

# **PROBUPHINE<sup>®</sup> (BUPRENORPHINE) IMPLANT**

## **PROBUPHINE REMS PROGRAM LIVE TRAINING: LECTURE SLIDES**

# Agenda

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- Introduction
- Probuphine (buprenorphine) implant
- Probuphine REMS Program
  - Probuphine REMS: Goal
  - Probuphine REMS: Mitigating Risks
  - Closed Distribution
  - HCPs Who Prescribe Probuphine
  - HCPs Who Perform Surgical Procedures
  - REMS Recertification Requirements
  - Roles/Responsibilities of Pharmacies
  - Patient Counseling and Resources
- Probuphine Insertion/Removal Procedures
  - Step by Step Insertion/Removal Procedures
  - Continuation of Therapy
  - Mitigating Complications and Risks of Insertion/Removal Procedures
- REMS Materials

# **Probuphine<sup>®</sup> (Buprenorphine) Implant**

# Probuphine (Buprenorphine) Implant



- Probuphine is an implantable formulation of buprenorphine
- Each implant contains 74.2 mg of buprenorphine, uniformly distributed throughout the ethylene vinyl acetate co-polymer (EVA) matrix
- 4 Probuphine implants are inserted subdermally in the upper arm in an office procedure and deliver continuous, stable blood levels of buprenorphine for **6 months**
- Probuphine surgical procedures can only be performed by HCPs who have successfully completed the live training program
- Dosage will be 4 Probuphine implants
- Supplied in a kit containing 4 individually packaged implants and sterile disposable applicator

# Probuphine Indication

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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 Subutex or Suboxone sublingual tablet or generic equivalent.

# Probuphine REMS Program

# REMS

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- A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration (FDA) to ensure the benefits of a drug outweigh its risks
- **Fedson Inc.** has worked with the FDA to develop the Probuphine REMS Program

# Probuphine REMS: Goal

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The goal of the Probuphine REMS is to mitigate the risk of complications of migration, protrusion, expulsion and nerve damage associated with the insertion and removal of Probuphine and the risks of accidental overdose, misuse and abuse by:

- a) Ensuring that healthcare providers are educated on the following:
  - a) proper insertion and removal of Probuphine
  - b) risk of complications of migration, protrusion, expulsion and nerve damage associated with the insertion and removal of Probuphine
  - c) risks of accidental overdose, misuse and abuse if an implant comes out or protrudes from the skin
- b) Ensuring pharmacies are certified and only provide Probuphine to healthcare settings in which a certified prescriber is practicing
- c) Informing patients about the risks of complications of migration, protrusion, expulsion and nerve damage associated with insertion and removal, as well as the risks of accidental overdose, misuse and abuse if an implant comes out or protrudes from the skin



# Probuphine REMS: Mitigating Risks

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- Mitigating complications associated with the insertion/removal
  - Inform HCPs on risks associated with the insertion/removal
    - Migration
    - Protrusion
    - Expulsion
    - Nerve damage
  - HCPs will be educated, trained and demonstrate proficiency on:
    - Proper and aseptic insertion/removal procedures
    - Appropriate care of the incision/removal site
    - Managing complications associated with insertion/removal
    - Referring patients when there are concerns regarding the incision/insertion site if HCP is certified as an HCP Who Prescribes

# Probuphine REMS: Mitigating Risks

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- Mitigating the risks of accidental overdose, misuse, and abuse if Probuphine comes out or protrudes from the skin
  - Buprenorphine in Probuphine can be extracted and then abused in a manner similar to other opioids
  - Probuphine should not be dispensed to patients for self-administration
  - Patients must be informed of the risks of:
    - Insertion/removal of Probuphine
    - Accidental overdose, misuse, and abuse, if an implant comes out or protrudes from the skin
    - The importance of appropriate wound care

# Closed Distribution

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- Certification Pathways:
  - HCP Who Prescribes
  - HCP Who Performs Probuphine Surgical Procedures
  - HCP Who Prescribes and Performs Surgical Procedures (Dual)
  - Pharmacies
- Probuphine will be distributed through a Closed Distribution System ONLY to certified pharmacies and HCPs Who Prescribe Probuphine and either
  - Are certified to insert or
  - Make arrangements for a certified HCP Who Performs Probuphine Surgical Procedures to perform the procedure
- Certification is required to perform the insertion and removal procedures

# HCPs who Prescribe Probuphine: Roles and Responsibility

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- To become certified to prescribe Probuphine in the REMS Program, HCP must:
  1. Review the Prescribing Information for Probuphine, including Instructions for Use.
  2. Take the **Probuphine REMS Program Live Training: Lecture and Practicum**, and successfully complete the **Probuphine REMS Program Knowledge Assessment**.
  3. Enroll in the Probuphine REMS Program by completing the **Probuphine REMS Program Prescriber Enrollment Form**.
- After enrollment, prescriber must:
  - Counsel patients using **What You Need to Know about Probuphine: A Patient's Guide**, and give a copy to the patient.
  - Ensure Probuphine surgical procedures are performed in your healthcare setting by a HCP who is certified to insert Probuphine. Patients must be monitored to ensure Probuphine is removed by a HCP who is certified to insert.
  - Maintain documentation of insertion/removal of Probuphine in each patient's medical record. Use the **Probuphine REMS Program Insertion/Removal Log** or another method/system (e.g., electronic health record) specific to HCP's practice.
  - Not loan or sell Probuphine.
  - Not transfer Probuphine except to certified inserters.

# HCPs who Perform Probuphine Surgical Procedures: Roles and Responsibility

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- To become certified to perform Probuphine surgical procedures in the Probuphine REMS Program, HCPs must:
  1. Review the Prescribing Information for Probuphine, including Instructions for Use.
  2. Have performed a surgical procedure in the 3 months immediately preceding enrollment in the Probuphine REMS Program.
  3. Take the **Probuphine REMS Program Live Training: Lecture and Practicum**, and successfully complete the **Probuphine REMS Program Knowledge Assessment**, as well as meet the **Probuphine REMS Program Criteria for Procedural Competency**.
  4. Enroll in the Probuphine REMS Program by completing the **Probuphine REMS Program HCP Who Performs Probuphine Surgical Procedures Enrollment Form** or **Probuphine REMS Program HCP Dual Enrollment Form**.

# HCPs who Perform Probuphine Surgical Procedures: Roles and Responsibility (cont.)

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- After enrollment, HCPs who perform Probuphine surgical procedures must:
  - Ensure that the facility where the procedure is being conducted has appropriate equipment to perform insertions/removals of Probuphine. Patients must be monitored to ensure Probuphine is removed by a HCP who is certified to insert.
  - Counsel each patient on risks associated with Probuphine and provide each patient a copy of the **Probuphine Medication Guide**.
  - Document the insertion/removal of Probuphine, using the **Probuphine REMS Program Insertion/Removal Log** or by other method/system (e.g., electronic health record) specific to HCP's practice.
  - Assess the patient's need for removal of Probuphine during treatment.
  - Recertify in the Probuphine REMS Program annually.

# HCPs who Perform Probuphine Surgical Procedures: Roles and Responsibility (cont.)

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- Insert and remove Probuphine only in healthcare settings in which a certified prescriber is practicing.
- Maintain records of the insertion and removal of Probuphine, including the date, serial number, number of implants inserted, name of the healthcare provider performing the procedure, and anatomical location of each implant for each patient by using the **Probuphine REMS Program Insertion/Removal Log** or by other method/system (e.g., electronic health record) specific to HCP's practice.
- Comply with audits by Fedson Inc., or third party, to ensure that all processes and procedures are in place and are being followed.

# Probuphine

## REMS Recertification Requirements

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- Only HCPs who perform Probuphine surgical procedures or Dual need to be recertified every 12 months, by obtaining the ***Probuphine REMS Program Healthcare Provider Who Performs Probuphine Surgical Procedures Recertification Form*** from the Probuphine REMS Program website and submitting via Fax provided in the form.
  - Notification 60 days prior to recertification deadline.
- HCPs who perform Probuphine surgical procedures will be subject to audit if they do not have operating privileges and choose to recertify by attesting to completing ten **successful** procedures in the past year.
  - Successful insertion and removal procedures exclude attempted procedures that require assistance of other surgical specialties for completion.
  - Removal procedures assisted by imaging prior to completion can be included, provided the HCP successfully removal all implants identified by imaging without involving additional surgical consultations.
- HCPs who perform Probuphine surgical procedures may use the **Probuphine REMS Program Procedure Record for Recertification** (found in the Probuphine REMS Program website) to document each Insertion/Removal procedure should they be audited



# Probuphine REMS Program Recertification Requirements<sup>1</sup>

I have <u>current</u> operating privileges at hospitals or out-patient surgical centers: (Select the “yes” or “no” Column below that Applies)		
If YES ↓	If NO ↓	
I must review the <b>Probuphine REMS Program Surgical Procedures Recertification Video</b> found on the Probuphine REMS website <b>every year</b> .	Number of Probuphine procedures in the past 12 months (Select the Row that applies)	
	≥10  Performed 10 or more successful <sup>2</sup> procedures (comprised of at least five insertions and five removals) →	I must review the <b>Probuphine REMS Program Surgical Procedures Recertification Video</b> found on the Probuphine REMS website <b>every year</b> .  I understand that I should keep documentation of all successfully completed procedures on the <b>Probuphine REMS Program Procedure Record for Recertification</b> or another record of my choosing - which must be provided to the Probuphine REMS Program if I am audited.
	<10  Performed less than 10 successful <sup>2</sup> procedures (comprised of at least five implantations and five removals) →	I must (annually): <ul style="list-style-type: none"> <li>• attend a <b>Probuphine REMS Program Live Training: Lecture and Practicum</b> session</li> <li>• successfully complete the <b>Probuphine REMS Program Knowledge Assessment</b> test</li> <li>• meet the <b>Probuphine REMS Program Criteria for Procedural Competency</b></li> </ul>

<sup>1</sup> Denotes the minimal requirements. Healthcare Providers should utilize the tools provided for recertification as needed to ensure proper insertion/ removal of Probuphine is conducted in accordance with the Probuphine REMS Program.

