

Initial REMS Approval: 05/2016  
Last modified/revised: 06/2016

NDA 204442 Probuphine<sup>®</sup> (buprenorphine) Implant CIII  
Opioid Partial Agonist  
Braeburn Pharmaceuticals, Inc.  
47 Hulfish Street, Suite 441  
Princeton, NJ 08542  
(609) 751-5375

## **RISK EVALUATION AND MITIGATION STRATEGY (REMS)**

### **I. GOALS:**

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:
  - proper insertion and removal of Probuphine
  - risk of complications of migration, protrusion, expulsion and nerve damage associated with the insertion and removal of Probuphine
  - risks of accidental overdose, misuse and abuse if an implant comes out or protrudes from the skin
- b) 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.

### **II. REMS ELEMENTS:**

#### **A. Medication Guide**

A Medication Guide will be dispensed with each Probuphine prescription in accordance with 21 CFR 208.24.

#### **B. Elements to Assure Safe Use**

1. Health care providers who prescribe Probuphine must be specially certified.
  - a. To become specially certified to prescribe Probuphine in the Probuphine REMS Program, healthcare providers must:
    - i. Review the Prescribing Information for Probuphine.

- ii. Complete the *Probuphine REMS Program Live Training: Lecture and Practicum*, and successfully complete the *Probuphine REMS Program Knowledge Assessment*.
  - iii. Enroll in the Probuphine REMS Program by completing the *Probuphine REMS Program Prescriber Enrollment Form*.
- b. As a condition of certification, prescribers must:
- i. Review the *What You Need to Know about Probuphine: A Patient's Guide* with each patient to counsel regarding the risks of insertion and removal, accidental overdose, misuse and abuse and the importance of appropriate wound care and provide the patient a copy.
  - ii. Maintain documentation of insertion and removal of Probuphine in each patient's medical record using the *Probuphine REMS Program Insertion/Removal Log* or by using another method/system (e.g., electronic health record) specific to the healthcare provider's practice.
- c. Braeburn Pharmaceuticals, Inc (Braeburn) must:
- i. Ensure that healthcare providers who prescribe Probuphine are specially certified, in accordance with the requirements described above.
  - ii. Provide live training for prescribers to ensure that healthcare providers can complete the certification process for the Probuphine REMS Program.
  - iii. Ensure that healthcare providers are notified when they have been certified by the Probuphine REMS Program.
  - iv. Maintain a validated, secure database of healthcare providers who are certified to prescribe Probuphine in the Probuphine REMS Program.
  - v. Ensure that healthcare providers meet the REMS certification requirements and de-certify non-compliant healthcare providers who do not maintain compliance with certification requirements.
  - vi. Ensure that certified prescribers are provided access to the database of healthcare providers who are certified to insert Probuphine.
  - vii. Provide the *Probuphine REMS Program Prescriber Enrollment Form* and the Prescribing Information to healthcare providers who (1) attempt to order Probuphine and are not yet certified, or (2) inquire about how to become certified.

The following materials are part of the REMS and are appended:

- *Probuphine REMS Program Prescriber Enrollment Form*
- *Probuphine REMS Program What You Need to Know about Probuphine: A Patient's Guide*
- *Probuphine REMS Program Slides for Live Training: Lecture and Practicum*
- *Probuphine REMS Program Knowledge Assessment*
- *Probuphine REMS Program Insertion/Removal Log*
- *Probuphine REMS Program website, [www. PROBUPHINEREMS.com](http://www.PROBUPHINEREMS.com)*

2. Healthcare providers who insert<sup>1</sup> Probuphine must be specially certified.
  - a. To become specially certified to insert Probuphine in the Probuphine REMS Program, healthcare providers must:
    - i. Review the Prescribing Information for Probuphine.
    - ii. Attest to performing a surgical procedure in the three months immediately preceding enrollment in the Probuphine REMS Program.
    - iii. Complete the *Probuphine REMS Program Live Training: Lecture and Practicum*, which includes training on the proper removal procedure for Probuphine.
    - iv. Successfully complete the *Probuphine REMS Program Knowledge Assessment* and meet the *Probuphine REMS Program Criteria for Procedural Competency*.
    - v. Enroll in the Probuphine REMS Program by completing the *Probuphine REMS Program Healthcare Provider who Performs Probuphine Surgical Procedures Enrollment Form* or *Probuphine REMS Program Healthcare Provider Dual Enrollment Form*.
  - b. As a condition of certification, healthcare providers who insert Probuphine must:
    - i. Agree to insert/remove Probuphine in a healthcare setting in which a prescriber certified in the Probuphine REMS Program is also practicing.
    - ii. Ensure that the facility where the procedure is being conducted has the appropriate equipment to perform insertions and removals of Probuphine.
    - iii. Review the Medication Guide with each patient to counsel them regarding the risks of insertion and removal; accidental overdose, misuse, and abuse;

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<sup>1</sup> For the purpose of this REMS, the term insert refers to the dispensing of medication.

and the importance of appropriate wound care, and provide the patient a copy.

- iv. Document the insertion of Probuphine, including the date, serial number, number of implants inserted, name of healthcare provider performing the procedure, and location of implants for each patient by using the *Probuphine REMS Program Insertion/Removal Log* or by using another method/system (e.g., electronic health record) specific to the healthcare provider's practice.
- v. Recertify in the Probuphine REMS Program annually.

c. Braeburn must:

- i. Maintain a process to ensure that healthcare providers who inquire about becoming certified to insert Probuphine attest to performing a surgical procedure in the three (3) months immediately preceding enrollment in the Probuphine REMS Program.
- ii. Ensure that healthcare providers who insert Probuphine are specially certified, in accordance with the requirements described above.
- iii. Provide live training and competency evaluation for healthcare providers who insert Probuphine to ensure that healthcare providers can complete the certification process for the Probuphine REMS Program.
- iv. Ensure that healthcare providers are notified when they have been certified as a healthcare provider who inserts Probuphine by the Probuphine REMS Program.
- v. Maintain a validated, secure database of healthcare providers who are certified to perform insertions in the Probuphine REMS Program.
- vi. Ensure that healthcare providers meet the REMS certification requirements and de-certify non-compliant healthcare providers who do not maintain compliance with the REMS requirements.
- vii. Ensure that healthcare providers who insert Probuphine have access to a database of certified prescribers.
- viii. Provide the *Probuphine REMS Program Healthcare Provider Who Performs Probuphine Surgical Procedures Enrollment Form* and the

Prescribing Information to healthcare providers who inquire about how to become certified to insert Probuphine.

- ix. Notify healthcare providers who insert Probuphine before their certification is due to expire of the need to recertify in the Probuphine REMS Program and provide the *Probuphine REMS Program Healthcare Provider who Performs Probuphine Surgical Procedures Recertification Form*.
- x. Make available the *Probuphine REMS Program Surgical Procedures Recertification Video* by September 30, 2016. The video must be consistent with the *Probuphine REMS Program Surgical Procedures Recertification Video* transcript.

The following materials are part of the REMS and are appended:

- *Probuphine REMS Program Healthcare Provider Who Performs Probuphine Surgical Procedures Enrollment Form*
- *Probuphine REMS Program Healthcare Provider Dual Enrollment Form*
- *Probuphine REMS Program Criteria for Procedural Competency*
- *Probuphine REMS Program Procedure Record for Recertification*
- *Probuphine REMS Program Healthcare Provider Who Performs Probuphine Surgical Procedures Recertification Form*
- *Probuphine REMS Program Surgical Procedures Recertification Video transcript*

3. Each patient is subject to certain monitoring **for removal** of Probuphine.
  - a. Patients having Probuphine removed must be monitored to ensure that removal is performed by a healthcare provider who is certified to insert. Healthcare providers certified to insert Probuphine are trained in removal procedures as well.<sup>2</sup>
  - b. Healthcare providers who remove Probuphine must document the removal of Probuphine, including, the date, serial number, number of implants removed, name of healthcare provider performing the procedure, and location of implants for each patient by using the *Probuphine REMS Program Insertion/Removal Log* or by using another method/system (e.g., electronic health record) specific to the healthcare provider's practice.
  - c. Braeburn must ensure that the *Probuphine REMS Program Insertion/Removal Log* is available to healthcare providers for patient monitoring.

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<sup>2</sup> Healthcare providers removing Probuphine in emergency situations, or as a result of a complicated removal requiring the involvement of a surgical specialist, are exempt from the certification requirement.

4. Probuphine must be inserted only in healthcare settings in which a certified prescriber is practicing.

Braeburn must ensure that Probuphine will only be inserted in healthcare settings in which a certified prescriber is practicing.

### C. Implementation System

1. Braeburn must ensure that Probuphine is only distributed to healthcare settings in which a certified prescriber is practicing by:
  - a. Ensuring that wholesalers/distributors who distribute Probuphine comply with the program requirements for wholesalers/distributors. The wholesaler/distributor must:
    - i. Put processes and procedures in place to verify, prior to distributing Probuphine, that the healthcare providers who prescribe Probuphine are certified.
    - ii. Comply with requests to be audited by Braeburn, FDA, or a third party acting on behalf of Braeburn or FDA to ensure that all processes and procedures are in place and are being followed for the Probuphine REMS Program. In addition, wholesalers/distributors must maintain appropriate documentation and make it available for audits.
    - iii. Provide distribution data to Braeburn.
  - b. Ensuring that wholesalers/distributors maintain distribution records of all shipments of Probuphine and provide the data to Braeburn.
2. Braeburn must monitor distribution data.
3. Braeburn must audit the wholesalers/distributors within 60 calendar days after the wholesaler/distributor is authorized to ensure that all processes and procedures are in place and functioning to support the requirements of the Probuphine REMS Program. Corrective action must be instituted by Braeburn if noncompliance is identified.
4. Braeburn must maintain and make available to wholesalers/distributors a validated, secure database of healthcare providers who are certified to prescribe in the Probuphine REMS Program.
5. Braeburn must maintain records of Probuphine distribution and dispensing, certified prescribers, certified inserters, and wholesalers/distributors to meet REMS requirements.
6. Braeburn must maintain a Probuphine REMS Program Call Center (1-866-397-8939) and Probuphine REMS Program website ([www.PROBUPHINEREMS.com](http://www.PROBUPHINEREMS.com)). The REMS Program website will include the option to print the Prescribing Information, Medication Guide and Probuphine REMS materials. The *Probuphine REMS Program Surgical Procedures Recertification Video* must be available for viewing September 30, 2016. The Probuphine product website will include a prominent REMS-specific link to the Probuphine REMS Program Website.

7. Braeburn must ensure that within 5 calendar days of REMS approval the Probuphine REMS Program website is fully operational (with the exception of the *Probuphine REMS Program Surgical Procedures Recertification Video*) and the REMS materials listed in or appended to the Probuphine REMS document are available through the Probuphine REMS Program website or by calling the Probuphine REMS Program Call Center.
8. Braeburn must continuously monitor the certified prescribers and healthcare providers who are certified to insert Probuphine to ensure the requirements of the Probuphine REMS Program are being met. Braeburn must institute corrective action if noncompliance is identified.
9. Annually, Braeburn must audit 10% (or a total of 15; whichever is greater) of the inserters who recertify within 90 calendar days of recertification to ensure that all processes and procedures are in place and functioning to support the requirements of the Probuphine REMS Program. The certified inserters must also be included in Braeburn's ongoing annual audit plan. Braeburn must institute corrective action if noncompliance is identified.
10. Braeburn must take reasonable steps to improve implementation of and compliance with the requirements in the Probuphine REMS Program based on monitoring and evaluation of the Probuphine REMS Program.

#### **D. Timetable for Submission of Assessments**

Braeburn must submit REMS Assessments for Probuphine to the FDA at 6 months and 1 year from the date of the REMS approval and then annually thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 calendar days before the submission date for that assessment. Braeburn must submit each assessment so that it will be received by the FDA on or before the due date.

**PROBUPHINE<sup>®</sup> REMS Program**  
**Healthcare Provider Who Prescribes Enrollment Form**  
(for completion by healthcare providers who will only prescribe Probuphine)

Probuphine is only available from healthcare providers who are certified in the Probuphine REMS Program to prescribe Probuphine. Probuphine may only be inserted or removed by healthcare providers who have successfully completed a live training program on the insertion and removal procedures and become certified to insert Probuphine implants. Patients must be monitored to ensure that Probuphine is removed by a healthcare provider certified to insert in the Probuphine REMS program.

**Healthcare Providers Who Prescribe Agreement**

By signing this form, I attest that:

1. I understand that Probuphine is only available to patients through healthcare providers who are certified in the Probuphine REMS Program and that I must comply with the program requirements to prescribe Probuphine.
2. I have reviewed and understand the *Probuphine Prescribing Information*, the *Probuphine Instructions for Use*, and successfully completed the *Probuphine REMS Program Live Training: Lecture and Practicum* and the *Probuphine REMS Program Knowledge Assessment*.
3. I understand the risks of migration, protrusion, expulsion, and nerve damage associated with insertion/removal of Probuphine and the risks of accidental overdose, misuse, and abuse associated with Probuphine.
4. I will provide each patient with a copy of *What You Need to Know about Probuphine: A Patient's Guide* and counsel each patient about:
  - a. The risks associated with insertion and removal of Probuphine
  - b. The risks of accidental overdose, misuse, and abuse, if an implant comes out or protrudes from the skin.
  - c. The importance of appropriate wound care
5. I will order Probuphine only from an authorized wholesaler/distributor.
6. I will not transfer Probuphine outside the healthcare setting to anyone who is not certified as a Healthcare Provider Who Prescribes in the Probuphine REMS Program.
7. I understand that Probuphine may only be inserted by healthcare providers who are certified in the Probuphine REMS Program specifically to insert Probuphine.

8. I understand that patients having Probuphine removed must be monitored to ensure the removal is performed by a healthcare provider who is certified to insert and is trained on the proper removal procedure for Probuphine.
9. I will make arrangements for a healthcare provider who is certified in the Probuphine REMS Program to insert Probuphine to perform the insertion and removal procedures in the healthcare setting in which I am practicing.
10. I will ensure that the Healthcare Provider Who Inserts/Removes Probuphine in the healthcare setting in which I am practicing documents the insertion and removal of Probuphine, including the date, serial number, number of implants inserted/removed, name of individual performing the procedure, and location of implants for individual patients on the *Probuphine REMS Program Insertion/Removal Log* or by using another method or system (e.g. electronic health record) specific to the healthcare provider's practice; and I will maintain such documentation of insertion and removal of Probuphine in each patient's medical record.
11. I understand that the Probuphine REMS Program may contact me via phone, mail, or email to survey me on the REMS Program requirements.
12. I understand personnel from the Probuphine REMS Program may contact me via phone, mail or email to gather or to provide information related to the Probuphine REMS Program.
13. I will report any adverse events associated with the insertion/removal of Probuphine and the risks of accidental overdose, misuse and abuse to Braeburn Pharmaceuticals at 1-844-859-6341.

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Prescriber's Signature

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Date

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**Print Name**

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**NPI #**

**Please print the following information clearly and legibly in order to more easily process your enrollment in the Probuphine REMS Program.**

First Name: \_\_\_\_\_

Last Name: \_\_\_\_\_

Practice or Healthcare Facility Name: \_\_\_\_\_

Practice or Healthcare Facility Street Address: \_\_\_\_\_

City: \_\_\_\_\_ State: \_\_\_\_\_ Zip: \_\_\_\_\_

Are you a: MD  DO

Clinical Specialty: Addiction Medicine  Family Medicine  Internal Medicine  Psychiatry  Other \_\_\_\_\_

Telephone #:	Fax #:
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E-mail:	Confirm E-mail:
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Preferred Method of Communication (please select one):  Fax  Email

**For more information, please contact the *Probuphine REMS Program* at 1-866-397-8939 or on line at *ProbuphineREMS.com*.**

## **PROBUPHINE<sup>®</sup> REMS Program**

### **Healthcare Provider Who Performs Probuphine Surgical Procedures<sup>1</sup> Enrollment Form**

(for completion by healthcare providers who will only insert/remove Probuphine)

Probuphine is only available from healthcare providers who are certified in the Probuphine REMS Program to prescribe Probuphine. Probuphine may only be inserted or removed by healthcare providers who have successfully completed a live training program on the insertion and removal procedures and become certified to insert Probuphine implants. Patients must be monitored to ensure that Probuphine is removed by a healthcare provider certified to insert in the Probuphine REMS program.

#### **Healthcare Providers Who Insert/Remove Agreement**

By signing this form, I attest that:

1. I understand that Probuphine is only available to patients through healthcare providers who are certified by the Probuphine REMS Program.
2. I must comply with the program requirements to insert or remove Probuphine.
3. I have performed a surgical procedure in the last three months. This procedure was performed under local anesthesia, using aseptic technique, and included, at a minimum, making skin incisions or placing sutures.
4. I have reviewed and understand the *Probuphine Prescribing Information*, the *Probuphine Instructions for Use*, and successfully completed the *Probuphine REMS Program Live Training: Lecture and Practicum* and the *Probuphine REMS Program Knowledge Assessment*; and meet the *Probuphine REMS Program Criteria for Procedural Competency*.
5. I understand the risks of migration, protrusion, expulsion, and nerve damage associated with insertion/removal of Probuphine and the risks of accidental overdose, misuse, and abuse associated with Probuphine.

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<sup>1</sup> Patients having Probuphine removed must be monitored to ensure that removal is performed by a healthcare provider who is certified to insert. Healthcare providers certified to insert Probuphine are trained in removal procedures as well.

6. I understand the safe administration of Probuphine, including the proper insertion and removal techniques, as well as appropriate wound care.
7. I will provide each patient with a copy of the *Probuphine Medication Guide* prior to each insertion procedure and counsel each patient about:
  - a. The risks associated with the insertion and removal of Probuphine,
  - b. The risks of accidental overdose, misuse, and abuse, and if an implant comes out or protrudes from the skin.
  - c. The importance of appropriate wound care.
8. I will document patient counseling in the *Probuphine REMS Program Insertion/Removal Log* or by using another method or system (e.g. electronic health record) specific to my medical practice.
9. I will perform the insertion and removal procedures in a healthcare setting in which a prescriber certified in the Probuphine REMS Program is also practicing.
10. I will ensure that this clinical setting has appropriate equipment to perform the insertion and removal procedures described in the *Probuphine Instructions for Use*.
11. I will document the insertion and removal of Probuphine including the date, serial number, number of implants inserted/removed, name of individual performing the procedure, and location of implants for individual patients on the *Probuphine REMS Program Insertion/Removal Log* or by using another method or system (e.g. electronic health record) specific to the prescriber's medical practice.
12. The removed implant contains a significant amount of residual buprenorphine. I will dispose of Probuphine implants in compliance with facility procedure for a Schedule III drug product and per applicable local, state and federal regulations governing the disposal of pharmaceutical bio-hazardous waste.
13. I will not transfer Probuphine outside the healthcare setting to anyone who is not certified as a Healthcare Provider Who Prescribes in the Probuphine REMS Program.
14. I understand that I will need to recertify in the Probuphine REMS Program annually.
15. I understand that the Probuphine REMS Program may contact me via phone, mail, or email to survey me on REMS Program requirements.
16. I understand that I may request personnel from the Probuphine REMS program to provide training and support for my first Probuphine insertion and removal procedure.
17. I understand that personnel from the Probuphine REMS Program may contact me via phone, mail, or email to gather or to provide information related to the Probuphine REMS Program.

18. I will comply with requests to be audited by Braeburn Pharmaceuticals to ensure all recertification requirements are being followed for the Probuphine REMS Program, and appropriate documentation is available upon request.
19. I will report any adverse events associated with the insertion/removal of Probuphine and the risks of accidental overdose, misuse and abuse to Braeburn Pharmaceuticals at 1-844-859-6341.

