CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204442Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of New Drugs
Division of Anesthesia, Analgesia, and Addiction Products

NDA/BLA #s:	204442
Products:	Probuphine (buprenorphine) subdermal implant
SPONSOR:	Titan Pharmaceuticals
FROM:	Judith A. Racoosin, MD, MPH
DATE:	see DARRTS signature

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity (NME).

Probuphine is a buprenorphine subdermal implant intended 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. The pre- and postmarketing experience of other subdermal implants (e.g., Norplant and other implantable levonorgestrel products) indicates that there are specific risks that must be considered with this dosage form. For example, a Division of Bone, Reproductive, and Urology Products consultation (12/11/15) noted the following:

> *First, pooled incidences of bleeding in the Probuphine program, including implant site hemorrhage/hematoma and incision site bleeding (10.9%) is much higher than that (of hematoma) observed in the Implanon clinical program (0.1%). Second, implant site infections were seen at a relatively high rate for a simple procedure in the setting of subdermal implant insertion (4.0% overall).*

Postmarketing experience with subdermal implants has documented clinically significant implant migrations that may result in nerve damage or other complications such as bleeding, infection, or altered strength/ range of motion. Cases of migration of the implant to lung vasculature and parenchyma have also been reported, some cases within a short (<6 months) interval after placement.

Additionally, because it is a possibility that the Probuphine subdermal implant could protrude from the skin or be expelled, the Probuphine risks overlap with those of the BTOD (Buprenorphine for the Treatment of Opioid Dependence) REMS products in that, if expelled or inappropriately removed, Probuphine poses the risks of accidental overdose, misuse, and abuse.

The BTOD (Buprenorphine for the Treatment of Opioid Dependence) REMS was approved in February 2013 for generic oral transmucosal buprenorphine products with the following goals:

- Mitigate the risks of accidental overdose, misuse, and abuse
- Inform prescribers, pharmacists, and patients of the serious risks associated with buprenorphine-containing products

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use is necessary for Probuphine (buprenorphine) to ensure the benefits of Probuphine (buprenorphine) outweigh the (1) risks of accidental overdose, abuse and misuse; and (2) risks of complications of migration, protrusion, expulsion, and nerve damage associated with the insertion and removal of Probuphine (buprenorphine).

In reaching this determination, we considered the following:

A. Probuphine (buprenorphine) 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 (e.g., doses of no more than 8 mg per day of Subutex or Suboxone sublingual tablet equivalent or generic equivalent). The estimated number of patients in the United States classified with dependence on or abuse of pain relievers is 1.7 million persons, and over 200,000 were classified with dependence on or abuse of heroin. This estimate is based the 2007 National Survey on Drug Use and Health.[1]

B. Opioid dependence is a serious and life-threatening condition associated with morbidity and mortality due to overdose, blood-borne and sexually-transmitted diseases, and a variety of psychosocial consequences.

C. Probuphine (buprenorphine) is effective in the treatment of opioid dependence as measured by maintenance of stability in stable patients as measured by low levels of illicit drug use and retention in treatment. .

[1]Substance Abuse and Mental Health Services Administration, Office of Applied Studies (2008). *Results from the 2007 National Survey on Drug Use and Health: National Findings* (NSDUH Series H-34, DHHS Publication No. SMA 08-4343). Rockville, MD.

D. Treatment with buprenorphine may continue indefinitely; however, Probuphine (buprenorphine) is only approved for use in one site in each upper arm (six-month duration per implantation). Post Marketing Requirements (PMRs) are being required to evaluate use of the Probuphine (buprenorphine) subdermal implant in other parts of the body.

E. Known or potential adverse events associated with Probuphine include abuse and accidental overdose leading to potentially lethal respiratory depression. Abuse and accidental overdose are common in the population of patients addicted to opioids, as are hepatic events attributable to blood-borne illnesses and use of other hepatotoxic substances. Other serious adverse events related to the subdermal implant include bleeding, infection, and side effects related to potential migration of the implant.

F. Probuphine (buprenorphine) is not a new molecular entity.

In accordance with section 505-1 of the FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for Probuphine (buprenorphine). FDA has determined that Probuphine (buprenorphine) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Probuphine (buprenorphine). FDA has determined that Probuphine (buprenorphine) is a product for which patient labeling could help prevent serious adverse effects and that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use, Probuphine (buprenorphine). Under section 505-1 of the FDCA, FDA has also determined that a Medication Guide is necessary to ensure the benefits of the drug outweigh the risk(s) of complications of migration, protrusion, expulsion and nerve damage associated with the insertion and removal of PROBUPHINE (buprenorphine hydrochloride), and the risks of accidental overdose, misuse, and abuse.

The elements of the REMS include:

- A Medication Guide;
- Elements to assure safe use to ensure that each patient receives Probuphine (buprenorphine) subdermal implant from certified prescribers and inserters in the same health care setting, and that patients are subject to certain monitoring;
    - Healthcare providers have particular experience or training, or are specially certified
    - Pharmacies, practitioners, or health care settings that dispense the drug are specially certified
    - The drug is dispensed to patients only in certain health care settings
    - Each patient using the drug is subject to certain monitoring
- An implementation system to ensure that Probuphine is only dispensed in healthcare settings in which a certified prescriber is practicing, and that healthcare providers who dispense the drug are specially certified;
- And a timetable for submission of assessments of the REMS.

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/s/

JUDITH A RACOOSIN
05/25/2016

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REVIEW

Date:	May 25, 2016
Reviewer(s):	Donella Fitzgerald, Pharm. D. Risk Management Analyst Division of Risk Management (DRISK)
Team Leader:	Kim Lehrfeld, Pharm. D. DRISK
Director:	Cynthia LaCivita, Pharm. D. DRISK
Subject:	Rationale and final review for the Probuphine REMS
Drug Name(s):	Probuphine (buprenorphine HCl) implant
Therapeutic Class:	Opioid partial agonist
Dosage and Route:	80 mg per rod for subdermal implant
Application Type/Number:	NDA 204442
Submission Number:	ORIG-1
Applicant/sponsor:	Braeburn Pharmaceuticals, on behalf of Titan Pharmaceuticals, Inc.
OSE RCM #:	2015-2115

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EXECUTIVE SUMMARY

The purpose of this review is to document the Division of Risk Management's (DRISK) evaluation of the proposed risk evaluation and mitigation strategy (REMS) for Probuphine (buprenorphine HCl), NDA 204442, submitted by Braeburn Pharmaceuticals on behalf of Titan Pharmaceuticals, Inc. Braeburn originally submitted a proposed REMS on August 27, 2015, and amended their proposed REMS submission on December 7, 2015, February 11, 2016, April 4, 2016, May 4, 2016, May 18, 2016, May 23, 2016, May 24, 2016 and May 25, 2016.Probuphine is a buprenorphine implant with a proposed indication 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).

The Sponsor's proposed REMS includes a Medication Guide (MG), elements to assure safe use (ETASU) [prescriber certification, certification of dispensers, a monitoring requirement regarding safe removal, and healthcare setting certification], an implementation system and a timetable for submission of assessments.

The goal of the Probuphine REMS Program 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 if an implant comes out or protrudes from the skin . During the review process, it was determined that labeling alone is not sufficient to mitigate the risks associated with Probuphine. A REMS with elements to assure safe use is necessary to ensure that the benefits of Probuphine outweigh the risks.

1 INTRODUCTION

The purpose of this review is to document the Division of Risk Management's (DRISK) evaluation of the proposed risk evaluation and mitigation strategy (REMS) for Probuphine (buprenorphine HCl), NDA 204442, submitted by Braeburn Pharmaceuticals on behalf of Titan Pharmaceuticals, Inc. Braeburn originally submitted a proposed REMS on August 27, 2015, and amended their proposed REMS submission on December 7, 2015, February 11, 2016, April 4, 2016, May 4, 2016, May 18, 2016, May 23, 2016, May 24, 2016 and May 25, 2016. The proposed REMS includes a Medication Guide (MG), elements to assure safe use (ETASU) [prescriber certification, certification of dispensers, a monitoring requirement regarding safe removal, and healthcare setting certification], an implementation system and a timetable for submission of assessments. The Medication Guide has been reviewed under separate cover by the Division of Medical Policy Programs (DMPP) and Office of Prescription Drug Promotion (OPDP).

1.1 PRODUCT BACKGROUND

Probuphine was submitted as a 505(b)(2) application. Probuphine contains buprenorphine, a partial opioid agonist. It 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). The likely prescribers are practitioners in Opioid Treatment Centers (OTC) and office-based treatment programs under the Drug Addiction Treatment Act of 2000 (DATA-2000). Training under the REMS is required for healthcare providers who will prescribe and insert in OTC and office-based treatment programs. The implant consists of four Probuphine rods, each 26mm x 2.5mm, containing 80 mg of buprenorphine HCl. They are inserted subdermally in the inner side of the upper arm to provide sustained delivery of buprenorphine for six months. At the end of six months, the implants must be removed. If treatment is continued, a new set of implants can be inserted in the opposite arm.

REMS for Other Buprenorphine Products

Probuphine is a buprenorphine-containing subdermal implant. Buprenorphine is a mixed partial agonist opioid receptor modulator approved in October 2002. On December 22, 2011 the FDA determined that a REMS was necessary to mitigate the risks of accidental overdose, misuse and abuse, as well as, inform patients, prescribers and pharmacists of the serious risks associated with buprenorphine products.[1] Buprenorphine products were the first narcotic drugs available for the treatment of opioid dependence in an office-based treatment program under DATA-2000. Currently, buprenorphine is available in sublingual (SL) tablets. In combination with naloxone HCl, an opioid antagonist, the dosage forms include SL tablets, SL film and buccal film.

1.2 REGULATORY HISTORY

October 31, 2012: Titan submitted a NDA for Probuphine, which included a proposed REMS (Seq. No. 0000).

March 21, 2013: Psychopharmacologic Drugs Advisory Committee (PDAC) meeting was held to discuss the Probuphine NDA. When asked if the proposed REMS was adequate to address the risks of complications associated with the insertion procedure and abuse, misuse and accidental overdose, the committee voted: 5-yes, 4-no and 6-abstain. The four members who voted "no" expressed concerns that providers would not be trained properly on insertion/removal. The six members that abstained noted that the Sponsor presented a modified REMS that was not previously described in the briefing materials.

April 30, 2013: A Complete Response was issued for deficiencies in clinical benefit and instructed the Sponsor to conduct a *Human Factors Usability Evaluation*.

August 27, 2015: Titan resubmitted Probuphine, NDA 204442, with a proposed REMS. The submission did not include a REMS supporting document.

November 23, 2015: The Agency sent Braeburn comments on their August 27, 2015 REMS submission. The FDA recommended revision of the goal, additional

[1] Division of Analgesia, Anesthesia and Addiction Products (DAAAP) REMS approval letter for Suboxone (buprenorphine) (NDA 020732) dated December 22, 2011.

requirements for prescriber certification and the development of an assessment criteria for HCP seeking certification to insert Probuphine.

December 7, 2015: The Sponsor amended the submission to include an amended proposed REMS document, REMS appended materials, and REMS supporting document addressing the Agency's comments from November 23, 2015.

January 12, 2016: A PDAC meeting was held to discuss the safety and efficacy of Probuphine. The panel discussed whether the REMS is adequate to address the risks of potential complications associated with the insertion and removal procedures, and abuse, misuse and accidental overdose. The Committee was asked to vote on the following question: Does the efficacy, safety, and risk-benefit profile of Probuphine support the approval of this application for a population of patients previously stable on a regimen of sublingual buprenorphine. The committee members voted: 12-yes and 5-no.

February 2, 2016: The Agency sent Braeburn comments on their December 7, 2015 REMS submission. The FDA recommended revision of the goal, along with a prerequisite and recertification requirement for HCP Who Perform Probuphine Surgical Procedures.

February 11, 2016: Braeburn submitted a REMS Amendment reflecting REMS comments provided on February 2, 2016.

February 19, 2016: The Agency issued a Major Amendment, extending the PDUFA date from February 27, 2016 to May 27, 2016.

March 24, 2016: The Agency sent Braeburn comments on their February 11, 2016 REMS submission. The FDA recommended revision of the goal, addition of ETASU C and an auditing requirement for HCP Who Perform Probuphine Surgical Procedures.

April 4, 2016: Braeburn submitted a REMS Amendment reflecting REMS comments provided on March 24, 2016.

April 22, 2016: The Agency sent Braeburn comments on their April 4, 2016 REMS submission. The FDA recommended changes to the REMS document to reflect the inclusion of a recertification video available post-approval.

May 4, 2016: Braeburn submitted a REMS Amendment, reflecting REMS comments provided on April 22, 2016.

May 13, 2016: The Agency sent Braeburn comments on their May 4, 2016 REMS submission. The FDA recommended the addition of ETASU E to the REMS Program.

May 16, 2016: The Agency sent Braeburn comments on their May 4, 2016 REMS submission. The FDA recommended changes in the REMS training program slides and other materials.

May 18, 2016: Braeburn submitted a revised REMS document and materials, via email, reflecting REMS comments provided on May 13 and May 16, 2016.

May 20, 2016: The Agency sent Braeburn comments on their May 18, 2016 REMS submission. The FDA recommended editorial changes. These changes were not intended to significantly impact the REMS.

May 23, 2016: Braeburn submitted a REMS Amendment reflecting REMS comments provided on May 20, 2016. The Agency sent Braeburn comments on their May 23, 2016 submission. The FDA recommended that Braeburn make minor edits to the REMS document and materials. These changes were not intended to significantly impact the REMS.

May 24, 2016: Braeburn submitted a REMS Amendment reflecting REMS comments provided on May 23, 2016. The FDA recommended that Braeburn make minor edits to the REMS document and materials. These changes were not intended to significantly impact the REMS.

May 25, 2016: Braeburn submitted a REMS Amendment reflecting REMS comments provided on May 23, 2016. These materials are the subject of this review.

2 MATERIALS REVIEWED

2.1 SUBMISSIONS

The following submissions, listed by date received, were reviewed from NDA 204442 for the proposed Probuphine REMS:

- Braeburn, on behalf of Titan Pharmaceuticals, Inc. Proposed REMS for Probuphine, NDA 204442, received August 27, 2015 (eCTD Seq No. 0030)
    - Amendment received December 7, 2015 (eCTD Seq No. 0049)
    - Amendment received February 11, 2016 (eCTD Seq No. 0061)
    - Amendment received April 4, 2016 (eCTD Seq No. 0071)
    - Amendment received May 4, 2016 (eCTD Seq No. 0079)
    - Amendment received May 18, 2016 (email submission)
    - Amendment received May 23, 2016 (email submission)
    - Amendment received May 24, 2016 (eCTD Seq No. 0082)
    - Amendment received May 25, 2016 (eCTD Seq No. 0084)

2.2 OTHER MATERIALS INFORMING OUR REVIEW

The following is a list of materials that were used to inform this review:

- Probuphine Complete Response Letter. Division of Anesthesia, Analgesia and Addiction Products (DAAAP), dated April 30, 2013.
- Bunting J., Final REMS Review of Probuphine, dated April 30, 2013.
- REMS Oversight Committee meeting minutes, dated February 28, 2013.
- Psychopharmacologic Drugs Advisory Committee (PDAC) meeting minutes, dated March 21, 2013.
- PDAC briefing materials, dated March 21, 2013.
- PDAC briefing materials, dated January 12, 2016.

- Shah, M., Division of Medication Error and Prevention Analysis (DMEPA) Human Factors Results, Label and Labeling Review for Probuphine, dated January 22, 2016.
- Fitzgerald D., REMS Review of Probuphine, dated November 23, 2015.
- Sewell C., Division of Bone, Reproductive and Urologic Products (DBRUP). Internal Consult for Probuphine, dated December 11, 2015
- Skeete R., Clinical Review for Probuphine, dated February 2, 2016.
- Fitzgerald D., REMS Review of Probuphine, dated February 2, 2016.
- Sullivan M., DAAAP. Probuphine Major Amendment Letter, dated February 19, 2016.
- Fitzgerald D., REMS Review of Probuphine, dated March 24, 2016.
- Walker M., Toombs L., Patient Labeling Review of Probuphine, dated April 13, 2016.
- Fitzgerald D., REMS Review of Probuphine, dated April 22, 2016.
- Fitzgerald D., REMS Review of Probuphine, dated May 25, 2016.

3 OVERVIEW OF THE CLINICAL DEVELOPMENT PROGRAM

Evidence of efficacy for Probuphine for use in opioid-dependent patients who are clinically stable and on no more than 8 mg a day of sublingual buprenorphine (equivalent to 8 mg/day or less buprenorphine as Suboxone tablet) is derived from a single controlled trial, PRO-814. PRO-814 was a randomized, double-blind, double dummy, active-controlled, multicenter trial that evaluated the safety and efficacy of four 80-mg Probuphine rods inserted as implants in adult outpatients with opioid dependence who were on ≤8 mg SL buprenorphine and considered clinically stable by their treating healthcare provider.[2]

3.1 SUMMARY OF EFFICACY

The sponsor sought to establish analgesic efficacy with results from a single phase 3 clinical trial, PRO-814. PRO-814 was a randomized, double-blind, double-dummy, active-controlled, multicenter study of 177 adult outpatients with opioid dependence who were stabilized on less than or equal to 8 mg/day sublingual buprenorphine (SL BPN). The study consisted of 3 phases: a screening phase (up to 3 weeks in duration), a 24-week maintenance phase, and a 2-week follow-up phase. There was a screening visit, 12 maintenance phase visits, a post-treatment telephone contact, and a follow-up visit.

Urine toxicology samples were collected at screening, at each scheduled monthly visit during the maintenance phase, and at 4 random times during the maintenance phase, for a total of 10 urine toxicology samples for each subject who completed the trial and provided all samples.

[2] PDAC briefing materials, dated January 12, 2016.

The primary endpoint was a comparison of the individual responders in each treatment arm, where response was defined as having at least 4 out of 6 months negative for illicit opioid use based on urine toxicology and patient self-report obtained by questionnaire. Using the primary imputation penalty for missing urine testing results and adjusting urine toxicology results for subject self-report, the proportion of responders was 96.4% in the Probuphine arm and 87.6% in the SL BPN arm. The proportion of responders computed by the Sponsor was statistically significantly higher in the Probuphine arm (P = 0.034). This indicates that the proportion of responders among patients blindly switched to Probuphine was non-inferior to the proportion of responders who continued on sublingual buprenorphine.

The clinical reviewer's analysis of the response rates, though still favorable, were lower than reported by the Sponsor. These differences were due to the Sponsor excluding three Probuphine patients (2 lost to follow-up, 1 incarcerated) who received the study medication in the intent-to-treat (ITT) population. The urine toxicology data did not address missing and incomplete urine sample analysis. Also, the unrestricted use of rescue buprenorphine was not addressed in the reported efficacy results. The clinical reviewer determined that "the responder rate depends on a number of assumptions about missing data and also assumes that use of supplemental buprenorphine is not an indicator of inadequacy of treatment. When analyzed under different assumptions, the response rates, though still favorable, were lower than reported by the Sponsor." [3]

3.2 SUMMARY OF SAFETY

Safety of Probuphine was primarily evaluated through examination of the three Phase 3 studies; PRO-814 from the current submission, and PRO-805 and 806, from the original NDA submission. However, for deaths, serious adverse effects (SAEs) and withdrawals due to treatment emergent adverse effects (TEAEs), data from the two open label (OL) extension studies (PRO-807, PRO-811), a pharmacokinetic study (TTP-400-02-01) and a comparative bioavailability study (PRO-810) was analyzed. The entire safety database included a total of 647 participants.

No deaths were observed in the Probuphine treated patients during the clinical program. There was, however, one death in a sublingual buprenorphine patient in Study PRO-806. The death was attributed to a heroin overdose.

Serious adverse events (SAEs) were reported in 10 (4%) of the patients randomized to Probuphine in the controlled trials, 7 (6%) of the patients randomized to placebo, and 9 (5%) of the patients randomized to sublingual buprenorphine. Additionally, 3 SAEs were reported in patients continuing on Probuphine in the open-label extensions and in one patient who completed placebo treatment in the controlled studies and was started on Probuphine in the open-label extension. SAEs present across all pooled studies for Probuphine, SL BPN and placebo were infections. Bronchitis, pneumonia, limb abscess and gastroenteritis were all observed, though none were identified as drug-related.

[3] PDAC briefing materials, dated January 12, 2016.

Cellulitis at the removal site was also identified for a patient in the placebo group. This AE was noted to be related to the procedure, not the drug itself.

Other serious AEs related to the procedure were expulsions, extrusions and complicated removals. Three patients experienced implant expulsions during the course of the clinical program and an additional three patients were reported to have implant extrusions (one patient experienced both). Complicated removals, defined as "failure to remove all implants during the first attempt – thus necessitating imaging studies to locate all implants and a second removal attempt"[4] occurred 16 times in the early stages (Study 805) of the clinical program. All of these complications occurred in patients treated with Probuphine.

The most frequently reported treatment emergent adverse effects (TEAEs) in general, for studies PRO-805, PRO-806 and PRO-814 were headache (12.6% Probuphine, 10.1% placebo/SL BPN), insomnia (8.4% Probuphine, 11.4% placebo/SL BPN) and nasopharyngitis (8.7% Probuphine, 6.9% placebo/SL BPN). These were followed by upper respiratory tract infections and nausea, which occurred in 8.1% Probuphine, 7.3% placebo/SL BPN and 6.5% Probuphine, 4.7% placebo/SL BPN respectively.

The most common type of event leading to study discontinuation involved problems with the implant site of Probuphine. Implant site pain, inflammation, hematoma and infection accounted for 3% of Probuphine, 4% of SL BPN and 2% of placebo site reactions causing patients to leave the study. All of these events occurred during Study PRO-805 and its extension, PRO-807. These two studies used different insertion/removal procedures than later studies (PRO-806, 811, 814) which incorporated a new insertion/removal instrument and technique. The DAAAP clinical reviewer stated, "The overall rate of implant-site related AEs was reduced from roughly half of all patients receiving implants to about a quarter after implementation of the new insertion device and training procedures."[5]

Other AEs of special interest during the safety evaluation of Probuphine were hepatic effects and QT prolongation. Current labeling for buprenorphine contains a warning for hepatitis/hepatic events, and use in patients with Long QT Syndrome. Data from the Probuphine clinical program revealed no new hepatic or cardiac safety concerns beyond those previously identified in buprenorphine clinical trials and postmarketing surveillance.

Overall, the most notable adverse events for Probuphine were related to the surgical procedures for insertion and removal of the implants. DAAAP consulted with both the Division of Medication Error Prevention and Analysis (DMEPA) and the Division of Bone, Reproductive and Urologic Products (DBRUP) to analyze the safety findings pertaining to the Probuphine insertion and removal procedures.

[4] Sewell C. Division of Bone, Reproductive and Urologic Products (DBRUP). Internal Consult for Probuphine, dated December 11, 2015.

[5] Skeete R., PDAC briefing materials, dated January 12, 2016.

Division of Medication Error Prevention and Analysis Consult Review

In the Complete Response letter sent on April 30, 2013, the Agency informed the Sponsor of the need to conduct a Human Factor Study (HFS) on the Probuphine training program. The purpose of the study was to determine if "the Probuphine training program is sufficient to impart necessary skills to a variety of providers who may not all have surgical experience (non-proceduralists) as well as validate the proposed training program's design and materials."[6] The HFS results were submitted on August 27, 2015 in response to the CR letter.

An analysis of the HFS results by DMEPA resulted in the determination that the submitted training program was not validated and did not support the safe and effective use of Probuphine. There were three primary reasons cited for this conclusion:

1. The study did not adequately simulate training decay
2. Implant removal after 6 months of implantation and the development of fibrotic tissue was not modeled, thus limiting the ability to assess training on removal
3. The results included task failures and use errors that indicated some proceduralists who received the training were unable to perform insertion and removal procedures successfully (the Sponsor did not include non-proceduralists)

Despite these findings, DMEPA indicated in their review that there would be providers who are able to safely insert and remove Probuphine. They recommended that the insertion and removal procedures be limited to proceduralists, the inclusion of a final practicum to test adequate performance, a recertification requirement and an evaluation of the criterion used to qualify Master Trainers.

Division of Bone, Reproductive and Urologic Products Consult Review

DAAAP consulted DBRUP, as the insertion and removal procedures of Probuphine are similar to that of implantable contraceptives. DBRUP was asked to provide a clinical perspective on the interpretation of the HFS results, the proposed training program and certification requirements for HCPs performing Probuphine surgical procedures. In their consult review, DBRUP compared the safety profile of Probuphine to implantable contraceptives. DBRUP concluded the following:

1. In comparison to contraceptive implants, Probuphine had higher incidences of bleeding, complicated removals, and implant site infection during the clinical trials; but that these procedure-related risks were predominately minor and self-limiting.
2. Serious but rare risks identified by DBRUP related to the insertion and removal procedures were migration, complicated removals and nerve damage.
3. As the risks of migration, complicated removals and nerve damage are more likely to occur in cases of improper insertion or removal, DBRUP stressed the importance of HCP's knowledge of proper surgical procedure.

