CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
21-306

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	June 30, 2010
To:	Bob Rappaport, MD, Director Division of Anesthesia and Analgesia Products (DAAP)
Thru:	Claudia Karwoski, Pharm.D., Director Division of Risk Management (DRISK)
From:	**Scientific Lead:** Jeanne Perla, Ph.D., Risk Management Analyst **Team Members:** **DRISK** Gita Toyserkani, Pharm.D., MBA, Acting Team Leader Marcia Britt, Ph.D., Health Education Reviewer Brian Gordon, MA, Social Science Reviewer **Division of Pharmacovigilance II** Afrouz Nayernama, Pharm.D., Safety Evaluator **Division of Drug Marketing, Advertising and Communication** Mathilda Fienkeng, Pharm.D., Regulatory Review Officer Twyla Thompson, Pharm.D., Regulatory Review Officer **Office of Compliance Division of Risk Management and Surveillance** Agnes Plante, BSN, RN, Consumer Safety Officer
Subject:	Review of Risk Evaluation and Mitigation Strategy (REMS)
Drug Name(s):	Butrans™ (buprenorphine) Transdermal System
Application Type/Number:	NDA 21-306
Applicant/sponsor:	Purdue Pharma Inc
OSE RCM #:	RCM: 2009-1865

1 INTRODUCTION AND BACKGROUND

This memo is in response to a request from the Division of Anesthesia and Analgesia Products (DAAP) to the Division of Risk Management (DRISK) to review the proposed Risk Evaluation and Mitigations Strategy (REMS) for Butrans (buprenoprine) Transdermal System.

Butrans™ (buprenorphine) Transdermal System is a transdermal system providing systemic delivery of buprenorphine over a 7-day period. Butrans™ is an opiate partial agonist with the proposed indication for the relief of moderate to severe chronic pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time. Butrans will be available in 5mcg/h, 10 mcg/h, and 20 mcg/h patches. Butrans™ is not intended for use as an as-needed analgesic nor is it intended for use in the treatment of opioid dependence.

Purdue submitted a proposed REMS on September 25, 2009 with their Complete Response to the not approvable action letter of August 31, 2001. The proposed REMS consisted of a Medication Guide, a communication plan, and a timetable for submission of assessments.

The Agency has been considering a class REMS for long-acting and extended release opioid products, to address the risks of abuse, misuse, and overdose. Until the Agency has determined the elements of the class opioid REMS, DAAP with input from OSE, has decided that an interim REMS for these opioids will be required as these products are approved. The Sponsor was informally notified of this requirement on February 1, 2010.

Purdue submitted an interim proposed REMS on February 18, 2010 and amended on June 22 and 29, 2010 based on Agency comments. The REMS includes a Medication Guide, Element to Assure Safe Use, specifically a plan to ensure Healthcare providers who prescribe Butrans™ will receive training, and a timetable for submission of assessment of the REMS.

Once the elements of the class-wide opioid REMS are determined, Purdue will be notified to resubmit a REMS incorporating these elements.

2 MATERIAL REVIEWED

2.1 DATA AND INFORMATION SOURCES

1. Proposed REMS received September 25, 2009
2. Proposed REMS amendment, received February 18, 2010
3. Proposed REMS amendment, received June 22, 2010
4. Proposed REMS amendment, with final REMS proposal received June 29, 2010

2.2 ANALYSIS TECHNIQUES

The submission was reviewed for conformance with Title IX, Subtitle A, Section 901 of the Food Drug Administration Amendments Act of 2007 (FDAAA) and responsiveness to comments submitted to Purdue as part of the ongoing review.

3 RESULTS OF REVIEW

3.1 SAFETY CONCERNS

Safety concerns identified by Purdue, DAAP, and OSE are the potential for abuse, misuse, overdose, and addiction to Butrans™, as well as the risk of use of Butrans™ 10 mcg/h, and 20 mcg/h patches in non-opioid-tolerant individuals.

3.2 PROPOSED REMS

The June 29, 2010 final proposed REMS submission contains the following:

3.2.1 GOALS:

1. To inform patients and healthcare professionals about the potential for abuse, misuse, overdose, and addiction of Butrans™
2. To inform patients and healthcare professionals about the safe use of Butrans™

3.2.2 Medication Guide (MG)

In accordance with 21 CFR 208.24, a Medication Guide will be dispensed with each Butrans™ prescription. Purdue Pharma L.P. will ensure that the Medication Guide is available for distribution to patients receiving a prescription for Butrans™ by providing sufficient numbers to distributors and authorized dispensers.

1. One copy of the Full Prescribing Information, which includes the Medication Guide, will be packaged with each carton of Butrans™.
2. Two separate additional Medication Guides will also be packaged with each carton of Butrans™.
3. Per 21CFR 208.24(d) the label on each carton of Butrans™ will include prominent and conspicuous statement:
   a. instructing authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed (eg, "Attention Dispenser: Accompanying Medication Guide must be provided to each patient upon dispensing"); and
   b. stating how the Medication Guide is provided.
4. Medication Guides will also be available from Purdue Pharma L.P. Field Sales representatives, through an Internet presence at www.butransrems.com, and from Purdue's Medical Services Department (1-888-726-7535).

3.2.3. Elements to Assure Safe Use

1. Healthcare providers who prescribe Butrans™ will receive training.

   a. Purdue will ensure that training will be provided to healthcare providers who prescribe Butrans™. To become trained, each prescriber will be provided with the

Butrans™ Educational materials.

The training includes the following:

i) Proper patient selection;
ii) Appropriate Butrans™ dosing and administration;
iii) General principles of safe opioid use, including information about opioid abuse and how to identify patients who are at risk for addiction;
iv) Potential abuse, misuse, addiction, and overdose from exposure to opioids including Butrans™;
v) Risks associated with Butrans™, including:
    1.) Overdose in patients who have not developed tolerance to the sedating or respiratory-depressant effects of opioids when using initial dose greater than 5 mcg/hour;
    2.) The risk of addiction from exposure to Butrans™;
    3.) The risk of unintentional exposure to Butrans™ in persons for whom it was not prescribed, including accidental exposure to children; and
    4.) Temperature-dependent increases in buprenorphine released from the system resulting in possible overdose and death;
vi) Information to counsel patients and caregivers on the need to store opioid analgesics safely out of reach of children and household acquaintances, the need to properly dispose of unused drugs when no longer needed by the patient and not to share drugs with anyone for any reason; and
vii) Importance of dispensers providing each patient a Medication Guide each time the product is dispensed and instructing the patient to read it.

b. Purdue will ensure that no later than 3 weeks prior to first availability of Butrans™ to healthcare professionals, a Dear Healthcare Professional letter will be mailed to prescribers most experienced in treating chronic pain with opioid agonists, including, pain specialists, physiatrists, and primary care physicians. This letter is designed to convey and reinforce the risks of abuse, misuse, overdose, and addiction of Butrans™ as well as the need to complete the Butrans™ REMS Education Program. The letter will be available on the Purdue website (www.butransrems.com) for 1 year.

c. The mailing will also include the following Butrans™ REMS Educational Program materials:
    i. Medication Guide for Butrans™ (including Instructions for Use)
    ii. Prescribing Butrans™ (buprenorphine) Transdermal System CIII: A Training Guide for Healthcare Providers
    iii. Butrans™ Training Confirmation Form for Healthcare Providers

d. Additional printed educational material will be available through Purdue Pharma L.P. Field Sales distribution and by calling the Purdue Medical Services Department toll free number (1-888-726-7535).

e. The educational material will also be available for download at

www.butransrems.com.

f. Purdue will maintain a list of all prescribers who have completed the Butrans™ REMS Educational Program.

Prescribers will be re-trained every two years or following substantial changes to the Butrans™ REMS. Substantial changes may include changes in the Full Prescribing Information for Butrans™, in the Medication Guide for Butrans™, or in the REMS for Butrans™ that requires substantial modification of the educational materials.

The following materials are part of the REMS and are appended to the REMS document:

i. Dear Healthcare Professional Letter for Butrans™
ii. Medication Guide for Butrans™ (including Instructions for Use)
iii. The Healthcare Provider Guide, "Prescribing Butrans™ (buprenorphine) Transdermal System CIII: A Training Guide for Healthcare Providers"
iv. Butrans™ Training Confirmation Form for Healthcare Providers

Reviewer comment:

Purdue requested that the mailing date of the DHCP letter be mailed 3 weeks prior to first availability of Butrans™ to healthcare professionals, rather than "within 60 days of approval" as was specified in the Agency's REMS comments emailed June 14, 2010. The reason for this request was that the Sponsor (b) (4) *and therefore, preferred using the timeframe of 3 weeks prior to the first availability of the drug.*

DRISK consulted the Office of Compliance (OC) and they agreed to alter the timeframe closer to launch but requested the date of drug launch, date(s) of the mailing(s) to Healthcare Professionals, number of recipients, and identify the sources for the mailing lists (for example, AMA) be included in the information needed for assessments in the Approval letter.

Purdue was notified June 23, 2010, June 25, 2010 and June 28, 2010 of additional revisions needed to be made to the Healthcare Professional Training Guide (Appendix 1).

3.2.4 Implementation System

Because Butrans™ can be approved without the Elements to Assure Safe Use described under FDCA 505-1(f)(3) (B), (C), and (D) of the Act, an implementation system is not required.

3.2.5. Timetable for Submission of Assessments

Purdue Pharma L.P. will submit REMS Assessments to FDA every 6 months for the first year from the date of approval of the REMS, and annually thereafter. To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare

the submission, the reporting interval covered by each assessment will conclude no earlier than 60 days before the submission date for that assessment. Purdue Pharma L.P. will submit each assessment so that it will be received by the FDA on or before the due date.

The REMS Assessment Plan was summarized in the REMS Supporting Document and will be included in the approval letter. The information needed for assessment will include at a minimum:

1. An evaluation of patients' understanding of the serious risks of Butrans™ (buprenorphine) Transdermal System.
2. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.
3. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.
4. A report on the status of the training program for healthcare providers.
5. Date of drug launch; date(s) of the mailing(s) to Healthcare Professionals; number of recipients; identify the sources for the mailing lists (for example, AMA).
6. An evaluation of healthcare providers' awareness and understanding of the serious risks associated with Butrans™ (buprenorphine) Transdermal System (for example, through surveys of healthcare providers).
7. Specification of measures that would be taken to increase awareness if surveys of healthcare providers indicate that healthcare provider awareness is not adequate.
8. An analysis and summary of surveillance and monitoring activities for abuse, misuse, overdose, and addiction and any intervention taken resulting from signals of abuse, misuse, overdose, and addiction.
9. An analysis to evaluate Butrans™ (buprenorphine) Transdermal System utilization patterns including use in non-opioid tolerant patients.
10. With respect to REMS goals, an assessment of the extent to which the elements to assure safe use are meeting the goals or whether the goals or such elements should be modified.

