

Risk Evaluation and Mitigation Strategy (REMS) Document

Probuphine® (buprenorphine) REMS Program

I. Administrative Information

Application Number: NDA 204442

Application Holder: Titan Pharmaceuticals, Inc.

Initial REMS Approval: 05/2016

Most Recent REMS Update: 11/2018

II. REMS Goal

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:

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

III. REMS Requirements

Titan Pharmaceuticals, Inc. must ensure that healthcare providers, patients, pharmacies, and wholesalers-distributors comply with the following requirements:

1. Healthcare providers who prescribe Probuphine must:

- | | |
|----------------------------------|---|
| To become certified to prescribe | <ol style="list-style-type: none">1. Review the Prescribing Information including the Instructions for Use.2. Take the Live Training: Lecture and Practicum provided by the REMS Program.3. Successfully complete the Knowledge Assessment and submit it to the REMS Program.4. Enroll in the REMS by completing the Prescriber Enrollment Form and submitting it to the REMS Program. |
|----------------------------------|---|
-

-
- | | |
|-----------------------------|---|
| Before treatment initiation | <ol style="list-style-type: none">5. Counsel the patient on the risks of insertion and removal, accidental overdose, misuse and abuse and the importance of appropriate wound care using the What You Need to Know about Probuphine: A Patient's Guide.6. Provide the patient the What You Need to Know about PROBUPHINE: A Patient's Guide. |
|-----------------------------|---|
-

- | | |
|--------------|---|
| At all times | <ol style="list-style-type: none">7. Not loan or sell Probuphine.8. Not transfer Probuphine, except to certified inserters.9. Maintain records of insertion and removal of Probuphine, including the date, serial number, number of implants inserted, name of healthcare provider performing the procedure, and anatomical location of each implant in each patient's medical record by using the Insertion/Removal Log or by using another method/system (e.g., electronic health record). |
|--------------|---|
-

2. Healthcare providers who insert and remove¹ Probuphine must:

- | | |
|-------------------------------|--|
| To become certified to insert | <ol style="list-style-type: none">1. Have performed a surgical procedure in the three months immediately preceding enrollment in the REMS.2. Review the Prescribing Information including the Instructions for Use.3. Take the Live Training: Lecture and Practicum provided by the REMS Program.4. Successfully complete the Knowledge Assessment and submit it to the REMS Program.5. Successfully complete the Criteria for Procedural Competency.6. Enroll in the REMS by completing the Healthcare Provider Who Performs Probuphine Surgical Procedures Enrollment Form or Healthcare Provider Dual Enrollment Form and submitting it to the REMS Program. |
|-------------------------------|--|
-

- | | |
|------------------|---|
| Before insertion | <ol style="list-style-type: none">7. Have the appropriate equipment to perform insertions and removals of Probuphine on-site.8. Counsel the patient on the risks of insertion and removal; accidental overdose, misuse, and abuse; and the importance of appropriate wound care using the Medication Guide. Provide a copy to the patient. |
|------------------|---|
-

- | | |
|-----------------|---|
| After insertion | <ol style="list-style-type: none">9. Complete the Insertion/Removal Log or use another method/system (e.g., electronic health record) to document the date, serial number, number of implants inserted, name of healthcare provider performing the procedure, and anatomical location of each implant for each patient. |
|-----------------|---|
-

¹ 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.

During treatment	10. Assess the patient's need for removal of Probuphine.
Before removal	11. Have the appropriate equipment to perform insertions and removals of Probuphine on site.
After removal	12. Complete the Insertion/Removal Log or use another method system (e.g., electronic health record) to document the date, serial number, number of implants removed, name of healthcare provider performing the procedure, and anatomical location of each implant for each patient.
To maintain certification to insert; every year	13. Complete the Healthcare Provider Who Performs Probuphine Surgical Procedures Recertification Form and the recertification training requirements as described in the Healthcare Provider Who Performs Probuphine Surgical Procedures Recertification Form .
At all times	<p>14. Insert and remove Probuphine only in healthcare settings in which a certified prescriber is practicing.</p> <p>15. Maintain records of the insertion and removal of Probuphine, including the date, serial number, number of implants inserted, name of healthcare provider performing the procedure, and anatomical location of each implant for each patient by using the Insertion/Removal Log or by using another method/system (e.g., electronic health record).</p> <p>16. Comply with audits carried out by Titan Pharmaceuticals, Inc. or a third party acting on behalf of Titan Pharmaceuticals, Inc. to ensure that all processes and procedures are in place and are being followed.</p>

3. Patients who are prescribed Probuphine:

Before treatment initiation	1. Receive counseling from the prescriber on the risks of Probuphine insertion and removal, accidental overdose, misuse and abuse and the importance of appropriate wound care using the What You Need to Know about Probuphine: A Patient's Guide .
Before insertion	2. Receive counseling from the healthcare provider who inserts Probuphine on the risks of Probuphine insertion and removal, accidental overdose, misuse and abuse and the importance of appropriate wound care using the Medication Guide .
During treatment	3. Be monitored for the need to remove Probuphine.
At all times	4. Get Probuphine removed by a healthcare provider who is certified to insert Probuphine.

4. Pharmacies that dispense Probuphine must:

- | | |
|---------------------------------|---|
| To become certified to dispense | <ol style="list-style-type: none">1. Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS Program on behalf of the pharmacy.2. Have the authorized representative enroll in the REMS Program by completing the Pharmacy Enrollment Form and submitting it to the REMS Program.3. Train all relevant staff involved in dispensing that Probuphine is dispensed only to healthcare settings in which a certified prescriber is practicing and that the drug is not dispensed directly to the patient.4. Establish processes and procedures to verify that Probuphine is provided to a healthcare setting in which a certified prescriber is practicing and the drug is not dispensed directly to the patient. |
|---------------------------------|---|
-

- | | |
|-------------------|---|
| Before dispensing | <ol style="list-style-type: none">5. Verify that the prescriber who will receive the drug is certified to prescribe Probuphine. |
|-------------------|---|
-

- | | |
|---------------------------------------|---|
| To maintain certification to dispense | <ol style="list-style-type: none">6. Have a new authorized representative enroll in the REMS Program by completing the Pharmacy Enrollment Form if the authorized representative changes. |
|---------------------------------------|---|
-

- | | |
|--------------|--|
| At all times | <ol style="list-style-type: none">7. Not distribute, transfer, or sell Probuphine, except to healthcare settings in which a certified prescriber is practicing.8. Maintain records of staff training and of all processes and procedures including compliance with those processes and procedures.9. Maintain and submit records of all shipments of Probuphine to Titan Pharmaceuticals, Inc.10. Comply with audits carried out by Titan Pharmaceuticals, Inc. or a third party acting on behalf of Titan Pharmaceuticals, Inc. to ensure that all processes and procedures are in place and are being followed. |
|--------------|--|
-

5. Wholesalers-Distributors that distribute Probuphine must:

- | | |
|--------------------------|--|
| To be able to distribute | <ol style="list-style-type: none">1. Establish processes and procedures to ensure that the drug is distributed only to certified pharmacies and to healthcare settings in which a certified prescriber is practicing.2. Train all relevant staff involved in distributing Probuphine on the process and procedures to verify that prescribers and pharmacies are certified. |
|--------------------------|--|
-

At all times

3. Distribute only to certified pharmacies and to healthcare settings in which a certified prescriber is practicing.
 4. Maintain records of all processes and procedures including compliance with those processes and procedures.
 5. Maintain and submit records of all shipments of Probuphine to Titan Pharmaceuticals, Inc..
 6. Comply with audits carried out by Titan Pharmaceuticals, Inc. or a third party acting on behalf of Titan Pharmaceuticals, Inc. to ensure that all processes and procedures are in place and are being followed.
-

Titan Pharmaceuticals, Inc. must provide training to healthcare providers who prescribe and/or insert Probuphine.

The training includes the following educational materials: [Live Training: Lecture and Practicum](#), [Knowledge Assessment](#), [Criteria for Procedural Competency](#), and [Surgical Procedures Recertification Video](#). The training for initial certification must be live. The training for recertification must be provided online via video, and as live training.

To support REMS Program operations, Titan Pharmaceuticals, Inc. must:

1. Establish and maintain a REMS Program website, www.PROBUPHINEREMS.com. The REMS Program website will include the capability to complete pharmacy certification/enrollment online, and the option to print the Prescribing Information including Instructions for Use, [Medication Guide](#), and REMS materials. All product websites for consumers and healthcare providers must include prominent REMS-specific links to the REMS Program website. The REMS Program website must not link back to the promotional product website(s).
2. Make the REMS Program website fully operational and all REMS materials available through website and call center within 30 calendar days of REMS modification (mm/dd/2018).
3. Establish and maintain a REMS Program call center for REMS participants at 1-866-397-8939.
4. Establish and maintain a validated, secure database of all REMS participants who are certified in the Probuphine REMS Program.
5. Ensure that healthcare providers who are certified to insert are able to view the [Probuphine Surgical Procedures Recertification Video](#) on the REMS website for recertification.
6. Ensure that healthcare providers who are certified to prescribe and/or insert are able to access the [Insertion/Removal Log](#) for patient monitoring.
7. Provide information on training, the enrollment process, 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.
8. Maintain a process to ensure that healthcare providers who want to become certified to insert Probuphine have performed a surgical procedure in the three months immediately preceding enrollment in the Probuphine REMS Program.
9. Provide [Pharmacy Enrollment Form](#) and the Prescribing Information to pharmacies who (1) attempt to dispense Probuphine and are not yet certified or (2) inquire about how to become certified.
10. Notify healthcare providers who insert Probuphine before their certification is due to expire of the need to recertify in the Probuphine REMS Program based on the recertification training requirements

described in the [Healthcare Provider who Performs Surgical Procedures Recertification Form](#) and provide the [Healthcare Provider who Performs Surgical Procedures Recertification Form](#).

11. Notify prescribers, inserters, and pharmacies within 7 calendar days after they become certified in the REMS Program.
12. Provide certified prescribers, certified healthcare providers who insert Probuphine, certified pharmacies, and wholesalers-distributors access to the database of these participants.

To ensure REMS participants' compliance with the REMS Program, Titan Pharmaceuticals, Inc. must:

13. Verify annually that the authorized representative's name and contact information correspond to those of the current designated authorized representative for the enrolled pharmacy. If different, the pharmacy must be required to re-enroll with a new authorized representative.
14. Maintain adequate records to demonstrate that REMS requirements have been met, including, but not limited to records of: Probuphine distribution and dispensing; certification of prescribers, inserters, and pharmacies; wholesaler-distributors, and audits of REMS participants. These records must be readily available for FDA inspections.
15. Establish a plan for addressing non-compliance with REMS Program requirements.
16. Monitor certified prescribers, certified healthcare providers who insert, certified pharmacies and wholesaler-distributors to ensure the requirements of the Probuphine REMS Program are being met. Take corrective action if noncompliance is identified, including decertification.
17. Audit 15 inserters within 90 calendar days of recertification to ensure that all processes and procedures are in place, functioning, and support the REMS Program requirements. The certified inserters must also be included in Titan Pharmaceuticals, Inc.'s **ongoing annual audit plan**.
18. Audit pharmacies no later than 60 calendar days after the pharmacy is certified to ensure that all REMS processes and procedures are in place, functioning, and support the REMS Program requirements.
19. Audit wholesaler-distributors no later than 60 calendar days after they are authorized to distribute the drug to ensure that all REMS processes and procedures are in place, functioning, and support the REMS Program requirements.
20. 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.

IV. REMS Assessment Timetable

Titan Pharmaceuticals, Inc. must submit REMS Assessments at 6 months and 1 year from the date of the initial REMS approval (05/26/2016) and 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. Titan Pharmaceuticals, Inc. must submit each assessment so that it will be received by the FDA on or before the due date.

V. REMS Materials

The following materials are part of the Probuphine REMS:

Enrollment Forms

Prescriber:

1. [Prescriber Enrollment Form](#)
2. [Healthcare Provider Dual Enrollment Form](#)

inserter:

3. [Healthcare Provider Who Performs Probuphine Surgical Procedures Enrollment Form](#)
4. [Healthcare Provider Dual Enrollment Form](#)
5. [Healthcare Provider Who Performs Probuphine Surgical Procedures Recertification Form](#)
6. [Procedure Record for Recertification](#)

Pharmacy:

7. [Pharmacy Enrollment Form](#)

Training and Educational Materials

Prescriber:

8. [Live Training: Lecture and Practicum](#)
9. [Knowledge Assessment](#)

inserter:

10. [Live Training: Lecture and Practicum](#)
11. [Knowledge Assessment](#)
12. [Criteria for Procedural Competency](#)
13. [Surgical Procedures Recertification Video](#)

Patient:

14. [Medication Guide](#)
15. [What You Need to Know About Probuphine: A Patient's Guide](#)

Patient Care Form

16. [Insertion/Removal Log](#)

Other Materials

17. [REMS Program Website](#)

PROBUPHINE[®] 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 not loan or sell Probuphine.
6. I will not transfer Probuphine, except to certified inserters.
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 maintain records of the insertion and removal of Probuphine, including the date, serial number, number of implants inserted/removed, name of individual performing the procedure, and anatomical 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 Titan Pharmaceuticals at 1-844-859-6341.

Prescriber's 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 Specify: _____

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 www.ProbuphineREMS.com.

PROBUPHINE[®] REMS Program

Healthcare Provider Who Preforms Probuphine Surgical Procedures¹ 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 three months immediately preceding enrollment in the REMS. This procedure was performed under local anesthesia, using aseptic technique, and included, at a minimum, making skin incision 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.

¹ 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 assess the patient's need for removal of Probuphine.
11. I will ensure that this clinical setting has appropriate equipment to perform the insertion and removal procedures described in the *Probuphine Instructions for Use*.
12. I will maintain records of the insertion and removal of Probuphine including the date, serial number, number of implants inserted/removed, name of individual performing the procedure, and anatomical 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.
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 will not distribute, transfer, loan, or sell Probuphine outside the healthcare setting to anyone who is not certified as a prescriber in the Probuphine REMS Program.
15. I understand that I will need to recertify in the Probuphine REMS Program annually.
16. I understand that the Probuphine REMS Program may contact me via phone, mail, or email to survey me on REMS Program requirements.
17. 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.

18. 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.
19. I will comply with requests to be audited by Titan Pharmaceuticals, or a third party, to ensure all processes and procedures are in place and are being followed for the Probuphine REMS Program, and appropriate documentation is available upon request.
20. I will report any adverse events associated with the insertion/removal of Probuphine and the risks of accidental overdose, misuse and abuse to Titan 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 specify: _____

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 www.ProbuphineREMS.com.

PROBUPHINE[®] REMS Program Healthcare Provider Dual¹ 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 three months immediately preceding enrollment in the REMS. 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.

¹ 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 not loan or sell Probuphine.
10. I will not transfer Probuphine except to certified inserters.
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 assess the patient's need for removal of Probuphine.
13. I will maintain records of the insertion and removal of Probuphine including the date, serial number, number of implants inserted/removed, name of individual performing the procedure, and anatomical 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.
14. 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.
15. I understand that I will need to recertify in the Probuphine REMS Program annually.
16. I understand that the Probuphine REMS Program may contact me via phone, mail, or email to survey me on REMS Program requirements.
17. I understand that I may request personnel from the Probuphine REMS Program to provide training and support for my first Probuphine insertion and removal.
18. 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.

19. I will comply with requests to be audited by Titan Pharmaceuticals, or a third party, to ensure all processes and procedures are in place and are being followed for the Probuphine REMS Program, and appropriate documentation is available upon request.
20. I will report any adverse events associated with the insertion/removal of Probuphine and the risks of accidental overdose, misuse and abuse to Titan 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 Specify: _____

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 www.ProbuphineREMS.com.

PROBUPHINE REMS Program
Pharmacy Enrollment Form

Instructions

Probuphine® (buprenorphine) implant is only available through the Probuphine Risk Evaluation and Mitigation Strategy (REMS) Program. Before Probuphine is provided, pharmacies must:

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

The **Probuphine REMS Program Pharmacy Enrollment Form** contains two sections:

- “Authorized Representative Information and Responsibilities” section – page 2
- “Dispensing Pharmacy Information” section – page 3

The authorized representative will ensure that each dispensing pharmacy location meets the REMS requirements for permission to order and dispense Probuphine. For the initial enrollment, both sections of the **Probuphine REMS Program Pharmacy Enrollment Form** must be submitted for each dispensing pharmacy location. To add additional dispensing pharmacy locations after the initial enrollment, you may complete just the “Dispensing Pharmacy Information” section. The certification will be confirmed by the REMS Program prior to shipping Probuphine.

If a designated authorized representative changes, the new authorized representative must complete and sign a new **Probuphine REMS Program Pharmacy Enrollment Form**, including a “Dispensing Pharmacy Information” section for each location.

Enrollment can be done online, by fax, email, or mail.

- To enroll **online**, please go to www.PROBUPHINEREMS.com.
- For enrollment via **FAX**, please complete all required fields on the form and fax the section(s) to 1-866-413-1135.
- For enrollment via **e-mail**, please complete all required fields on the form and email the section(s) to probuphinerems@titanpharm.com.
- For enrollment via **mail** please complete all required fields on the form and mail the section(s) to PROBUPHINE REMS Program, 1901 Eastpoint Parkway, Louisville, KY 40223.

Probuphine is only available to certified pharmacies. For questions about the Probuphine REMS Program or how to enroll, visit www.PROBUPHINEREMS.com or contact the Probuphine REMS Program at 1-866-397-8939.

**PROBUPHINE REMS Program
Pharmacy Enrollment Form**

Authorized Representative Information and Responsibilities

AUTHORIZED REPRESENTATIVE INFORMATION

Role

<input type="checkbox"/> Pharmacist	<input type="checkbox"/> Other _____
-------------------------------------	--------------------------------------

Contact details

First name:	Last name:	Middle initial:
-------------	------------	-----------------

Pharmacy Name:

Address:

City:	State:	Zip:
-------	--------	------

Telephone number:	Alternate telephone number:	Office fax:
-------------------	-----------------------------	-------------

Email:	Preferred method of communication:
--------	------------------------------------

I am the authorized representative designated by my pharmacy to carry out the certification process and oversee implementation of and compliance with the REMS. By signing this form, I agree, on behalf of myself and my pharmacy, with the REMS requirements. As a condition of certification, I agree to:

- Complete and sign the **Probuphine REMS Program Pharmacy Enrollment Form** and submit it to the REMS.
- Train all relevant staff involved in dispensing that Probuphine is only dispensed in healthcare settings in which a certified prescriber is practicing and is not dispensed directly to the patient.
- Establish processes and procedures to verify that Probuphine is provided to a healthcare setting in which a certified prescriber is practicing, and the drug is not dispensed directly to the patient.
- Verify that the healthcare provider who will receive the drug is certified to prescribe Probuphine.
- Have a new authorized representative enroll in the REMS by completing **Probuphine REMS Program Pharmacy Enrollment Form** if the authorized representative changes.
- Not distribute, transfer, or sell Probuphine, except to healthcare settings in which a certified prescriber is practicing.
- Maintain records of staff training and of all processes and procedures including compliance with those processes and procedures.
- Maintain records of all shipments of Probuphine and submit to Titan.
- Comply with audits carried out by Titan or a third party acting on behalf of Titan to ensure that all processes and procedures are in place and are being followed.

I understand that this enrollment applies to my pharmacy for which I am the designated authorized representative.

