosing should be very cautious to avoid triggering iatrogenic acute NOWS in the neonate.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Subdermal	Sterile subdermal implant, 80 mg buprenorphine hydrochloride	Ethylene Vinyl Acetate (EVA)

Each PROBUPHINE (buprenorphine hydrochloride subdermal implant) is a sterile, single, off-white, soft, flexible, rod-shaped ethylene vinyl acetate (EVA) implant, 26 mm in length and 2.5 mm in diameter, containing 80 mg of buprenorphine hydrochloride (equivalent to 74.2 mg of buprenorphine).

One PROBUPHINE kit consists of four individually packaged sterile implants (for a total of 320 mg buprenorphine hydrochloride to be delivered over 6 months) and one individually packaged sterile disposable applicator.

7 WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

General

PROBUPHINE (buprenorphine hydrochloride subdermal implant) is recommended only for the treatment of opioid dependence and, as other opioid substitution medications, should be used within the framework of medical, social and psychological support as part of a comprehensive opioid dependence treatment program.

Abuse potential

PROBUPHINE contains buprenorphine, a Schedule I 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.

Abuse of buprenorphine poses a risk of overdose and death. This risk is increased with the concomitant abuse of buprenorphine and alcohol or other substances, especially benzodiazepines. Consider these risks and the patient's stability in treatment for opioid dependence when determining whether PROBUPHINE is appropriate for the patient.

Proper assessment of the patient, periodic re-evaluation of therapy, and proper handling and storage of PROBUPHINE are appropriate measures that help to limit misuse, abuse, and diversion of opioid drugs.

Monitor all patients receiving PROBUPHINE and refer patients who have conditions indicative of diversion or progression of opioid dependence and addictive behaviors to more intensive and structured treatments for substance use.

Cardiovascular

PROBUPHINE may produce orthostatic hypotension in ambulatory patients.

QTc prolongation:

Buprenorphine products have been associated with QTc prolongation (see **ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology**). PROBUPHINE has been observed to prolong the QTc interval in some subjects participating in clinical trials. PROBUPHINE should not be used in patients with a history of Long QT Syndrome or an immediate family member with this condition, or those taking Class IA antiarrhythmic medications (e.g., quinidine, procainamide, disopyramide), Class IC antiarrhythmic medications (e.g., flecainide, propafenone) or Class III antiarrhythmic medications (e.g. amiodarone).

QTc prolongation may lead to an increased risk of ventricular arrhythmias including torsade de pointes. Torsade de pointes is a polymorphic ventricular tachyarrhythmia. Generally, the risk of torsade de pointes increases with the magnitude of QTc prolongation produced by the drug. Torsade de pointes may be asymptomatic or experienced by the patient as dizziness, palpitations, syncope, or seizures. If sustained, torsade de pointes can progress to ventricular fibrillation and sudden cardiac death.

Particular care should be exercised when inserting PROBUPHINE to patients who are suspected to be at an increased risk of experiencing torsade de pointes during treatment with a QTc-prolonging drug (see **DRUG INTERACTIONS**).

Risk factors for torsade de pointes in the general population include, but are not limited to, the following: female gender; age ≥ 65 years; baseline prolongation of the QTc interval; presence of pathological genetic variants affecting cardiac ion channels or regulatory proteins, especially congenital long QT syndromes; family history of sudden cardiac death at < 50 years of age; cardiac disease (e.g., myocardial ischemia or infarction, congestive heart failure, cardiomyopathy, conduction system disease); history of arrhythmias; electrolyte disturbances (e.g., hypokalemia, hypomagnesemia, hypocalcemia) or conditions leading to electrolyte disturbances (e.g., persistent vomiting, eating disorders); bradycardia; acute neurological events (e.g., intracranial or subarachnoid haemorrhage, stroke, intracranial trauma); diabetes mellitus; and autonomic neuropathy.

When drugs that prolong the QTc interval are prescribed, healthcare professionals should counsel their patients concerning the nature and implications of the ECG changes, underlying diseases and disorders that are considered to represent risk factors, demonstrated and predicted drug-drug interactions, symptoms suggestive of arrhythmia, risk management strategies, and other information relevant to the use of the drug. Patients should be advised to contact their healthcare provider immediately to report any new chest pain or discomfort, changes in heartbeat, palpitations, dizziness, lightheadedness, fainting, or changes in or new use of other medications.

Concomitant Use of CYP3A4 Inhibitors

The concomitant use of PROBUPHINE with cytochrome P450 3A4 inhibitors such as ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, nefazodone, verapamil, diltiazem, amiodarone, amprenavir, fosamprenavir, aprepitant, fluconazole, erythromycin and grapefruit juice may result in an increase in buprenorphine plasma concentrations, which could increase dose-related toxicity, including potential fatal respiratory depression and QTc prolongation. In this situation, special patient care and observation is appropriate (see **DRUG INTERACTIONS**).

Dependence/Tolerance

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.

Patients treated with PROBUPHINE who experience a delay between removal of implants and insertion of new implants should be maintained on their previous dose of sublingual buprenorphine (i.e., the dose from which they were transferred to PROBUPHINE treatment). Patients who elect to discontinue PROBUPHINE treatment without continuing on other buprenorphine treatment should be monitored for withdrawal. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

Driving and Operating 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, especially for the first 24-48 hours following initial insertion. Caution patients about driving or operating hazardous machinery until they are reasonably certain that PROBUPHINE does not adversely affect their ability to engage in such activities.

Elevation of Cerebrospinal Fluid Pressure

Buprenorphine, like other opioids, may elevate cerebrospinal fluid pressure and is contraindicated in patients with a history of seizure, head injury, intracranial lesions, and other circumstances when 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.

Endocrine

Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

Gastrointestinal

Constipation is a common side effect of opioids. PROBUPHINE is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction (e.g., bowel obstruction or strictures) or any diseases/conditions that affect bowel transit (e.g., ileus of any type).

Buprenorphine may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

Hepatic/Biliary/Pancreatic

Hepatitis, hepatic events

Cases of cytolytic hepatitis and hepatitis with jaundice have been observed in individuals receiving sublingual buprenorphine for the treatment of opioid dependence, both in clinical trials and through post-marketing adverse event reports.

The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of death, hepatic failure, hepatic necrosis, hepatorenal syndrome, and hepatic encephalopathy. In many cases, the presence of pre-existing liver enzyme abnormalities, infection with hepatitis B or hepatitis C virus, concomitant usage of other potentially hepatotoxic drugs, and ongoing injection drug abuse may have played a causative or contributory role. In other cases, insufficient data were available to determine the etiology of the abnormality. The possibility exists that buprenorphine had a causative or contributory role in the development of the hepatic abnormality in some cases. Liver function tests are recommended prior to initiation of treatment to establish a baseline. Periodic monitoring of liver function during treatment is also recommended.

A biological and etiological evaluation is recommended when a hepatic event is suspected.

Monitor patients with declining hepatic function for side effects resulting from increased exposure to buprenorphine. Patients may require removal of PROBUPHINE implants (see **DOSAGE AND ADMINISTRATION**).

Hepatic impairment

PROBUPHINE is contraindicated in patients with severe hepatic impairment. Because

PROBUPHINE cannot be titrated, its use in patients with moderate hepatic impairment may not be appropriate.

Patients who develop moderate to severe hepatic impairment while being treated with PROBUPHINE should be monitored for signs and symptoms of toxicity or overdose caused by increased levels of buprenorphine, and patients may require removal of PROBUPHINE implants (see **Special Populations**).

Hematologic

Patients on anti-coagulant therapy such as warfarin were excluded from pivotal trials for PROBUPHINE. Use of PROBUPHINE in those patients should be cautious.

Immune

Allergic reactions to buprenorphine and/or EVA are possible. Cases of hypersensitivity to buprenorphine sublingual tablets have been reported both in clinical trials and in the post-marketing experience. Cases of bronchospasm, angioneurotic edema, and anaphylactic shock have been reported. The most common signs and symptoms include rashes, urticaria, and pruritus. A history of hypersensitivity to buprenorphine or EVA is a contraindication to PROBUPHINE use.

Implant breakage

Breakage of PROBUPHINE implants following insertion in patients is not expected to have an effect on the buprenorphine pharmacokinetics profile (see **ACTION AND CLINICAL PHARMACOLOGY**). In a nonclinical study in dogs, 30-40% of the implants in the PROBUPHINE-treated animals were broken over the course of treatment. However, this did not result in significant differences in the buprenorphine pharmacokinetic parameters in these animals; although some slight differences in terms of the tissue response and behavior were noted (see **NON-CLINICAL TOXICOLOGY**).

Neurologic

Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol)

PROBUPHINE should be used with caution during concomitant administration of other opioid analgesics, general anaesthetics, phenothiazines and other tranquilizers, sedative-hypnotics, antidepressants, antipsychotics, antihistamines, benzodiazepines, centrally-active anti-emetics and other CNS depressants. Respiratory depression, hypotension and profound sedation, coma or death may result. When such combination therapy is contemplated, a reduction in the dose of the CNS depressant should be considered and patients should be carefully monitored. PROBUPHINE should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects including death (see **CONTRAINDICATIONS and ADVERSE REACTIONS, Sedation, and DRUG INTERACTIONS**).