Reviewer comments:

As part of the negotiations of the final Butrans™ REMS, comments came from the OC regarding the information needed for Assessments and requested to include the date of the shipment of the DHCL letter and the number of mailings.

Purdue did not submit the survey instruments or methodologies. Without the survey instruments and methodologies there is insufficient information to complete a review of the patient and prescriber surveys. Purdue was informed to submit for review the detailed plans that will be used to evaluate patients' and prescribers' understanding about the risks associated with and safe use of Butrans™ at least 90 days before the evaluation will be conducted. General comments about what should be included in the patient and prescriber methodologies and survey instruments were sent to Purdue April 28, 2010 (Appendix 2).

4 DISCUSSION AND CONCLUSION

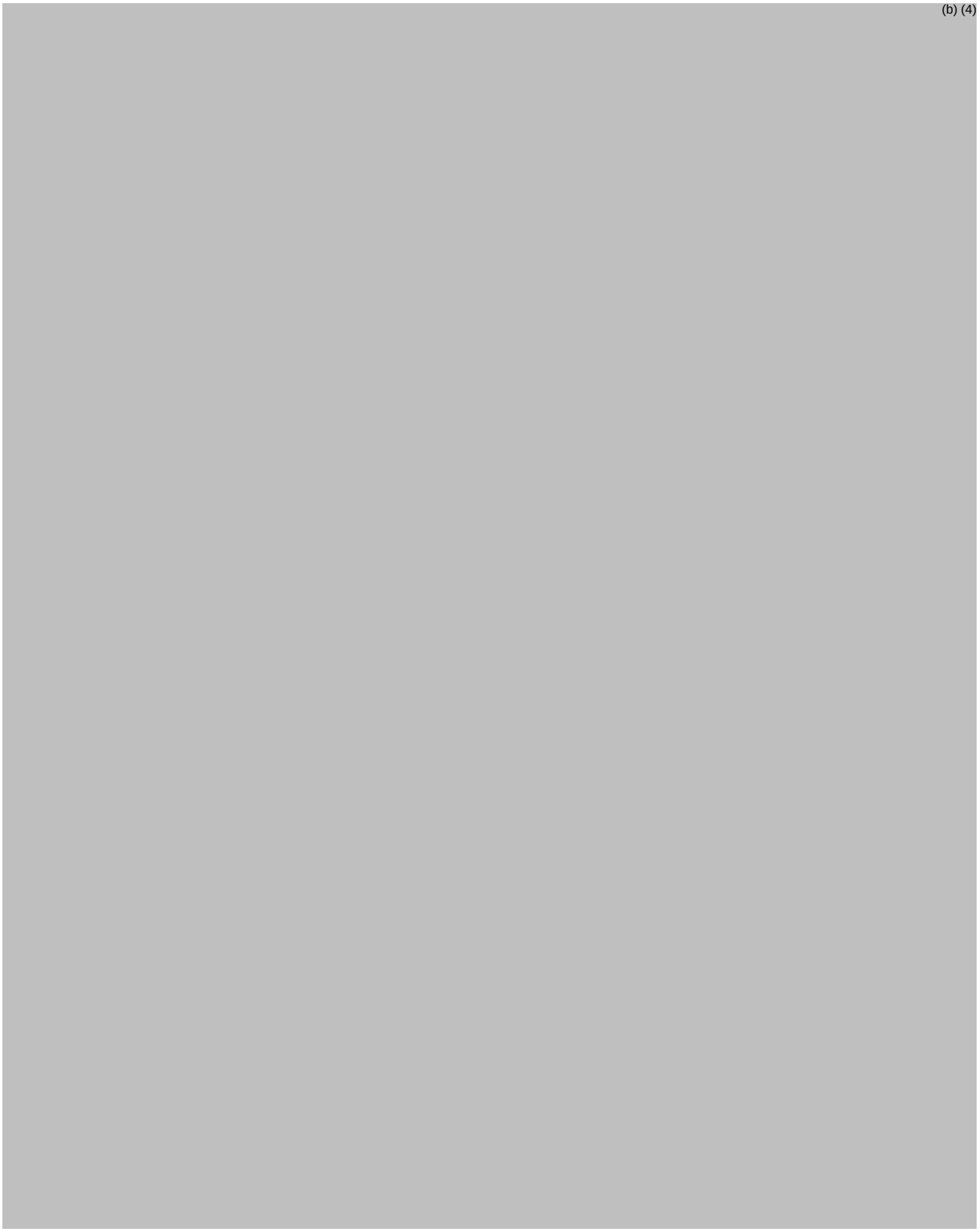
An interim REMS will be implemented by Purdue until a class-wide opioid REMS has been approved. The proposed REMS dated June 29, 2010 contains the required REMS elements which includes a Medication Guide, element to assure safe use, and a timetable for submission of assessments and meets the criteria identified by the FDA as necessary for this REMS at this time. The REMS Supporting Document outlines the information that the Sponsor will use to assess the effectiveness of the REMS in meeting the goals. Purdue did not submit the survey instruments or methodologies; however this information is not required to approve the REMS.

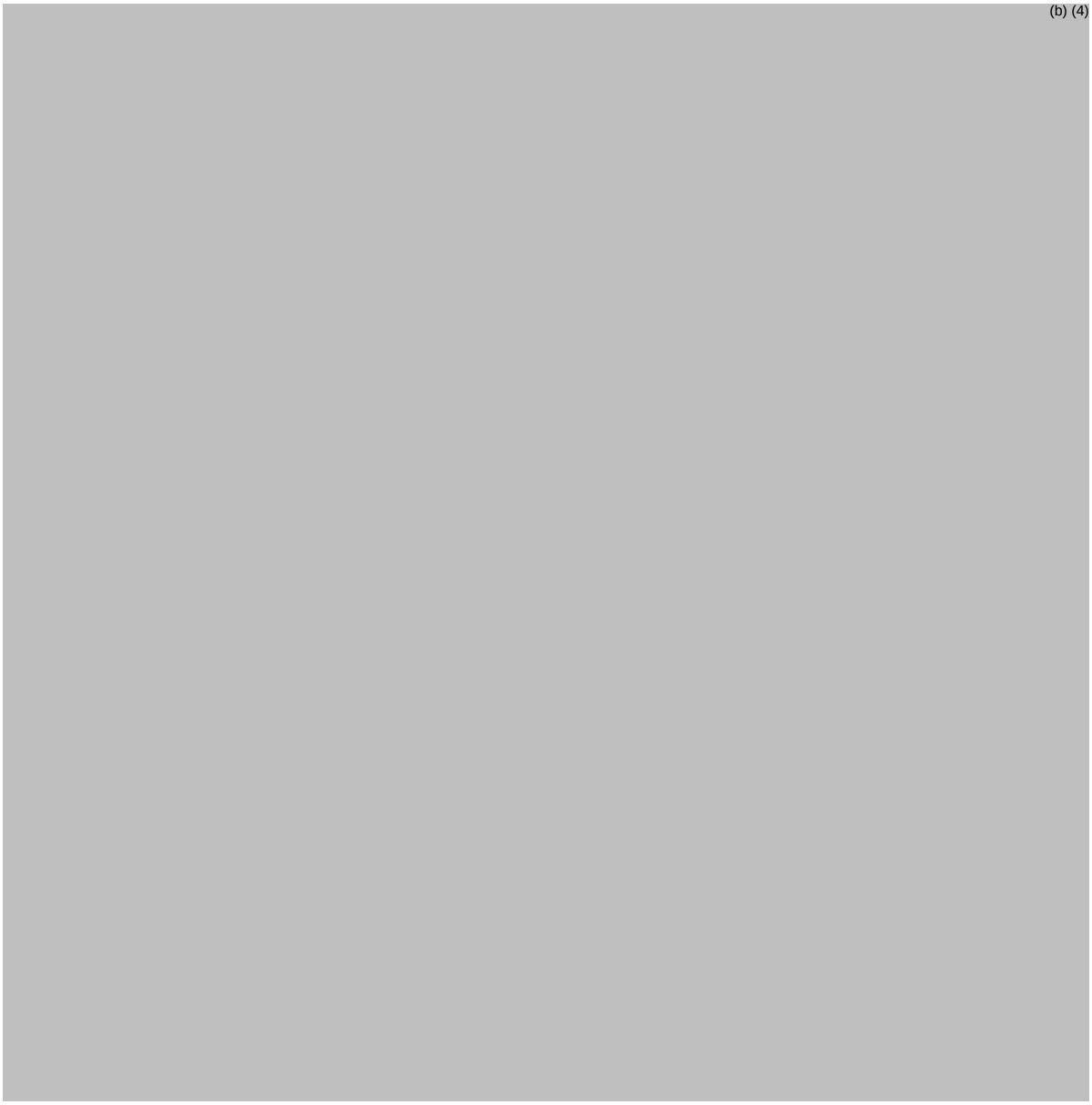
Based on our current understanding of the risks of Butrans™, DRISK believes that a REMS comprised of the components included in the June 29, 2010 proposed REMS is appropriate and should be approved until a class-wide opioid REMS is established.

Please consult DRISK once the survey instruments and methodologies haven been submitted by the Sponsor.

Appendix 1: Comments on the Butrans™ Healthcare Provider Training Guide sent to the sponsor June 23, 2010 and June 25, 2010

To maintain consistency with the FPI, revise the following sections:




(b) (4)

Appendix 2: Comments on Survey Methodology and Instruments sent to the sponsor April 28, 2010.

Submit for review the detailed plans that will be used to evaluate patients' and prescribers' understanding about the risks associated with and safe use of Butrans. This information **does not** need to be submitted for FDA review prior to approval of your REMS, however it should be submitted at least 90 days before the evaluation will be conducted. The submission should be coded "REMS Correspondence." The submission should include all methodologies and instruments that will be used in the evaluations.