Pharmacy Authorized Representative Signature:	Date: (MM/DD/YYYY)
---	--------------------

**PROBUPHINE REMS Program
Pharmacy Enrollment Form**

Dispensing Pharmacy Information			
Pharmacy Name:			
Street Address:			
City:	State:	Zip:	
Facility identifiers (provide at least 1)	NPI:	NCPDP:	DEA:
Authorized Representative Name:			
Dispensing Pharmacy Point of Contact Name:			
Telephone number:	Alternate telephone number:	Office fax:	
Email:	Preferred method of communication:		
I am the designated authorized representative for this pharmacy location			
Pharmacy Authorized Representative Signature:		Date: (MM/DD/YYYY)	

PROBUPHINE[®] (BUPRENORPHINE) IMPLANT

PROBUPHINE REMS PROGRAM LIVE TRAINING: LECTURE SLIDES

Agenda

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

Probuphine[®] **(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

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

- 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
- **Titan Pharmaceuticals** has worked with the FDA to develop the Probuphine REMS Program

Probuphine REMS: Goal

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

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

Probuphine REMS: Mitigating Risks

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

Probuphine REMS: Mitigating Risks

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

Closed Distribution

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

HCPs who Prescribe Probuphine: Roles and Responsibility

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

HCPs who Perform Probuphine Surgical Procedures: Roles and Responsibility

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

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

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

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

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

Probuphine

REMS Recertification Requirements

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

Probuphine REMS Program Recertification Requirements¹

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 Probuphine REMS Program Surgical Procedures Recertification Video found on the Probuphine REMS website every year .	Number of Probuphine procedures in the past 12 months (Select the Row that applies)	
	<p>≥10</p> <p>Performed 10 or more successful² procedures (comprised of at least five insertions and five removals) →</p>	<p>I must review the Probuphine REMS Program Surgical Procedures Recertification Video found on the Probuphine REMS website every year.</p> <p>I understand that I should keep documentation of all successfully completed procedures on the Probuphine REMS Program Procedure Record for Recertification or another record of my choosing - which must be provided to the Probuphine REMS Program if I am audited.</p>
	<p><10</p> <p>Performed less than 10 successful² procedures (comprised of at least five implantations and five removals) →</p>	<p>I must (annually):</p> <ul style="list-style-type: none"> attend a Probuphine REMS Program Live Training: Lecture and Practicum session successfully complete the Probuphine REMS Program Knowledge Assessment test meet the Probuphine REMS Program Criteria for Procedural Competency

¹ 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.

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

Roles/Responsibilities of Pharmacies

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

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

REMS Materials

- **List of Materials for HCPs:**

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

- **List of Materials for Pharmacies**

- Probuphine REMS Program Pharmacy Enrollment Form

REMS Materials (cont.)

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

Patient Counseling and Resources

Patient Counseling

- 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

- 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

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

Patient Education:

Risk of Accidental Overdose, Abuse, Misuse

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

Probuphine Insertion and Removal Procedures

Insertion and Removal

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

Probuphine Kit

Probuphine Kits contain:

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



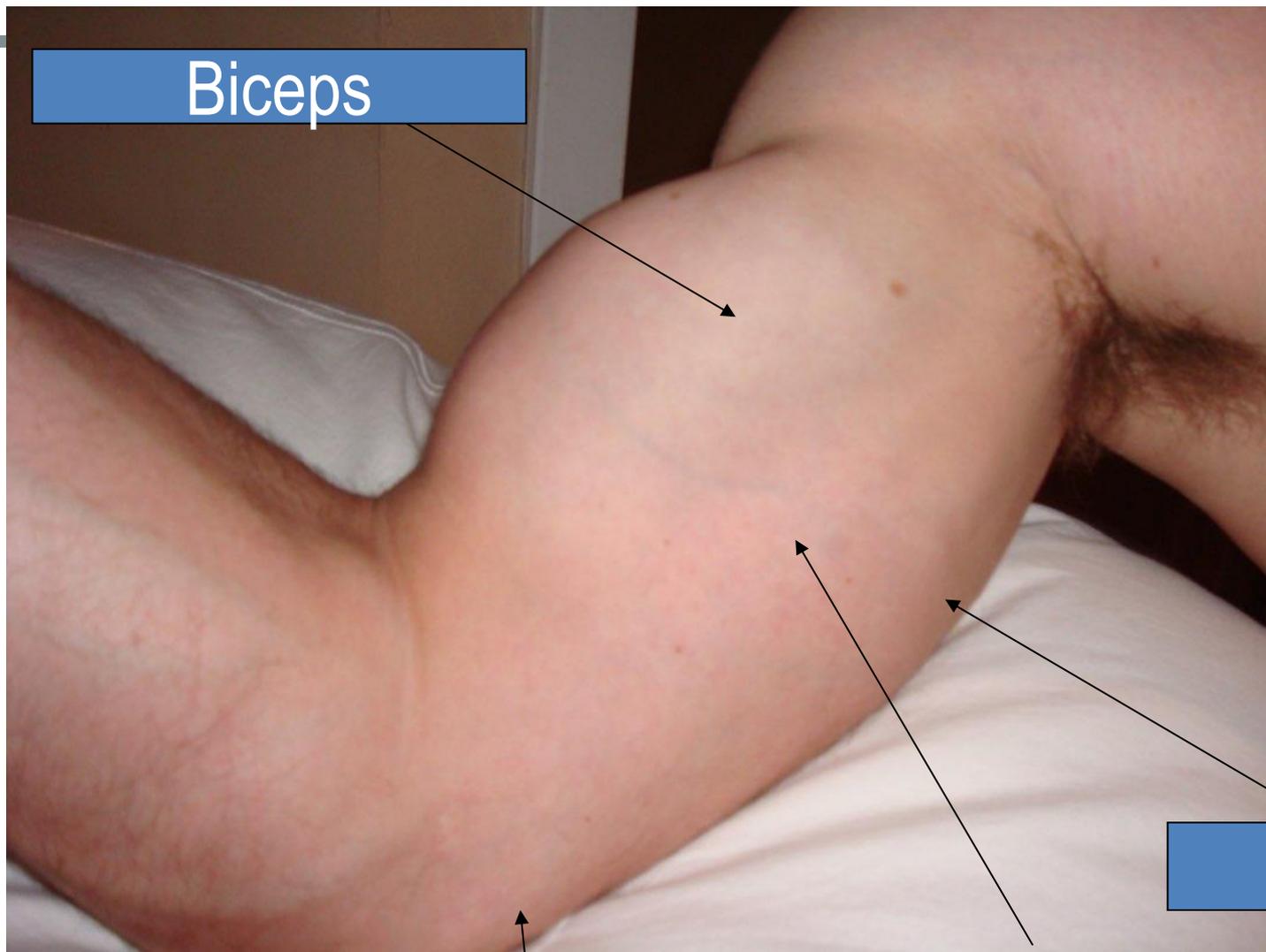
NOTE: The Serial Number for the kit is located on the back of the kit, in the bottom left hand corner. The Serial Number should be recorded in the Probuphine REMS Program Insertion/Removal Log for tracking and accountability (including, for example, to track adverse events).

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

Insertion/Removal Procedure Training Objectives

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

Brachium



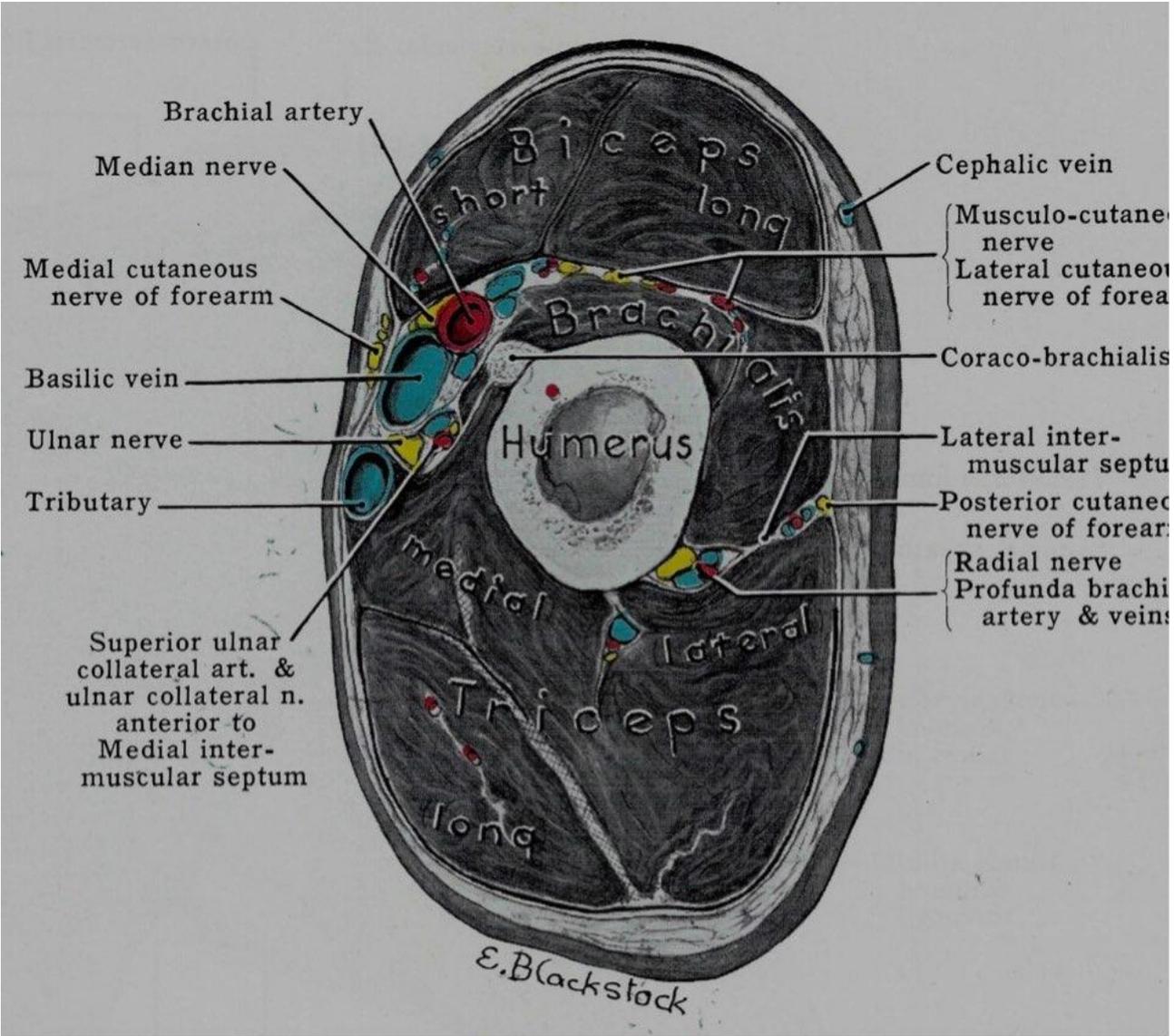
Biceps

Triceps

Medial epicondyle

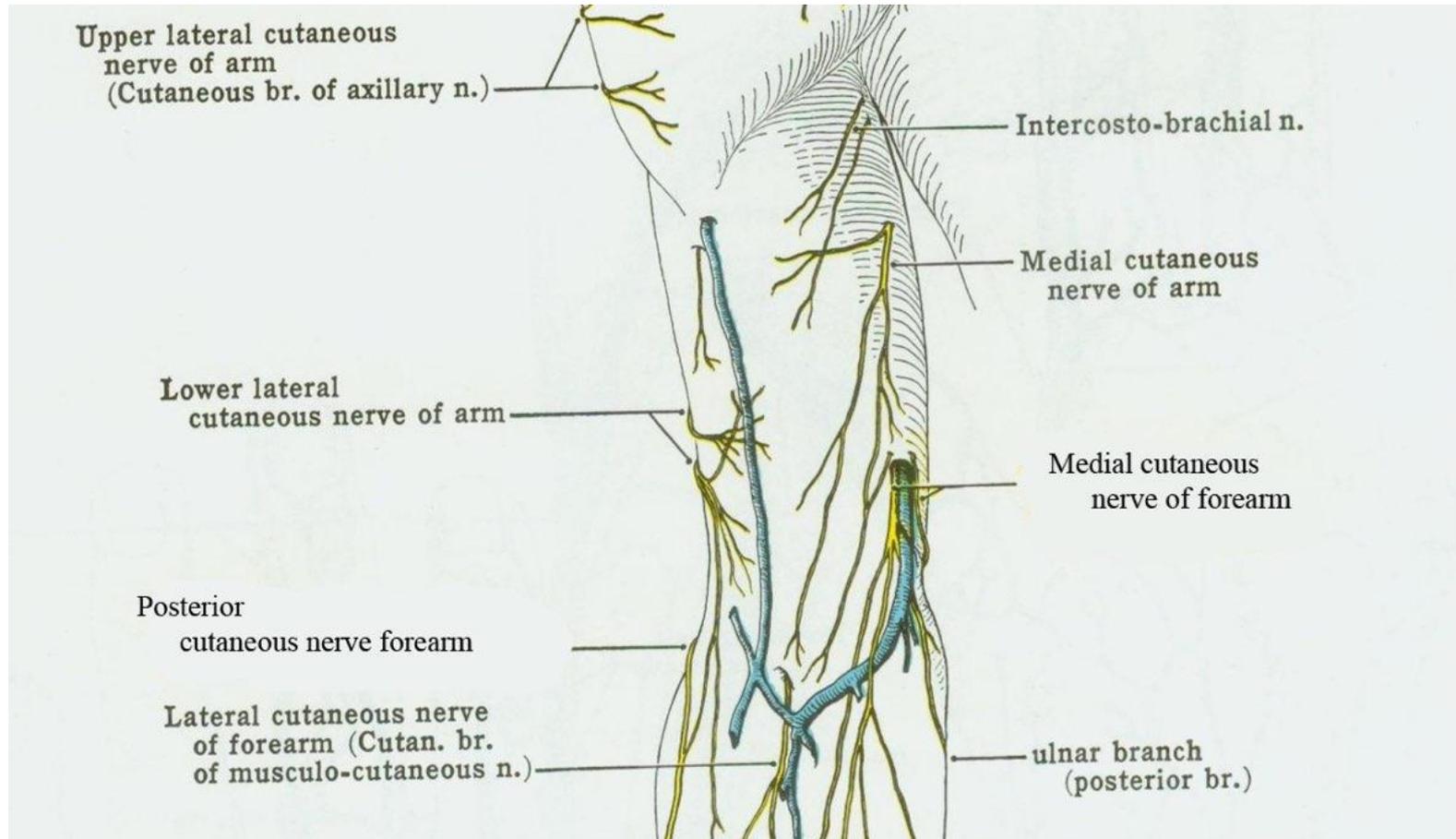
Medial Bicipital Groove

Brachium Cross Section



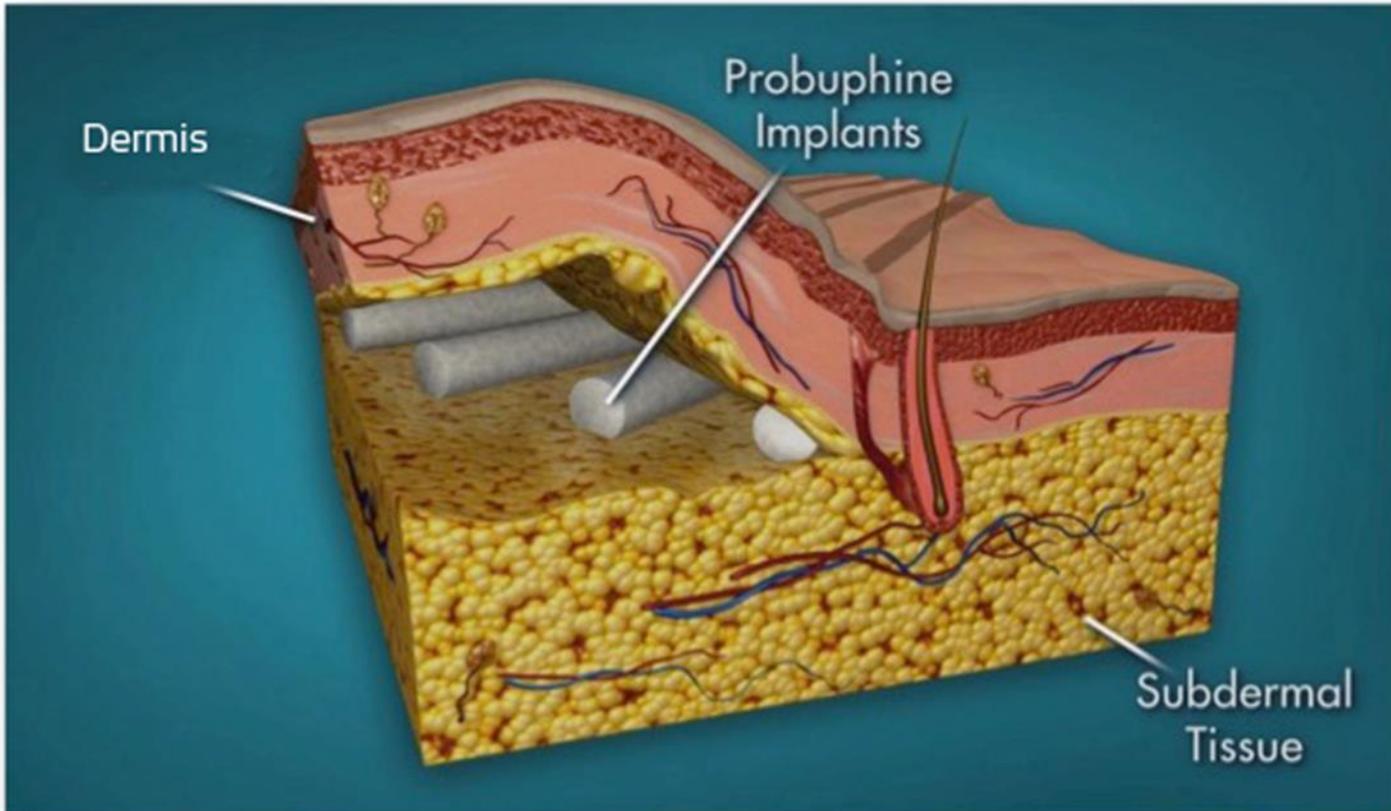
It is important to avoid the neurovascular bundle that underlies the subcutaneous plane.

Brachium Cutaneous Nerves



The medial cutaneous nerve lies within the subcutaneous tissue.

Correct Subdermal Insertion



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

Insertion of Probuphine

Probuphine Insertion Procedure Equipment

- 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 Titan 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.



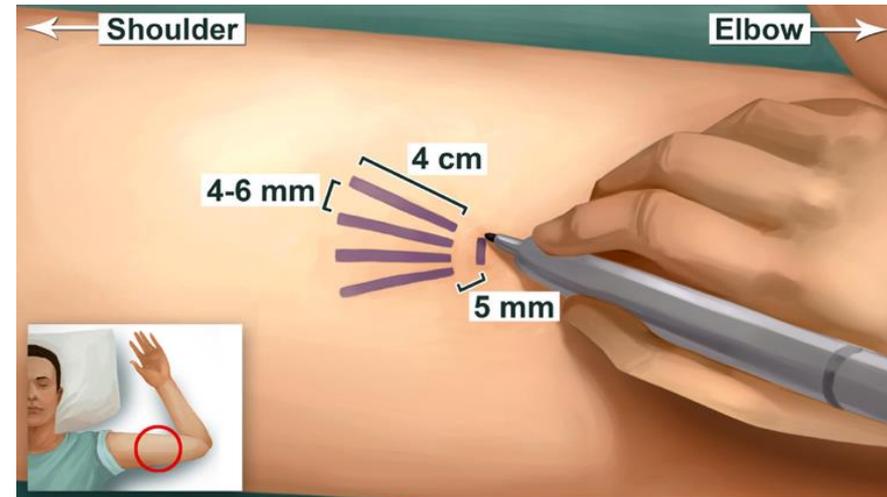
Step 2. Identify the insertion site, which is at the inner side of the upper arm about 8-10 cm (3-4 inches) above the medial epicondyle of the humerus in the sulcus between the biceps and triceps muscle. Having the patient flex the biceps muscle may facilitate identification of the site.