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics (see **DRUG**

INTERACTIONS). If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with PROBUPHINE, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already on PROBUPHINE, prescribe a lower than usual initial dose of the benzodiazepine or other CNS depressant and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when PROBUPHINE is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Warn patients of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs (see **DRUG INTERACTIONS**).

Use in Patients with Convulsive or Seizure Disorders

The buprenorphine in PROBUPHINE may aggravate convulsions in patients with convulsive disorders and may induce or aggravate seizures in some clinical settings. Therefore, PROBUPHINE should not be used in these patients (see **CONTRAINDICATIONS**).

Serotonin syndrome

Serotonin toxicity, also known as serotonin syndrome, is a potentially life-threatening condition and has been reported with buprenorphine, including PROBUPHINE, particularly during combined use with other serotonergic drugs (See **DRUG INTERACTIONS**).

Serotonin toxicity is characterised by neuromuscular excitation, autonomic stimulation (e.g. tachycardia, flushing) and altered mental state (e.g. anxiety, agitation, hypomania). In accordance with the Hunter Criteria, serotonin toxicity diagnosis is likely when, in the presence of at least one serotonergic agent, one of the following is observed:

- Spontaneous clonus
- Inducible clonus or ocular clonus with agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia and body temperature >38°C and ocular clonus or inducible clonus.

If concomitant treatment with PROBUPHINE and other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see **DRUG INTERACTIONS**). If serotonin toxicity is suspected, discontinuation of the serotonergic agents should be considered.

Respiratory and Central Nervous System (CNS) Depression

Clinically significant respiratory depression and death may occur in patients receiving PROBUPHINE. Some cases of death due to respiratory depression have been reported, particularly when buprenorphine was used in combination with benzodiazepines, when high dose buprenorphine was administered to non-opioid dependent individuals, or with concomitant administration of buprenorphine with other depressants such as alcohol or other opioids. Patients should be warned of the potential danger of the self-administration of benzodiazepines or other CNS depressants while under treatment with PROBUPHINE, particularly when PROBUPHINE is misused or abused (see **DRUG INTERACTIONS**).

PROBUPHINE should not be used in patients with compromised respiratory function (e.g., chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression) (see **CONTRAINDICATION**).

Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, removal of PROBUPHINE may be required.

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.

Opioid Withdrawal with Abrupt Discontinuation of PROBUPHINE Treatment

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

If PROBUPHINE implants are not to be immediately replaced upon removal, maintain patients on their previous dosage of sublingual buprenorphine until PROBUPHINE treatment is resumed (see **DOSAGE AND ADMINISTRATION**). Patients who elect to discontinue PROBUPHINE treatment should be monitored for withdrawal with consideration given to use of a tapering dose of transmucosal buprenorphine.

Precipitation of Opioid Withdrawal Syndrome

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 switched from a full agonist to PROBUPHINE (see **INDICATION**).

Neonatal Opioid Withdrawal Syndrome (NOWS)

Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening.

Neonatal withdrawal has been reported in infants of women treated with buprenorphine during pregnancy. Time to onset of withdrawal symptoms ranged from Day 1 to Day 8 of life with most occurring on Day 1 (69%). Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea, convulsions, and failure to gain weight. The most commonly-reported manifestations include abnormal crying, agitation, hypertonia, tremor myoclonus, and convulsions.

Due to the long half-life of buprenorphine, neonates should be monitored for several days at the end of pregnancy to detect potential NOWS.

Risks from Concomitant Use with Alcohol, Benzodiazepines or Other CNS Depressants

The co-ingestion of alcohol with PROBUPHINE should be avoided as it may result in dangerous additive effects, causing serious injury or death (see **WARNINGS AND PRECAUTIONS, Neurologic and DRUG INTERACTIONS**).

Concomitant use of opioids with benzodiazepines or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death (see **WARNINGS AND PRECAUTIONS, Neurologic and DRUG INTERACTIONS**).

- Reserve concomitant prescribing of PROBUPHINE and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Follow patients for signs and symptoms of respiratory depression and sedation.

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. Patients requiring opioid therapy for analgesia may be treated with a high-affinity full opioid analgesic under the supervision of a physician, with particular attention to respiratory function. Higher doses may be required for analgesic effect. Therefore, a higher potential for toxicity exists with opioid administration. If opioid therapy is required as part of anesthesia, patients should be continuously monitored in an anesthesia care setting by persons not involved in the conduct of the surgical or diagnostic procedure. The opioid therapy must be provided by individuals specifically trained in the use of anesthetic drugs and the management of the respiratory effects of potent opioids, specifically the establishment and maintenance of a patent airway and assisted ventilation.

Renal

Renal elimination plays a relatively small role in the overall clearance of buprenorphine; therefore, dose modification based on renal function is generally not required. However, metabolites of buprenorphine accumulate in patients with advanced renal failure. Caution is recommended when dosing patients with severe renal impairment ($CL_{cr} < 30$ ml/min), which may require dose adjustment (see **ACTION AND CLINICAL PHARMACOLOGY**).

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.

It is essential to insert PROBUPHINE subdermally so that each implant is palpable after insertion. It is also essential to confirm proper placement by palpation immediately after insertion. If PROBUPHINE is inserted too deeply (intramuscular or in the fascia), neural or vascular injury may occur.

Incomplete insertions or infections may lead to protrusion or expulsion. Accidental exposures to

PROBUPHINE can result from protrusion or expulsion of the implants.

Improper insertion may lead to complicated removal if the implant is inserted too deeply, is not palpable, or has migrated. Deep insertions may lead to difficulty localizing the implant; additional surgical procedures may be required in order to remove the implant. Injury to deeper neural or vascular structures in the arm may occur when removing deeply inserted implants (see **DOSAGE AND ADMINISTRATION**).

All Healthcare Professionals must successfully complete a live training program on the insertion and removal procedures and become certified in the PROBUPHINE Education Program, prior to performing insertions or removals of PROBUPHINE implants.

Skin

Infection at Implant Site

Infection may occur at the site of the insertion or removal. Excessive palpation shortly after insertion of the implants may increase the chance of infection. Improper removal carries risk of implant-site infection.

Sexual Function/Reproduction

Long-term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility.

General Precautions

PROBUPHINE should be administered with caution in debilitated patients and those with myxedema or hypothyroidism; adrenal cortical insufficiency (e.g., Addison's disease); CNS depression or coma; toxic psychoses; prostatic hypertrophy or urethral stricture; acute alcoholism; delirium tremens; or kyphoscoliosis. 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.

7.1 Special Populations

7.1.1 Pregnant Women

The use of PROBUPHINE in pregnant women or in women of childbearing potential requires that the benefits of its use be weighed against the risk to the foetus. The risks associated to PROBUPHINE should be discussed with the patient. The use of a formulation allowing for dosage adjustment may also be considered during pregnancy.

Buprenorphine can cross the placental barrier and can be life-threatening for the foetus if administered to the mother. Opioid dependence in pregnancy is associated with adverse obstetrical outcomes in the neonate such as low birth weight, preterm birth, respiratory depression and foetal death. There are no adequate and well-controlled studies of PROBUPHINE use in pregnant women; therefore, it should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

PROBUPHINE use during pregnancy may result in Neonatal Opioid Withdrawal Syndrome (NOWS) (e.g. hypertonia, neonatal tremor, neonatal agitation, myoclonus, or convulsions). The syndrome is generally delayed for several hours to several days after birth. Due to the long half-life of buprenorphine, neonatal monitoring for several days is advised to monitor for the risk of NOWS. Newborns should also be observed for poor feeding, diarrhea, irritability, tremor, rigidity, and seizures, and managed accordingly (see **WARNINGS AND PRECAUTIONS, Neonatal Opioid Withdrawal Syndrome (NOWS) and OVERDOSAGE**).

Studies have been conducted to evaluate neonatal outcomes in women exposed to buprenorphine during pregnancy. Limited published data on malformations from trials, observational studies, case series, and case reports on buprenorphine use in pregnancy have not shown an increased risk of major malformations. Based on these studies the incidence of NOWS is not clear and there does not appear to be a dose-response relationship.

Reproductive and developmental studies in rats and rabbits identified adverse events at clinically relevant doses following intramuscular or subcutaneous administration. Embryo-fetal death was observed in both rats and rabbits administered buprenorphine during the period of organogenesis at doses approximately 6 and 0.3 times, respectively, the human sublingual dose of 16 mg/day of buprenorphine. Pre- and postnatal development studies in rats demonstrated increased neonatal deaths and dystocia, at approximately 0.3 and 3 times greater the human sublingual dose at 16 mg/day of buprenorphine. Increases in skeletal abnormalities were noted in rats and rabbits administered buprenorphine daily during organogenesis at a dose of approximately 0.6 and 6 times the human sublingual dose of 16 mg/day of buprenorphine, respectively. In a few studies, some events such as acephalous and omphalocele were observed but these findings were not clearly treatment-related. Embryo-fetal death was also observed in both rats and rabbits. Based on the animal data, advise pregnant women of the potential risk to a fetus.

