CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-044

Chemistry Review(s)

Chemistry Review Data Sheet

NDA 21-044

Chem. Rev. # 6 dated 13-Jul-2004

PALLADONE™
Hydromorphone Hydrochloride Extended Release Capsules
12mg, 16mg, 24mg , 32mg
For use in opioid tolerant patients only

Purdue Pharma L.P.

Pramod Maturu, PhD. MBA
Division of Anesthetics, Critical Care, and Addiction Drug Products , HFD-170

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-044

2. REVIEW # 6

3. REVIEW DATE – 12-Jul-2004

4. REVIEWER: Pramod Maturu, PhD, MBA

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original NDA	28-Dec-1998
Review #1	24-Jun-1999
Amendment	20-Jul-1999
Review #2	16-Aug-1999
Agency's letter	27-Sep-1999
Amendment	11-Nov-1999 (Revised dissolution spec.)
Review #3	14-Dec-1999
Agency's letter	29-Dec-1999
Agency's letter	14-Jan-2000
Amendment	30-Mar-2001
Amendment	13-Aug-2001
Review #4	28-Sep-2001
Agency's letter	4-Oct-2001
Amendment	12-Mar-2002
Amendment	29-Apr-2002
Amendment	01-Aug-2002
Amendment	05-Aug-2002
T-con	04-Sep-2002 (FDA expressed concern regarding the potential mutagenicity of morphinone impurity in commercially available Hydromorphone HCl)
Amendment	06-Sep-2002

T-con	13-Sep-2002 (FDA expressed concern regarding the labels for the blister pack for the different dosage strengths, and requested more differentiation, e.g., color coding)
Review #5	13-Sep-2002
Agency's communication	04-Jun-2003 (FDA expressed agreement that lowering of the specification for morphinone impurity can be a phase-IV post marketing commitment).

6. SUBMISSIONS BEING REVIWED:

Submission(s) Reviewed	Document Date
Amendment	04-Oct-2002
Amendment	26-Nov-2002
Amendment	17-May-2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Purdue Pharma L.P.
Address:	One Stamford Forum, Stamford, CT 06901-3431
Representative:	Richard J. Fanelli, PhD, Senior Director U.S. Regulatory Affairs
Telephone:	203-588-8365

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Palladone™ CII
b) Non-Proprietary Name (USAN): Hydromorphone Hydrochloride Extended Release Capsules
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: Amendment dated 17-May-2004 is a complete response addressing the Agency's concern regarding the potential mutagenicity of morphinone impurity in Hydromorphone HCl that was cited in the approvable action letter on 13-Sep-2002.

10. PHARMACOL. CATEGORY: Proposed indication for use is for the management of persistent, moderate to severe pain in patients requiring continuous, around-the-clock opioid analgesic for weeks or longer.

11. DOSAGE FORM: Capsule.

12. STRENGTH/POTENCY: 12mg, 16mg, 24mg, and 32mg per capsule (12mg-cinnamon, 16mg-pink, 24mg-blue, and 32mg-white).

13. ROUTE OF ADMINISTRATION: Oral.

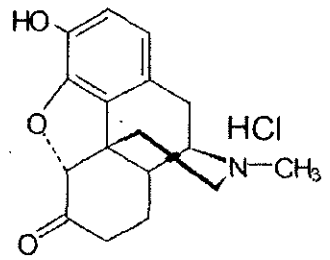
14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



$C_{17}H_{19}NO_3 \cdot HCl$ MW 321.81

The chemical name is 4,5α-epoxy-3-hydroxy-17 methylmorphinan-6-one hydrochloride.

17. RELATED/SUPPORTING DOCUMENTS:

This note is to inform that DMFs listed below are not cited on Form 356h.

Type/Number	Subject	Holder	Status	Review Date	Letter Date
DMF	Hydromorphone HCl USP		Adequate	7/13/04 Dr.Maturu	
DMF			Adequate *	12/19/00 Dr.Klein	
DMF			Adequate *		
DMF			Adequate *		
DMF			Adequate *	12/19/00 Dr.Klein	
DMF			Adequate *		
DMF			Adequate *		
DMF			Adequate *		
DMF			Adequate	12/19/00 Dr.Klein	
DMF			Adequate *		
DMF			Adequate *		
			Adequate **		

* USP test results for bottles and closures (submission dated 7.20.99) were in compliance with USP standards and they were considered adequate upon review in prior chem.

RELATED DOCUMENTS (if applicable):

IND 38,424 for Hydromorphone HCl extended release capsules, Purdue Pharma LP.