\_\_\_\_\_  
Healthcare Provider Signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
Print Name

\_\_\_\_\_  
NPI #

**Please print the following information clearly and legibly in order to more easily process your enrollment in the Probuphine REMS Program.**

\_\_\_\_\_  
First Name:

\_\_\_\_\_  
Last Name:

\_\_\_\_\_  
Practice or Healthcare Facility Name:

\_\_\_\_\_  
Practice or Healthcare Facility Street Address:

\_\_\_\_\_  
City:

\_\_\_\_\_  
State:

\_\_\_\_\_  
Zip:

Are you a: MD  DO  PA  NP  Other: \_\_\_\_\_

Clinical Specialty: Addiction Medicine  Family Medicine  Internal Medicine  Psychiatry  Other: \_\_\_\_\_

\_\_\_\_\_  
Telephone #:

\_\_\_\_\_  
Fax #:

\_\_\_\_\_  
E-mail:

\_\_\_\_\_  
Confirm E-mail:

Preferred Method of Communication (please select one):  Fax  Email

**For more information, please contact the *Probuphine REMS Program* at 1-866-397-8939 or on line at *ProbuphineREMS.com*.**

## **PROBUPHINE<sup>®</sup> REMS Program Healthcare Provider Dual<sup>1</sup> Enrollment Form**

(for completion by healthcare providers who will **prescribe, insert, and remove** Probuphine)

Probuphine is only available from prescribers who are certified in the Probuphine REMS Program to prescribe Probuphine. Probuphine may only be inserted or removed by healthcare providers who have successfully completed a live training program on the insertion and removal procedures and become certified to insert Probuphine implants. Patients must be monitored to ensure that Probuphine is removed by a healthcare provider certified to insert in the Probuphine REMS program.

### **Healthcare Providers Who Prescribe, Insert, and Remove Agreement**

By signing this form, I attest that:

1. I understand that Probuphine is only available to patients through healthcare providers who are certified by the Probuphine REMS Program.
2. I must comply with the program requirements to prescribe, insert, and remove Probuphine.
3. I have performed a surgical procedure in the last three months. This procedure was performed under local anesthesia, using aseptic technique, and included, at a minimum, making skin incisions or placing sutures.
4. I have reviewed and understand the *Probuphine Prescribing Information*, the *Probuphine Instructions for Use*, and successfully completed the *Probuphine REMS Program Live Training: Lecture and Practicum*, the *Probuphine REMS Program Knowledge Assessment*; and meet the *Probuphine REMS Program Criteria for Procedural Competency*.
5. I understand the risks of migration, protrusion, expulsion, and nerve damage associated with insertion/removal of Probuphine and the risks of accidental overdose, misuse, and abuse associated with Probuphine.
6. I understand the safe administration of Probuphine, including the proper insertion and removal procedures, as well as appropriate wound care.

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<sup>1</sup> Patients having Probuphine removed must be monitored to ensure that removal is performed by a healthcare provider who is certified to insert. Healthcare providers certified to insert Probuphine are trained in removal procedures as well.

7. I will provide each patient with a copy of the *Probuphine Medication Guide* prior to each insertion procedure along with a copy of *What You Need to Know about Probuphine: A Patient's Guide*, and counsel each patient about:
  - a. The risks associated with insertion and removal of Probuphine.
  - b. The risks of accidental overdose, misuse, and abuse, and abuse if an implant comes out or protrudes from the skin.
  - c. The importance of appropriate wound care.
8. I will document patient counseling on the *Probuphine REMS Program Insertion/Removal Log* or by using another method or system (e.g. electronic health record) specific to my medical practice.
9. I will order Probuphine only from an authorized wholesaler/distributor.
10. I will not transfer Probuphine outside the healthcare setting to anyone who is not certified as a Healthcare Provider Who Prescribes in the Probuphine REMS Program.
11. I will perform the insertion and removal procedures in a healthcare setting with appropriate equipment to perform the insertion and removal procedures as described in the *Probuphine Instructions for Use*.
12. I will document the insertion and removal of Probuphine including the date, serial number, number of implants inserted/removed, name of individual performing the procedure, and location of implants for individual patients on the *Probuphine REMS Program Insertion/Removal Log* or by using another method or system (e.g. electronic health record) specific to my medical practice; and I will maintain such documentation of insertion and removal of Probuphine in each patient's medical record.
13. The removed implant contains a significant amount of residual buprenorphine. I will dispose of Probuphine implants in compliance with facility procedure for a Schedule III drug product and per applicable local, state and federal regulations governing the disposal of pharmaceutical bio-hazardous waste.
14. I understand that I will need to recertify in the Probuphine REMS Program annually.
15. I understand that the Probuphine REMS Program may contact me via phone, mail, or email to survey me on REMS Program requirements.
16. I understand that I may request personnel from the Probuphine REMS Program to provide training and support for my first Probuphine insertion and removal.
17. I understand personnel from the Probuphine REMS Program may contact me via phone, mail, or email to gather or to provide information related to the Probuphine REMS Program.

18. I will comply with requests to be audited by Braeburn Pharmaceuticals to ensure all recertification requirements are being followed for the Probuphine REMS Program, and appropriate documentation is available upon request.
19. I will report any adverse events associated with the insertion/removal of Probuphine and the risks of accidental overdose, misuse and abuse to Braeburn Pharmaceuticals at 1-844-859-6341.

\_\_\_\_\_  
Healthcare Provider Signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
Print Name

\_\_\_\_\_  
NPI #

**Please print the following information clearly and legibly in order to more easily process your enrollment in the Probuphine REMS Program.**

\_\_\_\_\_  
First Name:

\_\_\_\_\_  
Last Name:

\_\_\_\_\_  
Practice or Healthcare Facility Name:

\_\_\_\_\_  
Practice or Healthcare Facility Street Address:

\_\_\_\_\_  
City:

\_\_\_\_\_  
State:

\_\_\_\_\_  
Zip:

Are you a: MD  DO

Clinical Specialty: Addiction Medicine  Family Medicine  Internal Medicine  Psychiatry  Other \_\_\_\_\_

\_\_\_\_\_  
Telephone #:

\_\_\_\_\_  
Fax #:

\_\_\_\_\_  
E-mail:

\_\_\_\_\_  
Confirm E-mail:

**Preferred Method of Communication (please select one):**  Fax  Email

**For more information, please contact the *Probuphine REMS Program* at 1-866-397-8939 or online at *ProbuphineREMS.com*.**

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

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

# Agenda

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- Introduction
- Probuphine (buprenorphine) implant
  - Indication
- Probuphine REMS Program
  - Goal of REMS Program
  - Mitigating Potential Risks
  - Roles/Responsibilities of Healthcare Providers (HCPs)
  - Certification Process for HCPs
  - Patient Counseling
- Probuphine Insertion/Removal Procedures
  - Step by Step Insertion/Removal Procedures
  - Complications and Risks of Insertion/Removal Procedures

# **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.
- **Braeburn Pharmaceuticals** has worked with the FDA to develop the Probuphine REMS Program 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 if an implant comes out or protrudes from the skin.

# Goal of Probuphine REMS

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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:

- Ensuring that healthcare providers are educated on the following:
  - Proper insertion and removal of Probuphine
  - Risk of complications of migration, protrusion, expulsion and nerve damage associated with the insertion and removal of Probuphine
  - Risks of accidental overdose, misuse and abuse if an implant comes out or protrudes from the skin
- 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

# What is the Probuphine REMS Program?

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- Probuphine is only available through this REMS Program
  - Healthcare Providers (HCPs) Who Prescribe must be certified to place an order for Probuphine
  - HCPs who insert Probuphine must be certified to perform the procedure
  - Only HCP who are certified to insert Probuphine can perform removal procedures
  - Probuphine will be distributed through a Closed Distribution System ONLY to HCPs Who Prescribe Probuphine and either (i) are certified to insert or (ii) make arrangements for a certified HCP Who Inserts to perform the procedures

# Probuphine REMS: Mitigating Potential Risks

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1. Mitigating complications associated with the insertion/removal
  - Inform HCPs on risks associated with the insertion/removal
    - Migration
    - Protrusion
    - Expulsion
    - Nerve damage
  - HCPs Who Prescribe will be educated/trained 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
  - HCPs who perform Probuphine surgical procedures 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

# Probuphine REMS:

## Mitigating Potential Risks, continued

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2. Mitigating the risks of accidental overdose, misuse, and abuse associated with Probuphine if an implant comes out or protrudes from the skin
  - Medication in Probuphine can be extracted and then abused in a manner similar to other opioids
  - HCPs must be properly educated, trained, pass the knowledge assessment, and be certified in the Probuphine REMS Program to prescribe and dispense Probuphine
  - Probuphine should not be dispensed to patients for self-administration
  - Prescribers must give patients **What You Need to Know About Probuphine: A Patient's Guide** counseling tool to inform patients about:
    - The risks of insertion/removal of Probuphine
    - The risks of accidental overdose, misuse, and abuse, if an implant comes out or protrudes from the skin
    - The importance of appropriate wound care
  - HCPs who perform Probuphine surgical procedure must give patients the **Probuphine Medication Guide** at each insertion procedure and counsel patients about:
    - The risks of insertion/removal of Probuphine
    - The risks of accidental overdose, misuse, and abuse, if an implant comes out or protrudes from the skin
    - The importance of appropriate wound care

# 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.
  2. Complete 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**.
  - 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

# 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.
  2. Attest to performing a surgical procedure in the 3 months immediately preceding enrollment in the Probuphine REMS Program.
  3. Complete 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
  - Recertify in the Probuphine REMS Program annually.

# 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 <b>the Probuphine REMS Program Surgical Procedures Recertification Video</b> found on the Probuphine REMS website <b>every year</b> .	<b>Number of Probuphine procedures in the past 12 months</b> (Select the Row that applies)	
	<p><b>≥10</b></p> <p>Performed 10 or more successful<sup>2</sup> procedures (comprised of at least five insertions and five removals) →</p>	<p>I must review <b>the Probuphine REMS Program Surgical Procedures Recertification Video</b> found on the Probuphine REMS website <b>every year</b>.</p> <p>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.</p>
	<p><b>&lt;10</b></p> <p>Performed less than 10 successful<sup>2</sup> procedures (comprised of at least five implantations and five removals) →</p>	<p>I must (annually):</p> <ul style="list-style-type: none"> <li>attend a <b>Probuphine REMS Program Live Training: Lecture and Practicum</b> session</li> <li>successfully complete <b>the 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.

# Probuphine

## REMS Recertification Requirements

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- Only HCPs who perform Probuphine surgical procedures 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.
- HCPs who perform Probuphine surgical procedures will be notified 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

# 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 (available in late 2016)
- 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 Patients**

- What You Need to Know about Probuphine: A Patient's Guide
- Probuphine Medication Guide
- Probuphine REMS Website

# **Patient Counseling, Medication Guide, & Care of the Incision**

# 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 the end of the 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 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.
- **After the Removal Procedure:** Return to the physician's office 7 days after the procedure to have your stitches removed. If you have absorbable stitches, return to have your incision checked to make sure it is healing well.

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

# 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 Procedure

# 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).

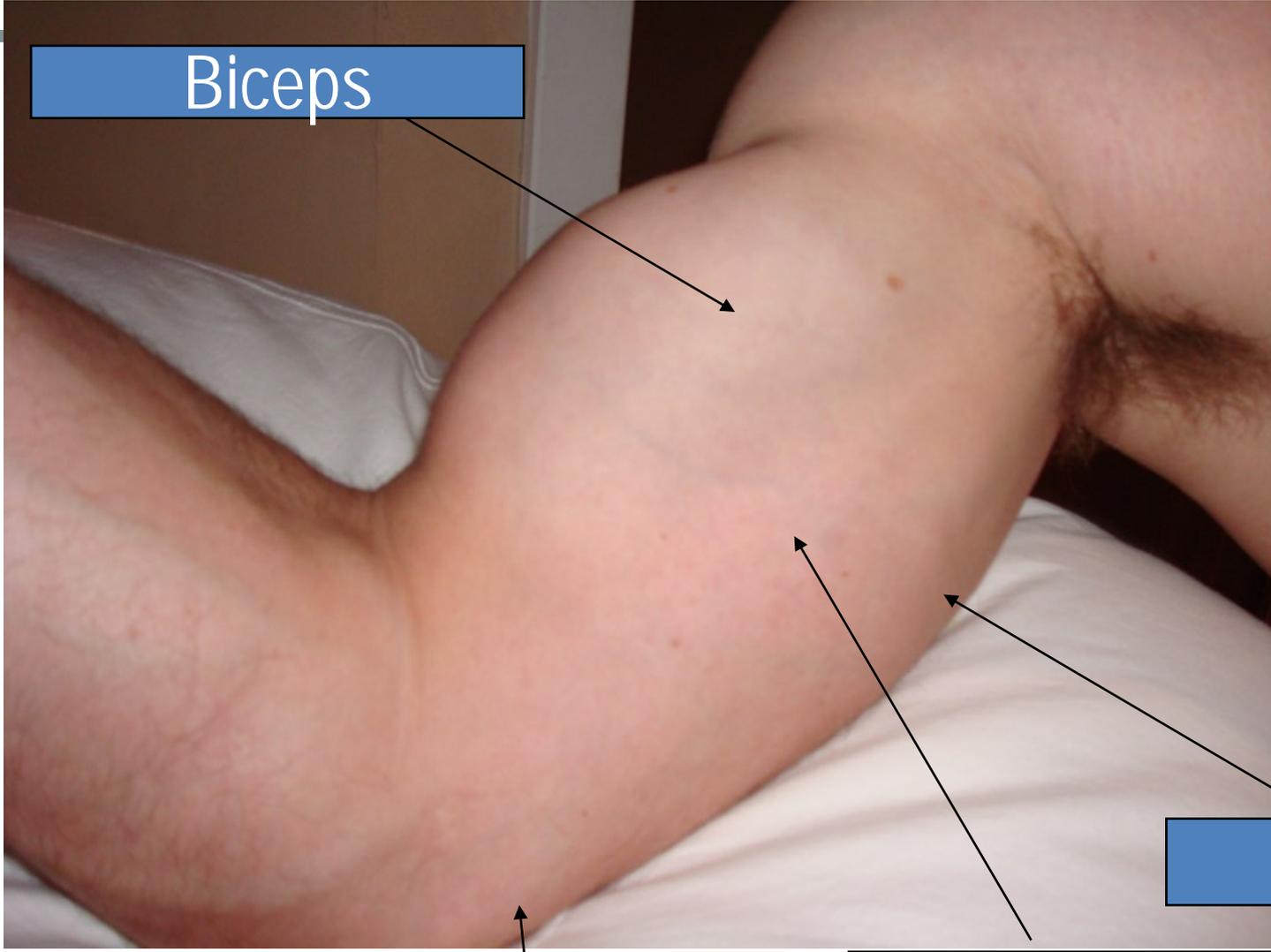
- Only a certified prescriber is allowed to order the Probuphine Kit.
- The only equipment from the kit that are needed for the insertion procedure are the Probuphine implants and the Probuphine Applicator.

# Insertion/Removal Procedure Training Objectives

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- Review anatomy of the brachium
- Insertion Procedure
- Implant Localization
- Removal Procedure
- Care of the Incision
- 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