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

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

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

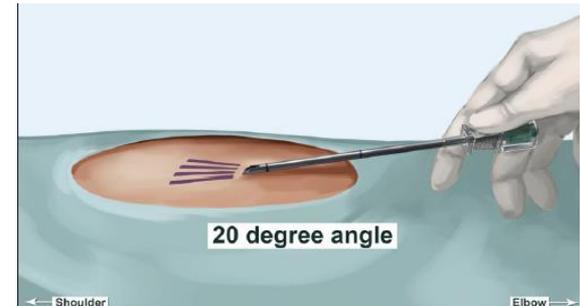


Figure 2

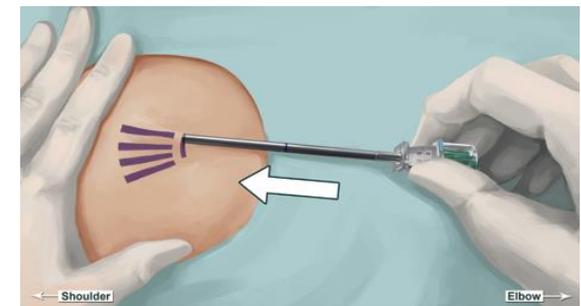
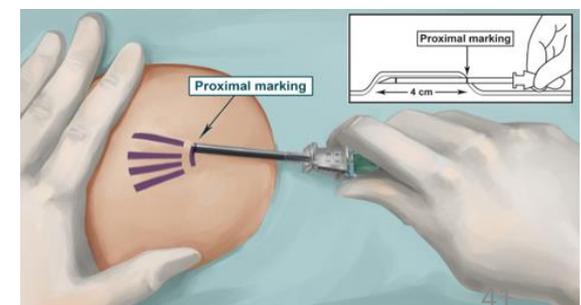


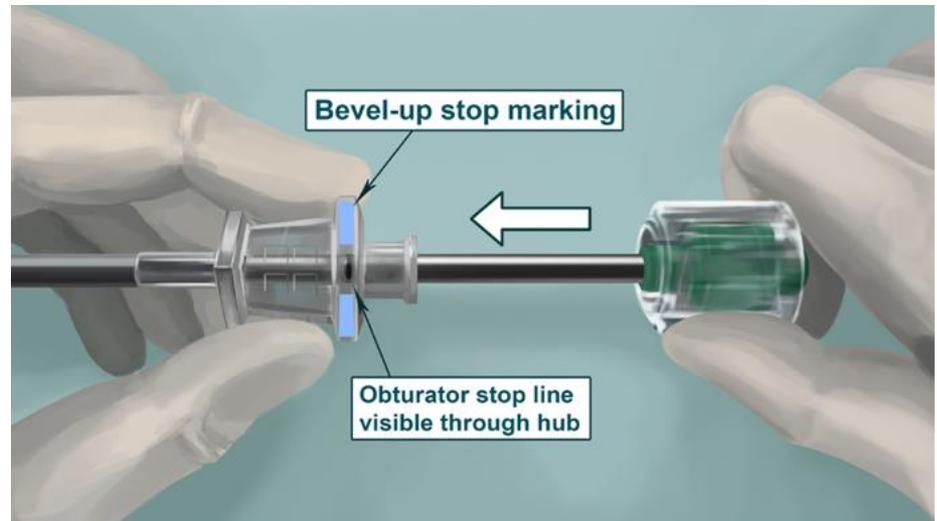
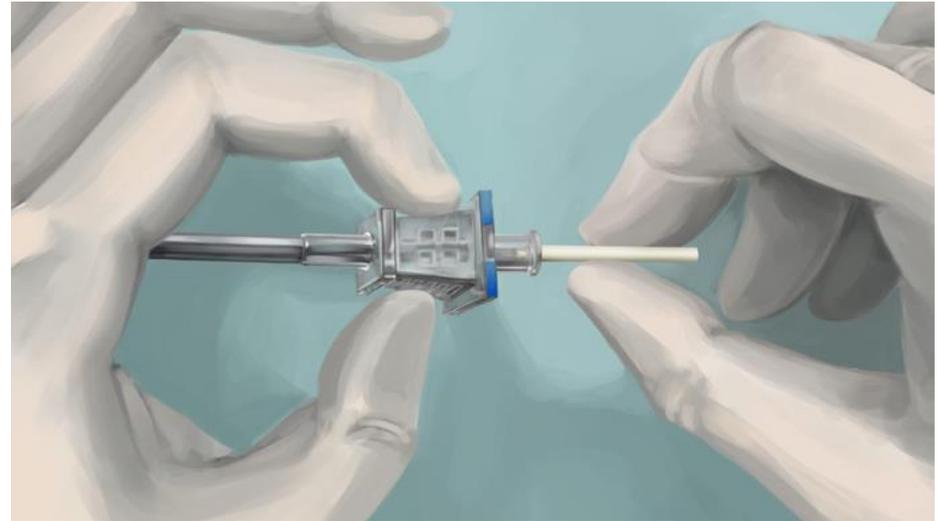
Figure 3



Insertion Procedure

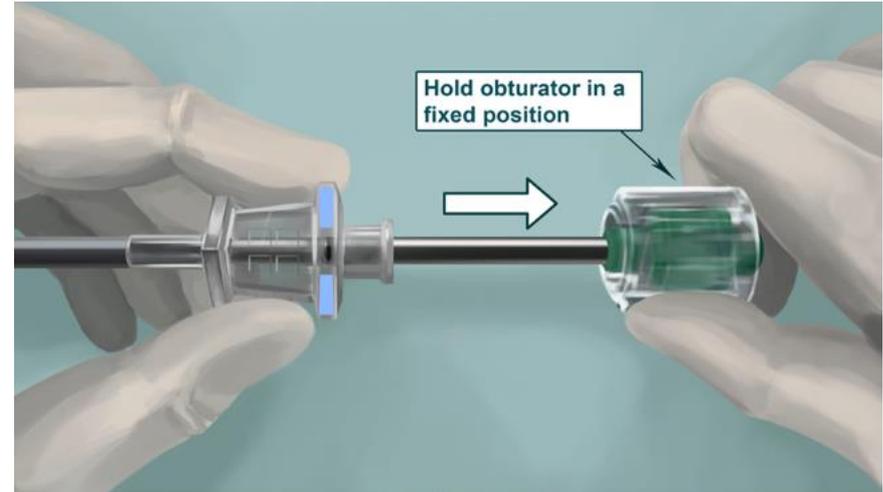
Step 15. While holding the cannula in place, unlock the obturator and remove the obturator.

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.

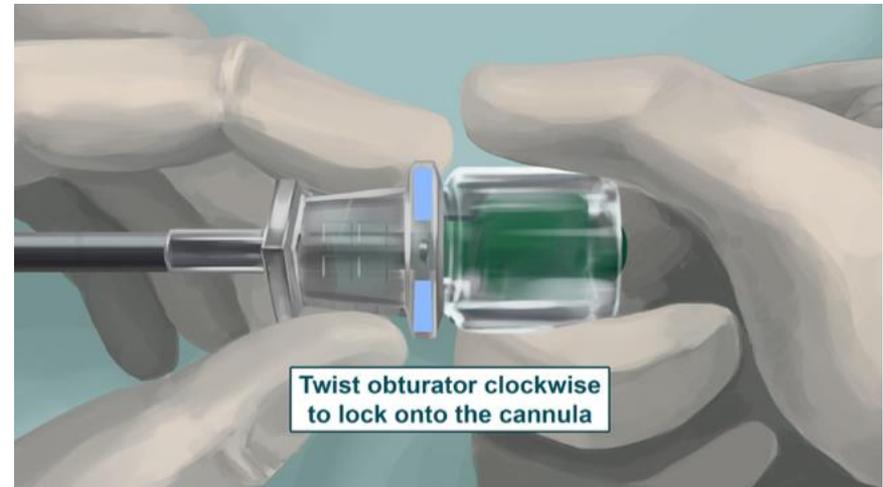


Insertion Procedure

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.



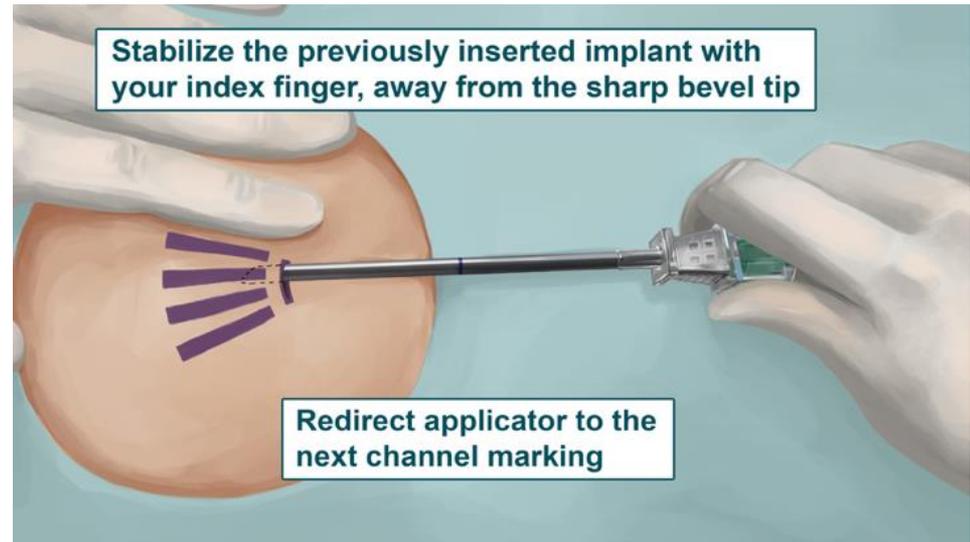
Step 18. Withdraw the cannula until the hub is flush with the obturator, and then twist the obturator clockwise to lock onto the cannula. Retract the applicator, bevel-up, until the distal marking of the cannula is visualized at the incision opening (the sharp tip remaining in the subcutaneous space).



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

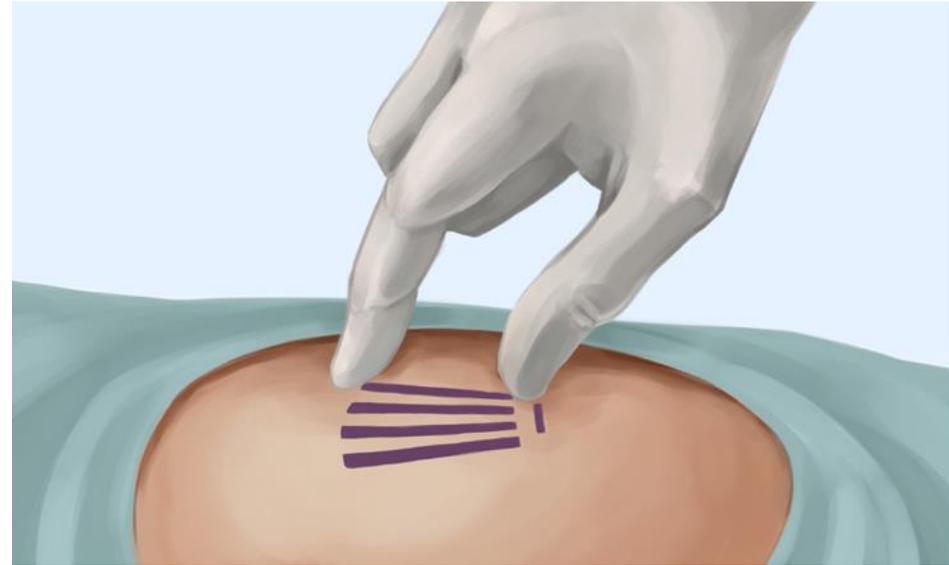
Step 20. Always verify the presence of each implant in the patient's arm by palpation of the arm immediately after the insertion. By palpating both ends of the implant, you should be able to confirm the presence of the 26 mm implant.

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

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

Step 26. The applicator is for single use only. Dispose of the applicator in accordance with the Centers for Disease Control and Prevention guidelines for hazardous waste.

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

Step 28. Complete the **PROBUPHINE REMS Program Insertion/Removal Log Form**.

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

Localization of Probuphine Implants

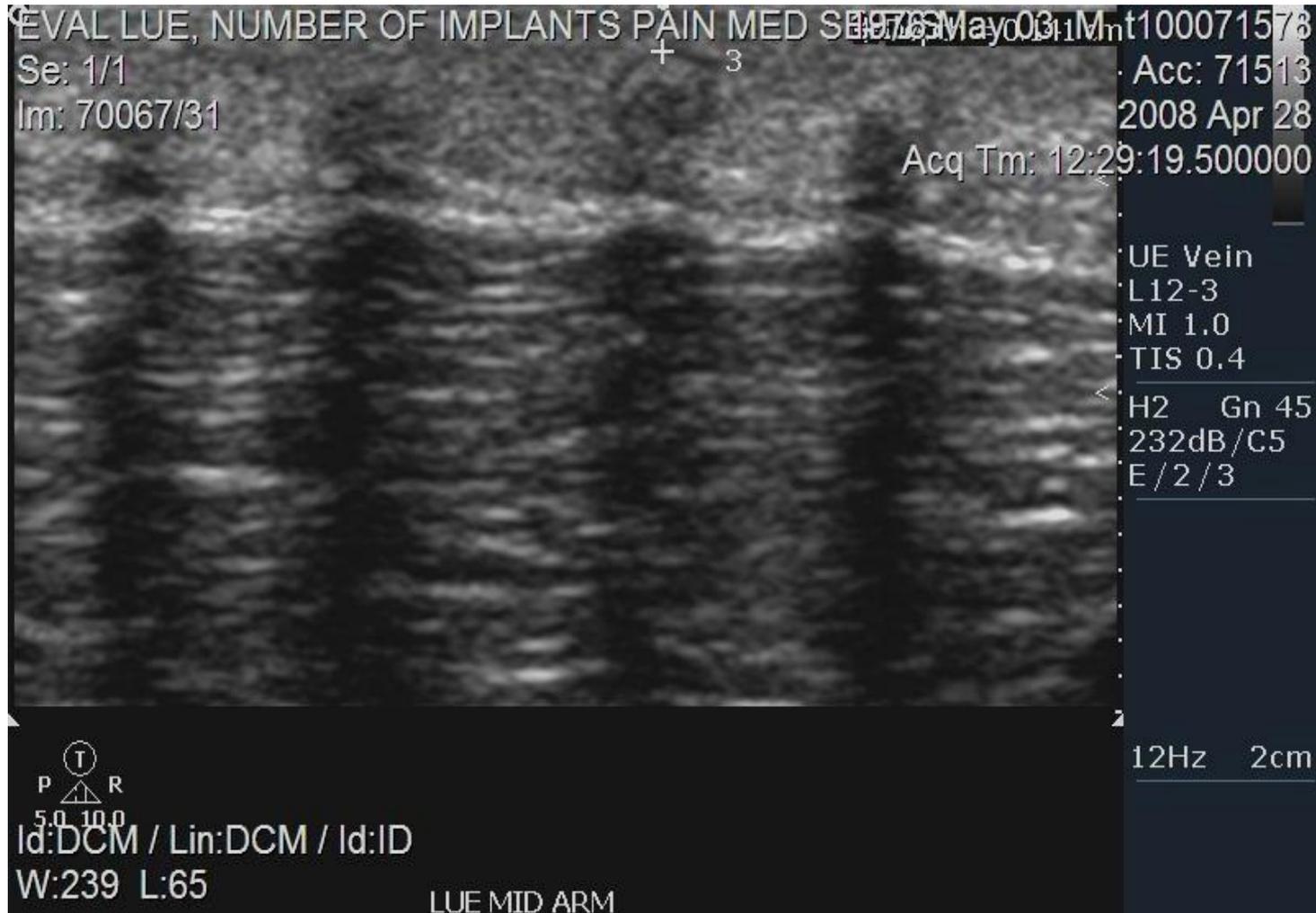
Probuphine Localization

- 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

- 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 1-844-859-6341 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

- 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 Titan upon request***

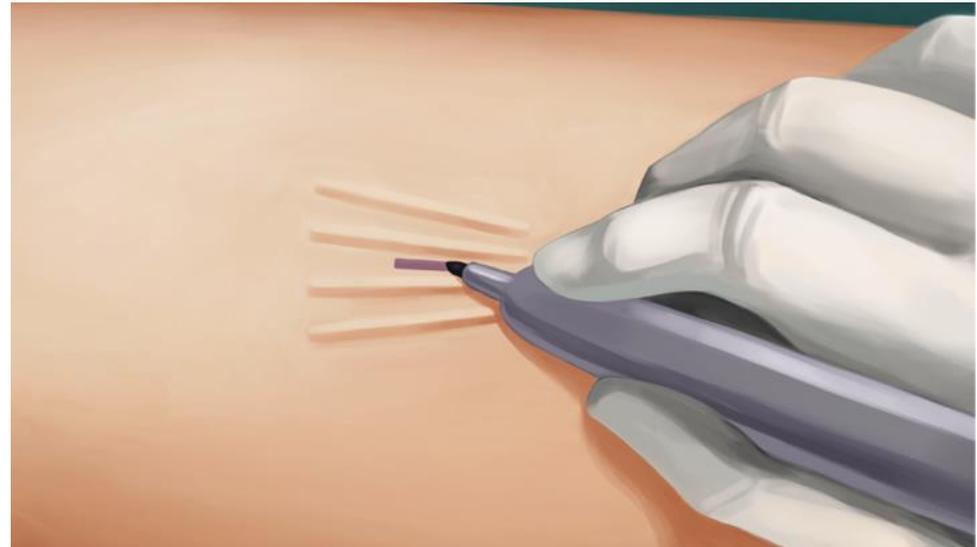
Removal Procedure

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

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

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

Step 4. Mark the location of the implants with 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

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.