<sup>2</sup> “Successful” implantation and removal procedures exclude attempted procedures that require assistance of other surgical specialties for completion. Removal procedures assisted by imaging studies prior to completion can be included, provided that the healthcare provider successfully removes all implants identified by imaging without involving additional surgical consultants.

# Roles/Responsibilities of Pharmacies

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Probuphine (buprenorphine) is only available through the Probuphine Risk Evaluation and Mitigation Strategy (REMS) Program, a restricted distribution program. To become certified to dispense Probuphine, pharmacies must:

- Designate an authorized representative.
- Complete and sign this ***Probuphine REMS Program Pharmacy Enrollment Form*** and submit it to the REMS Program.
- Agree to train all relevant staff involved in dispensing that Probuphine is only dispensed in healthcare settings in which a certified prescriber is practicing.
- Agree to verify that Probuphine is dispensed directly to healthcare settings in which a certified prescriber is practicing. **Probuphine must not be dispensed directly to a patient.**

# REMS Materials

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- **List of Materials for HCPs:**

- Probuphine REMS Program Healthcare Provider Who Prescribes Enrollment Form
- Probuphine REMS Program Healthcare Provider Who Performs Probuphine Surgical Procedures Enrollment Form
- Probuphine REMS Program Healthcare Provider Dual Enrollment Form
- Probuphine REMS Program Healthcare Provider Who Performs Probuphine Surgical Procedures Recertification Form
- What You Need to Know About Probuphine: A Patient's Guide
- Probuphine REMS Program Insertion/Removal Log
- Probuphine REMS Program Procedure Record for Recertification
- Probuphine REMS Program Live Training: Lecture and Practicum
- Probuphine REMS Program Surgical Procedures Recertification Video
- Probuphine REMS Program Knowledge Assessment
- Probuphine REMS Program Criteria for Procedural Competency
- Probuphine Medication Guide
- Probuphine Instructions for Use
- Probuphine REMS Website

- **List of Materials for Pharmacies**

- Probuphine REMS Program Pharmacy Enrollment Form

# REMS Materials (cont.)

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- **List of Materials for Patients**
  - What You Need to Know about Probuphine: A Patient's Guide
  - Probuphine Medication Guide
  - Probuphine REMS Website

# Patient Counseling and Resources

# Patient Counseling

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- All HCPs will provide patient counseling
- Two resources will be utilized for patient counseling:
  - **What You Need to Know about Probuphine : A Patient's Guide**
  - **Probuphine Medication Guide**
- HCPs who Prescribe Probuphine will counsel patients using **What You Need to Know about Probuphine: A Patient's Guide** prior to prescribing it for patients
- HCPs who perform Probuphine surgical procedures will counsel patients using the **Probuphine Medication Guide** prior to each insertion procedure (The Medication Guide is part of each Probuphine Insertion Kit)

# Patient Education on Potential Risks: Insertion and Removal of Probuphine

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- There are risks associated with Probuphine implants, including:
  - An implant may come out by itself, or an end of an implant may begin sticking out of the skin.
  - An implant may move (migrate). Probuphine or pieces of it can move into the blood vessels and to your lung, and could lead to death.
  - Injury or damage to nerves or blood vessels could occur.
  - Implants may be difficult to find if:
    - They are too deep for a doctor to feel
    - A patient tries to move them around under the skin
    - A patient has gained a lot of weight since they were inserted
  - Special procedures, tests, or a referral to a specialist may be needed to remove the implants if they are difficult to locate.

# Patient Education on Potential Risks: Insertion and Removal of Probuphine

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- Following are some common risks associated with any minor surgical procedure:
  - Itching, pain, irritation or redness, swelling, bleeding, or bruising at the insertion site
  - Scarring around the insertion site
- Appropriate care of the incision is important to reduce the risk of complications associated with the insertion and removal of Probuphine
- When to call a HCP right away
  - If the implants come out or an end of an implant starts sticking out of the skin
  - If there are symptoms of infection at the site after insertion or removal, including excessive or worsening itching, pain, irritation, redness or swelling
  - Any numbness or any weakness in the arm after the insertion or removal procedure
  - If there are symptoms suggesting the implant has migrated, such as weakness or numbness in the arm, or shortness of breath



# Patient Education:

## Risk of Accidental Overdose, Abuse, Misuse

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- There is a risk of accidental overdose, abuse and misuse for others if the implants come out and others are exposed to them
- Do not try to remove Probuphine implants yourself
  - Improper removal carries the risk of implant site infection
  - If you remove the implants, this may cause opioid withdrawal syndrome
- If the Probuphine implants come out:
  - Wash your hands if you have touched the Probuphine implants
  - Cover the area where they were inserted with a clean bandage
  - Do not allow others to touch or use the Probuphine implants, since this could be very dangerous
  - Put them in a plastic bag and bring them to your doctor right away
  - Keep the implants in a safe and secure place, away from others, especially children
  - Protect the implants from theft until you can return them to your doctor

# Probuphine Insertion and Removal Procedures

# Insertion and Removal

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- It may be of benefit during the insertion/removal process to have an assistant at all times.

# Probuphine Kit

## Probuphine Kits contain:

- Four Probuphine Implants
- Probuphine Applicator
- Patient ID Card
- Patient Chart Sticker
- Instruction for Use Booklet
- Probuphine Prescribing Information
- Probuphine Medication Guide



NOTE: The Serial Number for the kit is located on the back of the kit, in the bottom left hand corner. The Serial Number should be recorded in the Probuphine REMS Program Insertion/Removal Log for tracking and accountability (including, for example, to track adverse events).

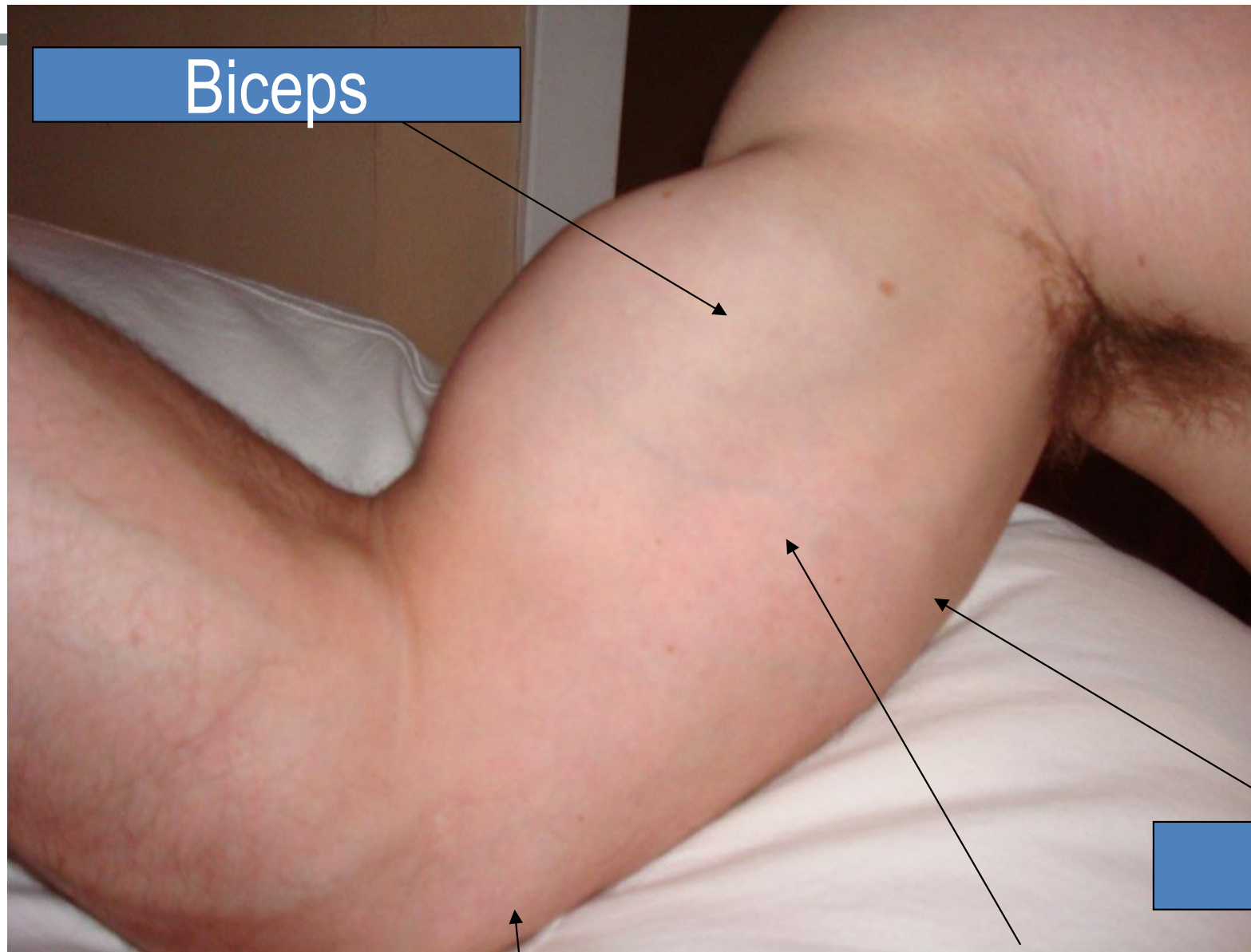
- The only equipment from the kit that are needed for the insertion procedure are the Probuphine implants and the Probuphine Applicator.