# Brachium



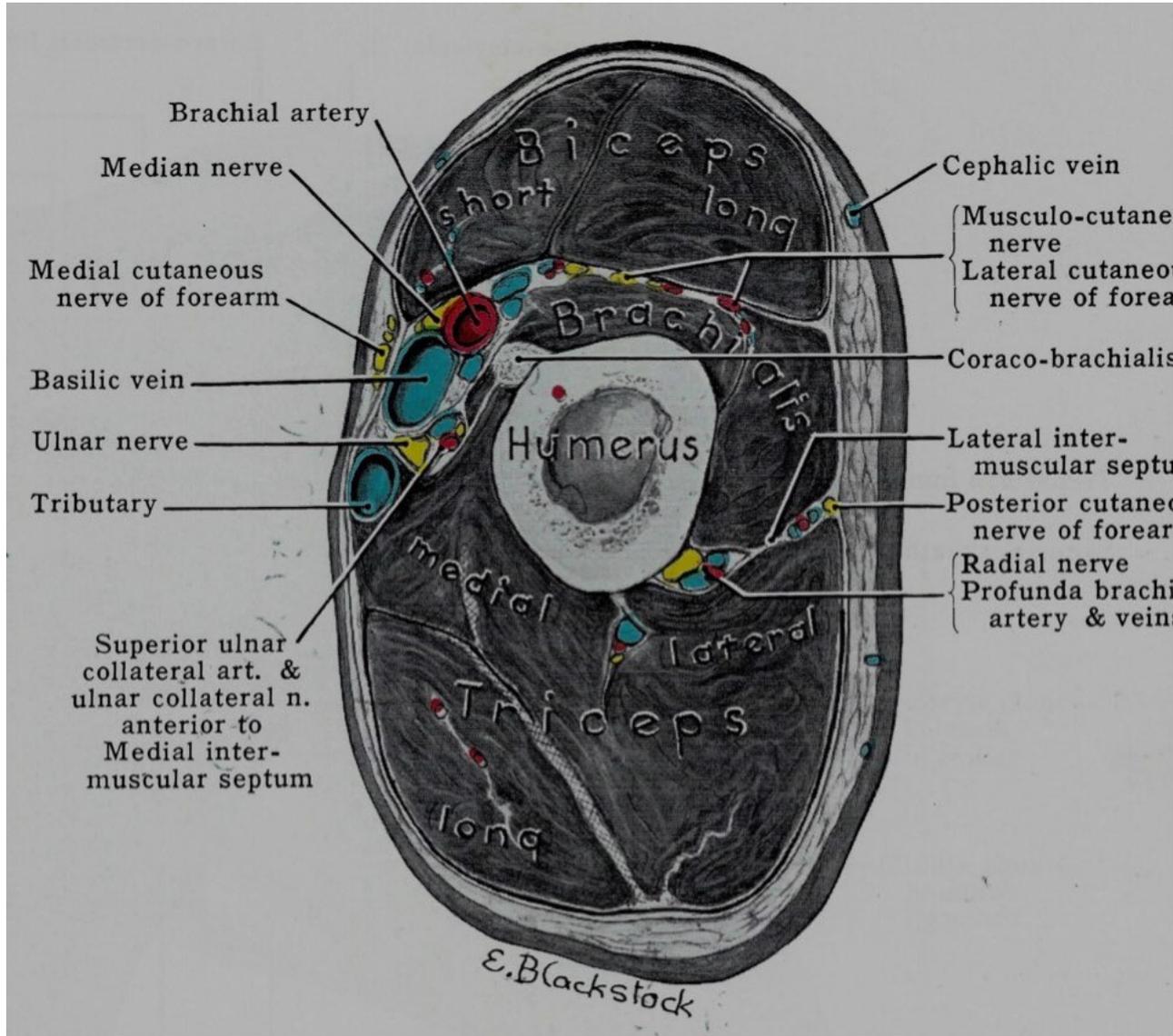
Biceps

Triceps

Medial epicondyle

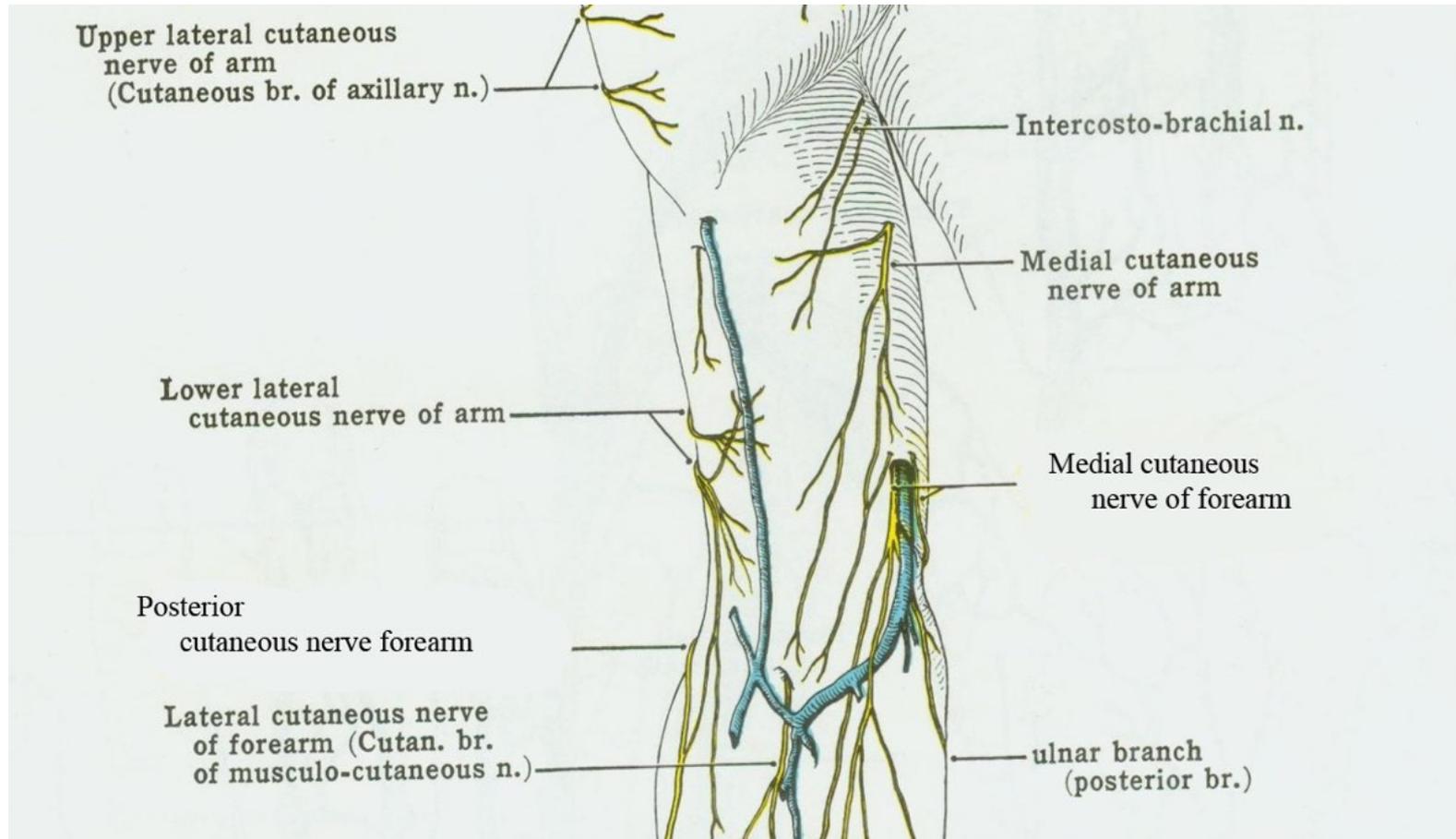
Medial Bicipital Groove

# Brachium Cross Section



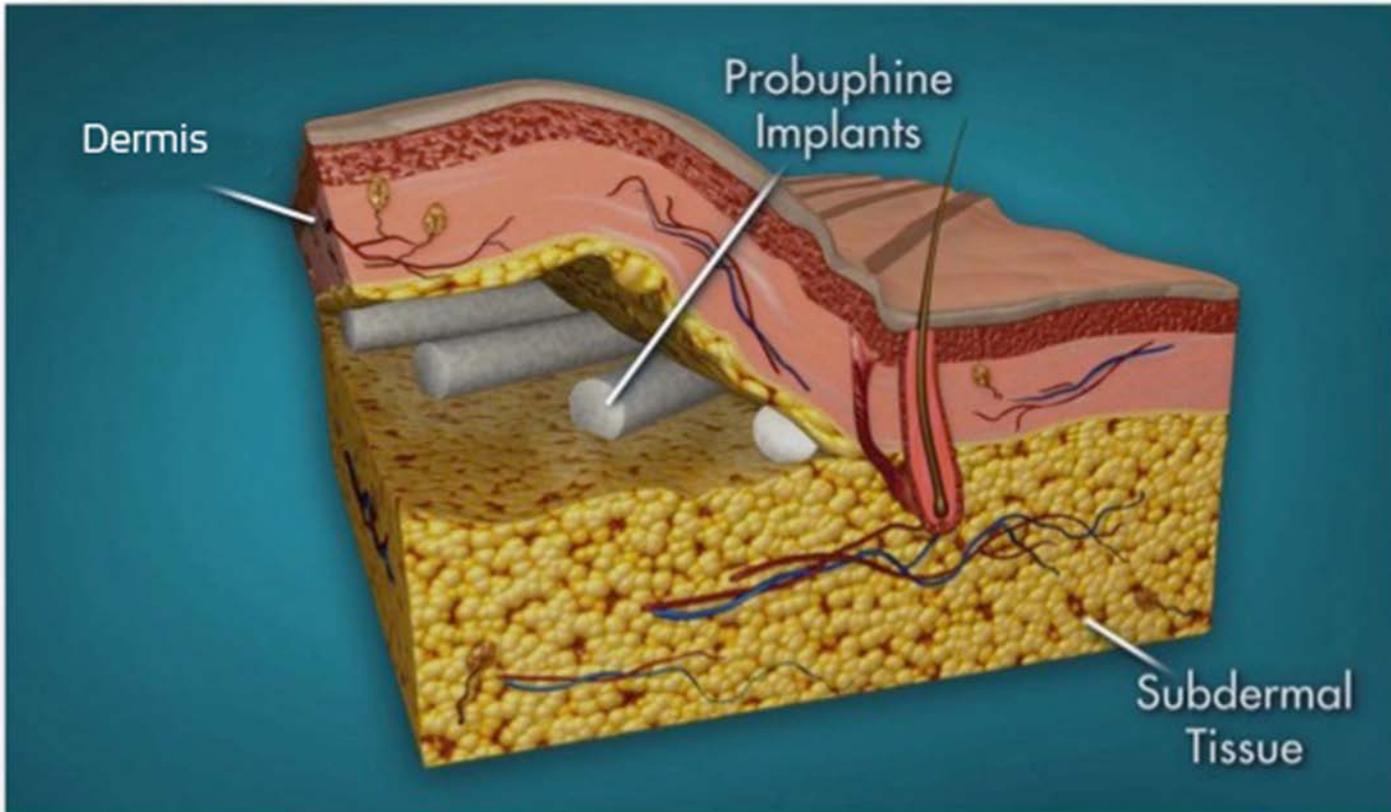
It is important to avoid the neurovascular bundle that underlies the subcutaneous plane.

# 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 Braeburn 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.



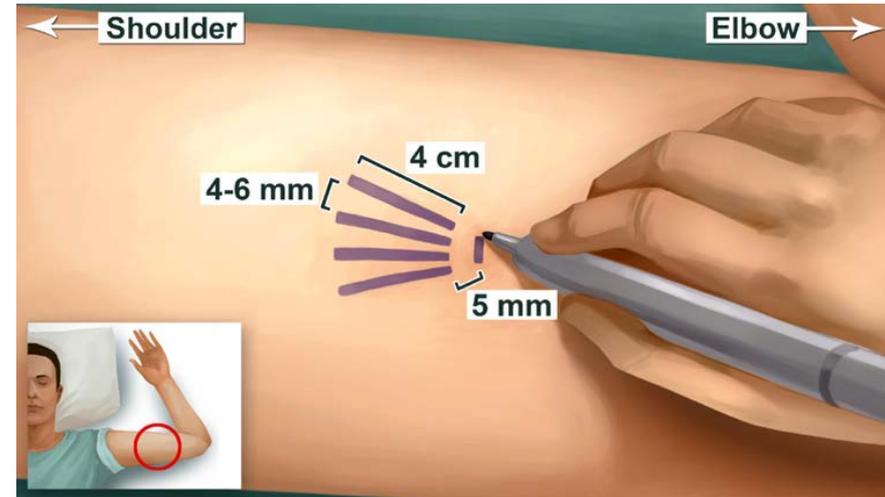
**Step 2.** Identify the insertion site, which is at the inner side of the upper arm about 8-10 cm (3-4 inches) above the medial epicondyle of the humerus in the sulcus between the biceps and triceps muscle. Having the patient flex the biceps muscle may facilitate identification of the site.



# 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

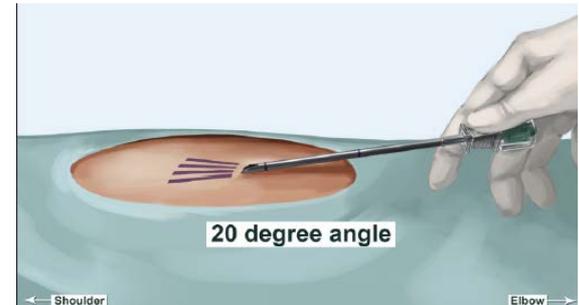


Figure 2

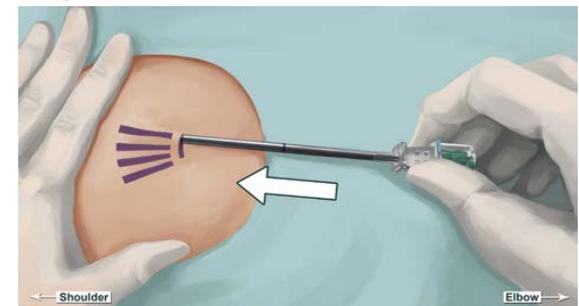
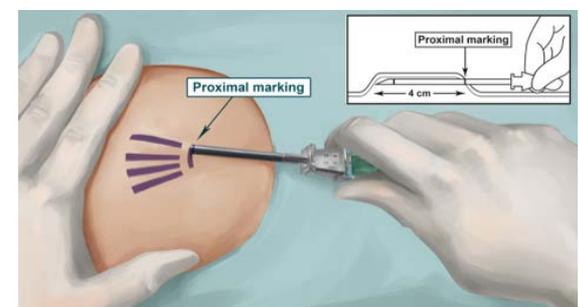


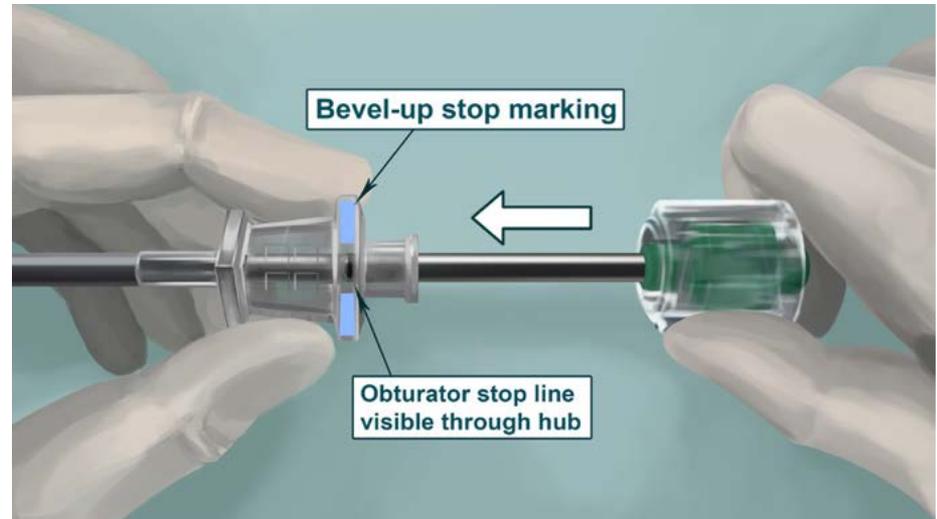
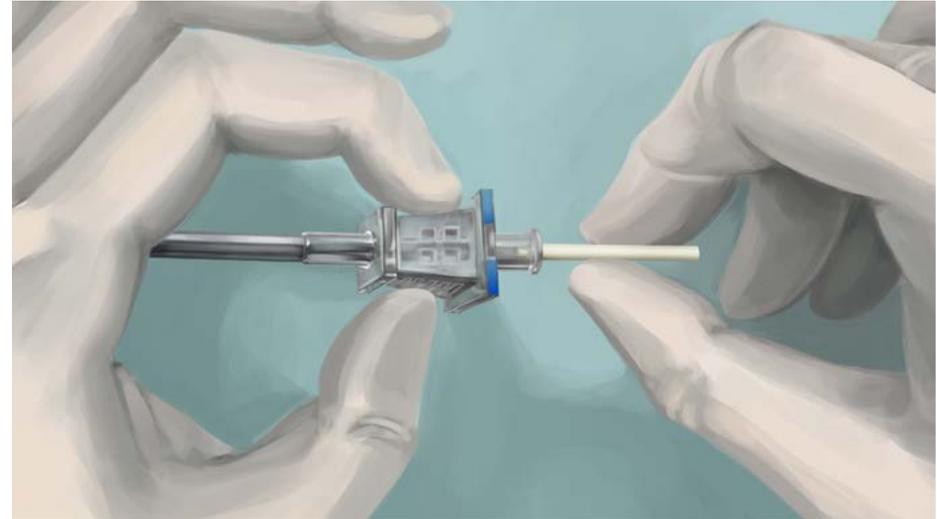
Figure 3



# Insertion Procedure

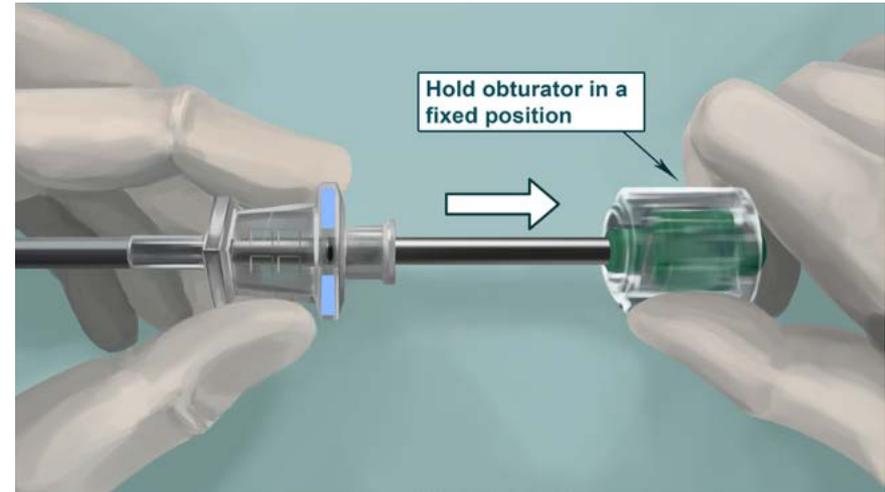
**Step 15.** While holding the cannula in place, unlock the obturator and remove the obturator.

**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.

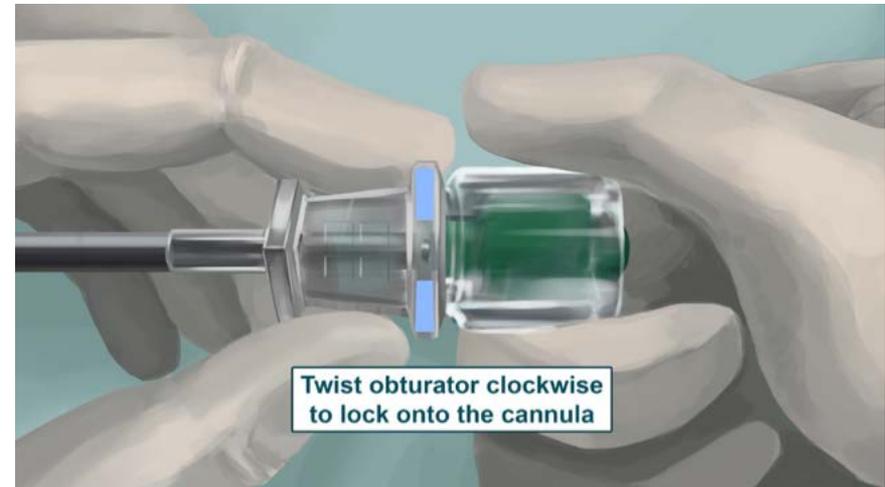


# Insertion Procedure

**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.



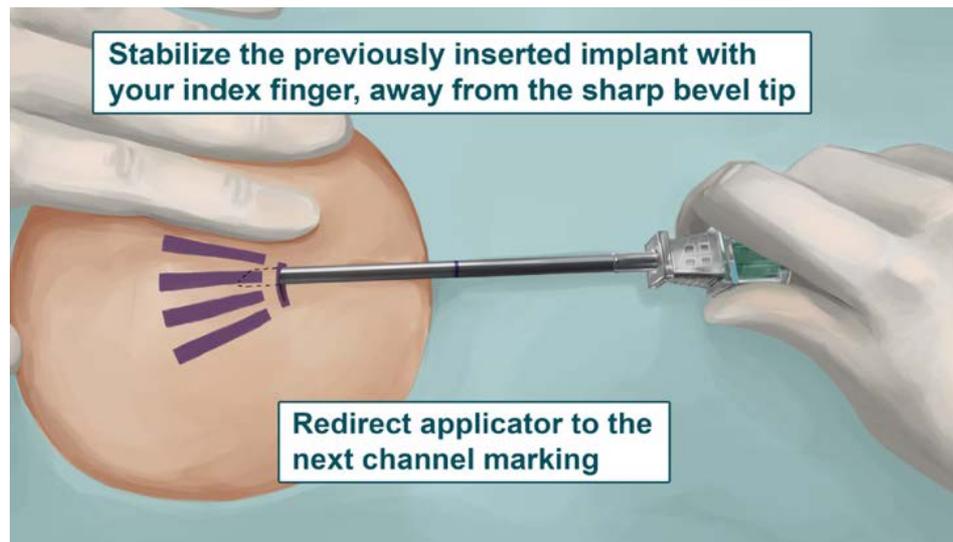
**Step 18.** Withdraw the cannula until the hub is flush with the obturator, and then twist the obturator clockwise to lock onto the cannula. Retract the applicator, bevel-up, until the distal marking of the cannula is visualized at the incision opening (the sharp tip remaining in the subcutaneous space).



# 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

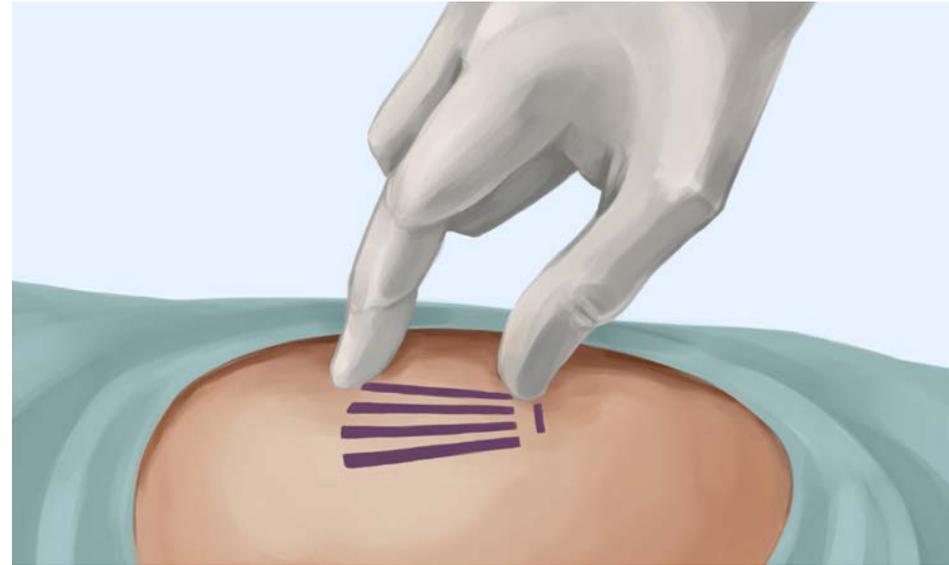
**Step 20.** Always verify the presence of each implant in the patient's arm by palpation of the arm immediately after the insertion. By palpating both ends of the implant, you should be able to confirm the presence of the 26 mm implant.

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 1-844-859-6341.



