

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204442Orig1s000

OTHER ACTION LETTERS



NDA 204442

COMPLETE RESPONSE

Titan Pharmaceuticals, Inc.
c/o: Allene M. Dodge; Regulatory Affairs Consultant
PO Box 711
Fox Island, WA 98333

Dear Ms. Dodge:

Please refer to Titan Pharmaceuticals' New Drug Application (NDA) dated October 29, 2012, received October 31, 2012, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Probuphine (buprenorphine hydrochloride implant) for subdermal use.

We acknowledge receipt of your amendments dated November 13, 15, and 16, and December 19 and 24, 2012, and January 11, 24, and 30, February 15 and 28, March 13, 18 (letter says 15), 27, and 29, and April 2, 5, 9, 16, and 25, 2013.

We also acknowledge receipt of your amendment dated April 2, 2013, which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

1. The clinical benefit that would be associated with the minor changes in drug taking behavior that were observed in the clinical trials has not been established. Provide additional data supporting the efficacy of Probuphine, including:
 - a. Opioid blockade study
Conduct a study to evaluate the ability of Probuphine to provide opioid blockade of relevant doses of agonists, in order to identify an effective opioid-blocking dose to be studied in future clinical trials.
 - b. Study of higher doses of Probuphine
Study substantially higher doses of Probuphine, ideally doses more closely approximating the plasma levels associated with sublingual doses of 12 to 16 mg/day. Examine factors such as Body Mass Index (BMI) and/or body weight as part of your dose finding exploration to ensure that a dose appropriate for a range of patient body types is identified. Ideally, the study should be a double-blind, double-dummy

comparison to sublingual buprenorphine, which should be provided under dosing conditions that more closely approximate the way treatment is usually provided.

Alternatively, if you are aware of data showing the clinical benefit of minor changes in drug use behavior, provide the data and a rationale supporting the clinical benefit of the patterns of drug use that were typically observed in the clinical trials.

2. Human Factors Usability Evaluation

There is a paucity of clinical experience with the insertion and removal procedures for the Probuphine rods. Since the “U-technique” for removal is not a commonly used procedure with implantable contraceptives, there is limited experience with this removal procedure. The proposed training that practitioners will receive to perform the procedures will provide only minimal experience for insertion and removal of the implants. Unlike the practitioners who perform procedures for implantable contraceptives, who are generally surgeons, the training program must be sufficient to impart the necessary skills to a variety of providers, who may not have surgical experience.

Therefore, you must conduct Human Factors testing of the training associated with Probuphine’s insertion and removal. These studies will capture findings which may suggest program modifications to prevent improper implant insertion and/or removal. In addition, they will validate the proposed training program’s design and materials. Conduct a comprehensive use-related risk analysis. This risk analysis should include: a comprehensive evaluation of all the steps involved in using the device, the errors that users might commit or the tasks they might fail to perform, the potential negative clinical consequences of use errors and task failures, the risk-mitigation strategies employed to reduce any moderate or high risks to acceptable levels, and the method of validating the risk-mitigation strategies.

LABELING

1. We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.
2. Please submit draft carton and container labeling revised as follows:
 - A. General Comments
 1. Per 21 CFR 201.15(b)(1) and 201.56(a)(2), remove (b) (4)
 2. Revise the established name to read buprenorphine hydrochloride implant.
 3. Revise the strength statement to read 80 mg buprenorphine hydrochloride.
 4. Ensure that the strength statement appears directly below the established name on the principal display panel of all product labels and labeling to consistently convey this critical information. For example:

Probuphine
(buprenorphine hydrochloride implant)
80 mg per implant

5. Relocate the scheduled drug designation (CIII) away from the established name. Ensure there is adequate white space between the established name and the CIII designation so that the CIII designation does not interfere with the readability of the established name.
6. Add the lot number and expiration date to the outside box.
7. If the model of care for this product ultimately changes to one where the patient may in fact handle this product at any portion of the use system, add the statement “Keep out of reach of children” on the container labels and carton labeling.

B. Pouch Container Label

1. Revise the contents statement to read “Contents: One implant containing 80 mg buprenorphine hydrochloride.”
2. Add a statement that reads “Sterile unless pouch is damaged or opened” so that practitioners understand that the pouches ensure the sterility of each individual rod.
3. Add a route of administration statement that reads “For Subdermal Administration Only.” Ensure the route of administration statement appears below the strength statement, “80 mg per implant” and before the “Contents” statement.
4. Relocate the “Rx only” statement to the bottom portion of the label away from the proprietary name, established name, and strength statement.

C. Kit Carton Labeling ((b)(4) Implant Kit (b)(4))

1. On the principal display panel, list the contents as follows:
Contents:
Four Probuphine implants, 80 mg buprenorphine hydrochloride per implant
One applicator
Prescribing information
Medication guide
2. Back Panel:
 - i. Add a statement that reads “Active ingredients: 80 mg buprenorphine hydrochloride per implant.”
 - ii. Add a statement that lists all inactive ingredients.
 - iii. Add the Dosage and Administration statement that reads: “A single use, sterile and disposable applicator is provided. Do not use if the package has been opened, or if the sterile barrier has been otherwise compromised. Please refer to package insert for complete product information. Insert Probuphine no later than the date printed on the Probuphine pouch container label.”

