APPLICATION NUMBER: 21-306

OTHER ACTION LETTER(s)
NDA 21-306

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

Attention: Lois Hinman
Sr. Director, US Regulatory Affairs

Dear Dr. Hinman:

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 for Norspan (buprenorphine transdermal system) 5, 10, and 20 mg.

We acknowledge receipt of your submissions dated November 28, December 15, and December 18, 2000, January 9, January 10, February 20, February 28, March 9, March 13, March 21, March 26, March 30, April 18, April 26, April 27, May 3, May 4, May 14, May 24, May 25, June 4, June 6, June 7, June 8, June 11, June 15, June 18, June 20, June 21, June 23, June 26, June 27, June 29, July 11, July 25, and July 26, 2001.

We also refer to your submissions dated June 28, July 16, July 19, July 23, July 30, August 3 and August 15, 2001. These submissions have not been reviewed in the current review cycle. You may incorporate these submissions by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125 (b). Before this application may be approved, however, it will be necessary for you to address the following.

1. Provide the criteria for qualifying the reference standard of buprenorphine at Purdue Pharma and Lohmann-Therapie Systems (LTS).

2. Revise the drug substance specifications to clarify that the total impurities include the known (b) and the unspecified species.

3. Provide the sampling plan for the assay of buprenorphine bulk drug substance including the number of samples and the locations from where they are obtained in the container.

4. Provide identification and acceptance criteria for each individual impurity recurring at and above (b) in buprenorphine drug substance.
5. Provide an acceptance criterion of less than (b) (4) for any individual unspecified impurity in buprenorphine drug substance.

6. Provide the impurity profile of the drug substance used in clinical trials and in the pre-clinical studies.

7. Provide information supporting the safety of each individual impurity in buprenorphine that has an acceptance criterion of equal to or more than (b) (4). Reference to the European Pharmacopoeia is insufficient justification for the safety.

8. Revise the drug substance specification sheet by deleting the disclaimer that (b) (4) is not present in the drug substance.

9. Resolve the discrepancy in the results of analysis of batch 6370 from (b) (4) and batch 7/51139/5, which is the sub-lotted batch from 6370. (b) (4) data indicate the presence of (b) (4)% of (b) (4) whereas the LTS data indicate its level to be (b) (4)%.

10. Submit revised certificates of analysis from LTS indicating the actual levels of each individual impurity present in all batches of buprenorphine used in the manufacture of Norspan.

11. Submit the certificate of analysis of lot 6531 obtained from (b) (4).

12. Coordinate with the drug substance manufacturer to provide consistent drug substance specifications in the referenced DMF and in the NDA.

13. Include system suitability parameters such as quantitation limit in the analytical procedure for the related substances in the buprenorphine drug substance.

14. State clearly how the retest period of two years is computed for the drug substance and provide supporting data.

15. Provide additional information from the published literature, or elsewhere, regarding the potential toxicity of the following chemical components of the Duro-Tak adhesives used in the manufacture of the drug product, with particular emphasis on dermal absorption and systemic toxicity (e.g. neurotoxicity, carcinogenicity), at the specified limits in the drug product:

   a. (b) (4)
16. Provide the following revised specification and data on Duro-Tak 387-2054 and 387-2051 polymers:

a. An upper limit on the solids contents.

b. The level of residual \[\text{(b)} \text{(4)}\] in the batches of Duro-Tak used in the manufacture of the buprenorphine transdermal system (BTDS) batches used in pre-clinical and clinical trials.

17. Provide updated specifications for oleyl oleate including the following:

a. The chemical names of stabilizers and their limits.

b. A specific ID test such as IR for QC release.

18. Provide the following revisions to the acceptance testing of levulinic acid.

a. Full release testing of levulinic acid will be carried out by LTS.

b. The retest parameters will include the melting point of the \[\text{(b)} \text{(4)}\] derivative.

19. Include testing of the melting point in the retesting of \[\text{(b)} \text{(4)}\].

20. Provide lower limits of acceptance of peel force for \[\text{(b)} \text{(4)}\], and \[\text{(b)} \text{(4)}\].

21. Provide DMF references for the \[\text{(b)} \text{(4)}\].

22. Establish an in-process test of solids content for the drug-free adhesive mass.

23. Provide an in-process test for viscosity of the drug-containing adhesive mass and drug-free adhesive mass.

24. Include \[\text{(b)} \text{(4)}\] and \[\text{(b)} \text{(4)}\] in the residual solvent testing of drug-free adhesive laminate.

25. Provide additional in-process controls over the \[\text{(b)} \text{(4)}\]
26. Provide a sampling plan for the in-process testing of [(b)(4)] which includes representative samples from the beginning, middle, and the end of the operations.

27. Clarify how long and under what conditions the bulk laminates and patches are stored prior to [(b)(4)] and provide data to support the maximum hold time.

28. Provide a detailed description of the sampling plan for drug-product-release testing. Include samples from the beginning and end of the manufacture in the testing of appropriate attributes.