# Insertion/Removal Procedure Training Objectives

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- Review anatomy of the brachium
- Insertion Procedure
- Implant Localization
- Removal Procedure
- Avoiding Complications & Important Potential Risks of:
  - Migration, protrusion, expulsion, and nerve damage
  - Insertion/Removal procedures
  - Accidental overdose, misuse, abuse associated if implant expulsion and protrusion occurs
- Care of the Incision

# Brachium



Biceps

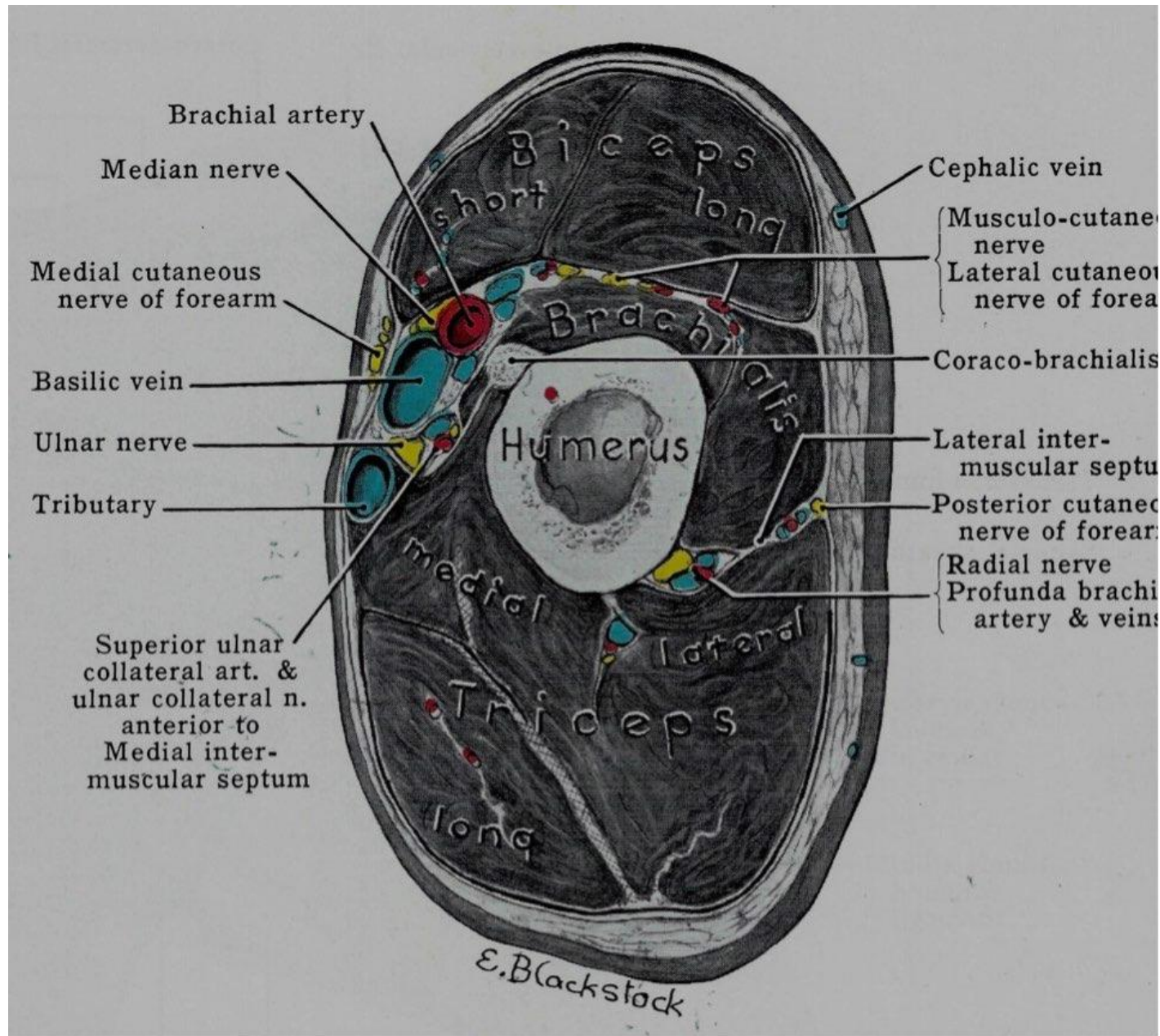
Triceps

Medial epicondyle

Medial Bicipital Groove

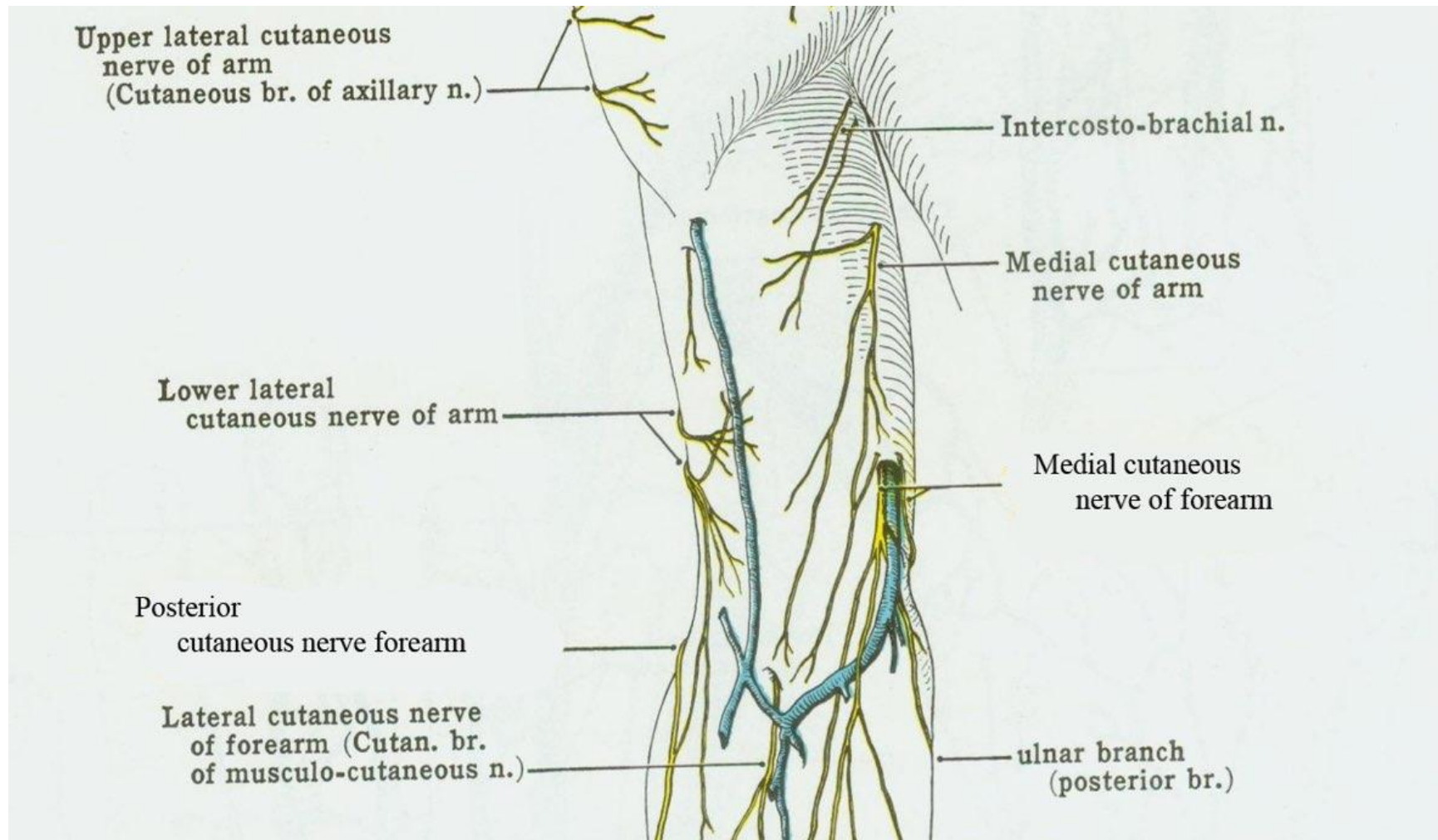


# Brachium Cross Section



It is important to avoid the neurovascular bundle that underlies the subcutaneous plane.