# 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

# 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

# Localization of Probuphine Implants

# Probuphine Localization

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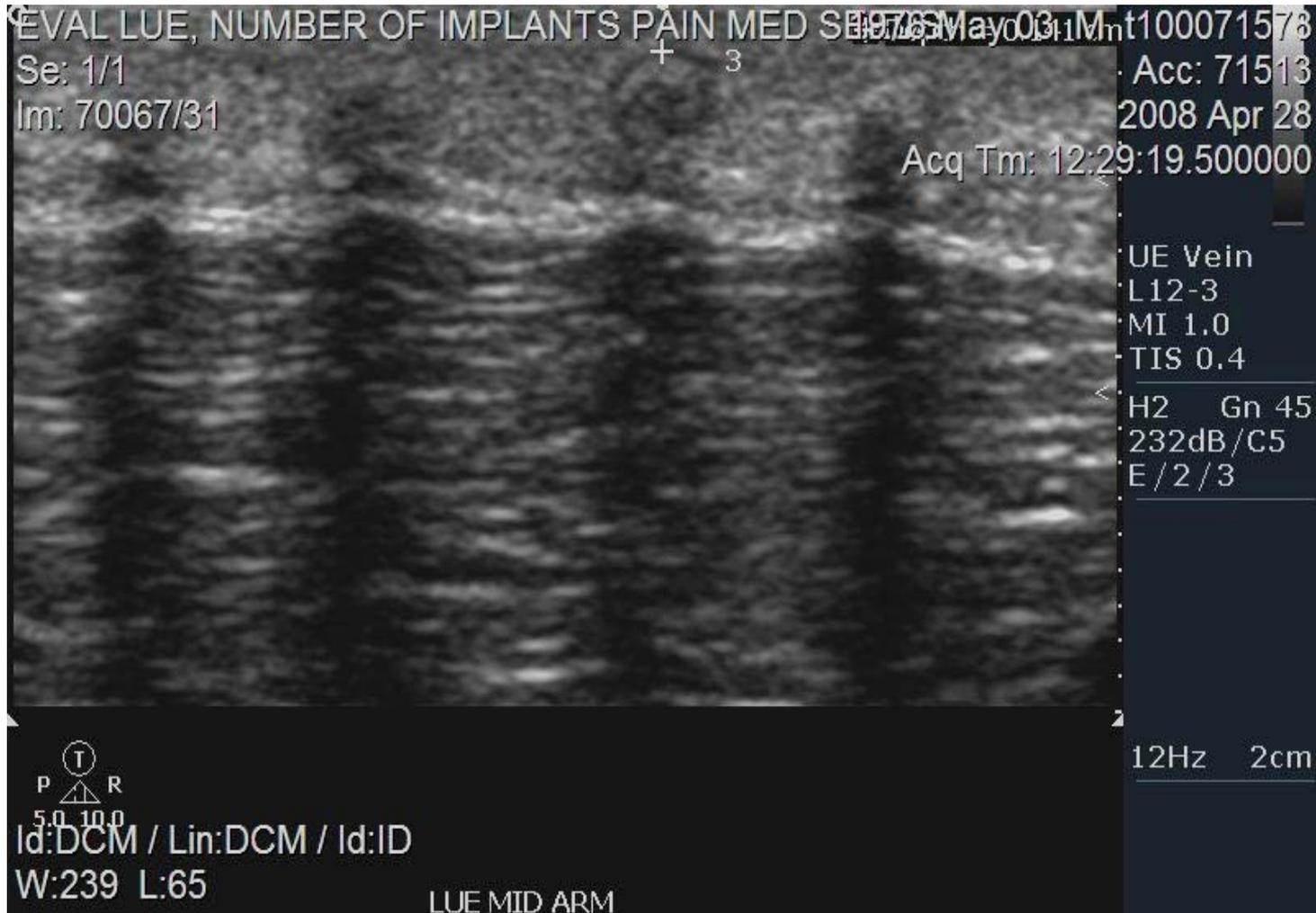
- Identify the location of the implants by consulting the PATIENT IDENTIFICATION CARD and/or THE PATIENT CHART STICKER.
  - The ***Probuphine REMS Program Insertion/Removal Log*** in the patient's chart or electronic health record can also be used to identify the location of the implants.
- The exact 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 Imagine (MRI)
- Note that Probuphine implants are not radiopaque and cannot be seen by X-ray or CT scan. Call 1-844-267-8675 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 Braeburn upon request*

# Removal Procedure

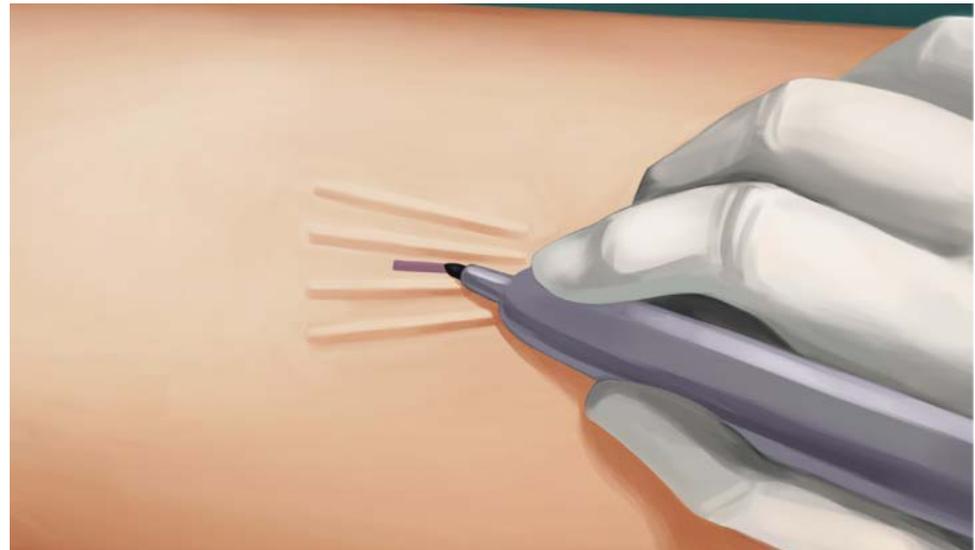
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**Step 1.** Have the patient lie on his/her back, with the implant arm flexed at the elbow and externally rotated, so that the hand is positioned next to the head.

**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.

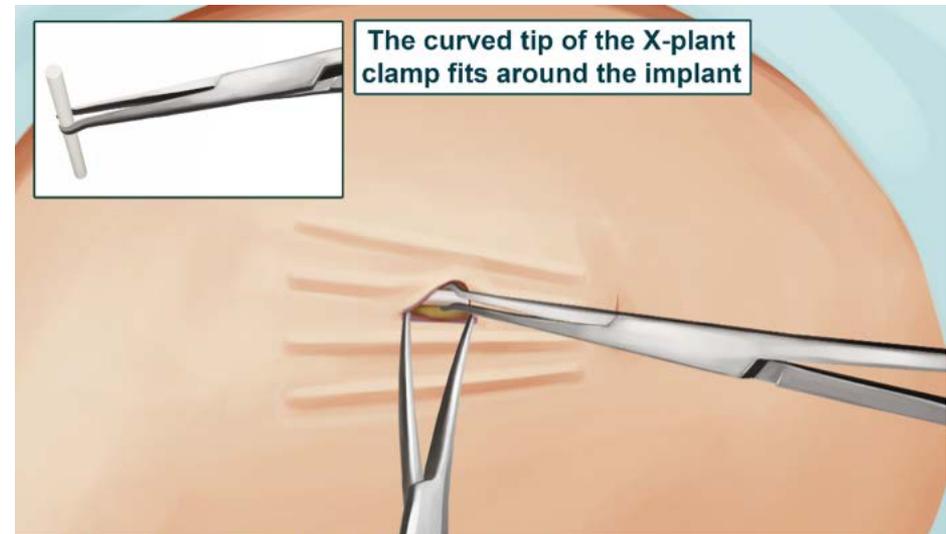
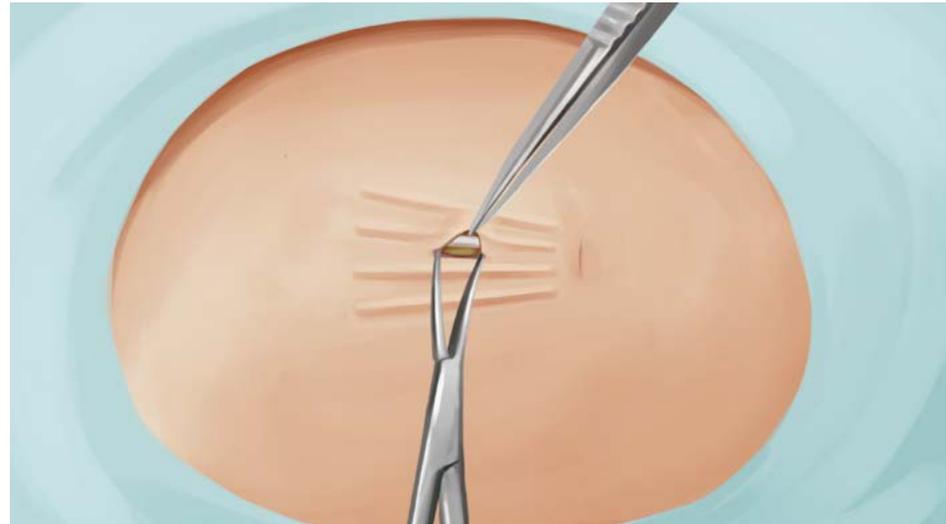
**Step 8.** Apply the sterile drape to the arm of the patient.

**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.**

# 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

---

- 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 Removal Procedure:** Return to the physician's office 7 days after the procedure to have your stitches removed. If you have absorbable stitches, return to have your incision checked to make sure it is healing well.

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

# 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

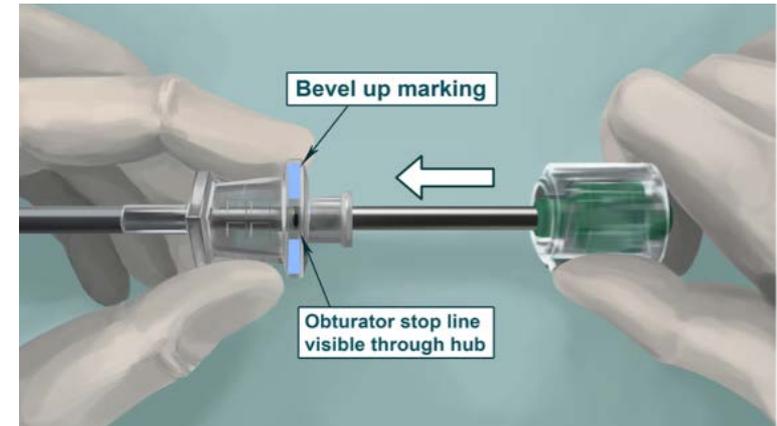
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- Insert only the TIP of the applicator, slightly angled no greater than ( $\sim 20^\circ$ ) to prevent neurovascular injury, at a depth of 3-4 mm below the skin
- Lower the applicator to a horizontal position
- Gently insert, while lifting the skin (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

# 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 **1-844-859-6341** 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 1-866-397-8939; OR
- Visit [www.PROBUPHINEREMS.com](http://www.PROBUPHINEREMS.com)
- To Report any suspected adverse reactions, please call 1-844-267-8675 (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

## **Probuphine REMS Program Knowledge Assessment**

### PROBUPHINE<sup>®</sup> (buprenorphine) Implant CIII Subdermal Use Only

To become certified in the Probuphine REMS Program as a Healthcare Provider Who Prescribes Probuphine or a Healthcare Provider Who Inserts Probuphine, you must answer all of the following questions correctly.

1. The goal of Probuphine REMS is to mitigate the risks 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.
  - a. True
  - a. False
2. Which are the potential risks of insertion and removal of Probuphine?
  - a. Migration
  - b. Protrusion or expulsion
  - c. Nerve damage
  - d. All of the above
3. Which of the following statements is/are true?
  - a. The certified Prescriber is responsible for ensuring that the healthcare provider inserting Probuphine has been certified.
  - b. Patients on Probuphine must be monitored to ensure removal of Probuphine is performed by a certified HCP.
  - c. Insertion procedures can only occur in the office in which a certified Prescriber is practicing.
  - d. All of the above
  - e. None of the above
4. Which of the following statements is/are **true**?
  - a. Probuphine can be dispensed to patients for self-administration.
  - b. Healthcare Providers Who Prescribe should use the patient counseling tool, **What You Need to Know about Probuphine: A Patient's Guide** to counsel patients about the risks and benefits of Probuphine therapy and give them a copy.
  - c. The medication in Probuphine can be extracted and then abused in a manner similar to other opioids.
  - d. B and C
  - e. All of the above

5. Which of the following are important risk messages to convey to patients?
- There is no need to keep the implants (should they come out) away from children.
  - Common risks associated with any minor surgical procedure (like the insertion of Probuphine implants) include itching, pain, irritation or redness, swelling, bleeding, bruising and scarring around the insertion site.
  - It is impossible for the implant to come out by itself.
  - Appropriate wound care is important to reduce the risk of complications associated with the insertion of Probuphine.
  - B and D
  - All of the above
6. When inserting the implants, the correct placement should be within the subdermal plane.
- True
  - False
7. When inserting the applicator through the incision, the angle of the applicator should not exceed which of the following?
- 10 degree angle
  - 20 degree angle
  - 45 degree angle
  - 90 degree angle
8. How far should the obturator be advanced to correctly position the implant?
- To the point where the plastic hub of the obturator locks with the plastic hub of the cannula.
  - To the point where the stop line on the obturator is level with the blue bevel-up marking on the cannula.
  - To the point where the stop line on the obturator is level with the distal marking on the cannula.
  - None of the above
9. Which one of the following is incorrect?
- After inserting the first implant:
- Withdraw the locked applicator to the level of the distal marking seen in the incision opening.
  - Withdraw the applicator completely from the incision and then re-insert it into the incision for the next implant.
  - When redirecting the applicator, stabilize the previously inserted implant to avoid fracturing or mal-positioning the previously inserted implant
  - Keep the bevel facing upward.
10. When inserting the implants, it is imperative to keep the bevel tip down throughout the procedure to ensure proper channel direction.
- True
  - False

11. Once the individual implant has been advanced to the final position within the cannula, and you are ready to insert the next implant, what is the next step?
  - a. Remove the entire applicator.
  - b. Keep the obturator fixed in position and retract the cannula along the obturator.
  - c. Force the implant into the tissues with the obturator.
  - d. Take a coffee break.
  
12. On removal, one of the implants is extracted in 3 pieces. To ensure that you have removed the entire implant what should the cumulative length be of all 3 pieces when measured?
  - a. 10 mm
  - b. 18 mm
  - c. 26 mm
  - d. 50 mm
  
13. What should be done in the event that an implant cannot be palpated prior to removal?
  - a. Reschedule the removal procedure. Order an ultrasound or MRI to locate the implant prior to removal.
  - b. Reschedule the removal procedure. Order a CT to locate the implant prior to removal.
  - c. Order an X-ray to locate the implant prior to removal.
  - d. Perform the removal procedure and explore the site for the non-palpable implant.
  
14. What should be done for an implant that has come out of the skin?
  - a. Ask the patient to dispose of the expelled implant.
  - b. Tell the patient to try to push the implant back under the skin.
  - c. Ask the patient to put the expelled implant in a plastic bag and bring it back to the office, then clean and close the expulsion site and insert a replacement implant in the same arm or contralateral arm.
  - d. None of the above
  
15. Which of the following measures is/are recommended to prevent post-operative complications (e.g. wound infection, hematoma, protruding implants, etc.)?
  - a. Advise the patient on proper care of the incision.
  - b. Ensure the placement of the implants is at least 5mm from the incision opening.
  - c. Apply a pressure bandage and cold compresses.
  - d. a. and b. only
  - e. a., b., and c.

Answer **True** or **False** for each of the statements associated with the following stem:  
 If an implant or implant fragment remains in the arm after a removal attempt, you should:

16. Request X-ray or CT imaging to locate the remaining implant or implant fragment(s).  
 True \_\_\_\_\_ False\_\_\_\_\_
  
17. Close the wound with sutures and have the patient return for imaging as soon as feasible followed by a second removal attempt on the day of localization.  
 True\_\_\_\_\_ False\_\_\_\_\_

## INSERTION

Trainees must demonstrate competency in performing the following techniques.

1	Identify insertion site (8-10 cm) above medial epicondyle of the humerus
2	Clean the insertion site with alcohol prep.
3	Mark insertion site with a surgical marker (2.5 – 3mm) and mark the tracks for each implant by drawing 4 lines with each line 4 cm in length and distributed 4-6 mm apart.
4	Put on sterile gloves.
5	Use aseptic technique to place sterile equipment and implants in sterile field.
6	Check applicator function by removing the obturator from the cannula and relocking it.
7	Clean insertion site with antiseptic solution (e.g., chlorhexidine) using gentle repeated back and forth strokes for 30 seconds.
8	Apply sterile drape.
9	Anesthetize insertion area.
10	After determining anesthesia is adequate and effective, make a shallow incision that is 2.5 – 3mm in length with a scalpel, lift skin with forceps.
11	Insert the tip of the applicator, with the bevel-up stop marking on the cannula facing upwards, into the opening (not to exceed a 20 degree angle) until the proximal marking on the cannula just disappears into the incision.
12	Unlock the obturator and remove the obturator. Then insert one implant into cannula and re-insert the obturator and advance obturator until the obturator stop marking reaches the bevel-up stop marking on cannula.
13	Hold obturator fixed in place, retract cannula along obturator, and lock obturator.
14	Stabilize the implant with finger while retracting the applicator (cannula and obturator) to distal marking.
15	Redirect applicator to the next channel marking and repeat steps 11-13 until all four implants have been inserted. Remove the applicator completely from the incision.
16	Verify presence of each implant by palpation.
17	Clean incision site and apply liquid adhesive and steri-strips.
18	Place small adhesive bandage over the insertion site.
19	Apply pressure bandage with sterile gauze.

**MAXIMUM INCISION LENGTH REQUIRED IS 3 mm**

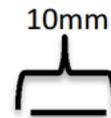


## REMOVAL

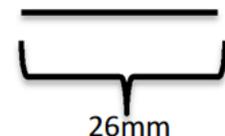
Trainees must demonstrate competency in performing the following techniques.

<b>1</b>	Reconfirm location of implants by palpation. IF ALL FOUR IMPLANTS CAN NOT BE PALPATED, DO NOT ATTEMPT TO REMOVE. REQUEST ULTRASOUND OR MRI.
<b>2</b>	Clean removal site properly with alcohol prep.
<b>3</b>	Using a surgical marker, mark location of the implants and mark location of incision site (7-10 mm) parallel to the axis of the arm between second and third implant.
<b>4</b>	Put on sterile gloves.
<b>5</b>	Use aseptic technique to place sterile equipment in sterile field.
<b>6</b>	Clean removal site with an antiseptic solution (e.g., chlorhexidine) using gentle repeated back and forth strokes for 30 seconds
<b>7</b>	Apply sterile drape.
<b>8</b>	Anesthetize incision site and subcutaneous space below implants (which helps to lift implants toward the skin, facilitating removal of the implants).
<b>9</b>	Confirm anesthesia is adequate and make a 7-10 mm incision parallel to the axis of the arm between 2 <sup>nd</sup> and 3 <sup>rd</sup> implants, along the marked tracks from step 3 above.
<b>10</b>	Pick up skin edge with a toothed forceps and separate the tissue above and below the first visualized implant. If necessary, use the scalpel to shave away adhered tissue.
<b>11</b>	Grasp the center of implant with X-plant clamp and apply gentle traction.
<b>12</b>	Remove implant.
<b>13</b>	After removal of each implant, confirm entire implant is removed by measuring 26 mm in total length, before proceeding to removal of the next implant.
<b>14</b>	Repeat steps 10 – 13 until all implants are removed.
<b>15</b>	Close the incision with sutures.
<b>16</b>	Place an adhesive bandage over the incision and wrap arm with pressure dressing.
<b>17</b>	Dispose of all implants in keeping with regulations governing disposal of biohazardous waste.

**MAXIMUM INCISION LENGTH REQUIRED IS 10 mm**



**EACH IMPLANT REMOVED SHOULD BE 26 mm**



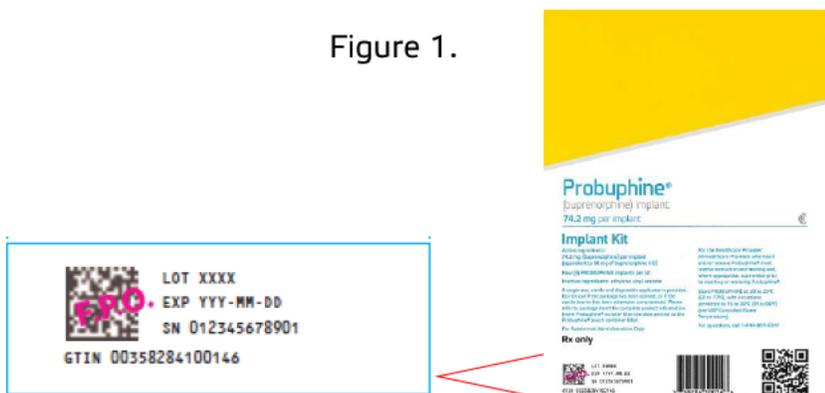
## PROBUPHINE® REMS Program Insertion/Removal Log

- Complete a new form each time a new set of implants are inserted, and document the removal of those implants on this same form.
- Consider this form as part of your patient’s medical records and store it accordingly.
- This form may also be repurposed for inclusion into an electronic health record.

Patient Information	
Patient Name:	
Patient ID:	
Patient received counseling including review of the Medication Guide:	<input type="checkbox"/> Yes <input type="checkbox"/> No
Probuphine Serial Number (located on the lower back left corner. See figure 1):	
<u>New</u> Probuphine Serial Number (If some of the implants are replaced, record the new Probuphine Serial Number from the replacement Probuphine kit.)	

Healthcare Providers Who Prescribe, Insert, and Remove Probuphine			
	Prescriber	inserter	Remover
Name (Please Print):			
Signature:			
NPI or other Clinician ID:			

Figure 1.