Labor or Delivery

Life-threatening respiratory depression may occur in the newborn if any opioid is administered to the mother during pregnancy. This risk is increased if another opioid is added to PROBUPHINE during labour and delivery. If any opioid was used in the mother during pregnancy, closely monitor neonate. Due to the long half-life of buprenorphine, neonatal monitoring for several days should be performed to monitor for the signs of respiratory depression or NOWS. Naloxone, a drug that counters the effects of opioids, should be readily available to treat potential respiratory depression. Naloxone dosing in neonates should be done with caution to avoid triggering an iatrogenic acute NOWS (see **WARNINGS AND PRECAUTIONS, Paediatrics**).

7.1.2 Breast-feeding

Buprenorphine can cross the placental barrier and is excreted in breast milk. Life-threatening respiratory depression may occur in the neonate if opioids are administered to the nursing mother. If PROBUPHINE is used in nursing mothers, closely monitor neonates for signs of respiratory depression. Naloxone, a drug that counters the effects of opioids, should be readily available to treat potential respiratory depression. Naloxone dosing should be done with caution to avoid triggering an iatrogenic acute NOWS (see **WARNINGS AND PRECAUTIONS, Neonatal Opioid Withdrawal Syndrome (NOWS) and OVERDOSAGE**).

Limited data from published literature have not reported adverse reactions in breastfed infants exposed to buprenorphine through breast milk, however nursing mothers taking buprenorphine should be advised to monitor the infant for increased drowsiness and breathing difficulties and infants should be regularly monitored by a healthcare professional.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for buprenorphine and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.

7.1.3 Paediatrics

Paediatrics (<18 years of age): No data is available for paediatrics. PROBUPHINE is not indicated in paediatrics.

Buprenorphine can cross the placental barrier and can be life-threatening for the foetus, if administered to the mother. (see **WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women, Labor or Delivery, Breast-feeding, WARNINGS AND PRECAUTIONS, Neonatal Opioid Withdrawal Syndrome (NOWS) and OVERDOSAGE**).

7.1.4 Geriatrics

Geriatrics (>65 years of age): No data is available for geriatrics. PROBUPHINE is not indicated in geriatrics. In general, drug use for an elderly patient should be done with caution, reflecting the greater frequency of decreased hepatic, renal, respiratory or cardiac function, concomitant disease or another drug therapy.

7.1.5 Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of sublingual buprenorphine has been evaluated in a pharmacokinetic study. While no clinically significant changes have been observed in subjects with mild hepatic impairment, the plasma levels have been shown to be higher and half-life values have been shown to be longer for buprenorphine in subjects with moderate and severe hepatic impairment.

The effect of hepatic impairment on the pharmacokinetics of implanted buprenorphine, such as PROBUPHINE, has not been studied, but since buprenorphine is extensively metabolized, the plasma levels can be expected to be higher in patients with moderate and severe hepatic impairment. Because PROBUPHINE cannot be titrated, it is contraindicated in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment. 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. If signs and symptoms of toxicity or overdose are observed, removal of PROBUPHINE implants may be required (see **DOSAGE AND ADMINISTRATION**).

7.1.6 Renal Impairment

Clinical studies of PROBUPHINE did not include subjects with renal impairment. No differences in buprenorphine pharmacokinetics were observed between 9 dialysis-dependent and 6 normal patients following IV administration of 0.3 mg buprenorphine.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Buprenorphine is a member of the opioid pharmacological class. The most commonly (>1%) reported TEAEs reported with this pharmacological class include constipation, headache, insomnia, asthenia, drowsiness, nausea and vomiting, fainting and dizziness, orthostatic hypotension, and sweating.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In the doubleblind double dummy pivotal study PRO-814, comparing PROBUPHINE to 8 mg sublingual buprenorphine (SL BPN), the most common TEAEs were nasopharyngitis, headache, implant site pain, and depression. Incidences of individual TEAEs were generally low and comparable between treatment groups. The incidence of depression was lower in the SL BPN group (2.2%) compared with the PROBUPHINE group (6.9%). A similar trend was observed for headache (3.4%, SL BPN; 6.9%, PROBUPHINE) and implant site pruritus (1.1%, SL BPN; 4.6%, PROBUPHINE).

Overall, 100 (56.8%) subjects experienced at least 1 (TEAE) during the study; 32 (18.2%) subjects had at least 1 implant site TEAE, and 89 (50.6%) subjects had at least 1 non-implant site TEAE.

Twelve (6.8%) subjects, 9 (10.1%) in the SL BPN group and 3 (3.4%) in the PROBUPHINE group, had at least 1 severe TEAE. All severe TEAEs were non-implant site events. None of the subjects died during the study.

Non-implant-site TEAEs

Table 1 shows the non-implant-site related adverse events for PROBUPHINE and the control group in the pivotal study 814. Adverse events were categorized using the Medical Dictionary for Regulatory Activities (MedDRA).

Table 1: Non-implant-site Treatment-Emergent Adverse Events Reported by ≥2% of Subjects in the PROBUPHINE arm for the pivotal study PRO-814

System Organ Class MedDRA Preferred Term	PROBUPHINE (N=87) n (%)	SL BPN (N=89) n (%)
GASTROINTESTINAL DISORDERS		
Constipation	4 (4.6)	0 (0.0)
Diarrhea	2 (2.3)	1 (1.1)

Vomiting	2 (2.3)	1 (1.1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Pain	2 (2.3)	1 (1.1)
INFECTIONS AND INFESTATIONS		
Nasopharyngitis	7 (8.0)	4 (4.5)
Gastroenteritis viral	4 (4.6)	3 (3.4)
Influenza	2 (2.3)	3 (3.4)
Urinary tract infection	4 (4.6)	3 (3.4)
Bronchitis	2 (2.3)	3 (3.4)
Sinusitis	2 (2.3)	2 (2.2)
Localized infection	2 (2.3)	0 (0.0)
NERVOUS SYSTEM DISORDERS		
Headache	6 (6.9)	3 (3.4)
Somnolence	2 (2.3)	0 (0.0)
PSYCHIATRIC DISORDERS		
Depression	6 (6.9)	2 (2.2)
Anxiety	3 (3.4)	4 (4.5)
VASCULAR DISORDERS		
Hypertension	2 (2.3)	2 (2.2)

Implant-site TEAEs

Table 2 shows the implant-site related adverse events for PROBUPHINE and the control group in the pivotal study 814.

Table 2: Implant-site Treatment-Emergent Adverse Events Reported by ≥2% of Subjects in the PROBUPHINE arm for the pivotal study PRO-814

System Organ Class MedDRA Preferred Term	PROBUPHINE (N=87) n (%)	SL BPN (N=89) n (%)
Implant site pain	4 (4.6)	4 (4.5)
Implant site pruritus	4 (4.6)	1 (1.1)

8.3 Less Common Clinical Trial Adverse Reactions (<2%)

Blood and Lymphatic System Disorders: anaemia.

Ear and Labyrinth Disorders: ear congestion.

Eye: eye discharge.

Gastrointestinal: dental caries, abdominal tenderness, gastric ulcer, nausea, oral pain.

General Disorders and Administration Site Conditions: implant site bruising, implant site erythema, implant site hemorrhage, feeling hot, feeling of body temperature change, oedema peripheral, pyrexia.

Infections and Infestations: acute sinusitis, cellulitis, ear infection, oral herpes, otitis media, pharyngitis streptococcal, purulent discharge, skin infection, tonsillitis, upper respiratory tract infection, viral pharyngitis, wound infection.

Injury, Poisoning and Procedural Complications: limb injury, tooth fracture, foot fracture, incision site complication, postoperative wound complication.

Investigations: alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyl transferase increased, weight increased.

Metabolism and Nutrition: decreased appetite, abnormal weight gain, hyperlipidemia, vitamin D deficiency.

Musculoskeletal and Connective Tissue Disorders: back pain, muscle spasm, pain in extremity, temporomandibular joint syndrome.

Nervous System Disorders: lethargy, convulsion, paresthesia.

Psychiatric Disorders: restlessness, attention deficit/hyperactivity disorder, bipolar I disorder, affective disorder, irritability, libido decreased, sleep disorder.

Reproductive System and Breast Disorders: cervical dysplasia.

Respiratory, Thoracic and Mediastinal Disorders: cough, dyspnea, oropharyngeal pain, yawning, sneezing, sinus congestion.

Skin and Subcutaneous Tissue Disorders: dermatitis contact, pruritus, alopecia, rash.

8.4 Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Results from the three 6-month, double-blind, PROBUPHINE Phase 3 studies show that mean changes in hematology, clinical chemistry, vital sign measurements and physical examination values over the course of each study were minimal and did not indicate any clinically meaningful trends.

8.5 Post-Market Adverse Reactions

Tables 3 and 4 list non- implant and implant adverse drug reactions reported during post-marketing surveillance. Adverse drug reactions are presented by MedDRA System Organ Class in order by preferred term.

