# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER:
## 21-306

## SUMMARY REVIEW

# Summary Review for Regulatory Action

| | |
|---|---|
| **Date** | (electronic stamp) |
| **From** | Sharon Hertz, M.D. |
| **Subject** | Division Director Summary Review |
| **NDA/BLA #**<br>**Supplement #** | 21-306/000 |
| **Applicant** | Purdue Pharma, LLC |
| **Date of Submission** | 30 September 2009 |
| **PDUFA Goal Date** | 30 June 2010 (extended 3 months) |
| | |
| **Proprietary Name / Established (USAN) names** | Butrans/buprenorphine transdermal system |
| **Dosage forms / Strength** | Transdermal system (patch) 5, 10, 20 mcg/hr |
| **Proposed Indication(s)** | 1. Relief of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time |

| **Material Reviewed/Consulted**<br>OND Action Package, including: | |
|---|---|
| CDTL Memo | Robert Shibuya, M.D. |
| Primary Medical Officer Review | Robert A. Levin, M.D. |
| Statistical | Jonathan Norton, Ph.D., Dionne Price, Ph.D. |
| Pharmacology Toxicology Review | Gary Bond, Ph.D., Adam Wasserman, Ph.D. |
| CMC Review | Zavier Ysern, Ph.D., Prasad Peri, Ph.D. |
| Clinical Pharmacology Review | Sheetal Agarwal, Ph.D., Suresh Doddapaneni, Ph.D. |
| QT Interdisciplinary Review Team | Christopher Tornoe, Ph.D., Christine Garnett, Ph.D., Lihan Yan, Ph.D., Monica Fiszman, M.D., Norman Stockbridge, M.D. |
| OSE/DRISK | Jeanne Perla, Ph.D., Gita Toyserkani, PharmD, Marcia Britt, Ph.D., Jodi Duckhorn, MA |
| OSE/DRISK | Latonia M. Ford, RN, BSN, MBA, Sharon R. Mills, BSN, RN, CCRP, Claudia Karwoski, PharmD |
| DDMAC | Mathilda Fienkeng, PharmD, Twyla Thompson, PharmD |
| DSI | Susan Liebenhaut, M.D., Jean Mulinde, M.D. |
| Office of Compliance | Agnes Plante, BSN, RN |
| OSE/DPV | Afrouz Nayernama, PharmD, Joanne Lee, PharmD, Robert Boucher, M.D. |
| OSE/DMEPA | Zachary Oleszczuk, PharmD, Kellie Taylor, PharmD, MPH, Carol Holquist, RPh |
| CSS | Chad J. Reissig, Ph.D., Lori Love, M.D., Ph.D., Michael Klein, Ph.D. |

# Signatory Authority Review Template

## 1. Introduction

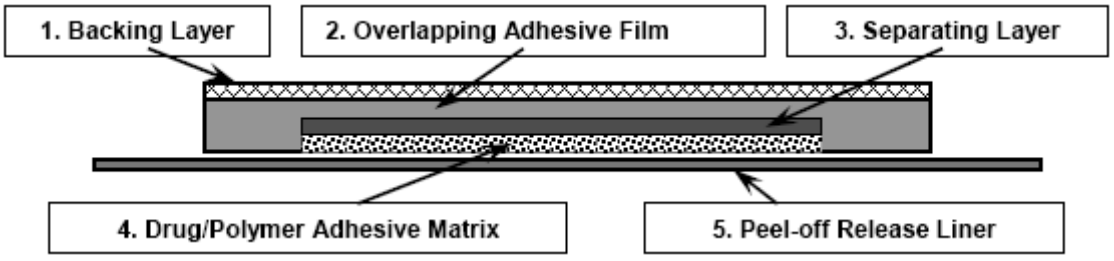
Butrans is a buprenorphine transdermal delivery system. Purdue Pharma, the Applicant, is seeking an indication for the management of moderate to severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time. This 505(b)(1) application represents a complete response to a Not Approvable action taken on August 31, 2001. There were numerous deficiencies that lead to the action including 49 CMC deficiencies, two nonclinical pharmacology/toxicology deficiencies, three clinical pharmacology deficiencies and 11 clinical deficiencies.