[6] Shaw M. Division of Medication Error Prevention and Analysis (DMEPA). Review for Probuphine, dated January 22, 2016.

DBRUP recommended that "mid-level practitioners not participate in Probuphine procedures unless they can demonstrate procedural experience equivalent to that of physicians who perform outpatient surgical procedures", and that the review team consider specifying the qualification of providers who will perform Probuphine surgical procedures.

4 SPONSOR'S PROPOSED REMS

The following summarizes the Sponsor's original proposed REMS submission, submitted August 27, 2015:

- Sponsor's Proposed REMS Goal
  To mitigate (1) the risks of complications related to the PROBUPHINE insertion and removal procedures and (2) the risks of PROBUPHINE misuse, abuse, and accidental overdose by:

  a) Educating and training (b) (4) on appropriate patient selection for PROBUPHINE, proper PROBUPHINE insertion and removal procedures, and the risks of misuse, abuse, and accidental overdose among patients treated with PROBUPHINE; and

  b) Establishing a Closed Distribution System that ensures PROBUPHINE is distributed directly and (b) (4) perform the insertion and removal procedures.

- REMS Elements
  - Medication Guide
  - Communication Plan
  - ETASU A – *Prescriber Certification*
    - Live lecture with knowledge assessment
  - ETASU B – *Inserter/Remover Certification*
    - Live lecture with knowledge assessment
    - Live practicum with "satisfactory completion"
  - Implementation System
    - Distribution to certified prescribers
  - Timetable for Submission of Assessments
    - 6 months, (b) (4)

The Sponsor amended their original submission on December 7, 2015, February 11, April 4, May 4, May 18, May 24 and May 25, 2016 based on feedback during the course of the review process from DAAAP, DRISK, DMEPA, DBRUP and the PDAC.

The following summarizes the Sponsor's proposed REMS submission, submitted on May 25, 2016:

- Sponsor's Proposed REMS Goal

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

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

b) Informing patients about the risks of complications of migration, protrusion, expulsion and nerve damage associated with insertion and removal, as well as, the risks of accidental overdose, misuse and abuse if an implant comes out or protrudes from the skin.

- REMS Elements
  - Medication Guide
  - ETASU A – *Prescriber certification*
    - Live lecture with knowledge assessment
    - Live practicum
  - ETASU B – *Inserter certification*
    - Live lecture with knowledge assessment
    - Live practicum with assessment of procedural competency
    - Recertification requirement
  - ETASU C – *Healthcare setting certification*
    - Practice setting of a certified prescriber
  - ETASU E – *Monitoring*
    - Removal of Probuphine by a certified inserter
  - Implementation System
    - Distribution to healthcare settings with a certified prescriber
  - Timetable for Submission of Assessments
    - 6 months, one year and annually thereafter

5 AGENCY PROPOSED REMS AND DISCUSSION

5.1 RATIONALE FOR A REMS

DRISK and the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) agree that a REMS is needed to ensure that the benefits outweigh the risks of serious adverse outcomes resulting from the insertion and removal of Probuphine and the risks of accidental overdose, misuse and abuse if an implant protrudes or expels from the skin.

The surgical procedures of inserting and removing the Probuphine rods are associated with serious risks including migration, protrusion, expulsion and nerve damage. Insertion and removal of the Probuphine rods requires a surgical procedure on the patient's inner arm.

Mandatory training with an assessment of procedural competency for all HCPs who perform Probuphine surgical procedures is necessary to mitigate the serious risks of Probuphine. The serious risks of migration, complicated removals and nerve damage are more likely to occur in cases of improper insertion and removal of the Probuphine rods. Therefore, educating HCPs about proper surgical procedures specific to Probuphine rods is essential. Requiring that they demonstrate procedural competency by passing an assessment further ensures healthcare providers have the skills necessary to correctly insert or remove the Probuphine rods. As demonstrated in the Human Factors study, not all HCPs who had surgical experience performed all steps correctly after training; this supports requiring all HCPs to pass an assessment of procedural competency in order to become certified to insert the Probuphine rods.

Ensuring that only HCPs who have performed a surgical procedure in the past 3 months take the training and become certified to insert Probuphine is necessary to mitigate the serious risks of Probuphine. This prerequisite requirement is necessary because only HCPs with some procedural experience are qualified to perform Probuphine surgical procedures and successfully complete the live practicum assessment of procedural competency. In the HFS, non-proceduralists were excluded from the user group, thus preventing an analysis of those with less surgical experience. DMEPA recommended non-proceduralists not be allowed to become certified. DBRUP recommended in their review that "mid-level practitioners not participate in Probuphine procedures unless they can demonstrate procedural experience equivalent to that of physicians who perform outpatient surgical procedures."

The training requirement for all Probuphine prescribers must be mandatory in order to ensure qualified, trained HCPs are performing Probuphine insertions and removals. The expected prescribers of Probuphine include psychiatrists, primary care physicians and other practitioners in private practice who provide addiction treatment. These prescribers who have limited experience in performing surgical procedures should not be performing Probuphine insertions and removals. However, Probuphine distribution is limited to HCFs where a certified prescriber is practicing. Thereby, Probuphine will be stored in facilities by prescribers who may not be qualified to perform Probuphine procedures. The mandatory training ensures all prescribers are informed how Probuphine implants are inserted and removed, that a HCP certified to insert must perform the Probuphine insertion procedure, and that patients must be monitored to ensure Probuphine is removed by a HCP certified to insert Probuphine. Additionally, prescribers are informed that if they intend to perform the insertion procedure in their office they must have the prerequisite requirements, undergo procedural training and pass a procedural competency assessment to become certified to perform the insertion procedure. Alternatively, prescribers are informed that they must arrange for another HCP, who is certified to insert Probuphine, to perform the insertion procedure for the prescriber's patients in their office.

In addition to certification of healthcare providers, patient education is necessary to ensure patients are aware of the serious risks of abuse, misuse and accidental exposure which can occur if the Probuphine implant protrudes or is expelled. Although the placement of Probuphine in a patient's arm makes it less available compared to buprenorphine tablets or films dispensed in bottles and potentially less likely to be

misused, abuse or accidentally overdosed, it is still possible. A REMS can help ensure patients are informed of actions to take to prevent abuse, misuse and accidental exposure to others not prescribed Probupine if an implant protrudes or is expelled. Both the prescriber and the HCP who inserts the product will be required to counsel the patient on the serious risks associated with Probuphine.

Finally, a REMS that includes a restricted distribution program can ensure that Probuphine is only distributed to the facility of certified prescribers who will ultimately insert the implant or arrange for insertion of the implant by a different certified HCP who inserts.

If approved, Probuphine's risks cannot be mitigated with labeling alone. A REMS is necessary to ensure the benefits outweigh serious adverse outcomes resulting from insertion and removal, the risks of migration, protrusion, expulsion and nerve damage, as well as, overdose, misuse and abuse if an implant protrudes or expels from the skin.

5.2 REMS GOAL

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

a) Ensuring that healthcare providers are educated on the following:

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

b) Informing patients about the risks of complications of migration, protrusion, expulsion and nerve damage associated with insertion and removal, as well as, the risks of accidental overdose, misuse and abuse if an implant comes out or protrudes from the skin.

We, DRISK [and DAAAP], recommended revising the REMS goal to target the achievement of particular health outcomes and knowledge related to the known safety risks and to minimize the risks associated with Probuphine. The Sponsor initially proposed a goal that did not identify specific risks to be mitigated. We determined that the most serious risks occur with the insertion and removal of Probuphine and proposed measurable HCP and patient educational objectives to support meeting the goal.[7] In consultation with the DAAAP clinical review team during this review cycle, it was determined that serious complications can also result from proper insertion and removal of Probuphine. DRISK's current thinking on the goal has evolved since the DRISK's

[7] DRISK Probuphine REMS Review. Reviewer: Donella Fitzgerald, dated November 23, 2015.

recommendation in the 2013 review cycle and the revised goal reflects these changes and the risks that need to be addressed by the REMS.[8]

Mitigating the risks of misuse, abuse and accidental overdose has consistently been part of the Probuphine REMS goal. What changed during the review cycle was the addition of a qualifying statement. During this review cycle DRISK and DAAAP also agreed that the risk of misuse, abuse and accidental overdose are of concern if an implant protrudes or comes out of the skin.[9] This distinction is reflected in the revised REMS goal.

5.3 MEDICATION GUIDE

A Medication Guide was included as a REMS element in the Sponsor's original and subsequent submissions for this review cycle. DRISK has maintained its concurrence with the Sponsor that a Medication Guide must be included as part of the REMS. The MG must be distributed to patients in accordance with 21 CFR 208.24. The HCP who inserts Probuphine must review the MG with the patient the day Probuphine is inserted. The Medication Guide has been reviewed under separate cover by DMPP and OPDP, in a collaborative review that found the MG to be acceptable.

5.4 COMMUNICATION PLAN

A communication plan (CP) was included as a REMS element in the Sponsor's original submission on August 27, 2015. DRISK's recommendation for including a CP has evolved since the Sponsor's first review cycle. The review team decided that a CP is not necessary to ensure that the benefits of Probuphine outweigh the risks.[10] The prescribing population for Probuphine is a small group of specialized HCPs and is limited to those working in Opioid Treatment Programs or DATA-2000 waived physicians. A CP is not necessary to support implementation of the REMS. In addition, since this REMS contains mandatory training for all HCPs who prescribe or perform Probuphine surgical procedures, a CP is not necessary to inform HCPs about the serious risks. The mandatory training replaces the need for mass mailings of educational materials to HCPs, therefore a CP is not a necessary risk mitigation tool for Probuphine.

5.5 ELEMENTS TO ASSURE SAFE USE

5.5.1 ETASU A – Healthcare Providers who Prescribe Certification

The Sponsor and Agency have been in agreement about the need for Prescriber Certification since Probuphine's first review cycle in 2013. On the proposed requirements of certification, however, Braeburn and the Agency did not initially align. In the Sponsor's original submission for this review cycle, they proposed that prescribers must attend the live lecture portion of the Probuphine training program, but not the live practicum session. The review team determined that participation in the *Live Practicum*

[8] DRISK Probuphine REMS Review. Reviewer: Donella Fitzgerald, dated March 24, 2016.

[9] DRISK Probuphine REMS Review. Reviewer: Donella Fitzgerald, dated November 23, 2015.

[10] DRISK Probuphine REMS Review. Reviewer: Donella Fitzgerald, dated November 23, 2015.

Training Session would increase prescriber's knowledge of the insertion and removal process, enabling them to better counsel the patient prior to insertion, respond to patient concerns and manage possible complications after the insertion. Therefore, DRISK and DAAAP recommended the REMS include the requirement that prescribers participate in the Live Practicum Training Session. (b) (4)

5.5.2 ETASU B – Healthcare Providers who Insert Certification[11]

The Sponsor and Agency have been in agreement about the need for inserter certification since the first review cycle for Probuphine in 2013. DRISK maintained concurrence that HCP who would be performing the procedures must attend and successfully complete both the *Live Lecture and Practicum Training*. A surgical prerequisite requirement to participate in the training program was added as a result of recommendations from both DMEPA and DBRUP. The training program initially included a written knowledge assessment for the lecture portion, but did not have an assessment developed for the practicum. DMEPA's consult review discussed the importance of developing clear assessment criteria for the practicum and recommended inclusion of an assessment in the training program. The review team agreed with DMEPA's recommendation. The Sponsor developed the *Criteria for Procedural Competency* in response to guidance provided by the Agency.

DRISK's recommended requirements under ETASU B have evolved since the first review cycle in 2013. The surgical prerequisite requirement was not required then; nor was the recertification requirement. The 2013 DRISK review recommended that the Sponsor offer re-training to those HCP who had not placed an order for Probuphine within six months of training, but it was not mandatory.[12]

During this review cycle the review team recommended Braeburn incorporate a recertification requirement for HCP who perform Probuphine surgical procedures. At the Advisory Committee meeting, members of the panel expressed concern that the proposed REMS did not address recertification of HCP performing Probuphine surgical procedures. DMEPA also recommended that the division reconsider the Sponsor's one-time training proposal. The review team agreed that recertification of HCP who perform Probuphine surgical procedures was necessary to ensure safe use. DBRUP provided the review team with proposed recertification requirements from a clinical perspective. This recommendation was communicated with the Sponsor and subsequently incorporated into the Probuphine REMS Program.

[11] For the purpose of this REMS, the term insert refers to the dispensing of medication.

[12] DRISK Final REMS Review of Probuphine. Reviewer: Jason Bunting, dated April 30, 2013.

5.5.3 **ETASU C – Healthcare Setting Certification**

Braeburn did not propose ETASU C as an element of the Probuphine REMS, however DRISK recommended including ETASU C to ensure Probuphine is only inserted in a setting in which a certified prescriber is practicing. It also provides assurance that both the dispensing (i.e. insertion) and monitoring occurs by a certified healthcare provider as the REMS requires. The language in ETASU C states "Probuphine must be inserted only in a healthcare setting in which a certified prescriber is also practicing."[13] Certified prescribers must ensure that Probuphine surgical procedures are performed by healthcare providers who are certified to insert Probuphine. In addition, patients who had Probuphine inserted must be monitored to ensure Probuphine is only removed by a HCP who is certified to insert.

As per FDAAA, ETASU B and C are supported by the implementation system. The implementation system states that Probuphine will be shipped only to sites that have a certified prescriber.

ETASU E – Monitoring

Braeburn did not propose ETASU E as an element of the Probuphine REMS. The Agency informed Braeburn that it was a necessary addition to incorporate removal of Probuphine in the REMS document. In Braeburn's August 2015 submission, removal of Probuphine was incorporated under ETASU B – Certification of HCP who insert and remove. During the Agency's internal clearance of the REMS document, it was determined that under FDAAA, ETASU B only applies to dispensing or administration (insertion in this case) of a drug, not removal. The removal of Probuphine carries the risks of nerve damage, scarring, infection and fractured implants, therefore because of these serious risks, the review team supported including ETASU E - monitoring (removal) in the REMS. ETASU E states "Patients must be monitored to ensure that removal of Probuphine is performed by a HCP certified in the insertion procedure." Since training on the proper removal of Probuphine is incorporated in the training program for healthcare providers who insert Probuphine rods, the risks associated with removal will be mitigated by this element.

5.6 IMPLEMENTATION SYSTEM

The Sponsor's implementation system submitted for this review cycle proposed that Probuphine is distributed to prescribers who are certified in the Probuphine REMS Program (ETASU A). The Agency recommended that Braeburn revise the implementation system to incorporate distribution to certified healthcare settings (ETASU C), to align with FDAAA. FDAAA supports distribution under ETASU B – certified dispenser and ETASU C – certified healthcare setting. Braeburn revised its implementation system, proposing that Probuphine be shipped only to healthcare settings in which a certified prescriber is also practicing. As stated above, in section 5.5.3, this

[13] DRISK Probuphine REMS Review. Reviewer: Donella Fitzgerald, dated March 24, 2016.

revision in the implementation system aligned the REMS with FDAAA and how Braeburn proposes to operationalize the Probuphine REMS Program.

5.7 TIMETABLE FOR SUBMISSION OF ASSESSMENTS

Braeburn originally proposed to submit assessments of the Probuphine REMS Program to the FDA at 6 months [redacted] (b) (4) DRISK and DAAAP agreed that the timetable for submission of assessments must be revised to submission of REMS Assessments 6 and 12 months from the date of approval, then annually thereafter.[14] This timetable is consistent with the timetable included for approved REMS with ETASU that have a restricted distribution program.

5.8 REMS ASSESSMENT PLAN

The REMS assessment plan must include, but is not limited to, the following:

1. **REMS Program Outreach and Communication**
   a) Number of *Probuphine REMS Prescriber Enrollment Forms* sent to prescribers who attempt to order Probuphine or inquire about certification
   b) Number and location of REMS training programs
      (1) Number of HCPs certified as prescribers, inserters/removers and dually certified at each program
2. **REMS Program Utilization**
   a) Number of certified HCPs who prescribe
      (1) Number of orders per certified prescriber
      (2) Degree, specialty, practice setting, and geographic location
      (3) Number of replacement kit orders shipped.
      (4) Number of times unused implants from replacement kits are returned per certified prescriber.
         (a) Number of unused implants from each replacement kit returned.
   b) Number of certified HCPs who insert
      (1) Degree, specialty and geographic location
      (2) Number of certified inserters that are re-certified by method of certification (i.e. live training, video)
         (a) If recertified by video, number of certified HCP who insert who have operating privileges versus those successfully performing 10 or more procedures
   c) Number of dual-certified HCPs who prescribe and insert
      (1) Number of orders per dual-certified prescriber
      (2) Degree, specialty and geographic location
      (3) Number of replacement kit orders shipped and returned per dual-certified prescriber

[14] DRISK Probuphine REMS Review. Reviewer: Donella Fitzgerald, dated November 23, 2015.

(4) Number of dual-certified prescribers that are re-certified by method of certification (i.e. live training, video)

(a) If recertified by video, number of certified HCPs who insert who have operating privileges versus those successfully performing 10 or more procedures

3. REMS Program Infrastructure and Performance

a) Number of non-certified prescribers attempting to prescribe Probuphine and corrective actions

b) Number of orders shipped to non-certified prescribers and corrective actions taken

c) Number of insertions/removals performed by a HCP not certified to insert or dually certified to prescribe and insert Probuphine and corrective actions taken

d) Summary of results of audits of 10% (or 15, whichever is greater) recertification forms for inserters/removers (beginning at the 24-month assessment)

e) Summary of call center calls; include corrective actions taken for any non-compliance identified through the call center by stakeholder type

f) Number of certified prescribers, inserters, and dual-certified healthcare providers that have been decertified and a summary of the reasons for decertification

g) Assessment of the distribution and use of the Medication Guide in accordance with 21 CFR 208.24 and the Probuphine REMS Program requirements

h) Report on failures to adhere to distribution requirements, and corrective actions taken to address noncompliance

4. Evaluation of knowledge

a) Healthcare Providers - Results of evaluation of healthcare provider's knowledge of the risk of complications of migration, protrusion, expulsion and nerve damage associated with the insertion and removal of Probuphine, and the risks of accidental overdose, misuse and abuse if an implant comes out or protrudes from the skin. Results should be stratified by certified prescriber, certified inserter, and dual-certified prescribers

b) Patients – Results of evaluation of patients' knowledge of the risk of complications of migration, protrusion, expulsion and nerve damage and the risks of accidental overdose, misuse and abuse if an implant comes out or protrudes from the skin.

5. Overall REMS evaluation

As required for assessments of an approved REMS under section 505-1(g)(3) the Applicant will include, with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

6 CONCLUSION

In conclusion, labeling alone is not sufficient to mitigate the risks associated with Probuphine. A REMS with ETASU is necessary to ensure the benefits outweigh 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. Ensuring that healthcare providers are educated about these risks, and that patients have been informed of them, are essential aspects of risk mitigation in this REMS program. To meet these objectives, a REMS with ETASU A, B, C and E, an implementation system and a timetable for submission of assessments are required to ensure that the benefits of Probuphine outweigh the risks.

7 RECOMMENDATION

On May 25, 2016, Braeburn submitted a REMS proposal amended based on Agency comments received during the review of Probuphine, NDA 204442. DRISK finds the proposed Probuphine REMS, appended materials and REMS supporting document, as submitted on May 25, 2016, acceptable. DRISK recommends approval of the REMS appended to this review.

8 ATTACHMENTS

Probuphine REMS document and appended materials

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DONELLA A FITZGERALD
05/25/2016

CYNTHIA L LACIVITA
05/25/2016
Concur

Department of Health and Human Services
Food and Drug Administration Center for
Drug Evaluation and Research Office of
Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

REMS REVIEW: INTERIM COMMENTS #5

Date:	May 25, 2016
Reviewer(s)	Donella Fitzgerald, Pharm.D., Risk Management Analyst Division of Risk Management (DRISK) Joan E. Blair, RN, MPH, Health Communications Analyst Division of Risk Management (DRISK)
Team Leader	Kim Lehrfeld, Pharm.D, DRISK
Director:	Cynthia LaCivita, Pharm.D. Division of Risk Management
Drug Name(s):	Probuphine (buprenorphine/ethylene vinyl acetate) implant
Therapeutic class and Dosage Form	Opioid Partial Agonist subdermal implants
OND Review Division	Division of Analgesia, Anesthesia and Addiction Products
Application Type/Number:	NDA 204442
Applicant/sponsor:	Braeburn Pharmaceuticals, on behalf of Titan Pharmaceuticals, Inc.
OSE RCM #:	2015-2115

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1 INTRODUCTION

The purpose of this review is to document the evaluation and provide comments on the proposed risk evaluation and mitigation strategy (REMS) for Probuphine, NDA 204442, submitted by Braeburn Pharmaceuticals (Braeburn) on behalf of Titan Pharmaceuticals, Inc. (Titan) as a 505(b)(2) application on August 27, 2015, and amended on December 7, 2015, February 11, 2016, April 4, 2016, and May 4, 2016.

1.1 BACKGROUND

Probuphine is a schedule III, buprenorphine-containing subdermal implant covered under the Drug Addiction Treatment Act of 2000 (DATA-2000). It has a proposed indication 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). The implants are 26mm x 2.5 mm rods, each containing 80 mg of buprenorphine HCl. Four rods are to be inserted subdermally in the inner side of the upper arm (about 8-10 cm above the medial epicondyle of the humerus) to provide sustained delivery of buprenorphine for six months. At the end of six months, implants can be inserted in the opposite arm if continued therapy is warranted.

Titan originally filed the application for Probuphine, NDA 204442, on October 31, 2012. A Complete Response was issued on April 30, 2013 for deficiencies in clinical benefit and human factors usability. The Agency recommended that the Applicant provide additional data supporting the efficacy of Probuphine, and a Human Factors study, complete with a comprehensive use-related risk analysis, for the insertion/removal training program.

Braeburn, on behalf of Titan, resubmitted Probuphine on August 27, 2015, with a proposed REMS. The resubmission included the results of a new randomized, double-blind, double-dummy Phase 3 study (PRO-814) that was conducted on 177 patients to support the clinical benefit of Probuphine in patients previously stabilized on 8mg or less of sublingual (SL) buprenorphine. The primary endpoint for PRO-814 was a responder analysis (using urine toxicology plus self-report) which evaluated the degree to which treatment with Probuphine resulted in the absence of objective evidence of opioid use. The Applicant states the proportion of responders was statistically significantly higher ($p = 0.034$), in the Probuphine group (96.4%) compared to the SL buprenorphine group (87.6%).

The Applicant stated the results of the Human Factors Study demonstrated healthcare providers with procedural experience were better able to perform the insertion procedure. An evaluation of the study has been conducted by the Division of Medication Error and Prevention Analysis (DMEPA).

The elements of the proposed REMS for Probuphine are a Medication Guide (MG), Elements to Assure Safe Use, Implementation Plan and a Timetable for Submission of Assessments.

1.2 REMS REGULATORY HISTORY

October 31, 2012: Titan submitted Probuphine, NDA 204442, with a proposed REMS (Seq. No. 0000).

February 28, 2013: A REMS Oversight Committee meeting was held to discuss the rationale for a REMS and to determine the minimum required elements.

March 21, 2013: Psychopharmacologic Drugs Advisory Committee meeting was held. The panel discussed if the proposed REMS was adequate to address the risks of complications associated with the insertion procedure and abuse, misuse and accidental overdose. The committee voted: 5-yes, 4-no and 6-abstain. The four members who voted "no" expressed concerns that providers would not be trained properly on insertion/removal. The six members that abstained noted that the Applicant presented a modified REMS that was not previously described in the briefing materials.

April 30, 2013: A Complete Response was issued for deficiencies in clinical benefit and human factors usability.

August 27, 2015: Braeburn, on behalf of Titan, resubmitted Probuphine, NDA 204442, with a proposed REMS. This submission did not include a Supporting Document (Seq. No. 0030).

January 12, 2016: A Psychopharmacologic Drugs Advisory Committee meeting was held to discuss the safety and efficacy of Probuphine. The panel discussed whether the REMS is adequate to address the risks of potential complications associated with the insertion and removal procedures, and abuse, misuse and accidental overdose. There was a vote on the following question: Does the efficacy, safety, and risk-benefit profile of Probuphine support the approval of this application for a population of patients previously stable on a regimen of sublingual buprenorphine? The committee members voted: 12-yes and 5-no.