### Care Transfer

Indicate the prescriber who will care for the patient post-insertion if/when it is different from the original prescriber. It is preferable that patients return to the inserter/remover with any complications related to the insertion/removal procedure.

Physician Name:	
NPI Number:	
Date:	
Signature:	

### Probuphine Implant Insertion and Removal Log

	Probuphine Insertion	Probuphine Removal
Date of Insertion or Removal:		
Indicate the following: <ul style="list-style-type: none"> <li>Exact Location of the Insertion and Removal sites</li> <li>Number of implants inserted or removed</li> </ul>		
If applicable, indicate the following: <ul style="list-style-type: none"> <li>Issues or difficulties with the procedure</li> <li>Reasons for why the insertion or removal procedure was not completed or performed – if known</li> <li>Adverse Events Related to the Implant Site</li> </ul>		

### Patient Contact Log

Note any actions taken to contact the patient for the removal of Probuphine implants, including dates.

Date	Details

# What is the Probuphine REMS Program?

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. Braeburn Pharmaceuticals has worked with the FDA to develop the Probuphine REMS Program 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.



## REMS Program Overview

- ✔ **Training** – for healthcare providers who prescribe and perform Probuphine surgical procedures on steps to mitigate the risks of complications related to the insertion and removal procedures, and the risks of accidental overdose, misuse, and abuse.

---

- ✔ **Certification** – for healthcare providers who prescribe Probuphine by completing the **Probuphine REMS Program Live Training: Lecture and Practicum**, the **Probuphine REMS Program Knowledge Assessment**, and enrollment in the Probuphine REMS Program.

---

- ✔ **Certification** – for healthcare providers who perform Probuphine surgical procedures by completing the **Probuphine REMS Program Live Training: Lecture and Practicum**, the **Probuphine REMS Program Knowledge Assessment**, the **Probuphine REMS Program Criteria for Procedural Competency** and enrollment in the Probuphine REMS Program.

---

- ✔ **Recertification**– Braeburn will notify clinicians in the database that the 12-month expiration of certification time point is approaching, and an attestation of having completed either online or live training for recertification will be required prior to placement of any additional orders from the healthcare provider. Use the **Probuphine REMS Program Healthcare Provider Who Performs Probuphine Surgical Procedures Recertification Form** to begin the recertification process. This form is available [here](#) or by clicking on the recertification button above. Healthcare providers will have a 30 day grace period to take corrective action to retain certification. If they are decertified they will need to attend the **Probuphine REMS Program Live Training: Lecture and Practicum** in order to regain certification.

---

- ✔ **Patient Counseling** – about the risks associated with the insertion and removal of Probuphine; the risks of accidental overdose, misuse, and abuse if the Probuphine implants come out or protrude from the skin; and when to contact the healthcare provider.

---

- ✔ **Closed Distribution** – only to healthcare providers certified in the Probuphine REMS Program.

## Materials for Healthcare Providers

- 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 Live Training: Lecture Slides [↓](#)
- Probuphine REMS Program Knowledge Assessment [↓](#)
- Probuphine REMS Program Criteria for Procedural Competency [↓](#)
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- Probuphine REMS Program Surgical Procedures Recertification Video [↓](#)
- Probuphine REMS Program Healthcare Provider Who Performs Probuphine Surgical Procedures Recertification Form [↓](#)
- What You Need to Know about Probuphine: A Patient's Guide [↓](#)
- Prescribing Information [↓](#)
- Probuphine Medication Guide [↓](#)
- Probuphine Instructions for Use [↓](#)

## Materials for Patients

- Probuphine Medication Guide [↓](#)
- What You Need to Know about Probuphine: A Patient's Guide [↓](#)



For any additional information about the Probuphine REMS Program, please call 1-866-397-8939

To Report any suspected adverse reactions, please call 1-844-267-8675

# Healthcare Providers

- + [Healthcare Providers Who Prescribe Probuphine](#)
- + [Healthcare Providers Who Perform Probuphine Surgical Procedures](#)
- + [Healthcare Providers Who Prescribe, Insert, and Remove Probuphine](#)
- + [Enroll in the Probuphine REMS Program Live Training: Lecture and Practicum](#)
- [Probuphine Re-Certification](#)

Braeburn will notify each prescriber and healthcare provider who performs Probuphine surgical procedures at least one month prior to the expiration of certification, and an attestation of having completed either online or live training for recertification will be required prior to placement of any additional orders from the healthcare provider. Use the ***Probuphine REMS Program Healthcare Provider Who Performs Probuphine Surgical Procedures Recertification Form*** to begin the recertification process. This form is available [here](#) or by clicking on the recertification button above.

Healthcare providers who perform Probuphine surgical procedures may be audited. The audit will, at a minimum, consist of a review of documentation to confirm compliance with the Probuphine REMS Program healthcare provider recertification requirements and if required will include an interview with the healthcare provider to discuss the documentation.

Please see below for the Probuphine REMS Recertification Training Requirements:

[VIEW REQUIREMENTS](#)

## Materials for Healthcare Providers

- Probuphine REMS Program Healthcare Provider Who Prescribes Enrollment Form [↓](#)
- Probuphine REMS Program Healthcare Provider Who Performs Probuphine Surgical Procedures Enrollment Form [↓](#)
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## Healthcare Providers

### - [Healthcare Providers Who Prescribe Probuphine](#)

Healthcare providers who prescribe Probuphine shall be specially certified. To become certified to prescribe Probuphine, healthcare providers shall:

- a. Review the Prescribing Information for Probuphine
- b. Complete the ***Probuphine REMS Program Live Training: Lecture and Practicum***
- c. Pass the ***Probuphine REMS Program Knowledge Assessment***
- d. Enroll in the Probuphine REMS Program by completing and signing the ***Probuphine REMS Program Healthcare Provider Who Prescribes Enrollment Form*** (form available at all live training sessions)

### + [Healthcare Providers Who Perform Probuphine Surgical Procedures](#)

### + [Healthcare Providers Who Prescribe, Insert, and Remove Probuphine](#)

### + [Enroll in the Probuphine REMS Program Live Training: Lecture and Practicum](#)

### + [Probuphine Re-Certification](#)

## Materials for Healthcare Providers

[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](#) 

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[Probuphine REMS Program Knowledge Assessment](#) 

[Probuphine REMS Program Criteria for Procedural Competency](#) 

[Probuphine REMS Program Insertion/Removal Log](#) 

[Probuphine REMS Program Procedure Record for Recertification](#) 

[Probuphine REMS Program Surgical Procedures Recertification Video](#) 

[Probuphine REMS Program Healthcare Provider Who Performs Probuphine Surgical Procedures Recertification Form](#) 

[What You Need to Know about Probuphine: A Patient's Guide](#) 

[Prescribing Information](#) 

[Probuphine Medication Guide](#) 

[Probuphine Instructions for Use](#) 



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# Healthcare Providers

## + Healthcare Providers Who Prescribe Probuphine

## - Healthcare Providers Who Perform Probuphine Surgical Procedures

Healthcare providers who perform Probuphine Surgical procedures must be specially certified. To become certified to insert Probuphine in the Probuphine REMS Program, healthcare providers must:

- Review the **Prescribing Information** for Probuphine.
- Attest to performing a surgical procedure in the three months immediately preceding enrollment in the Probuphine REMS Program.
- Complete the **Probuphine REMS Program Live Training: Lecture and Practicum**, which includes training on the proper removal procedure for Probuphine.
- Successfully complete the **Probuphine REMS Program Knowledge Assessment** and meet the **Probuphine REMS Program Criteria for Procedural Competency**.
- Enroll in the Probuphine REMS Program by completing the **Probuphine REMS Program Healthcare Provider Who Performs Probuphine Surgical Procedures Enrollment Form**.
- Obtain recertification annually to continue functioning as an inserter of Probuphine.

## + Healthcare Providers Who Prescribe, Insert, and Remove Probuphine

## + Enroll in the Probuphine REMS Program Live Training: Lecture and Practicum

## + Probuphine Re-Certification

## Materials for Healthcare Providers

Probuphine REMS Program Healthcare Provider Who Prescribes Enrollment Form [Download](#)

Probuphine REMS Program Healthcare Provider Who Performs Probuphine Surgical Procedures Enrollment Form [Download](#)

Probuphine REMS Program Healthcare Provider Dual Enrollment Form [Download](#)

Probuphine REMS Program Live Training: Lecture Slides [Download](#)

Probuphine REMS Program Knowledge Assessment [Download](#)

Probuphine REMS Program Criteria for Procedural Competency [Download](#)

Probuphine REMS Program Insertion/Removal Log [Download](#)

Probuphine REMS Program Procedure Record for Recertification [Download](#)

Probuphine REMS Program Surgical Procedures Recertification Video [Download](#)

Probuphine REMS Program Healthcare Provider Who Performs Probuphine Surgical Procedures Recertification Form [Download](#)

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# Healthcare Providers

+ [Healthcare Providers Who Prescribe Probuphine](#)

+ [Healthcare Providers Who Perform Probuphine Surgical Procedures](#)

- [Healthcare Providers Who Prescribe, Insert, and Remove Probuphine](#)

Healthcare providers who prescribe and perform Probuphine surgical procedures in a dual role shall be specially certified. To become certified to prescribe and perform Probuphine surgical procedures, healthcare providers shall:

- Review the **Prescribing Information** for Probuphine.
- Attest to performing a sterile procedure in the three months immediately preceding enrollment in the Probuphine REMS Program.
- Complete the **Probuphine REMS Program Live Training: Lecture and Practicum**, which includes training on the proper removal procedure for Probuphine.
- Successfully complete the **Probuphine REMS Program Knowledge Assessment** and meet the **Probuphine REMS Program Criteria for Procedural Competency**.
- Enroll in the Probuphine REMS Program by completing the **Probuphine REMS Program Healthcare Provider Dual Enrollment Form**.
- Obtain recertification annually to continue functioning as an inserter of Probuphine.

+ [Enroll in the Probuphine REMS Program Live Training: Lecture and Practicum](#)

+ [Probuphine Re-Certification](#)

## Materials for Healthcare Providers

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# Healthcare Providers

- + [Healthcare Providers Who Prescribe Probuphine](#)
- + [Healthcare Providers Who Perform Probuphine Surgical Procedures](#)
- + [Healthcare Providers Who Prescribe, Insert, and Remove Probuphine](#)
- [Enroll in the Probuphine REMS Program Live Training: Lecture and Practicum](#)

**Please fill in the information below to receive an email about the *Probuphine REMS Program Live Training: Lecture and Practicum***

\* indicates required

**Email Address \***

**First Name \***

**Last Name \***

**Phone Number \***

**Zip Code \***

**NPI Number \***

**Intended Role \***

**Email Format**

- html  
text

[Subscribe](#)

- + [Probuphine Re-Certification](#)

## Materials for Healthcare Providers

- Probuphine REMS Program Healthcare Provider Who Prescribes Enrollment Form [↓](#)
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For any additional information about the Probuphine REMS Program, please call 1-866-397-8939

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## Probuphine® REMS Recertification Training Requirements<sup>1</sup>

Your Training Requirements can be found at the intersection of the row and column you select below based upon your personal experience:

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><i>Probuphine REMS Program Surgical Procedures Recertification Video</i></b> found on the Probuphine REMS website <b>every year</b> .	<p><b>Number of Probuphine procedures in the past 12 months</b></p> <p>(Select the Row that applies)</p>	
	<p><b>10 or More &gt;</b></p> <p>Performed 10 or more successful<sup>2</sup> procedures (comprised of at least five insertions and five removals)</p>	<p>I must review the <b><i>Probuphine REMS Program Surgical Procedures Recertification Video</i></b> found on the Probuphine REMS website <b>every year</b>.</p> <p>I understand that I should keep documentation of all successfully completed procedures on the <b><i>Probuphine REMS Program Procedure Record for Recertification</i></b> or another record of my choosing - which must be provided to the Probuphine REMS Program if I am audited.</p>
	<p><b>Less than 10 &gt;</b></p> <p>Performed less than 10 successful<sup>2</sup> procedures (comprised of at least five implantations and five removals)</p>	<p>I must (annually):</p> <ul style="list-style-type: none"> <li>attend a <b><i>Probuphine REMS Program Live Training: Lecture and Practicum</i></b> session</li> <li>successfully complete the <b><i>Probuphine REMS Program Knowledge Assessment</i></b> test</li> <li>meet the <b><i>Probuphine REMS Program Criteria for Procedural Competency</i></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 HCP successfully removes all implants identified by imaging without involving additional surgical consultants.

CLOSE

# Probuphine REMS Recertification Training Requirements

Please answer the following questions to determine the recertification process that specifically applies to your situation. You may also check your recertification status by calling the Probuphine REMS Program at 1-866-397-8939.

**When last did you become certified/re-certified?\***

Under 12 Months

**Are you a healthcare provider with operating privileges at hospitals or out-patient surgical centers?\***

Yes  No

**Have you as a healthcare provider performed at least 5 successful insertions and 5 successful removals during past 12 months?\***

Yes  No

[SUBMIT](#)

## Materials for Healthcare Providers

[Probuphine REMS Program Healthcare Provider Who Prescribes Enrollment Form](#)

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[Probuphine REMS Program Knowledge Assessment](#)

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[Prescribing Information](#)

[Probuphine Medication Guide](#)

[Probuphine Instructions for Use](#)

## Materials for Patients

[Probuphine Medication Guide](#)

[What You Need to Know about Probuphine: A Patient's Guide](#)



For any additional information about the Probuphine REMS Program, please call 1-866-397-8939

To Report any suspected adverse reactions, please call 1-844-267-8675

# Probuphine REMS Recertification Training Requirements

Please answer the following questions to determine the recertification process that specifically applies to your situation. You may also check your recertification status by calling the Probuphine REMS Program at 1-866-397-8939.

You need to attend the ***Probuphine REMS Program Live Training: Lecture and Practicum.***

[CLICK HERE](#) to enroll for training.

[RESET FORM](#)

## Materials for Healthcare Providers

Probuphine REMS Program Healthcare Provider Who Prescribes Enrollment Form [Download](#)

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For any additional information about the Probuphine REMS Program, please call 1-866-397-8939

To Report any suspected adverse reactions, please call 1-844-267-8675

# Probuphine REMS Recertification Training Requirements

Please answer the following questions to determine the recertification process that specifically applies to your situation. You may also check your recertification status by calling the Probuphine REMS Program at 1-866-397-8939.

You need to watch the ***Probuphine REMS Program Surgical Procedures Recertification Video*** and fill out the ***Probuphine REMS Program Healthcare Provider Who Performs Probuphine Surgical Procedures Recertification Form***

[CLICK HERE](#) to watch the ***Probuphine REMS Program Surgical Procedures Recertification Video***

[CLICK HERE](#) to fill out and send the ***Probuphine REMS Program Healthcare Provider Who Performs Probuphine Surgical Procedures Recertification Form***. Please Fax to 609-423-0965

[RESET FORM](#)

## Materials for Healthcare Providers

[Probuphine REMS Program Healthcare Provider Who Prescribes Enrollment Form](#)

[Probuphine REMS Program Healthcare Provider Who Performs Probuphine Surgical Procedures Enrollment Form](#)

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# Probuphine REMS Recertification Training Requirements

Please answer the following questions to determine the recertification process that specifically applies to your situation. You may also check your recertification status by calling the Probuphine REMS Program at 1-866-397-8939.

You are not due for a recertification yet. Please check your status again before 1 year has passed from your last certification/recertification.

[RESET FORM](#)

## Materials for Healthcare Providers

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## Probuphine REMS Program Surgical Procedures Recertification Video

Available in late 2016

Heal

audit will, at a minimum, consist of a review of documentation to confirm compliance with the Probuphine REMS Program healthcare provider recertification requirements and if required will include an interview with the healthcare provider to discuss the documentation.

Please see below for the Probuphine REMS Recertification Training Requirements:

[VIEW REQUIREMENTS](#)

Training: Lecture Slides



Probuphine REMS Program  
Insertion/Removal Log



Probuphine REMS Program Procedure  
Record for Recertification



Probuphine REMS Program  
Surgical Procedures  
Recertification Video



Probuphine REMS Program Healthcare  
Provider Who Performs Probuphine  
Surgical Procedures Recertification  
Form



What You Need to Know about  
Probuphine: A Patient's Guide



[Click Here for Recertification](#)

[Prescribing Information](#)

[Medication Guide](#)

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# Patients

- + [What is Probuphine?](#)
- + [How does Probuphine Work?](#)
- + [What are the Risks Related to the Insertion and Removal of Probuphine Implants?](#)
- + [What Should I do After the Probuphine Implants Have Been Inserted?](#)
- + [Where Can I Get More Information About Probuphine?](#)

## Materials for Patients

[Probuphine Medication Guide](#) 

[What You Need to Know about Probuphine: A Patient's Guide](#) 



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# Patients

## - What is Probuphine?

- Probuphine is an implant that contains the medicine buprenorphine. Probuphine is used to treat certain adults who are addicted to (dependent on) opioid drugs (either prescription or illegal). Probuphine is a part of a complete treatment program that also includes counseling and behavioral therapy.
- Probuphine implants contain the opioid buprenorphine, which may cause physical dependence.

## + How does Probuphine Work?

## + What are the Risks Related to the Insertion and Removal of Probuphine Implants?

## + What Should I do After the Probuphine Implants Have Been Inserted?

## + Where Can I Get More Information About Probuphine?

## Materials for Patients

[Probuphine Medication Guide](#)



[What You Need to Know about Probuphine: A Patient's Guide](#)



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## Patients

### + What is Probuphine?

### - How does Probuphine Work?

- Four implants are inserted under the skin of your upper arm during a procedure done in your physician's office or Opioid Treatment Program (OTP).
- The implants remain in your arm for six months.
- After the six-month period, your doctor must remove the implants.
- If you wish to continue Probuphine, your doctor may insert new implants to continue treatment.
- The implants can be removed sooner if you want to stop treatment.
- Patients must continue to see their doctor at least every month while on Probuphine therapy.

### + What are the Risks Related to the Insertion and Removal of Probuphine Implants?

### + What Should I do After the Probuphine Implants Have Been Inserted?

### + Where Can I Get More Information About Probuphine?

## Materials for Patients

[Probuphine Medication Guide](#)



[What You Need to Know about Probuphine: A Patient's Guide](#)



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# Patients

## + What is Probuphine?

## + How does Probuphine Work?

## - What are the Risks Related to the Insertion and Removal of Probuphine Implants?

- There is a risk of accidental overdose, abuse, and misuse for others if the implants come out and others are exposed to them.
- There is a rare but serious risk that the drug implant, if inserted improperly, may move (migrate) into the blood vessels and to your lung, and could lead to death.
- An implant may come out by itself, or an end of an implant may begin sticking out of your skin.
- Injury or damage to nerves or blood vessels in your arm may happen during the insertion and/or removal procedures.
- Implants may be hard to find if:
  - They are too deep for your doctor to feel.
  - You try to move them around under your skin.
  - You have gained a lot of weight since they were inserted.
- Special procedures, tests, or a referral to a specialist may be needed to find and remove the implants if they are difficult to locate.
- There are common risks associated with any minor surgical procedure, such as:
  - Itching, pain, irritation or redness, swelling, bleeding, or bruising at the insertion site.
  - Scarring around the insertion site.

## + What Should I do After the Probuphine Implants Have Been Inserted?

## + Where Can I Get More Information About Probuphine?

## Materials for Patients

[Probuphine Medication Guide](#)



[What You Need to Know about Probuphine: A Patient's Guide](#)



For any additional information about the Probuphine REMS Program, please call 1-866-397-8939

To Report any suspected adverse reactions, please call 1-844-267-8675

# Patients

## + What is Probuphine?

## + How does Probuphine Work?

## + What are the Risks Related to the Insertion and Removal of Probuphine Implants?

## - What Should I do After the Probuphine Implants Have Been Inserted?

- Follow your doctor's instructions for wound care of the place where the implants were inserted or removed.
- Do not try to remove Probuphine implants yourself.
  - Improper removal carries the risk of implant site infection.
  - If you remove the implants, you could become sick with uncomfortable withdrawal signs and symptoms because your body has become used to this medicine.
- If the Probuphine implants come out:
  - Wash your hands if you have touched the Probuphine implants.
  - Cover the area where the implants were inserted with a clean bandage.
  - Do not allow others to touch or use the Probuphine implants, since this could be very dangerous.
  - Put the implants in a plastic bag and take the implants 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.