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	2.5-years expiry date request is within the estimates based on prediction limits approach and the confidence limits approach.	05-Sep-2002	Ms.Rosewitha Kelly
EES	Acceptable	05-May-2004	
Pharm/Tox	NDA can be approved with a phase IV commitment to decrease the impurity level of morphinone to an acceptable level of — ppm (or [ ] %).	10-Jun-2004	Dr.Suzna Thoroton-Jones
Biopharm	NDA acceptance range [ ] for the — dissolution time point was acceptable and it was validated by a biostudy (HD96-1206)	20-Oct-1999	Dr. Shinja Kim
LNC	Not consulted		
Methods Validation	Morphinone test method [ ] is suitable for regulatory purpose, and the method has a signal to noise ratio of [ ] solution.	7-Mar-2003	Dr. S. Nasir Ali, Director Science Branch, Philadelphia District, HFR-CE-160
ODS/DMETS	Acceptable trade name 'Palladone'. See review for labeling revisions.	12-Jul-2002	Dr. Nora Roselle
EA	Categorical exclusion from EA	26-Jun-1999	See CMC review #1.
Microbiology	N/A		

The Chemistry Review for NDA 21-044

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The reviewer recommends 'Approval' of the NDA from CMC perspective. CGMP compliance for the drug product-manufacturing site is acceptable to Office of Compliance based on EES dated 05-May-2004. Currently the FDA does not have an official guidance establishing acceptable levels for genotoxic impurities. To evaluate the risk benefit ratio of genotoxic impurities in pain medications, OND has addressed these impurities on a case by case basis, taking into consideration what is currently known regarding the level of the impurity, the maximum possible exposure to the impurity, the duration of treatment, the existing toxicological data, [ ] is present in Morphinone [ ] are structural alerts for mutagenicity. The applicant has added an interim specification for morphinone impurity at a level of [ ] for Hydromorphone HCl drug substance (e.g., submission dated 17-May-2004 volume 1 attachment 5 page 81) and completed the studies on genotoxic potential of morphinone. Morphinone showed positive genotoxicity in in-vitro CHO cells studies. The amendment dated 17-May-2004 is a complete response to Agency's approvable action letter dated 13-Sep-2002.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.

NDA can be approved from CMC perspective with a phase IV commitment to decrease the impurity level of morphinone to an acceptable level of [ ] A comment listed at the end of the review should be included in the action letter.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Palladone (Hydromorphone HCl extended release) capsules is indicated for oral administration for the management of persistent, moderate to severe pain in patients requiring continuous, around-the-clock opioid analgesic for weeks or longer. It is designed to provide delivery of Hydromorphone over 24 hours (once a day dosing), and it is supplied in opaque plastic bottles as 100s and in clear blister packs with 25 individually numbered blisters per card. It is a potent analgesic, about 8 times potent than morphine by oral route. It is supplied in 12mg, 16mg, 24mg, and 32mg capsule strengths. The color of each dosage strength capsule matches the color on the box.

Different dosage strength capsules are filled with identical pellets prepared by hot melt extrusion technology at [ ] Hydromorphone HCl. Pellets are sensitive to electrolytes (faster release) and to temperatures above [ ] (slower release). Out of all attributes for the stability, dissolution at 8hr-time point is the limiting factor for granting the expiration dating, and the 8hr dissolution specs for stability [ ] is based on IVIVC studies. Note that the prediction limits approach gave a shorter shelf life [ ] and the confidence limits approach gave a longer shelf life [ ] and the requested shelf life (2.5yrs) is within these limits, and it was granted. These shelf life estimates are based on — real time data.

Hydromorphone is prepared by [

] Hydromorphone HCl is [

] Tightening the morphinone impurity specification was conveyed to the applicant (Purdue Pharma) and the supplier of the drug substance [ ] on 4 September 2002. Process yield is about — at [ ]

The DMF holder [ ] had reported Morphinone [ ] study of hydromorphone HCl. These [ ] conditions are more drastic than pH gradient encountered in human GI tract, and there is no reported evidence that morphinone is absorbed from GI tract to plasma compartment to pose a safety risk.

B. Description of How the Drug Product is Intended to be Used

A once a day oral capsule formulation.

C. Basis for Approvability or Not-Approval Recommendation

The reviewer recommends 'Approval' of the NDA from CMC perspective with a phase IV commitment to decrease the impurity level of morphinone to an acceptable level of — ppm (or [ ]). The applicant has submitted a complete CMC response dated 17-May-2004 to the Agency's CMC comments in letter dated 13-Sep-2002. These are items 1 and 2 that pertain to GMP deficiencies observed during 6/2/02 inspection and for an updated drug substance specification sheet with an added test for morphinone with an interim acceptance criteria of less than — ppm — %).