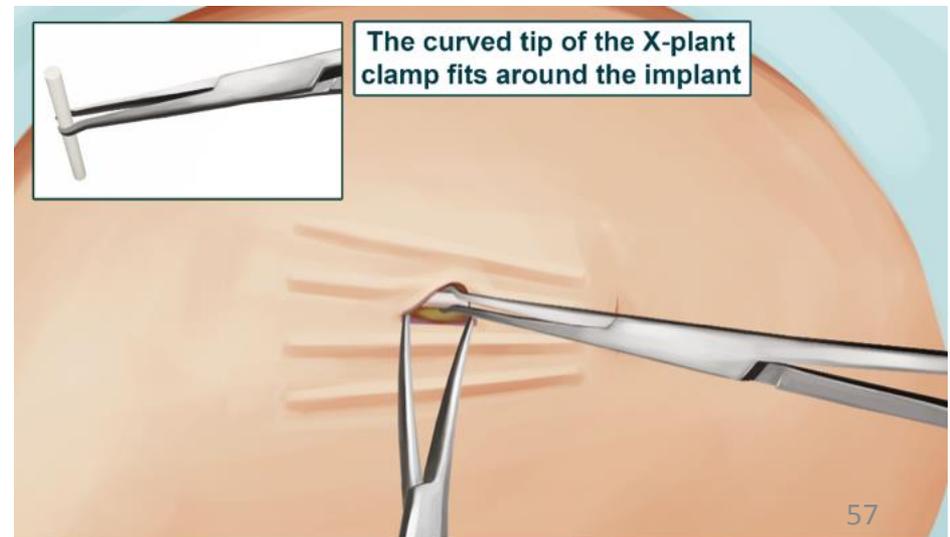
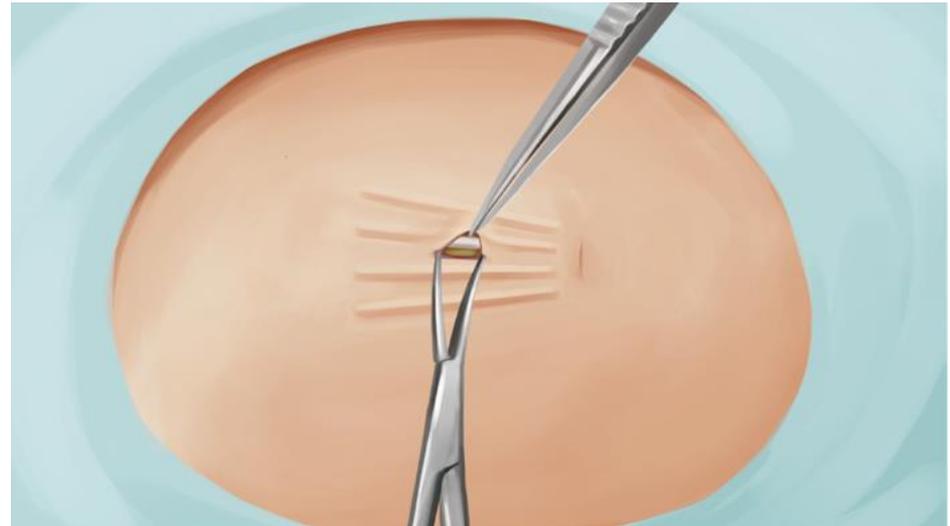
Step 8. Apply the sterile drape to the arm of the patient.

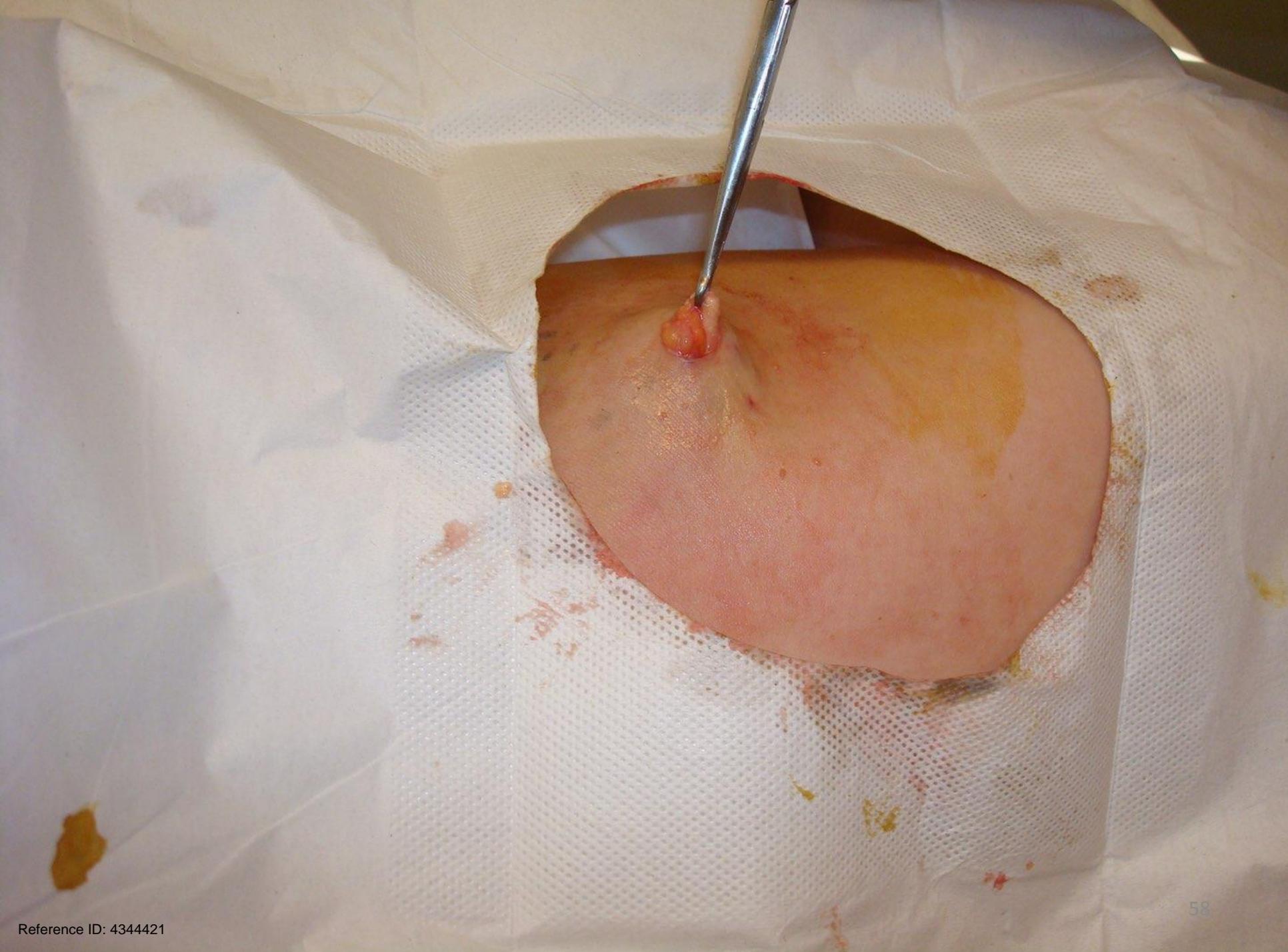
Step 9. Anesthetize the incision site and the subcutaneous space containing the implants (for example, by injecting 5-7 mL lidocaine 1% with epinephrine 1:100,000). Separate needles may be used for the incision site and the subcutaneous injections. NOTE: Be sure to inject the local anesthetic just beneath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

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

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

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

Step 21. The removed implant, contains a significant amount of residual buprenorphine, and must be handled with adequate security, accountability, and proper disposal, per facility procedure for a Schedule III drug product, and per applicable federal, state, and local regulations. Disposal of PROBUPHINE implants should also be in keeping with local state and federal regulations governing the disposal of pharmaceutical biohazardous waste.

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

Continuation of Therapy: Subsequent Insertion in the Contralateral Arm

- 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

- 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

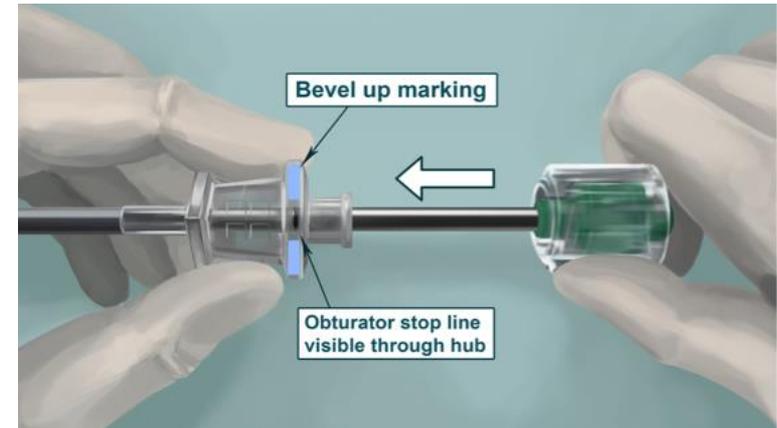
- There are risks associated with insertion/removal of Probuphine such as:
 - Migration
 - Protrusion
 - Expulsion
 - Nerve damage
- Proper training and education is needed to avoid complications associated with insertion/removal:
 - Ensuring proper aseptic insertion/removal procedures
 - NOTE: HCPs 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

- 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

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

Patient Education on Potential Risks: Care of the Incision Instructions

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 Insertion Procedure:** Keep steri-strips (the thin bandages sticking to your skin) on for 7 days after the procedure.

Patients may return the next day to check the wound.

When the patient comes back:

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

How to Address Spontaneous Expulsion of Implant

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

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

In Summary:

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

Probuphine REMS Resources

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

OR

- Visit www.PROBUPHINEREMS.com
- To Report any suspected adverse reactions, please call 1-844-859-6341 (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[®] (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?
 - a. There is no need to keep the implants (should they come out) away from children.
 - b. 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.
 - c. It is impossible for the implant to come out by itself.
 - d. Appropriate wound care is important to reduce the risk of complications associated with the insertion of Probuphine.
 - e. B and D
 - f. All of the above

6. When inserting the implants, the correct placement should be within the subdermal plane.
 - a. True
 - b. False

7. When inserting the applicator through the incision, the angle of the applicator should not exceed which of the following?
 - a. 10 degree angle
 - b. 20 degree angle
 - c. 45 degree angle
 - d. 90 degree angle

8. How far should the obturator be advanced to correctly position the implant?
 - a. To the point where the plastic hub of the obturator locks with the plastic hub of the cannula.
 - b. To the point where the stop line on the obturator is level with the blue bevel-up marking on the cannula.
 - c. To the point where the stop line on the obturator is level with the distal marking on the cannula.
 - d. None of the above

9. Which one of the following is incorrect?
After inserting the first implant:
 - a. Withdraw the locked applicator to the level of the distal marking seen in the incision opening.
 - b. Withdraw the applicator completely from the incision and then re-insert it into the incision for the next implant.
 - c. When redirecting the applicator, stabilize the previously inserted implant to avoid fracturing or mal-positioning the previously inserted implant
 - d. 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.
 - a. True
 - b. 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 – 3 mm) 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 – 3 mm 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

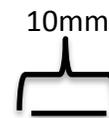


REMOVAL

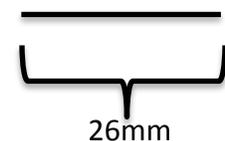
Trainees must demonstrate competency in performing the following techniques.

1	Reconfirm location of implants by palpation. IF ALL FOUR IMPLANTS CAN NOT BE PALPATED, DO NOT ATTEMPT TO REMOVE. REQUEST ULTRASOUND OR MRI.
2	Clean removal site properly with alcohol prep.
3	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.
4	Put on sterile gloves.
5	Use aseptic technique to place sterile equipment in sterile field.
6	Clean removal site with an antiseptic solution (e.g., chlorhexidine) using gentle repeated back and forth strokes for 30 seconds
7	Apply sterile drape.
8	Anesthetize incision site and subcutaneous space below implants (which helps to lift implants toward the skin, facilitating removal of the implants).
9	Confirm anesthesia is adequate and make a 7-10 mm incision parallel to the axis of the arm between 2 nd and 3 rd implants, along the marked tracks from step 3 above.
10	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.
11	Grasp the center of implant with X-plant clamp and apply gentle traction.
12	Remove implant.
13	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.
14	Repeat steps 10 – 13 until all implants are removed.
15	Close the incision with sutures.
16	Place an adhesive bandage over the incision and wrap arm with pressure dressing.
17	Dispose of all implants in keeping with regulations governing disposal of biohazardous waste.

MAXIMUM INCISION LENGTH REQUIRED IS 10 mm



EACH IMPLANT REMOVED IMPLANT SHOULD BE 26 mm





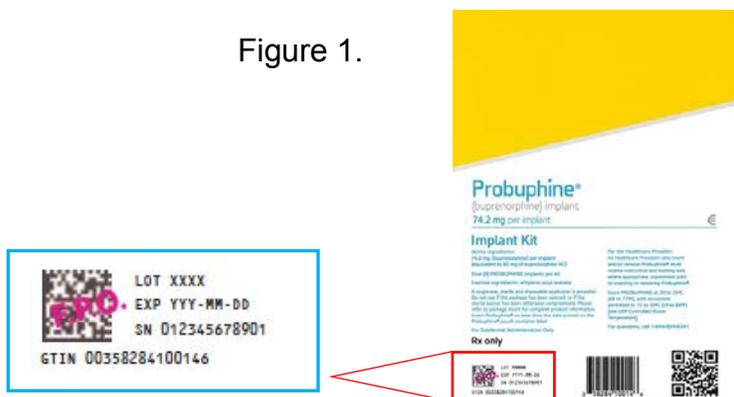
PROBUPHINE[®] REMS Program Insertion/Removal Log

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

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. Titan 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, insert and remove Probuphine on steps to mitigate the risks of complications related to the insertion and removal procedures, and the risks of accidental overdose, misuse, and abuse.

Materials for Healthcare Providers

Probuphine REMS Program Healthcare
Provider Who Prescribes Enrollment
Form



✔ **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.

✔ **Certification** – for pharmacies who dispense Probuphine by completing the ***Probuphine REMS Pharmacy Enrollment Form*** and enrollment in the Probuphine REMS Program.

✔ **Recertification**– Titan 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

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 

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 

implants come out or protrude from the skin; and when to contact the healthcare provider.

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

Prescribing Information



Probuphine Medication Guide



Probuphine Instructions for Use



Materials for Pharmacies

Probuphine REMS Pharmacy
Enrollment Form



Materials for Patients

Probuphine Medication Guide



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



Probuphine REMS Pharmacy
Enrollment Form



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 SUSPECTED ADVERSE REACTIONS, contact Titan at 1-844-859-6341
or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

[Privacy Policy](#)

[Terms of Use](#)

[Contact](#)

[Sitemap](#)

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](#)

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 [↓](#)

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 including the Instructions for Use
- b. Take the ***Probuphine REMS Program Live Training: Lecture and Practicum***
- c. Successfully complete 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 on this website and 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 

Probuphine REMS Program Live Training: Lecture Slides 

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 

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.
- Take 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**.
- Successfully complete the **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.

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 

Probuphine REMS Program Insertion/Removal Log 

Probuphine REMS Program Procedure Record for Recertification 

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, insert and remove 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 including the Instructions for Use.
- Attest to performing a sterile procedure in the three months immediately preceding enrollment in the Probuphine REMS Program.
- Take 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**.
- Successfully complete the **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.

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



Probuphine REMS Program Insertion/Removal Log



Probuphine REMS Program Procedure Record for Recertification



Probuphine REMS Program Surgical



Healthcare Providers

- + Healthcare Providers Who Prescribe Probuphine
- + Healthcare Providers Who Perform Probuphine Surgical Procedures
- + Healthcare Providers Who Prescribe, Insert, and Remove Probuphine
- Probuphine REMS Program Live Training Enrollment

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 *

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 

Probuphine REMS Program Insertion/Removal Log 

Probuphine REMS Program Procedure Record for Recertification 

Zip Code *

NPI Number *

Intended Role *

Submit

+ [Probuphine Re-Certification](#)

[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](#)



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

To report SUSPECTED ADVERSE REACTIONS, contact Titan at 1-844-859-6341 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

Probuphine REMS Program Live Training Enrollment

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 *

Submit



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

To report SUSPECTED ADVERSE REACTIONS, contact Titan at 1-844-859-6341 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

[Privacy Policy](#)

[Terms of Use](#)

[Contact](#)

[Sitemap](#)

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

Titan 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 annual 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 

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 

Probuphine REMS Program Insertion/Removal Log 

Probuphine REMS Program Procedure Record for Recertification 

Probuphine REMS Program Surgical 

Probuphine® REMS Recertification Training Requirements¹

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 <i>Probuphine REMS Program Probuphine Surgical Procedures Recertification Video</i> found on the Probuphine REMS website every year .	Number of Probuphine procedures in the past 12 months (Select the Row that applies)
	10 or More > Performed 10 or more successful ² procedures (comprised of at least five insertions and five removals)
	I must review the <i>Probuphine REMS Program Surgical Procedures Recertification Video</i> found on the Probuphine REMS website every year . I understand that I should keep documentation of all successfully completed procedures on the <i>Probuphine REMS Program Procedure Record for Recertification</i> or another record of my choosing - which must be provided to the Probuphine REMS Program if I am audited.

I must review the ***Probuphine REMS Program Probuphine Surgical Procedures Recertification Video*** found on the Probuphine REMS website **every year**.

10 or More >

Performed 10 or more successful² procedures (comprised of at least five insertions and five removals)

Probuphine REMS website **every year**.

I understand that I should keep documentation of all successfully completed procedures on the ***Probuphine REMS Program Procedure Record for Recertification*** or another record of my choosing - which must be provided to the Probuphine REMS Program if I am audited.

Less than 10 >

Performed less than 10 successful² procedures (comprised of at least five implantations and five removals)

I must (annually):

- attend a ***Probuphine REMS Program Live Training: Lecture and Practicum*** session
- successfully complete the ***Probuphine REMS Program Knowledge Assessment*** test
- meet the ***Probuphine REMS Program Criteria for Procedural Competency***

¹ 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.

² "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

Pharmacies

- Pharmacy Enrollment Form

Probuphine® (buprenorphine) is only available through the Probuphine Risk Evaluation and Mitigation Strategy (REMS) Program, a restricted distribution program. Only prescribers and pharmacies enrolled in the program can prescribe, insert/remove, dispense and receive Probuphine. Before Probuphine is provided, pharmacies must:

1. Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS Program on behalf of the pharmacy.
2. Have the authorized representative enroll in the REMS Program by completing the Pharmacy Enrollment Form and submitting it to the REMS Program.
3. Train all relevant staff involved in dispensing that Probuphine is dispensed only to healthcare settings in which a certified prescriber is practicing and that the drug is not dispensed directly to the patient.
4. Establish processes and procedures to verify that Probuphine is provided to a healthcare setting in which a certified prescriber is practicing and the drug is not dispensed directly to the patient.
5. Verify that the prescriber who will receive the drug is certified to prescribe Probuphine.

Materials for Pharmacies

Probuphine REMS Pharmacy
Enrollment Form



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](#)



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?

Materials for Patients

Probuphine Medication Guide



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



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.

Materials for Patients

Probuphine Medication Guide



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



- 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?**



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

To report SUSPECTED ADVERSE REACTIONS, contact Titan at 1-844-859-6341 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

[Privacy Policy](#)

[Terms of Use](#)

[Contact](#)

[Sitemap](#)

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.

Materials for Patients

[Probuphine Medication Guide](#)



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



- 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?



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

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?](#)

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

Materials for Patients

Probuphine Medication Guide



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



- ***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.

Probuphine Healthcare Provider Locator

Select "My Location" or enter your address or zip code to view closest Probuphine Healthcare Provider with the Probuphine Healthcare Provider Locator.

If you want someone to help you find a doctor you can email us at: probuphinelocator@titanpharm.com

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

Services

- Insert & Remove Probuphine
- Prescribe Probuphine
- Prescribe, Insert & Remove Probuphine

David Sternberg

Psychiatry Associates Chartered,
Lees Symmit, MO, 64063

913-209-9495

Services

Prescribe Probuphine



Probuphine Healthcare Provider Locator

Select "My Location" or enter your address or zip code to view closest Probuphine Healthcare Provider with the Probuphine Healthcare Provider Locator.

If you want someone to help you find a doctor you can email us at: probuphinelocator@titanpharm.com

Find Providers Near: Saint Louis, MO, USA Search Radius: Unlimited

Services

- Insert & Remove Probuphine Prescribe Probuphine Prescribe, Insert & Remove Probuphine

Sanjeev Kamat
3507 Texas Avenue, Saint Louis, MO, 63118
2.9 miles away
314-268-6195
Services
Prescribe Probuphine
[Show on Map](#) [Directions](#)

L.C. Tunstall-Robinson
5615 Pershing Ave., #26, Saint Louis, MO, 63112
4.8 miles away
314-361-0477





[Click Here for Recertification](#)

[Prescribing Information](#)

[Medication Guide](#)

[Healthcare Providers](#)

[Pharmacies](#)

[Patients](#)

[Probuphine Healthcare Provider Locator](#)

Search ...

