



Probuphine[®]

(buprenorphine) implant

INSERTION & REMOVAL INSTRUCTION BOOKLET

INDICATIONS & USAGE

Probuphine is indicated for the maintenance treatment of opioid dependence in patients who have achieved and sustained prolonged clinical stability on low-to-moderate doses of a transmucosal buprenorphine-containing product (i.e., doses of no more than 8 mg per day of Subutex or Suboxone sublingual tablet or generic equivalent).

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

Probuphine is not appropriate for new entrants to treatment and patients who have not achieved and sustained prolonged clinical stability, while being maintained on buprenorphine 8 mg per day or less of a Subutex or Suboxone sublingual tablet or generic equivalent.

Under the Drug Addiction and Treatment Act (DATA) codified at 21 United States Code (U.S.C.) 823(g) use of this product in the treatment of opioid dependence is limited to physicians who meet certain qualifying requirements, and who have notified the Secretary of Health and Human Services (HHS) of their intent to prescribe this product for the treatment of opioid dependence and have been assigned a unique identification number that must be included on every prescription.

INSERTION OF PROBUPHINE FOUR IMPLANTS

All Healthcare Providers who intend to prescribe Probuphine must successfully complete a live training program.

All Healthcare Providers 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. Information concerning the insertion and removal procedures can be obtained by calling 1-833-824-0824. The basis for successful use and subsequent removal of Probuphine is a correct and carefully-performed subdermal insertion of the four implants in accordance with the instructions.

As a prerequisite for participating in the live training program leading to certification, the Healthcare Provider 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. Further information is available at www.PROBUPHINEREMS.com or 1-833-824-0824.

Preparation

Prior to inserting Probuphine, carefully read the insertion instructions as well as the full prescribing information. Before insertion of Probuphine, confirm that:

- The patient does not have any contraindications for the use of Probuphine.
- 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 Medication Guide 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

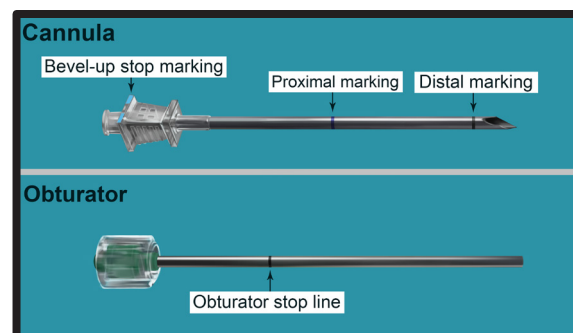
The following equipment is needed for implant insertion:

- 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
- EtOH prep
- Surgical Marker
- Antiseptic solution (e.g., chlorhexidine)
- Local anesthetic (1% lidocaine with epinephrine 1:100,000)
- 5mL syringe with 1.5 inch 25g needle
- Adson single tooth tissue forceps
- #15 blade scalpel
- 1/4 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)
- 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.

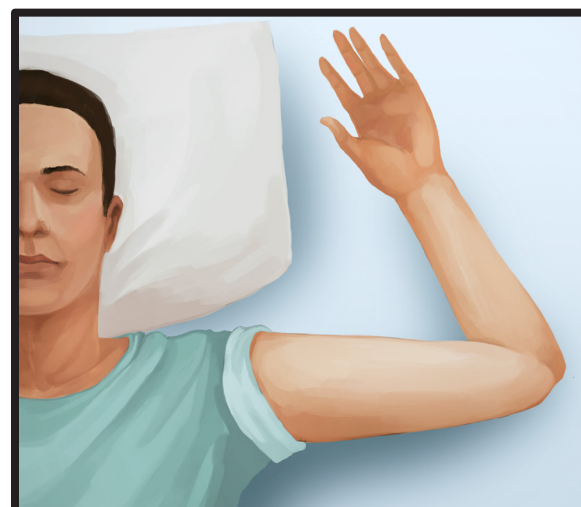
Figure 1



INSERTION PROCEDURE

Figure 2

- 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*).



