DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-044

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

Attention: Richard J. Fanelli, Ph.D.
Senior Director, US Regulatory Affairs

Dear Dr. Fanelli:

Please refer to your new drug application (NDA) dated December 28, 1998, received December 29, 1998, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Palladone ™ (hydromorphone hydrochloride extended-release) Capsules, 12-, 16-, 24-, and 32-mg.

We acknowledge receipt of your submissions dated February 12, March 5 and 8, April 16 and 29, July 15, 20, and 23, August 3, 12, and 26, September 15 and 30, October 11, and November 11, 17, and 18, 1999, March 29, May 3, August 7, 23, and 25, and October 5, and 17, 2000, March 30, April 6, and 20, June 19, July 7 and 20, August 8, 13, and 17, October 9 and 18, 2001, January 29, March 12, April 15 and 29, May 23, July 2 (2) and 24, August 1 (2) and 6, September 5, 6 (2), 9, 10, 11, 12, 13, and 18, October 4, 8, and 10, November 26, and December 10, 13, 19, and 23, 2002, January 21, March 12, May 12, July 30, August 26, September 2 and 15, October 14, November 4, and December 10, 2003, January 16 and 20, February 12, April 15, May 17 and 20, June 7, July 1, 6 (2), 7, 13, 19, 23, and 28, August 23, and September 9, 10, 13, 14 (2), 17, 20, (2), and 21(3), 2004.

The July 23, 2004, submission constituted a complete response to our July 16, 2004, action letter.

This new drug application provides for the use of Palladone (hydromorphone hydrochloride extended-release) Capsules 12-, 16-, 24-, and 32-mg for the management of persistent, moderate to severe pain in opiate-tolerant patients requiring continuous, around-the-clock analgesia with a high potency opioid for an extended period of time, generally weeks to months or longer.

We have completed our review of this application, as amended, and it is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text. Marketing of this drug product and related activities are to be in accordance with the substance and procedures of all FDA regulations and the commitments you have made regarding specific risk management and use described below.

Risk Management Program

We remind you that your Palladone Risk Management Program is an important part of the postmarketing risk management for Palladone. Your Risk Management Program must include the following components:

1. Labeling
    a. Package Insert

    b. MedGuide

2. Education
    a. Professional Labeling

    b. Healthcare Professional Education

    c. Patient and Caregiver Education

3. Surveillance
    a. Monitoring for significant safety issues, with initiation of specific interventions when monitoring reveals a safety issue and evaluation of the effectiveness of those interventions.

You have also committed to the following:

4. Launch Program
    a. Sales Force Training and Product Promotion

    b. Limited Rollout Proposal with Evaluation Metrics

5. Other components of your RMP
    a. Policies, procedures and interventions dealing with material handling and supply chain integrity.

    b. Participation in or support of broad-based coalitions seeking systems solutions leading to appropriate use and reduced abuse and diversion of scheduled analgesics.

The Palladone Risk Management Plan, as submitted on September 21, 2004, adequately addresses each of these requirements. Any change to the program must be discussed with FDA prior to its institution and is subject to FDA concurrence. We expect your continued cooperation to resolve any problems regarding the Palladone Risk Management Program that may be identified following approval of this application.

We remind you of your September 10, 2004 submission, our letter dated September 17, 2004, and the August 30, 2004 meeting with the Agency and your commitment to provide reports regarding serious adverse events in patients who have received Palladone. The reports and their contents are listed below:

Within 15 days of receipt

1. Expedited Safety Reporting as per 21CFR 314.80

2. In-transit cargo theft of Palladone reported through your supply chain management.

Monthly reports

All monthly reports will have a cut-off date of the last calendar day of the month and will be submitted to the FDA within two weeks of that date. Data analysis will not be required beyond what is usually done for these reports. The reports will be sorted and separated into appropriate categories and include the following:

1. MedWatch forms for all adverse events that have been finalized in your (b)(4) safety database associated with the following conditions that do not qualify for expedited reports. The reports will include:

    a. Labeled overdoses and deaths associated with Palladone Capsules.

    b. Reports of abuse, addiction and/or misuse (i.e., the use of the medication in a manner inconsistent with the labeling, whether willful or unintentional) associated with Palladone.

    c. Adverse events associated with reports of exposure to Palladone involving children 18 years of age or younger.

    d. Adverse events occurring in "opioid naïve" persons who use Palladone.

    e. Medication errors associated with the administration of Palladone.

    f. Reports of documented safety concerns identified via surveillance do not need to be submitted on MedWatch forms but should be submitted and clearly labeled in a format to allow review and analysis by FDA.

    g. Adverse events identified as items a, b, c, d, and e that will be submitted in the monthly report should also be submitted in the subsequent periodic report as normally required by the regulations 21CFR 314.80. This will ensure that the adverse events (AEs) are entered into the AERS database.