February 11, 2016: Braeburn submitted a REMS Amendment.

February 19, 2016: The Agency issued a Major Amendment, extending the PDUFA date from February 27, 2016 to May 27, 2016.

March 24, 2016: The Agency sent Braeburn comments on their February 11, 2016 REMS submission. The FDA recommended revision of the goal, addition of ETASU C and an auditing requirement for HCP Who Perform Probuphine Surgical Procedures.

April 4, 2016: Braeburn submitted a REMS Amendment reflecting REMS comments provided on March 24, 2016.

April 22, 2016: The Agency sent Braeburn comments on their April 4, 2016 REMS submission. The FDA recommended changes to the REMS document to reflect the inclusion of a recertification video available post-approval.

May 4, 2016: Braeburn submitted a REMS Amendment, reflecting REMS comments provided on April 22, 2016. These materials are the subject of this review.

1.3 MATERIALS INFORMING OUR REVIEW

1.3.1 SUBMISSIONS

- Braeburn, on behalf of Titan Pharmaceuticals Inc. Proposed REMS for Probuphine, received August 27, 2015 (eCTD Seq. No. 0030)
    - Amendment, received December 7, 2015 (eCTD Seq. No. 0049)
    - Amendment, received February 11, 2016 (eCTD Seq. No. 0061)
    - Amendment received April 4, 2016 (eCTD Seq No. 0071)
    - Amendment received May 4, 2016 (eCTD Seq No. 0079)

1.3.2 OTHER MATERIALS INFORMING OUR REVIEW

The following is a list of materials that were used to inform this review:

- Probuphine Complete Response Letter. Division of Anesthesia, Analgesia and Addiction Products (DAAAP), dated April 30, 2013.
- Bunting J., Final REMS Review of Probuphine, dated April 30, 2013.
- REMS Oversight Committee meeting minutes, dated February 28, 2013.
- Psychopharmacologic Drugs Advisory Committee (PDAC) meeting minutes, dated March 21, 2013.
- PDAC briefing materials, dated March 21, 2013.
- PDAC briefing materials, dated January 12, 2016.
- Shah, M., Division of Medication Error and Prevention Analysis (DMEPA) Human Factors Results, Label and Labeling Review for Probuphine, dated January 22, 2016.
- Sewell C., Division of Bone, Reproductive and Urologic Products (DBRUP). Internal Consult for Probuphine, dated December 11,
- Fitzgerald D., REMS Review of Probuphine, dated November 23, 2015.
- Fitzgerald D., REMS Review of Probuphine, dated February 2, 2016.
- Sullivan M., DAAAP. Probuphine Major Amendment Letter, dated February 19, 2016.
- Fitzgerald D., REMS Review of Probuphine, dated March 24, 2016.
- Fitzgerald D., REMS Review of Probuphine, dated April 22, 2016.
- Fitzgerald D., REMS Review of Probuphine, dated May 4, 2016.

2 PROPOSED REMS

2.1 REMS DOCUMENT

DRISK Comments:
The Probuphine REMS document has been revised to reflect the Agency's current thinking on how REMS documents are written and is attached to this review. The REMS document will continue to be revised and reviewed internally as details continue to be negotiated with the Applicant. Therefore, the REMS document should not be considered final.

2.2 REMS GOAL

No comments at this time.

2.3 REMS ELEMENTS

2.3.1 Medication Guide

The MG is currently under review by The Office of New Drugs, Division of Labeling. DRISK has no comments at this time.

2.3.2 Elements to Assure Safe Use

2.3.2.1 ETASU E – Monitoring

In the proposed REMS, removal of Probuphine is incorporated under ETASU B – Certification of HCP who insert and remove. During the Agency's internal clearance of the REMS document, it was determined that under FDAAA, ETASU B only applies to dispensing or administration (insertion in this case) of a drug, not removal. The removal of Probuphine carries the risks of nerve damage, scarring, infection and fractured implants, therefore because of these serious risks, the review team supports including ETASU E - monitoring (removal) in the REMS. Since training on the proper removal of Probuphine is incorporated in the training program for

healthcare providers who insert Probuphine rods, the risks associated with removal will be mitigated by this element.

DRISK Recommendation:

Revise the REMS document to include ETASU E – Monitoring. See attached redlined REMS document for proposed language.

2.3.3 Implementation System

No comments at this time.

2.3.4 Timetable for Submission of Assessments

No comments at this time.

2.3.5 Assessment Plan

See attached FDA proposed assessment plan. The Sponsor is advised to insert this into their REMS supporting document in their next submission.

3 CONCLUSION

DRISK recommends changes to the ETASU, supporting document and materials of the proposed Probuphine REMS. We have commented on the recommended changes and provided our rationale. The MG is currently under review by the Office of New Drugs, Division of Labeling.

4 RECOMMENDATIONS

DRISK advises that the above recommendations for the proposed Probuphine REMS, NDA 204442, be shared with the Applicant along with comments below *(Section 5: Comments for the Applicant*). DRISK requests that the Applicant respond to these comments by May 18, 2016 to facilitate further review of this submission. The comments below are based on DRISK's ongoing review.

5 COMMENTS FOR THE APPLICANT

The Agency has reviewed the proposed Probuphine REMS materials submitted on May 4, 2016. Based on our review and revisions of the Probuphine Prescribing Information (PI), we recommend revisions be made to the Probuphine REMS document, supporting document and materials.

Comments guiding their revisions are on the materials themselves as track change comments. Note that all REMS materials must reflect the most recent and eventually the final label, including Section 17 of the PI and the Medication Guide. The REMS materials must also align with the revised ***Probuphine Instructions for Use***.

Attachments

Documents sent on May 13, 2016:

- Probuphine REMS document
- 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 Program slides (25-77)
- Probuphine REMS Program Criteria for Procedural Competency
- Probuphine REMS Program Insertion/Removal Log
- What You Need to Know about Probuphine: A Patient's Guide
- Probuphine REMS Program Probuphine Surgical Procedures Recertification Video Script
- Probuphine REMS Website comments
- Probuphine REMS Program Assessment Plan

Documents sent on May 16, 2016:

- Probuphine REMS Program Healthcare Provider Who Performs Probuphine Surgical Procedures Recertification Form
- Probuphine REMS Program Procedure Record for Recertification
- Probuphine REMS Program Live Training Program slides (1-24)
- Probuphine REMS Program Knowledge Assessment

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/s/

DONELLA A FITZGERALD
05/25/2016

KIMBERLY LEHRFELD
05/25/2016

Department of Health and Human Services
Food and Drug Administration Center for
Drug Evaluation and Research Office of
Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

REMS REVIEW: INTERIM COMMENTS #4

Date:	April 22, 2016
Reviewer(s)	Donella Fitzgerald, Pharm.D., Risk Management Analyst Division of Risk Management (DRISK) Joan E. Blair, RN, MPH, Health Communications Analyst Division of Risk Management (DRISK)
Team Leader	Kim Lehrfeld, Pharm.D, DRISK
Director:	Cynthia LaCivita, Pharm.D. Division of Risk Management
Drug Name(s):	Probuphine (buprenorphine/ethylene vinyl acetate) implant
Therapeutic class and Dosage Form	Opioid Partial Agonist-antagonist subdermal implants
OND Review Division	Division of Analgesia, Anesthesia and Addiction Products
Application Type/Number:	NDA 204442
Applicant/sponsor:	Braeburn Pharmaceuticals, on behalf of Titan Pharmaceuticals, Inc.
OSE RCM #:	2015-2115

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1 INTRODUCTION

The purpose of this review is to document the evaluation and provide comments on the proposed risk evaluation and mitigation strategy (REMS) for Probuphine, NDA 204442, submitted by Braeburn Pharmaceuticals (Braeburn) on behalf of Titan Pharmaceuticals, Inc. (Titan) as a 505(b)(2) application on August 27, 2015, and last amended on April 6, 2016.

1.1 BACKGROUND

Probuphine is a schedule III, buprenorphine-containing subdermal implant covered under the Drug Addiction Treatment Act of 2000 (DATA-2000). The proposed indication is for the maintenance treatment of opioid dependence. Probuphine is intended for use in patients who are opioid-tolerant and have been stabilized on a sublingual buprenorphine [redacted] (b) (4) The implants are 26mm x 2.5 mm rods, each containing 80 mg of buprenorphine HCl. Four rods are to be inserted subdermally in the inner side of the upper arm (about 8-10 cm above the medial epicondyle of the humerus) to provide sustained delivery of buprenorphine for six months. At the end of six months, implants can be inserted in the opposite arm if continued therapy is warranted.

Titan originally filed the application for Probuphine, NDA 204442, on October 31, 2012. A Complete Response was issued on April 30, 2013 for deficiencies in clinical benefit and human factors usability. The Agency recommended that the Applicant provide additional data supporting the efficacy of Probuphine, and a Human Factors study, complete with a comprehensive use-related risk analysis, for the insertion/removal training program.

Braeburn, on behalf of Titan, resubmitted Probuphine on August 27, 2015, with a proposed REMS. The resubmission included the results of a new randomized, double-blind, double-dummy Phase 3 study (PRO-814) that was conducted on 177 patients to support the clinical benefit of Probuphine in patients previously stabilized on 8mg or less of sublingual (SL) buprenorphine. The primary endpoint for PRO-814 was a responder analysis (using urine toxicology plus self-report) which evaluated the degree to which treatment with Probuphine resulted in the absence of objective evidence of opioid use. The Applicant states the proportion of responders was statistically significantly higher ($p = 0.034$), in the Probuphine group (96.4%) compared to the SL buprenorphine group (87.6%).

The Applicant stated the results of the Human Factors Study demonstrated healthcare providers with procedural experience were better able to perform the insertion procedure. An evaluation of the study has been conducted by the Division of Medication Error and Prevention Analysis (DMEPA).

The elements of the proposed REMS for Probuphine are a Medication Guide (MG), Elements to Assure Safe Use, Implementation Plan and a Timetable for Submission of Assessments.

1.2 REMS REGULATORY HISTORY

October 31, 2012: Titan submitted Probuphine, NDA 204442, with a proposed REMS (Seq. No. 0000).

February 28, 2013: A REMS Oversight Committee meeting was held to discuss the rationale for a REMS and to determine the minimum required elements.

March 21, 2013: Psychopharmacologic Drugs Advisory Committee meeting was held. The panel discussed if the proposed REMS was adequate to address the risks of complications associated with the insertion procedure and abuse, misuse and accidental overdose. The committee voted: 5-yes, 4-no and 6-abstain. The four members who voted "no" expressed concerns that providers would not be trained properly on insertion/removal. The six members that abstained noted that the Applicant presented a modified REMS that was not previously described in the briefing materials.

April 30, 2013: A Complete Response was issued for deficiencies in clinical benefit and human factors usability.

August 27, 2015: Braeburn, on behalf of Titan, resubmitted Probuphine, NDA 204442, with a proposed REMS. This submission did not include a Supporting Document (Seq. No. 0030).

January 12, 2016: A Psychopharmacologic Drugs Advisory Committee meeting was held to discuss the safety and efficacy of Probuphine. The panel discussed whether the REMS is adequate to address the risks of potential complications associated with the insertion and removal procedures, and abuse, misuse and accidental overdose. There was a vote on the following question: Does the efficacy, safety, and risk-benefit profile of Probuphine support the approval of this application for a population of patients previously stable on a regimen of sublingual buprenorphine? The committee members voted: 12-yes and 5-no.

February 11, 2016: Braeburn submitted a REMS Amendment.

February 19, 2016: The Agency issued a Major Amendment, extending the PDUFA date from February 27, 2016 to May 27, 2016.

March 24, 2016: The Agency provided comments to the Sponsor on the proposed REMS.

April 4, 2016: Braeburn submitted a REMS Amendment.

April 6, 2016: Braeburn submitted a REMS Amendment.

1.3 MATERIALS INFORMING OUR REVIEW

1.3.1 SUBMISSIONS

- Braeburn, on behalf of Titan Pharmaceuticals Inc. Proposed REMS for Probuphine, received August 27, 2015 (eCTD Seq. No. 0030)
    - Amendment received December 7, 2015 (eCTD Seq. No. 0049)
    - Amendment received February 11, 2016 (eCTD Seq. No. 0061)
    - Amendment received April 4, 2016 (eCTD Seq No. 0071)
    - Amendment received April 6, 2016 (eCTD Seq No. 0072)

1.3.2 OTHER MATERIALS INFORMING OUR REVIEW

- Probuphine Complete Response Letter. Division of Anesthesia, Analgesia and Addiction Products (DAAAP), dated April 30, 2013
- DRISK Final REMS Review of Probuphine. Reviewer: Jason Bunting, dated April 30, 2013
- REMS Oversight Committee meeting minutes, dated February 28, 2013

- Psychopharmacologic Drugs Advisory Committee (PDAC) meeting minutes, dated March 21, 2013
- PDAC briefing materials, dated March 21, 2013
- PDAC briefing materials, dated January 12, 2016
- DMEPA Human Factors Results, Label and Labeling Review. Reviewer: Millie Shah, dated January 22, 2016
- DRISK Probuphine REMS Interim Comments. Reviewer: Donella Fitzgerald, dated November 23, 2015
- DRISK Probuphine REMS Interim Comments. Reviewer: Donella Fitzgerald, dated February 2, 2016
- DRISK Probuphine REMS Interim Comments. Reviewer: Donella Fitzgerald, dated March 24, 2016

2 PROPOSED REMS

2.1 REMS DOCUMENT

DRISK Comments:
The REMS document will continue to be revised and reviewed internally as details continue to be negotiated with the Applicant. Therefore, the REMS document should not be considered final.

2.2 REMS GOAL

No comments at this time.

2.3 REMS ELEMENTS

2.3.1 Medication Guide

The MG is currently under review by The Office of New Drugs, Division of Labeling. DRISK has no comments at this time.

2.3.2 Elements to Assure Safe Use

2.3.2.1 Heathcare Providers who Prescribe Certification

No comments at this time.

2.3.2.2 Heathcare Providers who Insert/Remove Certification

The Sponsor has expressed concerns with having a completed Probuphine REMS Insertion/Removal Recertification Video before the May 27, 2016 PDUFA date. To address this concern, DRISK consulted with the Safety Requirement Team (SRT), the Office of Regulatory Policy (ORP), the Office of Compliance (OC) and DAAAP to determine if an approval action could be taken with the Probuphine Insertion/Removal Recertification Video transcript being approved and the final, completed video being made available at a designated time post-approval. The review team has determined that the video transcript, which is to be based on the final, agreed upon Probuphine PI and IFU, will be sufficient to determine drug approval. If Probuphine is approved, after approval the final video must be:

- Submitted to the Agency six months prior to implementation.
- Consistent with the approved Probuphine REMS Insertion/Removal Recertification Video transcript

- Made available on the Probuphine REMS Website by an agreed upon date at least 3 months prior to implementation.

DRISK Recommendation

DRISK recommends the following redlined addition to the Healthcare Providers who Insert/Remove and the Implementation System sections of the REMS document:

2. Healthcare providers who insert/remove[1] Probuphine must be specially certified.
    b. To become specially certified to insert/remove Probuphine in the Probuphine REMS Program, healthcare providers must:
        i. Review the Prescribing Information for Probuphine.
        ii. Attest to performing a sterile procedure in the three months immediately preceding enrollment in the Probuphine REMS Program.
        iii. Complete the *Probuphine REMS Program Live Training: Lecture and Practicum*, (b) (4) successfully complete the *Probuphine REMS Program Knowledge Assessment*, (b) (4), meet the *Probuphine REMS Program Criteria for Procedural Competency*.
        iv. Enroll in the Probuphine REMS Program by completing the *Probuphine REMS Program Healthcare Provider who Inserts/Removes Probuphine Enrollment Form* or *Probuphine REMS Program Healthcare Provider Dual Enrollment Form*.

    c. As a condition of certification, healthcare providers who insert/remove must:
        i. Ensure that the facility where the procedure is being conducted has the appropriate equipment to perform insertions/removals of Probuphine.
        ii. Review the Medication Guide with each patient to counsel (b) (4) the risks associated with Probuphine and provide the patient a copy.
        iii. Document the insertion and removal of Probuphine, including the date, serial number, number of rods implanted/removed, name of healthcare provider performing the procedure, and location of rods for each patient by using the *Probuphine REMS Insertion/Removal Log* or by using another method/system (e.g., electronic health record) specific to the healthcare provider's practice.
        iv. Recertify in the Probuphine REMS Program annually.

    d. Braeburn must:
        i. Maintain a process to ensure that healthcare providers who inquire about becoming certified to insert/remove Probuphine attest to performing a sterile procedure in the three (3) months immediately preceding enrollment in the Probuphine REMS Program.
        ii. Ensure that healthcare providers who insert/remove Probuphine are specially certified, in accordance with the requirements described above.

[1] For the purpose of this REMS, the term insert/remove refers to the dispensing of medication.

iii. Provide live training and competency evaluation for healthcare providers who insert/remove to ensure that healthcare providers can complete the certification process for the Probuphine REMS Program

iv. Ensure that healthcare providers are notified when they have been certified as a healthcare provider who inserts/removes Probuphine by the Probuphine REMS Program.

v. Maintain a validated, secure database of healthcare providers who are certified to perform insertions/removals in the Probuphine REMS Program.

vi. Ensure that healthcare providers meet the REMS certification requirements and de-certify non-compliant healthcare providers who do not maintain compliance with the REMS requirements.

vii. Ensure that healthcare providers who insert/remove Probuphine have access to a database of certified prescribers.

viii. Provide the *Probuphine REMS Program Healthcare Provider who Inserts/Removes Enrollment Form* and the Prescribing Information to healthcare providers who inquire about how to become certified to insert/remove Probuphine.

ix. Notify healthcare providers who insert/remove Probuphine before their certification is due to expire of the need to recertify in the Probuphine REMS Program and provide the *Probuphine REMS Program Healthcare Provider* (b) (4) (b) (4) *Recertification Form*.

x. Braeburn must make available the *Probuphine REMS Program Insertion/Removal Recertification Video* by XXXX. The video must be consistent with the Insertion/Removal Recertification Video transcript.

C. Implementation System

1. Braeburn must ensure that Probuphine is only distributed to healthcare settings in which a certified prescriber is practicing by:
    a. Ensuring that wholesalers/distributors who distribute Probuphine comply with the program requirements for wholesalers/distributers. The wholesaler/distributer must:
        i. Put processes and procedures in place to verify, prior to distributing Probuphine, that the healthcare providers who prescribe Probuphine are certified.
        ii. Comply with requests to be audited by Braeburn, FDA, or a third party acting on behalf of Braeburn or FDA to ensure that all processes and procedures are in place and are being followed for the Probuphine REMS Program. In addition, wholesalers/distributors must maintain appropriate documentation and make it available for audits.
        iii. Provide distribution data to Braeburn.
    b. Ensuring that wholesalers/distributors maintain distribution records of all shipments of Probuphine and provide the data to Braeburn.
2. Braeburn must monitor distribution data.

3. Braeburn must audit the wholesalers/distributors within (b) (4) calendar days after the wholesaler/distributer is authorized to ensure that all processes and procedures are in place and functioning to support the requirements of the Probuphine REMS Program. Corrective action must be instituted by Braeburn if noncompliance is identified.
4. Braeburn must maintain and make available to wholesalers/distributors, a validated, secure database of healthcare providers who are certified to prescribe and healthcare providers who are certified to insert/remove Probuphine in the Probuphine REMS Program.
5. Braeburn must maintain records of Probuphine distribution and dispensing, certified prescribers, certified inserters/removers, and wholesalers/distributors to meet REMS requirements.
6. Braeburn must maintain a Probuphine REMS Program Call Center (866-397-8939) and Probuphine REMS Program website (www.PROBUPHINEREMS.com). The REMS Program website will include the option to print the Prescribing Information, Medication Guide and Probuphine REMS materials. The Probuphine product website will include a prominent REMS-specific link to the Probuphine REMS Program Website.
7. Braeburn must ensure that within 5 calendar days of REMS approval the Probuphine REMS Program website is fully operational (with the exception of the *Probuphine REMS Program Insertion/Removal Recertification Video* which will be available for viewing by XXXX) and the REMS materials listed in or appended to the Probuphine REMS document are available through the Probuphine REMS Program website or by calling the Probuphine REMS Program Call Center.
8. Braeburn must continuously monitor the certified prescribers and healthcare providers who are certified to insert/remove Probuphine to ensure the requirements of the Probuphine REMS Program are being met. Braeburn must institute corrective action if noncompliance is identified.
9. Braeburn must take reasonable steps to improve implementation of and compliance with the requirements in the Probuphine REMS Program based on monitoring and evaluation of the Probuphine REMS Program.

2.3.4 Timetable for Submission of Assessments

No comments at this time.

2.3.5 Supporting Document

No comments at this time.

3 CONCLUSION

DRISK recommends changes to the ETASU and Implementation System of the proposed Probuphine REMS document. We have commented on the recommended changes and provided our rationale. The MG is currently under review by the Office of New Drugs, Division of Labeling.

4 RECOMMENDATIONS

DRISK advises that the recommendations for the proposed Probuphine REMS, NDA 204442, be shared with the Applicant. The comments below *(Section 5: Comments for the Applicant*) should be shared with the Applicant. DRISK requests that the Applicant respond to these comments within 7 business days (9 calendar days) of receiving them, to facilitate further review of this submission. The comments below are based on DRISK's ongoing review.

5 COMMENTS FOR THE APPLICANT

The Agency has reviewed the proposed Probuphine REMS document and materials submitted on April 4th and 6th, 2016.

Submit the revised REMS document, the REMS supporting document, and revised REMS materials (excluding the *Probuphine REMS Program Recertification video transcript*) to your application (via the Gateway) by COB, **May 4, 2016**.

I. Probuphine REMS Document:

We have the following comments on the Probuphine REMS document. The REMS document will continue to be revised and reviewed internally as details continue to be negotiated with the Applicant. Therefore, the REMS document should not be considered final.

Elements to Assure Safe Use

A. Heathcare Providers who Prescribe Certification

No comments at this time.

B. Heathcare Providers who Insert/Remove Certification

The Agency acknowledges your concern with having an approved Probuphine REMS Insertion/Removal Recertification Video completed before the May 27, 2016 PDUFA date. The review team has determined that the video transcript, which is to be based on the final, agreed upon Probuphine PI and IFU, will be sufficient to determine drug approval. If Probuphine is approved, after approval the final video must be:

- Submitted to the Agency six months prior to implementation.
- Consistent with the approved Probuphine REMS Insertion/Removal Recertification Video transcript.
- Made available on the Probuphine REMS Website by an agreed upon date at least 3 months prior to implementation.

DRISK Recommendation

Make the following redlined addition to the Healthcare Providers who Insert/Remove and the Implementation System sections of the REMS document:

2. Healthcare providers who insert/remove[2] Probuphine must be specially certified.
    a. To become specially certified to insert/remove Probuphine in the Probuphine REMS Program, healthcare providers must:
        i. Review the Prescribing Information for Probuphine.
        ii. Attest to performing a sterile procedure in the three months immediately preceding enrollment in the Probuphine REMS Program.
        iii. Complete the *Probuphine REMS Program Live Training: Lecture and Practicum*, (b) (4) successfully complete the *Probuphine REMS Program Knowledge Assessment*, (b) (4) meet the *Probuphine REMS Program Criteria for Procedural Competency*.