Table 3: Non-implant-site Adverse Drug Reactions Collected Through Post-Marketing Surveillance

System Organ Class	Preferred Term
GASTROINTESTINAL DISORDERS	Abdominal pain upper Abdominal pain Oral pain
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Asthenia Chest pain Chills Crying Decreased activity Drug effect decreased Drug effect incomplete Drug ineffective Drug withdrawal syndrome Fatigue Feeling abnormal Feeling cold Gait disturbance Malaise Mass Peripheral swelling
INFECTIONS AND INFESTATIONS	Viral upper respiratory tract infection
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	Contusion Exposure during pregnancy Foreign body Injury Overdose
INVESTIGATIONS	Drug level increased Drug screen negative Drug screen positive Toxicologic test abnormal Weight decreased
METABOLISM AND NUTRITION DISORDERS	Appetite disorder
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Arthralgia Intervertebral disc disorder Limb discomfort
NERVOUS SYSTEM DISORDERS	Dizziness Hypersomnia Hypoaesthesia Migraine Movement disorder Sedation
PSYCHIATRIC DISORDERS	Abnormal dreams Agitation Depression suicidal Drug dependence Emotional distress Drug use disorder Initial insomnia Insomnia Nervousness Panic reaction Suicidal ideation Stress Thinking abnormal

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Rhinorrhoea
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Cold sweat Dry skin Hyperhidrosis Night sweats Pruritus Urticaria
SURGICAL AND MEDICAL PROCEDURES	Therapy cessation

Table 4: Implant-site Adverse Drug Reactions Collected Through Post-Marketing Surveillance

System Organ Class	Preferred Term
ADMINISTRATION SITE CONDITIONS	Implant site inflammation Implant site irritation Implant site scar Implant site swelling
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	Difficulty removing drug implant Drug administered at inappropriate site Incorrect drug administration duration Migration of implanted drug
PRODUCT ISSUES	Device breakage

Androgen deficiency: Post-marketing experience with opioids indicates that the chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions Box

Serious Drug Interactions

- The co-ingestion of alcohol with buprenorphine should be avoided as it may result in dangerous addictive effects, causing serious injury or death (see **WARNINGS AND PRECAUTIONS**).
- Risks from concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death (see **WARNINGS AND PRECAUTIONS**).
 - Reserve concomitant prescribing of **PROBUPHINE** and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
 - Consider dose reduction of CNS depressants in situations of concomitant prescribing.
 - Follow patients for signs and symptoms of respiratory depression and sedation.

9.2 Overview

Buprenorphine is metabolized by glucuronidation and also metabolized to norbuprenorphine primarily by CYP3A4; therefore, potential interactions may occur when **PROBUPHINE** is given concurrently with agents that affect CYP3A4 activity. The effects of co-administered inducers or inhibitors have been established in studies using transmucosal buprenorphine; the effects on buprenorphine exposure in patients treated with **PROBUPHINE** have not been studied, and the effects may be dependent on the route of administration.

Concomitant treatment with CYP3A4 inhibitors (e.g., ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, nefazodone, verapamil, diltiazem, amiodarone, amprenavir, fosamprenavir, aprepitant, fluconazole, erythromycin and grapefruit juice) may lead to elevated plasma concentrations with an increase in dose-related toxicity of buprenorphine including potentially fatal respiratory depression and QTc prolongation (see **WARNINGS AND PRECAUTIONS, Concomitant Use of CYP3A4 Inhibitors**). The above list of potentially interacting drugs is not comprehensive. Current information sources should be consulted for newly approved drugs that prolong the QTc interval, decrease electrolytes, or inhibit CYP3A, as well as for older drugs for which these effects have recently been established.

When patients transfer to **PROBUPHINE** treatment from a regimen of transmucosal buprenorphine used concomitantly with CYP3A4 inhibitors (see above paragraph), they should be monitored to ensure that the plasma buprenorphine level provided by **PROBUPHINE** is adequate. If patients already on **PROBUPHINE** require newly-initiated treatment with CYP3A4 inhibitors, they should be monitored for signs and symptoms of over- medication. If the concomitant medication cannot be reduced or discontinued, it may be necessary to remove the **PROBUPHINE** implants and treat the

patient with a formulation of buprenorphine that permits dose adjustments. Conversely, if a patient has been stabilized on PROBUPHINE in the setting of concomitant medication that is a CYP3A4 inhibitor, and the concomitant medication is discontinued, the patient should be monitored for withdrawal. If the dose of PROBUPHINE is not adequate in the absence of the concomitant medication, that patient should be transitioned back to a formulation of buprenorphine that permits dose adjustments.

CYP3A4 inducers may induce the metabolism of buprenorphine and, therefore, may cause increased clearance of the drug which could lead to a decrease in buprenorphine plasma concentrations, lack of efficacy or, possibly, development of an abstinence syndrome. It is not known whether the effects of CYP3A4 inducers are dependent on the route of administration of buprenorphine. Patients who transfer to PROBUPHINE treatment from a regimen of transmucosal buprenorphine used concomitantly with CYP3A4 inducers should be monitored to ensure that the plasma buprenorphine level provided by PROBUPHINE is maintained. If patients already on PROBUPHINE require newly-initiated treatment with CYP3A4 inducers, they should be monitored for withdrawal. If the dose of PROBUPHINE is not adequate in the absence of the concomitant medication, and the concomitant medication cannot be reduced or discontinued, that patient should be transitioned back to a formulation of buprenorphine that permits dose adjustments. Conversely, if a patient has been stabilized on PROBUPHINE in the setting of concomitant medication that is a CYP3A4 inducer, and the concomitant medication is discontinued, the patient should be monitored for signs and symptoms of over-medication. If the dose provided by PROBUPHINE is excessive in the absence of the concomitant inducer, it may be necessary to remove the PROBUPHINE implants and treat the patient with a formulation of buprenorphine that permits dose adjustments.

Additive Effects of Other CNS Depressants: PROBUPHINE (buprenorphine hydrochloride subdermal implant) should be used with caution in patients who are currently taking other CNS depressants or other drugs that may cause respiratory depression, hypotension, profound sedation, or may potentially result in coma. Such agents include antihistamines, antipsychotics, anxiolytics, barbiturates, benzodiazepines, centrally acting anti-emetics, clonidine and related substances, general anaesthetics, neuroleptics, other opioid derivatives (analgesic and antitussive), phenothiazines and sedatives or hypnotics. When such combined therapy is contemplated, a substantial reduction in the dose of one or both agents should be considered and patients carefully monitored (see **WARNINGS AND PRECAUTIONS**).

QTc Interval-Prolonging Drugs: The concomitant use of PROBUPHINE with other QTc interval-prolonging drugs should be avoided (see **WARNINGS AND PRECAUTIONS, Cardiovascular; ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology**). Drugs that have been associated with QTc interval prolongation and/or torsade de pointes include, but are not limited to, the examples in the following list. Chemical/pharmacological classes are listed if some, although not necessarily all, class members have been implicated in QTc interval prolongation and/or torsade de pointes: Class IA antiarrhythmics (e.g., quinidine, procainamide, disopyramide), Class III antiarrhythmics (e.g., amiodarone, sotalol, ibutilide, dronedarone), Class 1C antiarrhythmics (e.g., flecainide, propafenone), antipsychotics (e.g., chlorpromazine, pimozide, haloperidol, droperidol, ziprasidone, risperidone), antidepressants (e.g., fluoxetine, citalopram, tricyclic/tetracyclic antidepressants [e.g., amitriptyline, imipramine, maprotiline]), opioids (e.g., methadone), macrolide antibiotics and analogues (e.g., erythromycin, clarithromycin, azithromycin, tacrolimus), quinolone antibiotics (e.g., moxifloxacin, levofloxacin, ciprofloxacin), pentamidine, antimalarials (e.g., quinine, chloroquine), azole antifungals (e.g., ketoconazole, fluconazole,

voriconazole), domperidone, angrelide, ivabradine, 5-hydroxytryptamine (5-HT)₃ receptor antagonists (e.g., ondansetron), tyrosine kinase inhibitors (e.g., sunitinib, nilotinib, ceritinib, vandetanib), arsenic trioxide, histone deacetylase inhibitors (e.g., vorinostat), beta-2 adrenoceptor agonists (e.g., salmeterol, formoterol).

Drugs that Affect Electrolytes: The use of PROBUPHINE with drugs that can disrupt electrolyte levels should be avoided. Drugs that can disrupt electrolyte levels include, but are not limited to, the following: loop, thiazide, and related diuretics; laxatives and enemas; amphotericin B; high-dose corticosteroids; proton pump inhibitors.