1. Recruit respondents using a multi-modal approach. For example, patients might be recruited online, through physicians' offices, through pharmacies, managed care providers, or through consumer panels.
2. Explain how non-respondent follow-up or reminders will be completed and the planned frequency of the non-respondent follow-ups.
3. Explain how incentive or honorarium will be offered and the intended amount.
4. Explain how sites will be selected.
5. Submit for review any recruitment advertisements.
6. Define the sample size and confidence interval associated with that sample size.
7. Define the expected number of prescribers and patients to be surveyed, and how the samples will be determined (selection criteria)
8. Explain the inclusion criteria; that is, who is an eligible respondent. For example, a patient respondent might be:
    - Age 18 or older
    - Currently taking Butrans or have taken in past 3 months
    - Not currently participating in a clinical trial involving Butrans
9. Submit any screener instruments, and describe if any quotas of sub-populations will be used.
10. Explain how the surveys will be administered and the frequency of the surveys.
11. Offer respondents multiple options for completing the survey. This is especially important for inclusion of the lower literacy patient population. For example, surveys could be completed online, in writing or by mail, over the phone, or in person.
12. Explain how surveyors will be trained.
13. Explain controls used to compensate for the limitations or bias associated with the methodology
14. The patient sample should be demographically representative of the patients who use Butrans.

15. The prescriber sample should be demographically representative of the healthcare providers who prescribe or administer Butrans.
16. If possible and appropriate, the sample should be diverse in terms of: age, race, ethnicity, sex, socio-economic status, education level, geographically
17. Submit for review the introductory text that will be used to inform respondents about the purpose of the survey.
18. Potential respondents should be told that their answers will not affect their ability to receive or take (patients) or prescribe (prescribers) Butrans, and that their answers and personal information will be kept confidential and anonymous.
19. Respondents should not be eligible for more than one wave of the survey.
20. Results should be analyzed on an item-by-item or variable-by-variable basis. The data may be presented using descriptive statistics, such as sample size, mean, standard deviation, median, minimum and maximum (for continuous variables), and frequency distributions (for categorical variables).
21. Data may be stratified by any relevant demographic variable, and presented in aggregate. We encourage you to submit with your required assessments all methodology and instruments that were used to evaluate the effectiveness of the REMS.

With regard to the patient survey instrument:

22. The assessment is to evaluate the effectiveness of the REMS in achieving its goal by evaluating patients' knowledge of the serious risks associated with and safe use of Butrans. The assessment is not to evaluate consumer comprehension of the Medication Guide.
23. Respondents should not be offered an opportunity to read or see the Medication Guide again prior to taking the survey.
24. Submit for review the survey instruments (questionnaires and/or moderator's guide), including any background information on testing survey questions and correlation to the messages in the Medication Guide.
25. The patient knowledge survey should include a section with questions asking about the specific risks or safety information conveyed in the Medication Guide to see if the patient not only understands the information, but knows what to do if they experience the event.
26. Most of the risk-specific questions should be derived from information located in the "What is the Most Important Information I should know about Butrans?" section of the Medication Guide

27. The risk-specific questions should be non-biased, non-leading, multiple choice questions with the instruction to "select all that apply." Each question should have an "I don't know" answer option.
28. The order of the multiple choice responses should be randomized on each survey.
29. The order of the questions should be such that the risk-specific questions are asked first, followed by questions about receipt of the Medication Guide. Demographic questions should be collected last or as part of any screener questions.
30. Respondents should not have the opportunity or ability to go back to previous questions in the survey if the survey is conducted by telephone or online.
31. Explain if and when any education will be offered for incorrect responses.
32. Include questions about receipt of the Medication Guide in the patient survey as a way to fulfill the obligation to report on the distribution of the Medication Guide.
33. Just prior to the questions about receipt of the Medication Guide, include text explaining what is a Medication Guide. For example,

    Now we are going to ask you some questions about the Medication Guide you may have received with Butrans. The Medication Guide is a paper handout that contains important information about the risks associated with use of Butrans and how to use Butrans safely. Medication Guides always include the title "Medication Guide".
34. Use the following (or similar) questions to assess receipt and use of the Medication Guide.

a. Who gave you the Medication Guide for Butrans? (Select all that apply)
    a) My doctor or someone in my doctor's office
    b) My pharmacist or someone at the pharmacy
    c) Someone else - please explain:

       _____
    d) I did not get a Medication Guide for Butrans

b. Did you read the Medication Guide?
    - All,
    - Most,
    - Some,
    - None

c. Did you understand what you read in the Medication Guide?
    - All,
    - Most,
    - Some,
    - None

d. Did someone offer to explain to you the information in the Medication Guide?
    - o Yes, my doctor or someone in my doctor's office
    - o Yes, my pharmacist or someone at the pharmacy
    - o Yes, someone else – please explain:
      _____
    - o No

e. Did you accept the offer? Yes or No

f. Did you understand the explanation that was given to you?
    - o All,
    - o Most,
    - o Some,
    - o None

g. Did or do you have any questions about the Medication Guide? Yes or No (If Yes, list your question(s) below) Note: This is an open text field that should be grouped/coded by the sponsor prior to submitting to FDA

With regard to the prescriber survey instrument:

35. The assessment is to evaluate the effectiveness of the REMS in achieving its goal by evaluating prescribers' knowledge of the serious risks associated with and safe use of Butrans. The assessment is not to evaluate prescribers' comprehension of the educational materials.
36. Respondents should not be offered an opportunity to read or see any educational materials (prescribing information, communications, promotional materials, videos, etc.) prior to taking the survey.
37. Submit for review the survey instruments (questionnaires and/or moderator's guide), including any background information on testing survey questions and correlation to the messages in any educational materials.
38. The prescriber knowledge survey should include a section with questions asking about the specific risks and safety information conveyed in the educational materials.
39. Questions should be non-biased, non-leading, multiple choice questions with the instruction to "select all that apply." Each question should have an "I don't know" answer option.
40. The order of the multiple choice responses should be randomized on each survey.
41. The order of the survey questions should be such that the risk-specific questions are asked first, followed by questions about receipt of the educational materials. Demographic questions should be collected last or as part of any screener questions.

42. Respondents should not have the opportunity or ability to go back to previous questions in the survey if conducted by telephone or online.

43. Explain if and when any education will be offered for incorrect responses.

44. Use the following (or similar) questions to assess receipt and use of the educational materials.

a. Prior to today, which of the following were you aware of or received with regard to Butrans? (Select all that apply)

Full Prescribing Information	□	□
Medication Guide	□	□
Dear Healthcare Provider Letter	□	□
Prescribing Butrans: A Healthcare Professional Guide	□	□
Something else - please explain:	□	□
None of the above	□	□

b. Did you read the Full Prescribing Information?
   - All,
   - Most,
   - Some,
   - None
   - I did not receive the Butrans Full Prescribing Information

c. Did you read the Medication Guide?
   - All,
   - Most,
   - Some,
   - None
   - I did not receive the Butrans Medication Guide

d. Did you read the Dear Healthcare Provider Letter?
   - All,
   - Most,
   - Some,
   - None
   - I did not receive the Butrans Dear Healthcare Provider Letter

e. Did you read the Prescribing Butrans: A Healthcare Professional Guide?
    - All,
    - Most,
    - Some,
    - None
    - I did not receive the Prescribing Butrans: A Healthcare Professional Guide

f. Do you have any questions about any of the educational materials related to Butrans? Yes or No (If Yes, list your question(s) below) Note: This is an open text field that should be grouped/coded by the sponsor prior to submitting to FDA

Please let us know if you have any questions.

APPENDIX B

Butrans™ DEAR HEALTHCARE PROFESSIONAL LETTER

[Date]

[prescriber name]

[street address]

[city, state zip code]

Dear Prescriber:

The purpose of this communication is to notify you that a Risk Evaluation and Mitigation Strategy (REMS) has been instituted for Butrans™.

The Butrans™ REMS is deemed necessary by the U.S. Food and Drug Administration (FDA) to ensure that the benefits of Butrans outweigh its potential risk of misuse, abuse, overdose and addiction to Butrans. Butrans contains buprenorphine, a partial agonist at the mu-opioid receptor and a Schedule III controlled substance. Butrans can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing Butrans in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, overdose, and addiction.

Butrans™ is indicated for the management of moderate to severe chronic pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. Butrans has not been studied and is not approved for use in the management of addictive disorders.

The goals of the Butrans™ REMS program are:

Goal 1: To inform patients and healthcare professionals about the potential for misuse, abuse, and overdose from, and addiction to Butrans™.

Goal 2: To inform patients and healthcare professionals about the safe use of Butrans™.

Butrans™ is contraindicated in:

- patients who have significant respiratory depression
- patients who have severe bronchial asthma
- patients who have or are suspected of having paralytic ileus
- patients with known hypersensitivity to any of its components or the active ingredient, buprenorphine
- the management of acute pain or in patients who require opioid analgesia for a short period of time
- the management of post-operative pain, including use after out-patient or day surgeries
- the management of mild pain
- the management of intermittent pain (e.g., use on an as-needed basis [prn])

Safe Use, Storage and Disposal

The buprenorphine contained in Butrans™ is supplied in sealed transdermal systems in packages which pose little risk of exposure to health care workers. If the adhesive from the drug matrix accidentally contacts the skin, the area should be washed with water. Do not use soap, alcohol, or other solvents to remove the adhesive because they may enhance the absorption of the drug.

When changing the system, remove the Butrans™ patch, fold it over on itself, and flush it down the toilet. Alternatively, Butrans can be sealed in the Patch-Disposal Unit provided and then disposed of in the trash. Butrans should never be thrown away in the trash without sealing it in the Patch-Disposal Unit. Apply immediately after removal from the individually sealed package. Do not use a Butrans patch if the pouch seal is broken or the patch is cut, damaged, or changed in any way.

Misuse and Abuse

Abuse may occur by applying the transdermal system in the absence of legitimate purpose, or by ingesting buprenorphine extracted from the transdermal system. The risk of fatal overdose is further increased when buprenorphine is abused concurrently with alcohol or other CNS depressants, including other opioids and benzodiazepines.

In cases of overdose, remove Butrans™ immediately. Even in the face of improvement, continued medical monitoring is required because of the possibility of extended effects as opioid continues to be absorbed from the skin.

Due to the long terminal half-life of buprenorphine (approximately 26 hours) and the relatively short half-life of opioid antagonists, keep the patient under continued surveillance (at least 24 hours) and administer repeated doses of the antagonist according to the antagonist labeling as needed to maintain adequate respiration.

Naloxone may not be effective in reversing any respiratory depression produced by buprenorphine. High doses of naloxone, 10-35 mg/70 kg, may be of limited value in the management of buprenorphine overdose. The onset of naloxone effect may be delayed by 30 minutes or more. Doxapram hydrochloride (a respiratory stimulant) has also been used. Maintenance of adequate ventilation is essential when managing Butrans™ overdose and more important than specific antidote treatment with an opioid antagonist such as naloxone. Please see the full prescribing information for more information about treating overdose.