[2] For the purpose of this REMS, the term insert/remove refers to the dispensing of medication.

iv. Enroll in the Probuphine REMS Program by completing the *Probuphine REMS Program Healthcare Provider who Inserts/Removes Probuphine Enrollment Form* or *Probuphine REMS Program Healthcare Provider Dual Enrollment Form*.

b. As a condition of certification, healthcare providers who insert/remove must:

i. Ensure that the facility where the procedure is being conducted has the appropriate equipment to perform insertions/removals of Probuphine.

ii. Review the Medication Guide with each patient to counsel (b) (4) the risks associated with Probuphine and provide the patient a copy.

iii. Document the insertion and removal of Probuphine, including the date, serial number, number of rods implanted/removed, name of healthcare provider performing the procedure, and location of rods for each patient by using the *Probuphine REMS Insertion/Removal Log* or by using another method/system (e.g., electronic health record) specific to the healthcare provider's practice.

iv. Recertify in the Probuphine REMS Program annually.

c. Braeburn must:

i. Maintain a process to ensure that healthcare providers who inquire about becoming certified to insert/remove Probuphine attest to performing a sterile procedure in the three (3) months immediately preceding enrollment in the Probuphine REMS Program.

ii. Ensure that healthcare providers who insert/remove Probuphine are specially certified, in accordance with the requirements described above.

iii. Provide live training and competency evaluation for healthcare providers who insert/remove to ensure that healthcare providers can complete the certification process for the Probuphine REMS Program

iv. Ensure that healthcare providers are notified when they have been certified as a healthcare provider who inserts/removes Probuphine by the Probuphine REMS Program.

v. Maintain a validated, secure database of healthcare providers who are certified to perform insertions/removals in the Probuphine REMS Program.

vi. Ensure that healthcare providers meet the REMS certification requirements and de-certify non-compliant healthcare providers who do not maintain compliance with the REMS requirements.

vii. Ensure that healthcare providers who insert/remove Probuphine have access to a database of certified prescribers.

viii. Provide the *Probuphine REMS Program Healthcare Provider who Inserts/Removes Enrollment Form* and the Prescribing Information to healthcare providers who inquire about how to become certified to insert/remove Probuphine.

ix. Notify healthcare providers who insert/remove Probuphine before their certification is due to expire of the need to recertify in the Probuphine REMS Program and provide the *Probuphine REMS Program Healthcare Provider* (b) (4) (b) (4) *Recertification Form*.

x. Braeburn must make available the *Probuphine REMS Program Insertion/Removal Recertification Video* by XXXX. The video must be consistent with the Insertion/Removal Recertification video transcript.

C. Implementation System

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

the Probuphine REMS Program website or by calling the Probuphine REMS Program Call Center.

8. Braeburn must continuously monitor the certified prescribers and healthcare providers who are certified to insert/remove Probuphine to ensure the requirements of the Probuphine REMS Program are being met. Braeburn must institute corrective action if noncompliance is identified.

9. Braeburn must take reasonable steps to improve implementation of and compliance with the requirements in the Probuphine REMS Program based on monitoring and evaluation of the Probuphine REMS Program.

II. Probuphine REMS Materials:

General Comments:

Based on our review and revisions of the Probuphine Prescribing Information (PI) and the Probuphine REMS document, we recommend the following revisions be made to the Probuphine REMS materials.

Comments guiding their revision are included below or on the materials themselves as track change comments. Note that all REMS materials must reflect the most recent and eventually the final label, including Section 17 of the PI and the Medication Guide. The REMS materials must also align with the revised ***Probuphine Instructions for Use***.

- References to the "Probuphine REMS Program" should not be in italics, as it is not a REMS material. Make this change throughout all of the REMS materials.
- Submit each REMS material (except the training program PowerPoint slides and the REMS website screenshots) as separate MS Word documents with new track changes. Accept all track changes with which you agree and note any additional changes proposed by the applicant as new redlined track changes.
- Additionally, submit each REMS material as a separate clean MS Word version.
- Submit the training program's PowerPoint slides and the REMS website screenshots as pdf documents.
- In addition, submit revised pdf mocked up versions of all of the REMS materials reflecting graphic design principles as part of this submission. Many of the REMS materials submitted on April 6, 2016 do not reflect such principles and lack a cohesive and consistent design theme (i.e. color, font, logo, etc.) The use of good graphic design principles which are consistently presented across the REMS program materials will make them easily identifiable and more user-friendly for the stakeholders. Submitting pdf versions of the MS Word documents with minimal design is not acceptable.
- The design of all REMS materials should ensure that they are very legible when copied or printed in black and white. For example, avoid large sections of dark shaded background on all REMS materials, especially the patient guide.
- You may wish to use the graphic design theme already proposed on the Probuphine REMS website and pattern the other REMS materials after that, but still maintaining a different color-coded aspect of the enrollment and recertification forms to some extent. Note the following approved REMS programs as examples:
    - IONSYS REMS: http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=IndvRemsDetails.page&REMS=346
    - AVEED REMS: http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=IndvRemsDetails.page&REMS=313
    - SABRIL REMS: http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=IndvRemsDetails.page&REMS=346

Finally, all revised pdf versions must align with the most recent MS Word versions of each REMS material with each submission until approval.

Comments on Specific Materials

Redlined drafts of the following materials in MS Word are attached, which include comments regarding the final mocked up pdf versions as well:

a. Probuphine REMS Program Healthcare Provider Who Prescribes Enrollment Form
b. Probuphine REMS Program Healthcare Provider Who Inserts/Removes Enrollment Form
c. Probuphine REMS Program Healthcare Provider Dual Enrollment Form
d. Probuphine REMS Program Healthcare Provider (b) (4) Recertification Form
e. Probuphine REMS Program Procedure Record for Recertification
f. Probuphine REMS Criteria for Procedural Competency
g. Probuphine REMS Knowledge Assessment Test
h. Probuphine REMS Insertion/Removal Log
i. What You Need to Know about Probuphine: A Patient's Guide

Probuphine REMS Program Live Training: Lecture and Practicum

- Comments are on a separate MS Word document regarding general and slide-specific edits/comments.
- All content must be consistent with the PI, IFU, and recertification video.

REMS Website

- Comments are on a separate MS Word document regarding general and webpage-specific edits/comments.
- Answer the Agency's questions related to the REMS website in the cover letter which will accompany your next submission. This will help the Agency understand the full functionality of the REMS website.

Probuphine Medication Guide (MG)

- This was not reviewed as part of the REMS materials. However, patient messages in the MG should generally align with those in *What You Need to Know about Probuphine: A Patient's Guide.*

Probuphine Risk Messages

- Note the revised risk messages for HCPs and patients to reflect the revised REMS materials. These messages should be used to draft REMS assessment questions, as they reflect the most important messages for patients and HCPs. These Risk Messages must be incorporated into the REMS Supporting Document.

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/s/

DONELLA A FITZGERALD
04/22/2016

KIMBERLY LEHRFELD
04/22/2016

Department of Health and Human Services
Food and Drug Administration Center for
Drug Evaluation and Research Office of
Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

REMS REVIEW: INTERIM COMMENTS #3

Date:	March 22, 2016
Reviewer(s)	Donella Fitzgerald, Pharm.D., Risk Management Analyst Division of Risk Management (DRISK) Joan E. Blair, RN, MPH, Health Communications Analyst Division of Risk Management (DRISK)
Team Leader	Kim Lehrfeld, Pharm.D, DRISK
Director:	Cynthia LaCivita, Pharm.D. Division of Risk Management
Drug Name(s):	Probuphine (buprenorphine/ethylene vinyl acetate) implant
Therapeutic class and Dosage Form	Opioid Partial Agonist-antagonist subdermal implants
OND Review Division	Division of Analgesia, Anesthesia and Addiction Products
Application Type/Number:	NDA 204442
Applicant/sponsor:	Braeburn Pharmaceuticals, on behalf of Titan Pharmaceuticals, Inc.
OSE RCM #:	2015-2115

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1 INTRODUCTION

The purpose of this review is to document the evaluation and provide comments on the proposed risk evaluation and mitigation strategy (REMS) for Probuphine, NDA 204442, submitted by Braeburn Pharmaceuticals (Braeburn) on behalf of Titan Pharmaceuticals, Inc. (Titan) as a 505(b)(2) application on August 27, 2015, and amended on February 11, 2016.

1.1 BACKGROUND

Probuphine is a schedule III, buprenorphine-containing subdermal implant covered under the Drug Addiction Treatment Act of 2000 (DATA-2000). The proposed indication is for the maintenance treatment of opioid dependence. Probuphine is intended for use in patients who are opioid-tolerant and have been stabilized on a sublingual buprenorphine [redacted] (b) (4) The implants are 26mm x 2.5 mm rods, each containing 80 mg of buprenorphine HCl. Four rods are to be inserted subdermally in the inner side of the upper arm (about 8-10 cm above the medial epicondyle of the humerus) to provide sustained delivery of buprenorphine for six months. At the end of six months, implants can be inserted in the opposite arm if continued therapy is warranted.

Titan originally filed the application for Probuphine, NDA 204442, on October 31, 2012. A Complete Response was issued on April 30, 2013 for deficiencies in clinical benefit and human factors usability. The Agency recommended that the Applicant provide additional data supporting the efficacy of Probuphine, and a Human Factors study, complete with a comprehensive use-related risk analysis, for the insertion/removal training program.

Braeburn, on behalf of Titan, resubmitted Probuphine on August 27, 2015, with a proposed REMS. The resubmission included the results of a new randomized, double-blind, double-dummy Phase 3 study (PRO-814) that was conducted on 177 patients to support the clinical benefit of Probuphine in patients previously stabilized on 8mg or less of sublingual (SL) buprenorphine. The primary endpoint for PRO-814 was a responder analysis (using urine toxicology plus self-report) which evaluated the degree to which treatment with Probuphine resulted in the absence of objective evidence of opioid use. The Applicant states the proportion of responders was statistically significantly higher ($p = 0.034$), in the Probuphine group (96.4%) compared to the SL buprenorphine group (87.6%).

The Applicant stated the results of the Human Factors Study demonstrated healthcare providers with procedural experience were better able to perform the insertion procedure. An evaluation of the study has been conducted by the Division of Medication Error and Prevention Analysis (DMEPA).

The elements of the proposed REMS for Probuphine are a Medication Guide (MG), Elements to Assure Safe Use, Implementation Plan and a Timetable for Submission of Assessments.

1.2 REMS REGULATORY HISTORY

October 31, 2012: Titan submitted Probuphine, NDA 204442, with a proposed REMS (Seq. No. 0000).

February 28, 2013: A REMS Oversight Committee meeting was held to discuss the rationale for a REMS and to determine the minimum required elements.

March 21, 2013: Psychopharmacologic Drugs Advisory Committee meeting was held. The panel discussed if the proposed REMS was adequate to address the risks of complications associated with the insertion procedure and abuse, misuse and accidental overdose. The committee voted: 5-yes, 4-no and 6-abstain. The four members who voted "no" expressed concerns that providers would not be trained properly on insertion/removal. The six members that abstained noted that the Applicant presented a modified REMS that was not previously described in the briefing materials.

April 30, 2013: A Complete Response was issued for deficiencies in clinical benefit and human factors usability.

August 27, 2015: Braeburn, on behalf of Titan, resubmitted Probuphine, NDA 204442, with a proposed REMS. This submission did not include a Supporting Document (Seq. No. 0030).

January 12, 2016: A Psychopharmacologic Drugs Advisory Committee meeting was held to discuss the safety and efficacy of Probuphine. The panel discussed whether the REMS is adequate to address the risks of potential complications associated with the insertion and removal procedures, and abuse, misuse and accidental overdose. There was a vote on the following question: Does the efficacy, safety, and risk-benefit profile of Probuphine support the approval of this application for a population of patients previously stable on a regimen of sublingual buprenorphine? The committee members voted: 12-yes and 5-no.

February 11, 2016: Braeburn submitted a REMS Amendment.

February 19, 2016: The Agency issued a Major Amendment, extending the PDUFA date from February 27, 2016 to May 27, 2016.

1.3 MATERIALS INFORMING OUR REVIEW

1.3.1 SUBMISSIONS

- Braeburn, on behalf of Titan Pharmaceuticals Inc. Proposed REMS for Probuphine, received August 27, 2015 (eCTD Seq. No. 0030)
    - Amendment, received December 7, 2015 (eCTD Seq. No. 0049)
    - Amendment, received February 11, 2016 (eCTD Seq. No. 0061)

1.3.2 OTHER MATERIALS INFORMING OUR REVIEW

- Probuphine Complete Response Letter. Division of Anesthesia, Analgesia and Addiction Products (DAAAP), dated April 30, 2013
- DRISK Final REMS Review of Probuphine. Reviewer: Jason Bunting, dated April 30, 2013
- REMS Oversight Committee meeting minutes, dated February 28, 2013
- Psychopharmacologic Drugs Advisory Committee (PDAC) meeting minutes, dated March 21, 2013
- PDAC briefing materials, dated March 21, 2013
- PDAC briefing materials, dated January 12, 2016
- DMEPA Human Factors Results, Label and Labeling Review. Reviewer: Millie Shah, dated January 22, 2016

- DRISK Probuphine REMS Interim Comments. Reviewer: Donella Fitzgerald, dated November 23, 2015
- DRISK Probuphine REMS Interim Comments. Reviewer: Donella Fitzgerald, dated February 2, 2016

2 PROPOSED REMS

2.1 REMS DOCUMENT

DRISK Comments:
The Probuphine REMS document has been revised to reflect the Agency's current thinking on how REMS documents are written and is attached to this review. The REMS document will continue to be revised and reviewed internally as details continue to be negotiated with the Applicant. Therefore, the REMS document should not be considered final.

2.2 REMS GOAL

DRISK Comments:

The term "improper" should be removed from the REMS goal as serious complications could occur as a result of proper insertion and removal of Probuphine.

DRISK Recommendation:
DRISK recommends that the goal be revised to read:

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

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

b) Informing patients about the risks of complications of migration, protrusion, expulsion and nerve damage associated with insertion and removal, as well as, the risks of accidental overdose, misuse and abuse if an implant comes out or protrudes from the skin

2.3 REMS ELEMENTS

2.3.1 Medication Guide

The MG is currently under review by The Office of New Drugs, Division of Labeling. DRISK has no comments at this time.

2.3.2 Elements to Assure Safe Use

2.3.2.1 Heathcare Providers who Dispense[1] Certification

Recertification of HCPs who Insert/Remove

The Agency and Braeburn previously agreed that HCPs who Insert/Remove have different recertification requirements depending upon their experience over the past year. The Agency recommended that HCPs who Insert/Remove with operating privileges could recertify every two years. This differed from HCP without operating privileges who would recertify annually. HCPs with operating privileges would still need to annually interact with the REMS Program in order to submit an attestation stating they have current operating privileges, even though their recertification is required every two years. Therefore, this option would still result in annual burden even if recertification is only required every 2 years.

As a result, the review team believes requiring all HCP to recertify annually will prevent confusion by making the recertification timeframe consistent among all HCPs who Insert/Remove. Furthermore, annual recertification will provide assurance that safe use conditions for Probuphine are being reinforced yearly for all HCPs. Finally, this does not impose additional unnecessary burden since, in the initial proposal, HCPs with operating privileges would still need to contact the Probuphine REMS program annually. DRISK recommends HCPs who expect to complete at least 10 successful procedures annually and, therefore, intend to recertify via video, track the number of successful Probuphine insertion and removals they perform over the year. In order for Braeburn to verify these HCPs who Insert/Remove are compliant with the REMS recertification requirement which states they must have performed at least 10 successful procedures (comprised of at least 5 insertion and 5 removals), Braeburn must perform a specified amount of annual audits to confirm HCPs have competed the required number of procedures.

DRISK Recommendations:

Braeburn must revise the REMS document and materials to reflect an annual recertification requirement for all HCPs who Insert/Remove Probuphine. Braeburn must also add to the REMS materials the recommendation that HCPs who expect to complete at least 10 successful procedures (comprised of at least 5 insertions and 5 removals) annually and, therefore, intend to recertify via video, track the number of successful Probuphine insertion and removals they perform over the year. The following chart summarizes the recommended recertification requirements.

Healthcare Professional Background	**Recertification Requirements[1]**
I have current operating privileges at hospitals or ou patient surgical centers	I must review the *Probuphine Insertion/Removal Recertification Video* found on the Probuphine REMS website **every year.**
I have no operating privileges at hospitals or out-patient surgical centers, and in the past 12 months I have:	
Performed 10 or more successful* procedures (comprised of at least 5 insertions and 5 removals)	I must review the *Probuphine Insertion/Removal Recertification Video* found on the Probuphine REMS website **every year.** I understand I should keep documentation of all successfu completed procedures on the Probuphine REMS Program Procedure Record for Recertification or another record of your choosing which must be provided to the Probuphine REMS Program if I am audited.
Performed less than 10 successful* procedures (comprised of at least 5 implantations and 5 removals)	I must: • attend a *Probuphine REMS Program Live Trainir 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*

* "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.

Additionally, Braeburn must annually audit 10% or a total of 15 of these certified inserter/remover HCPs, whichever is greater.

To facilitate the new recommendation for HCP to track successful procedures and the new auditing requirements, Braeburn must create a new form entitled, "Probuphine REMS Program Procedure Record for Recertification". The purpose of the form is to serve as an optional tool for HCP who Insert/Remove to document the procedures they have completed. This form (or other documentation of the HCP's choosing) must be provided to the REMS Program by the HCPs if they are audited. This form must be available on the REMS website and also attached as an appendix to the Probuphine REMS Program Healthcare Provider (b) (4) *Recertification Form. See Section 5: Comments for the Applicant, for details on the form.*

2.3.2.2 Healthcare Setting Certification

As the REMS Document is reviewed within the Agency, additional revisions have been made. Previously, the Implementation System section of the Probuphine REMS document stated that wholesalers/distributors must ship Probuphine to certified Probuphine prescribers. However per FDAAA, the Implementation System only applies to either certified dispensers (ETASU B) or specific healthcare settings (ETASU C). In order to address this limitation of the Implementation System and ensure Probuphine is shipped to the appropriate certified practitioners, revise the REMS document to reflect that Probuphine must be inserted/removed only in a healthcare setting in which a certified prescriber is also practicing. We do not believe the addition of ETASU C fundamentally changes any aspect of the program. Rather, this change aligns with FDAAA and how Braeburn plans to operationalize the Probuphine REMS Progam.

DRISK Recommendations

Include Healthcare Setting Certification in the REMS document (see attached redlined REMS document).

2.3.3 Implementation System

Recertification of HCPs who Insert/Remove

DRISK Recommendation:
The Implementation System must be revised to state Braeburn will ensure HCP who Insert/Remove can recertify as required, as recommended above (section 2.3.2.1).

2.3.4 Timetable for Submission of Assessments

No comments at this time.

2.3.5 Supporting Document

(b) (4)

Assessment Plan

The Assessment Plan is currently under review. There are no comments at this time.

3 CONCLUSION

DRISK recommends changes to the goals, ETASU, Implementation System and Supporting Document of the proposed Probuphine REMS. We have commented on the recommended changes and provided our rationale. The MG is currently under review by the Office of New Drugs, Division of Labeling.

4 RECOMMENDATIONS

DRISK advises that the above recommendations for the proposed Probuphine REMS, NDA 204442, be shared with the Applicant along with comments below *(Section 5: Comments for*

the Applicant). DRISK requests that the Applicant respond to these comments within 6 days of receiving them, to facilitate further review of this submission. The comments below are based on DRISK's ongoing review.

5 COMMENTS FOR THE APPLICANT

The Agency has reviewed the proposed Probuphine REMS materials submitted on February 11, 2016. Based on our review and revisions of the Probuphine Prescribing Information (PI) and the Probuphine REMS document, we recommend the following revisions be made to the Probuphine REMS materials.

Comments guiding their revision are included below or on the materials themselves as track change comments. Note that all REMS materials must reflect the most recent and eventually the final label, including Section 17 of the PI and the Medication Guide. The REMS materials must also align with the revised ***Probuphine Instructions for Use***.

I. Submission Instructions:

Submit the revised REMS document, the REMS supporting document, and revised REMS materials (excluding the video script and video) to your application (via the Gateway) by COB, **April 4, 2016**.

- Submit each REMS material (except the training program PowerPoint slides and the REMS website screenshots) as separate MS Word documents with new track changes. Accept all track changes with which you agree and note any additional changes proposed by the applicant as new redlined track changes.
- Additionally, submit each REMS material as a separate clean MS Word version.
- Submit the training program's PowerPoint slides and the REMS website screenshots as pdf documents.
- In addition, submit pdf mocked up versions of all of the REMS materials reflecting graphic design principles as part of this submission.

II. Additional Questions:

In several places throughout the REMS training materials, there are references to multiple Probuphine "kits". It is our understanding that the Probuphine implants, applicator and written materials (including the PI, MG, IFU, Patient ID card, and Chart Sticker) comprise one kit. In addition, the Applicant's proposed REMS materials mention 2 other optional kits: the insertion kit and removal kit.

a. Describe the contents of each of the three kits.
b. Confirm that, (b) (4) each "kit" which contains the Probuphine implants has a clearly marked serial number for tracking purposes. How will the serial number be noted so that HCP who Insert/Remove can easily find this number to record on the *Probuphine REMS Insertion/Removal Log* and the *Probuphine REMS Procedure Record for Recertification Form*?
c. Describe how Braeburn plans to provide each of the specific types of certified HCPs with the X-clamp which is to be used in the removal procedure.
    i. Which of the 3 kits will contain the X-clamp?
    ii. If it won't be included in any of the "kits", will it be provided automatically with every Probuphine order or only the initial purchase?
    iii. Will it be available "upon request" to certified HCPs?

III. General Comments:

a. The Agency noted that the term "didactic" should be replaced by the term "lecture" since this accurately describes the presentation of the slides that is the first component of the live REMS training. Remove "didactic" from all REMS materials. To more clearly define the components of the REMS live training session, we recommend that you change the title of the live training sessions throughout all of the REMS materials, REMS Document, and REMS Supporting Document to: ***Probuphine REMS Program Live Training: Lecture and Practicum.***

b. The following materials will be reviewed outside of the REMS review. However, all references to Patient ID Card and Patient Chart Sticker must be consistently noted with the same titles throughout all of the REMS materials. This includes:
   i. **Patient ID Card:** This is referenced on training slides 22 and 42, in the training video frame 35 and 37 as components of the Probuphine Kit, and in the Criteria for Procedural Competency Checklist
   ii. **Patient Chart Sticker** (also called Patient Chart Label?): This is referenced on training slides 22 and 42 and in the training video frame 35 and 37 as components of the Probuphine Kit, and in the Criteria for Procedural Competency
   iii. (b) (4) (b) (4)

c. Note the exact titles of the REMS materials, which is how they should be presented consistently in all of the REMS materials and documents. In addition, be consistent throughout all of the REMS materials in your wording of "**insert/remove**" vs." insert or remove" and "**insert**" vs "implant" and "**implants**" vs. "rods." The words in **bold** text are preferred, other than in the patient materials.

d. All references to prerequisites for Inserters/Removers to attend the training session should align with the PI as follows: "As a prerequisite for participating in the live training program, the Healthcare Provider must have performed a surgical procedure in the last 3 months. Qualifying procedures should be performed under local anesthesia using aseptic technique, and include, but are not limited to, making skin incisions, or placing sutures. "

IV. REMS Document

The Probuphine REMS document has been revised to reflect the Agency's current thinking on how REMS documents are written and is attached to this review. The REMS document will continue to be revised and reviewed internally as details continue to be negotiated with the Applicant. Therefore, the REMS document should not be considered final.

a. REMS Goal

The term "improper" should be removed from the REMS goal as serious complications could occur as a result of proper insertion and removal of Probuphine. The revised goal should read:

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

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

b) Informing patients about the risks of complications of migration, protrusion, expulsion and nerve damage associated with insertion and removal, as well as, the risks of accidental overdose, misuse and abuse if an implant comes out or protrudes from the skin

b. Pharmacy Certification/Healthcare Providers who Dispense Certification(ETASU B)

Recertification of HCPs who Insert/Remove

The Agency and Braeburn previously agreed that HCPs who Insert/Remove have different recertification requirements depending upon their experience over the past year. The Agency recommended that HCPs who Insert/Remove with operating privileges could recertify every two years. This differed from HCP without operating privileges who would recertify annually. However, HCPs with operating privileges would still need to annually interact with the REMS Program in order to submit an attestation stating they have current operating privileges, even though their recertification is required every two years. Therefore, this option would still result in annual burden even if recertification is only required every 2 years.

As a result, the review team believes requiring all HCP to recertify annually will prevent confusion by making the recertification timeframe consistent among all HCPs who Insert/Remove. Furthermore, annual recertification will provide assurance that safe use conditions for Probuphine are being reinforced yearly for all HCPs. Finally, this does not impose additional unnecessary burden since, in the initial proposal, HCPs with operating privileges would still need to contact the Probuphine REMS program annually.

The Agency has revised the REMS document and materials to reflect an annual recertification requirement for all HCPs who Insert/Remove Probuphine. See appended, redlined REMS document and materials.

In addition, the Agency has revised the REMS materials to include the recommendation that HCPs who expect to complete at least 10 successful procedures (comprised of at least 5 insertions and 5 removals) annually and, therefore, intend to recertify via video, track the number of successful Probuphine insertion and removals they perform over the year.

The following chart, which is also included in the appended *Probuphine REMS Program Healthcare Provider* (b) (4) *Recertification Form*, summarizes the revised recertification requirements.