## 2. Background

Buprenorphine is a partial opioid agonist/antagonist listed in Schedule III of the Controlled Substances Act. There is a parenteral formulation approved for the management of pain and there are sublingual formulations with and without naloxone approved for the treatment of opioid addiction. Buprenorphine has not been approved previously for use in the management of chronic pain. Although a mu agonist opioid analgesic, buprenorphine is also a kappa antagonist and unlike full opioid agonists, is believed to have a ceiling effect. It is possible to precipitate opioid withdrawal in opioid-tolerant patients if converted to buprenorphine from a dose of opioid greater than 30 mg of morphine or equivalent. As noted, numerous deficiencies precluded approval of the original application including a failure to demonstrate efficacy.

## 3. CMC/Biopharmaceutics

The Butrans patch is formulated as a drug in matrix system. It is a rectangular transdermal patch formulated to provide release of buprenorphine for a period of seven days. The rate of drug release is controlled by the diffusion of the buprenorphine in the adhesive matrix through the skin. The patch consists of an outer backing layer, an adhesive film layer, a foil layer between the adhesive and the active drug in adhesive matrix and a peel off release liner as demonstrated in the following cross sectional cartoon of the product.



Butrans is manufactured in three different strengths, 5 mcg/h, 10 mcg/h, and 20 mcg/h containing 5 mg, 10 mg, and 20 mg of buprenorphine, respectively. Drug delivery is proportional to the drug containing surface area of drug in adhesive matrix.

As described in the CMC review, the numerous CMC deficiencies were addressed with the exception of reducing the amount of residual drug in the patch after use. The amount of residual buprenorphine is a concern from the perspective of availability of drug in the community for the purpose of intentional misuse. (b) (4) remains in the patch after use by the patient. However, there is no apparent risk to the patient, as the amount of buprenorphine in the drug is needed in order to create an adequate gradient for diffusion. Once the application period of 7 days is complete, the residual drug does not have an adequate concentration gradient to move across the patient's skin in any great amount. It was hoped that by reformulating the product, a change in excipients might permit the use of a smaller amount of buprenorphine to create the gradient and have a smaller residual. As the first transdermal patch with buprenorphine, there is no experience with alternate formulations; it is not yet known whether the residual can be reduced. An internal Agency working group in the Office of New Drug Quality Assessment, has been evaluating the scientific and regulatory issues associated with transdermal products. This group has been consulted and a summary of key points in this review follows:

- It is unclear from a pharmaceutical development basis how much reformulating effort will be required to minimize the residual buprenorphine in the drug product and still achieve similar efficacy characteristics. Therefore, in the absence of a specific guidance limiting the amount of residual drug in the transdermal patch a post approval commitment to reformulate the drug product is not currently being sought by the review team as an approvability issue.
- An OSE review of the postmarketing experience in Europe found that there were no reports of product failure associated with the use of transdermal buprenorphine products.
- Although the draft guidance on residual drug content in transdermal products is ready for publication, it is not out for public comment. The principles of this new guidance will be applied to all forth coming applications.

As summarized by Dr. Shibuya, the Biopharmaceutics review by Drs. Tapash Ghosh and Patrick Marroum assessed the impact of changes in in vitro dissolution rate and adhesion strength over storage on in vivo performance. Drs. Ghosh and Marroum found that the in vivo plasma concentrations vary widely. However, in conjunction with Drs. Sheetal Agarwal and Suresh Doddapaneni (Office of Clinical Pharmacology), the team felt that tightening the dissolution specifications and a post-approval commitment to collect dissolution data from 12 patches with the potential to require Level 3 testing would suffice in the interim (12-months). The Applicant agreed with this arrangement.

I concur with the conclusions reached by the chemistry reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 21 months. There are no outstanding issues.

## 4. Nonclinical Pharmacology/Toxicology

Studies assessing chronic dermal toxicity, carcinogenicity, toxicity of Duro-Tak adhesive and reproductive toxicity were submitted in this complete response and were reviewed. There is no evidence of carcinogenicity and the toxicity studies did not reveal any unexpected toxicity of concern. The reproductive toxicology studies did show increased stillbirths and early deaths resulting in a recommendation for Pregnancy Category C. I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

## 5. Clinical Pharmacology

Buprenorphine is highly bound to plasma proteins (96%). Buprenorphine is metabolized by CYP3A4 and by glucuronide conjugation. Norbuprenorphine is the only known active metabolite of buprenorphine. The bioavailability of a 7-day application of a single Butrans dose is 15%. Dose proportionality for the Butrans 5, 10 and 20 mg strengths was established for the 7-day application period. Application of external heat (i.e. heating pad) resulted in a 26-55% increase in buprenorphine plasma concentrations. A population PK analysis found that age, gender and ethnicity had no significant relationships to Cmax or AUC of buprenorphine.

