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Approval Package for:

APPLICATION NUMBER:

NDA 21-306

Trade Name: **Butrans**

Generic Name: **buprenorphine transdermal system**

Sponsor: **Purdue Pharma, LLC**

Approval Date: **6/30/2010**

Indications: **For the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time.**

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APPLICATION NUMBER:
21-306

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APPLICATION NUMBER:
21-306

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 021306 **NDA APPROVAL**

Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431

Attention: Richard Fanelli, Ph.D.
Executive Director, Regulatory Affairs

Dear Dr. Fanelli:

Please refer to your New Drug Application (NDA) dated November 3, 2000, received November 3, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Butrans (buprenorphine) Transdermal System for transdermal administration (5 mcg/hour, 10 mcg/hour, and 20 mcg/hour).

We acknowledge receipt of your amendments dated November 28, and December 15 (2) and 18 (2), 2000, January 9 and 10, February 28, March 9, 13, 21, 26, and 30, April 18, 26, and 27 (2), May 3, 4 (2), 14, 24, and 25, June 4, 6, 7, 8, 11, 15, 20, 21, 23, 26, 27, 28, and 29, July 11, 16, 19, 23 (2), 25, 26, and 30, and August 15 (2), 2001, September 25, October 8, 15, and 27, November 3, 5, 9, 10, 11, 13, 20, and 30, and December 9, 17, 28, and 30, 2009, January 7, 15, 27, and 28, February 3 and 18, March 1 (3), 5, 10, and 30, April 21 and 23, and June 16 (2), 22, 23, and 29, 2010.

The September 25, 2009, submission constituted a Complete Response to our August 31, 2001, Action Letter.

This new drug application provides for the use of Butrans (buprenorphine) Transdermal System for transdermal administration for the management of persistent, moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

Your application was not referred to an FDA advisory committee because Butrans is a member of a class of previously approved opioid drugs and the product did not raise significant safety or efficacy issues beyond those applicable to its class.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert and Medication Guide). Information on submitting SPL files using eLIST may be found in our Guidance for Industry *SPL Standard for Content of Labeling Technical Qs and As* at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your June 23, 2010, submission containing final printed carton and container labels.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages birth through six years because necessary studies are impossible or highly impracticable. This is because the numbers of pediatric patients meeting the indication are too small in number to make pediatric studies feasible.

We are deferring submission of your pediatric study for ages seven through sixteen years for this application because this product is ready for approval for use in adults and the pediatric study have not been completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

1655-1 Deferred pediatric study under PREA, a pharmacokinetic and safety study for the treatment of moderate to severe chronic pain requiring continuous, around-the-clock opioid treatment for an extended period of time in pediatric patients ages 7 through 16.

Final Protocol Submission:	April 7, 2011
Study Completion:	January 8, 2015
Final Report Submission:	June 30, 2015

Submit final study reports to this NDA. For administrative purposes, all submissions related to this required pediatric postmarketing study must be clearly designated "**Required Pediatric Assessment(s)**".

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments in your submission dated June 16, 2010. These commitments are listed below.

1655-2 Provide supporting data for adhesion strength of the drug containing adhesive and an updated adhesive laminate specification.

Final Report Submission: July 31, 2010

1655-3 Provide supporting data and an updated dissolution specification. You should collect dissolution data from 12 patches per every lot manufactured for the first year post approval.

Final Report Submission: June 30, 2011

Submit clinical protocols to your IND 050273 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Butrans (buprenorphine) Transdermal System to ensure the benefits of the drug outweigh the risks of abuse, misuse, overdose, and addiction.

In accordance with section 505-1 of FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Butrans (buprenorphine) Transdermal System poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Butrans (buprenorphine) Transdermal System. FDA has determined that Butrans (buprenorphine) Transdermal System is a product for which patient labeling could help prevent serious adverse effects and that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use Butrans (buprenorphine) Transdermal System. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Butrans (buprenorphine) Transdermal System.

Pursuant to 505-1(f)(1), we have also determined that Butrans (buprenorphine) Transdermal System can be approved only if elements necessary to assure safe use are required as part of a REMS to mitigate the risks of abuse, misuse, overdose, and addiction. The elements to assure safe use, specifically, your plan to ensure that Butrans (buprenorphine) Transdermal System will only be prescribed by healthcare providers who have particular training under 505-1(f)(3)(A), will mitigate the risks of abuse, misuse, overdose, and addiction.

Your proposed REMS, submitted on June 29, 2010, and appended to this letter, is approved. The REMS consists of a Medication Guide, elements to assure safe use, and a timetable for submission of assessments of the REMS.

Butrans (buprenorphine) Transdermal System delivers buprenorphine, a partial agonist at the mu-opioid receptor. When used for the management of persistent, moderate to severe, pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time, Butrans (buprenorphine) Transdermal System is considered to be a extended release opioid because it is delivered in a long-acting transdermal patch. As you know, we are considering what REMS elements should be implemented across the class of long-acting and extended-release opioids to address the risks of abuse, misuse, overdose, and addiction. Once that determination is made, we will notify you in writing and you will be required to submit a modified REMS incorporating those elements.

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

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. An evaluation of patients' understanding and practices regarding proper disposal of Butrans.
8. Specification of measures that would be taken to increase awareness if surveys of healthcare providers indicate that healthcare provider awareness is not adequate.
9. 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.
10. An analysis to evaluate Butrans (buprenorphine) Transdermal System utilization patterns including use in non-opioid tolerant patients.
11. 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.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(A), an assessment of the extent to which the elements to assure safe use are meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals or such elements should be modified.

Assessments of an approved REMS must also include, under section 505-1(g)(3)(B) and (C), information on the status of any postapproval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. With respect to any such postapproval study, you must include the status of such study, including whether any difficulties completing the study have been encountered. With respect to any such postapproval clinical trial, you must include the status of such clinical trial, including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to requirements under subsections (i) and (j) of section 402 of the Public Health Service Act. You can satisfy these requirements in your REMS assessments by referring to relevant information included in

the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in section 505-1(g) could result in enforcement action.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of FDCA.

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

NDA 021306 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 021306
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 021306
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

EXPIRATION DATING PERIOD

An expiration dating period of 21 months is granted for the Butrans (buprenorphine) Transdermal System 4-count carton configurations (5 mcg/hour, 10 mcg/hour, and 20 mcg/hour), stored at 25°C (77°F); excursions permitted between 15°C-30°C (59°F-86°F).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch
Food and Drug Administration
Suite 12B-05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Matt Sullivan, Regulatory Project Manager, at 301-796-1245.

Sincerely,

{See appended electronic signature page}

Sharon H. Hertz, M.D.
Deputy Director
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling (Package Insert and Medication Guide)
Carton and Container Labeling
REMS

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/

SHARON H HERTZ
06/30/2010