The applicant has submitted an updated drug substance specification sheet (added a test for morphinone with an interim acceptance criteria of less than [ ] and method validation documentation for the morphinone test, and they are acceptable. The applicant has completed genotoxic studies on morphinone besylate salt, and these were reviewed by Dr. Suzana Thoroton-Jones on 10 Jun-2004.

Morphinone test method [ ] is suitable for regulatory purpose (memorandum dated 3/7/2003), and the method has a signal to noise ratio [ ] solution, as per MV work at Philadelphia District.

Overall CGMP compliance is acceptable, as per EES dated 05-May-2004 from Office of Compliance. [

]

In Agency's action letter dated 13 September 2002, the applicant was informed that the Palladone ER capsules are effective for the management of persistent moderate to severe pain in patients requiring continuous around the clock opioid analgesia for an extended period of time.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Pramod Maturu, PhD/HFD-170------
Ravi S. Harapanhalli, PhD/-HFD-170-----
Sara Shepherd/HFD-170------

C. CC Block

Orig. NDA 21-044, HFD-170
R/D Init. by: Ravi Harpanhalli, PhD
File Name N21044_13July2004

15 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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

/s/

Pat Maturu
7/16/04 02:22:59 PM
CHEMIST

Ravi Harapanhalli
7/16/04 03:03:42 PM
CHEMIST
AP with commitment

NDA 21-044

Chem. Rev. #5

PALLADONE™
Hydromorphone Hydrochloride Extended Release Capsules
12mg, 16mg, 24mg , 32mg
For use in opioid tolerant patients only

Purdue Pharma L.P.

Pramod Maturu, PhD. MBA
Division of Anesthetics, Critical Care, and Addiction Drug Products , HFD-170

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-044

2. REVIEW # 5
   Previous reviews were dated as follows: review #1 was dated 24 June 1999, review #2 was dated 16 July 1999, review #3 was dated 14 December 1999, and review #4 was dated 28 September 2001.

3. REVIEW DATE – August 2002

4. REVIEWER: Pramod Maturu, PhD, MBA

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original NDA	28 Dec 1998

6. SUBMISSIONS BEING REVIWED:

Submission(s) Reviewed	Document Date
AZ	12 Mar 2002
BL	29 April 2002
BC	1 Aug 2002
BC	5 Aug 02
BC	6 Sept 02

7. NAME & ADDRESS OF APPLICANT:

Chemistry Review Data Sheet

Name:	Purdue Pharma L.P.
Address:	One Stamford Forum, Stamford, CT 06901-3431
Representative:	Richard Fanelli, PhD, Director US Regulatory Affairs
Telephone:	203-588-8365

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Palladone
b) Non-Proprietary Name (USAN): Hydromorphone HCl Extended Release Capsules
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: Resubmission of NDA is in response to the not approvable action letter on 4 Oct 2001.

10. PHARMACOL. CATEGORY: Opioid Analgesic.

11. DOSAGE FORM: Capsule.

12. STRENGTH/POTENCY: 12mg, 16mg, 24mg, and 32mg.

13. ROUTE OF ADMINISTRATION: Oral.

14. Rx/OTC DISPENSED: _X__Rx ___OTC

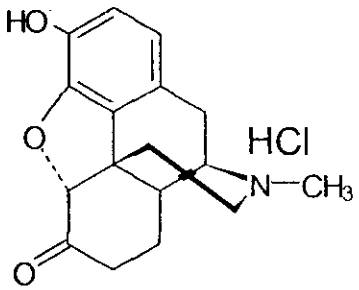
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:

_____SPOTS product – Form Completed

Chemistry Review Data Sheet

__X__ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



$C_{17}H_{19}NO_3 \bullet HCl$ MW 321.81

The chemical name is 4,5α-epoxy-3-hydroxy-17 methylmorphinan-6-one hydrochloride.

Appears This Way
On Original

17. RELATED/SUPPORTING DOCUMENTS:

Type/Number	Subject	Holder	Status	Review Date	Letter Date
DMF	Hydromorphone HCl USP		Inadequate	9./12/02 Dr.Maturu	
DMF			Adequate *	12/19/00 Dr.Klein	
DMF			Adequate *		
DMF			Adequate *		
DMF			Adequate *	12/19/00 Dr.Klein	
DMF			Adequate *		
DMF			Adequate *		
DMF			Adequate *		
DMF			Adequate	12/19/00 Dr.Klein	
DMF			Adequate *		
DMF			Adequate *		
			Adequate **		

* USP test results for bottles and closures (submission dated 7.20.99) were in compliance with USP standards , and they were considered adequate upon review in prior chem. Review #2.

RELATED DOCUMENTS (if applicable):

IND 38,424 for Hydromorphone HCl extended release capsules, Pudue Pharma LP.

