

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><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>

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