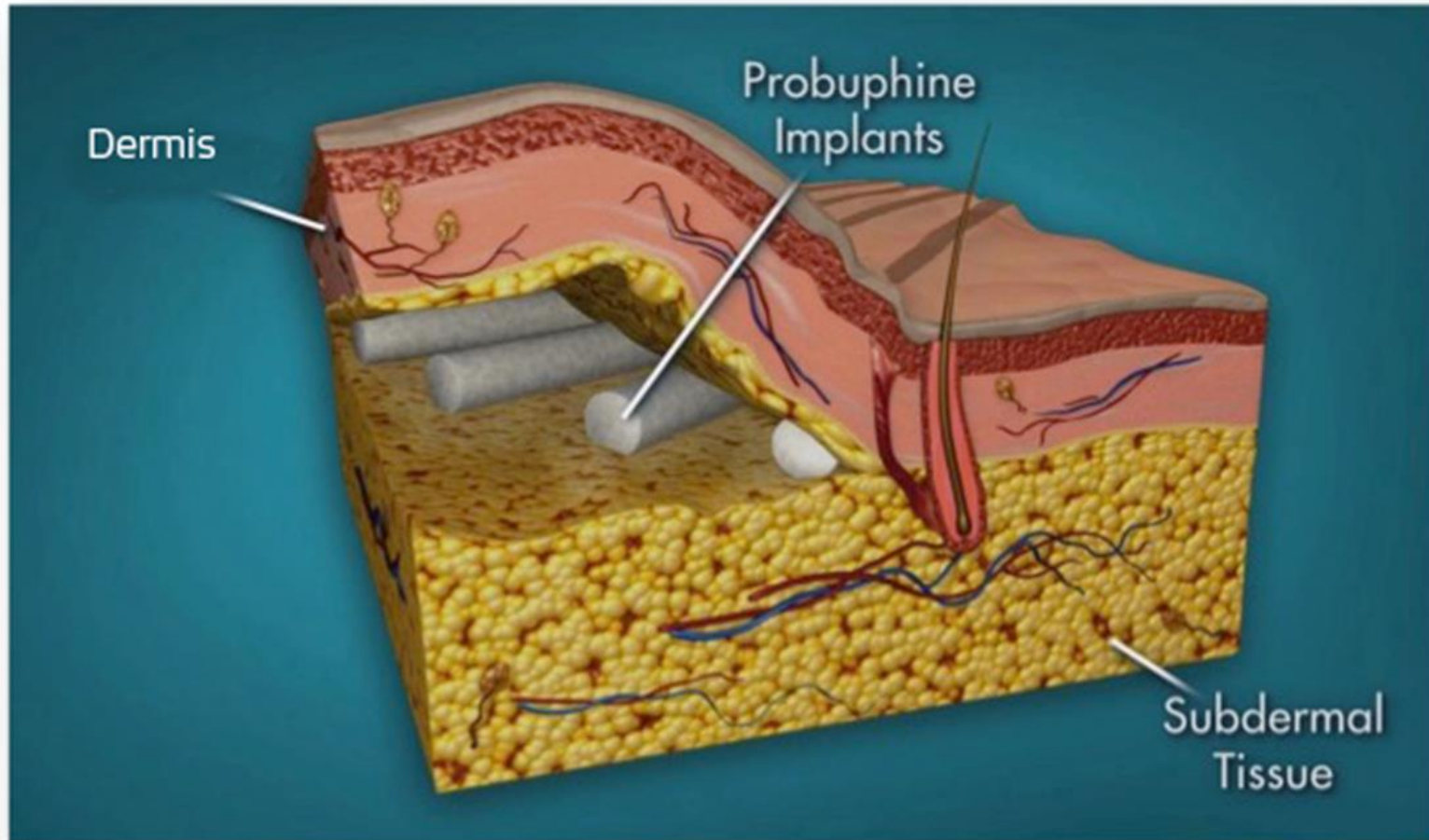
# Brachium Cutaneous Nerves



The medial cutaneous nerve lies within the subcutaneous tissue.



# Correct Subdermal Insertion



Careful and correct subdermal insertion is one of the keys to successful placement and will facilitate removal.

# Insertion of Probuphine

# Probuphine Insertion Procedure Equipment

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- 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
- 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., Matisol)
- 4 Probuphine implants (*included in the Probuphine Kit*)
- 1 Probuphine disposable applicator (*included in the Probuphine Kit*)

***NOTE: Insertion kits contain all of the equipment, except for exam table, instrument stand, a headlamp, 4 Probuphine implants and 1 Probuphine applicator. Insertion kits are available from Fedson Inc. upon request***

# Probuphine Applicator



## Cannula

Bevel-up stop marking

Proximal marking

Distal marking



## Obturator

Obturator stop line

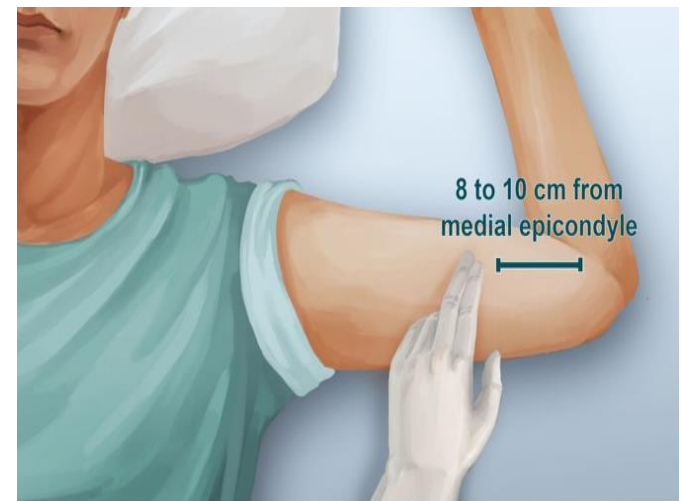


# Insertion Procedure

**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.



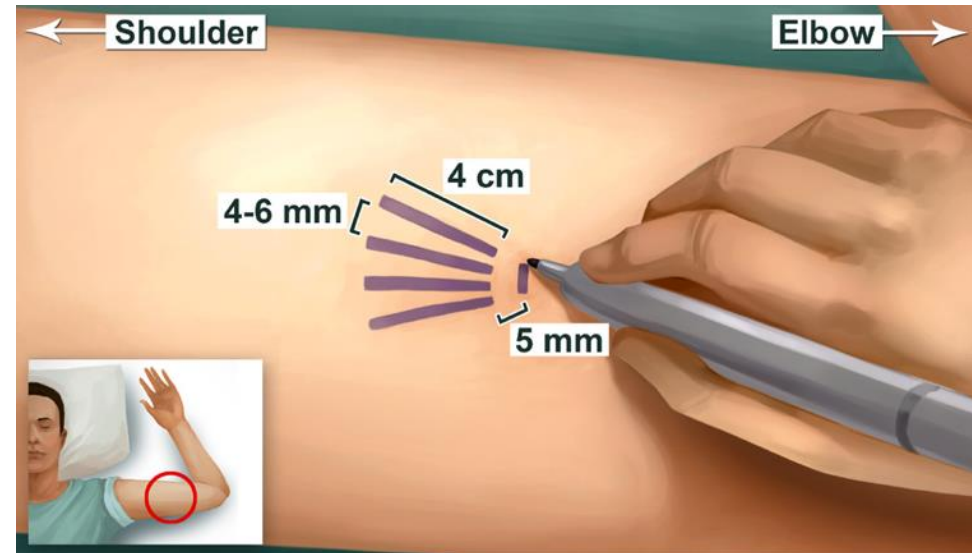
**Step 2.** Identify the insertion site, which is at the inner side of the upper arm about 8-10 cm (3-4 inches) above the medial epicondyle of the humerus in the sulcus between the biceps and triceps muscle. Having the patient flex the biceps muscle may facilitate identification of the site.