The deficiencies from the first cycle have been adequately addressed as described in the clinical pharmacology review and CDTL memo. While it was surprising that ketoconazole, a potent CYP3A4 inhibitor, did not appreciably increase the exposure to buprenorphine, there is data that, after sublingual administration, the Cmax and AUC of buprenorphine did increase in the presence of atazanavir. Atazanavir is a CYP3A4 inhibitor and a UGT1A1 inhibitor. Dr. Agarwal hypothesized that transdermal delivery of buprenorphine bypasses the first pass effect of oral administration and that may be why there was not an interaction with ketoconazole. Dr. Agarwal also notes that since buprenorphine is a high affinity substrate for CYP3A4, only a small amount of uninhibited enzyme activity may be needed for its metabolism.

The Applicant submitted a reanalysis of the pharmacokinetic data in patients with mild to moderate hepatic impairment. There was no data from patients with severe hepatic impairment so the recommendation is to begin patients with mild and moderate hepatic impairment patients on the lowest 5 mcg/h dose and to consider alternate analgesics in patients with severe hepatic impairment.

A thorough QT study (tQT study) was submitted and reviewed by the QT Interdisciplinary Review Team (QT IRT). While the study failed to exclude a 10 ms increase in QT for both therapeutic (10 mg) and supratherapeutic (40 mg) dose levels, the effect for the 10 mg strength was not consistent across time points. Dr. Garnett concludes that the therapeutic dose of Butrans 20 mg is considered to have no clinically meaningful effect on QT. In contrast, the maximum mean $\Delta\Delta$QTcF with the 40-mg dose exceeded the 10-ms threshold at 2 hours and at six additional timepoints. No significant relationship between buprenorphine concentrations and QTcI prolongation was identified. This finding is most likely because of the limited number of PK samples collected at 1, 13, and 23.5 h postdose and the limited range of concentrations within

each subject. The application site must be rotated with a 21-day break prior to re-using a site in order to avoid additional drug accumulation and an increase in exposure

I concur with the conclusions reached by the clinical pharmacology reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

## 6. Clinical Microbiology

N/A

## 7. Clinical/Statistical-Efficacy

Two clinical studies were conducted to support the efficacy of this product. Both studies were adequate and well-controlled and conducted in patients with moderate to severe chronic low back pain. Study BUP 3024 (Study 24) studied the drug in opioid-naïve patients; Study BUP3015 (Study 15) studied the drug in opioid-experienced patients who required between 30 and 80 mg of morphine or equivalent. In Study 24, patients were started on a Butrans 5 mcg/hr patch and titrated to a maximum of 20 mcg/hr of Butrans, as tolerated, and then randomized to remain on the titrated dose of Butrans or placebo. In Study 15, after tapering to no more than 30 mg of morphine per day, or equivalent, patients were titrated to a maximum of 20 mcg/hr of Butrans, as tolerated, and then randomized to remain on the titrated dose of Butrans, Butrans 5 mcg/hr or placebo. Efficacy was assessed after 12 weeks on the randomized treatment. Both studies demonstrated a statistically significantly greater treatment effect for the titrated dose buprenorphine treatment group as demonstrated in the following two tables from Dr. Shibuya's review.

**Table 1:** Analysis of Primary Efficacy Endpoint (pain intensity over the last 24 hours), Study 24

| Weeks/Visits | BTDS (n = 257) | Placebo (n = 284) |
|---|---|---|
| **Screening[a] (Visit 2)** | | |
| n | 257 | 284 |
| Mean (SD) | 7.24 (1.263) | 7.17 (1.223) |
| **Prerandomization[b] (Visit 3)** | | |
| n | 257 | 284 |
| Mean (SD) | 2.57 (1.283) | 2.56 (1.207) |
| **Double-blind Week 12 (Visit 8)** | | |
| n | 257 | 283[d] |
| Mean (SD) | 3.83 (2.738) | 4.38 (2.690) |
| **Repeated Measures Analysis/Least Squares Means (SE) at Week 12** | | |
| LS mean (SE) | 3.81 (0.166) | 4.39 (0.152) |
| **Treatment Comparison at Week 12** | | |
| Difference in LS means from placebo | −0.58 (0.225) | |
| *P* value vs placebo[c] | .0104 | |
| 95% CI for difference from placebo | (−1.02, −0.14) | |