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	2.5-years expiry date request is within the estimates based on prediction limits approach and the confidence limits approach.	5 Sept. 2002	Ms.Rosewitha Kelly
EES	Withhold	6 Sept 02	
Pharm/Tox	N/A		
Biopharm	NDA acceptance range [ ] for the dissolution time point was acceptable and it was validated by a biostudy (HD96-1206)	20 Oct 1999	Dr. Shinja Kim
LNC			
Methods Validation	Methods can be used for quality control and regulatory purpose.	18 Nov. 1999	Ms. Diana Amador Dir. Science Branch, SJN-DO, HFR-SE560
OPDRA	Acceptable trade name 'Palladone'. See review for labeling revisions.	12 July 2002	Dr. Nora Roselle
EA	Categorical exclusion from EA	26 June 1999	See CMC review #1.
Microbiology	N/A		

The Chemistry Review for NDA 21-044

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The reviewer recommends 'Approval' of the NDA from CMC perspective.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The firm will get the requested 2.5 yrs expiration dating for Palladone Capsules based on the statistical analysis of the stability data on 3 pellet lots based on matrixing and bracketing experimental design and that for any future extension of expiration dating, a prior approval supplement is required. The recommended expiration dating is based on the revised specifications for the drug product contained in the submission dated 12 March 2002 attachment 4 pages 113-115, and statistical analysis of the data set at 30C/60%RH storage condition with prediction limits and confidence limits. The prediction limits approach gave a shorter shelf life — and the confidence limits approach gave a longer shelf life , — , and the requested shelf life (2.5yrs) is within the estimates and it was granted.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Palladone (Hydromorphone HCl extended release) capsules is indicated for the relief of chronic moderate to severe pain. It is designed for oral administration to provide delivery of Hydromorphone over 24 hours (once a day dosing). It is a potent analgesic, about 8 times potent than morphine. It is supplied in 12mg, 16mg, 24mg, and 32mg capsule strengths filled with pellets prepared by hot melt extrusion technology at [ ] Hydromorphone HCl. Pellets are sensitive to electrolytes (faster release) and to temperatures above [ ] (slower release). Out of all attributes for the stability, dissolution at 8hr-time point is the limiting factor for granting the expiration dating. The 8hr dissolution specs for stability [ ] is based on IVIVC studies.

Hydromorphone is prepared by [

] Hydromorphone HCl is [

] Tightening the morphinone impurity specification

was conveyed to the applicant (Purdue Pharma) and the supplier of the drug substance on 4 September 2002. Process yield is about — , at

The DMF holder had reported Morphinone study of hydromorphone HCl. If reverse mutation assay studies by the applicant indicates that morphinone is mutagenic, then appropriate in vivo studies are needed to establish the safety of Palladone ER capsules.

B. Description of How the Drug Product is Intended to be Used

A once a day oral capsule formulation.

C. Basis for Approvability or Not-Approval Recommendation

The NDA was beset with several deficiencies and they were conveyed to the applicant in agency's letters dated 27 Sep 1999, 29 Dec 1999, 14 Jan 2000, and 4 Oct 2001. The applicant has submitted complete response dated 12 March 2002 to the agency's CMC comments in letter dated 4 Oct 2001. These are items 3 and 4 that pertain to stability and expiration dating for the drug product and an updated drug product specification sheet with tightened dissolution specification at 8hr-time point.

The applicant has requested 2.5 yrs expiry date and provided — real time data at 25C/60%RH and 30C/60%RH. Out of all attributes for the stability, dissolution was the limiting factor. Dissolution at 8 hr time point was not a problem for the drug product stored at 30C/60%RH but became a problem for the drug product stored at 25C/60%RH at the testing site due to an environmental excursion as a result of an unexpected malfunction This environmental excursion has retarded the dissolution at 8hr-time point presumably due to The applicant's hypothesis. However, 25C/60%RH storage condition was assigned to all countries in zones 1 and 2 (North America included) to support a room temperature label storage condition. See agency's letters dated 29 Dec 1999 and 14 Jan 2000 for the recommended dissolution specifications and time points. However, an acceptance range greater than 20% of the labeled content had to be validated by IVIVC data as per the Federal Register Notice on 29 Dec 2000 on page 83061. The NDA acceptance range for the 8hr dissolution time point for the mean was validated by a biostudy (HD96-1206) and this range was used to set the expiration dating for the drug product. Six capsules were tested at each stability test point as per the approved bracketing matrixing stability protocol. (See applicant's memo Dr. Chi-Wan Chen dated 10 June 1996).

NDA test methods for the drug product are satisfactory for quality control based on methods validation work at FDA Lab SJN-DO.