[Search](#)

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

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

Under 12 Months

Over 12 Months

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

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](#)

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?*

Over 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

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?*

Over 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

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 866-413-1135.

[RESET FORM](#)



[Click Here for Recertification](#)

[Prescribing Information](#)

[Medication Guide](#)

[Healthcare Providers](#)

[Pharmacies](#)

[Patients](#)

[Probuphine Healthcare Provider Locator](#)

Search ...

[Search](#)

Probuphine REMS Program Surgical Procedures Recertification Videos

Probuphine[®]
(buprenorphine) implant



Probuphine Implant Insertion Video



PART 1 080618

from Titan Pharmaceuticals, Inc.



Materials for Patients

[Probuphine Medication Guide](#)



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



Probuphine Implant Insertion Video



PART 1 080618

from Titan Pharmaceuticals, Inc.



Probuphine® REMS Program
Surgical Procedures Recertification Video



Probuphine Implant Removal Video



PART 2 080618

from Titan Pharmaceuticals, Inc.



PART II: Probuphine®

Materials for Patients

Probuphine Medication Guide



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



PART II: Probuphine® Removal Procedure



Probuphine Implant Manage Complications Video



PART III: Managing Complications





from Titan Pharmaceuticals, Inc.



PART III: Managing Complications



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

To report SUSPECTED ADVERSE REACTIONS, contact Titan at 1-844-859-6341
or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

[Privacy Policy](#)

[Terms of Use](#)

[Contact](#)

[Sitemap](#)

Thank you for enrolling

Probuphine[®]
(buprenorphine) implant



Thank you for your submission to Probuphine Rems Enrollment. We will review your submission and inform you about your status regarding Probuphine Rems Enrollment.

Materials for Patients

[Probuphine Medication Guide](#)



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



Probuphine REMS Website Privacy Statement

I. SCOPE OF THIS PRIVACY STATEMENT

This Privacy Statement describes the types of personal information Titan Pharmaceuticals, Inc. (“us,” “we” or “our”) collects through www.remsreviews.wpengine.com, (the “Site”), and the services offered through the Site, including the Titan Pathways Support and Services Program (“APSS”) and the Probuphine REMS Program (collectively with the Site and the APSS, the “Services”) and how we collect, use, and share that information. This Privacy Statement does not govern our collection of personal information through any website or other means, other than through the Services.

By using the Services, you explicitly accept, without limitation or qualification, our practices surrounding the collection, use, and sharing of personal information provided by you in the manner described in this Privacy Statement. If you do not agree with the terms of this Privacy Statement, please do not access, browse, or use the Services.

II. PERSONAL INFORMATION WE COLLECT

A. Information You Give Us

You do not have to give us any personal information to browse the Services. However, you may be asked to provide personal information to submit or request information from us, or to use the Services. Once you provide us with personal information about you, you are no longer anonymous to us. This information may include:

- Registration information. You may be asked to provide registration information to sign up for certain services, including without limitation your name, health care credentials if you are registering as a health care professional, email address, mailing address, telephone number, and fax number.
- Additional Information. Additional information you provide to us, including through comments, feedback, and emails.

B. Automated Information Collection

B. Automated Information Collection

We may collect certain information about your use of the Services through the use of tracking technologies or by other passive means. This “passively collected” information includes, but is not limited to, the domain name of the website that allowed you to navigate to the Services, search engines used, the internet protocol (IP) address used, the length of time spent on the Services, the pages you looked at on the Services, other websites you visited before and after visiting the Services, the type of internet browser you have, the frequency of your visits to the Services, and other relevant statistics, including the following:

- Log Information. When you access the Services, our servers automatically record information that your browser sends whenever you visit a website. These server logs may include information such as your web request, IP address, browser type, browser language, the date and time of your request, your computer operating system, mobile device and mobile operating system, name of your internet service provider or your mobile carrier, and one or more cookies (small text files containing a string of characters) that may uniquely identify your browser.
- Links. The Services may include links in a format that enables us to keep track of whether these links have been followed by IP addresses. We use this information to improve the quality of our products and design.
- URLs. When you visit or access the Services, we automatically receive the URL of the site from which you came and the site to which you are going when you leave the Services. Additionally, advertisers receive the URL of the page you were on when you click on an ad on the Services.
- Cookies. When you visit or access the Services, we send one or more cookies (small text files containing a string of characters) to your computer that uniquely identifies your browser. We use cookies to improve the quality of the Services by storing user preferences and tracking user trends. Most web browsers accept cookies automatically, but can be configured not to do so or to notify the user when a cookie is being sent. If you wish to disable cookies, refer to your browser help menu to learn how to disable cookies. Please note that if you disable cookies, you may not be able to use some customized features available through the Services.
- Web Beacons. Web beacons (also known as “pixel tags” or “clear GIFs”) are 1×1 single-pixel graphics that allow us to count the number of users who have visited or accessed the Services and to recognize users by accessing our cookies. We may employ web beacons to facilitate Services administration and navigation, to track the actions of users of the Services, to compile aggregate statistics about Services usage and response rates, and to provide an enhanced online experience for visitors to the Services. We may also include web beacons in HTML-formatted e-mail messages that we send to determine which e-mail messages were opened.

- Web Beacons. Web beacons (also known as “pixel tags” or “clear GIFs”) are 1×1 single-pixel graphics that allow us to count the number of users who have visited or accessed the Services and to recognize users by accessing our cookies. We may employ web beacons to facilitate Services administration and navigation, to track the actions of users of the Services, to compile aggregate statistics about Services usage and response rates, and to provide an enhanced online experience for visitors to the Services. We may also include web beacons in HTML-formatted e-mail messages that we send to determine which e-mail messages were opened.
- Aggregate Information. We may compile certain personal information and other information collected through the Services on an aggregate basis. This information may include, without limitation, the number of people who have visited the Services and other user demographics. Such aggregate information does not identify you individually.

III. HOW WE USE PERSONAL INFORMATION

Personal information collected through the Services may be used by us and our affiliates for purposes of:

- Responding to your questions and feedback;
- Providing the services you select through the Services;
- Confirming your eligibility to access certain products and Services;
- Contacting you, whether by email, postal mail, or telephone with information about the Services, our products, or our services;
- For such purposes as you may authorize at the time you submit the information;
- Auditing, research, and analysis to maintain, protect, and improve the Services and our services;
- Ensuring the technical functions of our network;
- Improving and customizing the content and layout of the Services;
- Developing new products and services; or

- Compiling personal information and other information collected through the Services on an aggregate basis.

IV. PERSONAL INFORMATION WE SHARE

We do not sell, rent, trade, or otherwise share personal information collected through the Services, except as described below:

- In Connection with our Offerings. The Services involves the sharing of certain personal information collected through the Services (i) in connection providing and administering the Services, including without limitation to health care providers and insurance institutions in connection with APSS, and (ii) as you otherwise provide your consent.
- Subsidiaries and Affiliates. We may share personal information with our subsidiaries and affiliates for the purposes for which you provided the information or as reasonably necessary for our internal administrative and business purposes.
- Service Providers. We work with third parties that provide services on our behalf. Such services may include website hosting, marketing, and website usage analytics. We may share personal information and non-personal information with these third parties for the purpose of enabling them to provide these services. We do not bear any responsibility for any actions or policies of such third parties.
- Consent. We may share personal information in accordance with any consent you provide.
- Required by Law. We may disclose personal information or any information collected through the Services if we are required to do so by law or pursuant to legal process, in response to a request from government officials or law enforcement authorities, or as necessary or appropriate in connection with an investigation of illegal activity.
- Certain Transactions. We may disclose or transfer personal information or any information collected through the Services to third parties who acquire all or a portion of our business, whether such acquisition is by way of merger, consolidation, or purchase of all or a portion of our assets, or in connection with any bankruptcy or reorganization proceeding brought by or against us.

V. AGGREGATE INFORMATION

We may compile personal information and other information collected through the Services on an aggregate basis. This information may

We may compile personal information and other information collected through the Services on an aggregate basis. This information may include, without limitation, the number of users who have registered for the Services, demographic information about users of the Services, and individual purchase preferences. Such aggregate information does not identify you individually. We may use aggregate information and share aggregate information with third parties for any of the purposes specified in this Privacy Statement, and for any other lawful purpose.

VI. Your Choices

A. Information You Provide

You can always choose whether or not to provide information on the Services. However, if you choose not to disclose certain information, you may not be able to register as a user of the Services, which may limit your access to certain portions of the Services.

B. Communications From Us

If at any time you decide that you no longer wish to receive notices from us regarding the Services, you may indicate this preference by contacting us at registration@titanpharm.com.

C. Do Not Track

Some web browsers may transmit “do-not-track” signals to websites with which the browser communicates. Titan web servers do not currently respond to these signals.

VII. INFORMATION STORAGE AND SECURITY

We employ reasonable security precautions to help protect against the loss, misuse, and alteration of personal information provided on or through the Services. However, no method of transmitting or storing data is completely secure. As a result, although we strive to protect personal information about you, we cannot guarantee the security of any information you transmit to us through or in connection with the Services. If you have reason to believe that personal information is no longer secure, please notify us immediately by contacting us in accordance with the last section below.

VIII. A SPECIAL NOTE ABOUT CHILDREN

VIII. A SPECIAL NOTE ABOUT CHILDREN

Children are not eligible to use the Services, and we ask that minors (children under the age of 18) not submit any personal information to us. If you are a minor, you can use the Services only in conjunction with your parents or guardians.

IX. EXTERNAL LINKS

The Services may contain links to various websites that we do not control. When you click on one of these links, you will no longer be transacting business through the Services. Third party websites maintain their own privacy policies, and we do not exercise any control over any of the third party websites that may be linked to the Services. If you visit a website that is linked to the Services, you should consult that website's privacy policy before providing any personal information. Please be aware that we are not responsible for the privacy practices of such other websites, and we are not liable for their misuse of personal information about you.

X. SPECIAL ADMONITIONS FOR INTERNATIONAL USE

The Services are hosted in the United States and are intended for use by residents of the United States of America only. All matters relating to the Services are governed exclusively by the laws of the New Jersey in the United States of America and not the jurisdiction in which you are located. If you are located outside of the United States of America and you contact us, please be advised that any information you provide to us will be transferred to the United States of America and that by submitting information, you explicitly authorize such transfer.

XI. UPDATES TO THIS PRIVACY STATEMENT

We may change or update the Site or any of our policies and procedures without prior notice. We will post a notice on the Services to advise you of any significant changes to this Privacy Statement and indicate via the "Last Updated" legend at the bottom of this Privacy Statement when it was most recently updated. Your continued use of the Site signifies your continued assent to the terms of this Privacy Statement, as updated or amended at that time.

XII. QUESTIONS REGARDING THIS PRIVACY STATEMENT

We may change or update the Site or any of our policies and procedures without prior notice. We will post a notice on the Services to advise you of any significant changes to this Privacy Statement and indicate via the “Last Updated” legend at the bottom of this Privacy Statement when it was most recently updated. Your continued use of the Site signifies your continued assent to the terms of this Privacy Statement, as updated or amended at that time.

XII. QUESTIONS REGARDING THIS PRIVACY STATEMENT

If you have any questions or comments regarding this Privacy Statement, please send us an email at registration@titanpharm.com.

This Privacy Statement is effective as of May 27, 2016.

Last Updated: September 4, 2018



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

To report SUSPECTED ADVERSE REACTIONS, contact Titan at 1-844-859-6341
or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

[Privacy Policy](#)

[Terms of Use](#)

[Contact](#)

[Sitemap](#)

Terms of Use

1. ACCEPTANCE OF TERMS AND CONDITIONS

This Terms of Use Agreement governs your use of the website located at www.remsreviews.wpengine.com (the "Site") which is owned and operated by Titan Pharmaceuticals, Inc. (the "Company," "we," "us" or "our"), and the services offered through the Site, including the Titan Pathways Support and Services Program ("APSS") and the Probuphine REMS Program (collectively with the Site and the APSS, the "Services"). By accessing, browsing or using the Services or any pages of the Services, you are indicating that you have read and acknowledge and agree to be bound by this Terms of Use Agreement and any additional terms and conditions applicable to certain areas of the Services and posted in those areas of the Services, which are incorporated herein by reference (collectively, "Terms and Conditions"), and the Company's Website Privacy Statement located at <https://probuphinerems.wpengine.com/privacy-statement/>. If you do not agree to every provision of these Terms and Conditions and the Company's Website Privacy Statement, please do not access, browse or use the Services.

These Terms and Conditions may be revised at any time for any reason, and we may provide you notice of these changes by any reasonable means, including by posting the revised version of the Terms and Conditions on the Services. You can determine when we last updated these Terms and Conditions by referring to the "Last Updated" legend at the bottom of these Terms and Conditions. By accessing, browsing or using the Services following the posting of changes to these Terms and Conditions, you accept such changes. You agree to use the Services for lawful purposes only in a manner consistent with any and all applicable rules, laws and regulations. Any use of the Services in a manner inconsistent with these Terms and Conditions is deemed unauthorized access and may subject the user to civil or criminal penalties. We strongly recommend that you periodically visit this page of the Services to review these Terms and Conditions.

2. MEDICAL INFORMATION

THE SERVICES MAY CONTAIN GENERAL INFORMATION RELATING TO CERTAIN MEDICAL CONDITIONS AND THEIR TREATMENT. SUCH INFORMATION IS FOR INFORMATIONAL PURPOSES ONLY. THE CONTENT OF THE SERVICES IS NOT INTENDED IN ANY WAY TO SUBSTITUTE FOR PROFESSIONAL MEDICAL ADVICE AND SHOULD NOT BE RELIED ON FOR MEDICAL DIAGNOSIS OR TREATMENT. ALWAYS SEEK THE ADVICE OF YOUR PHYSICIAN OR OTHER QUALIFIED HEALTH PROVIDER WITH ANY QUESTIONS YOU MAY HAVE REGARDING A MEDICAL CONDITION. NEVER DISREGARD MEDICAL ADVICE OR DELAY IN SEEKING IT BECAUSE OF SOMETHING YOU HAVE READ ON THE SERVICES. YOU SHOULD CONSULT WITH YOUR DOCTOR BEFORE USING ANY PRODUCT DISCUSSED ON THE SERVICES OR ON ANY OTHER WEBSITE

DISREGARD MEDICAL ADVICE OR DELAY IN SEEKING IT BECAUSE OF SOMETHING YOU HAVE READ ON THE SERVICES. YOU SHOULD CONSULT WITH YOUR DOCTOR BEFORE USING ANY PRODUCT DISCUSSED ON THE SERVICES OR ON ANY OTHER WEBSITE.

3. SERVICES CONTENT

The Services and all material on the Services or contained therein, all text, graphics, and other works on the Services, the Services' design and coding, all computer programs used and licensed in connection with the Services, the look and feel of the Services, and all data and reports generated by the Services (collectively, the "Services Content") are owned by us or a third party. These materials are protected under copyright, trademark and other laws. You may not copy, download, transmit, modify, distribute or republish the Services or any portion of the Services, including without limitation any of the Services Content without the prior written consent of Company. You may not sell, publicly display, create derivative works of, reverse engineer, assign, sub-license, transfer or otherwise exploit the Services or any Services Content. Use of any Services Content is prohibited without the prior written permission of Company. As long as you comply with these Terms and Conditions, Company grants you a personal, non-exclusive, non-transferable, non-sublicenseable right to access and make personal, non-commercial use of the Services in compliance with these Terms and Conditions. You shall not, and shall not permit anyone else to, directly or indirectly: (i) remove or alter proprietary notices or labels on or in the Services or Services Content; (ii) engage in any activity that interferes with or disrupts the Services or Services Content; (iii) engage in any fraudulent activity or activity that facilitates fraud; or (iv) otherwise act in violation of these Terms and Conditions. All rights not expressly granted herein are reserved.

4. COMPANY TRADEMARKS

All product and service names appearing in a typeface different from that of the surrounding text or with a trademark symbol, including without limitation the following:

PROBUPHINE®\

Titan Access Program™

are registered and unregistered trademarks and service marks owned by Company or its subsidiaries or affiliates or a third party. The absence of a name, trademark or logo in this list does not constitute a waiver of any and all intellectual property rights that Company has established in any of its goods, services, names or logos. These trademarks and all other trademarks, service marks, logos, and company names (each a "Mark") used in connection with the Services are the property of Company or third parties and shall remain the property of Company and such

“Mark”) used in connection with the Services are the property of Company or third parties and shall remain the property of Company and such third parties. Nothing contained in the Services shall be construed as granting, by implication or otherwise, any license or right to use any such Mark without the prior written permission of Company or such third party that may own such Mark. Your misuse of any such Mark, or any other Services Content, is strictly prohibited.

5. REGISTRATION

Some of the Services may require registration. Each registration is for a single user only. In consideration of your use of the Services, you agree to provide accurate, current and complete information about yourself or your company as requested on the Services registration form and to maintain and promptly update the information (including, in particular, your e-mail address) you provide as necessary to keep the information true, accurate, current and complete. By accepting these Terms and Conditions, you represent and warrant that you are 18 years of age or older and that, if you have accepted these Terms and Conditions on behalf of any business (such as a corporation, partnership, limited liability company or other organization) or other entity, you represent and warrant that you have legal authority to do so.

Any changes to your registration information should be made on the Services. If you provide information that is untrue, inaccurate, not current or incomplete, we may suspend or terminate your account and refuse any and all current or future use of the Services.

After you register on the Services, you may receive a password for your use of the Services. You are responsible for keeping your password confidential. You will be responsible for all uses and activity that occurs through your password or account. You will close the browser window for the Services at the end of each use, and you will immediately notify us of any unauthorized use of your password. We cannot and will not be liable for any loss or damage arising from your failure to comply with this Section 5.

6. LEGAL REQUIREMENTS

Where Company has a good faith belief that such action is necessary to comply with a judicial proceeding, court order, warrant, administrative order, civil investigative demand, subpoena, or other valid process, Company may disclose IP addresses, personal information, and any contents of the Services where it is legally compelled to do so. Please see the Company’s Website Privacy Statement located at <https://probuphinerems.wpengine.com/privacy-statement/> for additional information relating to the privacy and security of information collected hereunder.

7. YOUR USE OF THE SERVICES

7. YOUR USE OF THE SERVICES

You are solely responsible and liable for all data, information and other materials (“User Content”) that you submit, upload, post, e-mail or otherwise transmit (“Transmit”) in connection with the Services. In addition, we have no control over, and shall have no liability for, any damages resulting from the use (including without limitation republication) or misuse by any third party of information made public through the Services. IF YOU CHOOSE TO SUBMIT TO US, OR OTHERWISE MAKE ANY PERSONAL INFORMATION OR OTHER INFORMATION PUBLICLY AVAILABLE, YOU DO SO AT YOUR OWN RISK AND COMPANY SHALL HAVE NO RESPONSIBILITY OR LIABILITY THEREFOR.