2. Rx Patrol Reports that are reports of pharmacy level losses.

3. Media reports of any misuse/abuse/addiction/diversion cases involving Palladone Capsules.

Quarterly Reports

1. Periodic Safety Update Reports for Palladone Capsules as per 21 CFR 314.80

2. Research Abuse, Diversion, and Addiction-Related Surveillance (RADARS) System information on Palladone which will include the following:

    a. Beginning 6 months after the product is available, information will be provided on a quarterly basis alternating every three months between Summary Information without verification or analysis/synthesis and Full Report with analysis and synthesis of information.

    b. The information will include data from the Key Informant Network, Drug Diversion Study, Poison Control Centers, American Association for the Treatment of Opioid Dependence (AATOD) Study, and when available, usually once a year Federal Data sources will include Drug Abuse Warning Network (DAWN), National Survey on Drug Abuse Use and Health (NSDUH), and Treatment Episode Data Set (TEDS).

    c. Information will also be included to address FDA's "Minimum Candidate Rollout Metrics-2." The RADARS System will monitor for signals of abuse and diversion of Palladone and will include the outpatient drug use patterns in the following manner:

        (1) Use of sale and prescription data to monitor for disproportionate increases by geographic area

        (2) Look for inappropriate prescribing by using patient-level, prescription drug use longitudinal data to look for evidence of patients switching between insurance and cash payments and/or doctor/pharmacy shopping by geographic area.

3. The quarterly reports should also include:

    a. Interventions undertaken and known consequences/impacts

    b. External Advisory Board (EAB) meeting minutes

    c. Field force SOP findings

Six Month Reports

FDA's "Minimum Candidate Rollout Metrics-1," will be a semiannual report focused on serious adverse events, particularly overdose and deaths. These reports will also include your investigations to determine, where possible, whether the use was medical or nonmedical.

Report of Limited Rollout Evaluation Metrics

You will provide a report after distribution of Palladone Capsules begins that will include, but not be limited to, the Prior Therapy Report, Prescription by Specialty Report and the Primary Research Report of Key Messages.

1. The Prior Therapy Report will be clearly labeled and submitted not 15 months after dispensing of Palladone begins, but as part of the Six-Month Reports.

2. The Prescription by Specialty Report will be clearly labeled and submitted as part of the Quarterly Reports.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are deferring submission of your pediatric studies for ages 0-16 years until September 2009.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of this postmarketing study shall be reported annually according to 21 CFR 314.81. This commitment is listed below.

1. Deferred pediatric study under PREA for the use of Palladone (hydromorphone hydrochloride extended-release) Capsules 12-, 16-, 24-, and 32-mg for the management of persistent, moderate to severe pain in opiate-tolerant pediatric patients (0-16 years) requiring continuous, around-the-clock analgesia with a high potency opioid for an extended period of time, generally weeks to months or longer.

   Final Report Submission: September 24, 2009

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

We remind you of your agreement, submitted September 21, 2004, to decrease the level of the **(b)(4)** for the drug substance and submit a supplement for this change to the NDA by September 2006.

We have determined that Palladone poses a serious and significant public health concern requiring distribution of a Medication Guide under 21 CFR 208. This Medication Guide is necessary for patients' safe and effective use of Palladone.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, Medication Guide,) and labeling for immediate container and carton labels submitted September 20, 2004. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and unapproved new drug.

Please submit an electronic version of the FPL according to the guidances for industry titled *Providing Regulatory Submissions in Electronic Format – NDA* and *Providing Regulatory Submissions in Electronic Format-Content of Labeling*. Alternatively, except for the content of labeling, which must

be submitted electronically in PDF format, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-044**." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your September 10, 2004 submission, our letter dated September 16, 2004, and the following commitments to the Division of Drug Marketing, Advertising, and Communications (DDMAC):

1. Core launch material will be submitted to DDMAC at least 15 business days prior to actual use.

2. For the first 6 months following approval, any new core promotional material will be submitted at least 15 days prior to actual use for review and prior approval by DDMAC.

3. Items not considered core promotional material will be submitted at the time of first use.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

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

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

Sincerely,

{See appended electronic signature page}

Bob Rappaport, MD
Division Director
Division of Anesthetic, Critical Care,
and Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

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

/s/

Robert Meyer

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