Patient Counseling

Patients should also be advised to store opioid analgesics, including Butrans™, safely and out of the reach of children, other household members, visitors and pets.

Patients should be instructed against use by individuals other than the patient for whom it was prescribed.

You are strongly advised to discuss the risks associated with Butrans™ with your patients and/or their caregivers and encourage them to read the Medication Guide. This Medication Guide (including Instructions for Use) contains important information on the safe and effective use of Butrans. The Butrans Medication Guide should be provided by the pharmacist to patients every time Butrans is dispensed.

A REMS packet containing important information regarding the prescribing of Butrans™ accompanies this letter. Purdue Pharma L.P. encourages you to review the educational material that discuss the risk of misuse, abuse, overdose and addiction from exposure to opioids, how to identify patients who are at risk for addiction, information to counsel patients on proper safe storage of medications and patch application, removal and disposal.

Content of the Butrans™ REMS packet:

- Prescribing Butrans™ (buprenorphine) Transdermal System CIII: A Training Guide for Healthcare Providers
- Butrans™ Training Confirmation Form
- Butrans™ Medication Guide (including Instructions for Use)

As part of the REMS, the FDA has required that Purdue Pharma L.P. provide a Training Guide to healthcare providers. Healthcare providers are asked to please read the training guide received by mail or available at the Butrans™ REMS website (www.butransrems.com). The FDA has also required that a confirmation form be sent to healthcare providers to verify prescriber's understanding of the risks associated with Butrans and other information. After reading the Training Guide, healthcare providers are asked to please sign the confirmation form included in this mailing and to mail the confirmation form back in the self-addressed envelope. The confirmation form can also be completed online at the Butrans REMS website. Completion of this form does not affect your ability to prescribe Butrans. There is also an online training course containing the same word-for-word content as the Training Guide available on the Butrans REMS website.

Please report any adverse event information associated with the use of Butrans™ to Purdue Pharma L.P., at (888)726-7535 (prompt #2), or to the FDA MedWatch system by phone at (800)FDA-1088, by fax at (800)FDA-0178, or via the Internet at www.FDA.gov/medwatch.

Sincerely,

Craig J. Landau, MD
Chief Medical Officer

APPENDIX C

Butrans™ HEALTHCARE PROVIDER TRAINING GUIDE

Purdue

Butrans

HCP Training Guide

June 21, 2010

Cover

(HEADLINE) **Prescribing Butrans™ (buprenorphine) Transdermal System) CIII: A Training Guide for Healthcare Providers**

(Subhead) Healthcare Provider Training Guide

(Copy) **Please take the time to read the following pages before prescribing Butrans and review the accompanying Full Prescribing Information, along with the Medication Guide (including Instructions for Use)**

(HEADLINE) **TABLE OF CONTENTS**

(Copy)

(HEADLINE)

Introduction

(Copy)

Butrans is indicated for the management of moderate to severe chronic pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.[1]

Butrans is contraindicated in[1]:

- patients who have significant respiratory depression
- patients who have severe bronchial asthma
- patients who have or are suspected of having paralytic ileus
- patients who have known hypersensitivity to any of its components or the active ingredient, buprenorphine
- the management of acute pain or in patients who require opioid analgesia for a short period of time
- the management of post-operative pain, including use after out-patient or day surgeries
- the management of mild pain
- the management of intermittent pain (e.g., use on an as-needed basis [prn])

A Risk Evaluation and Mitigation Strategy (REMS) has been created to help assure the safe use of Butrans. The REMS has 2 goals:

Goal 1: To inform patients and healthcare professionals about the potential for misuse, abuse, and overdose from, and addiction to Butrans.

Goal 2: To inform patients and healthcare professionals about the safe use of Butrans.

The purpose of this *Training Guide for Healthcare Providers* is to provide prescribers with a highlight of safety information about Butrans so they can prescribe, dispense and counsel patients appropriately about the potential risks of Butrans including misuse, abuse, addiction and overdose. Please see the full prescribing information for detailed safety information and additional risks included in the Boxed Warning and described in the Warnings and Precautions section.

To help assure safe use of Butrans, it is important to remember that: [1]

- Butrans should always be prescribed at the lowest dose needed for pain relief.
- Butrans is not intended for use as an as-needed analgesic and not indicated for the management of postoperative pain, acute pain or mild pain.
- Patients and caregivers should be aware that hypotension, profound sedation, coma or respiratory depression may result if Butrans is added to a regimen that includes other CNS depressants (e.g., sedatives, anxiolytics [esp. benzodiazepines], hypnotics, neuroleptics, muscle relaxants, other opioids).[1]
- Patients and their caregivers should understand the directions for safe use of Butrans patches (e.g., where to apply, how often to apply, what to do if a patch falls off).

- Patients and caregivers should understand the need to store Butrans in a safe and secure place—out of the reach of children, household visitors and pets.
- Patients and caregivers should understand the need to dispose of used or unneeded Butrans patches by the "fold-and-flush" method. If the fold-and-flush method is not possible, a back-up method is by using the Self-adhesive Disposal Units that are supplied with the patches, which can then be discarded in the trash.

Part 1: Risks Associated with Butrans and Opioids

The risks associated with Butrans include:[1]

- The risk of overdose in opioid-naïve patients when using an initial dose greater than 5 mcg/hour.
- The risk of addiction from exposure to Butrans.
- The risk of unintentional exposure to Butrans in persons for whom it was not prescribed, including accidental exposure to children.
- The risk of temperature-dependent increase in buprenorphine released from the system resulting in possible overdose and death. Monitor patients wearing Butrans systems who develop fever or increased core body temperature due to strenuous exertion for opioid side effects and adjust the Butrans dose if necessary.

These risks will be discussed in this section.

Page 4

(HEADLINE) **RISK OF OVERDOSE WITH Butrans**

(Copy) It is important for all healthcare providers who prescribe opioid analgesics to understand the safety profiles of individual products. Indications and usage for different opioid analgesics vary and the Full Prescribing Information for any specific product should always be consulted before prescribing.

Following is important information about overdose risks with Butrans.

(Subhead) Risk of Overdose with Intact Patch

(Copy) Hypotension, profound sedation, coma or respiratory depression may result if Butrans is added to a regimen that includes other CNS depressants (e.g., sedatives, anxiolytics [esp. benzodiazepines], hypnotics, neuroleptics, muscle relaxants, other opioids). Therefore, use caution when deciding to initiate therapy with Butrans in patients who are taking other CNS depressants.[1]

Patients should be reminded to tell their doctor about all the medications they take because some may interact with Butrans leading to serious, life-threatening breathing

problems. Patients should also be instructed not to consume alcoholic beverages or medicines containing ethanol while using Butrans.[1]

Heat may increase the amount of buprenorphine that is absorbed from Butrans. Therefore, patients should be advised not to expose the patch to external heat sources such as heating pads, electric blankets, heat lamps and tanning lamps. In addition, they should not use saunas, hot tubs, heated water beds or sunbathe while wearing a Butrans patch.[1]

(Subhead) Risk of Overdose from Multiple Patch Application

(Copy) The dosage recommendation for Butrans is a single patch worn continuously for 7 days. Simultaneous application of multiple patches may produce buprenorphine plasma levels that could potentially result in hypoventilation and overdose. **Patients should be advised not to use more than one Butrans patch at the same time.**[1]

(Subhead) Signs of Overdose

(Copy) Acute overdosage with opioids, including Butrans, can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring and death. **In cases of overdose, patients and caregivers should be advised to remove the patch and get emergency help right away**[1]

(Subhead) Treatment of Overdose

(Copy) In cases of overdose, remove Butrans immediately. After removal of Butrans, the mean buprenorphine concentrations decrease approximately 50% in 12 hours (range 10-24 hours) with an apparent terminal half-life of approximately 26 hours[1]

In the treatment of Butrans overdosage, primary attention should be given to the maintenance of a patent airway, and of effective ventilation (clearance of CO_2) and oxygenation, whether by spontaneous, assisted or controlled respiration. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.[1]

Naloxone may not be effective in reversing any respiratory depression produced by buprenorphine. High doses of naloxone, 10-35 mg/70 kg, may be of limited value in the management of Butrans overdose. The onset of naloxone may be delayed by 30 minutes or more. Doxapram hydrochloride (a respiratory stimulant) has also been used. Since the duration of action of Butrans may exceed that of the antagonist, keep the patient under continued surveillance and administer repeated doses of the antagonist according to the antagonist labeling as needed to maintain adequate respiration. Maintenance of adequate ventilation is essential when managing Butrans overdose and more important than specific antidote treatment with an opioid antagonist such as naloxone.[1]

Do not administer opioid antagonists in the absence of clinically significant respiratory or circulatory depression secondary to buprenorphine overdose. In patients who are physically dependent on any opioid agonist including Butrans, an abrupt partial or

complete reversal of opioid effects may precipitate an acute abstinence (or withdrawal) syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. See the prescribing information for the specific opioid antagonist for details of its proper use.[1]

(Copy) **Please see accompanying Full Prescriber Information and Medication Guide (including Instructions for Use).**

Page 5

(HEADLINE) **RISK OF RESPIRATORY DEPRESSION**

(Copy) Respiratory depression is the chief hazard of Butrans. Respiratory depression occurs more frequently in elderly or debilitated patients as well as those suffering from conditions accompanied by hypoxia or hypercapnia when even moderate therapeutic doses may dangerously decrease pulmonary ventilation, and when opioids, including Butrans, are given in conjunction with other agents that depress respiration.