You agree that you will not, and will not permit anyone else to, directly or indirectly: (a) Transmit any User Content that is unlawful, harmful, threatening, abusive, hateful, obscene, harassing, tortious, defamatory, libelous, slanderous, pornographic, profane, vulgar, offensive, lewd, invasive of another’s privacy or racially, ethnically or otherwise objectionable; (b) use the Services to harm minors in any way or to stalk, threaten, or otherwise violate the rights of others, including without limitation others’ privacy rights or rights of publicity, or harvest or collect personal information, including e-mail addresses, about other users of the Services; (c) Transmit any User Content: (i) that you do not have the right to Transmit, under any law or contractual or fiduciary relationships, including, without limitation, any inside information or proprietary or confidential information; (ii) that infringes any patent, copyright, trademark or other intellectual property right or misappropriates any trade secret or right of privacy of any third-party; (iii) that constitutes unsolicited or unauthorized advertising or promotional materials, “spam,” “chain letters,” or pyramid schemes; or (iv) that contains any software routine, code, instruction or virus that is designed to disable, delete, modify, damage or erase software, hardware or data; (d) forge headers or otherwise manipulate identifiers in order to disguise any User Content Transmitted through the Services; (e) interfere with the Services or servers or networks used in connection with the Services; (f) interfere with the ability of others to use the Services; (g) copy, download, transmit, modify, reproduce, sell, resell, sub-license, distribute, publish create derivative works of, reverse engineer, assign, transfer or exploit for any commercial purposes, any portion of the Services, the Services Content or any User Content contained therein; (h) conduct your business using the Services in a way that is unfair, unlawful, or constitutes a deceptive business practice; (i) use any robot, spider, or other automatic device to monitor or copy portions of the Services or the Services Content without Company’s prior written permission; (j) include in any third party website any hypertext link to any page or location within the Services without Company’s prior written permission; (k) mirror or display the Services or any portion thereof in frames without Company’s prior written permission; or (l) impersonate any person or entity, including, but not limited to, other users of the Services, falsely state or otherwise misrepresent your affiliation with any person or entity, or express or imply that we endorse any statement you make.

You acknowledge and agree that Company may disclose or use any User Content that you Transmit for purposes that include, but are not limited to: (a) enforcing these Terms and Conditions; (b) complying with any laws, regulations or rules of any federal, state or local government or agency; (c) responding to claims that any User Content violates the rights of third parties; or (d) protecting the rights or property of Company, its customers or the public. With respect to User Content that you Transmit to the Services, you grant Company a perpetual,

Company, its customers or the public. With respect to User Content that you transmit to the Services, you grant Company a perpetual, worldwide, royalty-free, non-exclusive license to use, copy, excerpt, reproduce, display, publish, modify, distribute and create derivative works of such User Content in any form or media, and to allow others to do so, however, Company will only share personally identifiable information that you provide in accordance with Company's privacy statement at <https://probuphinerems.wpengine.com/privacy-statement/>. As between the parties, we own all right, title, and interest in and to all intellectual property rights in all materials, products or services developed by us, or on behalf of us by third parties, based on or including as a component thereof any such information as described above, and all generalized knowledge, skill, know-how and expertise relating to such information.

Company does not and cannot review all User Content posted to the Services, or created by users accessing the Services, and is not in any manner responsible for the content of any User Content. You acknowledge that by providing you with the ability to view and distribute user-generated content on the Services, Company is merely acting as a passive conduit for such distribution and is not undertaking any obligation or liability relating to any User Content or activities on the Services. However, Company reserves the right to block, remove, move or edit any of the submissions in its sole discretion.

8. LINKED SITES

Company has not reviewed all of the websites linked to the Services and is not responsible for the content of any third-party pages or any other websites linked to the Services. Nothing in the Services, including, without limitation, any links to other websites, should be construed as an endorsement of any products, services or information of any other persons or companies by Company. Your choice to link to any other website is at your own risk, and you agree to comply with all terms and conditions relating to such websites. Company reserves the right not to link, or to remove the link, to a particular website at any time. Any links to third party websites are provided as a convenience to you and are neither owned nor operated by Company. Company has no control over these linked websites and makes no representations or warranties with respect to these linked websites. Your viewing and use of any third party websites is at your sole discretion and risk.

9. SPECIAL ADMONITIONS FOR INTERNATIONAL USE

The Services are hosted in the United States and are intended for use by residents of the United States of America only. All matters relating to the Services are governed exclusively by the laws of the State of California in the United States of America and not the jurisdiction in which you are located. If you are located outside of the United States of America and you contact us, please be advised that any information you provide to us will be transferred to the United States of America and that by submitting information, you explicitly authorize such transfer.

10. INDEMNIFICATION

You agree to defend, indemnify and hold harmless Company, its subsidiaries and affiliates, business partners, contractors, clients and service providers, and their respective officers, employees, agents and representatives from and against any claims, liabilities, costs or damages, including reasonable attorneys' fees and paralegal fees through final appeals, made by any third party, relating to or arising from your use of the Services, any User Content that you Transmit to or through the Services, any violation of these Terms and Conditions by you, or any other act or omission by you, including your violation of any rights of another, arising from your use of the Services.

11. AVAILABILITY AND FEATURES

Availability and features of the Services are subject to change without notice.

12. TERMINATION

You acknowledge and agree that Company may terminate your access to use of the Services for any reason, including, without limitation, your violation of these Terms and Conditions. You agree that Company may terminate your access to and use of the Services without prior notice and without any liability to you or any third party. You acknowledge and agree that Company may modify, limit, suspend or discontinue the Services or any part of the Services at any time, without notice or liability to you. Company may also, from time to time, establish general rules and policies regarding use of the Services. Company will post such rules and policies on the Services, and you agree that your compliance with such rules and policies shall be a condition of your use or continued use of the Services. Company shall have no liability or responsibility with respect to any lost Services Content, User Content, or other data, such as the deletion of or failure to store Services Content, User Content, or other data. All provisions of these Terms and Conditions that by their nature should survive termination of your right to access and use the Services shall survive (including, but not limited to, all limitations on liability, releases, indemnification obligations, disclaimers of warranties, and intellectual property protections and licenses). Company reserves the right to, but has no obligation to, store or keep copies of any Services Content, User Content, or other information, unless otherwise required by law or court order.

13. DISCLAIMERS AND LIMITATION OF LIABILITY

13. DISCLAIMERS AND LIMITATION OF LIABILITY

COMPANY IS PROVIDING THE SERVICES AND ALL FEATURES OF THE SERVICES CONTENT ON AN "AS-IS," "AS-AVAILABLE" BASIS. YOU EXPRESSLY AGREE THAT YOUR USE OF THE SERVICES IS AT YOUR SOLE RISK. COMPANY DISCLAIMS ALL REPRESENTATIONS OR WARRANTIES OF ANY KIND TO THE EXTENT THAT THEY MAY BE EXCLUDED BY LAW, INCLUDING, BUT NOT LIMITED TO, WARRANTIES OF MERCHANTABILITY AND FITNESS FOR A PARTICULAR PURPOSE OR NON-INFRINGEMENT AS TO THE OPERATION OF THE SERVICES. COMPANY DOES NOT WARRANT THAT THE SERVICES WILL OPERATE IN AN UNINTERRUPTED, SECURE OR ERROR-FREE MANNER. COMPANY ASSUMES NO RESPONSIBILITY FOR AND MAKES NO WARRANTY OR REPRESENTATION AS TO THE ACCURACY, COMPLETENESS, RELIABILITY, CURRENTNESS, USEFULNESS, OR DECENCY OF THE SERVICES. COMPANY MAKES NO WARRANTY REGARDING THE QUALITY, SAFETY, OR LEGALITY OF THE SERVICES, AND COMPANY DOES NOT WARRANT THAT YOUR USE OF THE SERVICES WILL MEET YOUR REQUIREMENTS OR EXPECTATIONS.

YOU ASSUME TOTAL RESPONSIBILITY AND RISK FOR YOUR USE OF THE SERVICES. ANY SERVICES CONTENT DOWNLOADED OR OTHERWISE OBTAINED THROUGH YOUR USE OF THE SERVICES IS AT YOUR OWN RISK, AND YOU WILL BE SOLELY RESPONSIBLE FOR ANY DAMAGE DONE TO YOUR COMPUTER OR LOSS OF DATA THAT RESULTS FROM SUCH ACTIVITY.

IN NO EVENT SHALL COMPANY, OR ITS SUBSIDIARIES, AFFILIATES, OFFICERS, DIRECTORS, EMPLOYEES, OR AGENTS ("AFFILIATED ENTITIES") BE LIABLE, WHETHER IN CONTRACT, TORT (INCLUDING WITHOUT LIMITATION NEGLIGENCE) OR OTHERWISE FOR ANY INDIRECT, SPECIAL, INCIDENTAL, PUNITIVE, EXEMPLARY OR CONSEQUENTIAL DAMAGES, INCLUDING, BUT NOT LIMITED TO, LOSS OF DATA OR OTHER INTANGIBLES, INCOME OR PROFIT, LOSS OF OR DAMAGE TO PROPERTY OR CLAIMS OF THIRD PARTIES, EVEN IF COMPANY HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGES, ARISING OUT OF OR RESULTING FROM (1) THE USE OF OR INABILITY TO USE THE SERVICES, ANY SERVICES, OR THE USER CONTENT; (2) ANY TRANSACTION CONDUCTED THROUGH OR FACILITATED BY THE SERVICES; (3) ANY CLAIM ATTRIBUTABLE TO ERRORS, OMISSIONS, OR OTHER INACCURACIES IN THE SERVICES, ANY SERVICES AND/OR USER CONTENT; (4) UNAUTHORIZED ACCESS TO OR ALTERATION OF YOUR TRANSMISSIONS OR DATA; OR (5) ANY OTHER MATTER RELATING TO THE SERVICES, ANY SERVICES, OR THE USER CONTENT. YOU SPECIFICALLY AGREE THAT COMPANY IS NOT RESPONSIBLE OR LIABLE TO YOU OR ANYONE ELSE FOR ANY INFRINGEMENT OR VIOLATION OF YOUR RIGHTS BY ANY OTHER PARTY, INCLUDING, BUT NOT LIMITED TO, INTELLECTUAL PROPERTY RIGHTS, RIGHTS OF PUBLICITY, OR RIGHTS OF PRIVACY. YOUR SOLE AND EXCLUSIVE REMEDY FOR DISSATISFACTION WITH THE SERVICES IS TO STOP USING THE SERVICES. THE MAXIMUM LIABILITY OF COMPANY AND THE AFFILIATED ENTITIES FOR ALL DAMAGES, LOSSES AND CAUSES OF ACTION, WHETHER IN CONTRACT, TORT (INCLUDING WITHOUT LIMITATION NEGLIGENCE) OR OTHERWISE WILL BE THE TOTAL AMOUNT, IF ANY, PAID BY YOU TO COMPANY TO ACCESS AND USE THE SERVICES. IF YOU LIVE IN A JURISDICTION WHOSE LAWS PREVENT YOU FROM TAKING FULL RESPONSIBILITY AND RISK FOR YOUR USE OF THE SERVICES IN ACCORDANCE WITH THESE TERMS AND CONDITIONS, COMPANY'S LIABILITY IS LIMITED TO THE GREATEST EXTENT ALLOWED BY THE LAW OF THAT JURISDICTION.

14. GOVERNING LAW AND JURISDICTION

Company operates the Services from its offices in South San Francisco, California U.S.A. These Terms and Conditions and the transactions they contemplate, including without limitation their interpretation, construction, performance and enforcement shall be governed by the laws of the State of California, U.S.A. without reference to conflict or choice of law provisions, as applicable to contracts made and performed entirely within such State. The International Convention on the Sale of Goods, and other international treaties that are not mandatory with respect to contracts made and performed entirely in the United States, shall not apply. The exclusive forum for the resolution of any dispute relating to these Terms and Conditions shall be the state and federal courts in California, U.S.A., and you agree to personal jurisdiction of such courts over you with regard to any dispute relating to these Terms and Conditions and agree to service of process on you by e-mail to the address you have submitted on the Services, if any, and by any other means permitted by law.

15. NOTICE

All notices, demands, or consents given by you under these Terms and Conditions will be in writing and will be deemed given when delivered to Company at the following contact: Titan Pharmaceuticals, Inc. 400 Oyster Point Boulevard, Suite 505 South San Francisco, CA 94080-1958.

Any notices to you may be made via either e-mail or postal mail to the address in Company's records or via posting on the Services.

Please report any violations of these Terms and Conditions to Company at the contact listed above.

16. MISCELLANEOUS

You may not assign, sublicense or otherwise transfer any of your rights under these Terms and Conditions. If any provision of these Terms and Conditions is found to be invalid by any court having competent jurisdiction, the invalidity of that provision shall not affect the validity of the remaining provisions of this Agreement, which shall remain in full force and effect. Headings in these Terms and Conditions are for convenience only and shall have no legal meaning or effect. No action arising under this Agreement may be brought at any time more than twelve (12) months after the facts occurred upon which the cause of action arose. These Terms and Conditions, and not the conduct between us or any trade practice, shall control the interpretation of these Terms and Conditions between the parties respecting the Services. Company's failure to enforce a particular provision of these Terms and Conditions does not mean that Company waives the right to enforce it in the future; Company shall waive such a right only in writing.

These Terms and Conditions and all other written agreements duly executed between you and Company in connection with your use of the Services constitute the entire agreement between you and Company with respect to the subject matter hereof and supersede any prior or contemporaneous proposals, discussions, communications, or oral agreements heretofore made.

Last Updated: September 4, 2018



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

To report SUSPECTED ADVERSE REACTIONS, contact Titan at 1-844-859-6341
or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

[Privacy Policy](#)

[Terms of Use](#)

[Contact](#)

[Sitemap](#)



Contact

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 1-844-859-6341

Email

info@titanaccessprogram.com

Probuphine® REMS Program Surgical Procedures Recertification Video

Video Script
VERSION 19
Rev. 11/2018

The video will be divided into four sections with the option to play every section at once using "Play All."

The DVD disk menu should list:

- Play All
- Introduction
- Part I: Insertion of Probuphine®: Four Implants
- Part II: Probuphine® Removal Procedure and Reinsertion
- Part III: Managing Complications

SLIDE #	VIDEO	AUDIO
1	<p><u>TITLE APPEARS:</u></p> <p>Probuphine® REMS Program Surgical Procedures Recertification Video</p> <p>The Probuphine logo builds on in a stylized manner:</p> <p><u>GRAPHIC SCREEN:</u></p> <p>Probuphine (buprenorphine) implant Logo</p>	<p><u>MUSIC:</u></p> <p>We hear an energetic theme that motivates the flow of video images.</p>
2	<p><u>TEXT ON SCREEN:</u></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 that includes counseling and psychosocial support.</p>	<p><u>NARRATOR:</u></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, that is, 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 that includes counseling and psychosocial support.</p>
3	<p><u>TEXT ON SCREEN:</u></p> <p>Probuphine is not appropriate for new entrants</p>	<p><u>NARRATOR:</u></p> <p>Probuphine is not appropriate for new entrants to</p>

	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.	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.
4	<p><u>TEXT ON SCREEN:</u></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: http://buprenorphine.samhsa.gov/data.html</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 and remove Probuphine must successfully complete a live Probuphine REMS training program and be certified to prescribe and perform the procedures.</p>	<p><u>NARRATOR:</u></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 visit the DATA 2000 website.</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 and remove Probuphine must successfully complete a live Probuphine REMS training program and be certified to prescribe and perform the procedures.</p>
5	<p><u>TEXT ON SCREEN:</u></p> <p><u>Probuphine REMS Goal:</u></p> <p>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><u>NARRATOR:</u></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>
6	<p><u>TEXT ON SCREEN:</u></p> <p>a) Ensuring that healthcare providers are educated on the following:</p> <ul style="list-style-type: none"> • Proper insertion and removal of Probuphine • Risk of complications of migration, protrusion, expulsion, and nerve damage associated with the insertion and 	<p><u>NARRATOR:</u></p> <p>a) Ensuring that healthcare providers are educated on the following:</p> <ul style="list-style-type: none"> • Proper insertion and removal of Probuphine • Risk of complications of migration, protrusion, expulsion, and nerve damage associated with the insertion and removal

	<p>removal of Probuphine</p> <ul style="list-style-type: none"> • Risks of accidental overdose, misuse, and abuse if an implant comes out or protrudes from the skin <p>b) Ensuring pharmacies are certified and only provide Probuphine to healthcare settings in which a certified prescriber is practicing</p> <p>c) Informing patients about the risks of complications of migration, protrusion, expulsion, and nerve damage associated with insertion and removal, as well as, the risks of accidental overdose, misuse and abuse if an implant comes out or protrudes from the skin.</p>	<p>of Probuphine</p> <ul style="list-style-type: none"> • Risks of accidental overdose, misuse, and abuse if an implant comes out or protrudes from the skin <p>b) Ensuring pharmacies are certified and only provide Probuphine to healthcare settings in which a certified prescriber is practicing</p> <p>c) Informing patients about the risks of complications of migration, protrusion, expulsion, and nerve damage associated with insertion and removal, as well as, the risks of accidental overdose, misuse and abuse if an implant comes out or protrudes from the skin.</p>
7	<p><u>TEXT ON SCREEN:</u></p> <p>Healthcare providers who prescribe Probuphine must:</p> <ol style="list-style-type: none"> 1. Review the Prescribing Information, including the Instructions for Use 2. Take the <i>Probuphine REMS Program Live Training: Lecture and Practicum</i> 3. Successfully complete the <i>Probuphine REMS Program Knowledge Assessment</i> 4. Enroll into the Probuphine REMS Program by completing the <i>Prescriber Enrollment Form</i> 5. Counsel the patient on the risks of insertion and removal, accidental overdose, misuse and abuse and the importance of appropriate wound care using the <i>What You Need to Know about Probuphine: A Patient's Guide</i> 6. Provide the patient the <i>What You Need to Know about Probuphine: A Patient's Guide</i> 7. Not loan or sell Probuphine 8. Not transfer Probuphine except to certified inserters 9. Maintain records of the insertion and removal of Probuphine, in each patient's medical record using the <i>Probuphine REMS Program Insertion/Removal Log</i> or by using another method or system (e.g., electronic health record) specific to the healthcare provider's practice 	<p><u>NARRATOR:</u></p> <p>Healthcare providers who prescribe Probuphine must:</p> <ol style="list-style-type: none"> 1. Review the Prescribing Information, including the Instructions for Use 2. Take the <i>Probuphine REMS Program Live Training: Lecture and Practicum</i> 3. Successfully complete the <i>Probuphine REMS Program Knowledge Assessment</i> 4. Enroll into the Probuphine REMS Program by completing the <i>Prescriber Enrollment Form</i> and submitting it to the REMS Program 5. Counsel the patient on the risks of insertion and removal, accidental overdose, misuse and abuse and the importance of appropriate wound care using the <i>What You Need to Know about Probuphine: A Patient's Guide</i> 6. Provide the patient the <i>What You Need to Know about Probuphine: A Patient's Guide</i> 7. Not loan or sell Probuphine 8. Not transfer Probuphine except to certified inserters 9. And maintain records of the insertion and removal of Probuphine, including the date, serial number, number of implants inserted, name of healthcare provider performing the procedure, and anatomical location of each implant in each patient's medical record using the <i>Probuphine REMS Program Insertion/Removal Log</i> or by using another method or system (for example, electronic health record)

		specific to the healthcare provider's practice
8	<p><u>TEXT ON SCREEN:</u></p> <p>Healthcare providers who insert and remove Probuphine must:</p> <ul style="list-style-type: none"> • Have performed a surgical procedure in the 3 months immediately preceding enrollment in the Probuphine REMS Program • Review the Prescribing Information, including the Instructions for Use • Take the <i>Probuphine REMS Program Live Training: Lecture and Practicum</i> • Successfully complete the <i>Probuphine REMS Program Knowledge Assessment</i> • Successfully complete the <i>Probuphine REMS Program Criteria for Procedural Competency</i> • Enroll into the Probuphine REMS Program • Have the appropriate equipment to perform insertions and removals of Probuphine on-site • Counsel the patient on the risks of insertion and removal, accidental overdose, misuse and abuse and the importance of appropriate wound care using the <i>Medication Guide</i>. Provide a copy to the patient • Complete the <i>Probuphine REMS Program Insertion/Removal Log</i> or by using another method or system (e.g., electronic health record) to document the date, serial number, number of implants inserted, name of the healthcare provider performing the procedure, and anatomical location of each implant or each patient. • Insert and remove Probuphine only in healthcare settings in which a certified prescriber is practicing • Assess the patient's need for removal of Probuphine • Maintain documentation of the insertion and removal of Probuphine in each patient's medical record • Comply with audits carried out by Titan or a third party • <u>Recertify</u> in the Probuphine REMS 	<p><u>NARRATOR:</u></p> <p>Healthcare providers who insert and remove Probuphine in surgical procedures must:</p> <ul style="list-style-type: none"> • Attest to having performed a surgical procedure in the 3 months immediately preceding enrollment in the Probuphine REMS Program • Review the Prescribing Information, including the Instructions for Use • Take the <i>Probuphine REMS Program Live Training: Lecture and Practicum</i> • Successfully complete the <i>Probuphine REMS Program Knowledge Assessment</i> • Successfully complete the <i>Probuphine REMS Program Criteria for Procedural Competency</i> • Enroll into the Probuphine REMS Program by completing the <i>Healthcare Provider Who Performs Probuphine Surgical Procedures Enrollment Form</i> or <i>Healthcare Provider Dual Enrollment Form</i> and submitting it to the REMS Program • Have the appropriate equipment to perform insertions and removals of Probuphine on-site • Counsel each patient on the risks of insertion and removal, accidental overdose, misuse and abuse and the importance of appropriate wound care using the Medication Guide. Provide a copy to the patient. • Complete the <i>Insertion/Removal Log</i> or by using another method or system (for example, electronic health record) to document the date, serial number, number of implants inserted, name of the healthcare provider performing the procedure, and anatomical location of each implant or each patient • Insert and remove Probuphine only in healthcare settings in which a certified prescriber is practicing • Assess the patient's need for removal of Probuphine • Maintain documentation of the insertion and removal of Probuphine in each