NDA test material (12 mg Palladone ER cap. lot 3C60) used in Phase III clinical studies (HMP 3005 and 3006) was in compliance with the proposed acceptance criteria for release

and shelf life for the clinical study duration of [redacted] In HMP 3006 study, a greater proportion of subjects who had taken Palladone (HHER) had adequate analgesia compared to Placebo response (Dr. Thomas Permutt's review dated 7/16/02).

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Pramod Maturu, PhD/Aug 02
Dale Koble, PhD/Aug 02
Sara Shepherd/Aug 02

C. CC Block

Orig. NDA 21-044, HFD-170
R/D Init. by: Dale Koble, PhD
File Name C:\Data|wpfiles\N21044r5_Aug02.doc

30 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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

/s/

Pat Maturu
9/13/02 03:10:24 PM
CHEMIST

Dale Koble
9/13/02 03:29:22 PM
CHEMIST

DIVISION OF ANESTHETIC, CRITICAL CARE, AND DRUG ADDICITION (HFD-170)
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-044 **DATE REVIEWED:** Rev 28th September, 2001

REVIEW #:4 **REVIEWER: Pramod Maturu, PhD**

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT	August 13, 2001	August 14, 2001	
AMENDMENT	March 30, 2001	April 2, 2001	

NAME & ADDRESS OF APPLICANT: Purdue Pharma L.P.
One Stamford Forum
Stamford, CT 06901-3431

DRUG PRODUCT NAME

Proprietary:	Palladone capsules
Established:	Hydromorphone hydrochloride extended release capsules
Code Name/#:	
Chem.Type/Ther.Class:	

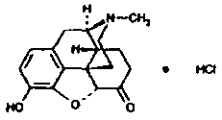
PHARMACOL. CATEGORY/INDICATION: Analgesic for management of moderate to severe pain

DOSAGE FORM:	Capsules extended release (Code 610)
STRENGTHS:	12, 16, 24 and 32 mg
ROUTE OF ADMINISTRATION:	Oral (Code 001)
Rx/OTC:	Rx _X_ OTC
SPECIAL PRODUCTS:	___ Yes ___ No X

(If yes, fill out the form for special products and deliver to TIA through team leader for data entry)

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Hydromorphone Hydrochloride (hye droe mor' fone). **USP.** $C_{17}H_{19}NO_3.HCl$. 321.80. [Hydromorphone is INN and BAN.] (1) Morphinan-6-one, 4,5-epoxy-3-hydroxy-17-methyl-, hydrochloride, (5α)-; (2) 4,5α-Epoxy-3-hydroxy-17-methylmorphinan-6-one hydrochloride. *CAS-71-68-1; CAS-466-99-9* [hydromorphone]. *Analgesic (narcotic).* (Astra); Dilaudid (Knoll); (Wyeth-Ayerst) *[Name previously used: Dihydromorphinone Hydrochloride.]*



SUPPORTING DOCUMENTS:

Type/Number	Subject	Holder	Status	Review Date	Letter Date
DMF	Hydromorphone HCl USP		Adequate	6.24.99 Dr.Maturu	
DMF			Adequate *	12/19/00 Dr.Kleine	
DMF			Adequate *		
DMF			Adequate *		
DMF			Adequate *	12/19/00 Dr.Kleine	
DMF			Adequate *		
DMF			Adequate *		
DMF			Adequate *		
DMF			Adequate	12/19/00 Dr.Kleine	
DMF			Adequate *		
DMF			Adequate *		
			Adequate **		

* USP test results for bottles and closures (submission dated 7.20.99) were in compliance with USP standards and they were considered adequate upon review in prior chem. Review #2.

RELATED DOCUMENTS (if applicable):

IND 38,424 for Hydromorphone HCl extended release capsules, Pudue Pharma LP.

CONSULTS :

Statistical consult: For expiry date recommendation for Palladone, see statistical review and evaluation of Ms. Rosewitha Kelly dated September 26, 2001. The applicant has requested — expiry date (Amendment dated August 13, 2001, page 1of 145 of stability report).

Biopharmaceutics: For acceptance criteria for dissolution for Palladone, see teleconference meeting minutes dated January 24, 2000. Page 2).

Imprint code: P-XL imprint code is considered acceptable under 21CFR206.10 (a) and (d) and 330.3. This position is supported by medical (see e-mail messages dated 6.13.01 from Bob Rappaport and John Jenkins).

Establishment inspections: An acceptable EER was issued by Compliance on 11th May 2001 for the mfg. sites for the drug substance and drug product.

CONCLUSIONS & RECOMMENDATIONS (p.9-10):

Child resistant blister package compliance with CPSC is not a part of CMC view. This issue should be addressed by HFD-170. Attached to this review as pages 21-25 are drug substance specifications, drug product specifications and post-approval stability protocol that were taken from the CD-ROM dated 29th December 1998.