**Table 4:** Primary Efficacy Analysis, Study 15

| Visits/Weeks | BTDS 5 (N = 221) | BTDS 20 (N = 219) | OxyIR® (N = 220) |
|---|---|---|---|
| **Screening**[a] | | | |
| n | 221 | 219 | 220 |
| Mean (SE) | 6.36 (0.075) | 6.46 (0.084) | 6.46 (0.079) |
| Median | 6.0 | 6.5 | 6.0 |
| Min, Max | 4, 10 | 1, 10 | 3, 10 |
| **Prerandomization**[b] | | | |
| n | 221 | 219 | 219 |
| Mean (SE) | 2.84 (0.075) | 2.91 (0.075) | 2.74 (0.074) |
| Median | 3.0 | 3.1 | 2.9 |
| Min, Max | 0, 7 | 0, 6 | 0, 5 |
| **Week 4** | | | |
| n | 154 | 176 | 184 |
| Mean (SE) | 3.79 (0.149) | 3.40 (0.128) | 3.14 (0.125) |
| Median | 4.0 | 3.0 | 3.0 |
| Min, Max | 0, 8 | 0, 8 | 0, 7 |
| **Week 8** | | | |
| n | 138 | 164 | 173 |
| Mean (SE) | 3.83 (0.162) | 3.35 (0.140) | 3.24 (0.145) |
| Median | 4.0 | 3.0 | 3.0 |
| Min, Max | 0, 9 | 0, 8 | 0, 10 |
| **Week 12** | | | |
| n | 127 | 142 | 154 |
| Mean (SE) | 4.02 (0.179) | 3.35 (0.139) | 3.26 (0.152) |
| Median | 4.0 | 3.0 | 3.0 |
| Min, Max | 0, 9 | 0, 9 | 0, 8 |
| **Overall Statistics**[c] | | | |
| Difference from BTDS 5 over weeks 4, 8, and 12 | | -0.67 (0.163) | -0.75 (0.161) |
| *P* value vs. BTDS 5 | | < .001 | < .001 |
| 95% CI for difference from BTDS 5 | | (-0.99, -0.35) | (-1.07, -0.44) |

The Applicant terminated Study 15 after only 74% of the planned accrual had completed. To ensure that there were no other reasons and to assess whether unblinding had occurred, the Division of Scientific Investigations was consulted to conduct a directed Sponsor inspection and they found no problems that would result in the data being unreliable in any way.

## 8. Safety

As noted by Drs. Levin and Shibuya, there were no unexpected safety concerns from the clinical trial data. No deaths were attributable to study drug. The adverse event profile was consistent with an opioid. There was local skin irritation at the site of patch placement and eight patients with serious adverse events related to the skin. One case of rash and one anaphylactoid reaction were attributed to Butrans.

Further review of the postmarketing data was requested of the Applicant who submitted reports of erythema, pruritus, dermatitis, vesicles, secretion/discharge, dryness, burns, and rashes at the

application site. The Applicant also conducted a latency analysis and found that the reactions can be immediate or late with 24% of reactions occurring following 100 days of Butrans treatment.

## 9. Advisory Committee Meeting

There was no advisory committee for this application as it did not represent an NME, nor was the indication novel.

## 10. Pediatrics

In keeping with the current approach used with other extended-release opioids indicated for moderate to severe chronic pain for an extended period of time, pediatric studies will be waived for pediatric patients below the age of 7 because the number of patients available for study is too small and studies are impracticable. The remainder of the pediatric population can be deferred because the adult studies are ready for approval. The required studies will be pharmacokinetic and safety studies since the efficacy associated with an opioid analgesics can be extrapolated to pediatric patients as young age 2. This plan was reviewed at the Pediatric Research Committee and approved.

## 11. Other Relevant Regulatory Issues

The Division of Scientific Investigations reported that the four sites inspected had no violations that would bring into question the acceptability of the data. There were no unblinding or other issues surrounding the Applicant's decision to prematurely terminate Study 15.

The Division of Medication Error Prevention and Analysis was consulted and recommended that the proprietary name, Butrans be changed to Butrans to reduce the risk of medication errors.

The Division of Pharmacovigilance was consulted to review the premarketing experience of transdermal buprenorphine outside of the U.S. There was no evidence of patch failure, leakage, or issues with matrix patch adhesion in the available data.

The Controlled Substance Staff (CSS) has made the following 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.