# Insertion Procedure

**Step 3.** Clean the 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 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 shape distribution 4-6 mm apart with the fan opening towards the shoulder.

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.

# Insertion Procedure

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**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.



# Insertion Procedure

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**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.



# Insertion Procedure

**Step 13.** Lift the edge of the incision opening with a 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) in to 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 1)

**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 2). 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 3).

Figure 1

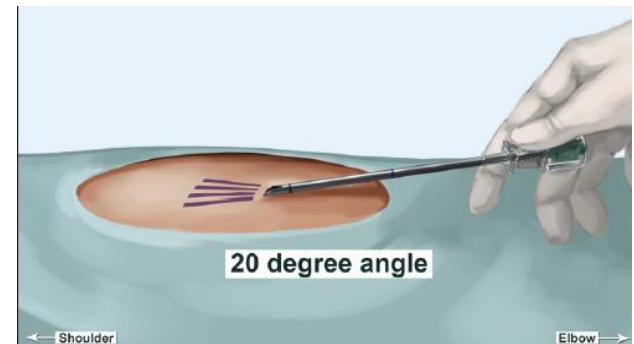


Figure 2

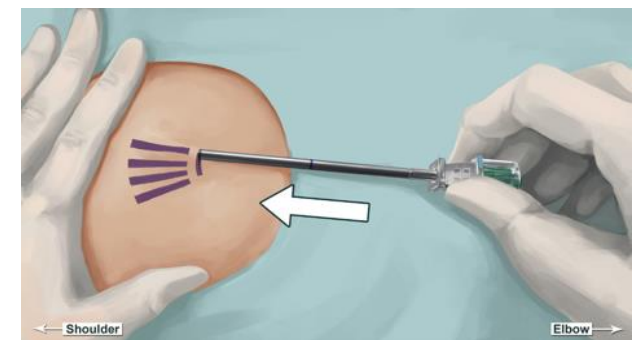
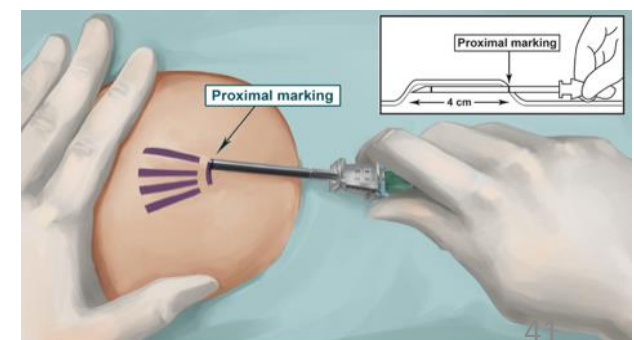


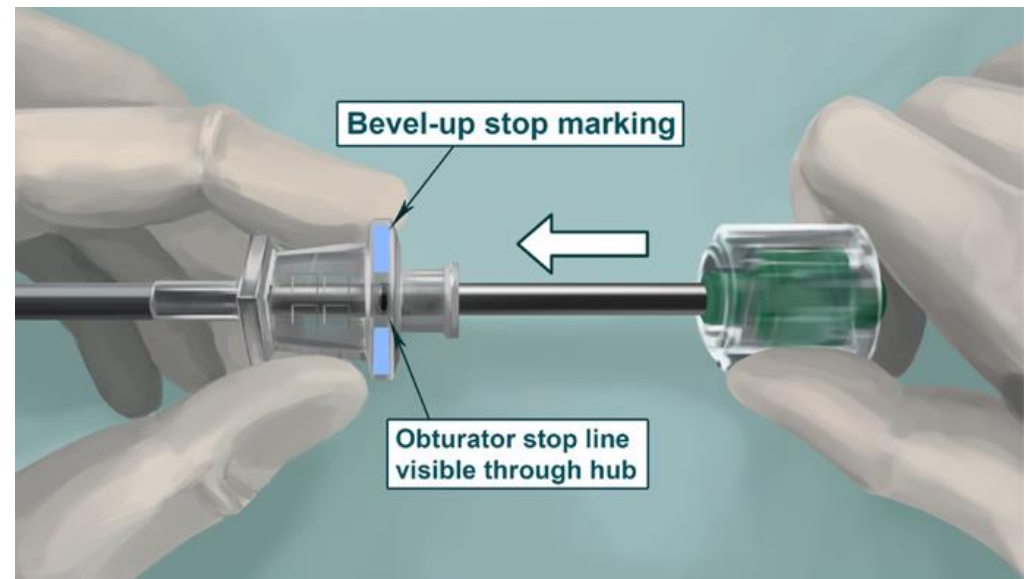
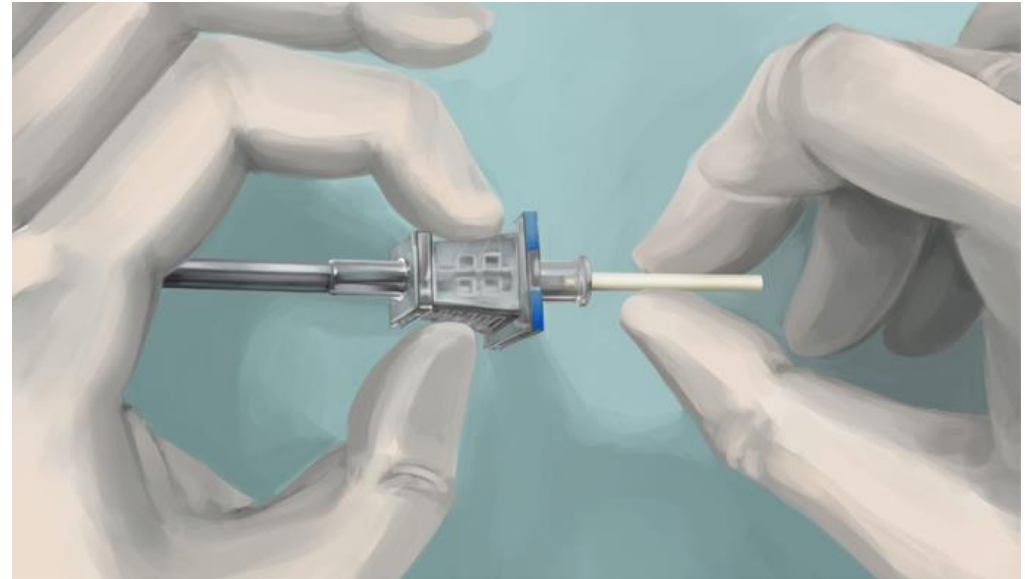
Figure 3



# Insertion Procedure

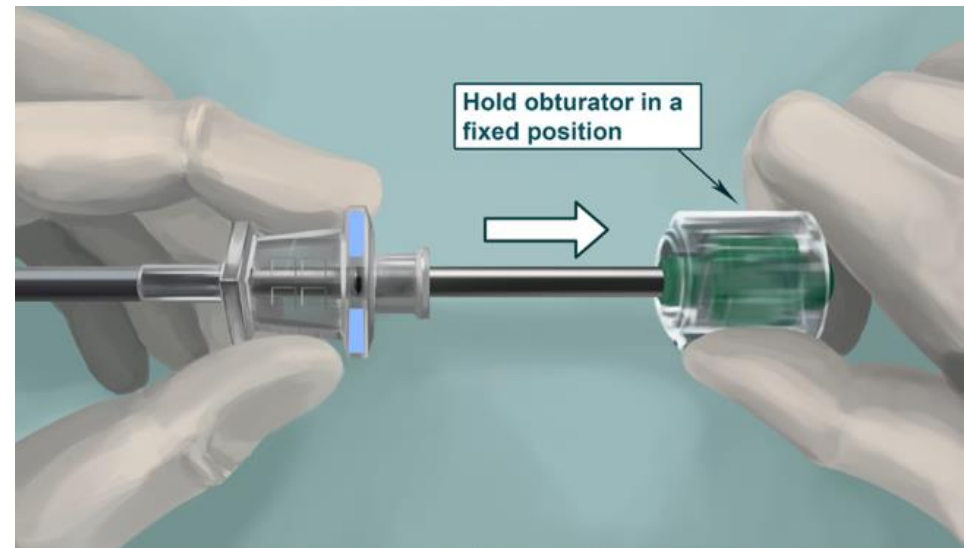
**Step 15.** While holding the cannula in place, unlock the obturator and remove the obturator.

**Step 16.** Insert one implant into the cannula, 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. 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.