## + Where Can I Get More Information About Probuphine?

## Materials for Patients

[Probuphine Medication Guide](#)



[What You Need to Know about Probuphine: A Patient's Guide](#)



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## Patients

- + [What is Probuphine?](#)
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- + [What Should I do After the Probuphine Implants Have Been Inserted?](#)
- [Where Can I Get More Information About Probuphine?](#)

### Read:

- ***What You Need to Know about Probuphine: A Patient's Guide*** The healthcare provider who prescribes Probuphine for you will give this guide to you to help you understand the risks and benefits of Probuphine. This helpful guide is also available by [clicking here](#).
- ***Probuphine Medication Guide*** The healthcare provider who inserts Probuphine will give this guide to you each time the implants are inserted. This medication guide is also available by [clicking here](#).

**Ask** your healthcare provider any questions you may have about Probuphine.

**Call** the Probuphine REMS Program at 1-866-397-8939.

## Materials for Patients

Probuphine Medication Guide



What You Need to Know about  
Probuphine: A Patient's Guide



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# Probuphine Healthcare Provider Locator

Find Providers Near: [My Location](#)  Search Radius

### Services

- 1. HCP Who Prescribes
- 2. HCP Who Inserts/Removes
- 3. HCP Who Prescribes, Inserts and Removes

**Sybil Marsh**  
6 Centerton Road, Moorestown, NJ, 08075  
555-555-5558

**Services**  
1. HCP Who Prescribes

[→ Show on Map](#)

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**Katherine Schmidt**  
4 Centerton Road, Moorestown, PA, 08063  
555-555-5556

**Services**  
3. HCP Who Prescribes. Inserts



For any additional information about the Probuphine REMS Program, please call 1-866-397-8939

To Report any suspected adverse reactions, please call 1-844-267-8675



[Click Here for Recertification](#)

[Prescribing Information](#)

[Medication Guide](#)

[Search](#)

## Contact Us

If you have any questions or require additional information, please contact the Probuphine REMS Program.

Phone Number  
1-866-397-8939

To Report any suspected adverse reactions, please call 1-844-267-8675

Email  
[probuphinerems@braeburnpharma.com](mailto:probuphinerems@braeburnpharma.com)



For any additional information about the Probuphine REMS Program,  
please call 1-866-397-8939

To Report any suspected adverse reactions, please call 1-844-267-8675



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- [Probuphine REMS Recertification Training Requirements](#)



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# Probuphine REMS Program Surgical Procedures Recertification Video

Video Script  
Version 11

The video will be divided into four sections with a play all.

Menu for a DVD disk should list:

- **Play All**
- **Insertion of Probuphine®: *Four Implants***
- **Probuphine® Removal Procedure and Reinsertion**
- **Managing Complications**

VIDEO	AUDIO
<p>1. GRAPHIC SCREEN</p> <p>Title appears:</p> <p><b>Probuphine® REMS Program Surgical Procedures Recertification Video</b></p> <p>The Braeburn Pharmaceuticals logo builds on in a stylized manner:</p> <p><b>Braeburn Pharmaceuticals, Inc.</b></p>	<p>Music: we hear an energetic theme that motivates the flow of video images.</p>
<p>2.</p> <p>Text on Screen:</p> <p>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).</p> <p>Probuphine should be used as part of a complete treatment program to include counseling and psychosocial support.</p>	<p style="text-align: center;">NARRATOR</p> <p>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.</p> <p>Probuphine should be used as part of a complete treatment program to include counseling and psychosocial support.</p>

<p>3. Text on Screen:</p> <p>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.</p>	<p>NARRATOR (voice-over)</p> <p>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.</p>
<p>4. Text on Screen:</p> <p>Under the Drug Addiction 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 or dispense this product for the treatment of opioid dependence and have been assigned a unique identification number that must be included on every prescription.</p> <p>Only DATA 2000 waived prescribers can prescribe Probuphine. For more information on DATA 2000, please go to: <a href="http://buprenorphine.samhsa.gov/data.html">http://buprenorphine.samhsa.gov/data.html</a></p> <p>Probuphine is only available to healthcare providers through the Probuphine REMS Program and all healthcare providers who intend to prescribe and/or insert Probuphine must successfully complete a live Probuphine REMS training program and be certified to prescribe and perform the procedures.</p>	<p>NARRATOR (voice-over)</p> <p>Under the Drug Addiction 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 or dispense this product for the treatment of opioid dependence and have been assigned a unique identification number that must be included on every prescription.</p> <p>Only DATA2000 waived prescribers can prescribe Probuphine. For more information on DATA2000, please visit the DATA 2000 website <a href="http://buprenorphine.samhsa.gov/data.html">http://buprenorphine.samhsa.gov/data.html</a></p> <p>Probuphine is only available to healthcare providers through the Probuphine REMS Program and all healthcare providers who intend to prescribe and/or insert Probuphine must successfully complete a live Probuphine REMS training program</p>

	and be certified to prescribe and perform the procedures.
<p>5. Text on screen:</p> <p>Probuphine REMS goal: 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:</p>	<p>NARRATOR (voice-over)</p> <p>The goal of 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:</p>
<p>6. Text on Screen:</p> <p>a) Ensuring that healthcare providers are educated on the following:</p> <ul style="list-style-type: none"> <li>- Proper insertion/removal</li> <li>- Risk of complications of migration, protrusion, expulsion and nerve damage associated with the insertion/removal</li> <li>- Risk of accidental overdose, misuse and abuse if an implant comes out or protrudes from the skin</li> </ul> <p>b) Informing patients about the risks of complications of migration, protrusion, expulsion and nerve damage associated with insertion/removal, as well as, the risks of accidental overdose, misuse and abuse if an implant comes out or protrudes from the skin.</p>	<p>NARRATOR (voice-over)</p> <p>a) Ensuring that healthcare providers are educated on the following:</p> <ul style="list-style-type: none"> <li>- Proper insertion/removal</li> <li>- Risk of complications of migration, protrusion, expulsion and nerve damage associated with the insertion/removal</li> <li>- Risk of accidental overdose, misuse and abuse if an implant comes out or protrudes from the skin</li> </ul> <p>b) Informing patients about the risks of complications of migration, protrusion, expulsion and nerve damage associated with insertion/removal, as well as, the risks of accidental overdose, misuse and abuse if an implant comes out or protrudes from the skin.</p>
<p>7. Text on Screen:</p> <p>Healthcare providers who prescribe</p>	<p>NARRATOR (voice-over)</p> <p>Probuphine REMS Program requires healthcare providers who prescribe</p>

<p>Probuphine must:</p> <ul style="list-style-type: none"> <li>- Review the Prescribing Information</li> <li>- Complete the <b><i>Probuphine REMS Program Live Training: Lecture and Practicum</i></b></li> <li>- Successfully complete the <b><i>Probuphine REMS Program Knowledge Assessment</i></b></li> <li>- Enroll into the Probuphine REMS Program by completing the <b><i>Probuphine REMS Program Prescriber Enrollment Form</i></b></li> <li>- Review the <b><i>What You Need to Know about Probuphine: A Patient's Guide</i></b> with the patient</li> <li>- And maintain documentation of the insertion and removal of Probuphine in each patient's medical record using the <b><i>Probuphine REMS Program Insertion/Removal Log</i></b> or by using another method/system (e.g., electronic health record) specific to the healthcare provider's practice.</li> </ul>	<p>Probuphine to:</p> <ul style="list-style-type: none"> <li>- Review the Prescribing Information</li> <li>- Complete the <b><i>Probuphine REMS Program Live Training: Lecture and Practicum</i></b></li> <li>- Successfully complete the <b><i>Probuphine REMS Program Knowledge Assessment</i></b></li> <li>- Enroll into the Probuphine REMS Program by completing the <b><i>Probuphine REMS Program Prescriber Enrollment Form</i></b></li> <li>- Review the <b><i>What You Need to Know about Probuphine: A Patient's Guide</i></b> with the patient</li> <li>- And maintain documentation of the insertion and removal of Probuphine in each patient's medical record, using the <b><i>Probuphine REMS Program Insertion/Removal Log</i></b> or by using another method or system, e.g., electronic health record, specific to the healthcare provider's practice.</li> </ul>
<p>8. Text on Screen:</p> <p>Healthcare providers who perform Probuphine surgical procedures must be specially certified and must:</p> <ul style="list-style-type: none"> <li>- Review the Prescribing Information</li> <li>- Attest to performing a surgical procedure in the 3 months prior to enrollment in the Probuphine REMS Program</li> <li>- Complete the <b><i>Probuphine REMS Program Live Training: Lecture and</i></b></li> </ul>	<p style="text-align: center;">NARRATOR (voice-over)</p> <p>Healthcare providers who perform Probuphine surgical procedures must be specially certified and must:</p> <ul style="list-style-type: none"> <li>- Review the Prescribing Information</li> <li>- Attest to performing a surgical procedure in the 3 months prior to enrollment in the Probuphine REMS Program</li> <li>- Complete the <b><i>Probuphine REMS Program Live</i></b></li> </ul>

<p><b>Practicum</b></p> <ul style="list-style-type: none"> <li>- Complete the <b>Probuphine REMS Program Knowledge Assessment</b></li> <li>- Meet the <b>Probuphine REMS Program Criteria for Procedural Competency</b></li> <li>- Enroll into the Probuphine REMS Program</li> <li>- Agree to insert/remove Probuphine in a healthcare setting in which a prescriber certified in the Probuphine REMS Program is also practicing</li> <li>- Ensure that the procedure is conducted in an appropriate facility</li> <li>- Review the <b>Medication Guide</b> with each patient about the risks associated with Probuphine and provide the patient a copy</li> <li>- Maintain documentation of the insertion and removal of Probuphine in each patient’s medical record, in the <b>Probuphine REMS Program Insertion/Removal Log</b> or by using another method/system (e.g., electronic health record) specific to the healthcare provider’s practice</li> <li>- AND, <u>recertify</u> in the Probuphine REMS Program annually</li> </ul>	<p><b>Training: Lecture and Practicum</b></p> <ul style="list-style-type: none"> <li>- Complete the <b>Probuphine REMS Program Knowledge Assessment</b></li> <li>- Meet the <b>Probuphine REMS Program Criteria for Procedural Competency</b></li> <li>- Enroll into the Probuphine REMS Program</li> <li>- Agree to insert and remove Probuphine in a healthcare setting in which a prescriber certified in the Probuphine REMS Program is also practicing</li> <li>- Ensure that the procedure is conducted in an appropriate facility</li> <li>- Review the <b>Medication Guide</b> with each patient about the risks associated with Probuphine and provide the patient a copy</li> <li>- Maintain documentation of the insertion and removal of Probuphine in each patient’s medical record, in the <b>Probuphine REMS Program Insertion/Removal log</b> or by using another method or system, e.g., electronic health record, specific to the healthcare provider’s practice</li> <li>- AND, recertify in the Probuphine REMS Program annually</li> </ul>
<p>9. Text on Screen:</p> <p>This video is intended to be used for recertification for healthcare providers who perform Probuphine surgical procedures.</p>	<p>NARRATOR (voice-over)</p> <p>This video is intended to be used for recertification for healthcare providers who perform Probuphine surgical procedures. This video is not intended to replace the live</p>

<p>This video is <u>not</u> intended to replace the live Probuphine REMS Training Program.</p>	<p>Probuphine REMS Training Program.</p>
<p>10. Text on Screen:</p> <p><b>Before inserting or removing Probuphine implants, be sure to read and thoroughly familiarize yourself with the <i>Probuphine Instructions for Use</i> as well as the <i>Prescribing Information</i>.</b></p>	<p>NARRATOR (voice-over)</p> <p>Before inserting or removing Probuphine implants, be sure to read and thoroughly familiarize yourself with the Instructions for Use as well as the prescribing information.</p>
<p>11. Graphic on Screen Titles appear:</p> <p><b>Part 1 Insertion of Probuphine®: <i>Four implants</i></b></p>	
<p>12. Graphic on Screen Title appears:</p> <p><b>Preparation</b></p> <p><b>Confirm the patient :</b></p> <ul style="list-style-type: none"> <li>• <b>Does not have any contraindications for the use of Probuphine</b></li> <li>• <b>Has had a medical history taken and physical examination</b></li> <li>• <b>Understands benefits and risks of Probuphine</b></li> <li>• <b>Has received a copy of the Medication Guide included in the packaging</b></li> <li>• <b>Does not have any questions prior to the procedure</b></li> <li>• <b>Does not have allergies to the antiseptic and anesthetic to be used during insertion</b></li> </ul>	<p>NARRATOR (voice-over)</p> <p>In preparation for the Probuphine insertion procedure you should confirm that your patient</p> <ul style="list-style-type: none"> <li>- Does not have any contraindications, including hypersensitivity to buprenorphine or ingredients in Probuphine, such as ethylene vinyl acetate.</li> <li>- Has had a medical history taken and physical examination.</li> <li>- Understands the benefits and risks of Probuphine.</li> <li>- Has received a copy of the Medication Guide included in the packaging.</li> <li>- Does not have any questions prior to the procedure</li> <li>- Does not have allergies to the antiseptic and anesthetic to be used during the insertion.</li> </ul>

<p>13. Text on Screen:</p> <p>Probuphine must be inserted under aseptic conditions.</p>	<p>NARRATOR (voice-over)</p> <p>Probuphine must be inserted under aseptic conditions.</p> <p>You may require an assistant to help set up the equipment. Ensure the assistant is functioning under aseptic conditions at all time.</p>
<p>14. Graphic on Screen:</p> <ul style="list-style-type: none"> <li>• Examination table</li> <li>• Instrument stand</li> </ul>	<p>NARRATOR (voice-over)</p> <p>The following equipment is needed for the insertion procedure.</p> <p>An examination table for the patient to lie on. An instrument stand and sterile tray</p>
<p>15. Graphic on Screen: (All the equipment will be shown on the screen and each will be highlighted one at a time with its name appearing for each.)</p>	<p>NARRATOR (voice-over)</p> <p><b>Adequate Lighting, such as a headlamp</b>  <b>Sterile Fenestrated drape;</b>  <b>Latex and talc-free sterile gloves;</b>  <b>Alcohol prep;</b>  <b>Surgical marker;</b>  <b>Antiseptic solution, for example chlorhexidine;</b>  <b>Local anesthetic, Lidocaine 1% with epinephrine 1:100,000;</b>  <b>5 milliliter syringe with 1.5 inch 25 gauge needle;</b>  <b>Adson single tooth tissue forceps;</b>  <b>#15 blade scalpel;</b>  <b>¼ inch thin adhesive strip, for example Steri-strip skin closures;</b>  <b>4x4 sterile gauze;</b></p>

	<p><b>Adhesive bandages;</b>  <b>3 inch pressure bandages;</b>  <b>Liquid adhesive, for example</b>  <b>Matisol</b>  <b>4 Probuphine implants</b>  <b>1 Probuphine applicator</b></p>
<p>16.  3D ANIMATION OF DEVICE</p> <p>NOTE: Cannula and Obturator will be labeled.</p>	<p style="text-align: center;">NARRATOR  (voice-over)</p> <p>The Probuphine® applicator is composed of two parts</p> <p>-- the cannula – and the obturator.</p> <p>It is important to note where each of the markings are located on both the cannula and the obturator</p> <p>The cannula markings include the Blue Bevel-up Marking, the Proximal Marking, and the Distal Marking.</p> <p>The obturator has a stop line marking. The two pieces come together and twist-lock to re-form the complete applicator assembly.</p>
<p>17.  Graphic on Screen:  Graphic on screen of the upper inner side of the arm and the location of the implant.</p>	<p style="text-align: center;">NARRATOR  (voice-over)</p> <p>The insertion procedure will now be demonstrated.</p> <p>Correctly performed sub-dermal insertion of the implants will facilitate their removal. Implants should be placed just under the skin to avoid the large blood vessels and nerves that lie deeper in the subcutaneous tissue in the sulcus between the biceps and the triceps muscles. If the implants are placed improperly, resulting in deep tissue location, the implants will be more difficult to</p>

	remove.
<p>18. footage depicting audio voiceover</p>	<p>NARRATOR (voice-over) Have the patient lie on his or her back with the intended arm flexed at the elbow and externally rotated, so that the hand is next to the head.</p>
<p>19. Graphic on Screen:  Graphically show 8-10 cm from medial epicondyle as well as delineation of the muscles and the sulcus</p>	<p>NARRATOR (voice-over) Identify the insertion site, which is at the inner side of the upper arm, approximately eight to ten centimeters or 3 to 4 inches above the medial epicondyle of the humerus, in the sulcus between the biceps and triceps muscles of the inner arm. Having the patient flex the biceps muscle may facilitate identification of the site.</p>
<p>20.  footage depicting audio voiceover</p>	<p>NARRATOR (voice-over) Clean the insertion site with alcohol prep pad prior to marking the skin.</p>
<p>21.  footage depicting audio voiceover</p>	<p>NARRATOR (voice-over) Using a surgical marker, draw a line to mark the location for the insertion. The implants will be inserted through a small 2.5 to 3 millimeter subdermal incision.  Then, mark the location of the four channel tracks— where each implant will be inserted by drawing four lines with each line 4 centimeter in length.</p>

	<p>The implants will be positioned in a close fan shape distribution 4 to 6 millimeters apart with the fan opening towards the shoulder. The closer the implants are to each other at time of insertion, the more easily they can be removed.</p> <p>There should be at least 5 millimeters between the incision and the implant when the implant is properly positioned.</p>
<p>22. footage depicting audio voiceover</p>	<p style="text-align: center;"><b>NARRATOR</b> (voice-over)</p> <p>Put on sterile gloves. It is important to carefully unwrap the sterile tray and remove the sterile gloves while not touching any of the contents inside the tray.</p> <p>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.</p> <p>Maintain the sterile field and do not touch anything that is not sterile or outside of the sterile field, once sterile gloves have been put on.</p>
<p>23. footage depicting audio voiceover</p>	<p style="text-align: center;"><b>NARRATOR</b> (voice-over)</p> <p>Check the applicator function by removing the obturator from the cannula and relocking it.</p>
<p>24. footage depicting audio voiceover</p>	<p style="text-align: center;"><b>NARRATOR</b> (voice-over)</p> <p>Clean the insertion site with an antiseptic solution, for example,</p>

	<p>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.</p>
<p>25. footage depicting audio voiceover</p>	<p>NARRATOR (voice-over) ...apply the sterile drape to the arm of the patient,</p>
<p>26. footage depicting audio voiceover</p>	<p>NARRATOR (voice-over) ...and anesthetize the insertion area at the incision site and just under the skin along the planned insertion channels using local anesthetic, for example, 5 milliliter lidocaine 1% with epinephrine 1:100,000)</p>
<p>27. footage depicting audio voiceover</p>	<p>NARRATOR (voice-over)  After you confirm the anesthesia is adequate and effective, make a shallow incision that is 2.5 to 3 millimeters in length.</p>
<p>28. Graphic on Screen:  Show the 20 degree angle and 3 to 4 mm below the skin for implant placement</p>	<p>NARRATOR (voice-over)  Lift the edge of the incision opening with an Adson single tooth tissue forceps. While applying counter-traction to the skin, insert only the tip of the applicator at a slight angle at no greater than 20 degrees, into the subdermal space with a depth of 3 to 4 millimeters below the skin, with the bevel-up stop marking on the</p>

	cannula facing upwards and visible with the obturator locked fully into the cannula.
<p>29. Text on Screen:</p> <p><b>Lower the applicator to a horizontal position, lift the skin up with the tip of the applicator but keep the cannula in the sub-dermal connective tissue.</b></p>	<p>NARRATOR (voice-over)</p> <p>Lower the applicator to a horizontal position, lift the skin up with the tip of the applicator but keep the cannula in the sub-dermal connective tissue.</p>
<p>30. Graphic on screen:</p> <p>Show cannula into the skin with proximal marking on cannula just going into skin (picture or graphic, applicator is horizontal to skin – See figure 7 in IFU)</p>	<p>NARRATOR (voice-over)</p> <p>While tenting, or lifting, gently advance the applicator sub-dermally along the channel marking on the skin until the proximal marking on the cannula just disappears into the incision.</p>
<p>31.</p>	<p>NARRATOR (voice-over)</p> <p>Holding the cannula in place, unlock and remove the obturator. Then, insert one Probuphine implant into the cannula.</p>
<p>32. Text on Screen:</p> <p><b>Gently push the obturator forward, keeping in mind that mild resistance should be felt, until the obturator stop line is level with the cannula bevel-up stop marking.</b></p> <p><b>The implant is now in position at the tip of the cannula. It is important not to force the implant beyond the end of the cannula with the obturator.</b></p> <p><b>There should be at least 5 mm</b></p>	<p>NARRATOR (voice-over)</p> <p>Reinsert the obturator into the cannula. Gently push the obturator forward, keeping in mind that mild resistance should be felt, until the obturator stop line is level with the cannula bevel-up stop marking.</p> <p>The implant is now in position at the tip of the cannula. It is important not to force the implant beyond the end of the cannula with the obturator.</p>