29. Provide adequate justification to conclude that [(b)(4)] is not a degradant in the drug product, or specify this as a degradant. The levels rose with time in batch 7/00499/6, and the forced degradation under acidic conditions resulted in the formation of this species, indicating that [(b)(4)] is a degradant.

30. Provide acceptance criteria for [(b)(4)] the third identified degradant in BTDS.

31. Provide acceptance criteria for each individual impurity recurring at and above [(b)(4)] in BTDS.

32. Provide an acceptance criterion of less than [(b)(4)] for any individual unspecified impurity in BTDS.

33. Provide safety information for each individual impurity in BTDS that has an acceptance criterion of equal to or greater than [(b)(4)].

34. Revise the *in vitro* release specifications as follows.

   a. Tighten the specifications to ensure the proper release profile of the drug product, at release, and through shelf life.

   b. Add an intermediate time point, e.g., 8 hours, in the testing.

   c. Include the USP<724> acceptance criteria of testing through L1, L2, and L3.

35. The adhesion and release strength data are wide and the respective specifications are even wider.

   a. Explain the observed data variability.

   b. Tighten the specifications to reflect the ranges observed for the batches used in the clinical studies, e.g., adhesion strength: [(b)(4)]; release strength: [(b)(4)]
c. Provide a summary, from the clinical trials, of drug product complaints relating to the adhesiveness of the patches.

d. Provide a specification for the adhesion strength of the drug-containing adhesive section of the BTDS.

36. The physical performance of the drug, and the drug product stability, may be related to residual levels of \[\text{(b)(4)}\]. Provide a test and acceptance criteria (minimum and maximum) for these residues or justification why this is not appropriate.

37. Provide the data on forced photodegradation of buprenorphine and BTDS.

38. Provide assay values of buprenorphine in the thermal stressing studies of BTDS.

39. Clarify whether the alkali treatment of BTDS was accompanied by loss in potency, and if so, was it accompanied by the formation of degradation products.

40. The detection and quantitation limits for \[\text{(b)(4)}\], and \[\text{(b)(4)}\] are \[\text{(b)(4)}\] respectively, whereas a \[\text{(b)(4)}\] percent threshold of identification based on total daily intake would amount to \[\text{(b)(4)}\]. Provide justification why the detection and quantitation limits of the procedure are considered adequate.

42. DMF indicates a potential change in the composition of the \[\text{(b)(4)}\]. Provide the composition of the \[\text{(b)(4)}\] used in the NDA stability studies and the one to be used for the commercial drug product.

43. At this time, agreement to a packaging equivalency protocol is premature pending resolution of other issues as detailed in this letter. Any changes in the composition or design of the pouch material should be reported to the Agency pursuant to the November 1999 Guidance on the Changes to A/NDAs.

44. Provide a test, test method, and acceptance criteria for \[\text{(b)(4)}\], or justification why this is not appropriate.

45. Provide an explanation for the lack of mass balance in the drug product stability data.

46. The stability data indicate that the adhesion strength and the release strength decrease with time. Provide data/justification to demonstrate that drug product at the end of
shelf-life performs acceptably for these attributes during patient use (see comment #35).

47. Provide moisture content data on three batches of the drug product that are part of the
primary stability studies.

48. A significant decrease is observed in dissolution (drug release) for the drug product
on stability.

a. Provide tightened dissolution specifications, and a shorter expiration dating
period (you have proposed 6 months), to ensure acceptable performance of the
drug product through its expiration dating period.

b. Provide the results of an investigation into the factors (e.g., raw materials,
manufacturing, packaging, etc.) which may have caused the observed wide
variability in stability for drug dissolution of the drug product.

49. Provide revised regression analyses of the stability data, including tests for
poolability and 95% confidence intervals, for the stability-indicating attributes: assay,
degraders, drug release, adhesion strength, and release strength. Provide separate
analyses for each strength and packaging vendor.

50. Deficiency letters were sent on August 31, 2001, to the holders of the following
DMFs: DMF (4), DMF (4), DMF (4), DMF (4), DMF (4), DMF (4)
DMF (4), DMF (4), DMF (4), DMF (4) and DMF (4).

51. Given the wide variability in plasma drug levels in the chronic toxicity studies
conducted in animals, and the fact that humans may require higher doses of
buprenorphine as they become tolerant to its effects, conduct an additional 6-month
chronic toxicity study in either rabbits or dogs at a maximum tolerated dose to fully
assess potential systemic toxicities that may be unrelated to buprenorphine’s known
pharmacological effects.

52. Your analyses of the hepatic impairment study were based on pooled data that do not
allow for a reasonable understanding of the correlation between the clinical stage of
disease and the pharmacokinetic profile. Reanalyze the data by degree of hepatic
impairment into separate subgroups for mild and moderate hepatic impairment.