Profound sedation, unresponsiveness, infrequent deep ("sighing") breaths or atypical snoring frequently accompany opioid-induced respiratory depression.[1]

Butrans should be used with extreme caution in patients with significant respiratory disorders or preexisting respiratory depression such as chronic obstructive pulmonary disease (COPD), cor pulmonale, decreased respiratory reserve (eg, kyphoscoliosis), hypoxia, and hypercapnia. In these patients, therapy with Butrans should be employed only under careful medical supervision, and then initiated at the lowest dose.[1]

Particular caution is advised if Butrans is administered to patients taking CNS/respiratory depressants, particularly benzodiazepines.[1]

(Copy) **Please see accompanying Full Prescriber Information and Medication Guide (including Instructions for Use).**

Page 6

(HEADLINE) **RISK OF ABUSE, MISUSE AND ADDICTION**

(Subhead) Butrans is a Schedule III Controlled Substance

(Copy) Butrans contains buprenorphine, a partial agonist at the mu-opioid receptor and a Schedule III controlled substance. Opioid agonists have potential for being abused, are sought by drug abusers and people with addiction disorders, and are subject to criminal

diversion.[1] Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, proper dispensing and correct storage and handling are appropriate measures that help to limit misuse and abuse of opioid drugs.[1]

Butrans is intended for transdermal use only. Compromising the transdermal delivery system will result in the uncontrolled delivery of buprenorphine and pose a significant risk to the abuser that could result in overdose and death. The risk of fatal overdose is further increased when Butrans is abused concurrently with alcohol or other CNS depressants, including other opioids and benzodiazepines. Abuse may occur by applying the transdermal system in the absence of legitimate purpose, or by swallowing, snorting or injecting buprenorphine extracted from the transdermal system.[1]

(Subhead) Addiction to Butrans is Possible

(Copy) There is a potential for drug addiction to develop following exposure to opioids, including Butrans. Concerns about abuse and addiction should not prevent the proper management of pain. However, all patients treated with opioids require careful monitoring for signs of abuse and addiction because use of opioid analgesic products carries the risk of addiction even during appropriate medical use.[1]

People who have abused prescription medications in the past may have a higher chance of abusing or developing addiction again when prescribed Butrans. Behaviors that suggest drug abuse exist on a continuum, and pain-relief seeking behavior can be mistaken for drug-seeking behavior. All patients treated with Butrans require careful monitoring for signs of addiction and drug abuse.[1]

(Copy) **Please see accompanying Full Prescriber Information and Medication Guide (including Instructions for Use).**

Page 7

(HEADLINE) MOST COMMON ADVERSE EVENTS

(Copy) The most common adverse events (≥5%) reported by patients treated with Butrans in the clinical trials were nausea, headache, application site pruritus, dizziness, constipation, somnolence, vomiting, application site erythema, dry mouth, and application site rash. [1]

Dizziness and somnolence may impair mental and/or physical ability required for the performance of potentially hazardous tasks (eg, driving, operating machinery). Patients should be cautioned accordingly.[1]

Please see accompanying Full Prescriber Information and Medication Guide (including Instructions for Use).

(HEADLINE) **ADDICTION DISORDER VERSUS PHYSICAL DEPENDENCE**

(Copy) Abuse and addiction are separate from physical dependence and tolerance.

(Subhead) Patients with Addiction Disorders:[2]

(Bullets)

- Suffer from a chronic, neurobiologic disease with genetic, psychosocial and environmental components
- Seek a drug in order to quickly affect the "reward center" of their brains
- Crave drugs and use them compulsively
- Continue abuse despite negative, even life-threatening, physical, mental and/or social consequences

(Subhead) Patients with Physical Dependence Who Do Not Have an Addiction Disorder:[2]

(Bullets)

- Experience a normal response to the ongoing use of certain medicines, including opioids
- Want sufficient medicine to reach opioid receptors to induce analgesia
- Take medicines to relieve pain—not to satisfy a craving for a psychic effect or to stave off withdrawal syndrome
- Can generally discontinue their medicine with mild to no withdrawal syndrome once their symptoms are gone by gradually tapering the dosage according to their doctor's orders

(Copy) **Please see accompanying Full Prescriber Information and Medication Guide (including Instructions for Use).**

(HEADLINE) **SCREENING FOR PATIENTS AT RISK FOR OPIOID ABUSE OR ADDICTION**

(Copy) Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed an opioid, and all patients receiving opioids should be routinely monitored for signs of misuse, abuse and addiction.

(Subhead) Patient/Family History[1]

(Copy) Persons at increased risk for opioid abuse include those with a personal or family history of substance use disorder (including drug or alcohol abuse or addiction) or mental illness (eg, major depression). Participation or recommended participation in drug abuse treatment programs should be determined. Patients who have undergone opioid detoxification in the past are at higher risk for re-emergence of substance use disorders.

(Subhead) Screening Tests and Physical Appearance

(Copy) Many drug abuse screening tests have been developed for use in clinical practice, including the CAGE and CAGE-AID Questionnaire, the Addiction Behaviors Checklist, the Opioid Risk Tool, The Michigan Alcohol Screening Test (MAST), and the Two-Item Conjoint Screening (TICS) for Alcohol & Other Drug Problems.[3,4,7]

(Copy) Physical screening may reveal signs of possible drug abuse. Initial screening clues may include unkempt appearance, ill-fitting clothes suggestive of weight loss/gain, sniffles, watery eyes, cough, nausea, lethargy, drowsiness, and nodding. Careful examination of skin may reveal marks caused by repeated injections.[5]

While these signs might suggest abuse, they should not be the only criteria for determining whether opioid abuse has occurred.

(Subhead) Laboratory Tests

(Copy) Laboratory signs that may suggest substance abuse include elevated mean corpuscular volume (MCV) and abnormal liver enzymes.[3,4,7]

Urine drug testing may yield unexpected results. The use of this technology requires understanding of specificity and sensitivity of the particular analytic method employed. Some urine tests for “opioids” or “opiates” that are immunoassay-based, whether for point-of-collection or laboratory use, do not, for example, reliably detect semisynthetic or synthetic opioid analgesics.[3,6]

All laboratory markers are nonspecific for alcohol or drug use and should be viewed as screens, not as diagnostic criteria.

(Subhead) Other Signs[1]

(Copy) Signs of compulsive drug use include covertly obtaining prescription medications from more than one physician, referred to as “Doctor Shopping,” concurrent abuse of related illicit drugs, altering or forging prescriptions, and repeated unsanctioned dose escalations despite warnings.

Other signs of compulsive drug use may be more subtle, including frequent visits to emergency rooms, and hoarding of drugs obtained from routine prescriptions.

(Subhead) When You Suspect Addiction or Drug Abuse

(Copy) Following are some suggestions about what to do if you suspect a patient is addicted to or abusing Butrans:[7]

- Remember, a person abusing drugs or affected by addictive disorder is in need of treatment for that disorder and any concomitant medical or mental conditions they have, although self-administered opioid analgesics may not be indicated
- Refer the patient to an addiction specialist or substance use treatment center, if warranted
- If you are not the primary care physician, always consult a patient's regular physician before initiating treatment with an opioid analgesic
- Contact authorities if you are threatened in any way

(Copy) **Please see accompanying Full Prescriber Information and Medication Guide (including Instructions for Use).**

Part 2: Patient Selection, Appropriate Dosing and Patient Instruction

Page 10

(HEADLINE) **PROPER PATIENT SELECTION**

(Bold Copy) **Careful patient selection is key to initiating the appropriate use of Butrans. The decision to use Butrans must balance the potential benefits with the risks of Butrans treatment. The following information should be reviewed when considering Butrans treatment for your patients.**

(Subhead) Patients Who May Be Appropriate for Treatment with Butrans

(Copy) Butrans is indicated for the management of moderate to severe chronic pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.[1]

Both opioid naïve and opioid experienced patients meeting the above indication may be appropriate to treat with Butrans.

Selection of patients for treatment with Butrans should be governed by the same principles that apply to the use of other modified-release opioid analgesics.[1]

(Subhead) Contraindications

(Copy) **Butrans is not intended for the management of intermittent pain (e.g., use on an as-needed basis [prn]).[1]**

Butrans is **not** indicated for the management of acute pain or in patients who require opioid analgesia for a short period of time.[1]

Butrans is **not** indicated for the management of post-operative pain, including use after out-patient or day surgeries[1]

Butrans is **not** indicated for the management of mild pain.[1]

For some patients, the risks associated with Butrans therapy outweigh any potential benefits, and therefore, its use is contraindicated in:[1]

- patients who have significant respiratory depression
- patients who have severe bronchial asthma
- patients who have or are suspected of having paralytic ileus
- patients with known hypersensitivity to any of its components or the active ingredient, buprenorphine
- the management of acute pain or in patients who require opioid analgesia for a short period of time
- the management of post-operative pain, including use after out-patient or day surgeries
- the management of mild pain
- the management of intermittent pain (e.g., use on an as-needed basis [prn])

The safety and effectiveness of Butrans in patients under the age of 18 years has not been established.[1]

Butrans has not been studied and is not approved for use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission, is limited to the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time.[1]

(Copy) **Please see accompanying Full Prescriber Information and Medication Guide (including Instructions for Use).**

(HEADLINE) **PROPER PATIENT SELECTION (CONT'D)**

(Subhead) Patients Who Require Close Supervision

(Copy) Use extreme caution when prescribing Butrans for patients with significant respiratory disorders or preexisting respiratory depression such as COPD, cor pulmonale, decreased respiratory reserve (e.g., kyphoscoliosis), hypoxia and hypercapnia. Butrans therapy should be employed only under careful medical supervision in these patients and then initiated with the lowest.[1]

(Subhead) Warnings and Precautions

(Copy) Avoid use of Butrans in:[1]

- Patients with increased risk of hypotension and circulatory shock
- Patients with Long QT Syndrome or a family history of Long QT Syndrome
- Patients taking Class IA or Class III anti-arrhythmic medications (e.g., quinidine, procainamide, disopyramide)
- Patients taking other CNS depressants (e.g., sedatives, anxiolytics, hypnotics, neuroleptics, muscle relaxants, other opioids)
- Patients with head injuries.
- Patients with biliary tract disease, including acute pancreatitis.
- Patients with severe hepatic impairment

Butrans may cause somnolence, dizziness, alterations in judgment and alterations in levels of consciousness, including coma

(Subhead) Assess All Patients for Risks of Opioid Abuse or Addiction Before Starting Treatment with Butrans

(Copy) Patients should be assessed for risks of opioid abuse or addiction before they start treatment with Butrans. In addition to a complete medical history, it is important to obtain a detailed history of alcohol and other substance use in the patient and his or her family before initiating treatment with Butrans.[1,3]

Persons at increased risk for opioid abuse include those with a personal or family history of substance use disorders (including drug or alcohol abuse or addiction) or mental illness (eg, major depression).[1,3]

Documentation and maintenance of careful prescribing and treatment records is essential for supporting the evaluation, the reason for Butrans prescribing, the overall pain management plan, and any consultations received.[1,3] Documentation should include:

- Name, strength and quantity of the opioid prescribed
- Dose and frequency of administration
- Timeliness of requests for another prescription
- Initial and ongoing assessment of patients' pain
- Proper prescribing practices
- Periodic reevaluation of all therapy prescribed or recommended, including progress toward established treatment goals

(Copy) **Please see accompanying Full Prescriber Information and Medication Guide (including Instructions for Use).**

Page 12

(HEADLINE) **APPROPRIATE DOSING AND ADMINISTRATION**

(Subhead) Dosage Strengths

[*Pictures of patches inserted here.*]

(Copy) Butrans patches are available in three different strengths designed to release buprenorphine at a controlled rate of 5, 10 and 20 mcg/hour respectively.[1]

Each Butrans system provides continuous delivery of buprenorphine for 7 days.[1]

(Subhead) Starting Therapy

(Copy) It is critical to initiate the dosing regimen individually for each patient. Overestimating the Butrans dose when converting patients from another opioid medication can result in fatal overdose with the first dose.