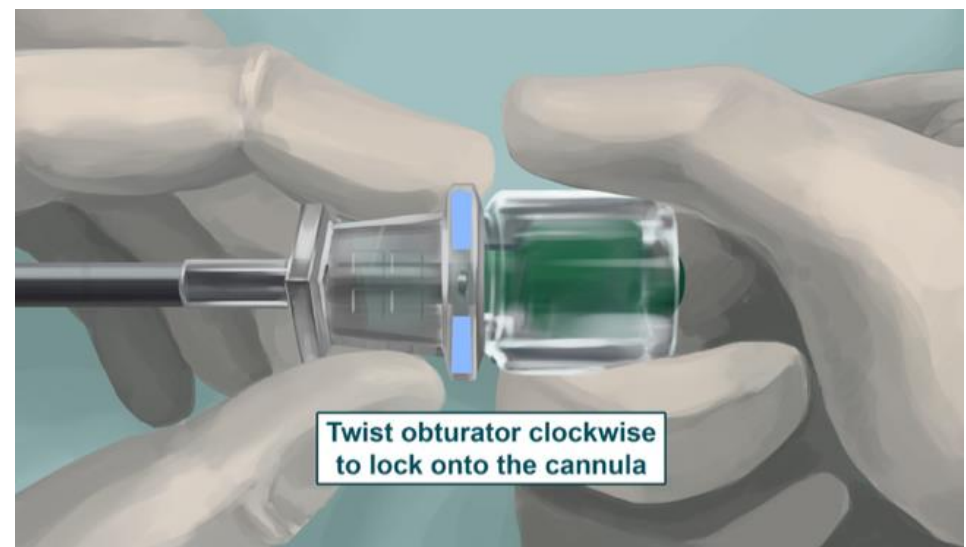


# Insertion Procedure

**Step 17.** While holding the obturator fixed in place on the arm, retract the cannula along the obturator, leaving the implant in place. 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.



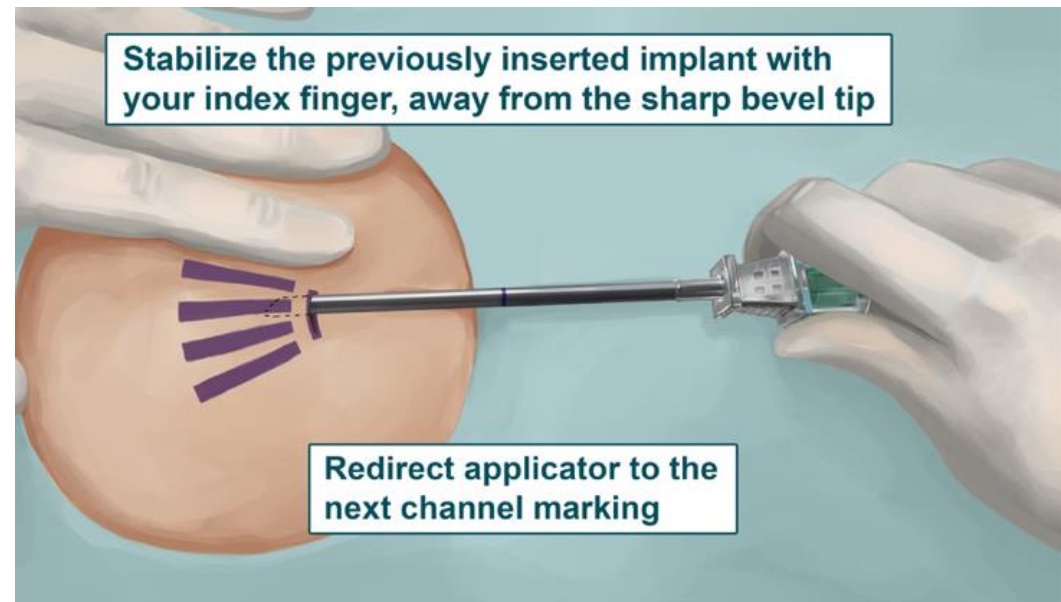
**Step 18.** Withdraw the cannula until the hub is flush with the obturator, and then twist the obturator clockwise to lock onto the cannula. Retract the applicator, bevel-up, until the distal marking of the cannula is visualized at the incision opening (the sharp tip remaining in the subcutaneous space).



# Insertion Procedure

**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.

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.



# Insertion Procedure

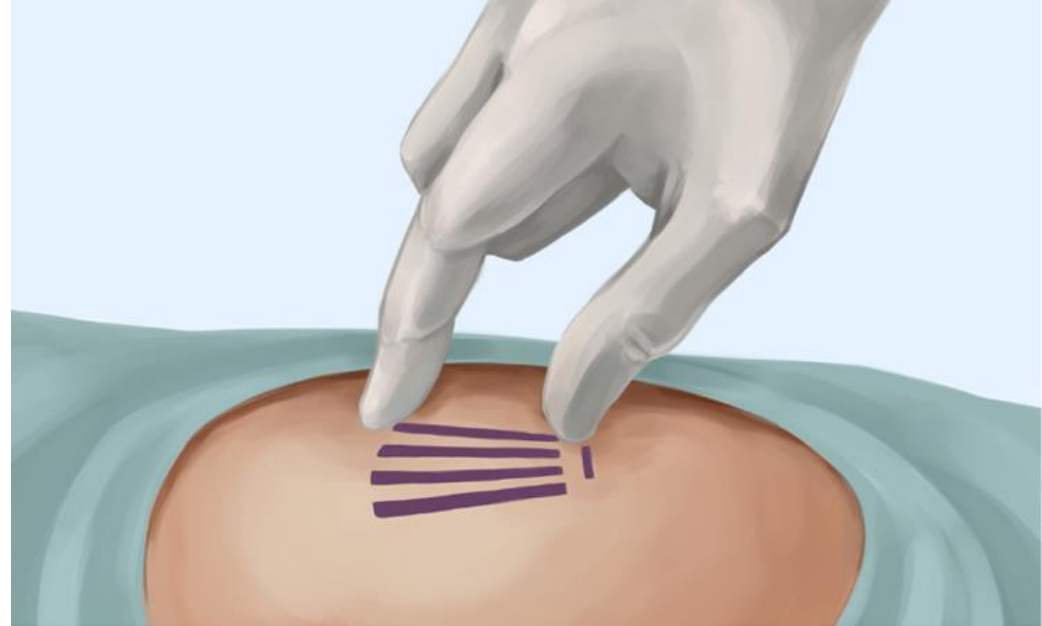
**Step 20.** Always verify the presence of each implant in the patient's arm by palpation of the arm immediately after the insertion. By palpating both ends of the implant, you should be able to confirm the presence of the 26 mm implant.

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 (10MHz 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 and MRI fail, please call 1-833-824-0824





# Insertion Procedure

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**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.

# Insertion Procedure

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**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 Program Insertion/Removal Log Form**.

- The Serial Number from the Probuphine Kit should be included for tracking and accountability purposes (for example, to track AEs) in the Probuphine REMS Program Insertion/Removal Log Form and include the log in the patient's chart – or by using another method or system (e.g. electronic health record)
- Record the procedure in the **Probuphine REMS Program Procedure Record for Recertification** to document each insertion/removal procedure should they be audited