9.3 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 5: Established or Potential Drug-Drug Interactions with Buprenorphine

Proper/Common Name	Source of Evidence	Effect	Clinical comment
Benzodiazepines	T	This combination may result in death due to respiratory depression of central origin, therefore patients should be closely monitored when prescribed this combination.	This combination must be avoided where there is risk of misuse or abuse. Patients should be warned that it is extremely dangerous to self-administer non-prescribed benzodiazepines while taking buprenorphine, and should also be cautioned to use benzodiazepines concurrently with this product only as prescribed.
Other central nervous system depressants	T	Combining central nervous system depressants with buprenorphine increases central nervous system depressant effects.	The reduced level of alertness can make driving and using machines hazardous. Example central nervous system depressants are: other opioids (e.g. methadone, analgesics, antitussives), certain antidepressants, sedative H ₁ -receptor antagonists, barbiturates, anxiolytics, neuroleptics, clonidine and related substances.
Serotonergic Agents	T	Coadministration of PROBUPHINE with a serotonergic agent may increase the risk of serotonin syndrome, a potentially life-threatening condition.	Due to the risk of serotonin syndrome, PROBUPHINE should be used with caution when co-administered with MAO inhibitors, SSRIs, SNRIs, serotonin-precursors (such as L-tryptophan, oxitriptan), certain muscle relaxants (such as cyclobenzaprine) and other serotonergic drugs (e.g. triptans, certain tricyclic antidepressants, lithium, tramadol, tapentadol and St. John's Wort).

Antiretrovirals	CT	Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are metabolized principally by CYP3A4. Efavirenz, nevirapine, and etravirine are known CYP3A4 inducers, whereas delavirdine is a CYP3A4 inhibitor. Significant pharmacokinetic interactions between NNRTIs and buprenorphine have been shown in clinical studies, but these pharmacokinetic interactions did not result in any significant pharmacodynamic effects.	Caution is warranted and therapeutic concentration monitoring is recommended.
Opioid analgesics	T	The analgesic properties of other opioids may be reduced in patients receiving treatment with buprenorphine/naloxone for opioid dependence. Adequate analgesia may be difficult to achieve when administering a full opioid agonist in patients receiving buprenorphine. Conversely, the potential for overdose should be considered with higher than usual doses of full agonist opioids, such as methadone or analgesics, especially when attempting to overcome buprenorphine partial agonist effects, or when buprenorphine plasma levels are declining.	Patients with a need for analgesia and opioid dependence treatment may be best managed by multidisciplinary teams that include both pain and opioid dependence treatment specialists.
Anticholinergic Drugs	T	The concomitant use of anticholinergic drugs may increase the risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.	Monitor patients for signs of urinary retention or reduced gastric motility when PROBUPHINE is used concomitantly with anticholinergic drugs.
Diuretics	T	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Muscle Relaxants	T	Buprenorphine may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.	Monitor patients receiving muscle relaxants (such as cyclobenzaprine) and PROBUPHINE for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of the muscle relaxant as necessary.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.4 Drug-Food Interactions

Interactions with food have not been established.

9.5 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.6 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established

9.7 Drug-Lifestyle Interactions

The concomitant use of alcohol should be avoided (see **WARNINGS AND PRECAUTIONS and Serious Drug Interactions Box**).

10 ACTION AND CLINICAL PHARMACOLOGY

The nature of the PROBUPHINE matrix formulation blends the active ingredient (buprenorphine) with the inactive ingredient (ethylene vinyl acetate or EVA) in a manner that limits the extraction and solubility of buprenorphine after breakage of the implant.

Cardiac Electrophysiology: Buprenorphine has been associated with concentration-dependent prolongation of the QTc interval in randomised, double-blind, placebo- and positive-controlled ECG assessment studies in healthy subjects.

10.1 Mechanism of Action

Buprenorphine is a partial agonist at the mu- opioid receptor and the ORL-1 (nociceptin) receptor. Buprenorphine is also an antagonist at the kappa and delta opioid receptors. Buprenorphine has a high affinity for mu-receptors, therefore reducing the binding ability, and thus the activity, of other opioids on these receptors. Buprenorphine's activity in opioid maintenance treatment is attributed to its slowly reversible link with the mu-opioid receptors in the brain, which prolongs activity at the receptor, leading to reduced opioid withdrawal symptoms.

Buprenorphine is a kappa-receptor antagonist, but the clinical relevance of this finding has not been established. Like other opioid agonists, buprenorphine may produce increases in cerebrospinal fluid pressure, cause altered mental status, mental clouding or amnesia following intravenous administration.

Subjective Effects

Comparison of buprenorphine with full opioid agonists such as methadone suggest that buprenorphine produces typical opioid effects, which are limited by a ceiling effect in the case of buprenorphine.

Buprenorphine opioid agonist ceiling effects were also observed in a double-blind parallel group, dose ranging comparison of single doses of 1, 2, 4, 8, 16 or 32 mg buprenorphine sublingual solution (comparable approximately to 1.5 mg, 3 mg, 6 mg, 12 mg, 24 mg and 48 mg, respectively, of the tablet form), oral methadone (15, 30, 45 or 60 mg) and placebo. The treatments were given in ascending dose order at intervals of at least one week to 16 opioid experienced, non-dependent male subjects. Both drugs produced typical opioid agonist effects. For all measures for which drugs produced an effect, buprenorphine produced a dose-related response but, in each case, there was a dose which produced no further effects. In contrast, the highest dose of methadone (60 mg) always produced the greatest effect.

Physiological Effects

Buprenorphine effects were also assessed in opioid-experienced subjects administered 12 mg sublingually or up to 16 mg by IV injection to examine cardiovascular, respiratory and subjective effects at doses comparable to those used for treatment of opioid dependence.

Compared to placebo, there were no statistically significant differences among any of the treatment conditions for blood pressure, heart rate, respiratory rate, O₂ saturation or skin temperature across time. Systolic blood pressure was higher for the 8 mg buprenorphine IV group than placebo. Minimum and maximum effects were similar across all treatments. Subjects remained responsive to low voice and responded to computer prompts. Some subjects showed irritability, but no other changes were observed.

The respiratory effects of sublingual buprenorphine solution (1, 2, 4, 8, 16 or 32 mg) were compared to those of oral methadone (15, 30, 45 or 60 mg) in non-dependent, opioid experienced healthy male volunteers. In this study, hypoventilation not requiring mechanical intervention was reported more frequently after buprenorphine sublingual solution doses of 4 mg and higher (4 mg solution comparable approximately to a 6 mg tablet dose) than after methadone at the tested doses. Both drugs decreased O₂ saturation to the same degree.

10.2 Pharmacokinetics

Table 6: Overall Mean (SD) Plasma Buprenorphine Pharmacokinetic Parameters Following Treatment with PROBUPHINE Implants

	C _{max} (ng/mL)	T _{max} (hr) ^a	AUC _{0-t}
Day 1 n=9	4.89 (1.110)	12 (9.0, 36)	113.13 (27.737)

Day 1, AUC_{0-t} represents the AUC from Day 1 Hour 0 through Day 2 Hour 36, relative to the time of implantation.

^aMedian (minimum, maximum) reported for T_{max}.

Absorption:

After PROBUPHINE insertion, an initial buprenorphine peak was observed and the median T_{max} occurred at 12 hours after insertion. After the initial buprenorphine peak, the plasma buprenorphine concentrations decreased slowly and steady-state plasma buprenorphine concentrations were reached by approximately Week 4. Mean steady-state plasma buprenorphine concentrations were approximately 0.5 to 1 ng/mL and were maintained for approximately 20 weeks (Week 4 through Week 24) in a 24-week treatment period. At steady state, the buprenorphine concentrations were stable and comparable to the buprenorphine plasma concentration in patients on 8 mg per day of sublingual buprenorphine at steady state.

Distribution:

Buprenorphine is highly lipophilic, which leads to rapid penetration of the blood brain barrier. Buprenorphine is approximately 96% protein bound, primarily to alpha and beta globulin.

Metabolism:

Buprenorphine undergoes both N-dealkylation to norbuprenorphine and glucuronidation. The N-dealkylation pathway is mediated primarily by the CYP3A4. Norbuprenorphine, the major metabolite, can further undergo glucuronidation. Norbuprenorphine has been found to bind to opioid receptors in vitro; however, it has not been studied clinically for opioid-like activity.

Elimination:

Buprenorphine is essentially eliminated in the feces by biliary excretion of the glucuroconjugated metabolites (approximately 70%), the rest being eliminated in the urine. In feces, almost all of the buprenorphine and norbuprenorphine were free (buprenorphine, 33% free and 5% conjugated; norbuprenorphine, 21% free and 2% conjugated). In urine, most of buprenorphine and norbuprenorphine were conjugated (buprenorphine, 1% free and 9.4% conjugated; norbuprenorphine, 2.7% free and 11% conjugated).

Special Populations and ConditionsHepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of implanted buprenorphine product, such as PROBUPHINE, has not been studied.

The disposition of buprenorphine was determined in a pharmacokinetics study after administering a 2.0/0.5 mg buprenorphine/naloxone sublingual tablet in subjects with varied degrees of hepatic impairment as indicated by their Child-Pugh score. The disposition of buprenorphine in patients with hepatic impairment was compared to disposition in subjects with normal hepatic function. In subjects with mild hepatic impairment, the changes in mean C_{max} , AUC_{0-last} , and half-life values of buprenorphine were not clinically significant. For subjects with moderate and severe hepatic impairment, mean C_{max} , AUC_{0-last} , and half-life values of buprenorphine were increased (see **CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION**).

11 STORAGE, STABILITY AND DISPOSAL

Store PROBUPHINE at 15°C to 30°C.

Store PROBUPHINE with adequate security and accountability, and out of reach and sight of children. Disposal of PROBUPHINE implants should be in keeping with recommendations governing the disposal of pharmaceutical biohazardous waste.