- **Consider the following when selecting the initial dose of Butrans:**[1]The total daily dose, potency, and specific characteristics of the opioid the patient has been taking previously
- The reliability of the relative potency estimate used to calculate the equivalent buprenorphine dose needed (when converting from other opioids or opioid-combination products)
- The patient's degree of opioid tolerance to respiratory-depressant and sedation effects of opiods
- The age, general condition and medical status of the patient
- Concurrent non-opioid analgesic and other medications
- The type and severity of the patient's pain
- The balance between pain control and adverse drug experiences
- Risk factors for abuse, addiction or diversion, including personal or family history of abuse, addiction or diversion

The following dosing recommendations, therefore, can only be considered as suggested approaches to what is actually a series of clinical decisions over time in the management of the pain of each individual patient.

The initial application

Steady-state plasma levels of buprenorphine are achieved by 72 hours during the first Butrans patch application. The dose should not be increased before 72 hours of wear. During the initial application of Butrans, patients should use short-acting analgesics as needed until analgesic efficacy with Butrans is attained.[1]

Opioid-Naïve Patients

For opioid-naïve patients, initiate treatment with Butrans 5 mcg/hour. Thereafter, individually titrate the dose as described in Section 2.3 of FPI. Dose Titration to a level that provides adequate analgesia and minimizes side effects. Dose may be titrated to the next higher level after a minimum of 72 hours.

Conversion from Other Opioids to Butrans

There is a potential for buprenorphine to precipitate withdrawal in patients who are already on opioids. For conversion from other opioids to Butrans (see Table 1), taper the patient's current around-the-clock opioids for 7 days to no more than 30 mg of morphine or equivalent per day before beginning treatment with Butrans. Patients may use short-acting analgesics as needed until analgesic efficacy with Butrans is attained.

For patients whose daily dose was less than 30 mg of oral morphine or equivalent, initiate treatment with Butrans 5 mcg/hour. For patients whose daily dose was between 30 and 80 mg morphine equivalents, initiate treatment with Butrans 10 mcg/hour (see Table 1). Thereafter, individually titrate the dose as described in Section 2.3 of FPI Dose Titration.

Table 1: Dose Estimation for Conversion of Oral Morphine Equivalents to Butrans

Current Opioid Analgesic	**Current Daily Dose**	
Oral Morphine Equivalent	<30 mg	30-80 mg
Recommended Butrans Starting Dose	**5 mcg/hour**	**10 mcg/hour**

Use caution when prescribing Butrans to opioid-experienced patients requiring high doses of opioids (more than 80 mg/day of oral morphine equivalents). Butrans 20 mcg/hour may not provide adequate analgesia for patients requiring greater than 80 mg/day oral morphine equivalents.

(HEADLINE) **APPROPRIATE DOSING AND ADMINISTRATION (CONT'D)**

For patients with renal impairment

No dosage adjustment of Butrans is required for patients with renal impairment.[1]

For patients with hepatic impairment

Start patients with mild to moderate hepatic impairment with the Butrans 5 mcg/hour dose. Thereafter, individually titrate the dose to a level that provides adequate analgesia and tolerable side effects, under the close supervision of the prescriber. Butrans has not been evaluated in patients with severe hepatic impairment. As Butrans is only intended for 7-day application, consider use of an alternate analgesic that may permit more flexibility with the dosing in patients with severe hepatic impairment.[1]

For patients at increased risk of hepatotoxicity (e.g., patients with a history of excessive alcohol intake, intravenous drug abuse or liver disease), baseline and periodic monitoring of liver function during treatment with Butrans is recommended. A biological and etiological evaluation is recommended when a hepatic event is suspected.[1]

(Subhead) Dose Titration

(Copy) Based on the patient's requirement for supplemental short-acting analgesics, upward titration may be instituted with a minimum Butrans titration interval of 72 hours, based on the pharmacokinetic profile and time to reach steady state levels. Titration of Butrans should be based on the amount of supplemental opioid required, the severity of the patient's pain, and the patient's ability to tolerate bupenoprhine. Individually titrate the dose, under close supervision, to a level that provides adequate analgesia with tolerable side effects.[1]

The maximum Butrans dose is 20 mcg/hour. Do not exceed a dose of one 20 mcg/hour Butrans system due to the risk of QTc interval prolongation. In a clinical trial, Butrans 40 mcg/hour (given as two Butrans 20 mcg/hour systems) resulted in prolongation of the QTc interval.[1]

During periods of changing analgesic requirements, including initial titration, there should be frequent contact between the prescriber, other members of the healthcare team, the patient, and the caregiver/family. Patients and caregiver/family members should be advised of the potential side effects.[1]

Page 14

(HEADLINE) **APPROPRIATE DOSING AND ADMINISTRATION (CONT'D)**

(Subhead) Maintenance of Therapy and Supplemental Analgesia

(Copy) The intent of the titration period is to establish a patient-specific weekly Butrans dose that will maintain adequate analgesia with tolerable side effects for as long as pain management is necessary. Immediate-release opioid and non-opioid medications can be used as supplemental analgesia during Butrans therapy.[1]

During chronic opioid analgesic therapy with Butrans, reassess the continued need for around-the-clock opioid analgesic therapy periodically.[1]

(Subhead) Cessation of Therapy

(Copy) When the patient no longer requires therapy with Butrans, taper the dose gradually to prevent signs and symptoms of withdrawal in the physically-dependent patient; consider introduction of an appropriate immediate-release opioid medication. Undertake discontinuation of therapy as part of a comprehensive treatment plan.[1]

(Subhead) Drug-Drug Interactions

(Copy) Hypotension, profound sedation, coma or respiratory depression may result if Butrans is added to a regimen that includes other CNS depressants (e.g., sedatives, anxiolytics [esp. benzodiazepines], hypnotics, neuroleptics, muscle relaxants, other opioids).

Therefore, use caution when deciding to initiate therapy with Butrans in patients who are taking other CNS depressants.

Butrans, like other opioids, may interact with skeletal muscle relaxants to enhance neuromuscular blocking action and increase respiratory depression.[1]

(Copy) **Please see accompanying Full Prescriber Information and Medication Guide (including Instructions for Use).**

(HEADLINE) **APPLICATION, REMOVAL AND DISPOSAL**

THIS SECTION OF THE BROCHURE IS DESIGNED FOR HEALTHCARE PROFESSIONALS RESPONSIBLE FOR INSTRUCTING PATIENTS ABOUT THE APPLICATION AND PROPER REMOVAL AND DISPOSAL OF THE PATCH.

(Subhead) Eight Possible Application Sites

(Copy) Butrans should be applied to the upper outer arm, upper chest, upper back or the side of the chest. These recommendations provide eight (8) possible application sites.[1]

Butrans should be rotated among the 8 skin sites. After patch removal, a minimum of 21 days should pass before re-applying a patch to the same skin site for maximal pharmacokinetic consistency.[1]

Butrans should be applied immediately after removal from the individually sealed package. Patients should not use a Butrans patch if the seal on the protective pouch is broken or the patch is cut, damaged or changed in any way.[1]

Butrans should be applied to a hairless or nearly hairless skin site. If none are available, the hair at the site should be clipped, not shaven. The patch should not be applied to irritated skin or skin that is not intact. If the application site must be cleaned, it should be done with water only. Soaps, alcohol, oils, lotions or abrasive devices should not be used as these can potentially alter the absorption characteristics of the delivery system, leading to possible under treatment of pain or overdose. The skin should be allowed to dry before the patch is applied.[1]

(Subhead) Managing Adhesion Problems

(Copy) If problems with adhesion of Butrans occur, the edges of the patch may be taped with first-aid tape. If problems with adhesion persist Butrans may be secured with a transparent adhesive film dressing (e.g., Bioclusive™ or Tegaderm™).[1]

If Butrans falls off during the 7 days dosing interval, patients should dispose of the patch properly and place a new Butrans patch on a different skin site. **Patches that fall off should not be reapplied, but must be discarded properly.[1]**

(Subhead) Two Methods of Proper Disposal

(Copy) Patients should be instructed about proper disposal of Butrans patches. When a patch is removed, it should be folded over on itself, and flushed down the toilet. Alternatively, for patients who do not want to flush the patch down the toilet, the Butrans patch can be sealed in the Patch-Disposal Unit provided and then disposed of in the trash. A Butrans patch should never be thrown away in the trash without sealing it in the Patch-Disposal Unit.[1]

(Copy) **Please see accompanying Full Prescriber Information and Medication Guide (including Instructions for Use).**

(HEADLINE) **WHAT YOU NEED TO TELL PATIENTS ABOUT Butrans**

(Copy) **Patients and caregivers must be told to carefully read the Butrans Medication Guide that is provided with each Butrans prescription. It is extremely important to remind them that the important safety information in the Medication Guide could have changed since their last Butrans prescription was filled**.