<p><b>between the incision and the implant when the implant is properly positioned.</b></p>	<p>There should be at least 5 millimeters between the incision and the implant when the implant is properly positioned.</p>
<p>33. Text on Screen:</p> <p><b>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 sub-dermal position.</b></p>	<p>NARRATOR (voice-over)</p> <p>While holding the obturator fixed in place on the arm, retract the cannula along the obturator, leaving the implant in place.</p> <p>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 sub-dermal position.</p>
<p>34. Graphic on Screen:</p> <p>Show applicator bevel-up and cannula tip in the skin with distal marking of the cannula visible right outside the incision opening</p>	<p>NARRATOR (voice-over)</p> <p>Withdraw the cannula until the hub is flush with the obturator, and then twist the obturator clockwise to lock onto the cannula.</p> <p>Retract the applicator, bevel up, until the distal marking of the cannula can be visualized at the incision opening -- the sharp tip will remain in the sub-dermal space.</p>
<p>35. footage depicting audio voiceover</p>	<p>NARRATOR (voice-over)</p> <p>Redirect the applicator to the next channel marking while stabilizing the previously inserted implant with your index finger, away from the sharp tip.</p>
<p>36. footage depicting audio voiceover</p>	<p>NARRATOR (voice-over)</p> <p>Repeat these steps to insert each of the three remaining implants through</p>

	<p>the same incision, placing implants in a close fan-shaped distribution 4 to 6 millimeters apart at the top of the implant. Once all implants are in place you can remove the applicator.</p>
<p>37. Text on Screen:</p> <p><b>By palpating both ends of the implant, you should be able to confirm the presence of each 26 mm implant.</b></p> <p>Graphic in Screen: <b>Palpation of inserted implants after insertion.</b></p>	<p>NARRATOR (voice-over)</p> <p>Always verify the presence of each implant by palpation in the patient's arm immediately after each implant insertion.</p> <p>By palpating both ends of the implant, you should be able to confirm the presence of each 26 millimeter implant.</p>
<p>38. Text on Screen:</p> <p><b>If you cannot feel each of the four implants or are in doubt of their presence prior to removal procedure, reschedule the removal procedure. Refer to a radiologist to confirm their location first – via an Ultrasound or if necessary, Magnetic Resonance Imaging (MRI).</b></p> <p><b>Attempt removal <u>only</u> after localization and depth has been confirmed by these measures.</b></p> <p><b>Probuphine implants are not radio-opaque and cannot be seen by X-rays or CT scan.</b></p> <p><b>If Ultrasound or MRI fail, call 1-844-859-6341 to report the event for surveillance purposes.</b></p>	<p>NARRATOR (voice-over)</p> <p>If you cannot feel each of the four implants or are in doubt of their presence prior to removal procedure, reschedule the removal procedure. Refer to a radiologist to confirm their location first – via an Ultrasound or if necessary, Magnetic Resonance Imaging.</p> <p>Attempt removal only after localization and depth has been confirmed by these measures.</p> <p>Note, however, that Probuphine implants cannot be seen by X-rays or CT scans.</p> <p>In the event of failure to locate through ultrasound or MRI, please call 1-844-859-6341 to report this event to the company for surveillance purposes.</p>
<p>39.</p>	

<p>footage depicting audio voiceover</p>	<p>NARRATOR (voice-over)</p> <p>Apply pressure to the incision site for approximately five minutes if necessary.</p> <p>Clean the incision site and surrounding skin. Apply liquid adhesive to the skin margins and allow to dry before closing the incision with the quarter inch thin adhesive strip, for example Steri-strip skin closers.</p>
<p>40. footage depicting audio voiceover</p>	<p>NARRATOR (voice-over)</p> <p>Place a small adhesive bandage over the insertion site.</p>
<p>41. Text on Screen:</p> <p><b>Inform the patient that the pressure bandage can be removed in 24 hours and the adhesive bandage can be removed in three to five days.</b></p> <p><b>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.</b></p>	<p>NARRATOR (voice-over)</p> <p>Apply a pressure bandage with sterile gauze to minimize bruising. Inform the patient that the pressure bandage can be removed in 24 hours and the adhesive bandage can be removed in three to five days.</p> <p>Instruct the patient to apply an ice pack on his or her arm for 40 minutes every two hours for the first 24 hours and as needed.</p>
<p>42. Text on Screen</p> <p><b>Instruct patient on proper wound care, signs and symptoms of infection, including: redness, swelling, fever, drainage, localized heat, malaise, and continued or increasing pain</b></p>	<p>NARRATOR (voice-over)</p> <p>Be sure to explain proper wound care of the insertion site as well as signs and symptoms of infection, including redness, swelling, fever, drainage, localized heat, malaise, and continued or increasing pain</p>

<p>around the surgical site.</p>	<p>around the surgical site</p>
<p>43. Text on Screen:</p> <p>Finally,</p> <ol style="list-style-type: none"> <li>1) <b>Complete the Patient Identification Card and give it to the patient to keep.</b></li> <li>2) <b>Complete the Patient Chart Sticker and affix it to the patient medical record.</b></li> <li>3) <b>Ensure that the patient takes the Medication Guide and explain proper care of the insertion site.</b></li> <li>4) <b>Ask the patient if they have any questions.</b></li> <li>5) <b>Complete the <i>Probuphine REMS Program Insertion/Removal Log</i> provided to you and place it in the patient’s chart. Be sure to record the serial number of the Probuphine Kit used in the procedure for tracking and accountability purposes (e.g., tracking adverse events) in the log.</b></li> <li>6) <b>If desired, note this procedure on your running <i>Probuphine REMS Program Procedure Record for Recertification</i> should you wish to document your procedures for auditing purposes.</b></li> </ol>	<p style="text-align: center;">NARRATOR (voice-over)</p> <p>Finally, Complete the Patient Identification Card and give it to the patient to keep.</p> <p>Also, complete the Patient Chart Sticker and affix it to the patient medical record or scan or input into electronic medical record. Ensure that the patient takes the Medication Guide and explain proper care of the insertion site. Ask the patient if they have any questions.</p> <p>Complete the <b><i>Probuphine REMS Program Insertion/Removal Log</i></b> provided to you and place it in the patient’s chart. Be sure to record the serial number of the Probuphine kit used in the procedure for tracking and accountability purposes, for example, tracking adverse events, in the log. If desired, note this procedure on your running Probuphine REMS Program Procedure Record for Recertification, should you wish to document your procedures for auditing purposes.</p>
<p>44.</p> <p>Title appears:</p> <p><b>Dispose of all equipment labeled “For Single Use Only”</b></p>	<p style="text-align: center;">NARRATOR (voice-over)</p> <p>The applicator is for single use only and should be disposed in accordance with the Centers for Disease Control and Prevention</p>

	guidelines for hazardous waste.
<p>45. Text on Screen:</p> <p><b>((Serious) adverse events ((S)AEs) and insertion and removal related events need to be reported to the company at 1-844-859-6341. Report the Probuphine Kit serial number in order to facilitate tracking of adverse events.</b></p>	
<p>46. GRAPHIC SCREEN The Braeburn Pharmaceuticals logo builds on in a stylized manner:</p> <p><b>Braeburn Pharmaceuticals, Inc.</b></p>	<p>NARRATOR (voice-over) -- from Braeburn Pharmaceuticals.</p>

## PART 2:

### Probuphine® Removal Procedure

<p>47. Text on Screen:</p> <p><b>Before initiating the removal procedure, carefully read the instructions for removal and consult the Patient Identification Card and/or the Patient Chart Sticker for the location of the implants. Location of the implants can also be found on the <i>Probuphine REMS Program Insertion/Removal Log</i> that was filled out during the insertion procedure.</b></p>	<p>NARRATOR (voice-over)</p> <p>Before initiating the removal procedure, carefully read the instructions for removal and consult the Patient Identification Card and/or the Patient Chart Sticker for the location of the implants. Location of implants can also be found on the <b><i>Probuphine REMS Program Insertion/Removal Log</i></b></p> <p>The exact location of all 4 implants in the arm should be verified by</p>
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<p><b>Verify exact location of all 4 implants by palpation.</b></p> <p><b>Non-palpable implants should always be located prior to attempted removal.</b></p> <p><b>Suitable methods to locate implants are:</b></p> <ul style="list-style-type: none"> <li>- <b>Ultrasound with high frequency linear array transducer at 10 MHz or greater, or</b></li> <li>- <b>Magnetic Resonance Imaging (MRI)</b></li> </ul>	<p>palpation. If all of the implants are not palpable or you are in doubt of their presence use other methods to confirm the presence of the implants.</p> <p>Non-palpable implants should always be first located prior to removal. Suitable methods to locate the implants are: Ultrasound with a high frequency linear array transducer at 10 mega-hertz or greater, or with Magnetic Resonance Imaging.</p>
<p>48. Text on Screen:</p> <p>Probuphine implants cannot be seen by X-ray or CT scan.</p> <p>In the event of failure to locate through ultrasound or MRI, call: 1-844-859-6341 to report the event.</p>	<p style="text-align: center;">NARRATOR (voice-over)</p> <p>Note that Probuphine implants are not radiopaque and cannot be seen by X-ray or CT scan. In the event of failure to locate through ultrasound or MRI, please call 1-844-859-6341 to report this event to the company for surveillance purposes.</p>
<p>49. Text on Screen:</p> <p><b>After localization of a non-palpable implant, removal should be performed under ultrasound guidance.</b></p> <p><b>Exploratory surgery without knowledge of the exact location of all implants is strongly discouraged.</b></p> <p><b>Removal of deeply inserted implants should be conducted with caution in order to prevent injury to deeper neural or vascular structures in the arm and be performed by healthcare providers familiar with the anatomy of the arm.</b></p>	<p style="text-align: center;">NARRATOR (voice-over)</p> <p>After localization of a non-palpable implant, removal should be performed under ultrasound guidance.</p> <p>Exploratory surgery without knowledge of the exact location of all implants is strongly discouraged.</p> <p>Removal of deeply inserted implants should be conducted with caution in order to prevent injury to deeper neural or vascular structures in the arm and be performed by healthcare providers familiar with the anatomy of the arm.</p>

<p><b>A surgical specialist consulted to assist with a difficult removal does not need to be certified in the Probuphine REMS Program.</b></p>	<p>Note that a surgical specialist consulted to assist with a difficult removal does not need to be certified in the Probuphine REMS Program.</p>
<p>50. Text on Screen:</p> <p>Probuphine must be removed under aseptic conditions.</p>	<p>NARRATOR (voice-over)</p> <p>Probuphine must be removed under aseptic conditions.</p> <p>You may require an assistant to help set up the equipment and assist with some of the removal procedures. Ensure the assistant is functioning under aseptic conditions at all times.</p>
<p>51. Graphic on Screen:</p> <ul style="list-style-type: none"> <li>• <b>Exam table</b></li> <li>• <b>Instrument stand</b></li> </ul>	<p>NARRATOR (voice-over)</p> <p>The following equipment is needed for implant removal: An examination table for the patient to lie on, an instrument stand,</p>
<p>52. Graphic on Screen:</p> <p>(Graphic of all equipment. Each equipment will be highlighted, with name of item appearing for each.)</p>	<p>NARRATOR (voice-over)</p> <p>Sterile Tray; Adequate lighting, for example a headlamp; Sterile fenestrated drape; Latex and talc-free sterile gloves; Alcohol prep; Antiseptic solution, for example chlorhexidine; Surgical marker; Local anesthetic, 1% lidocaine with epinephrine 1;100,000; 5 mL syringe with 1.5 inch 25 gauge</p>

	<p>needle;  Adson single tooth tissue forceps;  Mosquito forceps;  Two X-plant clamps, which are vasectomy fixation clamps with 2.5 millimeter ring diameter;  Iris scissors;  Needle driver;  #15 blade scalpel;  Sterile ruler  4x4 sterile gauze;  Adhesive bandage;  3-inch pressure bandage;  and sutures such as 4-0 Prolene with an FS-2 cutting needle.  sutures may be absorbable</p>
<p>53.  footage depicting audio voiceover</p>	<p>NARRATOR  (voice-over)  Have the patient lie on his or her back with the implant arm flexed at the elbow and externally rotated, so that the hand is next to the head.</p>
<p>54.  footage depicting audio voiceover</p>	<p>NARRATOR  (voice-over)  Reconfirm the location of all implants by palpation. The patient should have 4 implants.</p>
<p>55.  footage depicting audio voiceover</p>	<p>NARRATOR  (voice-over)  Clean the removal site with an alcohol prep pad prior to marking the skin.  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.</p>

<p>56. footage depicting audio voiceover</p>	<p>NARRATOR (voice-over) Put on sterile gloves.</p>
<p>57. footage depicting audio voiceover</p>	<p>NARRATOR (voice-over) It is important to carefully unwrap the sterile tray and remove the sterile gloves while not touching any of the contents inside the tray.</p> <p>Using aseptic technique, place the sterile equipment on the sterile field of the instrument stand.</p> <p>Maintain the sterile field and do not touch anything that is not sterile or outside of the sterile field, once sterile gloves have been put on.</p>
<p>58. footage depicting audio voiceover</p>	<p>NARRATOR (voice-over) Clean the removal site with an antiseptic solution, for example 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. Do not blot or wipe away.</p>
<p>59. footage depicting audio voiceover</p>	<p>NARRATOR (voice-over) Apply the sterile drape to the arm of the patient.</p>

<p>60. footage depicting audio voiceover</p>	<p style="text-align: center;"><b>NARRATOR</b> (voice-over)</p> <p>Anesthetize the incision site and the subcutaneous space containing the implants, by injecting 5 to 7 milliliters lidocaine 1% with epinephrine 1:100,000.</p> <p>Separate needles may be used for the incision site and the subcutaneous injections. Injecting anesthetic just underneath each of the implants will help lift the implants toward the skin surface, facilitating removal. Injecting superficially is not recommended as it will obscure your view of the implants.</p>
<p>61. footage depicting audio voiceover</p>	<p style="text-align: center;"><b>NARRATOR</b> (voice-over)</p> <p>After determining that anesthesia is adequate and effective, make a 7 to 10 millimeter incision with a scalpel, parallel to the axis of the arm, between the second and third implants.</p>
<p>62. footage depicting audio voiceover</p>	<p style="text-align: center;"><b>NARRATOR</b> (voice-over)</p> <p>Lift the skin edge with an Adson single tooth forceps, and separate the tissues above and below the first visualized implant using an iris scissors or a curved mosquito forceps.</p> <p>Grasp the center of the implant with the X-plant clamp and apply gentle traction.</p> <p>Use the technique of spreading and closing with either the iris scissors or mosquito forceps to separate the fibrous tissue. If the implant is</p>

	<p>encapsulated, use the scalpel to shave the tissue sheath and carefully dissect the tissue around the implant.</p> <p>The implant can then be removed.</p>
<p>63. footage depicting audio voiceover</p>	<p style="text-align: center;">NARRATOR (voice-over)</p> <p>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.</p> <p>At this point, you may require the use of your second X-plant clamp to remove the implant, as well as an assistant to hold the second X-plant clamp.</p> <p>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.</p>
<p>64. footage depicting audio voiceover</p>	<p style="text-align: center;">NARRATOR (voice-over)</p> <p>Confirm that the entire implant, which is 26 millimeters long, has been removed by measuring its length. If a partial implant - less than 26 millimeters -- is removed, the remaining piece should be removed by following the same removal instructions.</p>

	<p>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.</p>
<p>65. footage depicting audio voiceover</p>	<p>NARRATOR (voice-over)</p> <p>When all the implants have been removed, clean the incision site and close the incision with either continuous or interrupted sutures.</p>
<p>66. footage depicting audio voiceover</p>	<p>NARRATOR (voice-over)</p> <p>Place an adhesive bandage over the incision.</p> <p>Use the sterile gauze and apply gentle pressure for five minutes to the incision site to ensure hemostasis.</p> <p>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.</p>
<p>67. Text on Screen: <b>Counsel the patient on proper aseptic incision site care.</b></p> <p><b>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.</b></p>	<p>NARRATOR (voice-over)</p> <p>Counsel the patient on proper aseptic incision site care.</p> <p>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.</p>
<p>68. Text on Screen: <b>1. Instruct patient on proper wound care, signs and symptoms of infection,</b></p>	<p>NARRATOR (voice-over)</p> <p>Counsel the patient on proper wound care, signs and symptoms of</p>

<p>including redness, swelling, fever, drainage, localized heat, malaise, and continued or increasing pain around the surgical site.</p> <ol style="list-style-type: none"> <li>2. Schedule follow-up appointment for the sutures to be removed.</li> <li>3. Complete the <i>Probuphine REMS Program Insertion/Removal Log</i> and place it in the patient's chart.</li> <li>4. If desired, note this procedure on your own <i>Probuphine REMS Program Procedure Record for Recertification</i> - should you wish to document your procedures for auditing purposes.</li> </ol>	<p>infection including redness, swelling, fever, drainage, localized heat, malaise, and continued or increasing pain around the surgical site. Schedule an appointment with the patient for the sutures to be removed.</p> <p>Complete the <i>Probuphine REMS Program Insertion/ Removal Log</i> provided to you and place it in the patient's chart</p> <p>If desired, note this procedure on your own <i>Probuphine REMS Program Procedure Record for Recertification</i> – should you wish to document your procedures for auditing purposes.</p>
<p>69. Text on Screen:</p> <p>The removed implant, contains significant amount of residual buprenorphine, and 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.</p> <p>Disposal of Probuphine implants should also be in keeping with local, State, and Federal regulations governing the disposal of pharmaceutical biohazardous waste</p>	<p>NARRATOR (voice-over)</p> <p>The removed implant, contains significant amount of residual buprenorphine, and must be handled with adequate security, accountability, and proper disposal, per facility procedure for a Schedule three drug product, and per applicable Federal, State, and local regulations.</p> <p>Disposal of Probuphine implants should also be in keeping with local, State, and Federal regulations governing the disposal of pharmaceutical biohazardous waste.</p>
<p>70. Text on Screen:</p> <p><b>Continuation of Therapy: Subsequent Insertion in the Contralateral Arm</b></p>	<p>NARRATOR (voice-over)</p> <p>Continuation of Therapy: subsequent insertion in the contralateral arm.</p>

<p>71. Graphic on Screen:</p> <p><b>Figure of one location on each arm.</b></p>	<p>NARRATOR (voice-over)</p> <p>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 months 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.</p>
<p>72. Graphic on Screen:</p> <p><b>Figure of one location on each arm.</b></p>	<p>NARRATOR (voice-over)</p> <p>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 of which they were transferred to Probuphine treatment, prior to additional Probuphine treatment.</p>
<p>73. Text on Screen:</p> <p>Transition patients back to transmucosal buprenorphine containing product for continued treatment, after two six-month treatments with Probuphine.</p>	<p>NARRATOR (voice-over)</p> <p>After one insertion in each arm, most patients should be transitioned back to transmucosal buprenorphine containing product for continued treatment.</p> <p>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.</p>

<p>74. Text on Screen:</p> <p>Neither re-insertion into previously-used administration sites, nor into sites other than the upper arm, have been studied.</p> <p>Avoid previously implanted sites because the effect of scarring and fibrosis in previously used insertion sites on either the effectiveness of Probuphine or safety of insertion have not been evaluated.</p> <p>Continuation of Probuphine after one insertion in each arm should be only 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 healthcare provider with PROBUPHINE procedures and related procedures, and the clinical need of the patient for ongoing treatment with subdermal medication.</p> <p>In most cases, patients should be transitioned back to a transmucosal buprenorphine-containing product for continued treatment.</p>	<p>NARRATOR (voice-over)</p> <p>Neither re-insertion into previously-used administration sites, nor into sites other than the upper arm, have been studied.</p> <p>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 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.</p>
<p>75. Text on Screen:</p> <p><b>((Serious) adverse events ((S)AEs) and insertion and removal related events (IRREs) need to be reported to the company at 1-844-859-6341. Report the Probuphine Kit serial number in order to facilitate tracking</b></p>	