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*).

Step 3. Clean insertion site with alcohol prep pad prior to marking the skin.

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

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 four 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. When using the 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 away.

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 5mL lidocaine 1% with epinephrine 1:100,000).

Figure 3

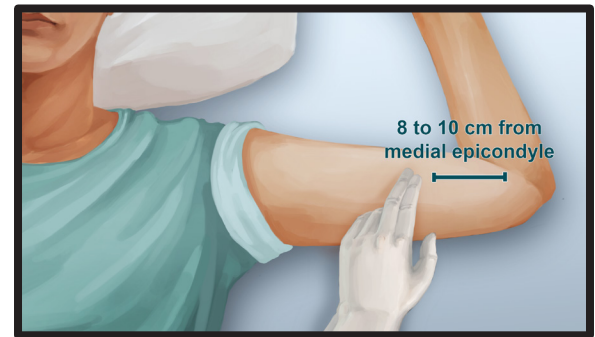
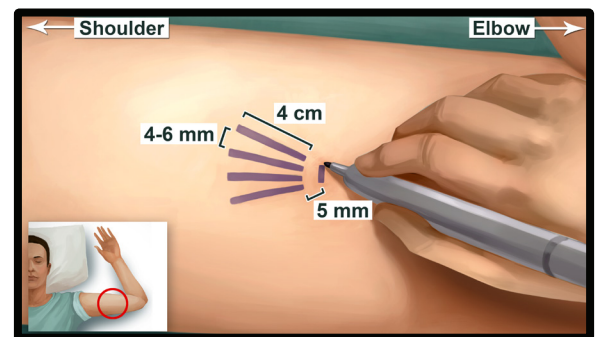


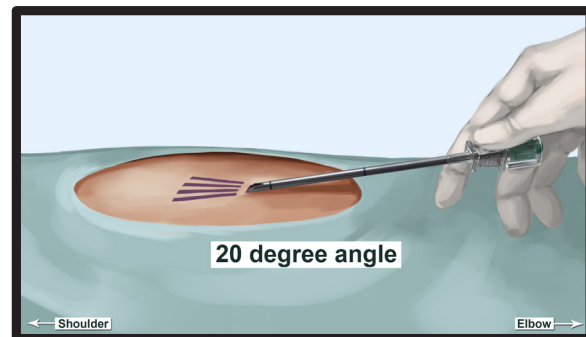
Figure 4



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

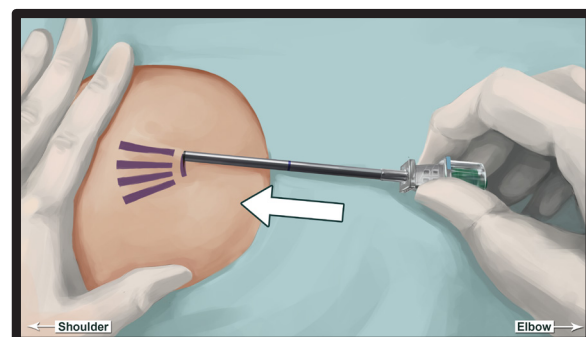
Step 13. Lift the edge of the incision opening with a tooth tissue forceps. While applying counter-traction to the skin, insert only the tip of the applicator at a slight angle (no greater than 20 degrees), into the subdermal space (depth of 3-4 mm below the skin), with the bevel-up stop marking on the cannula facing upwards and visible with the obturator locked fully in to 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 in to the incision (Figure 7).