Key points to discuss with patients and caregivers:

1. Butrans is an opioid narcotic pain medicine that can cause serious, life-threatening breathing problems. Patients or caregivers should call 911 immediately if the patient has trouble breathing, has diminished urge to breathe, has new-onset loud snoring, experiences extreme drowsiness with slow respiratory rate, or feels faint, very dizzy, confused or has any other unusual symptoms.[1]

2. Some medications can cause serious, life-threatening side effects when used with Butrans. Patients should keep a list of all their medications to show their doctor and pharmacist.[1]

3. Heat can increase the amount of buprenorphine absorbed through the skin. Patients should not use heat sources such as heating pads, electric blankets, heat lamps and tanning lamps, in addition, they should not use saunas, hot tubs, heated water beds or sunbathe while wearing a Butrans patch.[1]

4. Butrans is federally-controlled substance because it has the potential to be abused. Abusing Butrans, or not using it exactly as directed, can be dangerous, causing an overdose and possibly death. Patients and caregivers should be reminded to follow instructions for use carefully and never give Butrans to anyone else even if they have the same symptoms.[1]
5. Butrans is a narcotic opioid painkiller that can be a target for theft by people who abuse prescription medicines. Patients should store Butrans in a safe and secure place.[1]
6. Patients should be especially careful to keep Butrans away from children. Any exposure to a Butrans patch in children (touching, sticking to skin, chewing or swallowing) is dangerous. [1]
7. A single Butrans patch should be worn continuously around-the-clock for 7 days. After one week, the patch should be removed and patients should wait at least 21 days (3 weeks) before applying a patch to the same skin site. Application of patches should be rotated among the 8 possible application sites.[1]
8. Patients should not use more than one Butrans patch at the same time unless recommended by their doctor.[1]
9. If a Butrans patch falls off, the patient should throw it away (using proper disposal steps) and apply a new patch on a different skin site. Patients should not touch the sticky side of the patch (the part that contains drug) with their fingers and should always wash their hands after applying a patch.[1]
10. After removing a Butrans patch, the patient or caregiver should fold the patch over itself and flush it down the toilet. Alternatively, a Butrans patch can be sealed in the Self-adhesive Patch-Disposal Unit and then thrown in the trash. A Butrans patch should never be thrown in the trash without sealing it in the Self-adhesive Patch-Disposal Unit.[1]

(Copy) **Please see accompanying Full Prescriber Information and Medication Guide (including Instructions for Use).**

(HEADLINE) **REFERENCES**

(References)

1. Butrans™ [Full Prescribing Information]. Purdue Pharma LP; Stamford, CT.
2. Savage SR, Joranson DE, Covington EC, et al. Definitions related to the medical use of opioids: evolution towards universal agreement. *J Pain Symptom Management*. 2003; 26(1):655-667.
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APPENDIX D

Butrans™ TRAINING CONFIRMATION FORM

(Logo) **Butrans™ (BUPRENORPHINE TRANSDERMAL DELIVERY SYSTEM)**

(HEADLINE) **Butrans™ TRAINING CONFIRMATION FORM FOR HEALTHCARE PROVIDERS**

Completion of this form and questions does not affect your ability to prescribe Butrans™.

By signing the confirmation form you are helping to ensure patient safety through appropriate training.

I attest that I have read and understand the REMS Education materials for Butrans™.

Signature	**Date**

(Copy)

Prescriber Name *(Please Print)*		Professional Degree
Specialty		DEA, ME, or NPI Number *(please circle)*
Affiliation *(if any)*		
Address		
City	State	Zip Code
Telephone #		Fax #
Email Address		

Please answer the following questions to verify your understanding of the information contained in the Butrans™ REMS Education Materials.

Please return this signed form and completed questions (both pages) in the pre-addressed envelope provided.

Completion of the form and questions does not affect your ability to prescribe Butrans™.

1. Which of the following is the most significant, serious adverse event risk with Butrans™?
   - ☐ Myocardial infarction
   - ☐ Constipation
   - ☐ Dizziness
   - ☐ Respiratory depression
   - ☐ Drowsiness

2. Which of the following persons are at increased risk of opioid abuse? *(check all that apply)*
   - ☐ Individuals who have cancer pain
   - ☐ Individuals with a personal history of substance abuse
   - ☐ Individuals with a family history of substance abuse
   - ☐ Individuals with mental illness (e.g., major depression)
   - ☐ Individuals with a family history of hypercholesterolemia

3. Butrans™ can be prescribed for use on an as-needed (prn) basis.
   - ☐ True
   - ☐ False

4. Butrans™ needs to be stored in a secure place away from children, pets, and household visitors.
   - ☐ True
   - ☐ False

5. Which of the following statements are true regarding the proper use of Butrans™? *(check all that apply)*
   - ☐ Butrans™ is contraindicated in patients with significant respiratory depression
   - ☐ Butrans™ does not interact with benzodiazepines to exacerbate respiratory depression
   - ☐ Butrans™ is safe to prescribe to a patient who has paralytic ileus
   - ☐ A high starting dose of Butrans™ should not be prescribed to opioid-naïve patients

6. Proper use of Butrans™ involves the following: (*check all that apply)*
   - ☐ Unused supplies should be stored indefinitely in unlocked cabinets
   - ☐ The Butrans™ transdermal system must not be altered in any manner
   - ☐ External heat sources should not be applied to the Butrans™ transdermal system
   - ☐ Butrans™ is intended for transdermal use on intact skin only

7. Butrans™ is approved for use for which type of pain? *(check all that apply)*
   - ☐ Management of acute pain
   - ☐ Management of moderate to severe chronic pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time
   - ☐ Management of post-operative pain
   - ☐ Management of mild pain

For more information, please visit www.butransrems.com or contact Purdue's Medical Services Department at 1-888-726-7535.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21306	ORIG-1	PURDUE PHARMA LP	Butrans (buprenorphine) Transdermal System

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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/

JEANNE P PERLA
06/30/2010

GITA A AKHAVAN TOYSERKANI
06/30/2010
Concur for Claudia Karwoski

REMS Interim Review Comments

Drug Name:	**BLA/NDA:**	**Date:** 4-21-10
Butrans (Buprenorphine Transdermal Delivery System)	#21-306	**Comment Set #1**
DRISK Scientific Lead: Jeanne Perla, Ph.D., Risk Management Analyst		**Reviewers:** **DRISK** Gita Toyserkani, Pharm.D. Acting Team Leader Marcia Britt, Ph.D., Health Education Reviewer Jodi Duckhorn, MA. Social Science Reviewer **DDMAC** Mathilda Fienkeng Pharm.D., Regulatory Review Officer **Office of Compliance Division of Risk Management and Surveillance** Agnes Plante BSN, RN, Consumer Safety Officer
RCM #: 2009-1865		

Materials Reviewed:

1. The following proposed REMS materials submitted on February 17, 2010 were reviewed:
    a. Proposed REMS Document
    b. Proposed REMS Supporting Document
    c. Healthcare Provider Training Guide

Introduction:

During a telephone conference on February 22, 2010, Purdue was notified that a Medication Guide and Communication Plan would not be adequate to ensure adequate training of healthcare providers to address the labeled risks and to prevent the occurrence of serious adverse events associated with those risks. Purdue was informed that the REMS for Butrans must contain a Medication Guide, elements to assure safe use, specifically healthcare provider training under 505-1(f)(3)(A), and a timetable for the submission of assessments of the REMS, to ensure that the benefits of Butrans outweigh the risks. Purdue submitted a proposed REMS on February 17, 2010.

Comments for the Sponsor

Please see **Appendix A** (**Appendix B** – clean version) for our revisions to the proposed REMS which is consistent with current Agency standards.

The spelling of Butrans has been changed to Butrans to be consistent with the PI. TM can be added after Butrans throughout the document. The REMS Supporting Document must reflect the below changes to be consistent with the REMS document. Please incorporate the necessary revisions and include all current versions of materials in appendices in the next submission.

A. Goals

The goals have been reviewed and found to be acceptable. We have minor editorial revisions.

B. Medication Guide

Comments on the Medication Guide will be provided under a separate review.

C. Elements to Assure Safe Use

1. Dear Healthcare Professional (DHCP)Letter
   A DHCP Letter will be included in the REMS under elements to assure safe use to inform healthcare professionals of the Butrans REMS and the need for Healthcare Provider training. Please develop and submit for review the DHCP letter.

   The DHCP letter must be mailed within 60 days of the approval of Butrans to prescribers most experienced in treating chronic pain with opioid agonists, including, pain specialists, physiatrists, and primary care physicians. This letter is designed to convey and reinforce the risks of abuse, misuse, overdose, and addiction of Butrans. The mailings must also include the Butrans REMS Educational Program materials.

   Additional printed educational material should be made available through field-force distribution, by calling the toll free number, and available for download at the Butrans website.

2. Healthcare Provider Training Guide
   See **Appendix C** (**Appendix D** for clean copy) for our revisions to the proposed Healthcare Provider Training Guide.

   i. The guide does not provide a comprehensive view of the safety information for Butrans. Place a sentence in the purpose statement section of the guide instructing healthcare providers to refer to the full Prescribing Information for detailed safety information about this product. A similar statement should be used throughout the guide.

   ii. Healthcare provider training guide needs to include the risks associated with Butrans including:
      a. The risk of overdose in opioid naïve patients when using initial dose greater than 5mcg/h.

b. The risk of addiction from exposure to Butrans
c. The risk of unintentional exposure to Butrans in persons for whom it was not prescribed, including accidental exposure to children.
d. The risk of temperature-dependent increases in buprenorphine released from the system resulting in possible overdose and death.

iii. Remove the following promotional language proposed in the training guide:

[redacted] (b) (4)

This is an inadequate communication of the indication. Although the presentation is consistent with the Highlights section of the draft PI and the limitation to its use is presented on page 4 of the proposed Guide, under "Proper Patient Selection", the introductory presentation does not adequately communicate the indication. Revise this presentation to include the limitations to its use relating to [redacted] (b) (4) for consistency with the draft full PI.

iv. Present the information in a manner consistent with the proposed PI. The sequence of information within the Guide is inconsistent with the proposed PI and may minimize the risks associated with Butrans.
a. Present the information regarding risks associated with Butrans prior to information on patient selection and dosage and administration
- The content and order of presentation of risk information within the "Risks Associated with Butrans and Opioids" section of the proposed Guide minimizes the risks associated with Butrans. For example, the risk information, including warnings and precautions are presented under the header, [redacted] (b) (4) which fails to adequately convey the severity of the potential fatal risks being communicated. Eliminate the heading, [redacted] (b) (4) and replace it with a heading consistent with the draft PI. [redacted] (b) (4) The most serious information should be presented first in a manner consistent with the proposed PI, under an appropriate header.

b. Information on sections 17 (Patient Counseling Information), and 16 (How supplied, Storage and Handling) of the proposed PI are presented before serious and potentially fatal risk information from section 5 (Warnings and Precautions) of the draft PI.

v. Proper Patient Selection Section

a. Assess All Patients for Risks of Opioid Abuse or Addiction Before Starting Treatment with Butrans subsection
    - There are six bulleted items included in the documentation for prescribing and treatment records. It is not clear of the source for the bulleted information. They are not found in the PI. Provide a reference for the list.

vi. Appropriate Dosing and Administration Section
a. Factors to consider when selecting the initial dose of Butrans subsection
    - (b) (4) . Please check the bullet and revise or delete.
    - Do not bold the information provided in the third bullet. Bolding places emphasis on the information suggesting superiority over the other bulleted items.
b. Patient with hepatic impairment subsection
    - Use verbatim language provided in the PI. Revise the sentence (b) (4)

vii. Side Effects Section
a. Treatment of Overdose subsection
    - Please include correct information. Be sure the information in the guide is verbatim with information provided in the full PI. The PI states that Naloxone may not be effective in reversing any respiratory depression produced by buprenorphine. The Treatment of Overdose section of the guide states Naloxone, an opioid antagonist, should be administered.

viii. Risk of Abuse, Misuse, and Addiction Section
a. Butrans is a Schedule III Controlled Substance subsection
    - The sentence, 'Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs' is found in this section of the PI. Add the sentence to the Risk of Abuse, Misuse, and Addiction/Butrans is a Scheduled III Controlled Substance section of the guide.

ix. Revise Table of Contents

3. Butrans Educational Confirmation Form

As part of the healthcare provider training, develop a form that the healthcare providers will return to the sponsor confirming they have completed the educational training. This form may request the following Prescriber Information:

1) Prescriber name and credentials
2) DEA registration Number
3) Specialty
4) Affiliation
5) Address
6) Office Phone
7) Office Fax
8) Email
9) Date form completed

We recommend that you include questions that can verify prescriber's understanding of the risks associated with Butrans, the indication for use proper dosing, safety information about proper administration and storage of Butrans, and the need for patient counseling.

