CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-306

OTHER REVIEW(S)

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: June 23, 2010

To: Bob Rappaport, M.D., Director
Division of Anesthesia and Analgesia Products

Through: Michael Klein, Ph.D., Director Controlled Substance Staff
Lori A. Love, M.D., Ph.D., Lead Medical Officer
Controlled Substance Staff

From: Chad J. Reissig, Ph.D., Pharmacologist

Subject: **NDA 21-306 BuTrans (Buprenorphine transdermal)**
Indication: moderate to severe chronic pain
Dosages: 5, 10 & 20 mg transdermal system
Company: Purdue Pharmaceuticals

Materials reviewed: Epidemiological data from drug abuse surveillance systems (e.g. DAWN, RADARS)

This memorandum is a response to the Division of Anesthesia and Analgesia Products (DAAP) questions regarding the CSS perspective of residual buprenorphine in used BuTrans product, as a follow up to our review of NDA 21-306.

Conclusions:

In an assessment of the potential for misuse, abuse and diversion of BuTrans, CSS has determined that:

- Buprenorphine is abused and diverted, but not to the same extent as other opioids.

- The United Nations International Narcotics Control Board's (INCB) position on residual active pharmaceutical ingredient (API) in transdermal opioid products does not apply to buprenorphine products.

- Products that are identical to BuTrans (e.g. Norspan) are currently marketed in Canada and several other countries.

- Transtec is an approved buprenorphine patch in Spain. The lowest dose of Transtec contains the same amount of buprenorphine per cm^2 as the highest dose

of BuTrans. Transtec is worn for 4 days (in comparison to 7 days with BuTrans). After use, the amount of residual buprenorphine in each patch is similar.

Butrans 20 vs. Transtec 35					
Patch	Delivery rate (µg/hour)	Surface (cm^2)	Total Bup Content (mg)	Residual Bup after 4 days use	Residual Bup after 7 days use
Butrans 20 mg 7 day	20	25	20	(b) (4)	
Transtec 35 mg 4 day	35	25	20		

The Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) system uses four programs to analyze rates of abuse, misuse, and diversion. As seen below, rates of misuse, abuse, and diversion of methadone were greater than buprenorphine.

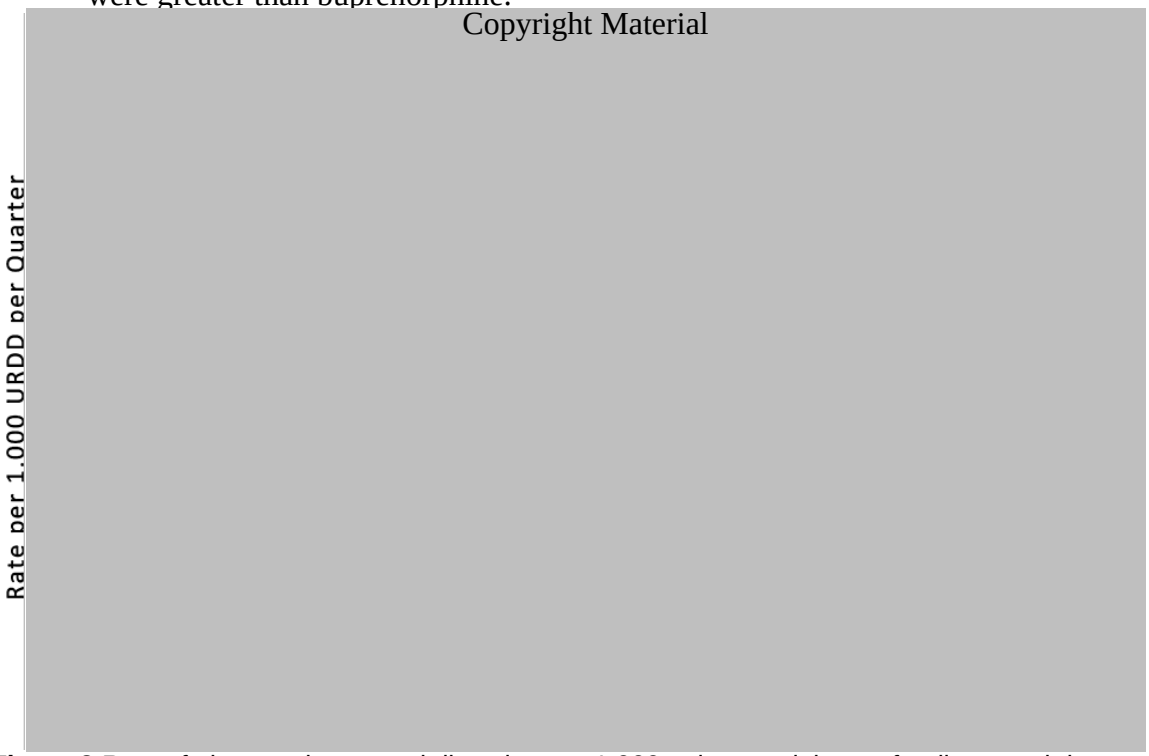

Figure 2 Rate of abuse, misuse, and diversion per 1,000 unique recipients of a dispensed drug (URDD), RADARS System, 2003–2007, United States (Dasgupta et al., 2010)

- The Drug Abuse Warning Network (DAWN) provides national estimates of drug-related emergency department visits. DAWN reports lower emergency department room visits with buprenorphine relative to methadone.

YEAR	2004	2005	2006	2007	2008
Total ED visits	2,537,722	3,009,025	3,441,855	3,998,228	4,383,494
Buprenorphine/combinations	1,001	3,161	6,733	10,229	19,491
Methadone	48,864	53,425	60,180	69,506	89,194

Recommendations:

- We refer the Division to the CSS memorandum of May 7, 2010 by Chad Reissig, Ph.D., Pharmacologist, for our review recommendations.
- We have no additional recommendations related to approval.

Reference List

1. Dasgupta N, Bailey EJ, Cicero T, Inciardi J, Parrino M, Rosenblum A, Dart RC (2010) Post-marketing Surveillance of Methadone and Buprenorphine in the United States. Pain Med

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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/s/

CHAD REISSIG
06/23/2010

LORI A LOVE
06/23/2010

MICHAEL KLEIN
06/23/2010

COPY

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: December 14, 2000

To: Cynthia G. McCormick, M.D., Director
Division of Anesthetic, Critical Care and Addiction Drug Products, HFD-170

From: Ann-Kathryn Yelovich, M.D., Medical Officer
Katherine Bonson, Ph.D., Pharmacologist
Controlled Substance Staff, HFD-009

Through: Deborah B. Leiderman, M.D., Director
Controlled Substance Staff, HFD-009

Subject: Filing Issues for NDA 21-306, Norspan BTDS (buprenorphine transdermal system)

Clinical abuse liability issues:

Sponsor should:

- Indicate if formal measures of withdrawal or drug-liking were used in any clinical studies.