Figure 6



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

Figure 7

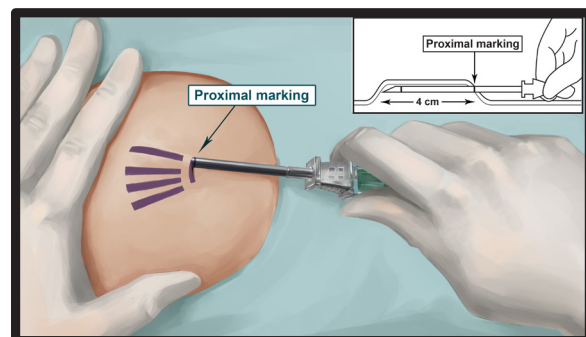
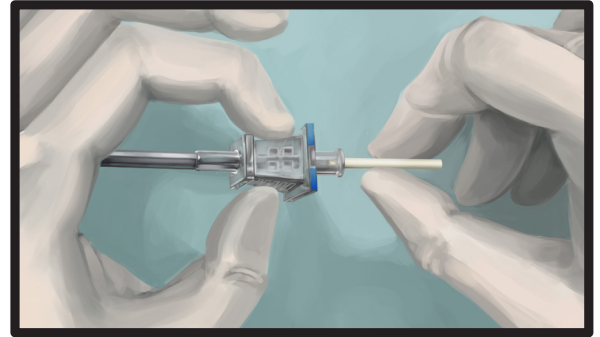


Figure 8



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 9

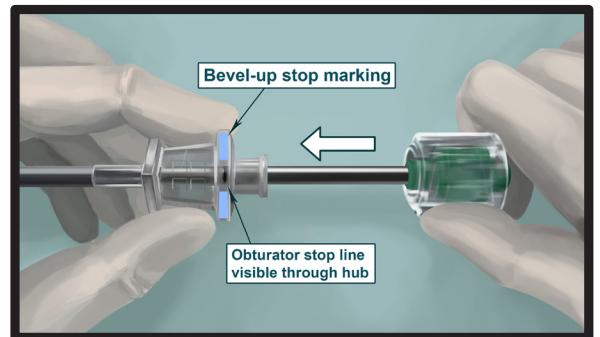


Figure 10

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.

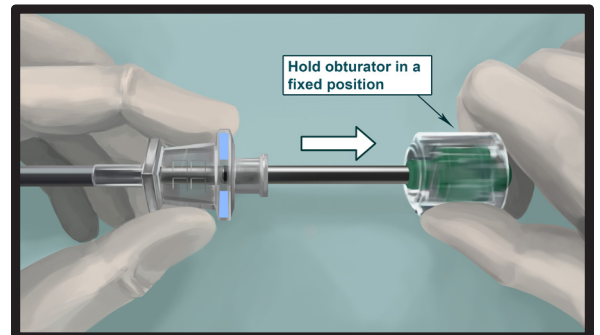


Figure 11

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).

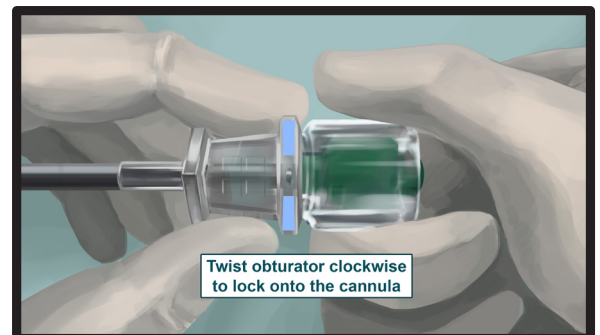
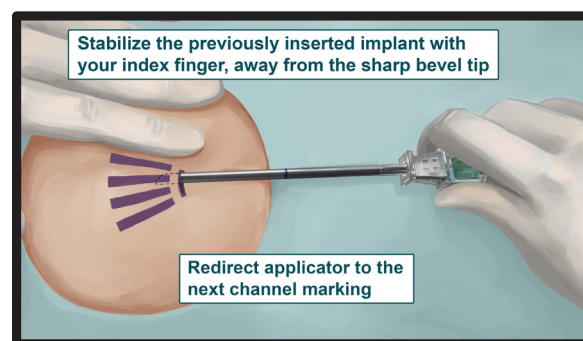