<p><b>of adverse events.</b></p>	
<p>76. Graphic on Screen:</p> <p>The Braeburn Pharmaceuticals logo builds on in a stylized manner:</p> <p><b>Braeburn Pharmaceuticals, Inc.</b></p>	<p>NARRATOR (voice-over) -- from Braeburn Pharmaceuticals.</p>

### **PART 3: Managing Complications**

<p>77. Text on Screen:</p> <p>Managing Spontaneous Expulsion of Probuphine</p>	
<p>78. Graphic on Screen: (NEED TO DECIDE) Animation showing an implant falling out of the arm</p>	<p>NARRATOR (voice-over)</p> <p>If spontaneous expulsion of the implant occurs after insertion, the following steps should be taken.</p>
<p>79. Text on Screen:</p> <ul style="list-style-type: none"> <li>- Schedule two appointments for the patient to return to the office of the inserting healthcare provider (HCP) as soon as possible and to the office of the prescribing HCP.</li> <li>- 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's office to determine whether the full implant has been expelled.</li> </ul>	<p>NARRATOR (voice-over)</p> <ul style="list-style-type: none"> <li>• 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.</li> <li>• 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's office to determine whether the full implant has been expelled.</li> </ul>

<p>80. footage depicting audio voiceover</p>	<p>NARRATOR (voice-over)</p> <ul style="list-style-type: none"> <li>If the patient returns the expelled implant, measure it to ensure that the entire implant was expelled, 26 millimeter in length.</li> </ul>
<p>81. footage depicting audio voiceover</p>	<p>NARRATOR (voice-over)</p> <ul style="list-style-type: none"> <li>Dispose the removed implant in keeping with local, state and federal regulations governing the disposal of pharmaceutical biohazardous waste, after measuring.</li> </ul>
<p>82. footage depicting audio voiceover</p>	<p>NARRATOR (voice-over)</p> <ul style="list-style-type: none"> <li>Examine the incision site for infection. If infected, treat appropriately and determine if remaining implants need to be removed.</li> </ul>
<p>83. Graphic on Screen</p> <p><b>Doctor palpating arm or 2D Graphic overlay on arm</b></p>	<p>NARRATOR (voice-over)</p> <ul style="list-style-type: none"> <li>If the expelled implant is not intact, palpate the insertion location to identify the location of any remaining partial implant. Remove implant using the techniques described in the Removal Procedure.</li> </ul>
<p>84. Text on Screen:</p> <p>Call 1-844-859-6341 to obtain a new kit</p>	<p>NARRATOR (voice-over)</p> <p>Call 1-844-859-6341 to obtain a</p>

<p>that will include four implants and return instructions for any unused implants.</p>	<p>new kit that will include four implants and return instructions for any unused implants.</p>
<p>85. Text on Screen:</p> <ul style="list-style-type: none"> <li>• 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.</li> <li>• Schedule an appointment to insert replacement implant(s).</li> <li>• Insert the replacement implant(s) in the same arm or either medially or laterally to in-situ implants. Alternatively, replacement implant(s) may be inserted in the contralateral arm.</li> <li>• Record the new serial number of the replacement kit on <b><i>the Probuphine REMS Program Insertion/Removal Log</i></b> Form.</li> </ul>	<p>NARRATOR (voice-over)</p> <ul style="list-style-type: none"> <li>• 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.</li> <li>• Schedule an appointment to insert replacement implant(s).</li> <li>• Insert the replacement implant(s) in the same arm or either medially or laterally to in-situ implants. Alternatively, replacement implant(s) may be inserted in the contralateral arm.</li> <li>• Record the new serial number of the replacement kit on the <b><i>Probuphine REMS Program Insertion/Removal Log Form</i></b>.</li> </ul>

<p>86. Text on Screen:</p> <p>Prevention of Deep Insertion</p>	
<p>87. Graphic on Screen: Animation depicting the difference between the correct depth vs too-deep insertion of the implants.</p>	<p>NARRATOR (voice-over)</p> <p>Correctly performed sub-dermal insertion of the implants will facilitate their removal. If the implants are placed improperly, resulting in deep</p>

	tissue location, the implants will be more difficult to remove.
88. Graphic on Screen: Animation depicting insertion of the implant under the skin in the subdermal space with large blood vessels and nerves beneath.	NARRATOR (voice-over)  In order to prevent deep insertion of the implants, the implants should be placed just under the skin to avoid the large blood vessels and nerves that lie deeper in the subcutaneous tissue in the sulcus between the biceps and the triceps muscles.
89. Graphic on Screen: Animation depicting the applicator, bevel-up, being inserted at 20 degrees and depth of 3 to 4 mm.	NARRATOR (voice-over)  After the shallow incision that is 2.5 to 3 millimeters has been made, insert only the tip of the applicator at a slight angle that is no greater than 20 degrees, into the subdermal space with a depth of 3 to 4 millimeters below the skin with the bevel-up stop marking on the cannula facing upwards and visible with the obturator locked fully into the cannula.
90. Graphic on Screen: Animation depicting the applicator being lowered to horizontal position.	NARRATOR (voice-over)  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.
91. Graphic on Screen: Animation depicting the applicator being inserted while tenting the skin, showing proximal marking disappearing into the incision.	NARRATOR (voice-over)  While tenting or 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.
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<p>92. Text on Screen:</p> <p>Non-palpable Implants and Complicated Removal Procedure</p>	
<p>93. Graphic on Screen:</p> <p>Picture of Patient Identification Card and Patient Chart Sticker</p> <p>Picture of a sample of <b>Probuphine REMS Program Insertion/Removal Log</b>, and location of the implants on the log</p>	<p style="text-align: center;">NARRATOR (voice-over)</p> <p>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. Location of the implants can also be found on the Probuphine REMS Program Insertion and Removal Log that was filled out during the patient's insertion procedure.</p> <p>The exact location of all implants in the arm should be verified by palpation.</p>
<p>94. Text on Screen:</p> <p>Non-palpable implants should always be located prior to attempted removal.</p>	<p style="text-align: center;">NARRATOR (voice-over)</p> <p>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.</p>
<p>95. Graphic on Screen:</p> <p>Picture of Ultrasound and MRI</p>	<p style="text-align: center;">NARRATOR (voice-over)</p> <p>Suitable methods to locate implants are: Ultrasound with a high frequency linear array transducer, 10 MHz or greater, or</p>

<p>Text on Screen:          Probuphine implants are not radiopaque and cannot be seen by X-ray or CT scan.</p>	<p>Magnetic resonance imaging or MRI.</p> <p>Note that Probuphine implants are not radiopaque and cannot be seen by X-ray or CT scan.</p>
<p>96.          Text on Screen:          If an implant or implant fragment is not removed during a removal attempt, the patient should undergo imaging for localization as soon as is feasible.</p> <p>The subsequent removal attempt should be performed on the same day of localization.</p> <p>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 be should closed with sutures in the interim.</p>	<p>NARRATOR          (voice-over)</p> <p>If an implant or implant fragment is not removed during a removal attempt, the patient should undergo imaging for localization as soon as is feasible.</p> <p>The subsequent removal attempt should be performed on the same day of localization.</p> <p>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 be should closed with sutures in the interim.</p>
<p>97.          Text on Screen:</p> <p>Report any event of failure to locate non-palpable implants using ultrasound or MRI, by calling 1-844-859-6341</p>	<p>NARRATOR          (voice-over)</p> <p>Report any event of failure to locate non-palpable implants using ultrasound or MRI, by calling 1-844-859-6341 for company surveillance purposes.</p>
<p>98.          Text on Screen:</p> <p><b>Exploratory surgery without knowledge of the exact location of all implants is strongly discouraged.</b></p> <p><b>Removal of deeply inserted implants should be conducted with caution in order to prevent injury to deeper neural or vascular structures in the</b></p>	<p>NARRATOR          (voice-over)</p> <p>Exploratory surgery without knowledge of the exact location of all implants is strongly discouraged.</p> <p>There is a greater risk of injury to neural and vascular structures during removal of implants located deeper than the subdermal space.</p> <p>As the anatomical location of these</p>

<p><b>arm and be performed by healthcare providers familiar with the anatomy of the arm.</b></p> <p><b>A surgical specialist consulted to assist with a difficult removal does not need to be certified in the Probuphine REMS Program.</b></p>	<p>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. Note that a surgical specialist consulted to assist with a difficult removal does not need to be certified in the Probuphine REMS Program.</p>
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<p>99. Text on Screen:  Prevention of Fractured/Bent Implant</p>	
<p>100. Prevention of Fractured/Bent Implant</p>	<p>NARRATOR (voice-over)</p> <p>In order to avoid fracturing or bending the implants, follow the steps below during insertion and removal procedures.</p>
<p>101. Graphic on Screen: Animation depicting the obturator pushed to bevel-up marking point. A second animation of the obturator being pushed above the implant channel to demonstrate improper location of the implants when the obturator is pushed beyond the bevel-up marking.</p>	<p>NARRATOR (voice-over)</p> <p>During insertion procedure, avoid pushing the obturator marking beyond the bevel up marking. If the obturator is pushed beyond the bevel marking, the implant will be PUSHED above the implant channel and inappropriately placed. The cannula is creating a channel for the implant to be placed, if the implant is pushed beyond the channel created by the cannula, the implant may fracture or bend.</p> <p>It is important to hold the obturator fixed in place and retract the cannula along the obturator to place the implant in the</p>

	channel that has been formed by the cannula.
102. Graphic on Screen: Animation or video demonstration of X-plant clamp grabbing the implant.	NARRATOR (voice-over)  During removal, it is important to not use a hemostat to pull the implant out, this will cause fractures. Use the X-plant clamp and use gentle traction with an X-plant clamp. Use an additional X-plant clamp as well as an assistant, if needed.

103. Text on Screen: Prevention of Incision Site Infection	
104. Text on Screen:  During insertion and removal procedures, it is essential to use and maintain aseptic technique at all times.  Graphic on Screen: Shots of insertion and removal tray in sterile field	NARRATOR (voice-over)  During insertion and removal procedures, it is essential to use and maintain aseptic technique at all times. It is important to ensure that all equipment is appropriately placed into the sterile field.
105. Graphic on Screen:  Use of chlorhexidine in the video of either insertion or removal video will be shown here to demonstrate again.	NARRATOR (voice-over)  Make sure that the insertion and removal sites are properly cleaned with the antiseptic solution, following the appropriate instructions carefully.
106. Graphic on Screen:  <b>Patient being handed instructions</b>	NARRATOR (voice-over)  Make sure that the patient is provided with the incision site care instructions and how to identify signs and symptoms

	of infections.
<p>107.</p> <p>Text on Screen:</p> <p>In summary, proper attention to technique and following the instructions for insertion and removal procedures will minimize potential problems and complications.</p>	<p>NARRATOR (voice-over)</p> <p>In summary, proper attention to technique and following the instructions for insertion and removal procedures will minimize potential problems and complications.</p>
<p>108.</p> <p>Text on Screen:</p> <p><b>Serious adverse events (SAEs) and insertion and removal related events (IRREs) need to be reported to the company at 1-844-859-6341. Report the Probuphine Kit serial number in order to facilitate tracking of adverse events.</b></p>	
<p>109.</p> <p>Graphic on Screen:</p> <p>The Braeburn Pharmaceuticals logo builds on in a stylized manner:</p> <p><b>Braeburn Pharmaceuticals, Inc.</b></p>	<p>NARRATOR (voice-over) -- from Braeburn Pharmaceuticals.</p>

## Probuphine<sup>®</sup> REMS Program Healthcare Provider Who Performs Probuphine Surgical Procedures Recertification Form

(for completion by healthcare providers who will **insert** or **remove** Probuphine. Please fax to 609-423-0965)

Probuphine may only be inserted by healthcare providers who are certified in the Probuphine REMS Program to perform these procedures. Patients having Probuphine removed must be monitored to ensure that removal is performed by a healthcare provider who is certified to insert. In addition, Probuphine is only available from healthcare providers who are certified in the Probuphine REMS Program to prescribe Probuphine. Annual recertification is required to maintain your certification to insert Probuphine. Based upon your healthcare provider background and the number of insertion/removal procedures you have completed; your recertification requirements are outlined below:

### Probuphine<sup>®</sup> REMS Recertification Training 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 ↓	
	<b>Number of Probuphine procedures in the past 12 months</b> (Select the Row that applies)	
	<b>≥10</b>  Performed 10 or more successful <sup>2</sup> procedures (comprised of at least five insertions and five removals) →	I must review the <b><i>Probuphine REMS Program Surgical Procedures Recertification Video</i></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><i>Probuphine REMS Program Procedure Record for Recertification</i></b> or another record of my choosing - which must be provided to the Probuphine REMS Program if I am audited.
I must review the <b><i>Probuphine REMS Program Surgical Procedures Recertification Video</i></b> found on the Probuphine REMS website <b>every year</b> .	<b>&lt;10</b>  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><i>Probuphine REMS Program Live Training: Lecture and Practicum</i></b> session</li> <li>• successfully complete the <b><i>Probuphine REMS Program Knowledge Assessment</i></b> test</li> <li>• meet the <b><i>Probuphine REMS Program Criteria for Procedural Competency</i></b></li> </ul>

Your Training Requirements can be found at the intersection of the row and column you select below based upon your personal experience

<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.

To maintain your certification to insert Probuphine, you must attest that you have completed the following requirements:

### **Healthcare Providers Who Perform Probuphine Surgical Procedures Recertification Agreement**

By signing this form, I attest that:

I meet one of the following recertification requirements (please select):

- I am a HCP with operating privileges at hospitals or out-patient surgical centers and I have reviewed the **Probuphine REMS Program Surgical Procedures Recertification Video** within the past 12 months of my last Probuphine REMS certification.
- I am a HCP with no operating privileges at hospitals or out-patient surgical centers. I have performed 10 or more successful\* procedures (comprised of at least five insertions and five removals) during the past 12 months and I have reviewed the **Probuphine REMS Program Surgical Procedures Recertification Video**.
- I am a HCP with no operating privileges at hospitals or out-patient surgical centers. I have performed less than 10 successful\* procedures (comprised of at least five insertions and five removals) during the past 12 months and have repeated and successfully completed the **Probuphine REMS Program Live Training: Lecture and Practicum** on \_\_\_\_\_ (insert date).

I further attest to the following:

1. I understand that Probuphine is only available through healthcare providers who are certified by the Probuphine REMS Program and that I must comply with the program requirements to insert/remove Probuphine.
2. I have reviewed and understand the **Probuphine Prescribing Information** and the **Probuphine Instructions for Use**.
3. I understand the risks of migration, protrusion, expulsion, and nerve damage associated with insertion/removal of Probuphine and the risks of accidental overdose, misuse, and abuse associated with Probuphine.
4. I understand the safe administration of Probuphine, including the proper insertion and removal techniques, as well as appropriate wound care.
5. I will provide each patient with a copy of the **Probuphine Medication Guide** prior to each insertion procedure and counsel each patient about:
  - a. The risks associated with the insertion and removal of Probuphine,
  - b. The risks of accidental overdose, misuse and abuse if an implant comes out or protrudes from the skin
  - c. The importance of appropriate wound care.

6. I will document patient counseling in the **Probuphine REMS Program Insertion/Removal Log** or by using another method or system (e.g. electronic health record) specific to my medical practice.
7. I will perform the insertion and removal procedures in a healthcare setting in which a prescriber certified in the Probuphine REMS Program is also practicing.
8. I will ensure that this healthcare setting has appropriate equipment to perform the insertion and removal procedures described in the **Probuphine Instructions for Use**.
9. I will document the insertion and removal of Probuphine including the date, serial number, number of implants inserted/removed, serial number, name of individual performing the procedure, and location of implants for individual patients on the **Probuphine REMS Program Insertion/Removal Log** or by using another method or system (e.g. electronic health record) specific to the prescriber's medical practice.
10. The removed implant contains a significant amount of residual buprenorphine. I will dispose of Probuphine implants in compliance with facility procedure for a Schedule III drug product and per applicable local, state and federal regulations governing the disposal of pharmaceutical bio-hazardous waste.
11. I will not transfer Probuphine outside the healthcare setting to anyone who is not certified as a Healthcare Provider Who Prescribes in the Probuphine REMS Program.
12. I understand that I will need to recertify in the Probuphine REMS Program annually.
13. I understand that the Probuphine REMS Program may contact me via phone, mail, or email to survey me on the REMS Program requirements.
14. I understand that personnel from the Probuphine REMS Program may contact me via phone, mail, or email to gather or to provide information related to the Probuphine REMS Program.
15. I will comply with requests to be audited by Braeburn Pharmaceuticals to ensure all recertification requirements are being followed for the Probuphine REMS Program, and appropriate documentation is available upon request.
16. I will report any adverse events associated with the insertion/removal of Probuphine and the risks of accidental overdose, misuse and abuse to Braeburn Pharmaceuticals at 1-844-859-6341.

Healthcare Provider Signature	Date
<b>Print Name</b>	<b>NPI #</b>

**Please print the following information clearly and legibly in order to more easily process your enrollment in the Probuphine REMS Program.**

First Name: \_\_\_\_\_

Last Name: \_\_\_\_\_

Practice Name: \_\_\_\_\_

Street Address: \_\_\_\_\_

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City: \_\_\_\_\_ State: \_\_\_\_\_ Zip: \_\_\_\_\_

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Are you a: MD  DO  PA  NP  Other -  
Please specify: \_\_\_\_\_

Clinical Specialty: Addiction Medicine  Family Medicine  Internal Medicine  Psychiatry  Other \_\_\_\_\_

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Telephone #:	Fax #:
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E-mail:	Confirm E-mail:
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Preferred Method of Communication (please select one):  Fax  Email

**For more information, please contact the *Probuphine REMS Program* at 1-866-397-8939 or online at [www.ProbuphineREMS.com](http://www.ProbuphineREMS.com).**

# What You Need to Know About Probuphine: A Patient's Guide

## What is Probuphine?

- PROBUPHINE is an implant that contains the medicine buprenorphine. PROBUPHINE is used to treat certain adults who are addicted to (dependent on) opioid drugs (either prescription or illegal). PROBUPHINE is part of a complete treatment program that also includes counseling and behavioral therapy.
- Probuphine implants contain the opioid buprenorphine, which may cause physical dependence.



## How does Probuphine work?

- Four implants are inserted under the skin of your upper arm during a procedure done in your physician's office or Opioid Treatment Program (OTP).
- The implants remain in your arm for six months.
- After the six-month period, your doctor must remove the implants.
- If you wish to continue Probuphine, your doctor may insert new implants to continue treatment.
- The implants can be removed sooner if you want to stop treatment.
- Patients must continue to see their doctor at least every month while on Probuphine therapy.

## What are the Risks Related to the Insertion and Removal of Probuphine Implants?

- There is a risk of accidental overdose, abuse, and misuse for others if the implants come out and others are exposed to them.
- There is a rare but serious risk that the drug implant, if inserted improperly, may move (migrate) into the blood vessels and to your lung, and could lead to death.
- An implant may come out by itself, or an end of an implant may begin sticking out of your skin.
- Injury or damage to nerves or blood vessels in your arm may happen during the insertion and/or removal procedures.
- Implants may be hard to find if:
  - They are too deep for your doctor to feel.
  - You try to move them around under your skin.
  - You have gained a lot of weight since they were inserted.
- Special procedures, tests, or a referral to a specialist may be needed to find and remove the implants if they are difficult to locate.

- There are common risks associated with any minor surgical procedure, such as:
  - Itching, pain, irritation or redness, swelling, bleeding, or bruising at the insertion site.
  - Scarring around the insertion site.

## What Should I do After the Probuphine Implants Have Been Inserted?

- Follow your doctor's instructions for wound care of the place where the implants were inserted or removed.
- Do not try to remove Probuphine implants yourself.
  - Improper removal carries the risk of implant site infection.
  - If you remove the implants, you could become sick with uncomfortable withdrawal signs and symptoms because your body has become used to this medicine.
- If the Probuphine implants come out:
  - Wash your hands if you have touched the Probuphine implants.
  - Cover the area where the implants were inserted with a clean bandage.
  - Do not allow others to touch or use the Probuphine implants, since this could be very dangerous.
  - Put the implants in a plastic bag and take the implants 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.

## Where Can I Get More Information About Probuphine?

There is a **Probuphine Medication Guide** that the healthcare provider who inserts the Probuphine implants will give you each time the implants are inserted. You can also find more information at [www.ProbuphineREMS.com](http://www.ProbuphineREMS.com) or by calling the Probuphine REMS Program at 1-844-859-6341.

## What Should I Do if I Have More Questions?

Please use the space below to write down any other questions you have for your doctor. You can ask them at your next appointment or when you return to start Probuphine.

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