- Provide case report forms and narratives for all of the following patients: patients in appendices 5 and 6 of Abuse Liability Volume 1 (AL V 1); patients who are presented in the Executive Summary of AL V 1, including patients whose numbers are not italicized (e.g., patient from BP 96-0304 who is referred to on p. 76 of AL V 1); patients who showed signs and symptoms of abuse, dependence, or withdrawal involving any substance or signs or symptoms of difficulty tolerating any substance; patients who lost their patches or did not return them; patients who had a history of drug or alcohol abuse or dependence prior to participating in the studies.

- Provide a more detailed explanation of what appendices 5 and 6 are and why patients in these appendices were chosen. Examples of some questions are as follows:
  A) How do appendices 5, 5.1A, and 5.1B relate to each other?
  B) If appendix 5 includes greater than or equal to 10% of patients with the highest scores for abuse or withdrawal, why does the word "no" appear in the columns for overdose, abuse, and withdrawal in appendix 5?

C) What do the titles of appendix 5.1A and 5.1B mean?
D) How were the scores in appendix 5.1A and 5.1B generated?
E) Why are there comments in appendix 6 that do not appear to be related to overdose, abuse, or withdrawal?
F) Why are there many patient listings with no comments in appendix 6?

- Identify the criteria determining inclusion of cases in Executive Summary of AL V 1.

- Provide an explanation of how the Executive Summary in AL V 1 correlates to the appendices. For example, patient 20226 suffered a serious and significant adverse event suggestive of overdose, abuse, or withdrawal (p. 58 of Executive Summary), but is not listed in appendix 5 (which is a listing of greater than or equal to 10 % of patients with the highest total scores for abuse or withdrawal).

- Provide an explanation for why only certain patients are included in the overdose summary table (appendix 8 of AL V 2). One case is clearly listed as involving BTDS. The Sponsor should provide data on the total number of patients who overdosed with the patch and information should be provided on whether any patients extracted medication from a patch.

- Provide all data from and a complete description of study BP 96-0304 which included a patient whose respiratory rate decreased following application of a 20 mg patch.

- Provide data, if collected, from patients following removal of BTDS that assessed whether withdrawal was present.

- Identify the area(s) of the body intended for BTDS application. Patches for abuse liability studies should be placed on the same area of the body upon which patches will be placed for analgesia. Discuss sites of body intended for patch application and the relationship between methodology in the pk/pd studies and instructions/use of the to be marketed product.

- Provide data demonstrating whether there is continued drug absorption following removal and replacement of BTDS, to mimic transfer of BTDS from a patient to another individual. In particular, data should be submitted testing the removal and reapplication of BTDS patches to skin with a secure adhesive tape, such as duct tape.

- Provide a complete description of and complete results of the external heat study (BP 98-1204).

- Provide any additional data, if available, regarding heat application to the patch (e.g., through a hot water bottle or heating pad) and changes in the absorption of buprenorphine from BTDS.

- Determine whether acute discontinuation of BTDS leads to the development of tolerance, craving and/or withdrawal symptoms that would indicate physical dependence.

- Address the potential risk for abuse, diversion and overdose of BTDS, given that large amounts of buprenorphine remains in the patch following removal from a patient.

Chemical extraction issues:

Sponsor should:

- Test extraction of buprenorphine from BTDS using acetone, methanol, ether, ethylacetate and ethanol.

- Test an extraction condition for each solvent that tests whether heating and stirring of the patch or patch pieces for varying amounts of time increases the extractability of BTDS.

- Provide more specific descriptions of the analytical methodology.

- Clarify which BTDS batch will be marketed, since the chemical extraction studies and the clinical abuse liability studies should be conducted on the product intended for marketing.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: December 19, 2000

To: Cynthia G. McCormick, M.D., Director
Division of Anesthetic, Critical Care and Addiction Drug Products, HFD-170

From: Ann-Kathryn Yelovich, M.D., Medical Officer and
Katherine Bonson, Ph.D., Pharmacologist
Controlled Substance Staff, HFD-009

Through: Deborah B. Leiderman, M.D., Director
Controlled Substance Staff, HFD-009

Subject: Filing Issues for NDA 21-306, Norspan BTDS (buprenorphine transdermal system)

Clinical abuse liability issues:

- Indicate if formal measures of withdrawal or drug-liking were used in any clinical studies.

- Give us the location of case report forms and narratives for all of the following patients: patients in appendices 5 and 6 of Abuse Liability Volume 1 (AL V 1); patients who are presented in the Executive Summary of AL V 1, including patients whose numbers are not italicized (e.g., patient from BP 96-0304 who is referred to on p. 76 of AL V 1); patients who showed signs and symptoms of abuse, dependence, or withdrawal involving any substance or signs or symptoms of difficulty tolerating any substance; patients who lost their patches or did not return them; patients who had a history of drug or alcohol abuse or dependence prior to participating in the studies.

- Please identify whether discontinuation of BTDS use leads to the development of tolerance, craving and/or withdrawal symptoms that would indicate physical dependence.

- Please provide a risk management plan that addresses the potential risk for abuse, diversion and overdose of BTDS, given that large amounts of buprenorphine remains in the patch following removal from a patient.

Chemical extraction issues:

- Please locate studies that test extraction of buprenorphine from BTDS using other solvents (such as acetone, methanol, ether ethylacetate and ethanol).

- Please locate studies that test whether heating and stirring of the patch or patch pieces for varying amounts of time in each solvent increases the extractability of BTDS.

- Clarify which BTDS patch will be marketed, since the chemical extraction studies and the clinical abuse liability studies should be conducted on the product intended for marketing.

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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/s/

MATTHEW W SULLIVAN

06/23/2010

These CSS filing reviews do not appear to have been checked into DFS at the time they were created. They were discovered while creating the June 2010, action package, and were checked into DARRTS for archival purposes.

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:	May 10, 2010
To:	Bob Rappaport, MD, Director **Division of Anesthesia and Analgesia Products (DAAP)**
Through:	Claudia Karwoski, Pharm D, Director **Division of Risk Management (DRISK)** Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer, Acting Team Leader **Division of Risk Management**
From:	Latonia M. Ford, RN, BSN, MBA Patient Product Information Reviewer **Division of Risk Management**
Subject:	DRISK Review of Patient Labeling (Medication Guide and Instructions for Use)
Drug Name(s):	Butrans (buprenorphine) Transdermal System
Application Type/Number:	NDA 21-306
Applicant/sponsor:	Purdue Pharma L.P.
OSE RCM #:	2009-1865

1 INTRODUCTION

This review is written in response to a request by the Division of Anesthesia and Analgesia Products (DAAP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) and Instruction for Use for Butrans (buprenorphine) Transdermal System.