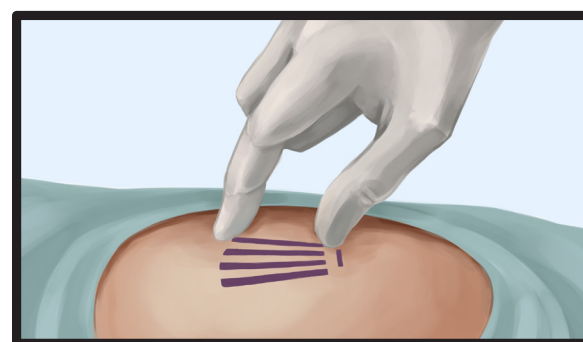
Figure 12

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 16 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.



Step 20. Always verify the presence of each implant by palpation in 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 four implants, or are in doubt of each 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 Probuphine implants are not radiopaque and cannot be seen by X-ray or CT scan. If ultrasound or MRI fail call 1-833-824-0824.

Figure 13



Step 21. Apply pressure to the incision site for approximately five 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 1/4 inch thin adhesive strip (butterfly strip) (for example Steri-strip skin closures).

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 three to five days.

- Step 25.** Complete the PATIENT IDENTIFICATION CARD and give it to the patient to keep. Also, complete the PATIENT CHART STICKER and affix it to the patient medical record or scan or input into electronic medical record. Provide the patient with the Medication Guide and explain proper care of the insertion site.
- Step 26.** The applicator is for single use only. Dispose of the applicator in accordance with the Centers for Disease Control and Prevention guidelines for hazardous waste.
- Step 27.** Instruct the patient to apply an ice pack on his/her arm for 40 minutes every two hours for first 24 hours and as needed.
- Step 28.** Complete the Probuphine REMS Insertion/Removal Log Form.

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

- Schedule two appointments for the patient to return to the office of the inserting healthcare provider as soon as possible and to the office of the prescribing healthcare provider.
- 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 provider 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 (26mm).
- Dispose of the removed implant in keeping with local, state and federal regulations governing the disposal of pharmaceutical biohazardous waste, after measuring.
- Examine incision site for infection. If infected, treat appropriately and determine if 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 techniques described above.
- Call 1-833-824-0824 to obtain a new kit that will include four implants and return instructions for any unused implants.
- The prescribing healthcare provider 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.
- Record the new serial number on the Probuphine REMS Program Insertion/Removal Log form.



PROBUPHINE

REMOVAL PROCEDURE

Before initiating the removal procedure, read the instructions for removal. Identify the location of the implants by consulting the PATIENT IDENTIFICATION CARD and/or THE PATIENT CHART STICKER. The exact location of all implants in the arm (patients will have four implants) should be verified by palpation. If all 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.

Report any event of failure to locate non-palpable implants using MRI or ultrasound, by calling 1-833-824-0824 for company surveillance purposes.

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 providers familiar with this anatomy. A surgical specialist consulted to assist with a difficult removal does not need to be certified in the REMS program.

Preparation

Before removal of Probuphine, confirm that the patient does not have allergies to the antiseptic or the anesthetic that will be used.

IMPLANTS SHOULD BE REMOVED UNDER ASEPTIC CONDITIONS

The following equipment is needed 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
- EtOH prep
- Antiseptic solution (e.g., chlorhexidine)
- Surgical marker
- Local anesthetic (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 alcohol prep pad prior to marking the skin.

Step 4. Mark the location of the implants with the 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*).

Step 5. Put on sterile gloves.

Step 6. Using the 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. When 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 away.