12 SPECIAL HANDLING INSTRUCTIONS

Handle with adequate security and accountability.

PART II: SCIENTIFIC INFORMATION

13. PHARMACEUTICAL INFORMATION

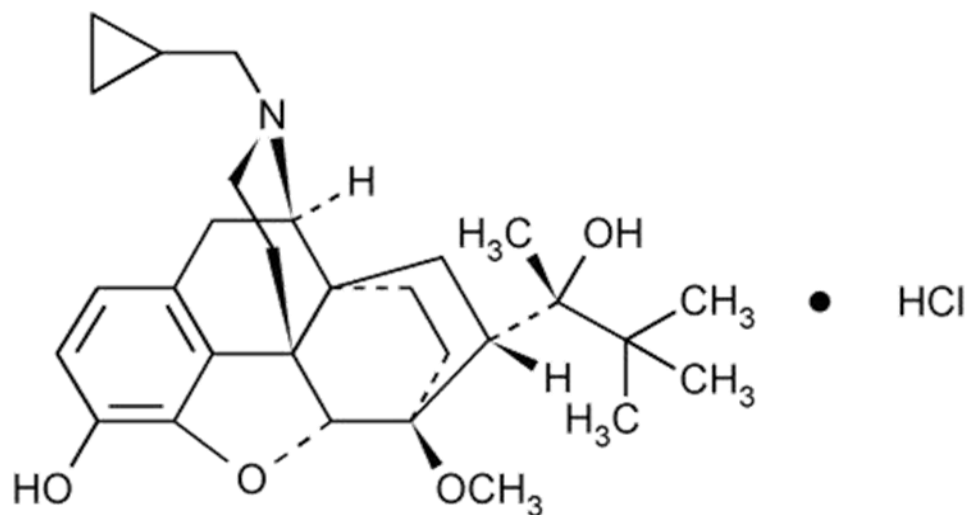
Drug Substance

Proper name: buprenorphine hydrochloride (HCl)

Chemical name: 6,14-Ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)- α - (1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-3-hydroxy-6- methoxy- α -methyl, hydrochloride,[5 α 7 α (S)].

Molecular formula and molecular mass: $C_{29}H_{41}NO_4 \cdot HCl$ and the molecular weight is 504.10 g/mol.

Structural formula:



Physicochemical properties: Buprenorphine is an odorless white, or almost white, substance which crystallizes from various organic solvents. It is usually crystalline and exhibits distinct X-ray powder patterns. Slightly soluble in water. Freely soluble in methanol. Very slightly soluble in acetone and isopropyl alcohol. Practically insoluble, or insoluble in ethyl acetate and tetrahydrofuran.

14. CLINICAL TRIALS

Trial Design and Study Demographics

The efficacy of PROBUPHINE was assessed in a 6-month, phase 3, double-blind, active-controlled study (Study PRO-814; Table 7):

Table 7: Characteristics of PROBUPHINE pivotal clinical trial PRO-814

Trial design	Treatment Groups ^a	Study subjects (n)	Duration
Randomized, double-blind, double-dummy multi-center, Active-comparator control	PROBUPHINE ^a	84	24 weeks
	SL buprenorphine	89	

SL = sublingual.

^a N = total number enrolled (Intent-to-Treat group).

Study 814 was conducted in clinical settings under the care of one or more physicians specializing in dependence medicine and/or psychiatry. The study enrolled male and female adults aged 18-65 who met the DSM-IV-TR definition for current opioid dependence and satisfied other protocol-specified inclusion and exclusion criteria.

This study was conducted in a patient population already at a steady maintenance dose of buprenorphine prior to enrolment, i.e. who had received 8 mg or less of sublingual buprenorphine over the last 90 days.

Table 8 provides demographics, including age, gender, and race for study 814.

Table 8: Summary of Demographic and Baseline Characteristics for Study PRO-814 (Intent-to-Treat Population)

	PRO-814	
	PROBUPHINE	SL BPN
Number of subjects	84	89
Age (mean [SD])	38 (11.0)	39 (10.8)
Age 18-35 (%) ^a	49.4%	50.6%
Male (%)	59.8	58.4
White (%)	94.3	95.5
Black (%)	3.4	2.2
Addiction diagnosis in last 5 years (%)	48.8	56.2

SD = standard deviation; SL BPN = sublingual buprenorphine.

^a Age category of 18-35 was selected based on approximate study median age values.

Study Results

Study PRO-814

The primary efficacy variable for study PRO-814 was the responder rate, where a responder was defined as a subject with no more than 2 of 6 months with any evidence of illicit opioid use (based on a composite of both urine toxicology testing results and self-report results). A total of 10 urine samples (4 random and 6 scheduled) were collected over 6 months. For the primary efficacy variable, a test of non-inferiority of PROBUPHINE versus the active control SL buprenorphine (PROBUPHINE - SL BPN) was conducted using a 20% delta margin.

Table 9 presents the proportion of responders in the intent-to-treat (ITT) population. In this analysis, the proportion of responders was 87.6% in the SL buprenorphine group and 96.4% in the PROBUPHINE group. The 2-sided 95% confidence interval (CI) (0.009, 0.167) of the proportion difference (PROBUPHINE – SL buprenorphine) was well above the predefined successful margin for noninferiority. Table 9 also presents a description the proportion of patients with no evidence of illicit opioid in their urine samples using 2 different imputation methods.

Table 9: Proportion (%) of responders and proportion of patients with no evidence of illicit opioid use based on a composite of both urine analysis and self-report

	PROBUPHINE (N=84)	SL BPN (N=89)	Proportion difference (95% CI) (PROBUPHINE - SL BPN)
Responders ^a	96.4	87.6	8.8 (0.9, 16.7) p=0.034 ^c
Patients with no evidence of illicit opioids ^a	78.6	64.0	14.6 (1.3, 27.9) p=0.034
Patients with no evidence of illicit opioids ^b	60.7	49.4	11.3 (-3.4, 26) p=0.13622

a: Missing samples considered positive for illicit opioid

b: Missing samples or use of rescue medication considered positive for illicit opioid

c: Based on the Chi-Square test for superiority claim

Abbreviations: CI, Confidence Interval; SL BPN Sublingual Buprenorphine

Two additional studies in patients who were new entrants to buprenorphine treatment suggested that PROBUPHINE should not be used in patients who are new entrants to buprenorphine treatment or who have not achieved and sustained prolonged clinical stability on low doses of a transmucosal buprenorphine-containing product, i.e., doses of no more than 8 mg per day.

15. NON-CLINICAL TOXICOLOGY

General Toxicology

In a 10-month chronic toxicity study in dogs, each animal was implanted with 24 EVA placebo implants or 24 PROBUPHINE implants containing nominally 82-90 mg of buprenorphine each; an additional 6 PROBUPHINE implants were implanted in the PROBUPHINE-treated cohort at month 8.5 to maintain plasma exposure at >80% of steady-state levels. Systemic effects noted in this study included transient lethargy and reduced food consumption on Day 1, findings consistent with the pharmacological profile of PROBUPHINE. Slight irritation was noted at the site of implantation with PROBUPHINE implants compared with control placebo (EVA) implants. Two animals with PROBUPHINE implants also showed signs of inflammation and infection however, both conditions were resolved by the end of the study with antibiotic treatment. In addition, at termination time, upon removal from the tissue, 30-40% of implants were broken in the PROBUPHINE-treated group as compared to none in the control placebo (EVA) group and a greater number of the PROBUPHINE-treated animals had areas or patches of incomplete hair growth/alopecia located on the side, flank or chest. The C_{max} and AUC_{0-last} levels in this study were about 13 and 15 times, respectively, the human clinical exposure levels estimated for a maximum 5 PROBUPHINE implant dose extrapolated over a 24-week treatment duration.

Carcinogenicity

Carcinogenicity studies testing PROBUPHINE have not been completed.

Carcinogenicity studies of buprenorphine were conducted in Sprague-Dawley rats and CD-1 mice. Buprenorphine was administered in the diet for 27 months to rats at equivalent doses of 0.6, 5.5, and 56 mg/kg body weight/day (approximately 2, 13, and 99 times the steady state exposure from PROBUPHINE on an AUC basis). A statistically significant dose-related increase in Leydig cell tumors occurred. In an 86-week study in CD-1 mice, buprenorphine was not carcinogenic when administered in the diet at equivalent doses up to 100 mg/kg body weight/day (approximately 53 times the steady state exposure from PROBUPHINE on an AUC basis).

Mutagenicity

Buprenorphine was studied in a series of tests utilizing gene, chromosome, and DNA interactions in both prokaryotic and eukaryotic systems. Results were negative in yeast (*Saccharomyces cerevisiae*) for recombinant, gene convertant, or forward mutations; negative in *Bacillus subtilis* "rec" assay; negative for clastogenicity in Chinese hamster ovary, bone marrow, and spermatogonia cells; and negative in the mouse lymphoma L5178Y assay.