- iv. Add a statement that reads: “For the Healthcare Provider: All health care providers who insert and/or remove Probuphine must receive instruction and training and, where appropriate, supervision prior to inserting or removing Probuphine.”

D. Applicator Container Label and Carton Labeling

Revise the presentation of the information to highlight the applicator device. The title of “applicator” should have equal or greater prominence to that of the proprietary name. Revise the statement of identity to appear similar to “Applicator for Probuphine (buprenorphine hydrochloride implant)” [REDACTED] (b) (4)

E. Patient Chart Label

We note the Patient Chart Label is not listed in the contents section of the Implant Kit labeling [REDACTED] (b) (4). Please provide an explanation how the Patient Chart Label will be provided to the physician.

F. Patient Identification Card

We note the Patient Identification Card is not listed in the contents section of the Implant Kit labeling [REDACTED] (b) (4). Please provide an explanation how the Patient Identification Card will be provided to the physician and patient.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the 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)].

We acknowledge receipt of your proposed REMS, included in your submission dated October 29, 2012, and amended on March 13, 2013 and April 2, 2013, which contains a Medication Guide, communication plan, elements to assure safe use, implementation system and a timetable for submission of assessments of the REMS. In accordance with section 505-1 of the FDCA, we agree that a REMS will be necessary for Probuphine (buprenorphine hydrochloride implant), if it is approved, to ensure that the benefits of the drug outweigh the risks of complications that could result from improper technique associated with the implantation/removal procedure of Probuphine (buprenorphine hydrochloride implant) and the risks of misuse, abuse, and accidental overdose associated with Probuphine treatment.

The REMS, should it be approved, will create enforceable obligations. We will continue discussion of your proposed REMS after your complete response to this action letter has been submitted.

Under 21 CFR 208.24(d), you are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided. You should submit marked up carton and container labels of all strengths and formulations with the required statement alerting the dispenser to provide the Medication Guide. We recommend one of the following statements, depending upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

- “Dispense the enclosed Medication Guide to each patient.” or
- “Dispense the accompanying Medication Guide to each patient.”

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

POSTMARKETING REQUIREMENTS UNDER 505(o)(3)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

FDA has determined that, if NDA 204442 is approved, an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the unexpected serious risk of QT prolongation with Probuphine (buprenorphine hydrochloride implant).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that, if NDA 204442 for Probuphine (buprenorphine hydrochloride implant) for subdermal use is approved, you will be required to conduct the following:

Conduct a clinical trial to assess the risk of QT prolongation with subdermal buprenorphine, i.e., a thorough QT (tQT) trial.

Any additional specific details of this required postmarketing clinical trial, including a timetable and annual reporting requirements, will be described more fully in the approval letter for this application, if it is approved.

If you complete this trial prior to re-submitting your application, you may include the final report and relevant data sets in your Complete Response submission to facilitate review of the information.

ADDITIONAL COMMENTS:

1. As already discussed at your pre-NDA meeting, you should evaluate the effect of scarring or inflammation at previously implanted sites on the re-implantation and bioavailability of Probuphine. Probuphine has never been administered in an implant site that was previously used. Scarring or other local tissue changes may have an impact on drug delivery, or on the feasibility of re-implantation. Because opioid addiction is a chronic,

relapsing disorder, it is conceivable that long-term or even life-long pharmacologic treatment will be required by some patients.

Should this evaluation reveal that sites cannot be re-used, study implantation sites other than the arm.

2. Consider conducting a study of Probuphine in patients with lower sublingual buprenorphine requirements. The current dosing regimen of Probuphine may well be appropriate for some patients. In particular, it may provide an adequate dose for patients who are in long-term, stable, recovery and are maintained on low (6 mg or less) doses of sublingual buprenorphine. These patients require less close clinical supervision and clinical interaction than patients early in treatment, and are likely to be the ideal candidates for a drug product which permits very infrequent contact with the treatment provider.
3. Consider modifying the implant to include a radio-opaque marker to facilitate removal when the implants cannot be palpated, or migrate from the implantation site.
4. We do not believe the mg/m^2 body surface area-derived safety margins modified from the reference sublingual label as described in the Pregnancy, (b) (4) and Fertility sections of the proposed label are appropriate.

In order to support nonclinical labeling of Probuphine doses which produce exposures within or in excess of the exposure levels of the listed drug during any portion of the implants usage you will need to provide a persuasive exposure-based scientific justification for safety margins described in nonclinical sections which may require bridging toxicokinetic studies. Otherwise you will need to conduct reproductive toxicology studies necessary to support sections 8.1 *Pregnancy* and carcinogenicity studies described in 13.1 *Carcinogenesis, Mutagenesis, and Impairment of Fertility*.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Lisa E. Basham, Senior Regulatory Health Project Manager, at (301) 796-1175.

Sincerely,

{See appended electronic signature page}

Bob A. Rappaport, M.D.
Director
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

BOB A RAPPAPORT
04/30/2013