Purdue Pharma L.P. submitted an original 505 (b) (1) New Drug Application, 21-306, for Butrans (buprenorphine) Transdermal System on November 3, 2000. FDA issued a Not Approvable (NA) action letter on August 31, 2001, for NDA 21-306. On September 25, 2009, Purdue Pharma L.P. submitted a complete response to the Agency's NA letter. The proposed indication for Butrans is for the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time.

The Applicant's proposed Risk Evaluation and Mitigation Strategy (REMS) for Butrans (buprenorphine) Transdermal system is currently under review by DRISK and will be provided under a separate cover.

Please let us know if DAAP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant.

2 MATERIAL REVIEWED

- Draft Butrans (buprenorphine) Transdermal System Prescribing Information (PI) submitted September 25, 2009, revised by the review division throughout the review cycle and provided to DRISK on March 8, 2010.
- Draft Butrans (buprenorphine) Transdermal System Medication Guide (MG) submitted September 25, 2009, revised by the review division throughout the review cycle and provided to DRISK on March 8, 2010.
- Draft Butrans (buprenorphine transdermal system) Instructions for Use (IFU) submitted September 25, 2009, revised by the review division throughout the review cycle and provided to DRISK on March 8, 2010.

3 RESULTS OF REVIEW

In our review of the MG and IFU, we have:

- simplified wording and clarified concepts where possible

- ensured that the MG and IFU are consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured consistency with the Medication Guides of similar products

Our annotated MG and IFU are appended to this memo. Any additional revisions to the PI should be reflected in the MG and IFU.

Please let us know if you have any questions.

41 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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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/s/

LATONIA M FORD
05/10/2010

CLAUDIA B KARWOSKI
05/10/2010
concur

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: May 7, 2010

To: Bob Rappaport, M.D., Director
Division of Anesthesia and Analgesia Products

Through: Michael Klein, Ph.D., Director Controlled Substance Staff
Lori Love, M.D., Ph.D., Lead Medical Officer
Controlled Substance Staff

From: Chad J. Reissig, Ph.D., Pharmacologist

Subject: **NDA 21-306 BuTrans (Buprenorphine transdermal)**
Indication: moderate to severe chronic pain
Dosages: 5, 10 & 20 mg transdermal system
Company: Purdue Pharmaceuticals

Materials reviewed: NDA submission located at:

\\CDSESUB1\EVSPROD\NDA021306

Initial CSS review by Maust et al., submitted July 24, 2001

This memorandum responds to a request from the Division of Anesthesia and Analgesia Products (DAAP) concerning the review of the Sponsor's New Drug Application (NDA). CSS has reviewed the NDA to evaluate the drug's abuse liability according to 21 CFR § 312.23.

Background

BuTrans is a transdermal system that contains 5, 10, and 20 mg of buprenorphine. BuTrans is being developed for the relief of moderate to severe pain. BuTrans is intended to provide around-the-clock treatment of pain for an extended period of time (up to 7 days).

Buprenorphine is a mu opioid partial agonist and kappa opioid receptor antagonist. Buprenorphine produces morphine-like effects at low doses, though as a partial mu opioid agonist, its maximal effects are expected to be less than the full agonists morphine and heroin. Buprenorphine is abused and diverted and is currently a Schedule III controlled substance.

NDA 21-306 was originally submitted by the Sponsor in November 2000. In response to the Sponsor's submission, FDA issued a not approvable (NA) action letter. The NA letter contained 62 deficiency items, two of which were identified by the Controlled Substance Staff (CSS).

Both of the issues were raised in the second End of Review meeting on April 2, 2002. The two items and the response from the Sponsor appear below (FDA responses from 2000 appear in **bold**):

Conclusions

We have concluded the following relative to the abuse and diversion risk of BuTrans:

- Buprenorphine abuse/overdose is a significant problem in countries where buprenorphine is marketed. An accessible outpatient dosage form of buprenorphine may lead to increased reports of misuse, abuse, and morbidity.

- Buprenorphine can be readily extracted from the BuTrans matrix and prepared for alternative routes of administration (e.g. injection).

- Considerable residual buprenorphine remains after use of the transdermal system. The BuTrans patch contains abou (b) (4) residual drug after seven days of use. For the high dose formulation (20 mg), this residual amount of drug is equal to about (b) (4) doses of (b) (4) mg buprenorphine. The large residual drug content of BuTrans may contribute to misuse, abuse, overdose, and diversion.

- Responses to CSS issues in the November 2000 NA letter (immediately below):

  November 2000 NA Letter (Item 60)

  Further characterize the abuse potential and risk of overdose of buprenorphine in the transdermal formulation. Examples of issues that need to be addressed, include, but are not necessarily limited to the following:

  a) Characterize the bioavailability and pharmacokinetic profile of buprenorphine through the buccal mucosal route in the presence of alcohol, a common accompaniment for orally or transmucosally abused drugs.

  Response to item 60 a): Existing buccal absorption data were sufficient to satisfy this request if a license agreement to reference the data was obtained. The Sponsor provided the right of reference for the buccal absorption data.

  b) The human abuse liability study was reviewed and found to be inconclusive because of the failure to investigate a full range of doses in order to produce low, moderate, and high reinforcing responses to buprenorphine. Failure to use a standard comparator, such as morphine, and failure to obtain plasma levels of buprenorphine renders the study uninterpretable. Repeat this study taking into consideration these design issues.

  Response to Item 60 b: Regarding the abuse potential of the drug product, in 2000 buprenorphine was listed in Schedule V or the Controlled Substances Act

(CSA); following reassessment in 2002, buprenorphine was rescheduled to Schedule III (Notice: Federal Register Vol 67 (No 55), 13114-13116, March 21, 2002; Final: Federal Register Vol 67 (No 194), 62354-62370, October 7, 2002). As buprenorphine is listed in Schedule III, additional human studies are not required.

November 2000 NA Letter (Item 61)

The potential for significant diversion of buprenorphine from Norspan is unacceptable for a controlled substance. This risk should be properly addressed by redesigning the patch or modifying the BTDS matrix to limit the residual buprenorphine upon completion of dosing and to reduce significantly the potential for extraction of buprenorphine from the matrix.

Response to item 61: Purdue submitted a risk evaluation and mitigation strategy (REMS) focused on educating prescribers and patients through a medication guide, full prescribing information, and a healthcare professional guide.

In addition, supplementing the REMS is the requirement for scissors to open each individual BuTrans pouch.

Instructions on BuTrans disposal are outlined by the Sponsor in the product labeling, instructing patients to flush used patches in the toilet (the "fold and flush method"). If this method is unavailable, the Sponsor developed a "patch disposal unit" which consists of a sealable, adhesive pouch that sequesters used BuTrans patches for disposal in the trash.

- Labeling and REMS.

The labeling and REMS strategy is an attempt to limit BuTrans diversion and abuse. Instructing patients on the "fold and flush" method and how to use the patch disposal unit may limit the diversion and extraction of the residual BuTrans buprenorphine content *when used as directed.* However, neither strategy is likely to deter a motivated individual from the misuse and abuse of the BuTrans product.