Healthcare Professional Background	**Recertification Requirements[1]**
I have current operating privileges at hospitals or out-patient surgical centers	I must review the *Probuphine Insertion/Removal Recertification Video* found on the Probuphine REMS website **every year.**
I have no operating privileges at hospitals or out-patient surgical centers, and in the past 12 months I have:	

Performed 10 or more successful* procedures (comprised of at least 5 insertions and 5 removals)	I must review the *Probuphine Insertion/Removal Recertification Video* found on the Probuphine REMS website **every year.** I understand I should keep documentation of all successfully completed procedures on the Probuphine REMS Program Procedure Record for Recertification or another record of your choosing which must be provided the Probuphine REMS Program if I am audited.
Performed less than 10 successful* procedures (comprised of at least 5 implantations and 5 removals)	I must: • 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*

* "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.

To facilitate the new recommendation for HCP to track successful procedures and the new auditing requirements, create a new form titled, "*Probuphine REMS Program Procedure Record for Recertification*". The purpose of the form is to serve as an optional tool for HCP who Insert/Remove to document the procedures they have completed. This form (or other documentation of the HCP's choosing) must be provided to the REMS Program by the HCPs if they are audited. This form must be available on the REMS website and also attached as an appendix to the *Probuphine REMS Program Healthcare Provider* (b) (4) *Recertification Form*. See Section V. Probuphine REMS Materials, e. *Probuphine REMS Program Procedure Record for Recertification* for details on the form.

In order to verify that HCPs who Insert/Remove are compliant with the REMS recertification requirements, Braeburn must perform annual audits of HCPs who Insert/Remove and do not have operating privileges. Braeburn must annually audit 10% or a total of 15 of these certified HCPs who insert/remove, whichever is greater. See appended, redlined REMS document and enrollment forms for details related to the audit requirement.

c. <u>Distribution Limited to Specific Healthcare Settings (ETASU C)</u>

Previously, the Implementation System section of the Probuphine REMS document stated that wholesalers/distributors must ship Probuphine to certified Probuphine prescribers. However per FDAAA, the Implementation System only applies to either certified dispensers (ETASU B) or specific healthcare settings (ETASU C). In order to address this limitation of the Implementation System and ensure Probuphine is shipped to the appropriate certified practitioners, revise the REMS document to reflect that Probuphine must be inserted/removed only in a healthcare setting in which a certified prescriber is also practicing. We do not believe the addition of ETASU C fundamentally changes any aspect of the program. Rather, this change aligns with FDAAA and how Braeburn plans to operationalize the Probuphine REMS Program. See appended, redlined REMS document for details.

d. Implementation System

Recertification of HCPs who Insert/Remove

The Implementation System must be revised to state Braeburn will ensure HCP who Insert/Remove can recertify as required.

V. REMS Supporting Document

(b) (4)

(b) (4)

VI. Probuphine REMS Materials (Specific Comments):

a. Probuphine REMS Program Healthcare Provider Who Prescribes Enrollment Form

- Color code this form in the final pdf version for easy identification
- A redlined draft is attached with additional edits.

b. Probuphine REMS Program Healthcare Provider Who Inserts/Removes Enrollment Form

- Color code this form in the final pdf version for easy identification
- A redlined draft is attached with additional edits.

c. Probuphine REMS Program Healthcare Provider Dual Enrollment Form

- Color code this form in the final pdf version for easy identification
- A redlined draft is attached with additional edits.

d. Probuphine REMS Program Healthcare Provider (b) (4) **Recertification Form**

- Color code this form in the final pdf version for easy identification
- A redlined draft is attached with additional edits.
- Note the revised recertification requirements on this form, which should be reflected in the training slides and REMS website content.

e. Probuphine REMS Program Procedure Record for Recertification *new!* (MS Word and pdf graphic design version need to be created)

- In order to verify that HCPs who Insert/Remove are compliant with the REMS recertification requirements, Braeburn must perform annual audits of HCPs who Insert/Remove and do not have operating privileges.

- To facilitate auditing, create a new form entitled, ***Probuphine REMS Program Procedure Record for Recertification.*** The purpose of the form is to serve as an optional tool for inserters/removers to document the procedures they have completed. This form can be provided to the REMS Program for documentation by the HCPs if they are audited. This form must be available on the REMS website and also attached as an appendix to the ***Probuphine REMS Program Healthcare Provider*** (b) (4)

[redacted](b) (4) ***Recertification Form.*** The new form would not include patient-specific information - only information about the inserter/remover and the number of procedures he/she has completed within the last 12 months, as documented by serial number.

- This new form should include spaces for the following information:
  - Name of inserter/remover
  - Location (practice name/address) of insertion/removal procedure
  - Date of each insertion/removal procedure
  - Serial Number
  - The following attestation:

"I attest that the insertion/removal procedures noted above were successful. "Successful" implantation and removal procedures exclude attempted procedures that require assistance of other surgical specialists 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."

  - Signature of inserter/remover

f. Probuphine REMS Program Live Training: Lecture and Practicum

- Note the new title
- Comments are on a separate MS Word document regarding general and slide-specific edits/comments.
- All content must be consistent with the PI, IFU, and recertification video.

g. Probuphine REMS Criteria for Procedural Competency

- A redlined draft is attached with additional edits.

h. Probuphine REMS Knowledge Assessment Test

- A redlined draft is attached with additional edits.

i. Probuphine REMS Insertion/Removal Log

- A redlined draft is attached with additional edits and multiple comments, including a bulleted list of information that should be collected using this form.

j. Probuphine Medication Guide

- Patient messages in MG must align with those in ***What You Need to Know about Probuphine: A Patient's Guide***.
- Agency comments will be forthcoming at a later date as part of the review of the PI.

k. What You Need to Know about Probuphine: A Patient's Guide (previously referred to as the Patient Counseling Tool)

- Note the ***new*** patient-friendly title: ***What You Need to Know about Probuphine: A Patient's Guide***.
- See specific track changes on the document.
- This tool should focus on the risks the REMS is intended to mitigate.

l. REMS Website

- Note additional track change comments and edits on separate the MS Word document.

m. Probuphine REMS Program Insertion/Removal Recertification Video

- Note the revised title
- All content must be consistent with the PI, IFU, and training slides.
- Note track change comments on the training video script you submitted.
- The Agency agrees that the primary purpose of this video is to enable the recertification of inserters/removers who have current operating privileges or those without operating privileges who have performed 10 or more successful procedures (consisting of at least 5 successful insertions and 5 removals) within the last 12 months.
- Topics of the video(s) would be:
  - Insertion Procedure
  - Removal Procedure
  - Managing Complications
    - Insertion
    - Removal
    - Post-insertion care and follow-up
- This must be placed on the website for viewing or downloading for recertification, if applicable.

n. Risk Message Map

- Note the revised Risk Message Map, with changes to the risk messages for HCPs and patients. These have already been integrated into the REMS materials, with the exception of the training slides.

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/s/

DONELLA A FITZGERALD
03/23/2016

KIMBERLY LEHRFELD
03/24/2016

Department of Health and Human Services
Food and Drug Administration Center for
Drug Evaluation and Research Office of
Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

REMS REVIEW: INTERIM COMMENTS #2

Date:	February 2, 2016
Reviewer(s)	Donella Fitzgerald, PharmD, Risk Management Analyst Division of Risk Management (DRISK) Joan E. Blair, RN, MPH, Health Communications Analyst Division of Risk Management (DRISK)
Team Leader	Kim Lehrfeld, Pharm.D, DRISK
Director:	Claudia Manzo, Pharm.D Division of Medication Error Prevention and Risk Management
Drug Name(s):	Probuphine (buprenorphine/ethylene vinyl acetate) implant
Therapeutic class and Dosage Form	Opioid Partial Agonist-antagonist subdermal implants
OND Review Division	Division of Analgesia, Anesthesia and Addiction Products
Application Type/Number:	NDA 204442
Applicant/sponsor:	Braeburn Pharmaceuticals, on behalf of Titan Pharmaceuticals, Inc.
OSE RCM #:	2015-2115

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1 INTRODUCTION

The purpose of this review is to document the evaluation and provide comments on the proposed risk evaluation and mitigation strategy (REMS) for Probuphine, NDA 204442, submitted by Braeburn Pharmaceuticals (Braeburn) on behalf of Titan Pharmaceuticals, Inc. (Titan) on August 27, 2015, as a 505(b)(2) application.

1.1 BACKGROUND

Probuphine is a schedule III, buprenorphine-containing subdermal implant covered under the Drug Addiction Treatment Act of 2000 (DATA-2000). The proposed indication is for the maintenance treatment of opioid dependence. Probuphine is intended for use in patients who are opioid-tolerant and have been stabilized on a sublingual buprenorphine [redacted] (b) (4) The implants are 26mm x 2.5 mm rods, each containing 80 mg of buprenorphine HCl. Four rods are to be inserted subdermally in the inner side of the upper arm (about 8-10 cm above the medial epicondyle of the humerus) to provide sustained delivery of buprenorphine for six months. At the end of six months, implants can be inserted in the opposite arm if continued therapy is warranted.

Titan originally filed the application for Probuphine, NDA 204442, on October 31, 2012. A Complete Response was issued on April 30, 2013 for deficiencies in clinical benefit and human factors usability. The Agency recommended that the Applicant provide additional data supporting the efficacy of Probuphine, and a Human Factors study, complete with a comprehensive use-related risk analysis, for the insertion/removal training program.

Braeburn, on behalf of Titan, resubmitted Probuphine on August 27, 2015, with a proposed REMS. The resubmission included the results of a new randomized, double-blind, double-dummy Phase 3 study (PRO-814) that was conducted on 177 patients to support the clinical benefit of Probuphine in patients previously stabilized on 8mg or less of sublingual (SL) buprenorphine. The primary endpoint for PRO-814 was a responder analysis (using urine toxicology plus self-report) which evaluated the degree to which treatment with Probuphine resulted in the absence of objective evidence of opioid use. The Applicant states the proportion of responders was statistically significantly higher ($p = 0.034$), in the Probuphine group (96.4%) compared to the SL buprenorphine group (87.6%).

The Applicant stated the results of the Human Factors Study demonstrated healthcare providers with procedural experience were better able to perform the insertion procedure. An evaluation of the study has been conducted by the Division of Medication Error and Prevention Analysis (DMEPA).

The elements of the proposed REMS for Probuphine are a Medication Guide (MG), Elements to Assure Safe Use, Implementation Plan and a Timetable for Submission of Assessments.

1.2 REMS REGULATORY HISTORY

October 31, 2012: Titan submitted Probuphine, NDA 204442, with a proposed REMS (Seq. No. 0000).

February 28, 2013: A REMS Oversight Committee meeting was held to discuss the rationale for a REMS and to determine the minimum required elements.

March 21, 2013: Psychopharmacologic Drugs Advisory Committee meeting was held. The panel discussed if the proposed REMS was adequate to address the risks of complications associated with the insertion procedure and abuse, misuse and accidental overdose. The committee voted: 5-yes, 4-no and 6-abstain. The four members who voted "no" expressed concerns that providers would not be trained properly on insertion/removal. The six members that abstained noted that the Applicant presented a modified REMS that was not previously described in the briefing materials.

April 30, 2013: A Complete Response was issued for deficiencies in clinical benefit and human factors usability.

August 27, 2015: Braeburn, on behalf of Titan, resubmitted Probuphine, NDA 204442, with a proposed REMS. This submission did not include a Supporting Document (Seq. No. 0030).

January 12, 2016: A Psychopharmacologic Drugs Advisory Committee meeting was held to discuss the safety and efficacy of Probuphine. The panel discussed whether the REMS is adequate to address the risks of potential complications associated with the insertion and removal procedures, and abuse, misuse and accidental overdose. There was a vote on the following question: Does the efficacy, safety, and risk-benefit profile of Probuphine support the approval of this application for a population of patients previously stable on a regimen of sublingual buprenorphine? The committee members voted: 12-yes and 5-no.

1.3 MATERIALS INFORMING OUR REVIEW

1.3.1 SUBMISSIONS

- Braeburn, on behalf of Titan Pharmaceuticals Inc. Proposed REMS for Probuphine, received August 27, 2015 (Seq. No. 0030)

1.3.2 OTHER MATERIALS INFORMING OUR REVIEW

- Probuphine Complete Response Letter. Division of Anesthesia, Analgesia and Addiction Products (DAAAP), dated April 30, 2013
- DRISK Final REMS Review of Probuphine. Reviewer: Jason Bunting, dated April 30, 2013
- REMS Oversight Committee meeting minutes, dated February 28, 2013
- Psychopharmacologic Drugs Advisory Committee (PDAC) meeting minutes, dated March 21, 2013
- PDAC briefing materials, dated March 21, 2013
- PDAC briefing materials, dated January 12, 2016
- DMEPA Human Factors Results, Label and Labeling Review. Reviewer: Millie Shah, dated January 22, 2016

2 PROPOSED REMS

2.1 GOAL

DRISK Comments:

The REMS goal should include an objective to require training on the proper insertion and removal of Probuphine.

DRISK Recommendation:
DRISK recommends that the goal be revised to read:

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

a) Ensuring that healthcare providers are educated on the following:

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

b) Informing patients about the risks of complications of migration, protrusion, expulsion and nerve damage associated with improper insertion and removal, as well as, the risks of accidental overdose, misuse and abuse if an implant comes out or protrudes from the skin

2.1 REMS DOCUMENT

The Probuphine REMS document has been revised to reflect the Agency's current thinking on how REMS documents are written and is attached to this review. The REMS document will continue to be revised and reviewed internally as details continue to be negotiated with the Applicant. Therefore, the REMS document should not be considered final.

2.2 REMS ELEMENTS

2.2.1 Medication Guide

The MG is currently under review by The Office of New Drugs, Division of Labeling. DRISK has no comments at this time.

2.2.2 Elements to Assure Safe Use

2.2.2.1 Healthcare Providers who Prescribe Certification

No comments at this time.

2.2.2.2 Heathcare Providers who Dispense[1] Certification

DRISK Comments:

Based upon feedback received in the Advisory Committee Meeting about training program concerns and DMEPA's review of the Human Factor's Study, the Agency has concluded that practitioners with recent procedural experience would be best suited to safely perform the Probuphine Insertion and Removal procedure.

Advisory Committee panel members also raised concerns about the absence of a recertification requirement for Inserters/Removers. This same concern was expressed in DMEPA's evaluation of the Human Factor Study results.

In the original email submission of the Applicant's draft slides for the AC meeting, there was a slide (b) (4) *This slide was removed from the Applicant's final slide deck after DRISK expressed concern that* (b) (4) *was not included in the proposed REMS or Supporting Document,* (b) (4) *It is unclear to DRISK* (b) (4)

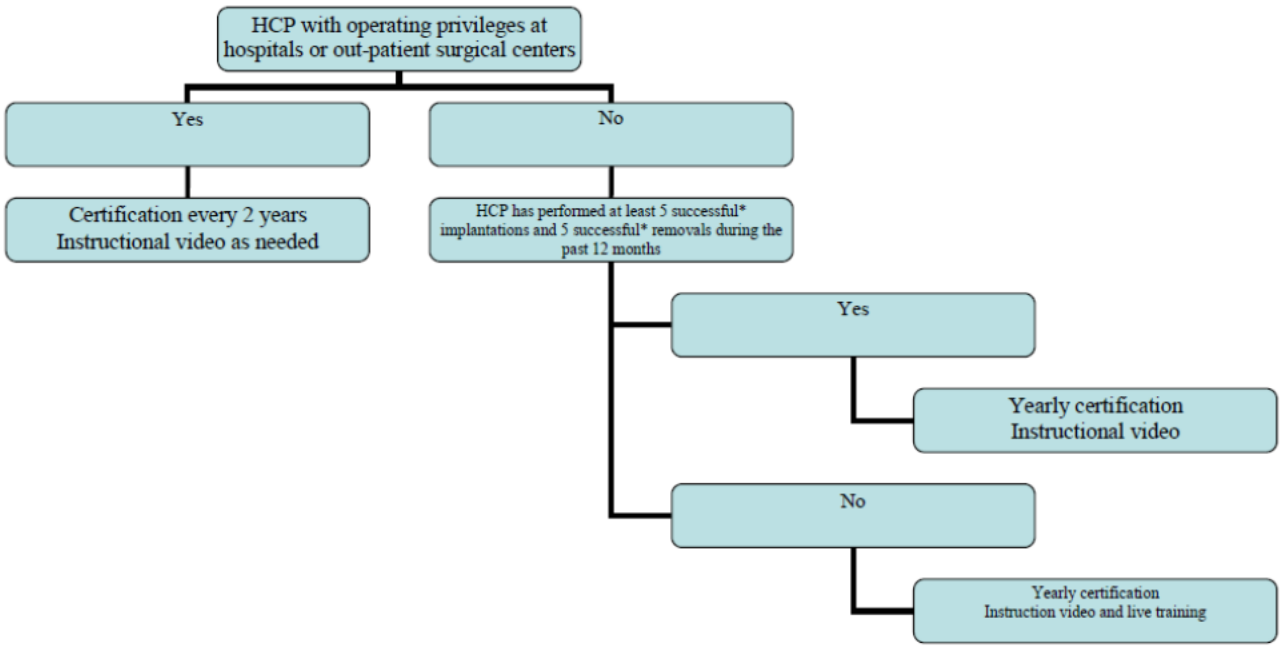
DRISK Recommendations:

Prerequisite for HCPs who Insert/Remove
DRISK recommends that the requirement of having performed a sterile procedure in the last 3 months, which includes (but is not limited to) using aseptic technique, injecting local anesthetic, making skin incisions, placing sutures, and removing foreign objects be included as a prerequisite for HCP to attend the training to certify as an Inserter/Remover of Probuphine. In addition, HCP who Insert/Remove must attest to having met this prerequisite at the time of enrollment in the Probuphine REMS Program.

Reinforcement of the Probuphine REMS Training Program
DRISK recommends the development of an instructional training video(s) to reinforce the skills learned at the Live Practicum Training. Three topics should be covered in the video(s): Insertion, Removal and Managing Complications. The video should show the procedures being conducted on a live model, and should be available online and for distribution to HCPs.

Recertification of HCPs who Insert/Remove
DRISK recommends that the Applicant include a recertification requirement for HCP who Insert/Remove Probuphine. Braeburn should provide a detailed explanation in the Supporting Document for whom the recertification requirement would apply and how the recertification process would be operationalized (via video or live training). The Agency's proposed recertification requirements are outlined below in the diagram. Note that some HCP may be able to recertify by reviewing online materials while others will need to attend live training. It is possible the Instructional Training Video(s) used to reinforce the REMS Training Program could be used to fulfill the recertification requirement, as well.

RECERTIFICATION REQUIREMENTS ALGORITHM



* "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.

Consider the use of a diagram such as one provided above to help explain the recertification requirements in the REMS Supporting Document and REMS materials, where applicable.

2.2.3 Implementation System

DRISK Recommendations:

Prerequisite for HCPs who Insert/Remove

The Implementation System must be revised to state that Braeburn will ensure HCP who Insert/Remove meet the prerequisite requirement for Inserter/Remover training, as recommended above (section 2.2.2.2).

Recertification of HCPs who Insert/Remove

The Implementation System must be revised to state Braeburn will ensure HCP who Insert/Remove can recertify as required, as recommended above (section 2.2.2.2).

Probuphine Insertion Procedure Locations

Braeburn should consult (b) (4) *If Braeburn decides* (b) (4) (b) (4) *the Applicant needs to include detailed information in the proposed REMS and Supporting Document.*

First Procedure Observation

Advisory Committee panel members discussed the limitations of using the pork loin model in the Live Practicum Training. A recommendation was made to require the observation of a Master Trainer during the first insertion/removal procedure. The first procedure observation is not necessary for all HCPs to ensure the safe use of Probuphine. However, Braeburn must offer HCP who Insert/Remove Probuphine the option to have their first insertion or removal procedure

observed since the Probuphine REMS training program does not offer training on a live patient. The Implementation System must be revised to state Braeburn will offer this additional support to newly certified HCP who Insert/Remove. Consider how this process would be coordinated and describe it in the REMS Supporting Document.

2.2.4 Timetable for Submission of Assessments

No comments at this time.

2.2.5 Supporting Document

(b) (4)

Additional Recommendations from section 2.2.2.2:

Prerequisite for HCPs who Insert/Remove
Inclusion of a prerequisite for Inserter/Remover training, as recommended above (section 2.2.2.2), would require a detailed explanation of how Braeburn would ensure this condition was met for each HCP before attending the Live Didactic and Practicum Training.

First Procedure Observation
Inclusion of an optional First Procedure Observation, as recommended above (section 2.2.2.2), would require a detailed explanation of how this process would be coordinated.

Probuphine Insertion Procedure Locations
If Braeburn decides to incorporate (b) (4) *(see section*

2.2.2.2), the Applicant needs to include detailed procedures (b) (4)

Recertification of HCPs who Insert/Remove
Inclusion of a recertification requirement, as recommended above (section 2.2.2.2), would require a detailed explanation of for whom it applies and how the recertification process would be handled.

3 CONCLUSION

DRISK recommends changes to the goals, ETASU, Implementation System and Supporting Document of the proposed Probuphine REMS. We have commented on the recommended changes and provided our rationale. The MG is currently under review by the Office of New Drugs, Division of Labeling.

4 RECOMMENDATIONS

DRISK advises that the above recommendations for the proposed Probuphine REMS, NDA 204442, be shared with the Applicant along with comments below *(Section 5: Comments for the Applicant*). DRISK requests that the Applicant respond to these comments within 14 days of receiving them, to facilitate further review of this submission. The comments below are based on DRISK's ongoing review.

5 COMMENTS FOR THE APPLICANT

The Agency has reviewed the proposed Probuphine REMS document, REMS Supporting document, and REMS materials submitted on December 7, 2015. Based on our review, discussion at the recent Advisory Committee, and revisions of the REMS goals and REMS document, we recommend the following revisions be made to the Probuphine REMS materials, including the addition of two new REMS materials.

Comments guiding their revision are included below or on the materials themselves as track change comments. Please note that all REMS materials must reflect the most recent and eventually the final label, including Section 17 of the PI and the Medication Guide. The REMS materials must also align with the revised ***Probuphine Instructions for Use*** based on recent comments sent by FDA to the sponsor.

Submit the revised REMS document, the REMS Supporting Document and revised materials to your application (via the Gateway) within 14 business days. Provide each REMS material noted above as a separate MS Word document with new track changes and as a separate clean MS Word version. Please accept all track changes with which you agree and noting any additional changes proposed by the applicant as new redlined track changes. Final pdf mocked up versions of the REMS materials are not required at this time as part of this submission.

I. REMS Document

The Probuphine REMS document has been revised to reflect the Agency's current thinking on how REMS documents are written and is attached to this review. The REMS document will continue to be revised and reviewed internally as details continue to be negotiated with the Applicant. Therefore, the REMS document should not be considered final.

a. REMS Goal

The goal of the REMS should be revised to include an objective to require training on the proper insertion and removal of Probuphine.

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

a) Ensuring that healthcare providers are educated on the following:

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

b) Informing patients about the risks of complications of migration, protrusion, expulsion and nerve damage associated with improper insertion and removal, as well as, the risks of accidental overdose, misuse and abuse if an implant comes out or protrudes from the skin

b. <u>Pharmacy Certification / Heathcare Providers who Dispense Certification (ETASU B)</u>

Prerequisite for HCPs who Insert/Remove

DRISK recommends that the requirement of having performed a sterile procedure in the last 3 months, which includes (but is not limited to) using aseptic technique, injecting local anesthetic, making skin incisions, placing sutures, and removing foreign objects be included as a prerequisite for HCP to attend the training to certify as an Inserter/Remover of Probuphine. (*Note*: This language, that will be included in the Probuphine PI, is currently under review by the Division of Analgesia, Anesthesia, and Addiction Products and may be further revised. The REMS materials must match the final, agreed upon PI.) In addition, HCPs who Insert/Remove must attest to having met this prerequisite at the time of enrollment in the Probuphine REMS Program. Revise the REMS document and the appropriate HCP Enrollment Forms to reflect this new prerequisite requirement.

Probuphine Insertion Procedure Locations

In the original email submission of the Applicant's draft slides for the AC meeting, there was a slide (b) (4) This slide was removed from the Applicant's final slide deck after DRISK expressed concern that the delivery concept was not included in the proposed REMS or Supporting Document (b) (4) It is unclear to DRISK (b) (4) If Braeburn decides (b) (4) the Applicant needs to include detailed information in the proposed

REMS Document and Supporting Document.