Results were equivocal in the Ames test: negative in studies in two laboratories, but positive for frame shift mutation at a high dose (5 mg/plate) in a third study. Results were positive in the Green-Tweets (*E. coli*) survival test, positive in a DNA synthesis inhibition (DSI) test with testicular tissue from mice, for both in vivo and in vitro incorporation of [³H] thymidine, and positive in unscheduled DNA synthesis test using testicular cells from mice.

Extracts of PROBUPHINE and EVA placebo implants were tested for genotoxicity in the bacterial reverse mutation (Ames), in vitro chromosome aberration, and in vivo mouse micronucleus assays. These studies showed that PROBUPHINE extracts were non-mutagenic in the bacterial reverse mutation assay. In addition, both extracts were non-clastogenic in the in vitro chromosome aberration assay and were non-clastogenic and did not damage the mitotic apparatus in the in vivo mouse bone marrow micronucleus assay.

Impairment of Fertility

Dietary administration of buprenorphine in the rat at dose levels of 500 ppm or greater (equivalent to approximately 47 mg/kg/day or greater; estimated exposure approximately 22 times the highest human daily dose from PROBUPHINE on an AUC basis) produced a reduction in fertility demonstrated by reduced female conception rates. A dietary dose of 100 ppm (equivalent to approximately 10 mg/kg/day; estimated exposure approximately 18 times the recommended human daily from PROBUPHINE on an AUC basis) had no adverse effect on fertility.

Reproduction studies of buprenorphine in rats demonstrated no evidence of impaired fertility at daily oral doses up to 80 mg/kg/day (estimated exposure approximately 100 times the human daily SL dose of 8 mg on a mg/m² basis) or up to 5 mg/kg/day IM or SC (estimated exposure was approximately 12 times the human daily SL dose of 8 mg on a mg/m² basis for IM dosing and 18 times the steady state exposure from PROBUPHINE on an AUC basis for SC dosing).

Tissue Irritation

PROBUPHINE implants were found to be a slight irritant as compared to placebo control implants in a 10-month chronic toxicity study in dogs (see **General Toxicology**) as well as in a 26-week study in rabbits. In addition, there was a marked inflammatory response observed at the implant-tissue interface in 1 of the 3 PROBUPHINE-treated rabbits; however, the significance of this finding is not known.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

^NPROBUPHINE[®]

Buprenorphine hydrochloride, Subdermal implant

Read this carefully before starting PROBUPHINE and each time PROBUPHINE is inserted. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about PROBUPHINE.

Serious Warnings and Precautions

- **Serious complications may happen from the insertion and removal of PROBUPHINE, including:**
 - Damage to nerve or blood vessels in your arm
 - Movement of an implant (migration) or pieces of it into blood vessels and your lungs. This could lead to death.
 - Call your healthcare professional right away if:
 - An implant sticks out of the skin or comes out by itself;
 - You have bleeding or symptoms of infection at the site after insertion or removal, including excessive or worsening itching, pain, irritation, redness, or swelling;
 - You have numbness or weakness in your arm or shortness of breath after the insertion or removal procedure.

- **QTc Prolongation:** medicines containing buprenorphine have been known to cause problems with how a heart beats (abnormal heart rhythm) in some people. Tell your healthcare professional if you have heart problems.

Before you start PROBUPHINE, you should tell your healthcare professional all the medications you are taking as well as changes to or any new medicines you start while you are on PROBUPHINE. Call your healthcare professional right away if you:

- Have pain or discomfort in your chest that was not there before;
- Have changes in how your heart beats (it beats too fast, skips a beat);
- Feel dizzy;
- Feel lightheaded or feel like you are going to pass out.

PROBUPHINE contains buprenorphine and belongs to the opioid class of drugs. The warnings and precautions below apply to all medicines in this class including PROBUPHINE.

- If an implant sticks out or comes out by itself, store it safely to prevent theft and misuse until you can take it to your healthcare professional. Never give your PROBUPHINE to anyone else, because it may harm them or cause death. Selling or giving away PROBUPHINE is against the law. **If a child accidentally comes into contact with an implant, get emergency help right away.**
- Life-threatening breathing problems can happen while using PROBUPHINE, especially if not used as directed. Babies are at risk of life-threatening breathing problems if their mothers take opioids while pregnant or nursing.
 - If you used PROBUPHINE while you were pregnant, whether for short or long periods of time, your baby can suffer life-threatening withdrawal symptoms after birth. This can occur in the days after birth and for up to 4 weeks after delivery. If your baby has any of the following symptoms:
 - Has changes in their breathing (such as weak, difficult or fast breathing);
 - Is not feeding well;
 - Is unusually difficult to comfort;
 - Has tremors (shakiness);
 - Has stiffness;
 - Has increased stools or diarrhea;
 - Is sneezing, yawning, vomiting, or has fever.

Get medical help right away for your baby.

What is PROBUPHINE used for?

PROBUPHINE is:

- Used to treat adults (18 years and older) who are dependent on opioid drugs.
- For adults who are currently taking no more than 8 mg of sublingual buprenorphine.
- A drug program used along with counseling and psychosocial support.

How does PROBUPHINE work?

PROBUPHINE contains buprenorphine. It works in a similar way as other opioid drugs that are used in the treatment of pain. When you stop taking opioid drugs, you can experience withdrawal. PROBUPHINE helps control the symptoms you feel when you are in withdrawal.

What are the ingredients in PROBUPHINE?

Medicinal ingredients: buprenorphine hydrochloride

Non-medicinal ingredients: ethylene vinyl acetate (EVA)

PROBUPHINE comes in the following dosage form:

Subdermal implant: containing 80 mg buprenorphine hydrochloride

Do not use PROBUPHINE if you:

- Are allergic to buprenorphine or to ethylene vinyl acetate (EVA);
- Have trouble breathing or other lung problems;
- Have any conditions that can cause you to have higher than normal carbon dioxide levels in your blood;
- Have any problems with your heart;
- Have low levels of potassium, calcium or magnesium in your blood;
- Have a condition where the small bowel does not work properly (paralytic ileus) or you have severe pain in your abdomen;
- Have serious problems with your liver;
- Suffer from severe central nervous system depression;
- Have or had a brain injury or medical condition that can cause growing pressure inside your head;
- Are at risk for seizures;
- Suffer from or have a history of alcoholism;
- Are under 18 years of age.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take PROBUPHINE. Talk about any health conditions or problems you may have, including if you:

- Have a history of illicit or prescription drug or alcohol abuse;
- Have problems with how your heart beats (abnormal heart rhythm) or you have a close family member with this problem who is taking medicines to treat it;
- Have low blood pressure;
- Have brain problem or recent head injury;
- Have problems with your gallbladder;
- Have adrenal gland problems such as Addison's disease;
- Have liver disease;
- Have heart disease;
- Have trouble breathing, asthma, sleep apnea or other respiratory problems;
- Have past or current depression and are taking medicines to treat it;
- Have severe kidney disease or kidney problems;
- Have severe mental problems or hallucinations (seeing or hearing things that are not really there);

- Have low thyroid hormone levels (hypothyroidism);
- Suffer from chronic or severe constipation;
- Have a curve in your spine that affects your breathing;
- Have problems urinating;
- In men: have an enlarged prostate gland;
- Have a history of keloid formations;
- Have connective tissue disease (such as scleroderma);
- Have a history of recurring MRSA (methicillin resistant Staphylococcus aureus) infections;
- Are going to have a planned surgery;
- Are taking or have taken a Monoamine Oxidase inhibitor (MAOi) (such as moclobemide or selegiline);
- Are pregnant or planning to become pregnant*;
- Are breastfeeding or planning to breastfeed*.

***Pregnancy and breast-feeding:** If you are pregnant or planning to become pregnant or you are breast-feeding or planning to breast-feed your baby your doctor will decide if you should use PROBUPHINE. The ingredient in PROBUPHINE can be transferred to your baby through breast milk, or while still in the womb. It can then cause life-threatening breathing problems in your unborn baby or nursing infant. It should only be used if the potential benefit justifies the potential risk to the fetus or baby. It is important that you discuss this with your healthcare professional.

Other warnings you should know about:

Driving and operating machinery: Before you do tasks, which may require special attention, you should wait until you know how you react to PROBUPHINE. PROBUPHINE can cause:

- Drowsiness;
- Dizziness;
- Lightheadness.

This can usually occur within the first few days after implant insertion.

Implant breakage: It is unlikely that the PROBUPHINE implants will break after their insertion under the skin. A broken implant should not affect how well PROBUPHINE works. If you think that an implant has broken, you should contact your healthcare professional.

Disorder of the adrenal gland: You may develop a disorder of the adrenal gland called adrenal insufficiency. This means that your adrenal gland is not making enough of certain hormones. You may experience symptoms such as:

- Nausea, vomiting;
- Feeling tired, weak or dizzy;
- Decreased appetite.

You may be more likely to have problems with your adrenal gland if you have been taking opioids for longer than one month. Your doctor may do tests, give you medication, and take you off PROBUPHINE.

Serotonin Syndrome: PROBUPHINE can cause serotonin syndrome, a rare but potentially life-threatening condition. It can cause serious changes in how your brain, muscles and digestive system work. You may develop serotonin syndrome if you take certain antidepressants or migraine medications while on PROBUPHINE treatment.