53. The assay used in study BP95-0901 was not validated and therefore, the
pharmacokinetic data from that study were not reported. As a trend toward an
exposure-response relationship was noted, samples from this study should be
reassayed and the data specifically analyzed to assess
pharmacokinetic/pharmacodynamic relationships.

54. You have not adequately addressed concerns pertaining to potential drug-drug
interactions between CYP450 inhibitors and BTDS. Provide data to adequately
address these concerns either from available literature or from in vivo drug-drug interaction studies.

55. You have not provided substantial evidence that the drug will have its intended clinical effect.

In Study BP99-0203, patients were counted as “successfully” treated if their pain evaluations indicated pain relief using a last-observation-carried-forward (LOCF) methodology, regardless of the reason for discontinuation. When patients who were discontinued due to a drug-related adverse event were re-classified as treatment failures, the difference between Norspan and placebo was no longer clinically or statistically significant. While the protocol specified a sample size that was to be sufficient for the demonstration of a statistically significant effect in both hip and knee subgroups, there was no beneficial effect of Norspan in patients with osteoarthritis of the hip compared to placebo in your analysis. In your primary efficacy analysis, the between-group difference in treatment successes is not very large, about 12%, which is notably different from the 30% between-treatment difference specified in the protocol.

While Study BP96-0604 met its protocol-specified primary endpoint, further review of the data calls into question the clinical relevance of the findings. The relatively favorable efficacy results in Norspan patients who dropped out (relative to placebo patients who dropped out) was a factor in the statistical demonstration of a superior effect of Norspan over placebo. Further review of the data indicates that both an endpoint analysis (i.e., an analysis using the last recorded observation on each randomized patient) and a completers’ analysis (i.e., an analysis using the last observation only on patients who completed the protocol) indicate no statistically significant difference between Norspan and placebo. Using only observed data (i.e., no LOCF), there is no clinically meaningful difference in pain reduction after day 60 between placebo- and Norspan-treated patients. Additionally, the magnitude of effect of the between-group difference in mean change from baseline for Pain on the Average and Pain Right Now is of questionable clinical significance.

These findings from Studies BP99-0203 and BP96-0604, coupled with the negative findings from Studies BP96-0101 and BP96-0102, fail to demonstrate the effectiveness of the product for the “management of patients with pain requiring continuous opioid analgesia.”

Submit the results of additional adequate and well-controlled studies of appropriate duration and in relevant target populations to provide evidence of the effectiveness of the product and the durability of the treatment effect.

56. The extent of errors and inconsistencies in the safety database and in the safety analyses, especially the clinical laboratory data, preclude meaningful interpretation of the safety data.

a. Submit safety data in clinical study reports and in an Integrated Summary
of Safety (ISS) that are accurate and presented in a clear manner. Safety data in
this context refer to the primary safety database, the tables and listings of safety
data in the text of the reports and ISS, the tables and listings in appendices, and
the text of the reports and of the ISS and their appendices.

b. Adverse events were not coded consistently. Code all adverse events in the
safety database in a consistent manner across all studies.

c. The intercurrent diseases and conditions that were reported in some of the
studies appear to be adverse events. Include in the analysis of adverse events an
analysis of intercurrent diseases and conditions, and address how not classifying
these events as adverse events may impact the reported rates of adverse events.
As part of this analysis, review all of the events classified under intercurrent
diseases and conditions to insure that none meet criteria for a serious adverse
event.

57. The safety analyses did not analyze the effect of BTDS dose on safety outcomes. For
all safety measures, include analyses in the ISS that focus on the relationship between
BTDS dose at the time of a safety measure and the outcome of the safety measure.

58. The electrocardiogram data do not analyze electrocardiographic intervals.
Include in the ISS analyses of electrocardiographic intervals (e.g., PR, QRS, QT,
QTc, etc) in view of reports of cardiotoxicity associated with other opioids.

59. A potential problem with the design of studies BP96-0604 and BP99-0203 was
the fact that during the titration period, patients could escalate from one dose to
the next dose before seven days – in fact, as early as three days after a dose had
been applied. Given the pharmacokinetic characteristics of BTDS, which suggest that
the maximum concentration is reached at about 107 hours, titration to a higher dose
after only 3 or 4 days on a lower dose may be premature, and may lead to either
excessive toxicity, overestimation of the minimum effective dose for a given patient,
or both. Address this issue, both in regard to the completed studies, and in the design
of future studies.

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.

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.

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.

62. Adequate adhesion characteristics of the patch should be ensured. This deficiency may affect the efficacy and diversion potential of this product.

Labeling comments and comments on the proposed risk management plan will be provided when the issues identified above have been adequately addressed.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug. The safety update should include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   • Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

   • Present tabulations of the new safety data combined with the original NDA data.

   • Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

   • For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common,
but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with this division to discuss what further steps need to be taken before the application may be approved.

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

If you have any questions, call Sara E. Shepherd, Regulatory Project Manager, at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

Cynthia McCormick, M.D.
Director
Division of Anesthetic, Critical Care, and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
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Cynthia McCormick
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