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 5-7mL lidocaine 1% with epinephrine 1:100,000). Separate needle 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-tooth tissue forceps and separate the tissues above and below the first visualized implant using an iris scissors or a 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 14

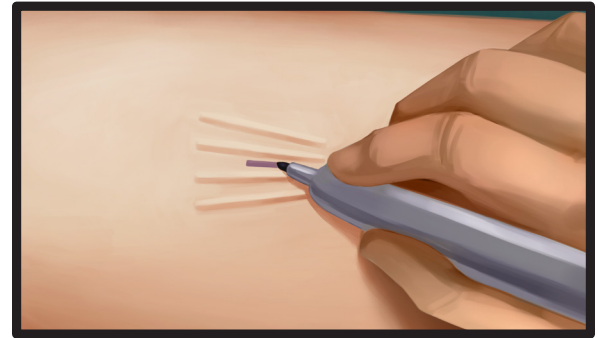


Figure 15

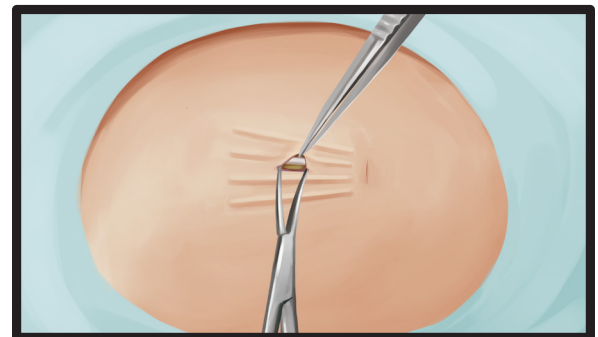
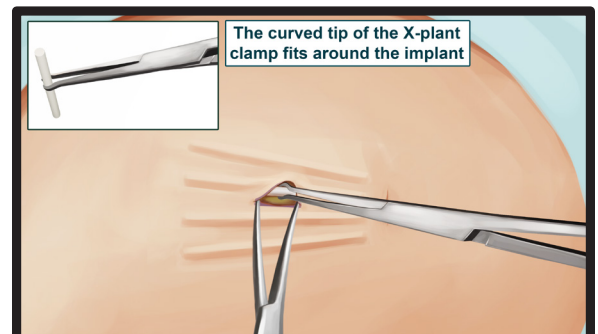


Figure 16





- 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 each implant confirm that the entire implant, which is 26mm long, has been removed by measuring its length. If a partial implant (less than 26 mm) is removed, the remaining piece 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 four 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 five 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 three to five 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 two hours for first 24 hours and as needed.
- Step 20.** Schedule an appointment for the sutures to be removed.
- Step 21.** The removed implant, contains a significant amount of residual buprenorphine. It must be handled with adequate security, accountability, and proper disposal, per facility procedure for a Scheduled III drug product, and per applicable federal, state, and local regulations. Disposal of Probuphine implants should also be in keeping with local, state, and federal regulations governing the disposal of pharmaceutical biohazardous waste.

Step 22. Complete the Probuphine REMS Program Insertion/
Removal Log Form.

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 of 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.

Continuation of Therapy: Subsequent Insertion of Probuphine in the Contralateral Arm

There is no clinical experience with insertion of Probuphine beyond a single insertion in each arm. If continued treatment is desired at the end of the first six- month treatment cycle, Probuphine implants may be replaced by new implants at the time of removal 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 be maintained on their previous dose of transmucosal buprenorphine (i.e., the dose from which they were transferred to Probuphine treatment) prior to additional Probuphine treatment.

There is no experience with inserting additional implants into other sites in the arm to recommend an approach to a second insertion into a previously-used arm. Neither re-insertion into previously-used administration sites, nor into sites other than the upper arm, have been studied. 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. After one insertion in each arm, additional cycles of treatment should only be considered if the potential benefits of continuing PROBUPHINE outweigh the potential risks of additional insertion and removal procedures, taking into account the experience of the health care provider with PROBUPHINE procedures and related procedures, and the clinical need of the patient for ongoing treatment with subdermal medication. In most cases, patients should be transitioned back to a transmucosal buprenorphine-containing product for continued treatment.