# Localization of Probuphine Implants



# Probuphine Localization

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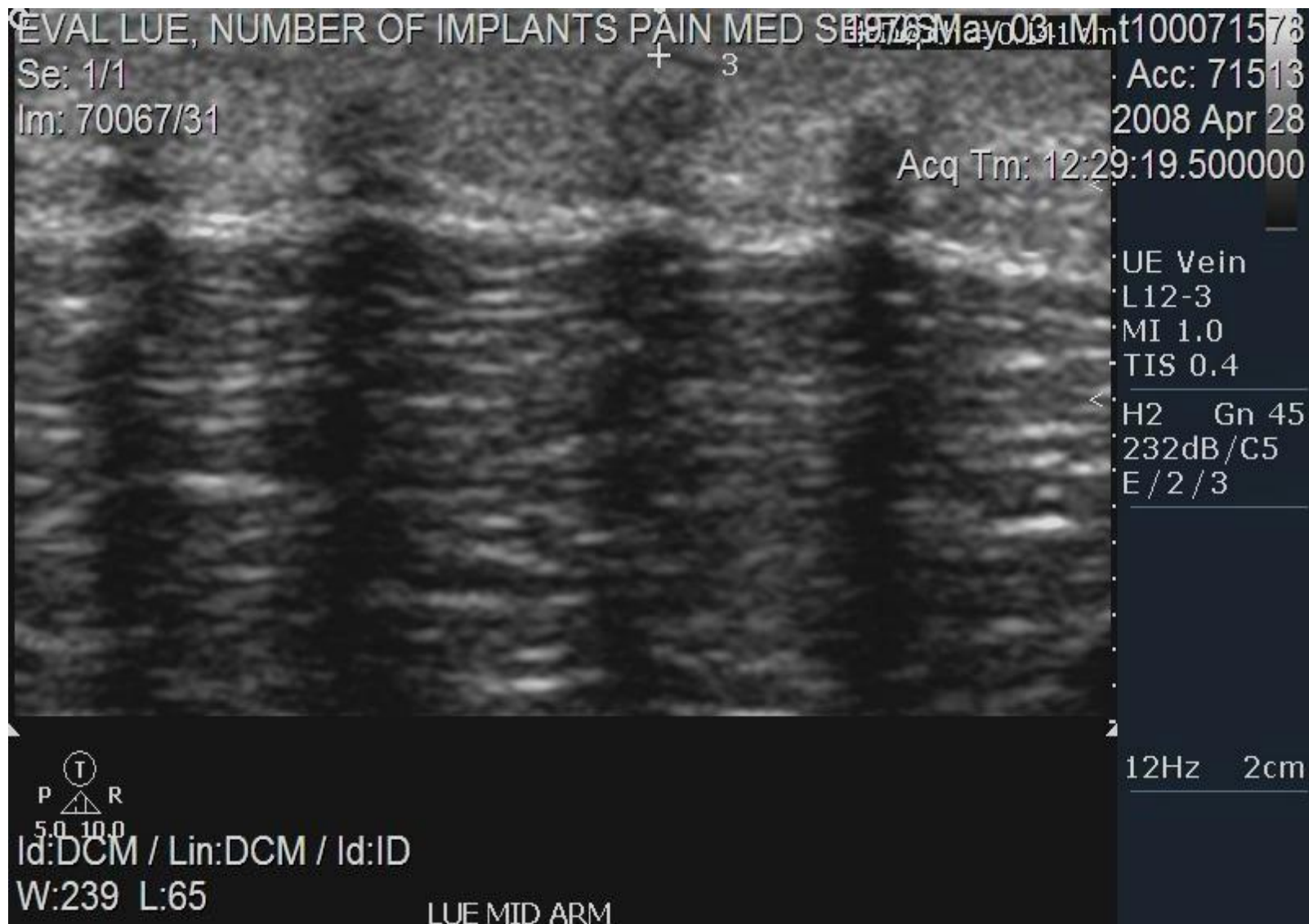
- Identify the location of the implants by consulting the PATIENT IDENTIFICATION CARD and/or THE PATIENT CHART STICKER.
  - The ***Probuphine REMS Program Insertion/Removal Log*** in the patient's chart or electronic health record can also be used to identify the location of the implants.
- The exact location of all implants in the arm (patients will have four implants) should be verified by palpation.

# Inability to Palpate Probuphine

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- 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 Image (MRI)
- Note that Probuphine implants are not radiopaque and cannot be seen by X-ray or CT scan. Call 1-833-824-0824 if you are unable to locate non-palpable implants using MRI or ultrasound.
- After localization of a non-palpable implant, removal should be performed under ultrasound guidance.
  - If implant(s) or implant fragment(s) are not removed during removal attempt, the patient should undergo imaging for localization as soon as feasible.
  - 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.
- Exploratory surgery without knowledge of the exact location of all implants is strongly discouraged.

# Probuphine Four Implants: Ultrasound Transverse Image



# Removal of Probuphine

# Probuphine Removal

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- Indications for removal
  - At the end of 6 months of treatment
  - Patient request
  - Medical indication
- Before initiating the removal procedure, read the instructions for removal.
- Counsel patients about removal procedure.
- **Do not attempt removal until the location of the implants have been verified by palpation or imaging.**
- Confirm no allergies to antiseptic and anesthetic.
- Prepare aseptic conditions.
- Allow 45 minutes for removals.

# Probuphine Removal Procedure Equipment

- An examination table for the patient to lie on
- Instrument stand and Sterile tray
- Adequate lighting (e.g., headlamp)
- Sterile fenestrated drape
- 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
- 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 bandages
- 3-inch pressure bandages
- Sutures (e.g., 4-0 Prolene™ with an FS-2 cutting needle)
  - May be absorbable

***NOTE: Removal kits contain all of the equipment, except for exam table, instrument stand, and a headlamp  
Removal kits are available from Fedson Inc. upon request***

# Removal Procedure

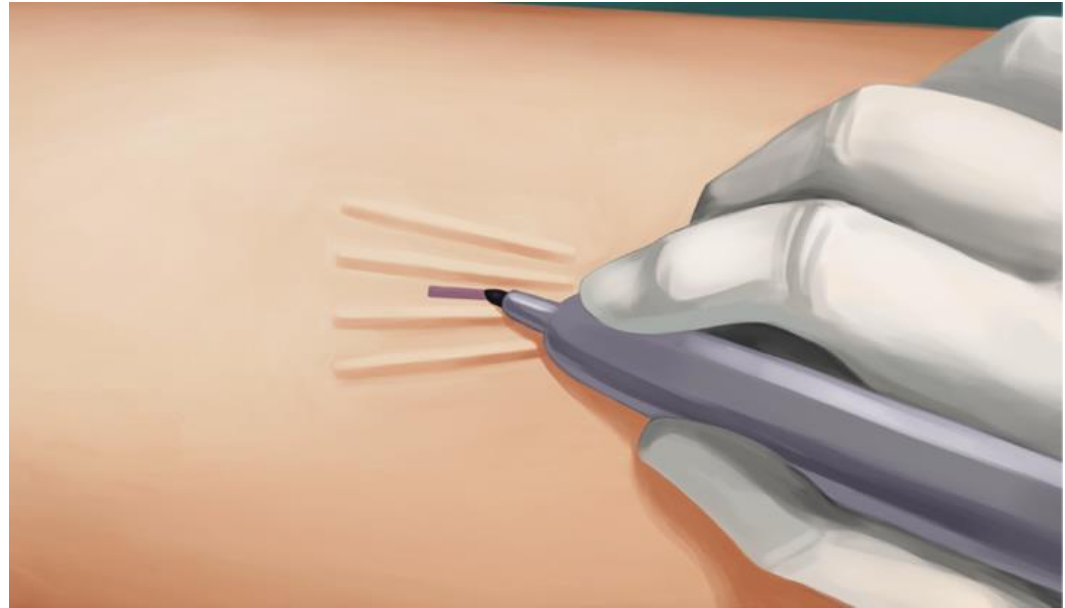
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**Step 1.** Have the patient lie on his/her back, with the implant arm flexed at the elbow and externally rotated, so that the hand is positioned next to the head.

**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 a surgical marker. In addition, mark the location of the incision, parallel to the axis of the arm, between the second and third implants.



# Removal Procedure

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**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. 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.

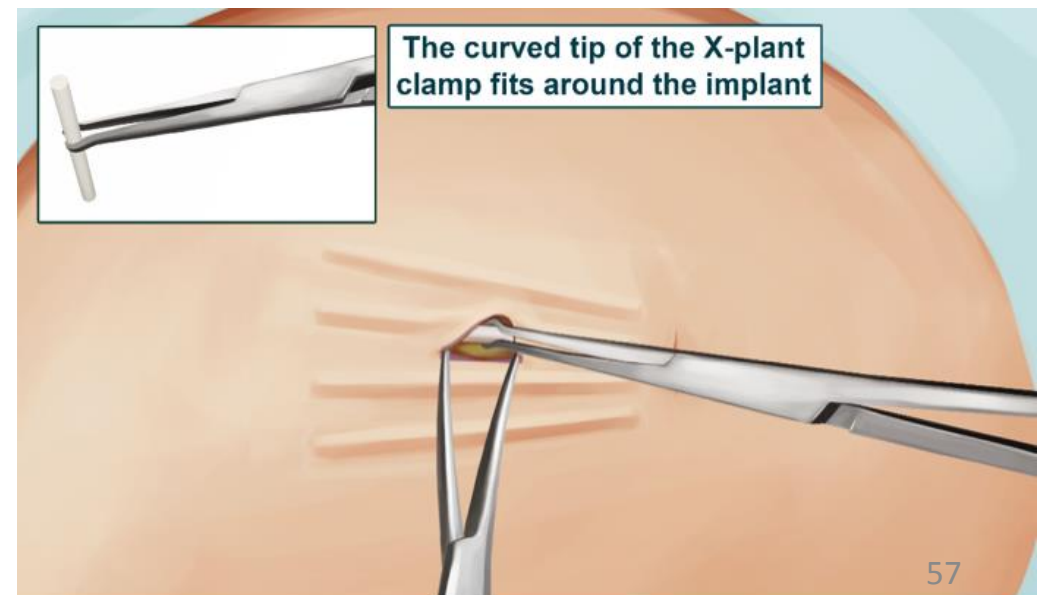
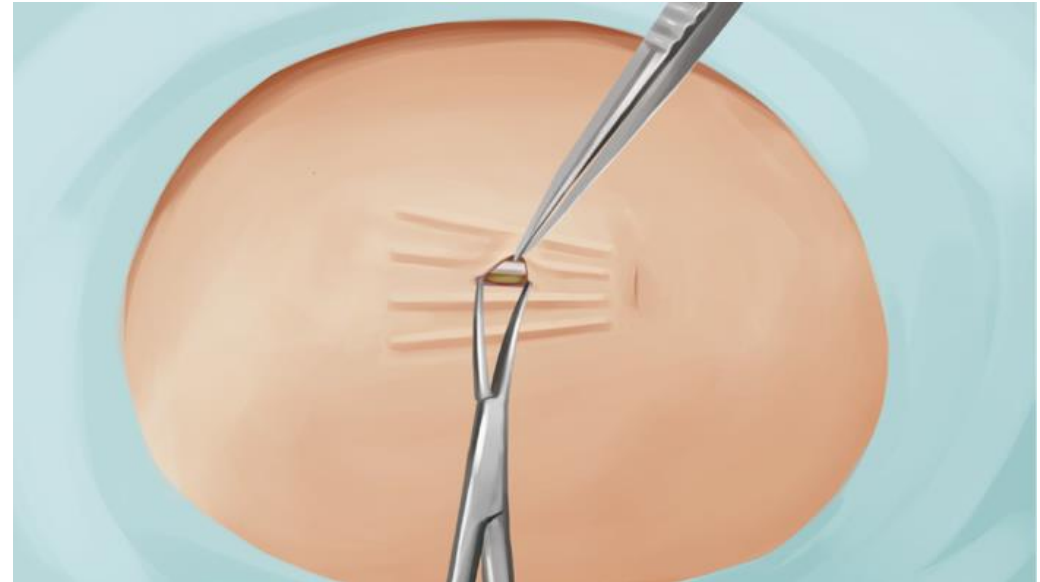
**Step 9.** Anesthetize the incision site and the subcutaneous space containing the implants (for example, by injecting 5-7 mL lidocaine 1% with epinephrine 1:100,000). Separate needles may be used for the incision site and the subcutaneous injections. NOTE: Be sure to inject the local anesthetic just 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 arm, between the second and the third implants.