The ability to circumvent, retrieve, or remove used BuTrans patches from the patch disposal unit is unknown.

The high buprenorphine content of BuTrans (in both used and unused patches) presents a significant abuse potential, risk of acute overdose, and diversion.

Because buprenorphine is easily extracted from BuTrans, and because (b) (4) of the drug remains in BuTrans after it has been used, BuTrans presents a significant risk for diversion, abuse and overdose.

Recommendations

The Sponsor should address the following concerns to minimize the risk of abuse and diversion of BuTrans:

- Reduce residual buprenorphine left over in the patch after use.
- Monitor the product for abuse, misuse, overdose, diversion and death.
- Conduct post marketing monitoring and surveillance of BuTrans to assess the ability of individuals to circumvent, retrieve, or remove used BuTrans patches from the patch disposal unit.

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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/s/

CHAD REISSIG
05/07/2010

LORI A LOVE
05/07/2010

MICHAEL KLEIN
05/07/2010

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY ADDENDUM

DATE: April 28, 2010

TO: Matthew Sullivan, Regulatory Project Manager
Robert A. Levin, M.D., Medical Officer
Division of Metabolic and Endocrine Products (DMEP)

FROM: Susan Leibenhaut, M.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: #21-306

APPLICANT: Purdue Pharma

DRUG: Buprenorphine Transdermal System

NME: No

THERAPEUTIC CLASSIFICATION: Standard review of a complete response (6 months)

INDICATION: relief of moderate to severe pain in patients requiring continuous opioid treatment for an extended period of time

CONSULTATION REQUEST DATE: March 4, 2010

DIVISION ACTION GOAL DATE: March 16, 2010
PDUFA DATE: March 30, 2010

I. BACKGROUND:

Purdue Pharma L.P. submitted NDA 21-306, a 505(b) application for BuTrans, a transdermal system providing systemic delivery of buprenorphine over a 7-day period, for the indication of the relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time. Clinical inspections were conducted in response to a routine audit request to assess data integrity and human subject protection for clinical trials conducted for approval. On February 26, 2010, the Division of Scientific Investigations, Good Clinical Practice Branch II, submitted a clinical inspection summary (CIS) for NDA 21-306 to the Division of Anesthesia, Analgesia and Rheumatology Products (DAARP). The CIS summarized the results of the requested inspections of clinical sites for the NDA.

During the NDA review, it was noted that a decision was made to terminate Protocol BUP3015 entitled "A Multicenter, Randomized, Double-Blind, Active Comparator Study to Determine the Efficacy and Safety of BTDS 20 or OxyIR® versus BTDS 5 in Subjects with Moderate to Severe Low Back Pain" due to "changing business conditions." On March 4, 2010, the review division requested audit of the sponsor to determine whether the applicant was unblinded when the decision was made to terminate the study. We are issuing the review of the sponsor inspection as an addendum to the original clinical inspection summary.

The inspection focused on:

A. Protocol BUP3015 entitled "A Multicenter, Randomized, Double-Blind, Active Comparator Study to Determine the Efficacy and Safety of BTDS 20 or OxyIR® versus BTDS 5 in Subjects with Moderate to Severe Low Back Pain" and also covered:

B. Protocol BUP3024 entitled "A Multi-center, Randomized, Double-blind, Placebo-controlled Study with an Open-label Run-in to Assess the Efficacy, Tolerability, and Safety of BTDS 10 or BTDS 20 Compared to Placebo in Opioid-naïve Subjects with Moderate to Severe Chronic Low Back Pain"

II. RESULTS (by Site):

Name of Inspected entity and Location	**Protocol #/ # of Subjects Enrolled/ Randomized**	**Inspection Dates**	**Final Classification**
Sponsor: Purdue Pharma One Stamford Forum Stamford, CT 06901-3431	BUP3015/ 662 subjects randomized BUP3024/ 541 subjects randomized	April 12 to 15, 2010	Pending (Preliminary classification NAI)

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations.

1. Purdue Pharma
One Stamford Forum, Stamford, CT 06901-3431

Note: Observations noted for this site are based on communications with the FDA investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Report (EIR).

a. **What was inspected**: This inspection covered sponsor/monitor activities related to the protocol included with the assignment (BUP3015) and an additional pivotal study (BUP3024). The following were addressed during this inspection: 1) Early termination of Study BUP3015 after 74% of the planned subjects had enrolled; firm personnel were interviewed and records were reviewed to determine the reason for early termination and whether or not the study had been unblinded when the decision was made to terminate. 2) Organization and Personnel; 3) Study Monitoring; 4) Data Management; 5) Quality Assurance, and 6) Drug Safety-method of tracking adverse events serious adverse events, deaths and discontinuations.

b. **General observations/commentary:** Purdue was involved in a patent dispute concerning oxycontin. As the case was in the courts, and the several rulings against Purdue unfolded, the company downsized, resulting in lay-off of workers and termination of development programs, and leasing the company building and moving to cheaper quarters. Studies BUP3011 and 3014 were terminated during the initial downsizing. In June 2005, after another ruling against Purdue, the decision was initially made to terminate Studies BUP3015 and 3019, but review of the enrollment numbers for Study BUP3015 suggested that continuing the subjects already enrolled would result in a study that would possibly have adequate power to demonstrate efficacy of the product. The statistician described this as “a balance between having a good study and the conditions at the time.” The firm provided meeting minutes of the deliberations during the downsizing and SOPs and study documents concerning database lock and unblinding. We found no evidence that the study had been unblinded prior to June 2005 when the decision was made to terminate.

The sponsor appears to have executed their responsibilities appropriately, and not significant issues were noted. No Form FDA 483 was issued to the sponsor.

c. **Assessment of data integrity:** Study BUP3015 appears to have been conducted adequately, and the data generated by this study may be used in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The sponsor inspection found no evidence of unblinding prior to the decision to terminate Study BUP3015 because of "changing business conditions." Actions by the company concerning this study appeared appropriate in the context of a patent dispute that affected many aspects of company activities. The data generated in support of the application appears reliable.

Note: The final classification for this inspection is pending. An addendum to this clinical inspection summary will be forwarded to the review division if additional observations of clinical and regulatory significance are discovered after reviewing the EIR for this inspection.

{See appended electronic signature page}

Susan Leibenhaut, M. D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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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/s/

SUSAN LEIBENHAUT
04/29/2010

TEJASHRI S PUROHIT-SHETH
04/29/2010

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

PRE-DECISIONAL AGENCY MEMO

Date: March 17, 2010

To: Matthew Sullivan – Regulatory Project Manager
Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)

From: Mathilda Fienkeng – Regulatory Review Officer
Twyla Thompson – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: **DDMAC draft labeling comments**
NDA 21-306 **Butrans (buprenorphine) Transdermal System for transdermal administration CIII**

DDMAC has reviewed the proposed product labeling (PI), for Butrans (buprenorphine) Transdermal System for transdermal administration CIII (Butrans), submitted for consult on October 7, 2009.