Serotonin syndrome symptoms include:

- Fever, sweating, shivering, diarrhea, nausea, vomiting;
- Muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination;
- Fast heartbeat, changes in blood pressure;
- Confusion, agitation, restlessness, hallucinations, mood changes, unconsciousness, and coma.

Sleep Apnea: Opioids can cause sleep-related breathing disorders including sleep apnea (breathing interruptions during sleep) and sleep-related hypoxemia (low level of oxygen in the blood). Your healthcare professional may decide to remove PROBUPHINE implants.

Treatment of short-term pain: When you are on PROBUPHINE treatment, there may be times when you need to take other medicines, including other opioids, to treat short-term pain. Since PROBUPHINE may make it difficult to get full pain relief from other opioids, you should tell your doctor that you are on PROBUPHINE treatment if they are treating you for pain.

Sexual Function/ Reproduction: Long term use of opioids may lead to a decrease in sex hormone levels. It may also lead to low libido (desire to have sex), erectile dysfunction or being infertile.

Monitoring and Laboratory Tests: Your doctor may do an electrocardiogram (ECG):

- Before you start your treatment.
- After your first dose and at regular intervals during your treatment.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious Drug Interactions

Taking:

- Other opioid medications (used to treat pain);
- Benzodiazepines (used to treat anxiety or sleep disorders);
- Alcohol;
- Or other central nervous system depressants (including street drugs)

while you are on PROBUPHINE treatment can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.

The following may interact with PROBUPHINE:

- Drugs used to treat an irregular heartbeat (such as quinidine, procainamide, disopyramide, flecainide, amiodarone, sotalol, ibutilide, dronedarone and propafenone).
- General anesthetics (used during surgery).
- Benzodiazepines or other drugs used to help you sleep or to help reduce anxiety.
- Drugs used to treat depression and mood disorders (such as nefaxodone, fluoxetine, citalopram, amitriptyline, imipramine and maprotiline).
- Drugs used to treat serious mental or emotional disorders (such as schizophrenia).
- Antipsychotics (such as chlorpromazine, pimozide, haloperidol, droperidol, ziprasidone and risperidone).
- Antihistamines (used to treat allergies).
- Drugs used to treat malaria (such as quinine and chloroquine).
- Drugs used for the treatment or prevention of vomiting (such as aprepitant, domperidone and ondansetron).
- Drugs used to treat muscle spasms and back pain (such as muscle relaxants, like cyclobenzaprine).
- Drugs used to treat viral infections (such as ritonavir, nelfinavir, amprenavir and fosamprenavir).
- Drugs used to treat fungal infections (such as ketoconazole, itraconazole, voriconazole and fluconazole).
- Drugs used to treat bacterial infections (such as troleandomycin, clarithromycin, erythromycin, azithromycin, tacrolimus, moxifloxacin, levofloxacin and ciprofloxacin).
- Drugs used to treat high blood pressure (such as diuretics, also known as “water pills,” verapamil and diltiazem).
- Drugs used to treat migraines (such as triptans).
- Warfarin (such as Coumadin) and other anticoagulants (used for the prevention or treatment of blood

clots).

- Monoxidase inhibitors (MAOi) (such as moclobemide or selegiline).
- Drugs that affect the level of electrolytes in your blood (such as diuretics, laxatives, high doses of corticosteroids and drugs used to reduce the amount of acid made by your stomach).
- Drugs used to treat certain types of cancer (such as sunitinib, nilotinib, ceritinib, vandetabib, arsenic trioxide and vorinostat).
- Drugs used to treat asthma or COPD (such as salmeterol and formoterol).
- Grapefruit juice.

How PROBUPHINE is used:

PROBUPHINE is a drug that comes in the form of an implant. 4 implants are inserted just underneath the skin in the inside of your upper arm.

The implants must only be inserted and removed by a certified Healthcare Professional who has received instruction and training.

Insertion of the implants:

- The implants are soft, flexible, and about the size of a matchstick.
- 4 implants are placed just under the skin on the inside of your upper arm by a minor surgical procedure.
- Your healthcare professional will cover the site where the implants were inserted with 2 bandages:
 - Leave the top bandage on for 24 hours.
 - Keep the smaller, bottom bandage clean, dry, and in place for 3 to 5 days.
- You should apply an ice pack to your arm where the implants were inserted, for 40 minutes every 2 hours for the first 24 hours and as you need.
- Your healthcare professional will fill out and give you a Patient Identification (ID) card. **You need to carry this card with you at all times.** The implants cannot be seen by x-ray or a CT scan. The card identifies that you are using PROBUPHINE and easily identifies where the implants can be found in your arm. It also shows the date your implants were inserted and the date they are to be removed.
- Your healthcare professional will decide how long the PROBUPHINE implants will stay in your arm.
- This card will help you to keep track of the date the implants are to be removed. Schedule an appointment with your healthcare professional to remove the implants on or before the removal date listed on your card.

You should tell your family members that you are using PROBUPHINE to treat your opioid dependence.

Removal of the implants:

Do not try to remove the implants yourself. This could lead to infection and you could go into opioid withdrawal. Ask your healthcare professional how to stop PROBUPHINE treatment.

- The 4 implants are removed by a minor surgical procedure.
- When the implants are removed, the insertion site will be closed with stitches.
- Your healthcare professional will cover the site where the implants were removed with 2 bandages:
 - Leave the top bandage on for 24 hours.
 - Keep the smaller, bottom bandage clean, dry, and in place for 3 to 5 days.
- You should apply an ice pack to your arm where the implants were inserted, for 40 minutes every 2 hours for the first 24 hours and as you need.
- Schedule an appointment with your healthcare professional to remove the stitches.

Interrupting or stopping your treatment: If the implants are not replaced with new ones at the same time they are removed, your doctor will prescribe the same dose of sublingual buprenorphine you were taking

before you started PROBUPHINE treatment. Take it until you can start your treatment again. If you are stopping your treatment, your doctor should monitor you for withdrawal. Your doctor may change your dose of sublingual buprenorphine if needed.

What should I do if PROBUPHINE implant sticks out of my skin or comes out by itself?

IMPORTANT:

- **Never give or allow others to touch or use the implant.** It contains buprenorphine and it can be dangerous.

If a PROBUPHINE implant comes out by itself or sticks out of your skin:

- Remove the implant and put it in a plastic bag. Try not to touch it with your bare hands. If you do, wash your hands right away.
- Cover the area where the implants were inserted with a clean bandage.
- **Store it:**
 - **Safely out of the reach and sight of children. If a child accidentally comes into contact with an implant get emergency help right away.**
 - **In a safe place where it cannot be stolen.**
- Contact your healthcare professional right away and take the implant to them as soon as possible.

Usual dose:

4 implants inserted just under the skin on the inside of your upper arm for up to 6 months.

Overdose:

PROBUPHINE will be implanted by your healthcare professional. It is unlikely that overdose could occur. However, if you notice:

- Your lips turning blue;
- Constriction of the pupils of your eyes (getting smaller);
- You are feeling sleepy or drowsy;
- You have trouble breathing;
- You have a slow heart beat.

Get medical help right away.

If you think you have taken too much PROBUPHINE, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using PROBUPHINE?

These are not all the possible side effects you may feel when taking PROBUPHINE. If you experience any side effects not listed here, contact your healthcare professional.

Side effects of PROBUPHINE include:

- Nausea;
- Vomiting;
- Abdominal pain;
- Constipation;
- Cold and flu like symptoms;
- Urinary tract infection;
- Bronchitis;
- Sinus infections;
- Feeling tired;

- Back pain;
- Headache;
- Toothache;
- Mouth and throat pain;
- Feeling depressed;
- Feeling anxious;
- Decreased sex drive (libido);
- Mild sweating;
- Bruising at the insertion or removal site;
- Scarring around the insertion site.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Get immediate medical help
	Only if severe	In all cases	
COMMON Infection at the insertion or removal site		x	
RARE Respiratory depression: slow, shallow or weak breathing			x
Allergic reactions: rash, hives, swelling of face, lips, tongue or throat, difficulty swallowing or breathing			x
Opioid withdrawal (if PROBUPHINE comes out of your arm or if you stop treatment): shaking, sweating more than normal, feeling hot or cold more than normal, runny nose, watery eyes, goose bumps, diarrhea, vomiting and muscle aches.		x	
Liver problems: your skin or the white part of your eyes turns yellow (jaundice), urine turns dark, stools turn light in color, stomach (abdominal) pain or nausea.		x	
Overdose: hallucinations, confusion, inability to walk normally, slow or weak breathing, extreme sleepiness, floppy muscle/low muscle tone, cold and clammy skin.			x
Complication of the insertion procedure: weakness or numbness in your arm, or shortness of breath			x

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

PROBUPHINE will be stored by your healthcare professional.

Keep any implant that has accidentally come out and been removed from your arm in a plastic bag safely away from the reach and sight of children and in a safe place where it cannot be stolen.

If you want more information about PROBUPHINE:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (<https://health-products.canada.ca/dpd-bdpp/index-eng.jsp>); the manufacturer's website, by emailing medinfo@gudknight.com, or by calling 1-844-483-5636.

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