# Removal Procedure

**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 a curved mosquito forceps. 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. 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.







# Removal Procedure

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**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 26 mm 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.

*NOTE: a ruler should be utilized to measure the removed implant*

# Removal Procedure

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**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.

# Removal Procedure

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

**Step 21.** The removed implant, contains a significant amount of residual buprenorphine, and must be handled with adequate security, accountability, and proper disposal, per facility procedure for a Schedule 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.**

# Continuation of Therapy: Subsequent Insertion in the Contralateral Arm

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- 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 in the instructions for use 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.

# Continuation of Therapy: Subsequent Insertion in the Contralateral Arm

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- 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 risk of additional insertion and removal procedures, taking into account the experience of the healthcare 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.

# Mitigating Complications and Risks of Insertion/Removal Procedures



# Mitigation of Complications Associated with Insertion/Removal Procedure

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- There are risks associated with insertion/removal of Probuphine such as:
  - Migration
  - Protrusion
  - Expulsion
  - Nerve damage
- Proper training and education is needed to avoid complications associated with insertion/removal:
  - Ensuring proper aseptic insertion/removal procedures
    - NOTE: HCPs Who perform Probuphine surgical procedure must demonstrate proficiency on proper technique for certification
  - Providing appropriate care of the insertion/removal site and instructions to patients
  - Appropriate management of complications

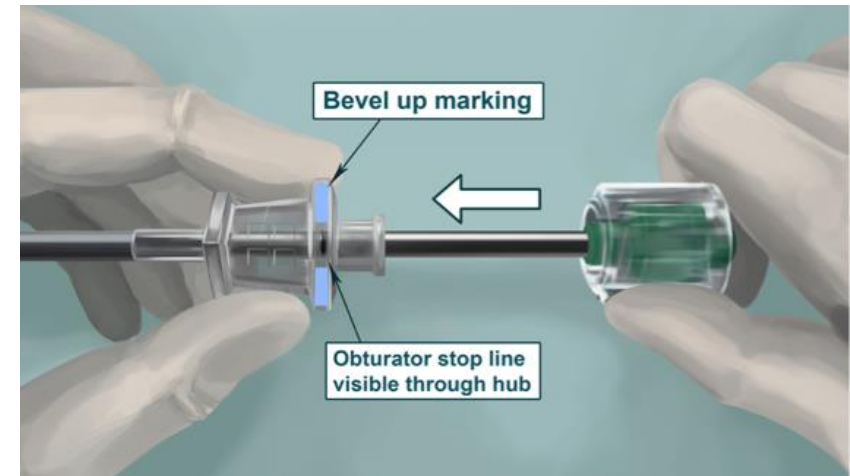
# Prevention of Deep Insertion

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- Insert only the TIP of the applicator, slightly angled no greater than ( $\sim 20^\circ$ ) to prevent neurovascular injury, at a depth of 3-4 mm below the skin.
- Lower the applicator to a horizontal position.
- Gently insert, while lifting the skin (tenting), the applicator until the **proximal marking** just disappears into the incision, without using force.
- Keep the applicator parallel to the surface of the skin.

# Prevention of a Fractured/Bent Implant

- During insertion:
  - Avoid pushing the beyond the bevel-up marking on the cannula
  - Withdraw cannula until hub is flush with obturator, twist the obturator clockwise to lock into the cannula
- During removal:
  - Apply gentle traction with X-plant clamp, use an assistant if needed.
  - Do not grasp the implant with hemostat
- If implant(s) or implant fragment(s) are not removed during a removal attempt, the following steps should be taken:
  - The patient should undergo imaging for localization. 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



# Prevention of Wound Infection

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- Adhere to aseptic technique.
- Prep skin with antiseptic solution (e.g., chlorhexidine) per product guidelines.
- Instruct patient on proper care of the incision.

# Patient Education on Potential Risks: Care of the Incision Instructions

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Explain proper care of the incision to the patient:

- Keep the incision site clean as directed by your physician.
- Keep the incision site clean and **dry** for at least 24 hours after the insertion or removal of implants. This includes avoiding showers/baths for the first 24 hours to keep the pressure dressing and inside bandage dry. Avoid any activities such as swimming or strenuous activities for the first week after the implants are inserted or removed.
- Apply an ice pack or a cold compress to your arm for 40 minutes every two hours for the first 24 hours and as needed after your procedure to reduce bruising and swelling.
- Remove the pressure dressing, but not the inside bandage 24 hours after the procedure.
- Remove the inside bandage 3-5 days after the procedure.
- After removal of the inside bandage, you should gently wash the wound area (insertion and removal site area) with soap and water and pat dry.
- Do not scratch, rub, or pick at the incision site, or put any liquids, ointment medications or any other product on the incision site.

# Patient Education on Potential Risks: Care of the Incision Instructions, continued

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- Protect the incision site from prolonged exposure to sunlight or tanning lamps while the incision is healing.
- Check for any signs and symptoms of infection, such as: increased pain, swelling, redness, fever, drainage of pus or pus-like material from the insertion and removal site. If any of these signs or symptoms appears, or if the incision site seems to be opening up, immediately contact the doctor who performed the insertion or removal procedure, the doctor who prescribed Probuphine for you, or another healthcare provider.
- **After the Insertion Procedure:** Keep steri-strips (the thin bandages sticking to your skin) on for 7 days after the procedure.

Patients may return the next day to check the wound.

When the patient comes back:

- Check for signs of infection: heat, redness, pain, pus
- Check for suture complications: knot failure, wound dehiscence

# How to Address Spontaneous Expulsion of Implant

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1. Schedule two appointments for the patient to return to the office of the inserting HCP as soon as possible and to the office of the prescribing HCP.
2. 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 HCP office to determine whether the full implant has been expelled.
3. If the patient returns the expelled implant, measure it to ensure that the entire implant was expelled (26 mm).
4. Dispose of the removed implant in keeping with local, state, and federal regulations governing the disposal of pharmaceutical biohazard waste, after measuring.
5. Examine the incision site for infection. If infected, treat appropriately and determine if remaining implants need to be removed.
6. 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 in the instructions for use for removal procedure.

# How to Address Spontaneous Expulsion of Implant

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7. Call **1-833-824-0824** to obtain a new kit that will include four implants and return instructions for any unused implants.
8. The prescribing HCP must carefully monitor patient until the implant is replaced to evaluate for withdrawal or other clinical indicators that supplemental transmucosal buprenorphine may be needed.
9. Schedule an appointment to insert replacement implant(s).
10. Insert the replacement implant(s) in the same arm either medially or laterally to in-situ implants. Alternatively, replacement implant may be inserted in the contralateral arm.
11. Record the serial number on the **Probuphine REMS Program Insertion/Removal Log.**



# Avoiding Complications: Insertion and Removal

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## **In Summary:**

**Proper attention to technique and following the instructions will minimize potential problems and complications.**

# Probuphine REMS Resources

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- For any additional information about the PROBUPHINE REMS Program, please call 1-833-824-0824;

OR

- Visit [www.PROBUPHINEREMS.com](http://www.PROBUPHINEREMS.com)
- To Report any suspected adverse reactions, please call 1-833-824-0824 (please remember to provide the serial number of the kit when reporting an adverse event).

# **Live Demonstration by Trainer: Insertion and Removal Procedures**

# Step by Step Insertion and Removal Procedures Training