

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:

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| 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. |
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| 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. |
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| 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). |
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2. Healthcare providers who insert and remove¹ Probuphine must:

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| 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. |
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| 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. |
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| 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. |
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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:

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

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| 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. |
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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.
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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](#)