This form should include the following statement: "Completion of this form does not affect your ability to prescribe Butrans" Additionally, we require that you maintain a list of all prescribers that have completed the Butrans REMS Educational Program training and provide a report on the status of the training program as part of your REMS assessment.

E. Timetable for Submission of Assessment

The proposed timetable for submission of assessment is acceptable. We have minor editorial revisions

F. REMS Supporting Document

1. All Changes in REMS Document should be reflected in the REMS Supporting Document.

2. The following information needs to be included in your REMS Supporting Document under "Information Needed for Assessment:"
   i. An evaluation of patients' understanding of the serious risks of Butrans.

   ii. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.

   iii. A report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.

   iv. A report on the status of the training program for healthcare providers.

v. An evaluation of healthcare providers' awareness and understanding of the serious risks associated with Butrans (for example, through surveys of healthcare providers).

vi. Specification of measures that would be taken to increase awareness if surveys of healthcare providers indicate that healthcare provider awareness is not adequate.

vii. An analysis and summary of surveillance and monitoring activities for abuse, misuse, overdose, and addiction and any intervention taken resulting from signals of abuse, misuse, overdose, and addiction.

viii. An analysis to evaluate Butrans (buprenorphine) utilization patterns including use in non-opioid tolerant patients.

ix. With respect to REMS goals, an assessment of the extent to which the elements to assure safe use are meeting the goals or whether the goals or such elements should be modified.

3. Survey Methodology:

Submit for review the detailed plans that will be used to evaluate patients' and prescribers' understanding about the risks associated with and safe use of Butrans. This information **does not** need to be submitted for FDA review prior to approval of your REMS, however it should be submitted at least 90 days before the evaluation will be conducted. The submission should be coded "REMS Correspondence." The submission should include all methodologies and instruments that will be used in the evaluations.

1. Recruit respondents using a multi-modal approach. For example, patients might be recruited online, through physicians' offices, through pharmacies, managed care providers, or through consumer panels.
2. Explain how non-respondent follow-up or reminders will be completed and the planned frequency of the non-respondent follow-ups.
3. Explain how incentive or honorarium will be offered and the intended amount.
4. Explain how sites will be selected.
5. Submit for review any recruitment advertisements.
6. Define the sample size and confidence interval associated with that sample size.
7. Define the expected number of prescribers and patients to be surveyed, and how the samples will be determined (selection criteria)
8. Explain the inclusion criteria; that is, who is an eligible respondent. For example, a patient respondent might be:

- Age 18 or older
- Currently taking Butrans or have taken in past 3 months
- Not currently participating in a clinical trial involving Butrans

9. Submit any screener instruments, and describe if any quotas of sub-populations will be used.
10. Explain how the surveys will be administered and the frequency of the surveys.
11. Offer respondents multiple options for completing the survey. This is especially important for inclusion of the lower literacy patient population. For example, surveys could be completed online, in writing or by mail, over the phone, or in person.
12. Explain how surveyors will be trained.
13. Explain controls used to compensate for the limitations or bias associated with the methodology
14. The patient sample should be demographically representative of the patients who use Butrans.
15. The prescriber sample should be demographically representative of the healthcare providers who prescribe or administer Butrans.
16. If possible and appropriate, the sample should be diverse in terms of: age, race, ethnicity, sex, socio-economic status, education level, geographically
17. Submit for review the introductory text that will be used to inform respondents about the purpose of the survey.
18. Potential respondents should be told that their answers will not affect their ability to receive or take (patients) or prescribe (prescribers) Butrans, and that their answers and personal information will be kept confidential and anonymous.
19. Respondents should not be eligible for more than one wave of the survey.
20. Results should be analyzed on an item-by-item or variable-by-variable basis. The data may be presented using descriptive statistics, such as sample size, mean, standard deviation, median, minimum and maximum (for continuous variables), and frequency distributions (for categorical variables).
21. Data may be stratified by any relevant demographic variable, and presented in aggregate. We encourage you to submit with your required assessments all methodology and instruments that were used to evaluate the effectiveness of the REMS.

With regard to the patient survey instrument:

22. The assessment is to evaluate the effectiveness of the REMS in achieving its goal by evaluating patients' knowledge of the serious risks associated

with and safe use of Butrans. The assessment is not to evaluate consumer comprehension of the Medication Guide.

23. Respondents should not be offered an opportunity to read or see the Medication Guide again prior to taking the survey.
24. Submit for review the survey instruments (questionnaires and/or moderator's guide), including any background information on testing survey questions and correlation to the messages in the Medication Guide.
25. The patient knowledge survey should include a section with questions asking about the specific risks or safety information conveyed in the Medication Guide to see if the patient not only understands the information, but knows what to do if they experience the event.
26. Most of the risk-specific questions should be derived from information located in the "What is the Most Important Information I should know about Butrans?" section of the Medication Guide
27. The risk-specific questions should be non-biased, non-leading, multiple choice questions with the instruction to "select all that apply." Each question should have an "I don't know" answer option.
28. The order of the multiple choice responses should be randomized on each survey.
29. The order of the questions should be such that the risk-specific questions are asked first, followed by questions about receipt of the Medication Guide. Demographic questions should be collected last or as part of any screener questions.
30. Respondents should not have the opportunity or ability to go back to previous questions in the survey if the survey is conducted by telephone or online.
31. Explain if and when any education will be offered for incorrect responses.
32. Include questions about receipt of the Medication Guide in the patient survey as a way to fulfill the obligation to report on the distribution of the Medication Guide.
33. Just prior to the questions about receipt of the Medication Guide, include text explaining what is a Medication Guide. For example,
    Now we are going to ask you some questions about the Medication Guide you may have received with Butrans. The Medication Guide is a paper handout that contains important information about the risks associated with use of Butrans and how to use Butrans safely. Medication Guides always include the title "Medication Guide".
34. Use the following (or similar) questions to assess receipt and use of the Medication Guide.

a. Who gave you the Medication Guide for Butrans? (Select all that apply)
    a) My doctor or someone in my doctor's office

b) My pharmacist or someone at the pharmacy
c) Someone else - please explain:

_____

d) I did not get a Medication Guide for Butrans

b. Did you read the Medication Guide?
   - o All,
   - o Most,
   - o Some,
   - o None

c. Did you understand what you read in the Medication Guide?
   - o All,
   - o Most,
   - o Some,
   - o None

d. Did someone offer to explain to you the information in the Medication Guide?
   - o Yes, my doctor or someone in my doctor's office
   - o Yes, my pharmacist or someone at the pharmacy
   - o Yes, someone else – please explain:

     _____

   - o No

e. Did you accept the offer? Yes or No

f. Did you understand the explanation that was given to you?
   - o All,
   - o Most,
   - o Some,
   - o None

g. Did or do you have any questions about the Medication Guide? Yes or No (If Yes, list your question(s) below) Note: This is an open text field that should be grouped/coded by the sponsor prior to submitting to FDA

With regard to the prescriber survey instrument:

35. The assessment is to evaluate the effectiveness of the REMS in achieving its goal by evaluating prescribers' knowledge of the serious risks associated with and safe use of Butrans. The assessment is not to evaluate prescribers' comprehension of the educational materials.

36. Respondents should not be offered an opportunity to read or see any educational materials (prescribing information, communications, promotional materials, videos, etc.) prior to taking the survey.

37. Submit for review the survey instruments (questionnaires and/or moderator's guide), including any background information on testing survey questions and correlation to the messages in any educational materials.

38. The prescriber knowledge survey should include a section with questions asking about the specific risks and safety information conveyed in the educational materials.
39. Questions should be non-biased, non-leading, multiple choice questions with the instruction to "select all that apply." Each question should have an "I don't know" answer option.
40. The order of the multiple choice responses should be randomized on each survey.
41. The order of the survey questions should be such that the risk-specific questions are asked first, followed by questions about receipt of the educational materials. Demographic questions should be collected last or as part of any screener questions.
42. Respondents should not have the opportunity or ability to go back to previous questions in the survey if conducted by telephone or online.
43. Explain if and when any education will be offered for incorrect responses.
44. Use the following (or similar) questions to assess receipt and use of the educational materials.

a. Prior to today, which of the following were you aware of or received with regard to Butrans? (Select all that apply)

Full Prescribing Information	□	□
Medication Guide	□	□
Dear Healthcare Provider Letter	□	□
Prescribing Butrans: A Healthcare Professional Guide	□	□
Something else - please explain:	□	□
None of the above	□	□

b. Did you read the Full Prescribing Information?
   - All,
   - Most,
   - Some,
   - None

- I did not receive the Butrans Full Prescribing Information

c. Did you read the Medication Guide?
   - All,
   - Most,
   - Some,
   - None
   - I did not receive the Butrans Medication Guide

d. Did you read the Dear Healthcare Provider Letter?
   - All,
   - Most,
   - Some,
   - None
   - I did not receive the Butrans Dear Healthcare Provider Letter

e. Did you read the Prescribing Butrans: A Healthcare Professional Guide?
   - All,
   - Most,
   - Some,
   - None
   - I did not receive the Prescribing Butrans: A Healthcare Professional Guide

f. Do you have any questions about any of the educational materials related to Butrans? Yes or No (If Yes, list your question(s) below) Note: This is an open text field that should be grouped/coded by the sponsor prior to submitting to FDA

Please let us know if you have any questions.

G. General Comments:

1. Resubmission Requirements: Submit the revised Proposed REMS with appended materials and the REMS Supporting Document. Please provide a track changes and clean version of all revised materials and documents.

2. Format Request: Please submit your proposed REMS and other materials in WORD format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS and appended materials be a single WORD document.

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21306	ORIG-1	PURDUE PHARMA LP	BuTrans (buprenorphine transdermal system)

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

/s/

JEANNE P PERLA
04/21/2010

GITA A AKHAVAN TOYSERKANI
04/22/2010