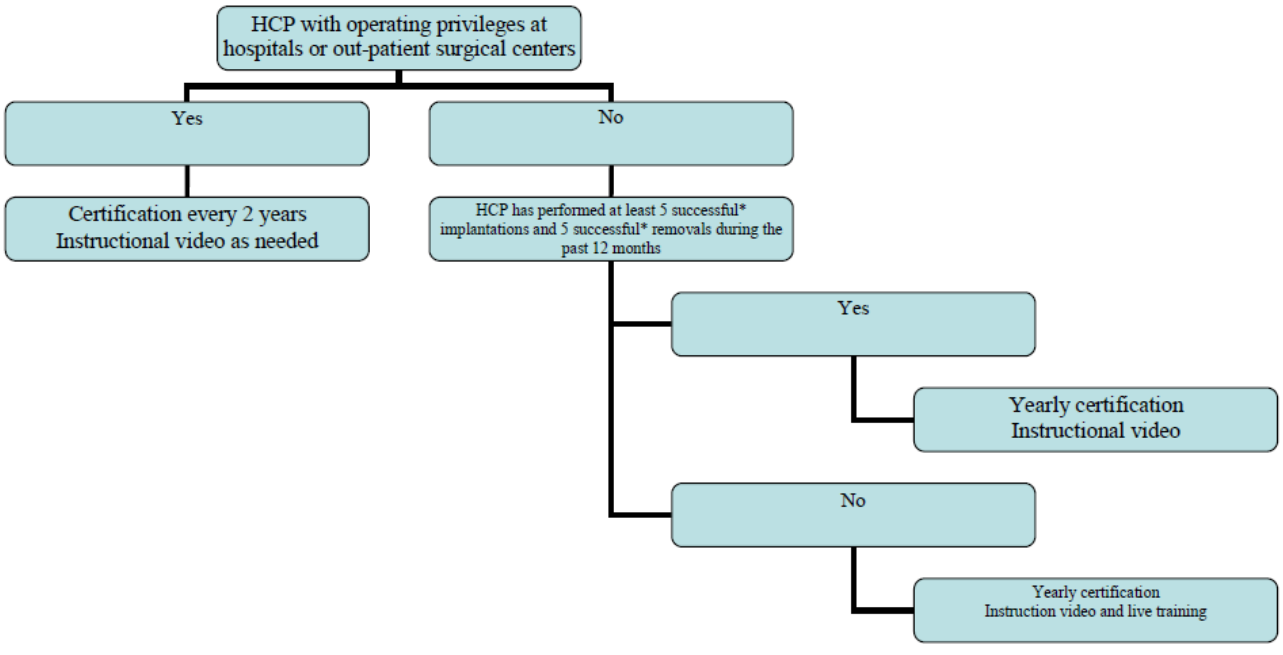
Reinforcement of the Probuphine REMS Training Program

DRISK recommends the development of an Instructional Training Video(s) to reinforce the skills learned at the Live Practicum Training. Three topics should be covered in the video(s): Insertion, Removal and Managing Complications. The video should show the procedures being conducted on a live model, and should be available on-line and for distribution to HCP. For additional information, see details on the **Instructional Training Videos** under **Probuphine REMS Materials** below.

Recertification of HCPs who Insert/Remove

DRISK recommends that the Applicant include a recertification requirement for HCP who Insert/Remove Probuphine. Braeburn should provide a detailed explanation in the Supporting Document for whom the recertification requirement would apply and how the recertification process would be operationalized (via video or live training). The Agency's proposed recertification requirements are outlined below in the diagram. Note that some HCP may be able to recertify by reviewing online materials while others will need to attend live training. It is possible the Instructional Training Video(s) used to reinforce the REMS Training Program could be used to fulfill the recertification requirement, as well.

RECERTIFICATION REQUIREMENTS ALGORITHM



* "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.

c. Implementation System

DRISK has the following comments on the Implementation System:

Prerequisite for HCPs who Insert/Remove

The Implementation System must be revised to state that Braeburn will ensure HCP who Insert/Remove meet the prerequisite requirement for Inserter/Remover training, as recommended above.

First Procedure Observation

Advisory Committee panel members expressed the limitations of using the pork loin model in the Live Practicum Training. A recommendation was made to require the observation of a Master Trainer during the first insertion/removal procedure. The Agency does not feel first procedure observation is necessary for all HCPs to ensure the safe use of Probuphine. However, Braeburn must offer HCP who Insert/Remove Probuphine the option to have their first insertion or removal procedure observed since the Probuphine REMS training program does not offer training on a live patient. The Implementation System must be revised to state Braeburn will offer this additional support to newly certified HCP who Insert/Remove. Consider how this process would be coordinated and describe it in the REMS Supporting Document.

Recertification of HCPs who Insert/Remove

The Implementation System must be revised to state Braeburn will ensure HCP who Insert/Remove can recertify as required, as recommended above.

d. Timetable for Submission of Assessments

DRISK has no comments on the Timetable for Submission of Assessments

II. REMS Supporting Document

(b) (4)

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[redacted] (b) (4)

III. Probuphine REMS Materials

- **Probuphine REMS Program Healthcare Provider Who Prescribes Enrollment Form**
  - Color code this form in the final pdf version for easy identification
  - A redlined draft is attached with additional edits.
- **Probuphine REMS Program Healthcare Provider Who Inserts/Removes Enrollment Form**
  - Color code this form in the final pdf version for easy identification
  - A redlined draft is attached with additional edits.
- **Probuphine REMS Program Healthcare Provider Dual Enrollment Form**
  - Color code this form in the final pdf version for easy identification
  - A redlined draft is attached with additional edits.
- **Probuphine REMS Program Healthcare Provider** [redacted] (b) (4) **Recertification Form *(new!)***
  - Please draft a form for inserters/removers to fill out where they can indicate the rationale for their recertification. It should include attestations based on what kind of recertification they need.
  - Color code this form in the final pdf version for easy identification
- **Probuphine REMS Training Program**
  - Please align all content (especially Slides #19-70) with the revised IFU, based on recent Agency comments regarding the IFU and the training slides. The Agency will review the slides further in the next round after the Sponsor has made revisions noted above.
  - Revise to include the updated REMS goal
  - Please note comments on a separate document re: the REMS portion of the training slides (Slides 1-18, 61, and 65)
  - Please provide additional information about the recertification requirements and the new form

- Please include information about Prerequisites for Inserters/Removers

  Text could include the following. However, it must match the final approved language in the PI:

  "At the time of the Probuphine REMS Training Program, the inserter/remover must have performed a sterile procedure in the last 3 months, which includes (but is not limited to) using aseptic technique, injecting local anesthetic, making skin incisions, placing sutures, and removing foreign objects."

- Please incorporate references to and information about recent updates to the REMS, (i.e. new components in the REMS, changes to the REMS document, and new REMS materials - such as the videos and the new recertification enrollment form, etc.)

- **Probuphine REMS Criteria for Procedural Competency**
  - Please align all content with the revised IFU, based on recent comments from the Agency.
  - Please note the change in the title of this form.
- **Probuphine REMS Knowledge Assessment Test**
  - Please align all content with the revised IFU, based on recent Agency comments.
  - See specific track changes on the document and the addition of two questions related to the REMS.
  - This knowledge assessment should include information applicable to both the prescriber and the inserter/remover. OR, consider developing two separate knowledge assessment test for both audiences.
- **Probuphine REMS Insertion/Removal Log**
  - The Agency has no comments on this REMS material at this time.
- **Probuphine Medication Guide**
  - Patient messages in MG must align with those in the patient counseling document.
  - For inclusion in the Probuphine packaging
  - For use by the inserter to inform patients of the risks associated with Probuphine.
  - Agency comments will be forthcoming at a later date as part of the review of the PI and will not be reviewed as part of the REMS development, even though the MG is a component of the REMS.
- **Probuphine REMS Patient Counseling Tool** (b) (4)
  - See specific track changes on the document, and note the added subtitle.
  - This tool should focus on the risks the REMS is intended to mitigate. Additional information was deleted in the document with track changes.
  - Please revise this tool to make it less of a consent form and more of a document that includes important patient risk messages the prescriber should review to help the patient understand and consider the risks of Probuphine therapy. These messages should use plain language, be patient-friendly, and be presented in a format for future reference by the patient once he/she is home. It should be given to patients to take home after the prescriber first discusses Probuphine therapy with the patient and before the patient returns for insertion of the rods.

- It should not require signatures on the part of the patient or prescriber, as a patient's consent can be obtained via a form the healthcare facility provides for all such procedures or one the sponsor proposes for use outside of the REMS.
- See the patient brochure for Prolia as a guide, which is located here: http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=IndvRemsDetails.page&REMS=43

- **REMS Website**
  - Note additional track change comments and edits on the MS Word document.
  - Submit screenshots showing all pages and aspects and functionality of the Probuphine REMS website, including online registration option for the live and didactic training sessions and online recertification of HCPs who Insert or Remove Probuphine, when live recertification is not required.
  - Ensure the Website has a way for HCP who Prescriber and HCP who Insert/Remove to identify other certified HCPs.
  - Each screenshot must be reviewed as part of the REMS program approval
  - Please include updated titles of the REMS materials and newly added REMS materials to the website screenshots

- **Instructional Training Videos** ***new!***
  - Develop three training videos, which will aid healthcare providers (particularly inserters/removers) in refreshing their knowledge and skills if they have not performed these procedures in several months - and for recertification.
  - Topics of the three videos would be:
    - Insertion Procedure
    - Removal Procedure
    - Managing Complications
      - Insertion
      - Removal
      - Post-insertion care and follow-up
  - The videos should illustrate actual insertion and removal procedures on a live patient or model and illustrate complications and how to address them.
  - These must be placed on the website for viewing or downloading for recertification, if applicable.
  - The videos should be made available after live training sessions for every certified healthcare provider or mailed to healthcare providers at a specified time after certification.
  - For the next submission, please submit the content outlines of each video, scripts, and possibly story boards for FDA's review - prior to shooting/ producing the videos.

- **Risk Message Map**
  - Please note the revised and FINAL Risk Message Map, with minor changes that have already been integrated into the attached REMS materials.

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/s/

DONELLA A FITZGERALD
02/02/2016

KIMBERLY LEHRFELD
02/02/2016

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

REMS REVIEW : INTERIM COMMENTS #1

Date:	November 23, 2015
Reviewer(s)	Donella Fitzgerald, PharmD, Risk Management Analyst Division of Risk Management (DRISK) Joan E. Blair, RN, MPH, Health Communications Analyst Division of Risk Management (DRISK)
Team Leader	Kim Lehrfeld, Pharm.D, DRISK
Deputy Division Director:	Reema Mehta, Pharm.D, MPH, DRISK
Drug Name(s):	Probuphine (buprenorphine/ethylene vinyl acetate) implant
Therapeutic class and Dosage Form	Opioid Partial Agonist-antagonist subdermal implants
OND Review Division	Division of Analgesia, Anesthesia and Addiction Products
Application Type/Number:	NDA 204442
Applicant/sponsor:	Titan Pharmaceuticals, Inc.
OSE RCM #:	2015-2115

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1 INTRODUCTION

The purpose of this review is to document the evalution and provide comments on the proposed risk evaluation and mitagation strategy (REMS) for Probuphine, NDA 204442, submitted on August 27, 2015, as a 505(b)(2) application.

1.1 BACKGROUND

Probuphine is a schedule III, buprenorphine-containing subdermal implant covered under the Drug Addiction Treatment Act of 2000 (DATA-2000). The proposed indication is for the maintenance treatment of opioid dependence. Probuphine is intended for use in patients who are opioid-tolerant and have been stabilized on a sublingual buprenorphine daily dose of 12-16 mg for at least three consecutive days. The implants are 26mm x 2.5 mm rods, each containing 80 mg of buprenorphine HCl. Four rods are to be inserted subdermally in the inner side of the upper arm (about 8-10 cm above the medial epicondyle of the humerus) to provide sustained delivery of buprenorphine for six months. At the end of six months, implants can be inserted in the opposite arm if continued therapy is warranted.

Titan originally filed the application for Probuphine, NDA 204442, on October 31, 2012. A Complete Response was issued on April 30, 2013 for deficiencies in clinical benefit and human factors usability. The Agency recommended that the Applicant provide additional data supporting the efficacy of Probuphine, and a Human Factors study, complete with a comprehensive use-related risk analysis, for the insertion/removal training program.

The Applicant resubmitted Probuphine on August 27, 2015, with a proposed REMS. The resubmission included the results of a new randomized, double-blind, double-dummy Phase 3 study (PRO-814) that was conducted on 177 patients to support the clinical benefit of Probuphine in patients previously stabilized on 8mg or less of sublingual (SL) buprenorphine. The primary endpoint for PRO-814 was a responder analysis (using urine toxicology plus self-report) which evaluated the degree to which treatment with Probuphine resulted in the absence of objective evidence of opioid use. The Applicant states the proportion of responders was statistically significantly higher ($p = 0.034$), in the Probuphine group (96.4%) compared to the SL buprenorphine group (87.6%).

The Applicant stated the results of the Human Factors Study demonstrated healthcare providers with procedural experience were better able to perform the insertion procedure. An evaluation of the study is currently being conducted by the Division of Medication Error and Prevention Analysis (DMEPA).

The elements of the proposed REMS for Probuphine are a Medication Guide (MG), Communication Plan (CP), Elements to Assure Safe Use, Implementation Plan and a Timetable for Submission of Assessments.

1.2 REMS REGULATORY HISTORY

October 31, 2012: Titan submitted Probuphine, NDA 204442, , with a proposed REMS (Seq. No. 0000).

February 28, 2013: A REMS Oversight Committee meeting was held to discuss the rationale for a REMS and to determine the minimum required elements.

March 21, 2013: Psychopharmacologic Drugs Advisory Committee meeting was held. The panel discussed if the proposed REMS was adequate to address the risks of complications associated with the insertion procedure and abuse, misuse and accidental overdose. The committee voted: 5-yes, 4-no and 6-abstain. The four members who voted "no" expressed concerns that providers would not be trained properly on insertion/removal. The six members that abstained noted that the Applicant presented a modified REMS that was not previously described in the briefing materials.

April 30, 2013: A Complete Response was issued for deficiencies in clinical benefit and human factors usability.

August 27, 2015: Titan resubmitted Probuphine, NDA 204442, with a proposed REMS. This submission did not include a Supporting Document (Seq. No. 0030).

1.3 MATERIALS INFORMING OUR REVIEW

1.3.1 SUBMISSIONS

- Titan Pharmaceuticals Inc. Proposed REMS for Probuphine, received August 27, 2015 (Seq. No. 0030)

1.3.2 OTHER MATERIALS INFORMAING OUR REVIEW

- Probuphine Complete Response Letter. Division of Anesthesia, Analgesia and Addiction Products, dated April 30, 2013
- DRISK Final REMS Review of Probuphine. Reviewer: Jason Bunting, dated April 30, 2013
- REMS Oversight Committee meeting minutes, dated February 28, 2013
- Psychopharmacologic Drugs Advisory Committee meeting minutes, dated March 21, 2013
- Psychopharmacologic Drugs Advisory Committee briefing materials, dated March 21, 2013

2 PROPOSED REMS

2.1 GOALS

Applicant's proposed:

To mitigate (1) the risks of complications related to the PROBUPHINE insertion and removal procedures and (2) the risks of PROBUPHINE misuse, abuse, and accidental overdose by:

- Educating and training (b) (4) on appropriate patient selection for PROBUPHINE, proper PROBUPHINE insertion

and removal procedures, and the risks of misuse, abuse, and accidental overdose among patients treated with PROBUPHINE; and

- Establishing a Closed Distribution System that ensures PROBUPHINE is distributed directly and (b) (4) perform the insertion and removal procedures.

DRISK Comments:

DRISK believes that the goal should specifically state what complications the REMS is mitigating. The complications should be unique to improper Probuphine insertion/removal, not common surgical procedures.

The risks of misuse, abuse and accidental overdose are of concern if an implant protrudes or comes out of the skin. This distinction should be apparent in the goal.

DRISK believes that the Probuphine REMS goal should not include language about the closed distribution system.

Throughout the REMS document, various terms were used to describe healthcare providers who will participate in the Probuphine REMS program. Consistency within the REMS document and materials is required.

DRISK Recommendations:

Include the complications of migration, protrusion, expulsion and nerve damage in the goal statement.

Specify that the risks of misuse, abuse and accidental overdose are present if an implant protrudes or comes out of the skin.

Remove the reference to the Closed Distribution System from the goal.

DRISK recommends the following terms to describe healthcare providers who will participate in the Probuphine REMS program:

- *Healthcare Providers who Prescribe*
- *Healthcare Providers who Insert/Remove*

Agency's proposed goal:

The goal of the Probuphine REMS is to mitigate the risk of complications of migration, protrusion, expulsion and nerve damage associated with the improper insertion and removal of Probuphine and the risks of accidental overdose, misuse and abuse if an implant comes out or protrudes from the skin by:

a) Ensuring that prescribers are educated on the following:

- *risk of complications of migration, protrusion, expulsion and nerve damage associated with the improper insertion/removal of Probuphine*
- *risks of accidental overdose, misuse and abuse if an implant comes out or protrudes from the skin*

b) *Ensuring that Probuphine is administered only to patients informed about the risks of complications of migration, protrusion, expulsion and nerve damage associated with the improper insertion and removal, as well as, the risks of accidental overdose, misuse and abuse if an implant comes out or protrudes from the skin.*

2.2 REMS ELEMENTS

2.2.1 Medication Guide

The MG is currently under review by The Office of New Drugs, Division of Labeling. DRISK has no comments at this time.

2.2.2 Communication Plan

Applicant's proposed:

(b) (4)

DRISK Comments:

A Communication Plan (CP) is not necessary to ensure that the benefits of Probuphine outweigh the risks. The prescribing population for this medication is limited to those working in Opioid Treatment Programs or DATA 2000 waived. A mass mailing would not be necessary to target these specific practitioners. Additionally, since this program requires that healthcare providers who prescribe and insert Probuphine are certified in the REMS program, additional Dear Healthcare Provider (DHCP) letters are not necessary to reach these HCPs.

DRISK Recommendations:

We recommend removing the CP as a component of the Probuphine REMS Program.

2.2.3 Elements to Assure Safe Use

2.2.3.1 Prescriber Certification

Applicant's proposed requirements:

(b) (4)

(b) (4)

DRISK Comments:

DRISK, the Division of Anesthesia, Analgesia and Addiction Products (DAAAP) and the Division of Bone, Reproductive and Urological Products (consulted by DAAAP) believe that prescribers should participate in the Didactic Training and the Live Practicum Training Session. Demonstration of procedural competency (b) (4) *would be required for HCP who insert/remove Probuphine. Participation in the Live Practicum Training Session would increase their knowledge of the insertion/removal process, enabling them to better counsel the patient prior to insertion, respond to patient concerns and manage possible complications after the insertion.*

DRISK believes the responsibility of ensuring that the inserting facility has the proper equipment belongs to the HCP who inserts/removes Probuphine, (b) (4) *The practitioner actually performing the procedure should determine and attest that all necessary equipment is available.*

All (b) (4) *must be removed from the REMS document.* (b) (4)

(b) (4)

Consistency within the REMS document and materials is required.

DRISK Recommendations:

DRISK recommends the additional requirement of the Live Practicum Training Session (b) (4)

DRISK recommends removing (b) (4)

DRISK recommends removing [redacted] *from the REMS document.*

DRISK recommends the following terms to describe healthcare providers who will participate in the Probuphine REMS program:

- *Healthcare Providers who Prescribe*
- *Healthcare Providers who Insert/Remove*

2.2.3.2 Heathcare Providers who Dispense[1] Certification

Applicant's proposed requirements:

[redacted]

DRISK Comments:

DRISK believes the responsibility of ensuring that the inserting facility has the proper equipment belongs to the Healthcare Provider who Inserts/Removes, [redacted] *The practitioner performing the procedure should determine and attest that all necessary equipment is available.*

Additionally, [redacted] *needs further explanation.* [redacted]

[redacted] *Consistency within the REMS document and materials is required.*

DRISK Recommendations:

DRISK recommends the additional requirement of attesting to performing the procedure in an office that includes the proper equipment for insertion and

[1] For the purpose of this REMS, the term dispense refers to the dispensing for administration of medication, including insertion and removal.

removal procedures be included for the Healthcare Provider who Inserts/Removes Probuphine.

DRISK recommends the development of assessment criteria to be used in the evaluation of procedural competency.

DRISK recommends the following terms to describe healthcare providers who will participate in the Probuphine REMS program:

- *Healthcare Providers who Prescribe*
- *Healthcare Providers who Insert/Remove*

2.2.4 Implementation System

Applicant's proposed:

(b) (4)

(b) (4)

DRISK Comments:

We do not believe (b) (4) *to be a necessary component of this REMS.*

(b) (4)

The Didactic and Live Practicum Training Session should be provided to all healthcare providers enrolled in the Probuphine REMS program. Prescribers who will not perform insertions/removals (b) (4) *should participate in the practicum training.*

Some of the tools and materials that are proposed should not be part of the Probuphine REMS materials. (b) (4) *Should Titan desire to use these materials, they will be used outside of the REMS program.*

The (b) (4) *Form should be renamed.*

DRISK Recommendations:

Remove (b) (4) *from the Implementation System.*

Remove the requirement (b) (4) *from the Implementation System.*

Include Didactic and Live Practicum Training for all healthcare providers enrolled in the Probuphine REMS program in the Implementation System. Specify that prescribers who will not perform insertions/removals (b) (4) *should participate in the practicum training.*

Remove [redacted] (b) (4)

Rename the following materials:

- [redacted] (b) (4) *Form should be renamed Probuphine REMS Program Patient Counseling Tool*
- [redacted] (b) (4) *Form should be renamed Probuphine REMS Program Prescriber Enrollment Form*
- [redacted] (b) (4) *Form should be renamed Probuphine REMS Program Healthcare Provider who Inserts/Removes Enrollment Form*

2.2.5 Timetable for Submission of Assessments

Applicant's proposed:

Braeburn Pharmaceuticals will submit assessments of the PROBUPHINE REMS program to the FDA at 6 months, [redacted] (b) (4). To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment will conclude no earlier than 60 days before the submission date of the assessment. Braeburn Pharmaceuticals will submit each assessment so that it will be received by the FDA on or before the due date. [redacted] (b) (4)

DRISK Comments:
For a REMS with ETASU, the Agency's standard timeframe for assessments is six months, one year and annually thereafter.

DRISK Recommendations:
DRISK recommends the Applicant change their timetable for submission of assessments to six months, one year and annually thereafter.

2.2.6 Supporting Document

The Applicant did not submit a supporting document with the proposed REMS submission. The REMS supporting document should provide a thorough explanation of the rationale for and supporting information about the content of the proposed REMS. It should include a description of how and when each REMS element will be implemented and should specify the rationale for overall timelines and milestones. Additionally, it must describe the distribution process for Probuphine from distributer/wholesaler to patient. Refer to *Guidance for Industry Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications,* available on the following FDA website: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm184128.pdf

3 CONCLUSION

DRISK recommends changes to the goals, CP, ETASU, Implementation System and Timetable for Submission of Assessments sections of the proposed Probuphine REMS. We have commented on the recommended changes and provided our rationale. Additionally, we require the submission of a REMS supporting document, as outlined in the *REMS Guidance for Industry Format and Content*. The MG is currently under review by the Office of New Drugs, Division of Labeling.

4 RECOMMENDATIONS

DRISK advises that the above recommendations for the proposed Probuphine REMS, NDA 204442, be shared with the Applicant along with comments below *(Section 5: Comments for the Applicant*). DRISK requests that the Applicant respond to these comments within 7 to 14 days of receiving them, to facilitate further review of this submission. The comments below are based on DRISK's preliminary review.

5 COMMENTS FOR THE APPLICANT

The Office of Surveillance and Epidemiology, DRISK is currently reviewing the proposed REMS document and REMS materials for Probuphine, NDA 204442 that was received August 27, 2015. DRISK has the following comments, below, in response to the Applicant's proposal.

REMS Document

Communication Plan

A Communication Plan (CP) is not necessary to ensure that the benefits of Probuphine outweigh the risks. Since this program requires that healthcare providers who prescribe and insert Probuphine are certified in the REMS program, additional Dear Healthcare Provider (DHCP) letters are not necessary to reach these HCPs. Remove the CP as a component of the Probuphine REMS Program.