	<p>Program annually. Complete the <i>Healthcare Provider Who Performs Probuphine Surgical Procedures Recertification Form</i> and the recertification training requirements as described in the form.</p>	<p>patient's medical record</p> <ul style="list-style-type: none"> Comply with audits carried out by Titan or a third party to ensure that all processes and procedures are in place and are being followed. AND recertify annually by completing the <i>Healthcare Provider Who Performs Probuphine Surgical Procedures Recertification Form</i> and the recertification training requirements as described in that form.
9	<p><u>TEXT ON SCREEN:</u></p> <p>This video is intended to be used for recertification for healthcare providers who perform Probuphine surgical procedures. This video is <u>not</u> intended to replace the live Probuphine REMS Training Program.</p>	<p><u>NARRATOR:</u></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 Probuphine REMS Training Program.</p>
10	<p><u>TEXT ON SCREEN:</u></p> <p>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>.</p>	<p><u>NARRATOR:</u></p> <p>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>.</p>
11	<p><u>TITLE APPEARS:</u></p> <p>Part 1 Insertion of Probuphine®: <i>Four Implants</i></p>	<p><u>NARRATOR:</u></p> <p>Part 1 Insertion of Probuphine®: <i>Four Implants</i></p>
12	<p><u>TITLE APPEARS:</u></p> <p>PREPARATION</p> <p>Confirm that the patient:</p> <ul style="list-style-type: none"> Does not have any contraindications including hypersensitivity to buprenorphine or ingredients in Probuphine, such as ethylene vinyl acetate Has had a medical history taken and physical examination Understands the benefits and risks of Probuphine Has received a copy of the <i>Medication Guide</i> included in the packaging Does not have any questions prior to the procedure 	<p><u>NARRATOR:</u></p> <p>Preparation.</p> <p>Confirm that the patient:</p> <ul style="list-style-type: none"> Does not have any contraindications, including hypersensitivity to buprenorphine or ingredients in Probuphine, such as ethylene vinyl acetate Has had a medical history taken and physical examination Understands the benefits and risks of Probuphine Has received a copy of the <i>Medication Guide</i> included in the packaging Does not have any questions prior to the procedure

	<ul style="list-style-type: none"> Does not have allergies to the antiseptic and anesthetic to be used during insertion 	<ul style="list-style-type: none"> Does not have allergies to the antiseptic and anesthetic to be used during the insertion
13	<p><u>TEXT ON SCREEN:</u></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 times.</p>	<p><u>NARRATOR:</u></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 times.</p>
14	<p><u>LIVE ACTION:</u></p> <ul style="list-style-type: none"> Examination table Instrument stand 	<p><u>NARRATOR:</u></p> <p>The following equipment is needed for the insertion procedure.</p> <p>An examination table for the patient to lie on.</p> <p>An instrument stand and sterile tray.</p>
15	<p><u>2D ANIMATION ON SCREEN:</u></p> <p>(All the equipment will be shown on the screen and each will be highlighted one at a time).</p>	<p><u>NARRATOR:</u></p> <p>Adequate Lighting, such as a headlamp Sterile fenestrated drape Latex and talc-free sterile gloves Alcohol prep Surgical marker Antiseptic solution (for example, chlorhexidine) Local anesthetic (Lidocaine 1% with epinephrine 1:100,000) 5 milliliter syringe with 1.5 inch 25 gauge needle Adson single tooth tissue forceps #15 blade scalpel ¼ inch thin adhesive strip (for example, Steri-Strip skin closures) 4x4 sterile gauze Adhesive bandages 3-inch pressure bandages Liquid adhesive (for example, Mastisol) 4 Probuphine implants 1 Probuphine applicator</p>
16	<p><u>3D ANIMATION ON SCREEN:</u></p> <p>Cannula and Obturator will be labeled as well as its markings.</p>	<p><u>NARRATOR:</u></p> <p>The Probuphine applicator is composed of two parts: the cannula and the obturator.</p> <p>It is important to note where each of the markings</p>

		<p>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. The obturator has a stop line marking. The two pieces come together and twist-lock to reform the complete applicator assembly.</p>
17	<p><u>GRAPHIC ON SCREEN:</u></p> <p>Graphic on screen of the upper inner side of the arm and the location of the implant.</p>	<p><u>NARRATOR:</u></p> <p>The insertion procedure will now be demonstrated.</p> <p>Correctly performed subdermal insertion of the implants will facilitate their removal. Implants should be placed just under the skin to avoid the large blood vessels 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 remove.</p>
18	<p><u>LIVE ACTION ON SCREEN:</u></p> <p>Footage depicting audio over.</p>	<p><u>NARRATOR:</u></p> <p>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>
19	<p><u>LIVE ACTION ON SCREEN:</u></p> <p>Show 8–10 cm from medial epicondyle as well as delineation of the muscles and the sulcus</p>	<p><u>NARRATOR:</u></p> <p>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>
20	<p><u>LIVE ACTION ON SCREEN:</u></p> <p>Footage depicting audio voiceover.</p>	<p><u>NARRATOR:</u></p> <p>Clean the insertion site with an alcohol prep pad prior to marking the skin.</p>
21		<p><u>NARRATOR:</u></p> <p>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.</p> <p>Mark the location of the four channel tracks—that</p>

	<p><u>LIVE ACTION ON SCREEN:</u></p> <p>Footage depicting audio voiceover to show clear channel marking.</p>	<p>is, where each implant will be inserted. Draw four lines with each line measuring 4 centimeters 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 the 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>
22	<p><u>LIVE ACTION ON SCREEN:</u></p> <p>Footage depicting audio voiceover.</p>	<p><u>NARRATOR:</u></p> <p>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>Put on the sterile gloves.</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 the sterile gloves have been put on.</p>
23	<p><u>LIVE ACTION ON SCREEN:</u></p> <p>Footage depicting audio voiceover.</p>	<p><u>NARRATOR:</u></p> <p>Check the applicator function by removing the obturator from the cannula and relocking it.</p>
24	<p><u>LIVE ACTION ON SCREEN:</u></p> <p>Footage depicting audio voiceover.</p>	<p><u>NARRATOR:</u></p> <p>Clean the insertion site with an antiseptic solution (for example, 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>
25	<p><u>LIVE ACTION ON SCREEN:</u></p> <p>Footage depicting audio voiceover.</p>	<p><u>NARRATOR:</u></p> <p>Apply the sterile drape to the arm of the patient...</p>
	<p><u>LIVE ACTION ON SCREEN:</u></p>	<p><u>NARRATOR:</u></p>

26	<p>Footage depicting audio voiceover and proper aspiration of lidocaine.</p> <p><u>TEXT ON SCREEN:</u></p> <p>ALWAYS ASPIRATE BEFORE EVERY INJECTION</p>	<p>...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 milliliters of lidocaine 1% with epinephrine 1:100,000).</p>
27	<p><u>LIVE ACTION ON SCREEN:</u></p> <p>Footage depicting audio voiceover showing shallow incision.</p>	<p><u>NARRATOR:</u></p> <p>After you confirm the anesthesia is adequate and effective, make a shallow incision that is 2.5 to 3 millimeters in length.</p>
28	<p><u>2D ANIMATION ON SCREEN:</u></p> <p>Show the 20 degree angle and 3-4 mm below the skin for implant placement (Live footage, then transition to animation, then transition to still from footage).</p>	<p><u>NARRATOR:</u></p> <p>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 of 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.</p>
29	<p><u>TEXT ON SCREEN:</u></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 subdermal connective tissue.</p>	<p><u>NARRATOR:</u></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 subdermal connective tissue.</p>
30	<p><u>2D ANIMATION ON SCREEN:</u></p> <p>Show cannula going into the skin with proximal marking on cannula just going into the skin (picture or graphic, applicator is horizontal to skin – See figure 7 in IFU)</p>	<p><u>NARRATOR:</u></p> <p>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.</p>
31	<p><u>2D ANIMATION ON SCREEN:</u></p> <p>Animation describing the narration.</p>	<p><u>NARRATOR:</u></p> <p>Holding the cannula in place, unlock and remove the obturator. Then, insert one Probuphine implant into the cannula.</p>
32	<p><u>2D ANIMATION ON SCREEN:</u></p> <p>Show reinsertion of obturator, stop markings, insertion of implant, etc.</p> <p><u>TEXT ON SCREEN:</u></p>	<p><u>NARRATOR:</u></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</p>

	<p>It is important to not force the implant beyond the end of the cannula with the obturator.</p> <p>There should be at least 5 mm between the incision and the implant when the implant is properly positioned.</p>	<p>marking. The implant is now in position at the tip of the cannula.</p> <p>It is important not to force the implant beyond the end of the cannula with the obturator.</p> <p>There should be at least 5 millimeters between the incision and the implant when the implant is properly positioned.</p>
33	<p><u>2D ANIMATION ON SCREEN:</u></p> <p>Show retraction of cannula along obturator.</p> <p><u>TEXT ON SCREEN:</u></p> <p>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.</p>	<p><u>NARRATOR:</u></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>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.</p>
34	<p><u>2D ANIMATION/LIVE ACTION ON SCREEN:</u></p> <p>Show withdrawal of cannula then transition to live action of twist lock of the obturator. Final shot will contain graphic image of sharp tip.</p>	<p><u>NARRATOR:</u></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 subdermal space.</p>
35	<p><u>LIVE ACTION ON SCREEN:</u></p> <p>Show beginning of redirection then transition to 2D animation.</p> <p><u>2D ANIMATION ON SCREEN:</u></p> <p>Show redirection and stabilizing implant with index finger.</p>	<p><u>NARRATOR:</u></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>
36	<p><u>LIVE ACTION ON SCREEN:</u></p> <p>Footage depicting audio voiceover.</p>	<p><u>NARRATOR:</u></p> <p>Repeat these steps to insert each of the three remaining implants through 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>
37	<p><u>GRAPHIC ON SCREEN:</u></p>	<p><u>NARRATOR:</u></p>

	<p>Palpation of inserted implants after insertion.</p> <p><u>TEXT ON SCREEN:</u></p> <p>By palpating both ends of the implant, you should be able to confirm the presence of each 26 mm implant.</p>	<p>Always verify the presence of each implant by palpation on 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>
38	<p><u>TEXT ON SCREEN:</u></p> <p>If you cannot feel each of the four implants or are in doubt of their presence prior to the 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).</p> <p>Attempt removal <u>only</u> after localization and depth have been confirmed by these measures.</p> <p>Probuphine implants are not radiopaque and cannot be seen by X-ray or CT scan.</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><u>NARRATOR:</u></p> <p>If you cannot feel each of the four implants or are in doubt of their presence prior to the 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 have been confirmed by these measures.</p> <p>Probuphine implants are not radiopaque and cannot be seen by X-ray or CT scan.</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>
39	<p><u>LIVE ACTION ON SCREEN:</u></p> <p>Footage depicting audio voiceover.</p>	<p><u>NARRATOR:</u></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 it to dry before closing the incision with quarter-inch thin adhesive strips, such as Steri-Strips skin closures.</p>
40	<p><u>LIVE ACTION ON SCREEN:</u></p> <p>Footage depicting audio voiceover.</p>	<p><u>NARRATOR:</u></p> <p>Place a small adhesive bandage over the insertion site.</p>
41	<p><u>LIVE ACTION ON SCREEN:</u></p> <p>Show wrapping of pressure bandage.</p> <p><u>TEXT ON SCREEN:</u></p> <p>Inform the patient that the pressure bandage</p>	<p><u>NARRATOR:</u></p> <p>Apply a pressure bandage with sterile gauze to minimize bruising.</p> <p>Inform the patient that the pressure bandage can be removed in 24 hours and the adhesive</p>

	<p>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>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>
42	<p><u>TEXT ON SCREEN:</u></p> <p>Be sure to explain proper wound care of the insertion site as well as signs and symptoms of infection including:</p> <p>Redness, swelling, fever, drainage, localized heat, malaise, and continued or increasing pain around the surgical site.</p>	<p><u>NARRATOR:</u></p> <p>Be sure to explain proper wound care of the insertion site as well as signs and symptoms of infection including:</p> <p>Redness, swelling, fever, drainage, localized heat, malaise, and continued or increasing pain around the surgical site.</p>
43	<p><u>TEXT ON SCREEN:</u></p> <p>PATIENT COUNSELING</p> <ol style="list-style-type: none"> 1. Complete the Patient Identification Card and give it to the patient to keep. 2. Complete the Patient Chart Sticker and affix it to the patient medical record or scan or input into their electronic medical record. 3. Ensure that the patient takes the Medication Guide and explain proper care of the insertion site. 4. Ask the patient if they have any questions. 5. 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. 6. 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. 	<p><u>NARRATOR:</u></p> <p>Patient counseling.</p> <p>Complete the Patient Identification Card and give it to the patient to keep.</p> <p>Complete the Patient Chart Sticker and affix it to the patient medical record or scan or input into their electronic medical record.</p> <p>Ensure that the patient takes the Medication Guide and explain proper care of the insertion site.</p> <p>Ask the patient if they have any questions.</p> <p>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, for example, tracking adverse events, in the log.</p> <p>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.</p>

44	<p><u>TITLE APPEARS:</u></p> <p>Dispose of all equipment labeled “For Single Use Only”</p>	<p><u>NARRATOR:</u></p> <p>The applicator is for single use only and should be disposed in accordance with the Centers for Disease Control and Prevention guidelines for hazardous waste.</p>
45	<p><u>TEXT ON SCREEN:</u></p> <p>Serious adverse events (SAEs) and insertion and removal related events need to be reported to the company at 1-844-859-6341 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. Report the Probuphine Kit serial number in order to facilitate tracking of adverse events.</p>	<p><u>NARRATOR:</u></p> <p>Serious adverse events (SAEs) and insertion and removal related events need to be reported to the company at 1-844-859-6341 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. Report the Probuphine Kit serial number in order to facilitate tracking of adverse events.</p>
46	<p><u>GRAPHIC ON SCREEN: NARRATOR:</u></p> <p>The Titan Pharmaceuticals logo builds on in a stylized manner.</p> <p>Titan Pharmaceuticals, Inc.</p>	<p><u>NARRATOR:</u></p> <p><u>Titan Pharmaceuticals.</u></p>

Part 2: Probuphine® Removal Procedure

47	<p><u>TITLE APPEARS:</u></p> <p>Part II: Probuphine® Removal Procedure</p>	<p><u>MUSIC:</u></p> <p>We hear an energetic theme that motivates the flow of video images.</p> <p><u>NARRATOR:</u></p> <p>Part II: Probuphine Removal Procedure</p>
48	<p><u>TEXT ON SCREEN:</u></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.</p> <p>Location of the implants can also be found on the <i>Probuphine REMS Program Insertion/Removal Log</i>.</p> <p>The exact location of all four implants in the</p>	<p><u>NARRATOR:</u></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.</p> <p>Location of the implants can also be found on the <i>Probuphine REMS Program Insertion/Removal Log</i>.</p> <p>The exact location of all four implants in the arm should be verified by palpation. If all of the</p>

	<p>arm should be verified by 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 located first prior to attempted removal.</p> <p>Suitable methods to locate the implants are:</p> <ul style="list-style-type: none"> • Ultrasound with high frequency linear array transducer at 10 MHz or greater • Magnetic Resonance Imaging (MRI) 	<p>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 located first prior to removal.</p> <p>Suitable methods to locate the implants are: Ultrasound with a high frequency linear array transducer at 10 megahertz or greater, or with Magnetic Resonance Imaging.</p>
49	<p><u>TEXT ON SCREEN:</u></p> <p>Probuphine implants are not radiopaque and cannot be seen by X-ray or CT scan.</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><u>NARRATOR:</u></p> <p>Probuphine implants are not radiopaque and cannot be seen by X-ray or CT scan.</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>
50	<p><u>TEXT ON SCREEN:</u></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>A surgical specialist consulted to assist with a difficult removal does not need to be certified in the Probuphine REMS Program.</p>	<p><u>NARRATOR:</u></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>A surgical specialist consulted to assist with a difficult removal does not need to be certified in the Probuphine REMS Program.</p>
51	<p><u>TEXT ON SCREEN:</u></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</p>	<p><u>NARRATOR:</u></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</p>

	under aseptic conditions at all times.	under aseptic conditions at all times.
52	<p><u>LIVE ACTION FOOTAGE:</u></p> <ul style="list-style-type: none"> • Examination table • Instrument stand. 	<p><u>NARRATOR:</u></p> <p>The following equipment is needed for implant removal:</p> <p>An examination table for the patient to lie on.</p> <p>An instrument stand.</p>
53	<p><u>2D ANIMATION ON SCREEN:</u></p> <p>(Graphic of all equipment. Each equipment will be highlighted).</p>	<p><u>NARRATOR:</u></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 (Lidocaine 1% with epinephrine 1:100,000) 5 milliliter syringe with 1.5 inch 25-gauge needle Adson single tooth tissue forceps Mosquito forceps Two X-plant clamps, which are vasectomy fixation clamps with a 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</p> <p>Sutures may be absorbable</p>
54	<p><u>LIVE ACTION ON SCREEN:</u></p> <p>Footage depicting audio voiceover.</p>	<p><u>NARRATOR:</u></p> <p>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>
55	<p><u>LIVE ACTION ON SCREEN:</u></p>	<p><u>NARRATOR:</u></p> <p>Reconfirm the location of all the implants by</p>

	Footage depicting audio voiceover.	palpation. The patient should have four implants.
56	<u>LIVE ACTION ON SCREEN:</u> Footage depicting audio voiceover.	<u>NARRATOR:</u> 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.
57	<u>LIVE ACTION ON SCREEN:</u> Footage depicting audio voiceover.	<u>NARRATOR:</u> It is important to carefully unwrap the sterile tray and remove the sterile gloves while not touching any of the contents inside the tray.
58	<u>LIVE ACTION ON SCREEN:</u> Footage depicting audio voiceover.	<u>NARRATOR:</u> Put on sterile gloves. Using aseptic technique, place the sterile equipment on the sterile field of the instrument stand. Maintain the sterile field and do not touch anything that is not sterile or outside of the sterile field, once the sterile gloves have been put on.
59	<u>LIVE ACTION ON SCREEN:</u> Footage depicting audio voiceover.	<u>NARRATOR:</u> Clean the removal site with an antiseptic solution (for example, 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. Do not blot or wipe away.
60	<u>LIVE ACTION ON SCREEN:</u> Footage depicting audio voiceover.	<u>NARRATOR:</u> Apply the sterile drape to the arm of the patient.
61	<u>LIVE ACTION ON SCREEN:</u> Footage depicting audio voiceover and proper aspiration of lidocaine. <u>TEXT ON SCREEN:</u>	<u>NARRATOR:</u> Anesthetize the incision site and the subcutaneous space containing the implants by injecting 5 to 7 milliliters of lidocaine 1% with epinephrine 1:100,000.

	ALWAYS ASPIRATE BEFORE EVERY INJECTION	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.
62	<u>LIVE ACTION ON SCREEN:</u> Footage depicting audio voiceover.	<u>NARRATOR:</u> After you confirm 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.
63	<u>LIVE ACTION ON SCREEN:</u> Footage depicting audio voiceover. <u>2D ANIMATION ON SCREEN:</u> Show scalpel shaving off tissue around the implant.	<u>NARRATOR:</u> Lift the skin edge with an Adson single-toothed 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.
64	<u>LIVE ACTION ON SCREEN:</u> Footage depicting audio voiceover.	<u>NARRATOR:</u> 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, as well as an assistant to hold the second X-plant clamp. 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.
65	<p><u>TEXT ON SCREEN:</u></p> <p>Confirm that the entire implant, which is 26 mm 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><u>NARRATOR:</u></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>
66	<p><u>LIVE ACTION ON SCREEN:</u></p> <p>Footage depicting audio voiceover.</p>	<p><u>NARRATOR:</u></p> <p>When all the implants have been removed, clean the incision site and close the incision with either continuous or interrupted sutures.</p>
67	<p><u>LIVE ACTION ON SCREEN:</u></p> <p>Footage depicting audio voiceover.</p>	<p><u>NARRATOR:</u></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 a sterile gauze to minimize bruising. The pressure bandage can be removed in 24 hours and the adhesive bandage in three to five days.</p>
68	<p><u>TEXT ON SCREEN:</u></p> <p>Counsel the patient on proper aseptic incision site care.</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><u>NARRATOR:</u></p> <p>Counsel the patient on proper aseptic incision site care.</p> <p>Instruct the patient to apply an ice pack on his or her arm for 40 minutes every two hours for the first the 24 hours and as needed.</p>
69	<p><u>TEXT ON SCREEN:</u></p> <p>1. Counsel the patient on proper wound care. The signs and symptoms of infection include: redness, swelling, fever, drainage, localized heat, malaise, and continued or increasing pain around the surgical site.</p>	<p><u>NARRATOR:</u></p> <p>Counsel the patient on proper wound care. The signs and symptoms of infection include: redness, swelling, fever, drainage, localized heat, malaise, and continued or increasing pain around the surgical site.</p>

	<ol style="list-style-type: none"> 2. Schedule a follow-up appointment for the sutures to be removed. 3. Complete the <i>Probuphine REMS Program Insertion/Removal Log</i> and place it in the patient's chart. 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. 	<p>Schedule a follow-up appointment for the sutures to be removed.</p> <p>Complete the <i>Probuphine REMS Program Insertion/ Removal Log</i> 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>
70	<p><u>TEXT ON SCREEN:</u></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 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><u>NARRATOR:</u></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>
71	<p><u>TITLE ON SCREEN:</u></p> <p>Continuation of Therapy: Subsequent Insertion in the Contralateral Arm</p>	<p><u>NARRATOR:</u></p> <p>Continuation of Therapy: Subsequent Insertion in the Contralateral Arm.</p>
72	<p><u>GRAPHIC ON SCREEN:</u></p> <p>Figure of one location on each arm.</p>	<p><u>NARRATOR:</u></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>
73	<p><u>GRAPHIC ON SCREEN:</u></p> <p>Figure of drawn implant lines on patient's arm.</p>	<p><u>NARRATOR:</u></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</p>

		buprenorphine—that is, to the same dose they received as part of transferring to the Probuphine treatment—prior to receiving additional Probuphine treatment.
74	<p><u>TEXT ON SCREEN:</u></p> <p>After one insertion in each arm, most patients should be transitioned back to a 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><u>NARRATOR:</u></p> <p>After one insertion in each arm, most patients should be transitioned back to a 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>
75	<p><u>TEXT ON SCREEN:</u></p> <p>Neither reinsertion 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>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.</p> <p>In most cases, patients should be transitioned back to a transmucosal buprenorphine-containing product for continued treatment.</p>	<p><u>NARRATOR:</u></p> <p>Neither reinsertion 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.</p> <p>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.</p> <p>In most cases, patients should be transitioned back to a transmucosal buprenorphine-containing product for continued treatment.</p>
76	<p><u>TEXT ON SCREEN:</u></p> <p>Serious adverse events (SAEs) and insertion and removal related events need to be reported to the company at 1-844-859-6341 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. Report the</p>	<p><u>NARRATOR:</u></p> <p>Serious adverse events (SAEs) and insertion and removal related events need to be reported to the company at 1-844-859-6341 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. Report the</p>

	Probuphine Kit serial number in order to facilitate tracking of adverse events.	Probuphine Kit serial number to facilitate tracking of adverse events.
77	<p><i>GRAPHIC ON SCREEN: NARRATOR:</i></p> <p>The Titan Pharmaceuticals logo builds on in a stylized manner.</p> <p>Titan Pharmaceuticals, Inc.</p>	<p><i>NARRATOR:</i></p> <p><u>Titan Pharmaceuticals.</u></p>

Part 3: Managing Complications

78	<p><u>TEXT ON SCREEN:</u></p> <p>Part III: Managing Complications</p>	<p><u>MUSIC:</u></p> <p>We hear an energetic theme that motivates the flow of video images.</p> <p><u>NARRATOR:</u></p> <p>Part III: Managing Complications</p>
79	<p><u>TEXT ON SCREEN:</u></p> <p>Managing Spontaneous Expulsion of Probuphine®</p>	<p><u>NARRATOR:</u></p> <p>Managing Spontaneous Expulsion of Probuphine</p>
80	<p><u>2D ANIMATION ON SCREEN:</u></p> <p>Animation showing an implant falling out of the arm.</p>	<p><u>NARRATOR:</u></p> <p>If spontaneous expulsion of the implant occurs after insertion, the following steps should be taken.</p>
81	<p><u>TEXT ON SCREEN:</u></p> <ul style="list-style-type: none"> 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. 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. 	<p><u>NARRATOR:</u></p> <ul style="list-style-type: none"> Schedule two appointments for the patient to return to the office of the inserting healthcare provider as soon as possible and to the office of the prescribing healthcare provider. Instruct the patient to place the implant in a plastic bag, store it safely out of reach of children, and to bring it to the healthcare provider's office to determine whether the full implant has been expelled.

82	<p><u>LIVE ACTION ON SCREEN:</u></p> <p>Footage depicting audio voiceover.</p>	<p><u>NARRATOR:</u></p> <ul style="list-style-type: none"> If the patient returns the expelled implant, measure it to ensure that the entire implant was expelled. The implant is 26 millimeters in length.
83	<p><u>LIVE ACTION ON SCREEN:</u></p> <p>Footage depicting audio voiceover.</p>	<p><u>NARRATOR:</u></p> <ul style="list-style-type: none"> Dispose the removed implant in keeping with local, state, and federal regulations governing the disposal of pharmaceutical biohazardous waste, after measuring.
84	<p><u>TEXT ON SCREEN:</u></p> <p>Examine the incision site for infection.</p> <p><u>LIVE ACTION SCREEN:</u></p> <p>Show doctor examining patient's arm</p>	<p><u>NARRATOR:</u></p> <ul style="list-style-type: none"> Examine the incision site for infection. If infected, treat appropriately and determine if remaining implants need to be removed.
85	<p><u>LIVE ACTION ON SCREEN:</u></p> <p>Doctor palpating arm.</p> <p><u>TEXT ON SCREEN:</u></p> <p>Remove the implant using the techniques described in the Removal Procedure.</p>	<p><u>NARRATOR:</u></p> <ul style="list-style-type: none"> If the expelled implant is not intact, palpate the insertion location to identify the location of any remaining partial implant. Remove the implant using the techniques described in the Removal Procedure.
86	<p><u>TEXT ON SCREEN:</u></p> <p>Call 1-844-859-6341 to obtain a new kit that will include four implants and return instructions for any unused implants.</p>	<p><u>NARRATOR:</u></p> <p>Call 1-844-859-6341 to obtain a new kit that will include four implants and return instructions for any unused implants.</p>
87	<p><u>TEXT ON SCREEN:</u></p> <ul style="list-style-type: none"> The prescribing healthcare provider must carefully monitor the patient until the implant is replaced to evaluate for withdrawal or other clinical indicators that supplemental transmucosal buprenorphine may be needed. Schedule an appointment to insert replacement implant(s). 	<p><u>NARRATOR:</u></p> <ul style="list-style-type: none"> The prescribing healthcare provider must carefully monitor the patient until the implant is replaced to evaluate for withdrawal or other clinical indicators that supplemental transmucosal buprenorphine may be needed. Schedule an appointment to insert a replacement implant or implants.

	<ul style="list-style-type: none"> Insert the replacement implant(s) in the same arm or either medially or laterally to in-situ implants. <i>Alternatively, replacement implant(s) may be inserted in the contralateral arm.</i> Record the new serial number of the replacement kit on the Probuphine REMS Program Insertion/Removal Log. 	<ul style="list-style-type: none"> Insert the replacement implant or implants in the same arm or either medially or laterally to in-situ implants. Alternatively, a replacement implant or implants may be inserted in the contralateral arm. Record the new serial number of the replacement kit on the Probuphine REMS Program Insertion/Removal Log.
88	<p><u>TEXT ON SCREEN:</u></p> <p>Prevention of Deep Insertion</p>	<p><u>NARRATOR:</u></p> <p>Prevention of Deep Insertion</p>
89	<p><u>2D ANIMATION ON SCREEN:</u></p> <p>Animation depicting the difference between the correct depth vs. too deep insertion of the implants.</p>	<p><u>NARRATOR:</u></p> <p>Correctly performed subdermal insertion of the implants will facilitate their removal. If the implants are placed improperly, resulting in deep tissue location, the implants will be more difficult to remove.</p>
90	<p><u>2D ANIMATION ON SCREEN:</u></p> <p>Animation depicting insertion of the implant under the skin in the subdermal space with large blood vessels and nerves beneath.</p>	<p><u>NARRATOR:</u></p> <p>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.</p>
91	<p><u>2D ANIMATION ON SCREEN:</u></p> <p>Animation depicting the applicator, bevel-up, being inserted at 20 degrees and depth of 3 to 4 mm.</p>	<p><u>NARRATOR:</u></p> <p>After the shallow incision that is 2.5-3 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 3-4 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.</p>
92	<p><u>2D ANIMATION ON SCREEN:</u></p> <p>Animation depicting the applicator being lowered to horizontal position.</p>	<p><u>NARRATOR:</u></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 subdermal connective tissue.</p>
93	<p><u>2D ANIMATION ON SCREEN:</u></p> <p>Animation depicting the applicator being inserted</p>	<p><u>NARRATOR:</u></p> <p>While tenting, or lifting, gently advance the</p>

	while tenting the skin, showing proximal marking disappearing into the incision.	applicator subdermally along the channel marking on the skin until the proximal marking on the cannula just disappears into the incision.
94	<u>TEXT ON SCREEN:</u> Non-palpable Implants and Complicated Removal Procedure	<u>NARRATOR:</u> Non-palpable Implants and Complicated Removal Procedure
95	<u>GRAPHIC ON SCREEN:</u> Picture of Patient Identification Card and Patient Chart Sticker. Picture of a sample of Probuphine REMS Program Insertion/Removal Log , and location of the implants on the log. <u>LIVE ACTION ON SCREEN:</u> Show palpation of implants on the arm.	<u>NARRATOR:</u> Before initiating the removal procedure, read the instructions for removal. Identify the location of the implants by consulting the Patient Identification Card and/or the Patient Chart Sticker. The location of the implants can also be found on the Probuphine REMS Program Insertion/Removal Log that was filled out during the patient's insertion procedure. The exact location of all implants in the arm should be verified by palpation.
96	<u>TEXT ON SCREEN:</u> If all of the implants are not palpable, use other methods to confirm the presence of the implants. Non-palpable implants should always be located prior to attempted removal.	<u>NARRATOR:</u> 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.
97	<u>TEXT ON SCREEN:</u> Methods for locating implants <u>GRAPHIC ON SCREEN:</u> Picture of Ultrasound and MRI <u>TEXT ON SCREEN:</u> Probuphine implants are not radiopaque and cannot be seen by X-ray or CT scan.	<u>NARRATOR:</u> Suitable methods to locate implants are: Ultrasound with a high frequency linear array transducer, 10 Megahertz or greater, or, Magnetic Resonance Imaging, or MRI. Probuphine implants are not radiopaque and cannot be seen by X-ray or CT scan.
98	<u>TEXT ON SCREEN:</u> 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. The subsequent removal attempt should be	<u>NARRATOR:</u> 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. The subsequent removal attempt should be

	<p>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 should be closed with sutures in the interim.</p>	<p>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 should be closed with sutures in the interim.</p>
99	<p><u>TEXT ON SCREEN:</u></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><u>NARRATOR:</u></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>
100	<p><u>TEXT ON SCREEN:</u></p> <p><i>Exploratory surgery without knowledge of the exact location of all implants is strongly discouraged.</i></p> <p><i>There is a greater risk of injury to neural and vascular structures during removal of implants located deeper than the subdermal space. As the anatomical location of these structures must be taken into consideration during the removal of deeply inserted implants, the procedure should only be attempted by healthcare providers familiar with this anatomy.</i></p> <p><i>A surgical specialist consulted to assist with a difficult removal does not need to be certified in the Probuphine REMS Program.</i></p>	<p><u>NARRATOR:</u></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. As the anatomical location of these structures must be taken into consideration during the removal of deeply inserted implants, the procedure should only be attempted by healthcare providers familiar with this anatomy.</p> <p>A surgical specialist consulted to assist with a difficult removal does not need to be certified in the Probuphine REMS Program.</p>
101	<p><u>TEXT ON SCREEN:</u></p> <p>Prevention of Fractured/Bent Implant</p>	<p><u>NARRATOR:</u></p> <p>Prevention of Fractured/Bent Implant</p>
102	<p><u>TEXT ON SCREEN:</u></p> <p>In order to avoid fracturing or bending of the implants, the following steps below should be used during insertion and removal procedure.</p>	<p><u>NARRATOR:</u></p> <p>In order to avoid fracturing or bending of the implants, the following steps should be used during insertion and removal procedure.</p>
103	<p><u>2D ANIMATION ON SCREEN:</u></p> <p>Animation depicting the obturator pushed to bevel-up marking point and insertion of an implant.</p> <p>A second animation of the obturator being pushed above the implant channel to</p>	<p><u>NARRATOR:</u></p> <p>During the 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.</p>

	demonstrate improper location of the implants when the obturator is pushed beyond the bevel-up marking.	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. It is important to hold the obturator fixed in place and retract the cannula along the obturator to place the implant in the channel that has been formed by the cannula.
104	<u>2D ANIMATION ON SCREEN:</u> Animation or video demonstration of X-plant clamp grabbing the implant.	<u>NARRATOR:</u> 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.
105	<u>TEXT TITLE ON SCREEN:</u> Prevention of Incision Site Infection	<u>NARRATOR:</u> Prevention of Incision Site Infection
106	<u>TEXT ON SCREEN:</u> During insertion and removal procedures, it is essential to use and maintain aseptic technique at all times. <u>LIVE ACTION ON SCREEN:</u> Shots of removal tray in sterile field.	<u>NARRATOR:</u> 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.
107	<u>2D GRAPHIC ON SCREEN:</u> Use of chlorhexidine in the video of the insertion or removal video will be shown here to demonstrate again.	<u>NARRATOR:</u> Make sure that the insertion and removal sites are properly cleaned with the antiseptic solution, following the appropriate instructions carefully.
108	<u>LIVE ACTION ON SCREEN:</u> Patient being handed instructions.	<u>NARRATOR:</u> Make sure that the patient is provided with the incision site care instructions and how to identify signs and symptoms of infections.
109	<u>TEXT ON SCREEN:</u> In summary, proper attention to technique and following the instructions for insertion and removal procedures will minimize potential problems and complications.	<u>NARRATOR:</u> In summary, proper attention to technique and following the instructions for insertion and removal procedures will minimize potential problems and complications.
110	<u>TEXT ON SCREEN:</u>	<u>NARRATOR:</u>

	<p>Serious adverse events (SAEs) and insertion and removal related events need to be reported to the company at 1-844-859-6341 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. Report the Probuphine Kit serial number in order to facilitate tracking of adverse events.</p>	<p>Serious adverse events (SAEs) and insertion and removal related events need to be reported to the company at 1-844-859-6341 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. Report the Probuphine Kit serial number in order to facilitate tracking of adverse events.</p>
111	<p>GRAPHIC ON SCREEN: NARRATOR:</p> <p>The Titan Pharmaceuticals logo builds on in a stylized manner.</p> <p>Titan Pharmaceuticals, Inc.</p>	<p>NARRATOR:</p> <p><u>Titan Pharmaceuticals.</u></p>

Owner: Titan Pharmaceuticals, Inc
FDA Version 19
Script: Five Way Media, LLC.
Pages: 27

Probuphine[®] Training
Video Nov2018

Probuphine[®] REMS Program Healthcare Provider Who Performs Surgical Procedures Recertification Form

(for completion by healthcare providers who will **insert** or **remove** Probuphine. Please fax to 1-866-413-1135)

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[®] REMS Recertification Training Requirements¹

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 ↓	
	Number of Probuphine procedures in the past 12 months (Select the Row that applies)	
	≥10 Performed 10 or more successful ² procedures (comprised of at least five insertions and five removals) →	I must review the <i>Probuphine REMS Program Surgical Procedures Recertification Video</i> found on the Probuphine REMS website every year . I understand that I should keep documentation of all successfully completed procedures on the <i>Probuphine REMS Program Procedure Record for Recertification</i> or another record of my choosing - which must be provided to the Probuphine REMS Program if I am audited.
I must review the <i>Probuphine REMS Program Surgical Procedures Recertification Video</i> found on the Probuphine REMS website every year .	<10 Performed less than 10 successful ² procedures (comprised of at least five implantations and five removals) →	I must (annually): <ul style="list-style-type: none"> attend a <i>Probuphine REMS Program Live Training: Lecture and Practicum</i> session successfully complete the <i>Probuphine REMS Program Knowledge Assessment</i> test meet the <i>Probuphine REMS Program Criteria for Procedural Competency</i>

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

¹ 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.

² “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 an 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

_____ (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 maintain records of 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 anatomical 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 distribute, transfer, loan, or sell Probuphine outside the healthcare setting to anyone who is not certified as a prescriber 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 Titan Pharmaceuticals, or a third party, to ensure all processes and procedures are in place and 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 Titan 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 Name: _____

Street Address: _____

City: _____ State: _____ Zip: _____

Are you a: MD DO PA NP Other specify: _____

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 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 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.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JUDITH A RACOOSIN
11/01/2018