The following comments are provided using the updated proposed PI sent via email on March 12, 2010 by Matt Sullivan. If you have any questions about DDMAC's comments, please do not hesitate to contact us

Carton and Container Labeling

DDMAC notes that the tradename presentation within the full PI has been revised. We recommend revising the tradename on the carton and container labeling to be consistent with the PI.

51 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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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/s/

MATHILDA K FIENKENG
03/17/2010

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:	March 5, 2010
To:	Bob Rappaport, MD, Director Division of Anesthesia, Analgesia and Rheumatology Products
Through:	Kellie Taylor, PharmD, MPH, Associate Director Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis
From:	Zachary Oleszczuk, PharmD, Acting Team Leader Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name(s):	Butrans (Buprenorphine) Transdermal System 5 mcg/hour, 10 mcg/hour, and 20 mcg/hour
Application Type/Number:	NDA 021306
Applicant:	Purdue Pharma L.P.
OSE RCM #:	2009-1861

EXECUTIVE SUMMARY

Butrans (Buprenorphine) Transdermal System is a partial agonist opioid transdermal patch. This patch is similar to other analgesic transdermal patches and has some of the same risks associated with the opioid products such as respiratory depression, accidental exposure to used and discarded patches, and intentional abuse of used or discarded patches. The Applicant also proposes a novel disposal system as an alternate to the "fold and flush" method, which is the preferred method of discarding patches to minimize the risk of accidental exposure to children and pets or intentional abuse of used patches or discarded patches.

We evaluated the proposed patches, container labels, carton labeling, package insert labeling, patient package insert labeling, medication guide labeling, and disposal system for Butrans submitted by the Applicant on September 25, 2009, and November 20, 2009, using Failure Mode and Effects Analysis (FMEA) [1] and our previous experience with other marketed transdermal patches. The proposed labels and labeling lack the use of color differentiation, are inconsistent with the information presented, and have some warning statements that are not prominent. Additionally, the novel disposal system may introduce some confusion since the consumers and healthcare professionals will be unfamiliar with the disposal system.

The container labels and carton labeling should be revised to incorporate the use of color differentiation to help minimize the risk of confusion between the multiple strengths. The information presented throughout the labels and labeling should be consistent and warnings should be included or made more prominent to reduce the risk of inappropriate use of the patch and accidental exposure. Additionally, warning statements can be added to the disposal system to help minimize confusion that could lead to medication errors.

1 INTRODUCTION

This review is written in response to a request from the Division of Anesthesia, Analgesia and Rheumatology Products (DARRP) for assessment of the patches, container labels, carton labeling, insert labeling, patient package insert labeling, medication guide labeling, and disposal system for Butrans (buprenorphine transdermal system) for their vulnerability to medication errors.

2 METHODS AND MATERIALS

2.1 ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE

Since, Butrans is currently marketed in foreign countries, DMEPA conducted a search of the Adverse Event Reporting System (AERS) on January 26, 2010 using the active ingredient name "buprenorphine" and the verbatim terms "Butr%" and "bupren%" along with the MedDRA reaction terms "Medication Errors" (HLGT), "Product Quality Issue" (PT) and "Product Label Issue" (HLT). The tradename 'Butrans' was not used as a proprietary name because the name does not appear as a tradename in the AERS drug database.

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were grouped together into cases. If an error occurred, the staff reviewed the cases to determine if the root cause could be associated with the labels, labeling, or packaging configuration of the product, and thus pertinent to this review. Those cases that did not describe a medication error were excluded from further analysis. The cases that did describe a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors.

Our search of the Adverse event database did not identify any cases of medication errors reports involving Butrans. However, since medication errors are known to be under reported and this product is currently marketed in foreign markets only, a negative AERS result can not guarantee that errors are not occurring, only that the errors are not being reported to the FDA.

2.2 LABELS AND LABELING

The Applicant submitted patches (Appendix A) container labels (see Appendix B), carton labeling (see Appendix C), insert labeling (no image), patient package inset labeling (no image), medication guide (no image), and instructions for use labeling (no image) for Butrans (buprenorphine transdermal system) on September 25, 2009. Additionally the Applicant submitted the disposal system (no image) on November 20, 2009. DMEPA used Failure Mode and Effects Analysis (FMEA)[2] in our evaluation of the labels and labeling.

3 CONCLUSIONS AND RECOMMENDATIONS

Our evaluation of the labels and labeling noted areas where the presentation of information can be improved to minimize the potential for medication errors. Additionally, our evaluation noted that the novel disposal system proposed by the Applicant may be a source of confusion among patient and healthcare providers since they will be unfamiliar with the disposal system. Since the disposal system is in the same shape as the patch (rectangle) and is adhesive, patients may confuse the disposal system for the transdermal patch, particularly if they are unaware of the existence of a disposal system. Our postmarketing experiences with other transdermal patches have seen similar situations where patients applied only a protective overlay that was included with those patches because the patients believed that the overlays were the actual patch. Additionally, DMEPA is not sure if the disposal system will help to minimize the risk of intentional abuse since the disposal system could be cut open and the patch would then be exposed. However, DMEPA believes that the disposal system could provide an alternative to the "fold and flush" method which may help to minimize the risk of unintentional exposure in children and pets. However, the disposal system can be improved to help minimize the risk of confusion that could lead to medication errors and we provide recommendations in section 3.2.

Section 3.1, Comments to the Division, contains our recommendations for the package insert labeling, and patient package insert labeling. Section 3.2, Comments to the Applicant contain our recommendations for the patch labels, container labels, carton labeling, and disposal system. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have questions or need clarifications, please contact Abolade Adeolu, OSE Regulatory Project manager, at 301-796-4264.

[2] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3.1 COMMENTS TO THE DIVISION

3.1.1 General Comments

1. Presenting the capital '-T-' in the middle of the name 'BuTrans' is representative of tall-man lettering which is typically reserved for differentiating known look-alike established name pairs or in rare circumstances for proprietary name pairs to help reduce the risk of name confusion resulting in medication error. Since 'BuTrans' is not a name that has been involved in name confusion the capitalization of the letter 'T' is inappropriate. We request that all instances of the proprietary name in the labels and labeling be revised so that only the first letter is a capital letter followed by all lower cases letters, 'Butrans', to avoid the inappropriate use of tall-man letters.
2. Revise all references to the unit 'hour' to be expressed as the word 'hour' to provide consistency throughout the labels and labeling and to avoid confusion that can be caused by the use of abbreviations that have multiple meanings. Currently, the labels and labeling utilize three different expressions ('h', 'hr', and 'hour') to represent the unit 'hour'. In the expression of strength (i.e. 5 mcg/h, 10 mcg/h, and 20 mcg/h) throughout the labels and labeling, the abbreviation 'h' is used to represent the unit 'hour'. On the container label the statement "Each transdermal system delivers 5 mcg buprenorphine per hr" uses the abbreviation 'hr' to represent the unit 'hour'. A similar statement "Each transdermal system delivers 5 mcg buprenorphine per hour" that appears on the carton labeling use the word 'hour' to express the unit of time. Although, we acknowledge that all three expressions can be interpreted as 'hour' in the medical community, the two abbreviations ('h' and 'hr') also have other recognized meanings that can be found in standard references for abbreviations. Additionally, the use of abbreviations in labels and labeling can lead to prescribing habits that may result in medication errors. If the use of an abbreviation for 'hour' is necessary because of inadequate space, revise all abbreviations to use 'hr' and be consistent whenever the abbreviation is used.
3. (b) (4)

3.1.2 Package Insert

1. There are three statements in the "Indication and Usage" section that give instructions when Butrans is not to be used or for when Butrans is not intended. Similar products such as Duragesic repeat instructions when Duragesic should not be used or for when Duragesic is not intended in both the "Indication for Usage" section and the "Contraindications" section. DMEPA questions if the following statements should repeated in the "Contraindications" section and including the statements in the highlights:

(b) (4)

(b) (4)

2. Include the statement (b) (4) in the "Warnings and Precautions" section of the highlights if it is concluded that the patch (b) (4).
3. Although the statement "Do not use Butrans if the patch is cut, damaged, or changed in any way" (b) (4), the statement should also appear in the "Dosage and Administration Section". Include the statement "Do not use Butrans if the patch is cut, damaged, or changed in any way" to the "Dosage and Administration" section.
4. Considering revising the statement " (b) (4) The statement should be presented as "Butrans 5 mcg/hour Transdermal System (45 mm by 45 mm matrix patch)". This should be done for each of the three strengths.
5. Revise section 17.1 "Information for Patient and Caregivers" to include an additional instruction (b) (4)

3.1.3 Patient Package Insert

1. Consider revising the statement (b) (4) The statement should be revised as "Keep Butrans patch in its unopened protective pouch until you are ready to use it."
2. Considering revising the section (b) (4)
3. The section 4 "Disposing of Butrans Patch" the instructions for disposing the patch using the toilet come before the instructions for disposing the patch using the disposal system. DMEPA recommends placing the instruction for disposal of the preferred methods first, however DMEPA will defer to the Division for which method is the preferred method.

3.2 COMMENTS TO THE APPLICANT

A. GENERAL COMMENTS

1. Revise all instances of the presentation of the proprietary name throughout the labels and labeling to presented with only the first letter as capital letter followed by all lower cases letters, 'Butrans', to avoid the appearance of tall-man letters. Presenting the capital '-T-' in the middle of the name 'BuTrans' is representative of tall-man lettering which is typically reserved for differentiating known look-alike established name pairs or in rare circumstances for proprietary name pairs to help reduce the risk of name confusion resulting in medication error. Since 'BuTrans' is not a name that has been involved in name confusion, the capitalization of the letter 'T' is inappropriately applied.

2. Revise all references to the unit 'hour' to be expressed as the word 'hour' to provide consistency throughout the labels and labeling and to avoid confusion that can be caused by the use of abbreviations that have multiple meanings. Currently, the labels and labeling utilize three different expressions ('h', 'hr', and 'hour') to represent the unit 'hour'. In the expression of strength (i.e. 5 mcg/h, 10 mcg/h, and 20 mcg/h) throughout the labels and labeling, the abbreviation 'h' is used to represent the unit 'hour'. On the container label the statement "Each transdermal system delivers 5 mcg buprenorphine per hr" uses the abbreviation 'hr' to represent the unit 'hour'. A similar statement "Each transdermal system delivers 5 mcg buprenorphine per hour" that appears on the carton labeling use the word 'hour' to express the unit of time. Although, we acknowledge that all three expressions can be interpreted as 'hour' in the medical community, the two abbreviations also have other recognized meanings that can be found in standard references for abbreviations. Additionally, the use of abbreviations in labels and labeling can lead to prescribing habits that may result in medication errors. If the use of an abbreviation for 'hour' is necessary because of inadequate space, revise all abbreviations to use 'hr' and be consistent whenever the abbreviation is used.

3. The controlled symbol competes for prominence with the proprietary name and strength. Reduce the size of the control symbol so it is not the most prominent information on the labels and labeling.

4. (b) (4)

B. PATCHES

(b) (4)

C. CONTAINER LABELS

1. Revise the color of the expression of strength to help differentiate the different strengths. Currently all the strengths are highlighted with (b) (4) and may be confused because of the use of the same color.
2. Revise the statement (b) (4) The new statement should read "Each transdermal system delivers 5 mcg buprenorphine per hour for seven days".
3. Include the total drug content of the transdermal system in a manner that does not compete with the prominence of expression of strength or the rate of drug release.
4. Include warning statements on the principal display panel to help minimize the inappropriate use of the transdermal system. We have seen inappropriate use with other similar transdermal systems through our postmarketing experiences and similar products list warning statements on the container label to help minimize the risk of inappropriate use of those products. (b) (4) . Statements such as these warnings should be included on the principal display panel.
5. The net quantity statement is confusing and can be revised to be easier to understand. (b) (4)

D. CARTON LABELING

1. Revise the color of the expression of strength to help differentiate the different strengths. Currently all the strengths are highlighted with (b) (4) and may be confused because of the use of the same color.
2. Revise the statement (b) (4) The new statement should read "Each transdermal system delivers 5 mcg buprenorphine per hour for seven days".
3. Include warning statements on the principal display panel to help minimize the inappropriate use of the transdermal system. We have seen inappropriate use with other similar transdermal systems through our postmarketing experiences similar products list warning statements on the carton labeling to help minimize the risk of inappropriate use of those products.. (b) (4) . Statements such as these warnings should be included on the principal display panel.

4. The net quantity statement is confusing. (b) (4) Revise the net quantity statement to delete the phrase " (b) (4) and present as the net quantity as "Contains 4 transdermal systems and 4 disposal systems".
5. The warning statement (b) (4) Additionally, the warning statement could be made more prominent by bolding the text.
6. Include the total drug content of the transdermal system in a manner that does not compete with the expression of strength or the rate of drug release.

E. DISPOSAL SYSTEM

Include a prominent statement such as "Disposal Unit: does not contain active drug" on the Disposal System to help clearly differentiate the disposal system from the patch. Such a statement should indicate what the Disposal System is and that it does not contain active drug. Since the Disposal System is in the same shape as the patch (rectangle) and is adhesive, patients may confuse the disposal system for the patch, particularly if they are unaware of the existence of a disposal system. Our postmarketing experiences with other transdermal patches have seen similar situations where patients applied only the protective overlays that are included with those patches because the patients believed that the overlays were the actual patch.

6 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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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/s/

ZACHARY A OLESZCZUK
03/05/2010

KELLIE A TAYLOR
03/05/2010

CAROL A HOLQUIST
03/05/2010

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:	March 4, 2010
To:	Bob Rappaport, M.D, Director Division of Anesthesia, Analgesia and Rheumatology Products (DAARP) Office of New Drugs
Through	Robert Boucher, MD, MPH, FACS, Director Joann Lee, Pharm.D, Acting Team Leader Division of Pharmacovigilance II (DPV II) Office of Surveillance and Epidemiology
From:	Afrouz Nayernama, Pharm.D. Safety Evaluator Division of Pharmacovigilance II (DPV II) Office of Surveillance and Epidemiology
Subject:	AERS reports of products failure associated with the use of transdermal buprenorphine products
Drug Name(s):	Buprenorphine transdermal
Application Type/Number:	NDA- 021306
OSE RCM #:	2010-463

1 INTRODUCTION

In preparation for BuTrans (buprenorphine transdermal system) NDA review, the Division of Anesthesia, Analgesia and Rheumatology Products (DAARP) requested an AERS review of drug product failure associated with the use of all currently available transdermal buprenorphine products. Buprenorphine is marketed in Europe[1] under different trade names (BuTrans, Norspan, Transtec, Sectran, Transect and Restiva).

2 METHODS AND MATERIAL

2.1 DATA SOURCE

The AERS database was searched on March 1, 2010 for reports of drug product failure associated with the use of transdermal buprenorphine drug products.

2.2 SEARCH CRITERIA

Two separate AERS searches were conducted.

The criteria for the first AERS search are as follows:

- Drug: buprenorphine (generic name)
- MedDRA Search Terms: Device component findings (HLT) and Therapeutic and non-therapeutic responses (HLT)
- Route of administration: transdermal
- Search dates: 1969-3/1/2010

The criteria for the second AERS search are as follows:

- Drug: buprenorphine (generic name)
- MedDRA Search Terms: All adverse events
- Route of administration: transdermal
- Search dates: 1969-3/1/2010

3 RESULTS

The first AERS search, as of March 1, 2010 resulted in 4 foreign cases. One case was eliminated because the reported events were not associated with the use of buprenorphine patch. The review of the case narratives in the 3 remaining cases did not reveal any type of transdermal patch failure, leakage or other issue with the matrix patch adhesion adverse events. The 4 cases were also retrieved from the second AERS search (see Appendix A for the summary of the reported adverse events).

[1] Buprenorphine transdermal system is not currently available in the U.S.

As of 03/01/2010, the AERS database contained a total of 97 (all foreign) adverse event reports in association with buprenorphine transdermal system (BuTrans, Norspan, Transtec, Sectran, Transect and Restiva).The cases were individually reviewed, duplicates were consolidated (N=19), and non-transdermal buprenorphine cases were eliminated (N=17). A total of 61 unique foreign reports remained for further analysis.

The review of the case narratives of the 61 unique cases did not reveal any type of transdermal patch failure, leakage or any issue with the matrix patch adhesion adverse events (see appendix A for the summary of the reported adverse events).

AERS Limitations:

AERS collects reports of adverse events from health care professionals and consumers submitted to the product manufacturers or directly to the FDA. The main utility of a spontaneous reporting system, such as AERS, is to identify potential drug safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for particular product or used for comparing risk between products.

Appendix A

Table 1. Summary of adverse events (N= 61)

#	ISR #	Drug name (trade name)	Comments/reported events
1	4208177 & 4215795	Transtec 20 mg daily	Confusion, fluctuating vigilance, attention problems, myoclonia, disorientation
2	4236056	Transtec	Nausea/vomiting and dizziness, not a primary suspect drug, multiple concomitant drug
3	4320628	Buprenorphine patch 17.5 mg	Insomnia and visual hallucination
4	4567508	Transtec	Death, collapsed due to drug interaction (additive analgesic effect) with Palladone
5	4659828	Transtec 35 mcg/hr	Somnolence, Withdrawal symptoms, concomitant medications: Palladone
6	4791200	Transtec 35mcg/hr	Severe sedation required naloxone
	4803849 & 4805327	Transtec 35 mcg/hr	Panic attack
8	4805489 4871026	Transtec 35 mcg/hr	Sedation, somnolence, depression, aggression of coronary artery disease, tachy fibrillation
9	4884360 4885966 4889248 4889254 4891788 4891789 4891969	Buprenorphine transdermal 35 mcg/hr,	Literature report, Clinical study, post-marketing surveillance study in 1317 patients: adverse reactions were reported in 10% of patients
10	4894865	Transtec 35mcg/hr	Restlessness, increased blood pressure and pulse
11	4978874	Transtec 35 mcg/hr	Restlessness, anorexia, withdrawal syndrome, nausea
12	4998047	Buprenorphine (?)	Respiratory depression and peripheral coldness, concomitant med: Tramadol
13	5006548	Buprenorphine transdermal	Literature report: buprenorphine transdermal is a good drug delivery method for MI/angina, pt did not experienced any chest pain during having an MI
14	5031763	Transtec 35 mcg/hr	Death, intentional overdose, respiratory failure, pulmonary edema, concomitant meds: morphine, codeine
15	5040244	Transtec 70 mcg x 2 patch, buprenorphine 2 mg tablet	Within 1 hour experienced withdrawal symptoms, violent, shaking, respiratory problems (?), heart rate uncontrolled, hospitalized and received sedation, suspected AEs resulted from buprenorphine antagonistic effect

#	ISR #	Drug name (trade name)	Comments/reported events
16	5106784	Trastec	Death, Withdrawal syndrome (fever) 12 hours after switching from morphine to Transtec
17	5124693	Norspan 5 then increased to 10 mg,	Death unknown cause, concomitant med: morphine
18	5134815	Transtec	Hallucination , inadequate pain relief, concomitant med: morphine
♣19	5136253 5141045	Transtec 35 mcg/hr increased to 52.5 mcg/hr,	Respiratory insufficiency, bradycardia, pupillary constriction, confusion, concomitant meds: codeine, morphine, Ifosfamide (suspected CYP-450 interaction)
20	5158557	Transtec 35 mcg/hr	Comatose, hyponatremia, vascular encephalopathy, apathy, concomitan med: venlafaxine
21	5159957	Transtec ½ patch for a month then increased to whole patch (35 mcg/hr)	Coma, transferred to hospital, received Narcan and responded
22	5187191	Buprenorfina plaster 35 mcg/hr	Loss of consciousness for long hours (14 hour), outcome not reported, concomitant meds: Lyric 375 mg/die(?)
23	5200256	Transtec	Confusion, concomitant med: Catapress
24	5220829 & 5225900	BuTrans	Immobile, increased tone, concomitant med: metoclopramide
25	5256033	Transtec 35 mcg/hr	Zombie state/condition, delusion
26	5349623	Transtec	Liver injury, elevated LFT, cholestatic , concomitant meds: Tramadol/apap
27	5395269	Norspan weekly	Withdrawal syndrome, convulsion, hot and cold sweat, required treatment with Valium
28	5530563 5531371 5535131	BuTrans	Paralysis, sleepiness
29	5614892	Norspan 20 mg,	Chest tightness, breathless, angiogram: blockage 50-70%
30	5657443	Transtec 35 mcg/hr increased to 52.5 mcg/hr,	Respiratory failure, concomitant med: Neurontin
31	5671594	Transtec	Difficulty breathing, somnolence, disorientation
♣32	5672463	Norspan	Death, Respiratory failure, possible withdrawal syndrome due to switching from morphine to Norspan

♣ The cases were also retrieved on the first AERS search

#	ISR #	Drug name (trade name)	Comments/reported events
33	5744826	Buprenorphine patch	Confusion
34	5779987	Transtec	Lower extremities edema, vomiting
35	5795852	Buprenorphine transdermal 20 mg	Confusion, decreased mobility
36	5838465	Transtec	Obstipation
37	5846651 5853830	Transtec	Coma and death, multiple concomitant medications
38	5874791	Buprenorphine transdermal	Visual hallucination
39	6064450	Bu Trans	Over sedation and difficult to arouse
40	6076530 6083802 6086318 6093386 6094850	Transect	Hepatitis, multiple medications are listed as the suspected drugs
41	6079381	Buprenorphine transdermal	Shortness of breath
42	6154960	Norspan	Confusion
43	6204747	Transtec 35 mcg/h	Steven-Johnson syndrome, Lamictal was the primary suspect drug, multiple concomitant meds
	6311320	Buprenorphine transdermal	Respiratory depression, concomitant medications: morphine, Duragesic patch
45	6421340	Norspan	Hallucination, concomitant medication/co-suspected med: Stalevo
46	6424458	Buprenorphine transdermal 35 mcg/hr	Overdose, decreased vigilance, concomitant med: morphine
47	6462753	Transec 20mg/ day	Somnolence, disorientation, hyponatremia
*48	6529504	Bu Trans	Not feeling well, uncomfortable in legs
49	6565609	Norspan	Loss of consciousness, concomitant med: fentanyl patch
50	6565611	Norspan	Hallucination
51	6565613	Norspan	Visual hallucination, fluid retention, nightmares, cold sweat
52	6566972	Norspan	Visual hallucination, confusion
53	6567028	Norspan	aphasia, aphonia, asthenia, cognitive disorder and

* The cases were also retrieved on the first AERS search.

#	ISR #	Drug name (trade name)	Comments/reported events
			Facial palsy
54	6567044	Norspan	confusion , constipation and visual hallucination
55	6567088	Norspan	Hallucination
56	6567114	Norspan	abnormal behavior and visual hallucination
57	6567132	Norspan	hallucination, headache, hypertension and nausea
58	6567207	Norspan	application site reaction, hallucination, nausea
			pyrexia and vomiting
59	6567285	Norspan 20	unresponsive to stimuli for an hour
60	6567286	Norspan 10 mg/day increased to 20 mg/day,	unresponsive to stimuli and hypersomnia once dose increased to 20 mg/day
61	6568076 6573909	Norspan 5 mg/day	Constipation, feeling of fullness

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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/s/

AFROUZ R NAYERNAMA
03/10/2010

ROBERT M BOUCHER
03/10/2010

45 DAY MEETING CHECKLIST

FILEABILITY:

On initial overview of the NDA application **(NDA 21-306):** **YES** **NO**

PROJECT MANAGEMENT:

(1) Do any of the following apply to this application (i.e., if YES, the application MUST BE REFUSED TO FILE under 314.100 (e) and there is no filing over protest):

(a) Is the drug product already covered by an approved application? NO

(b) Does the submission purport to be an abbreviated application under 314.55; however the drug product is not one for which FDA has made a finding that an abbreviated application is acceptable under 314.55(b)? NO

(c) Is the drug product subject to licensing by the FDA under the Public Service Act and Subchapter F of Chapter I of Title 21 of the CFR? NO

(2) Do any of the following apply to this application (i.e., if NO, the application MAY BE REFUSED TO FILE under 314.100 (d) and there is the potential for filing over protest):

Does the application contain a completed application form as required under 314.50 or 314.55 YES

(a) On its face, does the application contain the sections of an application required by regulation and Center guidelines? YES

(b) Has the applicant submitted a complete environmental assessment which addresses each of the items specified in the applicable format under 25.31 or has the applicant submitted evidence to establish that the product is subject to categorical exclusion under ~~25.24~~ of the CFR? YES (sec 4.5)

(c) On its face, is the NDA formatted in compliance with Center guidelines including integrated efficacy and safety summaries? YES

(d) Is the NDA indexed and paginated? YES

(e) On its face, is the NDA legible? YES

(f) Has the applicant submitted all required copies of the submission and various sections of the submission? YES

(g) Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor? YES

(h) Does the application contain a statement that all nonclinical laboratory studies was conducted in compliance with the requirements set forth in Part 58 or a statement why a study was not conducted in compliance with those YES (sec 5.7)

requirements??

(i) If required, has the applicant submitted carcinogenicity studies? YES (Phase 4)

(j) On its face, does the application contain at least two adequate and well-controlled clinical trials? YES

(k) Does the application contain a statement that all clinical trials were conducted in accord with the IRB/Declaration of Helsinki provisions of the CFR? YES

(l) Have all articles/study reports been submitted either in English or translated into English? YES

(m) Has the applicant submitted draft labeling in compliance with 210.56 and 210.57 of the CFR? YES

(n) Has the applicant submitted the required FRAUD POLICY notice? YES

(p) Has the applicant submitted copies of all package inserts (or their equivalent) from all countries in which this product has been previously approved for marketing? Have all non-English package inserts been translated? YES

(q) Has the applicant stated that the integrated summary of safety includes all safety data for this product of which they are aware from all sources, domestic and foreign? What is the cut-off date for the preparation of the ISS? YES

(r) If this is a CANDA submission, has the applicant submitted a statement to the archival NDA that the text, tables, and data in the CANDA and the archival hardcopy NDA are identical? If they are not identical, is there a letter to the archival NDA that specifies distinctly ALL of the differences in the two submissions? YES

(3) From a project management perspective, is this NDA fileable? If "no", please State on below why it is not. YES

_____

Project Manager/Sara E. Shepherd

_____

Supervisory Project Manager /Cathie Schumaker

/s/

Sara Shepherd
12/11/00 02:48:01 PM
CSO

Cathie Schumaker
12/12/00 09:34:03 AM
CSO