CSS has also made the following 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.

In a final memo, CSS states:

This follows up our earlier memos (see: CSS memos on June 23, 2010, and May 7, 2010). Although we would prefer that the actual amount of residual drug be reduced, CSS recommends the following:

- It is not necessary for the actual amount of residual drug to be reduced prior to approval.
- In contrast, we would like to assess the use of the disposal pouch as an alternative method for reducing the amount of drug that could be available for diversion and ultimate abuse.
- In order to assess the effectiveness of the Butrans pouch disposal system, the Sponsor should perform a survey-based, post marketing evaluation of the effectiveness of the pouch. This assessment should determine the frequency of use of the pouch disposal system and the "fold and flush" method for the disposal of used Butrans pouches.

Risk Evaluation and Mitigation Strategies (REMS)

A REMS was submitted as part of the initial resubmission and subsequently revised. The revised REMS consists of:

- Medication Guide
- Elements to Assure Safe Use
  - Prescriber training with retraining every two years
- Timetable for submission of assessments

The REMS appears to be acceptable with the final refinements from the Applicant.

There are no other unresolved relevant regulatory issues.

# 12. Labeling

The proprietary name of Butrans was found to be acceptable. Recommendations from OSE and DDMAC were conveyed to the applicant and incorporated into the labeling. The REMS was reviewed and, after revision, found to be adequate.

## 13. Decision/Action/Risk Benefit Assessment

- Regulatory Action - Approval

- Risk Benefit Assessment

There is adequate evidence of efficacy for this product with an adverse event profile consistent with most opioid analgesics. The one outstanding issue is the amount of residual buprenorphine in the patch once it is removed from the patient. The applicant was asked to attempt to reduce this residual. Not much work appears to have been done. Most products with transdermal delivery of drug require a gradient to support the diffusion of drug across the skin and into the systemic circulation. As a result, there will be a residual amount of drug left behind in the patch. The problem with residual drug, in this case buprenorphine, is not that it poses a safety risk to the patient, but rather, this results in excess drug in the community where there is potential for it to be unintentionally or intentionally misused or abused. Accidents can occur if household contacts come into contact with a used patch that is not properly discarded. For the only currently approved transdermal opioid patch, Duragesic, proper disposal consists of folding the sticky sides of the patch together and flushing it down the toilet. Flushing a folded patch is one possible disposal method for Butrans and the other is to use the disposal unit developed by the Applicant, consisting of a sticky surface, larger in area than the Butrans patch, that sticks together with the Butrans patch and the combination can then be discarded in the trash.

Intentional misuse and abuse of prescription opioid products is a major public health concern in the U.S. It is currently unknown whether a buprenorphine transdermal patch can be developed with a lower residual, but there will always be a residual amount of drug in order for these transdermal products to work. If it were possible to reduce the residual from the current amount, (b) (4) to (b) (4) or even (b) (4), it is unknown whether that would result in a difference in the abuse liability of the product. The Butrans patch contains 20 mg of buprenorphine, so with the current formulation, the residual would be approximately (b) (4) mg. While this might be attractive to some for the purpose of intentional abuse, it would require a directed effort to liberate the buprenorphine from the matrix in the patch, and, in contrast to more potent opioids, this amount of buprenorphine is not likely to be a sufficient dose to cause respiratory depression or death in most adults.

Therefore, I find the overall risk of this product to be adequately balanced by the findings of efficacy.

- Recommendation for Postmarketing Risk Management Activities
  Butrans will have a REMS with the following components:

- Medication Guide
- Elements to Assure Safe Use
    - Prescriber training with retraining every two years
- Timetable for submission of assessments

- Recommendation for other Postmarketing Study Commitments

    1. The Applicant will update the specifications (validated test and acceptance criterion) for drug containing laminate to include testing for the adhesive strength as agreed to in the 16-Jun-2010 amendment. The proposed adhesion strength of the drug containing adhesive laminate specification will be submitted to the Agency before July 31, 2010, when data from an adequate number of Butrans batches will be available to establish a specification.

    2. The Applicant's proposed acceptance criteria for dissolution in an amendment dated 16- Jun-2010 is accepted on an interim basis. The Applicant agrees to collect dissolution data from twelve patches for each lot manufactured within one year for each time point on release and stability. The data and an analysis of its relation to the dissolution specification will be submitted to FDA before June 30, 2011.

| 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/

SHARON H HERTZ
06/29/2010