The applicant has requested — expiry date for Palladone capsules and provided — real time data for — stability studies on a CDRom on August 13, 2001. Stability data contained [ ] Confidence limits (CL) for the mean was used for assay, and CL for individual observations was used for dissolution. The assay data and impurities data had not presented any problems. However, dissolution failures at — had presented problems. **The recommendation was not to grant the requested expiry date. See pages 26-27 for chemist's portion of letter to applicant.**

P. Maturu, Review Chemist

Dr. D. Koble, Acting Chemistry Team Leader

cc:
Org. NDA 21-044
HFD-170/Division File,PM (JMilstein)
HFD-820/PMaturu
HFD-820/TEAMLEADER (DKoble)
Filename: N21044r4srs3.doc
NOT APPROVED

23 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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

/s/

Pat Maturu
9/28/01 04:32:41 PM
CHEMIST

Dale Koble
9/28/01 04:44:38 PM
CHEMIST

DEC 2 9 1999

DIVISION OF ANESTHETIC, CRITICAL CARE AND ADDICTION DRUG PRODUCTS, HFD-170

Review of Chemistry, Manufacturing, and Controls

NDA #: 21-044

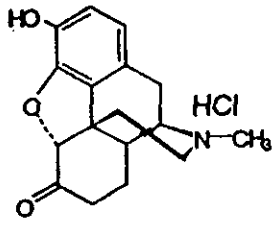
REVIEW #3 **DATE REVIEWED:** 12.14.99

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Correspondence	11.11.99	11.12.99	

NAME & ADDRESS OF APPLICANT:
Purdue Pharma LP, 100 Connecticut Avenue, Norwalk, CT 06850-3590

DRUG PRODUCT NAME
Proprietary: PALLADONE **(CII)**
Established: Hydromorphone HCl controlled release (HHCR)
Code Name/#: CAS# 71-68-1
Chem.Type/Ther.Class: 3 S

PHARMACOL. CATEGORY: Oral analgesic with Q24 dosing
DOSAGE FORM: Multi dose (MD) pellets in capsules.
Bulk pellets are prepared by hot melt extrusion at — Hydromorphone HCL. Pellets are filled into capsules with — mg fill weight for 12 mg capsules, — mg fill weight for 16 mg capsules, — mg fill weight for 24 mg capsules and — mg fill weight for 32 mg capsules.
STRENGTHS: 12, 16, 24 and 32mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: X **Rx** ____ **OTC**
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:
The chemical name for Hydromorphone hydrochloride is 4,5 alpha-epoxy-3-hydroxy-17 methylmorphinan-6-one hydrochloride.



$C_{17}H_{19}NO_3 \cdot HCl$ MW 321.81

RELATED DOCUMENTS: See chem.rev#1.

REMARKS:

The correspondence is a response to chemistry discipline initiated enquiry asking the applicant to reexamine the proposed dissolution specifications based on submitted dissolution data for the clinical lots to IND 38424 file.

Setting dissolution specifications for Palladone is likely to consume a lot of time based on Biopharm discipline input. Biopharm discipline has recommended the following dissolution specifications based on IVIVC studies. IVIVC slow dissolution lot CB26-16 was prepared at [ ] and IVIVC fast dissolution lot CB26-15 was prepared at [ ] The composition intended for US marketing is [ ] refers to [ ]

At hrs
At hrs
At hrs NLT [ ]

Chemistry.discipline has recommended the following dissolution specifications based on dissolution data for clinical lots and stability lots for all strengths, all packages and all storage conditions. Matrixing and bracketing was used to minimize the extent of stability testing for 4 strengths, 3 packages, 3 storage conditions, and 3 pellet lots (5K, 6K and 7K). Bioequivalency of pellet lot to kg pilot lot CB25-32 was studied under protocol HD96-1206.

At hrs
At hrs
At hrs NLT

In response to Biopharm and Chemistry inputs, the applicant has revised dissolution specs as follows.

At hrs
At hrs
At hrs NLT

The applicants reasoning is based on the exclusion of data for the blister package and 40C/75%RH storage condition. The revised dissolution specs for Palladone is acceptable given that the blisters used for stability testing are not child resistant type and given that child resistant blisters are required so as to comply with 16 CFR 1700.14 (a)(4) for controlled drugs.

The revised and acceptable dissolution specs include [redacted] intervals for all strengths, all lots, bottle packages, 25C/60%RH and 30C/60%RH storage data, by using [redacted] in USP [redacted] dissolution media [redacted]. Inclusion of [redacted] in dissolution media has increased % dissolution at [redacted] for the clinical lot CB25-34. See enclosed data.