Prescriber Certification (Element to Assure Safe Use A [ETASU A])

DRISK has the following comments on Prescriber Certification:

1. Add the requirement that Prescibers participate in the Live Practicum Training Session. (b) (4)
2. Remove (b) (4) from prescriber certification. (b) (4) .
3. Remove (b) (4) from the REMS document.
4. Use the following terms to describe healthcare providers who will participate in the Probuphine REMS program:
    - Healthcare Providers who Prescribe
    - Healthcare Providers who Insert/Remove

Pharmacy Certification / Heathcare Providers who Dispense Certification (ETASU B)

DRISK has the following comments on Pharmacy Certification:

1. The Agency considers "Healthcare Providers who Insert/Remove Probuphine" to be "dispensers" and "administrators" of Probuphine. In the REMS document, this certification is considered ETASU B.
2. Add the requirement of attesting to performing the procedure in an office that includes the proper equipment for insertion and removal procedures for the Healthcare Provider who Inserts/Removes Probuphine.
3. Develop assessment criteria to be used in the evaluation of procedural competency. This must be submitted for the Agency to review.
4. Use the following terms to describe healthcare providers who will participate in the Probuphine REMS program:
   - Healthcare Providers who Prescribe
   - Healthcare Providers who Insert/Remove

Implementation System

DRISK has the following comments on the Implementation System:

1. Remove [redacted] (b) (4) from the Implementation System.
2. Remove the requirement [redacted] (b) (4) from the Implementation System.
3. Include Didactic and Live Practicum Training for <u>all</u> healthcare providers enrolled in the Probuphine REMS program in the Implementation System. Specify that prescribers who will not perform insertions/removals [redacted] (b) (4) should participate in the practicum training.
4. Remove [redacted] (b) (4)
5. Rename the following materials:
   - [redacted] (b) (4) Form should be renamed Probuphine REMS Program Patient Counseling Tool
   - [redacted] (b) (4) Form should be renamed Probuphine REMS Program Prescriber Enrollment Form
   - [redacted] (b) (4) Form should be renamed Probuphine REMS Program Healthcare Provider [redacted] (b) (4) Enrollment Form

Timetable for Submission of Assessments

Change the timetable for submission of assessments to six months, one year and annually thereafter. For a REMS with ETASU, the Agency's standard timeframe for assessments is six months, one year and annually thereafter.

REMS Supporting Document

Submit a REMS Supporting Document. The Applicant did not submit a supporting document with the proposed REMS submission. The REMS supporting document should provide a thorough explanation of the rationale for and supporting information about the content of the proposed REMS. It should include a description of how and when each REMS element will be implemented and should specify the rationale for overall timelines and milestones. Additionally, it must describe the distribution process for Probuphine from distributer/wholesaler to patient. Refer to *Guidance for Industry Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications,* available on the following FDA website: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm184128.pdf

Probuphine REMS Risk Message Map

Please note the following Risk Message Map, which you should use to draft the REMS materials. This risk message map should also be inserted into the REMS Supporting Document.

Risk Messages for Healthcare Providers

Risk Message #1: Healthcare providers must take steps to mitigate complications associated with the improper insertion and removal of Probuphine.

- Healthcare providers should be informed about the possible risks associated with the improper insertion and removal of Probuphine such as:
  - migration
  - protrusion
  - expulsion
  - nerve damage
- All healthcare providers who prescribe Probuphine must be properly educated and trained on:
  - proper and aseptic insertion and removal procedures for Probuphine
  - appropriate wound care.
  - managing complications associated with the insertion and removal procedures of Probuphine.
- All healthcare providers who insert or remove Probuphine must be properly educated, trained, and demonstrate proficiency on proper and aseptic insertion and removal procedures.

Risk Message #2: Healthcare providers must take steps to mitigate the risks of accidental overdose, misuse, and abuse associated with Probuphine if a rod comes out or protrudes from the skin

- The medication in Probuphine can be extracted and then abused in a manner similar to other opioids.
- Healthcare providers must make proper patient selection prior to prescribing Probuphine.
- Healthcare providers must be properly educated, trained, pass the knowledge assessment, and be certified in the Probuphine REMS Program to prescribe and dispense Probuphine.
- Probuphine should not be dispensed to patients for self-administration.
- Prior to prescribing Probuphine, prescribers must use the Patient Counseling Tool to inform patients about:
    - the risks of accidental overdose, misuse, and abuse associated with Probuphine if the Probuphine rods come out or protrude from the skin
    - when to contact the healthcare provider
- Prior to Probuphine insertion, healthcare providers who will insert must give patients the Probuphine Medication Guide; and using the Medication Guide, counsel patients on:
    - the risks of accidental overdose, misuse, and abuse associated with Probuphine if the Probuphine rods come out or protrude from the skin
    - when to contact the healthcare provider

Risk Messages For Patients

Risk Message #1: There are risks associated with the improper insertion and removal of Probuphine

- Possible risks related to improper insertion and removal of the implants include:
    - An implant may come out by itself, or an end of an implant may begin sticking out of the skin.
    - Injury to nerves or blood vessels in your arm.
    - Implants may be difficult to locate if they were inserted too deeply, or manipulated by you, or if you have gained significant weight since insertion.
    - Special procedures or a referral to a specialist may be needed to remove the implants if they are difficult to locate.
- 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.
    - Infection at the site of the insertion or removal.
- Appropriate wound care is important to reduce the risk of complications associated with the insertion of Probuphine
- Call your healthcare professional right away
    - If you are no longer able to feel all four of the implants under your skin.

- If the implant comes out or the end of the implant starts sticking out of the skin.
- If you have excessive or worsening itching, pain, irritation or redness, swelling, bleeding, bruising, numbness, or scarring at the insertion site

Risk Message #2: There are risks of accidental overdose, misuse and abuse associated with the use of Probuphine if an implant comes out or the end of the implant starts sticking out of the skin.

- Do not try to remove Probuphine implants yourself.
- If the Probuphine rods protrude or come out:
  - Wash your hands if you touch the Probuphine rods.
  - Cover the area where they were inserted with a clean bandage.
  - Do not allow others to touch or use the Probuphine rods, since this could be very dangerous.
  - If the Probuphine rods come out, put them in a plastic bag and bring the rods to your doctor right away. Keep them away from others, especially children.

Based on our review, revision of the REMS goals, and development of risk messages, we recommend that the following materials be included in the Probuphine REMS. Comments guiding their revision or resubmission are included. Please note that all REMS materials must reflect the most recent and eventually the final label, including Section 17 of the PI and the Medication Guide.

Probuphine REMS Materials Proposed by the Agency:

- **Probuphine REMS Program Prescriber Enrollment Form**
  - For prescribing HCPs
  - Attestations in form may need to be revised following final approval of the REMS document
  - Enrollment forms will be available for completion following the live didactic training sessions
  - Will not be available online
  - Completion required prior to receiving Probuphine from the certified wholesaler
  - Color code this form for easy identification once final
  - A redlined draft is attached
- **Probuphine REMS Program Healthcare Provider who Inserts/Removes Enrollment Form**
  - For HCPs who have completed the live didactic training and demonstrated competency to insert and remove Probuphine.

- Attestations in form may need to be revised following final approval of the REMS document
- Removes the need to have a Designee Authorization Request Form
- Enrollment forms will be available for completion following the live didactic and Live Practicum Training Sessions
- Completion required prior to inserting or removing Probuphine
- Will not be available on line
- Color code this form for easy identification once final
- A redlined draft is attached

- **Probuphine REMS Program Healthcare Provider <u>Dual</u> Enrollment Form**
  - For HCPs who intend to prescribe, insert, and remove Probuphine and have completed the live didactic training and demonstrated competency to insert and remove Probuphine.
  - Attestations in form may need to be revised following final approval of the REMS document
  - Enrollment forms will be available for completion following the live didactic and Live Practicum Training Session
  - Will not be available online
  - Required prior to receiving Probuphine from the certified wholesaler and inserting and removing Probuphine
  - Color code this form for easy identification once final
  - A redlined draft is attached

- **Probuphine REMS Training Program**
  - for use at the didactic training sessions and available online for review purposes
  - May be developed as a power point presentation
  - See the Natpara, Lemtrada, Celgene, and other approved REMS programs as possible examples. A complete list of REMS programs with related materials may be found here: http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm
  - Should be revised to include the following information:
    - Indication
    - What is the Probuphine REMS
    - Risks that the Probuphine REMS will help to mitigate (complications from insertion/removal and the risks of accidental exposure, abuse, and misuse)

        - Initial and ongoing roles and responsibilities of the prescriber, inserter, and dual role prescriber/inserter
        - Certification process for the prescriber, inserter, and dual role prescriber/inserter
        - Content reflecting the risk messages for healthcare providers (see risk message map)
        - Content reflecting the risk messages for patients (see risk message map)
        - Importance of proper insertion and removal
        - Appropriate wound care (directed at HCPs with limited surgical experience who may need a review of this information)
        - Step by step content directly from the IFU (once the IFU has been finalized)

- **Probuphine REMS Program Criteria for Procedural Competency**
    - Will provide guidelines to determine if the healthcare providers who insert Probuphine and dual role prescribers/ healthcare providers who insert are competent to perform the insertion and removal of Probuphine.
    - Draft this document for trainers to use to determine if inserters are competent to insert and remove Probuphine after the Live Practicum Training Session.
- **Probuphine REMS Program Knowledge Assessment Test**
    - Revise questions to assess knowledge gained from the training program slides.
    - Should reflect content from the updated training programs slides (include insertion/removal complications, risk of accidental exposure, misuse, and abuse; and REMS program information)
    - Should include 10-15 multiple choice questions and true/false questions
- **Probuphine REMS Program Insertion/Removal Log**
    - Will document the insertion and removal of Probuphine, including specific information about where and when Probuphine was inserted and removed.
    - Will be included in patient's chart.
    - Revise as needed to reflect the updated Probuphine REMS document
- **Probuphine Medication Guide**
    - For inclusion in the Probuphine packaging
    - For use by the healthcare provider who inserts Probuphine to inform patients of the risks associated with Probuphine.

- **Probuphine REMS Program Patient Counseling Tool**
    - To be utilized by the prescriber when discussing the risks and benefits of Probuphine with the patient
    - May also be used with the Probuphine Medication Guide.
    - Should include information related to the risk messages for patients (see risk message map)
    - See the ER/LA Opioids REMS, Prolia REMS, Qsymia REMS, or other REMS' patient counseling documents/tools as examples. A complete list of REMS programs with related materials may be found here: http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm
- **Probuphine REMS Program Website**
    - Create a Probuphine REMS website.
    - Consider patterning it after approved REMS websites such as Opsumit, Aveed, or Natpara. A complete list of REMS programs with related materials and website screenshots may be found here: http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm
    - Include the following content:
        - Overview of REMS
        - REMS Program requirements
        - Role of and certification process for the prescriber, inserter, and dual role of the prescriber who also serves as the inserter
        - Provide links to the following REMS materials:
            - REMS Training Program slides
            - Probuphine REMS Criteria for Procedural Competency
            - Probuphine REMS Insertion and Removal Log
            - PI
            - Probuphine Medication Guide
            - Probuphine REMS Patient Counseling Tool
        - Include tabs which contain information for the prescriber, inserter, and the prescriber/inserter
        - Include a tab for patients, with basic information reflecting the risk messages and the medication guide.
        - Include a box on the home page that includes links to the REMS materials by audience type, e.g. Materials for Prescribers.
        - Adverse Reaction Reporting
        - Links for Privacy, Terms of Use, Contact information, etc. can be placed at bottom of web page
    - Submit screenshots showing all pages and aspects of the Probuphine REMS website. These screenshots can be submitted after the content of each web page is first reviewed by the Agency. This content may be shown in an MS Word document for the next submission.

- Healthcare provider enrollment, completion of the training program, or completion of the knowledge assessment will not be offered online, as they are important aspects of the didactic and Live Practicum Training Sessions.

General Comments for the Applicant:

Other materials previously submitted will not be part of the REMS, but may still be used; i.e., reviewed as part of the labeling.

Please note the attached track changed documents (redlined versions of the three enrollment forms).

Submit the revised proposed Probuphine (NDA 204442) REMS document within 7 days, via email, and note any requirements which you are not in agreement with the Agency. Submit the revised REMS document, the REMS supporting document and revised materials to your application (via the Gateway) within 14 days. Provide each REMS material noted above as a separate MS Word document with track changes (noting any additional changes proposed by the applicant as redlined track changes) and as a separate clean MS Word version.

6 APPENDIX

- Probuphine REMS Program Prescriber Enrollment Form - redlined
- Probuphine REMS Program Healthcare Provider who Inserts/Removes Enrollment Form - redlined
- Probuphine REMS Program Healthcare Provider Dual Enrollment Form - redlined

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/s/

DONELLA A FITZGERALD
11/24/2015

KIMBERLY LEHRFELD
11/24/2015

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Risk Evaluation and Mitigation Strategies (REMS) Review

Date:	April 30, 2013
Reviewer(s):	Jason Bunting, PharmD, Risk Management Analyst
	Division of Risk Management
Team Leader	Reema Mehta, PharmD, MPH, Team Leader
	Division of Risk Management
Division Director	Claudia Manzo, PharmD
	Division of Risk Management
Subject:	Review evaluates the Sponsor's proposed Risk Evaluation and Mitigation Strategy (REMS)
Drug Name(s):	Probuphine® (buprenorphine HCl/ethylene vinyl acetate)
Therapeutic Class:	Buprenorphine-containing implantable device for opioid dependence
Dosage and Route:	Subdermal implants (four or five) containing 80 mg each of buprenorphine
Application Type/Number:	NDA 204-442
Applicant/sponsor:	Titan Pharmaceuticals, Inc.
OSE RCM #:	2013-190 & 2013-193

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EXECUTIVE SUMMARY

DRISK has determined that a risk evaluation and mitigation strategy (REMS) is required for Probuphine® (buprenorphine HCl/ethylene vinyl acetate) subdermal implant to ensure the benefits outweigh the risks of complications due to improper implantation/removal technique and potential for accidental overdose, misuse, and abuse. The proposed minimum requirements for the REMS include a Medication Guide (MG), communication plan (CP), and elements to assure safe use (ETASU). The recommended ETASU include prescriber certification, certification of the individual who will administer the medication, and documentation of safe use conditions. An implementation system must also be required; including wholesaler/distributor enrollment to ensure Probuphine is only distributed to certified prescribers.

The proposed REMS has not been evaluated to determine if the requirements constitute an adverse determination under the Drug Addiction Treatment Act of 2000 (DATA-2000); the results of this evaluation are pending.

The Sponsor's proposed REMS, submitted on October 29, 2012 and amended on March 13, 2013, does not comply with the Controlled Substance Act (CSA) and DATA-2000 and does not contain the minimum requirements as recommended by DRISK. A REMS amendment submitted on April 2, 2013; however, it was not reviewed during this review cycle. Therefore, the Sponsor's proposed REMS is not recommended for approval.

1 INTRODUCTION

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested the Division of Risk Management (DRISK) review NDA 204-442, Probuphine® (buprenorphine HCl/ethylene vinyl acetate) subdermal implant, to assess the need for a risk evaluation and mitigation strategy (REMS) and review the proposed REMS submitted by Titan Pharmaceuticals, Inc. (Titan). This review documents DRISK's evaluation of the proposed REMS for Probuphine.

1.1 BACKGROUND

Probuphine is a Schedule III, buprenorphine-containing subdermal implant covered under the Drug Addiction Treatment Act of 2000 (DATA-2000). The proposed indication is for the maintenance treatment of opioid dependence to be used as part of a complete treatment program, including counseling and psychosocial support. Probuphine is available as a 25 mm x 2.5 mm rod-shaped implant and contains 80 mg buprenorphine HCl. Once implanted subdermally at the inner side of the upper arm (about 8-10 cm above the medial epicondyle of the humerus), it provides sustained delivery of buprenorphine for up to six months.

Currently, Subutex® (buprenorphine HCl) sublingual tablets and Suboxone® (buprenorphine HCl/ naloxone HCl) sublingual tablets and sublingual film, including generics as applicable, are approved for the treatment of opioid addiction. These products were the first narcotic drugs available for the treatment of opioid dependence in an office-based treatment program under DATA-2000. Probuphine was developed as an

alternative for practitioners and patients in the office-based setting utilizing an abuse deterrent formulation.

Probuphine is intended for use in patients who are opioid-tolerant and who are stabilized on a sublingual buprenorphine daily dose of 12-16 mg for a period of at least three consecutive days. After induction with sublingual buprenorphine, four Probuphine implants are surgically inserted subdermally in the upper arm. After two weeks of therapy, the patient is assessed to determine if a fifth implant is necessary to achieve appropriate therapeutic drug levels. Probuphine is removed after six months; new implants can be inserted in the opposite arm if continued therapy with Probuphine is warranted.

The serious risks of concern are the complications related to the surgical insertion and removal procedures of Probuphine and the possibility of misuse, abuse, and accidental overdose. (See Section 3.2 Safety Concerns for details).

1.2 REGULATORY HISTORY

On October 31, 2012, Titan submitted the NDA for Probuphine, which included a proposed REMS. The application was filed on December 30, 2012 and classified as a priority review with a user fee goal date of April 30, 2013.

DRISK formed a working group with representation from DAAAP, the Division of Medical Error Prevention and Analysis (DMEPA), the Division of Pharmacovigilance (DPV), the Division of Reproductive and Urologic Products (DRUP), the Controlled Substance Staff (CSS), and the Office of the Center Director (OCD). The working group met weekly, between January 23, 2013 and February 26, 2013, to identify what risks, if any, would need to be mitigated through a REMS to ensure the benefits of the drug outweigh the risks. Also, discussed at the weekly meetings were the Sponsor's proposed [redacted] (b) (4)

On February 15, 2013, the Agency met with the Drug Enforcement Administration (DEA) via teleconference to gain a better understanding regarding the regulations for buprenorphine-containing products covered under DATA-2000.

On February 19, 2013, the Agency met with Titan via teleconference to obtain clarification regarding the Sponsor's REMS proposal. Advice regarding the adequacy of their proposal or FDA recommended strategy was not provided at this meeting. On February 21, 2013, the team received written responses from Titan as a follow-up action item to the teleconference and an official resubmission of the proposed REMS was submitted to the NDA on March 13, 2013.

On February 28, 2013, the working group presented the rationale for a REMS for Probuphine and minimum required elements to the REMS Oversight Committee (ROC). The Agency's minimum requirements included a Medication Guide (MG), communication plan (CP), and elements to assure safe use (ETASU) (prescriber certification, restricted distribution, and documentation of safe use conditions). The ROC agreed with the working group's proposed REMS requirements.

Although not a NME, this product was referred to the Psychopharmacologic Drugs Advisory Committee (PDAC) due to the novel formulation and potential safety concerns associated with the implantation and removal procedures of the device. On March 19, 2013, DAAAP and DRISK met with the Sponsor via teleconference to inform them of the concerns regarding the proposed REMS that would be raised during the March 21st PDAC meeting. (b) (4)

On March 21, 2013, DRISK presented the Agency's concerns with the Sponsor's proposed REMS (submitted on March 13, 2013) to the PDAC. The Sponsor presented their proposed REMS to the PDAC, which the Agency had not had sufficient time to review or evaluate. During the PDAC, committee members asked the Sponsor clarifying questions to which the Sponsor responded and made further commitments regarding the REMS that had not yet been presented either at the meeting or in their official NDA submission.

The following question was asked of the PDAC members regarding the REMS:

> *Is the Risk Evaluation and Mitigation Strategy (REMS) proposed by the Applicant, which consists of restricted distribution and a training/certification program for healthcare professionals who will implant the product, adequate to address the risks of potential complications associated with the implantation procedure and abuse, misuse, and accidental overdose?*

The committee voted 5, yes; 4, no; and 6 abstain. The committee members who voted "Yes" noted that they believed the training was adequate, as proposed by the Sponsor, as was the restricted distribution system. Members who voted "No" expressed concerns with the training program and wondered not if providers could be trained, but if providers would be trained. These members also noted that potential complications such as abuse and misuse were not fully addressed. Those who abstained from voting cited that the Sponsor had presented a REMS that differed from the one described in the briefing materials and they could not come to a conclusion on its adequacy.

On March 26, 2013, during a post PDAC teleconference with the Sponsor, FDA asked that the Sponsor submit their revised proposed REMS to the NDA. The revised proposed REMS was submitted on April 2, 2013; however, it was not reviewed during this review cycle.

In order to continue development of the REMS for Probuphine, the working group needed an assessment of the proposed program and whether or not it constituted an adverse determination under DATA-2000. Therefore, on April 19, 2013, DRISK drafted a proposed REMS document for assessment by the Office of Regulatory Policy (ORP), Office of Center Director (OCD), and Office of Chief Counsel (OCC). Additionally, ORP, OCD, and OCC were requested to determine if consultation with DEA and SAMHSA was required to assess the program's compliance with applicable regulations. As of April 30, 2013, the results of the assessment by ORP/OCD/OCC are still pending.

2 MATERIALS REVIEWED

2.1 SUBMISSIONS

- Titan Pharmaceuticals Inc.'s Amended Proposed REMS for Probuphine® (buprenorphine HCl/ ethylene vinyl acetate) subdermal implant, received March 13, 2013: (eCTD Sequence No. 0011)
- Titan Pharmaceuticals Inc.'s Responses to the February 19, 2013 teleconference, received February 21, 2013: (eCTD Sequence No. 0009)
- Titan Pharmaceuticals Inc.'s Responses to the 60-Day letter, received February 15, 2013: (eCTD Sequence No. 0009)
- Titan Pharmaceuticals Inc. Proposed REMS for Probuphine® (buprenorphine HCl/ ethylene vinyl acetate) subdermal implant, received October 31, 2012. (eCTD Sequence No. 0000)

2.2 PERTINENT REGULATIONS

- Controlled Substances Act (CSA)
- Drug Addiction Treatment Act of 2000 (DATA-2000)

3 RESULTS OF REVIEW

3.1 OVERVIEW OF CLINICAL PROGRAM

The clinical safety and efficacy of Probuphine were evaluated in patients with opioid dependence as defined in the DSM-IV-TR in two double-blind placebo-controlled studies, PRO-805 and PRO-806, and two open-label extension studies, PRO-807 and PRO-811. Each study included an induction period with sublingual buprenorphine at a stable dose of 12-16 mg daily for a minimum of three consecutive days. Within 12-24 hours after the last induction dose of sublingual buprenorphine, four Probuphine or four placebo (PRO-805 and PRO-806 only) implants were surgically inserted in the patients' inner upper arm during an in-office procedure. In studies PRO-805 and PRO-806 efficacy was determined by urine toxicology screening, three times weekly, and self-reporting for use of illicit opioids; urine testing was done in studies PRO-807 and PRO-811, but less frequently. Positive self-report data were used in lieu of urine toxicology results where such were contrary to the self-reported data.

3.2 SAFETY CONCERNS

3.2.1 Complications related to the surgical insertion/removal of Probuphine

While the formulation of Probuphine is novel for buprenorphine and the patient setting, this implantable product, including the insertion/removal procedures, have many similarities with hormonal contraceptive implants (e.g., Norplant®). Complications related to the implantation procedure may include, but are not limited to, surgical complications (e.g., infection, bleeding, and scarring of implant site) and overdosing/underdosing. Some of these risks have been observed in the Probuphine clinical trials. While serious complications were not observed in the clinical trials, it is

the experience with hormonal contraceptive implants, in the post-marketing setting, that indicates additional adverse events related to the surgical implantation and removal procedures may be plausible. Moreover, the shorter therapeutic duration of Probuphine (six months vs. up to five years for contraceptive implants) requires more frequent implant replacement, adding to the concern for adverse events associated with insertion/removal procedures.

Additionally, Probuphine implants are expected to be managed by providers not in surgically-oriented specialties; while hormonal contraceptive implants are managed by surgical specialists, such as obstetricians/gynecologists. Thus, there is the concern for greater potential of procedure-related risks with Probuphine as compared to contraceptive implants. Based on a review by the Division of Epidemiology (DEPI) to investigate the top prescribers of oral buprenorphine formulations, the top prescriber specialties for the oral combination buprenorphine/naloxone products and single-ingredient buprenorphine products were General Practice/Family Medicine/Doctor of Osteopathy, Psychiatry, and Internal Medicine. A small proportion of prescriptions dispensed were written by physicians who may have training in surgical procedures. Therefore, Probuphine may be implanted by practitioners with no previous surgical experience; thereby, increasing the possibility of adverse events related to improper technique.

3.2.2 Abuse, misuse, and accidental overdose of Probuphine

While the novel formulation for Probuphine reduces the risk for potential abuse, misuse, and accidental overdose, these risks are not eliminated. The Sponsor claims surgical implantation makes it unlikely that patients or others, including children, would have access to the drug; thus, minimizing the potential for accidental exposure, misuse, abuse, and diversion. However, due to the nature of the intended patient population (i.e., patients who are addicted to opioids), patients may intentionally remove the implants after insertion to obtain access to buprenorphine for purposes of abuse and misuse. This is an important concern because the drug can easily be extracted from the implant by submerging in water or alcohol for a period of time. Additionally, from the clinical trials for Probuphine, 6/262 patients (2%) experienced expulsions or extrusions of implants; therefore, patients or others may be accidentally exposed to buprenorphine if expulsion or extrusion occurs, which can result in accidental overdose.

3.3 RATIONALE FOR REQUIRING A RISK EVALUATION AND MITIGATION STRATEGY

DRISK and DAAAP have determined that a REMS for Probuphine must be required to ensure the benefits outweigh the risks. In particular, the expected complications for the formulation combined with the anticipated prescribing population who will have limited to no surgical experience are the primary factors that may result in compromised patient safety. Additionally, while the risk of misuse, abuse, and accidental overdose for Probuphine is reduced via the formulation, it is not eliminated. The patient population is predisposed to misuse and abuse of drug substances. Furthermore, the implant can be removed from the site of implantation (intentionally or unintentionally), which can result in accidental cutaneous exposure of buprenorphine or intentional extraction of buprenorphine from the implant.

3.4 APPLICANT'S PROPOSED RISK EVALUATION AND MITIGATION STRATEGY

The Sponsor has proposed a REMS aimed at mitigating the risks of misuse, abuse, and diversion and also, the risks associated with the surgical insertion and removal of the implants. The following describes the Sponsor's proposed REMS, submitted on March 13, 2013.

3.4.1 Goals

The Sponsor's proposed goals are as follows:

(b) (4)

(b) (4)

In pursuit of these goals, the following elements will be implemented:

- Patient education through the Medication Guide and Probuphine Informed Consent.
- Healthcare professional education and training on appropriate patient selection and proper insertion and removal procedures.
- A closed distribution system that includes the use of a single Specialty Pharmacy/Distributor network.
- Administration to patients only in certain healthcare settings.

3.4.2 Medication Guide (MG)

The Sponsor has proposed that a MG for Probuphine will be included in each package of Probuphine (b) (4)

3.4.3 Communication Plan (CP)

The Sponsor has proposed sending letters to currently registered prescribers of buprenorphine for the treatment of opioid dependence in the Office Based Opioid Treatment (OBOT) setting and the Opioid Treatment Program (OTP) setting. The Sponsor has also proposed sending letters to organizations that provide training and certification for healthcare professionals to use buprenorphine in OBOT. These letters will provide an orientation to Probuphine and describe the additional requirement for training in insertion and removal.

3.4.4 Elements to Assure Safe Use (ETASU)

The Sponsor has proposed ETASU consisting of prescriber certification, pharmacy certification, and documentation of safe use conditions. Encompassed within the ETASU is a training program for health care providers (HCP), to mitigate the risk of complications due to surgical insertion and removal of Probuphine, and a restricted

distribution system, to ensure only the appropriate stakeholders handle the product to mitigate the risks of misuse, abuse, and accidental exposure.

3.4.4.1 ETASU A – Prescriber Certification

By law, physicians who prescribe/order opioids to treat opioid dependence must be practicing in a DEA registered OTP. Alternatively, DATA-2000 gives qualified physicians the opportunity to obtain a waiver from the registration requirements of the CSA to prescribe and dispense, in the office-based setting, opioids for the treatment of opioid addiction.

In addition to meeting these criteria, the Sponsor has proposed a training program for HCP's (b) (4)

(b) (4)

3.4.4.2 ETASU B – Pharmacy Certification

The Sponsor has proposed a certified central pharmacy that will be utilized to dispense Probuphine directly to the treating HCP within a closed distribution system. (b) (4)

(b) (4)

3.4.4.3 ETASU D – Documentation of Safe Use

The Sponsor has proposed the use of a Probuphine Informed Consent Form and Probuphine Distribution Logs to document the safe use of Probuphine. Patients and prescribers must sign a Patient Consent Form to attest they have read and understood the MG and discussed risks of Probuphine. A Probuphine Order/Receipt Log may be utilized to document the date, time, and amount of Probuphine order/received. A Probuphine Patient Log may be utilized to document the date, time, and location of the implants either inserted or removed for a specific patient, as well as, the disposal of the used implants, any attempts to contact a patient should they not return for removal of the implants, and the transfer of the patients' care to another provider. Patients will also receive a Patient Identification Card documenting the implantation.

3.4.5 Implementation System

The Sponsor has proposed that verification of REMS training will be conducted by the Specialty Pharmacy. (b) (4)

3.4.6 Timetable for Submission of Assessments

The Sponsor has proposed that assessments of the Probuphine REMS will be submitted (b) (4) (b) (4) To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment will conclude no earlier than 60 days before the submission date for that assessment time interval. The assessment will be sent to FDA on or before each due date.

3.4.7 Information Needed for Assessment

The Sponsor has proposed that the following will be submitted at each assessment reporting period:

(b) (4)

[redacted] (b) (4)

3.5 FDA INTERACTION WITH DEA

On February 15, 2013, DRISK, DAAAP, and CSS participated in a teleconference with DEA to clarify the regulations of the CSA. The objective of the meeting was to obtain a better understanding of the regulatory requirements for a buprenorphine-containing product covered under DATA-2000.

The key takeaway messages as it relates to the Probuphine [redacted] (b) (4) closed distribution system were:

- A pharmacy may only ship a prescription for a controlled substance to the ultimate user and at the ultimate user's address specified on the prescription.
- A manufacturer may distribute a controlled substance, including buprenorphine, directly to a physician's office for inventory maintained at the office, or office stock.
- If dispensing from office stock, a controlled substance may only be administered at the individual's registered location.
- Expired controlled substances must be disposed of through a reverse distributor and appropriate records must be kept. A controlled substance that has been partially used by the ultimate user must be disposed of by the ultimate user.
- If a prescription for a controlled substance is dispensed from a pharmacy to the ultimate user, there is no restriction on who may administer the controlled substance. If medication is administered from a physician's office stock, it must be administered "in the presence of" the qualified physician.
- A DATA-2000 waived physician may identify a designee (e.g., mid-level practitioner) to administer a buprenorphine product for drug addiction treatment provided the designee meets state requirements to do so. The designee does not have to be registered with DEA.

3.6 DRISK'S CONCERNS WITH THE SPONSOR'S PROPOSED REMS

[redacted] (b) (4) The closed distribution system is designed to ensure only the appropriate stakeholders handle the product to mitigate the risks of misuse, abuse, and accidental overdose. However, the review team has identified several inadequacies for the proposed REMS including the training program, [redacted] (b) (4) and the closed distribution system.

With regard to the proposed training program, the Sponsor has provided insufficient information to validate their proposed training program. Titan has not provided stakeholder input from physicians or other healthcare providers regarding the content and format of the proposed training program, nor have they conducted human factors studies to assess the effectiveness of the proposed training program.

The need for an enhanced training program was identified due to the number of improper implantation/removal procedures reported in PRO-805 and PRO-807. The proposed training program included in the Sponsor's REMS proposal was instituted in study PRO-806 and PRO-811. Also, there were additional improvements to the device and procedure that were instituted in PRO-806 and PRO-811 to mitigate the risk of complications due to improper technique (e.g., switching from a dull to sharp trocar). While the clinical trials did demonstrate an improvement in complications after the institution of the training program and device and procedure improvements, the Sponsor's submission indicates that the training materials are still in development and in a pilot phase. Additionally, it is not clear if the other interventions in the clinical trials combined with increased experience in performing the procedure contributed to the improvements. Therefore, sufficient data has not been provided to support the adequacy of the proposed training program. Furthermore, the Sponsor has proposed (b) (4)

(b) (4)

With regard to the closed distribution system, the Sponsor's proposal does not conform to the requirements included in Title 21 United States Code Controlled Substances Act (CSA). The CSA defines "dispense" in Section 802 (Definitions) as the following:

> *to deliver a controlled substance to an ultimate user or research subject by, or pursuant to the lawful order of, a practitioner, including the prescribing and administering of a controlled substance and the packaging, labeling or compounding necessary to prepare the substance for such delivery.*

Based on the working group's interpretation of the CSA and the feedback received during the February 15, 2013 meeting with the DEA, a pharmacy must dispense a controlled substance, pursuant to a prescription, directly to the patient (the ultimate user) and cannot ship a controlled substance directly to the DATA-2000 waived physician as the Sponsor has proposed; thus, the sponsor's proposed distribution system, which utilizes a pharmacy to ship to the provider and not the patient may not be in compliance with the CSA. Note; the Sponsor did present a revised closed distribution system at the PDAC meeting, which did not include a pharmacy to dispense Probuphine. The revised distribution system utilized a specialty distributor to supply Probuphine directly to qualified physician's offices.

3.7 DRISK'S RECOMMENDED MINIMUM REQUIREMENTS FOR THE PROBUPHINE REMS

The following proposal was provided to ORP/OCD/OCC on April 19, 2013; their review is pending.

3.7.1 Goals

The recommended goals of the Probuphine REMS are as follows:

1) To mitigate the risk of complications that could result from improper technique associated with the implantation/removal procedure of Probuphine
2) To inform prescribers of the complications that could result from improper technique associated with the implantation/removal procedure of Probuphine
3) To inform patients and prescribers of the risks of accidental overdose, misuse, and abuse associated with Probuphine

3.7.2 Medication Guide

A MG will be dispensed with each Probuphine prescription in accordance with 21 CFR 208.24. The Sponsor's proposal included a MG as a component of the proposed REMS.

3.7.3 Communication Plan

Titan will implement a communication plan to health care providers to support the implementation of the REMS. The communication plan will include a Dear Health Care Professional (DHCP) letter which will include information on the risks associated with the use of Probuphine and will explain the requirements of the REMS. Appended to the DHCP letter will be the Full Prescribing Information and Medication Guide. The DHCP letter and appended materials will be mailed to all physicians certified to treat opioid dependence under the Drug Addiction Treatment Act of 2000 (DATA 2000) and physicians practicing in an Opioid Treatment Program (OTP). Furthermore, the DHCP letter and appended materials will also be mailed to member lists of appropriate professional organizations.

The Sponsor's proposal included a CP as a component of the proposed REMS.

3.7.4 Elements to Assure Safe Use

ETASU, including prescriber certification, dispenser certification, and documentation of safe use conditions, are minimum requirements to ensure the benefits of Probuphine outweigh the risks of complications related to the surgical insertion and removal of Probuphine and the risks of abuse, misuse, and accidental overdose.

3.7.4.1 ETASU A – Prescriber Certification

Health care providers who prescribe[1] and dispense[2] Probuphine are specially certified.

[1] For the purposes of this REMS, the term prescribe refers to a medication order filled from an on-site inventory of medication.

Titan will ensure that physicians who prescribe and dispense Probuphine are specially certified in the Probuphine REMS. Probuphine is available only through a restricted distribution program called the Probuphine REMS.

A physician is qualified to undergo the REMS certification if the physician (a) is waived to treat opioid-dependent patients in the office-based opioid treatment (OBOT) setting under DATA-2000, or (b) is DEA registered to prescribe Probuphine in an Opioid Treatment Program (OTP).

To become certified, each physician must complete the Probuphine REMS Prescriber Enrollment Form and agree to do the following:

a. Successfully complete a live, company-sponsored Probuphine REMS training program on patient selection and the safe administration of Probuphine, including the proper insertion and removal techniques. Successful completion is defined as:

    i. Experiential training: the ability to perform the procedure utilizing the Probuphine Training Kit

    ii. Didactic training: completion of a Post-Training Knowledge Assessment Test with a score of 80% or more to demonstrate adequate understanding of material from the Probuphine Training Slides.

b. Provide patient counseling on the benefits and risks of Probuphine therapy, including risks of accidental overdose, misuse, and abuse; potential serious risks of Probuphine, including potential complications of the implantation/removal procedure; and appropriate wound care.

c. Provide each patient with a copy of the Medication Guide prior to each implantation procedure.

d. Document the implantation and removal of Probuphine, including the date, number of rods implanted/removed, name of individual performing the procedure, and location of rods for individual patients on the Probuphine Implantation/Removal Log and maintain a copy in the patient's medical records.

e. Ensure relevant staff are trained on the safe use of Probuphine, as described in the Probuphine Training Slides and Probuphine Implantation/Removal Guide

f. Complete a Designee Authorization Request Form to allow a designee to administer Probuphine in their presence once the designee has successfully completed the live, company-sponsored Probuphine REMS training program. A designee is defined as a mid-level practitioner or another contracted physician permitted by the REMS certified physician to perform the procedure at the DATA-2000 waived physician's office or OTP.

g. Order Probuphine only from a wholesaler/distributor that is enrolled in the Probuphine REMS program.

[2] For the purposes of this REMS, the term dispense refers to the administration of medication, including implantation and removal.

h. Maintain an on-site inventory of Probuphine based on current regulations as required by the DEA.

i. Ensure the REMS certified physician's facility has appropriate equipment available to perform the implantation and removal procedures.

Titan will:

a. Ensure that the Probuphine REMS program materials, including prescriber enrollment are available on the Probuphine REMS website or can be obtained by contacting Titan at 1-800-xxx-xxxx.

b. Ensure that a call center is available 24 hours a day, seven days a week, to address questions regarding the Probuphine REMS, the REMS training requirements, and the implantation/removal procedure.

c. Maintain a validated and secure database of all Probuphine certified physicians and authorized designees.

d. Monitor to ensure that only Probuphine REMS certified physicians are prescribing Probuphine.

e. Monitor certified physician compliance with the Probuphine REMS program, including patient counseling and appropriate documentation of the implantation and removal procedure

f. Ensure REMS certified physicians are adequately trained to prescribe and dispense Probuphine, including the following educational components:

    i. Procedure for implanting and removing Probuphine

    ii. Important patient counseling information, including wound care

    iii. Managing complications associated with the implantation and removal procedures of Probuphine

    iv. Potential for accidental overdose, misuse, and abuse

g. Follow-up with REMS certified physicians who have not placed an order for Probuphine within six months of training to offer re-training via the live, company sponsored Probuphine REMS training program

h. Provide supplemental training, including the live, company sponsored Probuphine REMS training program, upon request

i. Provide a Probuphine Implantation/Removal Guide to Probuphine REMS certified prescribers for reference after completion of the training program and upon request

j. Ensure that a list of enrolled wholesalers/distributors in the Probuphine REMS is available to Probuphine REMS certified physicians.

k. Ensure that Probuphine is distributed only by enrolled wholesalers/distributors to Probuphine REMS certified physicians.

l. Ensure that Probuphine is only dispensed and administered by a Probuphine REMS certified physician or a qualified designee.

m. Ensure the Probuphine REMS training program is available for all Probuphine REMS certified physicians and qualified designee(s) identified through the Designee Authorization Request Form

Reviewer Comments: DRISK's proposal includes a requirement for all HCPs who prescribe or administer Probuphine to complete a full range of clinical and procedure training. (b) (4) Additionally, further details are included above to outline the expected requirements for a certified prescriber/dispenser and the Sponsor.

The risks of accidental overdose, abuse, and misuse will be disseminated to HCPs using educational brochures similar to the brochures included in the approved Suboxone, Subutex, and Buprenorphine-containing Transmucosal products for Opioid Dependence (BTOD) REMS.

3.7.4.2 ETASU D – Documentation of Safe Use

Probuphine will only be dispensed to patients with evidence or other documentation of safe-use conditions.

a. Titan will ensure that certified physicians agree to only dispense and administer Probuphine to patients once the patient has received a copy of the Medication Guide and counseling regarding the following:

- Risks of accidental overdose, misuse, and abuse
- Potential serious risks of Probuphine, including potential complications of the implantation/removal procedure
- Appropriate wound care

b. Titan will provide certified physicians with a Probuphine Implantation/Removal Log to document the implantation and removal of Probuphine, including the date, number of rods implanted/removed, name of individual performing the procedure, and location of rods for individual patients.

The Sponsor's proposal included ETASU D as a component of the proposed REMS.

3.7.5 Implementation System

1. Titan will ensure that wholesalers/distributors who distribute Probuphine are enrolled in the Probuphine REMS Program. The wholesaler/distributer enrollment process is comprised of the following steps that must be completed by the wholesaler/ distributor's authorized representative, prior to receiving Probuphine for distribution:

   a. Complete and sign the Wholesaler/Distributor Enrollment Form and send it to Titan (by fax or mail). In signing the Wholesaler/Distributor Enrollment Form, each wholesaler/distributor is required to indicate that they understand that

Probuphine is available only through the Probuphine REMS Program and acknowledge that they must comply with the following Probuphine REMS Program requirements:

i. The Wholesaler/Distributor will ensure that Probuphine is only distributed to physicians in which certification in the Probuphine REMS Program has been validated.

ii. The Wholesaler/Distributor will cooperate with periodic audits or non-compliance investigations to ensure that Probuphine is distributed in accordance with the Probuphine REMS program requirements.

iii. Wholesalers/Distributors will be required to renew their enrollment in the Probuphine REMS program every three (3) years.

b. Titan will ensure that all forms are complete prior to enrolling a wholesaler/ distributor in the Probuphine REMS Program

c. Titan will notify wholesalers/distributors when they are enrolled in the Probuphine REMS Program and, therefore, able to distribute Probuphine.

The Wholesaler/Distributor Enrollment Form is part of the REMS and appended.

2. Titan will maintain a validated and secure database that includes a list of all certified physicians, which will be available to wholesalers/distributers to ensure distribution of the product only to certified physicians.
3. Titan will notify wholesalers/distributers before their enrollment is due to expire of the need to re-enroll in the Probuphine REMS program.
4. Titan will monitor physician certification compliance and address deviations by conducting prescriber audits.
    a. If a certified physician is found to be non-compliant with the Probuphine REMS, Titan will institute corrective action and may de-activate physicians for which re-training has proven ineffective, removing them from the Probuphine REMS program.
    b. Titan will perform regular on-site audits of certified physicians participating in the Probuphine REMS.
5. If there are substantial changes to the Probuphine REMS program, Titan will update all affected materials and notify certified prescribers and wholesalers/distributors of the changes, as applicable.
6. Based on monitoring and evaluation of the Probuphine REMS Elements to Assure Safe Use, Titan will take reasonable steps to improve implementation of these elements and to maintain compliance with the Probuphine REMS program requirements, as applicable.
7. Titan will develop and follow written procedures related to the implementation of the REMS.

Reviewer Comments: Due to the restricted distribution from an enrolled wholesaler/distributor directly to a certified prescriber, the prescriber will be required to

maintain an onsite inventory of Probuphine based on applicable regulations for maintaining such inventory.

3.7.6 Timetable for submission of assessments

Titan will submit REMS Assessments for Probuphine to the FDA at 6 months and 1 year from the date of the REMS approval (mmm dd, 2013), and then annually thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Titan will submit each assessment so that it will be received by the FDA on or before the due date.

4 DISCUSSION

A REMS for Probuphine is required to ensure the benefits outweigh the risks of complications due to improper implantation/removal technique and potential for accidental overdose, misuse, and abuse. The Sponsor has proposed a REMS for Probuphine consisting of a training program for HCP's, to minimize adverse events due to the implantation and removal procedures, and a tightly controlled distribution system, to minimize the risks of abuse, misuse, and diversion. Also, different models of care have been presented by the Sponsor to demonstrate how Probuphine will be utilized in the health care system.

DRISK's proposed minimum requirements for the REMS include a Medication Guide (MG), communication plan (CP), and elements to assure safe use (ETASU). The recommended ETASU include prescriber certification, certification of the individual who will administer the medication, and documentation of safe use conditions. An implementation system must also be required; including wholesaler/distributor enrollment to ensure Probuphine is only distributed to certified prescribers. Additionally, DRISK's proposed REMS includes a system that is minimally burdensome to ensure the benefits outweigh the risks. DRISK's proposed program accommodates the use of Probuphine in both OBOT and OTP settings.

Medication Guide

A MG must be provided to each patient prior to the implantation procedure to ensure the patient has adequate understanding of the potential complications that can arise from the procedure and appropriate wound care. The MG can be used by prescribers to counsel their patients prior to the procedure.

Communication Plan

A CP must be included in the Probuphine REMS to support implementation of the REMS for Probuphine once approved. The CP will be utilized to inform prescribers of the availability of the product via a restricted distribution REMS program and its applicable requirements. To ensure adequate dissemination, the CP should include a DHCP letter that is disseminated to all DATA-2000 waived prescribers, prescribers in OTPs, and relevant professional societies. Additionally, a REMS website should be maintained to ensure an alternative mechanism is available for HCPs to access the REMS related materials.

Elements to Assure Safe Use/Implementation System

The REMS must include a mandatory training program for physicians who will prescribe and administer Probuphine. The required training program will ensure that individuals who do not have a surgical background receive adequate experiential and didactic training to safely perform the procedure.

The training program proposed by the Sponsor is neither adequate nor validated. (b) (4) [redacted] Also, while the Sponsor claims that the training has been validated by the improvement in the clinical trials, as demonstrated by fewer adverse events related to the implantation and removal procedures in PRO-806 and PRO-811 versus PRO-805 and PRO-807; sufficient evidence has not been provided to demonstrate that the training will correlate to fewer adverse events in real world practice. Furthermore, the Sponsor should validate the training program through human factors testing prior to implementation.

DATA-2000 requires the physician who dispenses, or administers, buprenorphine for the treatment of opioid addiction in the office-based setting to be DATA-2000 waived. The DATA-2000 waived physician may allow the administration of buprenorphine by another individual only if the product is administered in his/her presence. DRISK's proposed REMS permits the administration of Probuphine by such an individual if the individual has undergone the REMS experiential and didactic training. The certified prescriber will be responsible for ensuring that the training has been completed prior to establishing such an individual as a designee to perform the procedure. (b) (4) [redacted] Sponsor's proposed model does not comply with the requirements set forth in DATA-2000.

In order to ensure that Probuphine is only administered by certified prescribers, the REMS must include a closed distribution system. Based on the CSA, inclusion of a pharmacy within the distribution system for a controlled substance requires the drug to be dispensed directly to an ultimate user, or patient. For Probuphine, this would result in the need for patients to transport Probuphine to a qualified HCP for administration. However, this model would permit patients to utilize non-certified HCPs to perform the insertion/removal procedure. Therefore, in order to ensure only certified prescribers administer Probuphine, the proposed REMS requires enrollment of wholesalers/ distributors. The enrolled wholesalers/distributors would ensure Probuphine is only distributed to HCPs trained and certified in the Probuphine REMS program. While this option may increase the burden on providers to maintain a controlled substance inventory in their office, it ensures that only adequately trained HCPs administer Probuphine.

Documentation of Safe Use

Documentation of safe use must be included in the Probuphine REMS to provide prescribers with the necessary tools to counsel patients regarding the risks associated with Probuphine and to document the implantation/removal procedure.

Prescribers will counsel patients on accidental overdose, misuse, and abuse, the complications related to the implantation/removal procedure, and wound care using the MG. The proposed Probuphine Implantation/Removal Log can be used to document the appropriate number and location of rods for each patient, which would be available when needed (e.g., the transfer of care to another provider, emergent situation). Additionally, the Sponsor can audit individual certified prescribers using the Probuphine Implantation/Removal Log to ensure compliance with the REMS requirements.

4.1 OUTSTANDING QUESTIONS

Under DATA-2000, Title 35, §3502(2)(C)(i) states that with respect to narcotic drugs in schedule III, IV, or V "the drugs or combinations of drugs have, under the Federal Food, Drug, and Cosmetic Act or section 351 of the Public Health Service Act, been approved for use in maintenance or detoxification treatment" and that (ii) The drugs or combinations of drugs have not been the subject of an adverse determination. Furthermore, DATA-2000 states that "an adverse determination is a determination published in the Federal Register and made by the Secretary, after consultation with the Attorney General, that the use of the drugs or combinations of drugs for maintenance or detoxification treatment requires additional standards respecting the qualifications of practitioners to provide such treatment, or requires standards respecting the quantities of the drugs that may be provided for unsupervised use."

ORP, OCD and OCC are still evaluating the Agency's proposed REMS to determine if a mandatory REMS prescriber training and certification requirement will constitute an adverse determination under DATA-2000. ORP, OCD, and OCC must also determine if additional consultation with DEA or SAMHSA is required to assess whether the proposed REMS complies with the CSA and DATA-2000. This evaluation is pending.

Finally, although the Sponsor has met with DEA and submitted a revised REMS to fully conform to all applicable regulations, the Sponsor has not provided any formal documentation from the DEA to substantiate the validity of their proposed REMS program.

5 CONCLUSION

The REMS proposed by DRISK has not been evaluated by the Agency to determine if the minimum requirements constitute an adverse determination under the Drug Addiction Treatment Act of 2000 (DATA-2000); the results of this evaluation are pending. Additionally, the Sponsor's proposed REMS, submitted on March 13, 2013, does not comply with applicable regulations and does not contain the minimum requirements as recommended by DRISK. Therefore, based on currently available information, the Sponsor's proposed REMS (submitted March 13, 2013) is not recommended for approval.

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/s/

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04/30/2013

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concur