CERTIFICATE OF ANALYSIS

Page 1 of 1

Product: Hydromorphone HCl CR 24 mg Capsules
Lot Number: CB25-34
Analysis Number:
Analysis Release Date: 5/31/96

Test Name	Specification	Results
[redacted]		

Approved by: [redacted] Date: 10-27-99

3 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

CONCLUSIONS & RECOMMENDATIONS:

Satisfactory revised dissolution specs were submitted

My recommendations are to accept revised dissolution specs, at [ ] and to fix PPI for Palladone with the following statements. Store the drug product at 25C CRT. Do not store at or above [ ].

P Maturu

P. Maturu, PhD, Review Chemist

12/16/99

A.D'Sa, PhD, Team Leader Chemistry

cc:
Orig. NDA 21044
HFD-170/Division File
HFD-170/PMaturu, AD'Sa, JGibbs
HFD-170/DFong
filename: C:\wpfiles\n21044r3.99.doc
ADEQUATE

4 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

DEC 2 2 1999

DIVISION OF ANESTHETIC, CRITICAL CARE AND ADDICTION DRUG PRODUCTS, HFD-170

Review of Chemistry, Manufacturing, and Controls

NDA #: 21-044

REVIEW #2 **DATE REVIEWED: 8.16.99**

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Correspondence	7.20.99	7.21.99	7.26.99

NAME & ADDRESS OF APPLICANT:
Purdue Pharma LP, 100 Connecticut Avenue, Norwalk, CT 06850-3590

DRUG PRODUCT NAME
Proprietary: PALLADONE
Established: Hydromorphone HCl controlled release (HHCR)
Code Name/#: CAS# 71-68-1
Chem.Type/Ther.Class: 3 S

PHARMACOL. CATEGORY: Oral analgesic with Q24 dosing

DOSAGE FORM: Multi dose (MD) pellets in capsules.

Bulk pellets prepared by hot melt extrusion at — Hydromorphone HCL were encapsulated with — mg fill weight for 12 mg capsules, — mg fill weight for 16 mg capsules, — mg fill weight for 24 mg capsules and —mg fill weight for 32 mg capsules.

STRENGTHS: 12, 16, 24 and 32mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: __X__ **Rx** _____ **OTC**

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:

4,5 alpha-epoxy-3-hydroxy-17 methylmorphinan-6-one hydrochloride. Molecular weight is 321.81. See USP 23 for structural formula.

RELATED DOCUMENTS: See chem.rev#1.

REMARKS:

Adequate and satisfactory responses were submitted to information request dated 18 June 99 based on chem. rev. #1 for this NDA.

See attachment 6 of correspondence for raw data.

CONCLUSIONS & RECOMMENDATIONS:

Satisfactory responses were submitted to the information request

Overall compliance is acceptable for the mfg. sites, as per EES dated 7 April 99.

Methods verification was initiated on 21 June 99. [

]

To show compliance with USP, satisfactory microbial contamination test results were submitted for the primary stability testing lots at release (10/96) and at [ ] retest (10/97). There was no micro consult.

To demonstrate HHCR capsules [ ] satisfactory assay and related substances results with no significant changes were submitted for [ ] studies. [ ]

Recommends approval of hot melts extrusion, novel technology, to manufacture Hydromorphone HCl controlled release ~~pellets~~ Capsules with Q24 dosing.

P. Maturu / 8.16.99
P. Maturu, PhD, Review Chemist

8/19/99
A.D'Sa, PhD, Team Leader Chemistry

cc:
Orig. NDA 21044
HFD-170/Division File
HFD-170/PMaturu, AD'Sa, JGibbs
HFD-170/DFong,CMoody
filename: C:\wpfiles\n21044r2.99
ADEQUATE

DIVISION OF ANESTHETIC, CRITICAL CARE AND ADDICTION DRUG PRODUCTS, HFD-170

Review of Chemistry, Manufacturing, and Controls

NDA #: 21-044

REVIEW #1 **DATE REVIEWED:** Rev 6.24.99

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	12.28.98	12.29.98	

NAME & ADDRESS OF APPLICANT:
Purdue Pharma LP, 100 Connecticut Avenue, Norwalk, CT 06850-3590

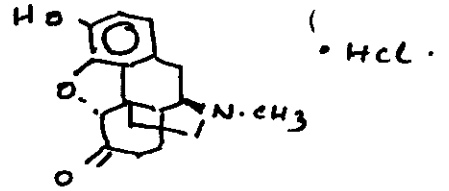
DRUG PRODUCT NAME

Proprietary: PALLADONE
Established: Hydromorphone HCl controlled release (HHCR)
Code Name/#: CAS# 71-68-1
Chem.Type/Ther.Class: 3 S

PHARMACOL. CATEGORY: Oral analgesic with Q24 dosing

DOSAGE FORM: Multi dose (MD) pellets in capsules.
Bulk pellets prepared by hot melt extrusion at — Hydromorphone HCL were encapsulated with — mg fill weight for 12 mg capsules, — mg fill weight for 16 mg capsules, — mg fill weight for 24 mg capsules and — mg fill weight for 32 mg capsules.
STRENGTHS: 12, 16, 24 and 32mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: __X__ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:
4,5 alpha-epoxy-3-hydroxy-17 methylmorphinan-6-one hydrochloride.
Mol. Wt. 321.81



RELATED DOCUMENTS: IND 38424, DMF [ ] for the drug substance, DMFs [ ] for the bottles, DMFs [ ] and — for the [ ] [ ] DMFs [ ] for the closures, DMF [ ] for [ ] DMF [ ] DMF [ ] DMF [ ] See chem. review notes for suitability of the DMFs.

REMARKS:

Original IND 38424 dated 2.14.92 [redacted]

[redacted] Original submission was reviewed by Paul Hillary and later reassigned to me. The [redacted] formulations in the original submission were prepared by [redacted]

[redacted]

Subsequent IND 38424 amendment dated 8.12.96 was for [redacted] HHCR capsules prepared by hot melt extrusion under biostudy HD95-0701, and it was reviewed by me. The [redacted] formulations were prepared [redacted]
Based on these results, HHCR pellet lot CB25-32 was used up to Phase III studies, under protocol nos. HD95-0701 (n=24 subjects), HD95-0702 (n=26), HD96-0505 (n=45), HD95-0801 (n=183) and HD95-0802 (n=151).

CMC details for the clinical lot CB25-32 (— kg) pellets: This pellet lot was formulated from [redacted] Hydromorphone HCL USP lot 960302 with [redacted] used at [redacted] purity. Pellets composition was — Hydromorphone HCl (HY), [redacted] Ethylcellulose and [redacted] Stearyl alcohol, prepared by hot melt extrusion. [redacted]

[redacted]

34 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

4.4. Environmental Assessment

21 CFR 25.31 describes certain FDA actions which do not significantly affect the quality of the human environment. Any such actions are subject to categorical exclusions and, therefore, ordinarily do not require the preparation of an environmental assessment (EA) or an Environmental Impact Statement (ES).

Purdue Pharma L.P. is claiming an exemption from the requirement for an EA based upon 21 CFR Part 25.31 (b) which allows for a categorical exclusion for an action on a New Drug Application (NDA). Based on estimated marketing figures, the expected introduction concentration (EIC) of Hydromorphone HCl into the aquatic environment is projected to be [ ], or approximately [ ]; than the level permitted under a categorical exclusion. To the best of Purdue Pharma L.P. knowledge, no extraordinary circumstances exist.

Appears This Way
On Original

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 21044/000
Org Code : 170
Priority : 3S

Sponsor: PURDUE PHARMA LP
1 STAMFORD FORUM
STAMFORD, CT 069013431

Stamp Date : 29-DEC-1998
PDUFA Date : 26-SEP-2004
Action Goal :
District Goal: 15-JUL-2002

Brand Name : PALLADONE (HYDROMORPHONE HCL)12/16/24
Estab. Name:
Generic Name: HYDROMORPHONE HCL
Dosage Form: (CONTROLLED RELEASE CAPSULE)
Strength : 12,16,24,32 MG

FDA Contacts:			
N. CHAMBERLIN	Project Manager	(HFM-602)	301-827-6342
P. MATURU	Review Chemist	(HFD-170)	301-827-7434
A. D SA	Team Leader	(HFD-320)	301-827-9044

Overall Recommendation:

ACCEPTABLE on 05-MAY-2004by J. D AMBROGIO(HFD-322) 301-827-9049

WITHHOLD on 14-MAY-2003by J. D AMBROGIO(HFD-322) 301-827-9049

WITHHOLD on 06-SEP-2002by R. WOODS (HFD-322) 301-827-9011

ACCEPTABLE on 11-MAY-2001by S. FERGUSON(HFD-322) 301-827-9009

WITHHOLD on 10-MAR-2000by HARTMANB

ACCEPTABLE on 26-MAY-1999by J. D AMBROGIO(HFD-322) 301-827-9049

ACCEPTABLE on 07-APR-1999by J. D AMBROGIO(HFD-322) 301-827-9049

Establishment : CFN : — FEI : —

—

—

DMF No: —— AADA:

Responsibilities: ——

Profile : CSN OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 05-MAY-04

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

Establishment : CFN : —— FEI : ——

——

——

——

DMF No: AADA:

Responsibilities: ——

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 05-MAY-04

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

Establishment : CFN : [redacted] FEI : [redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile : CTR OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 19-APR-04

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

---

9 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling