CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-044

Pharmacology Review(s)

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**21-044**
SERIAL NUMBER:	**N000 AZ**
DATE RECEIVED BY CENTER:	**07/23/2004**
DRUG NAME:	**hydromorphone hydrochloride extended-release (Palladone)**
INDICATION:	**management of moderate to severe pain in patients requiring continuous around-the clock opioid analgesia for an extended period of time**
SPONSOR:	**Purdue Pharma L.P.**
DOCUMENTS REVIEWED:	**1 of 1 volumes**
REVIEW DIVISION:	**Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170)**
PHARM/TOX REVIEWER:	**Suzanne R. Thornton-Jones, Ph.D.**
PHARM/TOX SUPERVISOR:	**R. Daniel Mellon, Ph.D.**
DIVISION DIRECTOR:	**Bob Rappaport, M.D.**
PROJECT MANAGER:	**Sara Stradley**

Date of review submission to Division File System (DFS): 23 September 2004

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on acceptability.
The NDA can be approved from a pharmacology/toxicology perspective with appropriate labeling revisions.

B. Recommendation for nonclinical studies.
None.

C. Recommendations on labeling.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity studies have been conducted in animals.

Hydromorphone was negative in the *in vitro* bacterial reverse mutation assay and in the *in vivo* mouse micronucleus assay. Hydromorphone was negative in the mouse lymphoma assay in the absence of metabolic activation, but was positive in the mouse lymphoma assay in the presence of metabolic activation. Morphinone, an impurity, tested as a besylate salt was negative in the *in vitro* bacterial reverse mutation assay and negative in the *in vivo* mouse micronucleus assay. Morphinone was positive in the Chinese Hamster Ovary Cell Chromosomal Aberration test in the absence and presence of metabolic activation.

Hydromorphone did not affect fertility in rats at oral doses up to 5 mg/kg which is equivalent to a 32 mg human daily oral dose based on body surface area.

Pregnancy

Pregnancy Category C

Hydromorphone was not teratogenic in female rats given oral doses up to 10 mg/kg or female rabbits given oral doses up to 50 mg/kg during the major period of organ development. Estimated exposures in the female rat and rabbit were approximately 3-fold and 6-fold higher than a 32 mg human daily oral dose based on exposure ($AUC_{0\text{-}24h}$). In rat pre- and post-natal studies, an increase in pup mortality and a decrease in pup body weight which was associated with maternal toxicity was observed at doses of 2 and 5 mg/kg/day. The maternal no effect level for hydromorphone was 0.5 mg/kg/day which is <1-fold lower than a 32 mg human daily oral dose on a body surface area. Hydromorphone had no effect on pup development or reproduction when given to female rats during the prenatal and postnatal periods up to a dose of

5 mg/kg which is equivalent to a 32 mg human daily oral dose on a body surface area.

Hydromorphone administration to pregnant Syrian hamsters and CF-1 mice during major organ development revealed teratogenicity likely the result of maternal toxicity associated with sedation and hypoxia. In Syrian hamsters given single subcutaneous doses from 14 to 278 mg/kg during organogenesis (gestation days 8-10), doses ≥ 19 mg/kg hydromorphone produced skull malformations (exencephaly and cranioschisis). Continuous infusion of hydromorphone (5 mg/kg, s.c.) via implanted osmotic mini pumps during organogenesis (gestation days 7-10) produced soft tissue malformations (cryptorchidism, cleft palate, malformed ventricals and retina), and skeletal variations (supraoccipital, checkerboard and split sternebrae, delayed ossification of the paws and ectopic ossification sites). The malformations and variations observed in the hamsters and mice were at doses approximately 3-fold higher and <1-fold lower, respectively, than the 32 mg human daily oral dose on a body surface area basis.

There are no adequate and well-controlled studies in pregnant women. Hydromorphone crosses the placenta. Palladone™ Capsules should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (see **Labor and Delivery**).

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings
No studies were submitted for review.

B. Pharmacologic activity
Hydromorphone is a selective mu-opioid receptor agonist with binding potency of 10-30 X greater than morphine, and pharmacological potency for analgesia for 4-10 X greater than that of morphine.

C. Nonclinical safety issues relevant to clinical use
No studies were submitted for review. In the previous review of the N000 AZ (05/18/2004) there was a positive genotoxicity finding for morphinone besylate. The manufacturing specification needs to be lowered to [ ]. The lowering of the specification as previously agreed with the Sponsor can be a Phase 4 post-marketing agreement.

Reviewer Signature Suzanne R. Thornton-Jones, Ph.D.

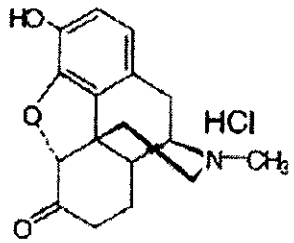
Supervisor Signature R. Daniel Mellon, Ph.D. Concurrence Yes X No ___

TABLE OF CONTENTS

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA NUMBER:	21-044
REVIEW NUMBER:	7
SEQUENCE NUMBER/DATE/TYPE OF SUBMISSION:	N000/26 July 2004/AZ
INFORMATION TO SPONSOR:	Yes (X) No ( )
SPONSOR:	Purdue Pharma L.P. One Stamford Forum Stamford, CT 06901-3431
MANUFACTURER FOR DRUG SUBSTANCE :	[redacted]
REVIEWER NAME:	Suzanne R. Thornton-Jones, Ph.D.
DIVISION NAME:	DACCADP
HFD #:	170
REVIEW COMPLETION DATE:	17 September 2004
DRUG:	
TRADE NAME:	Palladone™ Controlled Release Capsules
GENERIC NAME (LIST ALPHABETICALLY):	hydromorphone hydrochloride
CODE NAME:	NA
CHEMICAL NAME:	4,5α-epoxy-3-hydroxyl-17-methylmorphinan-6-one-hycrochloride
CAS REGISTRY NUMBER:	71-68-1
MOLE FILE NUMBER:	not specified
MOLECULAR FORMULA/MOLECULAR WEIGHT:	$C_{17}H_{19}NO_3 \cdot HCl/321.81$
STRUCTURE:	



RELEVANT INDS/NDAS/DMFS:	IND 38,424
DRUG CLASS:	opioid agonist
INTENDED CLINICAL POPULATION:	management of moderate to severe pain in patients requiring continuous around-the clock opioid analgesia for an extended period of time

CLINICAL FORMULATION:

Ingredient	Function	Unit Dosage Strength (mg/capsule)			
Pellets		**12**	**16**	**24**	**32**
Hydromorphone HCl,	USP Active Ingredient	12.0	16.0	24.0	32.0
Ethylcellulose,		( )	[ ]		
Steryl alcohol, NF					
Weight of Multi-Dose Pellets (mg/capsule)					
Capsules					
No. 2 Gelatin Capsule (					
No. 2 Gelatin Capsule (			[		
No. 1 Gelatin Capsule,	Blue				
No. 0 Gelatin Capsule (White					
Total Filled Capsule Weight			[		]

ROUTE OF ADMINISTRATION: oral

PROPOSED CLINICAL PROTOCOL: No new clinical studies were submitted.

BACKGROUND/PREVIOUS CLINICAL EXPERIENCE: The current submission contains the labeling revisions.

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Studies reviewed within this submission: Not applicable.
Studies not reviewed within this submission: Not applicable.

2.6.2 PHARMACOLOGY: No new studies were submitted.

2.6.3 PHARMACOLOGY TABULATED SUMMARY: No new studies were submitted.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS: No new studies were submitted.

2.6.6 TOXICOLOGY: No new studies were submitted.

2.6.7 TOXICOLOGY TABULATED SUMMARY: Not applicable.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Suggested labeling revisions are outlined below.

Revision 1 – The Sponsor proposed to make *in vitro* and *in vivo* concentration comparisons were are not appropriate.

Revision 2 -

Unresolved toxicology issues: None at this time.

Recommendations: None at this time.

Suggested labeling: (Note: strike-through indicates corrections to proposed label, double underlines indicate insertions/edits to the proposed label)

Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity studies have been conducted in animals.

Hydromorphone was negative in the *in vitro* bacterial reverse mutation assay and in the *in vivo* mouse micronucleus assay. Hydromorphone was negative in the mouse lymphoma assay in the absence of metabolic activation, but was positive in the mouse lymphoma assay in the presence of metabolic activation. Morphinone, an impurity, tested as a besylate salt was negative in the *in vitro* bacterial reverse mutation assay and negative in the *in vivo* mouse micronucleus assay. Morphinone was positive in the Chinese Hamster Ovary Cell Chromosomal Aberration test in the absence and presence of metabolic activation. C ;

J

Hydromorphone did not affect fertility in rats at oral doses up to 5 mg/kg which is equivalent to a 32 mg human daily oral dose based on body surface area. C J

Pregnancy

Pregnancy Category C

Hydromorphone was not teratogenic in female rats given oral doses up to 10 mg/kg or female rabbits given oral doses up to 50 mg/kg during the major period of organ development. Estimated exposures in the female rat and rabbit were approximately 3-fold and 6-fold higher than a 32 mg human daily oral dose based on exposure ($AUC_{0\text{-}24h}$). In rat pre-[3] and post-natal studies, an increase in pup mortality and a decrease in pup body weight which was associated with maternal toxicity was observed at doses of 2 and 5 mg/kg/day. The maternal no effect level for hydromorphone was 0.5 mg/kg/day which is <1-fold lower than a 32 mg human daily oral dose on a body surface area. Hydromorphone had no effect on pup development or reproduction when given to female rats during the prenatal and postnatal periods up to a dose of 5 mg/kg which is equivalent to a 32 mg human daily oral dose on a body surface area.[4]

Hydromorphone administration to pregnant Syrian hamsters and CF-1 mice during major organ development revealed teratogenicity likely the result of maternal toxicity associated with sedation and hypoxia. In Syrian hamsters given single subcutaneous doses from 14 to 278mg/kg during organogenesis (gestation days 8-10), doses ≥ 19 mg/kg hydromorphone produced skull malformations (exencephaly and cranioschisis). Continuous infusion of hydromorphone (5 mg/kg, s.c.) via implanted osmotic mini pumps during organogenesis (gestation days 7-10) produced soft tissue malformations (cryptorchidism, cleft palate,

malformed ventricals and retina), and skeletal variations (supraoccipital, checkerboard and split sternebrae, delayed ossification of the paws and ectopic ossification sites). The malformations and variations observed in the hamsters and mice were at doses approximately 3-fold higher and <1-fold lower, respectively, than the 32 mg human daily oral dose on a body surface area basis.[5]

There are no adequate and well-controlled studies in pregnant women. Hydromorphone crosses the placenta. Palladone™ Capsules should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (see **Labor and Delivery**).

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/s/

Suzanne Thornton-Jones
9/23/04 08:34:42 AM
PHARMACOLOGIST

R. Daniel Mellon
9/23/04 03:14:51 PM
PHARMACOLOGIST

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**21-044**
SERIAL NUMBER:	**N000 AZ**
DATE RECEIVED BY CENTER:	**05/18/2004**
DRUG NAME:	**hydromorphone hydrochloride extended-release (Palladone)**
INDICATION:	**management of moderate to severe pain in patients requiring continuous around-the clock opioid analgesia for an extended period of time**
SPONSOR:	**Purdue Pharma L.P.**
DOCUMENTS REVIEWED:	**2 of 2 volumes**
REVIEW DIVISION:	**Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170)**
PHARM/TOX REVIEWER:	**Suzanne R. Thornton-Jones, Ph.D.**
PHARM/TOX SUPERVISOR:	**R. Daniel Mellon, Ph.D.**
DIVISION DIRECTOR:	**Bob Rappaport, M.D.**
PROJECT MANAGER:	**Sara Stradley**

Date of review submission to Division File System (DFS): 10 June 2004

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on acceptability.
The NDA can be approved from a pharmacology/toxicology perspective. The potential genotoxicity of the morphinone impurity has been adequately assessed; however, the positive finding in the chromosome aberrations assay does not provide adequate qualification of safety. Appropriate labeling changes will be necessary to address the positive *in vitro* genotoxicity finding for morphinone. A Phase 4 post-marketing commitment will be necessary to decrease the impurity level to an acceptable level of [ ]

B. Recommendation for nonclinical studies.
None.

C. Recommendations on labeling
None.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings
The sponsor submitted a standard battery of genetic toxicology studies for the impurity morphinone as the besylate salt. An oral MTD for morphinone besylate following a single dose in male and female mice was 300 mg/kg, while an i.p. MTD was ≤60 mg/kg. Morphinone besylate was not mutagenic in the *in vitro* Ames bacterial reversion assay or clastogenic in the *in vivo* mouse micronucleus assay. Morphinone besylate was clastogenic in the Chinese Hamster Ovary chromosomal aberration assay -S9 (metabolic nonactivation) at concentrations ≥3.75 µg/mL and +S9 (metabolic activation) at 25 µg/mL following a 20 hr treatment period.

B. Pharmacologic activity
Hydromorphone is a selective mu-opioid receptor agonist with binding potency of 10-30 X greater than morphine, and pharmacological potency for analgesia for 4-10 X greater than that of morphine.

C. Nonclinical safety issues relevant to clinical use
Based on the positive result in one assay of the genotoxicity battery, morphinone has not been adequately qualified per ICH-S3A in the drug substance or per ICH-S3B in the drug product. Further, in light of the positive genotoxicity finding, the current manufacturing specification needs to be lowered to [ ] as previously conveyed to the Sponsor. The lowering of the specification as previously agreed with the Sponsor can be a Phase 4 post-marketing commitment.

Reviewer Signature Suzanne R. Thornton-Jones, Ph.D.

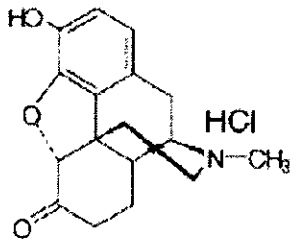
Supervisor Signature R. Daniel Mellon, Ph.D. Concurrence Yes X No ___

TABLE OF CONTENTS

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA NUMBER:	21-044
REVIEW NUMBER:	6
SEQUENCE NUMBER/DATE/TYPE OF SUBMISSION:	N000/18 May 2004/AZ
INFORMATION TO SPONSOR:	Yes ( ) No (X)
SPONSOR:	Purdue Pharma L.P. One Stamford Forum Stamford, CT 06901-3431
MANUFACTURER FOR DRUG SUBSTANCE :	[redacted]
REVIEWER NAME:	Suzanne R. Thornton-Jones, Ph.D.
DIVISION NAME:	DACCADP
HFD #:	170
REVIEW COMPLETION DATE:	09 June 2004
DRUG:	
TRADE NAME:	Palladone Controlled Release Capsules
GENERIC NAME (LIST ALPHABETICALLY):	hydromorphone hydrochloride
CODE NAME:	NA
CHEMICAL NAME:	4,5α-epoxy-3-hydroxyl-17-methylmorphinan-6-one-hycrochloride
CAS REGISTRY NUMBER:	71-68-1
MOLE FILE NUMBER:	not specified
MOLECULAR FORMULA/MOLECULAR WEIGHT:	$C_{17}H_{19}NO_3 \cdot HCl/321.81$
STRUCTURE:	



RELEVANT INDS/NDAS/DMFS:	IND 38,424
DRUG CLASS:	opioid agonist
INTENDED CLINICAL POPULATION:	management of moderate to severe pain in patients requiring continuous around-the clock opioid analgesia for an extended period of time

CLINICAL FORMULATION:

Ingredient	Function	Unit Dosage Strength (mg/capsule)			
Pellets		**12**	**16**	**24**	**32**
Hydromorphone HCl,		12.0	16.0	24.0	32.0
Ethylcellulose					
Steryl alcohol, NF					
Weight of Multi-Dose Pellets (mg/capsule)					
Capsules					
No. 2 Gelatin Capsule					
No. 2 Gelatin Capsule					
No. 1 Gelatin Capsule	Blue				
No. 0 Gelatin Capsule (White					
Total Filled Capsule Weight					

ROUTE OF ADMINISTRATION: oral

PROPOSED CLINICAL PROTOCOL: No new clinical studies were submitted.

BACKGROUND/PREVIOUS CLINICAL EXPERIENCE: In a teleconference held between the Agency and Sponsor regarding CMC issues on 04 September 2002 the Agency expressed a concern regarding the potential mutagenicity of the morphinone impurity observed in hydromorphone. C

J . The Sponsor agreed to conduct a standard genotoxicity *in vitro* and *in vivo* battery to assess the genotoxic potential of morphinone in the approval letter sent 13 September 2002. The current submission contains the genotoxicity studies for morphinone.

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Studies reviewed within this submission:

1. *Salmonella-Escherichia coli*/mammalian-microsome reverse mutation assay with a confirmatory assay using morphinone besylate. [Study no. 24911-0-409OECD (NDSE-650-GLP)], Volume 1, pp. 124.
2. Chromosomal aberrations in Chinese hamster ovary (CHO) cells using morphinone besylate. [Study no. 24911-0-449OECD (NDSE-732-GLP)], Volume 2, pp. 210.
3. A non-GLP single dose oral (gavage) and intraperitoneal toxicity study with morphinone besylate in CD-1 mice. [Study no. NDSE-776], Volume 2, pp. 316.
4. *In vivo* oral mouse micronucleus assay using morphinone besylate. [Study no. 24911-0-455OECD (NDSE-775-GLP], Volume 2, pp. 351.

Studies not reviewed within this submission: Not applicable.

2.6.2 PHARMACOLOGY: No new studies were submitted.

2.6.3 PHARMACOLOGY TABULATED SUMMARY: No new studies were submitted.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS: No new studies were submitted.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology: An oral MTD following a single dose in male and female mice was 300 mg/kg, while an i.p. MTD was ≤60 mg/kg.

Genetic toxicology: Morphinone besylate was not mutagenic in the *in vitro* Ames bacterial reversion assay or clastogenic in the *in vivo* mouse micronucleus assay. Morphinone besylate was clastogenic in the Chinese Hamster Ovary chromosomal aberration assay -S9 (metabolic nonactivation) at concentrations ≥3.75 µg/mL and +S9 (metabolic activation) at 25 µg/mL following a 20 hr treatment period.

Carcinogenicity: No new studies were reviewed.
Reproductive toxicology: No new studies were reviewed.
Special toxicology: No new studies were reviewed.

2.6.6.2 Single-dose toxicity:

Study title: A non-GLP single dose oral (gavage) and intraperitoneal toxicity study with morphinone besylate in CD-1 mice.

Key study findings:

- Mortality: [p.o.] 1/4 female mice at a dose of 300 mg/kg; [i.p.] all male and female mice at a dose of 150 and 300 mg/kg died within 4 hrs post-dose; 2/4 male and 1/4 female mice at a dose of 60 mg/kg died by SD 3.
- Clinical observations: hypoactivity, tremors, erect posture, and death following p.o. and i.p. administration
- Body weight/food consumption: [p.o.] decrease in 1/4 female mice at a dose of 300 mg/kg; [i.p.] decrease in male and female mice at a dose of 60 mg/kg
- MTD: [p.o.] male and female mice= 300 mg/kg; [i.p.] male and female mice ≤60 mg/kg

Study no.: NDSE-776
Volume #, and page #: 2, pp. 316
Conducting laboratory and location: Purdue Pharma L.P.
Date of study initiation: August 2003
GLP compliance/QA report: yes (X) no ( )
Drug, lot #, and % purity: morphinone besylate/1943-199-3/
Methods:

Doses: [oral] 100, 200, 300 mg/kg; [i.p.] 60, 150, 300 mg/kg
Species/strain: CD-1(ICR) BR mouse

Number/sex/group or time point (main study): 4 sex/group
Route, formulation, volume, and infusion rate: oral gavage @ 20 mL/kg; i.p. @ 30 mL/kg
Satellite groups used for toxicokinetics or recovery: NA
Age: 8-10 weeks
Weight: 22-30 g
Unique study design or methodology: All animals received a single dose.

Observation times and results:

Observations	Times	Results
Mortality	daily	One female mouse that received 300 mg/kg, p.o., was found dead on SD2. All other p.o. animals survived to scheduled euthanasia. All male and female mice receiving 150 and 300 mg/kg i.p. died within 4 hrs post-dose. Male and female mice (2/4 and 1/4, respectively) receiving 60 mg/kg died by SD 3.
Clinical signs	daily	Male and female mice at a dose of 300 mg/kg, p.o. exhibited hypoactivity, Straub tail, lethargy, and erect posture which appeared within 8 hrs post-dose but were gone by 24 hrs. Male and female mice at a dose of 60 mg/kg, i.p. exhibited hypoactivity, unkempt appearance, exophthalmia, and bilateral enopthalmia which appeared within 30 mins post-dose and lasted 3-4 hrs. Also observed at doses ≥150 mg/kg, i.p. was ataxia, twitching, tremors, and loss of righting reflex which appeared within 2-4 hrs and then animals were found dead. Female mice appeared to exhibit a higher incidence of clinical observations than male mice following i.p. administration.
Body weights	pre-dose, daily	Unremarkable for male mice following p.o. administration. One female mouse at a dose of 300 mg/kg, p.o. exhibited a decrease in body weight on SD2. Male (2/4) and female (1/4) mice at a dose of 60 mg/kg, i.p. exhibited a decrease in body weight by SD2.

Food consumption	daily	Unremarkable for male mice. One female mouse at a dose of 300 mg/kg and 200 mg/kg, p.o. exhibited a decrease in food consumption by SD2. Male mice (3/4) and 1/4 female mice at a dose of 60 mg/kg, i.p. exhibited a decrease in food consumption by SD2.

[Note: SD=study day]

2.6.6.3 Repeat-dose toxicity: No new studies were submitted.

2.6.6.4 Genetic toxicology

A. Study title: *Salmonella-Escherichia coli*/mammalian-microsome reverse mutation assay with a confirmatory assay using morphinone besylate.

Key study findings:

- Morphinone besylate was not mutagenic under these conditions.

Study no.: 24911-0-409OECD (NDSE-650-GLP)
Volume #, and page #: 1, pp. 124
Conducting laboratory and location: [ ]
Date of study initiation: 12 March 2003
GLP compliance/QA report: yes (X) no ( )
Drug, lot #, and % purity: morphinone besylate/02-OC-FP-071/ —
Methods:
Strains/species/cell line: *Salmonella typhimurium* TA1535, TA1537, TA98, TA100; *Escherichia coli* WP2uvrA
Doses used in definitive study: initial mutagenicity assay [-S9] 10-5000 µg/plate, [+S9] 33.3-5000 µg/plate
confirmatory assay 10-3330 µg/plate ±S9
Basis of dose selection: dose finding study at doses of 6.67-5000 µg/plate ±S9
Negative controls: DMSO or water (for sodium azide positive control)
Positive controls: [-S9] 2-nitrofluorene, sodium azide, ICR-191, 4-nitroquinoline-N-oxide
[+S9] benzo[a]pyrene, 2-aminoanthracene
Incubation and sampling times: incubation for 52±4 hrs at 37°C
Results:
Study validity: Plates were counted using an automated counter. Criteria for positive results included tester strains exhibited sensitivity to crystal violet or presence of the pKM101 plasmid, all strains were within the acceptable range for spontaneous revertants, a 3-fold increase over the control ±S9, a minimum of 3 non-toxic doses evaluable, no significant cytotoxicity (decrease in number of revertant colonies and/or thinning or disappearance of the bacterial background lawn), 2-fold increase in mean revertants compared to the control for TA98, TA100, WP2*uvr*A, and 3-fold increase over control for TA1535 and TA 1537.

Study outcome: In the dose range-finding assay cytotoxicity was observed in TA100 and WP2*uvr*A strains at concentrations ≥1000 µg/plate -S9 and at concentrations ≥3330 µg/plate +S9 as evidenced by an a concentration-related decrease in the number of revertants per plate. Also there was a reduction or absence of the bacterial background lawns in the TA100 strain at concentrations ≥1000 µg/plate ±S9.

In the initial mutagenicity assay cytotoxicity was observed –S9 in strains TA98, TA100, TA1537, and WP2*uvr*A at concentrations ≥2500 µg/plate and for strain TA1535 at concentrations ≥333 µg/plate. Cytotoxicity was observed +S9 in strains TA98 and WP2*uvr*A at concentrations ≥2500 µg/plate, and in strains TA100, TA1535, and TA1537 at concentrations ≥5000 µg/plate. Cytotoxicity was evidenced by a concentration-related decrease in the number of revertants per plate. Also there was a reduction or absence of the bacterial background lawns in the all strains at a concentration of 5000 µg/plate ±S9, and for TA1537 –S9 at concentrations ≥2500 µg/plate.

In the confirmatory assay cytotoxicity was observed –S9 in strains TA98, TA1535, and WP2*uvr*A at concentrations ≥1000 µg/plate and for strain TA100 and TA1537 at concentrations ≥3330 µg/plate. Cytotoxicity was observed +S9 in strains TA98, TA1535, and TA1537 at concentrations ≥1000 µg/plate, and in strains TA100 and WP2*uvr*A at concentrations ≥3330 µg/plate. Cytotoxicity was evidenced by a concentration-related decrease in the number of revertants per plate. Also there was a reduction or absence of the bacterial background lawns in all strains, except WP2*uvr*A, at a concentration of 3330 µg/plate ±S9. The positive control for WP2uvrA did not produce any revertants, therefore, the assay was repeated with the strain. For the repeat assay, the positive control produced a statistically significant increase in revertants and results of cytoxicity were the same as in the previous experiment.

Positive controls for all strains produced a significant increase in revertants, with the exception of WP2*uvr*A positive control mentioned above. Morphinone besylate was not mutagenic under these conditions.

B. Study title: Chromosomal aberrations in Chinese Hamster Ovary (CHO) cells using morphinone besylate

Key study findings:

- Morphinone besylate was clastogenic -S9 at concentrations ≥3.75 µg/mL and +S9 at 25 µg/mL following a 20 hr treatment period.

Study no.: 24911-0-449OECD (NDSE-732-GLP)
Volume #, and page #: 2, pp. 210
Conducting laboratory and location: [ ]
Date of study initiation: 03 March 2003
GLP compliance/QA report: yes (X) no ( )
Drug, lot #, and % purity: morphinone besylate/02-OC-FP-071, —
[Note: Morphinone base is — of the besylate salt, the concentrations were not corrected for the base content]

Methods:

Strains/species/cell line: Chinese Hamster Ovary (CHO-WBL) cells
Doses used in definitive study: 0.2-7.5 μg/mL -S9; 7.5-25 μg/mL +S9
Basis of dose selection: dose finding study at doses of 13.6-2000 μg/mL ±S9; 0.313-40 μg/mL –S9 and 0.625-60 μg/mL +S9
Negative controls: DMSO
Positive controls: [-S9] mitomycin C (MMC)
[+S9] cyclophosphamide (CP)
Incubation and sampling times: Cell cultures were incubated ± S9 for 3 and 20 hrs (confirmatory assay only) at 37°C. Following treatment, cells were washed, re-cultured and then harvested approximately 20 hrs after treatment initiation.

Results:

Study validity: Plates were manually counted. Criteria for positive results included the negative and vehicle control cultures contained < 5% cells with aberrations, the positive control produced significant increases in aberrations, and each assay had at least three analyzable concentrations.

Study outcome: Morphinone besylate was not soluble at concentrations ≥500 mg/mL, but was soluble at 200 mg/mL.

In the dose range-finding study incubated for 3 hrs there was significant cytotoxicity, demonstrated by a severe reduction in mitotic cells, at concentrations ≥39.5 μg/mL and all cells were dead at concentrations ≥80.7 μg/mL –S9. Cytotoxicity was also observed +S9 at concentrations ≥20 μg/mL. Positive controls produced statistically significant increases in chromosomal aberrations.

In the initial chromosomal aberration assay following a 3 hr incubation, reductions in mitotic indices were observed at 10, 15, 20, 30, and 40 μg/mL of 48%, 67%, 81%, 97%, and 100%, respectively, -S9. No significant increases in chromosomal aberrations were observed at concentrations of 1.25, 2.5, 5, and 10 μg/mL, and a slight increase in endoreplication in cultures treated with 10 μg/mL. A reduction in mitotic indices was also observed in cultures exposed to +S9 at concentrations of 2.5, 5, 10, 15, 20, 30, 40, 50, and 60 μg/mL of 19%, 25%, 57%, 54%, 66%, 70%, 96%, 100%, and 90%, respectively. No increases in chromosomal aberrations or polyploidy were observed at concentrations of 2.5, 5, 10, and 15 μg/mL, but there was significant increase in endoreplication in cultures treated with 15 μg/mL. Positive controls produced statistically significant increases in chromosomal aberrations.

In the confirmatory assay following a 20 hr incubation, reductions in mitotic indices were observed at 2.5, 3.75, 5, and 7.5 μg/mL –S9, respectively. Statistically significant increases in chromosomal aberrations were observed at concentrations ≥3.75μg/mL –S9. A reduction in mitotic indices was also observed +S9 at concentrations of 15, 20, 25, and 30 μg/mL of 25%, 17%, 4%, and 53%, respectively. A statistically significant increase in chromosomal aberrations was observed in cultures treated at a concentration of 25 μg/mL. Also at this concentration there was an increase in endoreplication, but no significant increase in polyploidy. Positive controls produced statistically significant increases in

chromosomal aberrations. Morphinone besylate was clastogenic -S9 at concentrations ≥3.75 µg/mL and +S9 at 25 µg/mL following a 20 hr treatment period.

C. Study title: *In vivo* oral mouse micronucleus assay using morphinone besylate.

Key study findings:

- Morphinone besylate was not clastogenic under these conditions.

Study no.: 24911-0-455OECD (NDSE-775-GLP)
Volume #, and page #: 8, pp. 2713
Conducting laboratory and location: [redacted]
Date of study initiation: 02 September 2003
GLP compliance/QA report: yes (X) no ( )
Drug, lot #, and % purity: morphinone besylate/02-OC-FP-071/ —

Methods:
Strains/species/cell line: — CD-1 (IGR) male mice (6/group)
Doses used in definitive study: oral gavage
[male mice] 50, 100, 200 mg/kg administered BID separated by 1 hr for total dose of 100, 200, 400 mg/kg as a, single oral gavage dose @ 15 mL/kg BID
Basis of dose selection: oral dose range-finding study @ 300 mg/kg and 450 mg/kg (divided into 2 doses separated by 1 hr); previous oral gavage range-finding study indicated an MTD of 300 mg/kg given as a single dose
Negative controls: water
Positive controls: cyclophosphamide (80 mg/kg, p.o.)
Incubation and sampling times: 24 and 48 hrs after administration

Results:
Study validity: Polychromatic erythrocytes/animal (2000) were counted and scored for micronucleated cells and 500 polychromatic erythrocytes/animal were counted to determine the polychromatic/normochromatic erythrocyte (PCE/NCE) ratio. Acceptance criteria included <0.4% micronucleated PCE's and within historical control data for the control group, positive control produced statistically significant increases in micronucleated PCEs compared to the control group, high dose produced toxicity and/or the PCE:NCE ratio is statistically significantly decreased.

Study outcome: In the dose range-finding study 1/4 male and 1/4 female mice at a dose of 450 mg/kg died on SD1. One female mouse at a dose of 300 mg/kg exhibited hypoactivity and squinted eyes. All other animals survived until scheduled euthanasia and there were no other clinical observations.

In the definitive study 2 male mice at a dose of 400 mg/kg died on SD1 and exhibited red discharge, squinted eyes, irregular respirations, hypoactivity, and/or a rough coat. A statistically significant decrease in the PCE:NCE ratio (i.e., bone marrow cytotoxicity) was observed at a dose of 400 mg/kg. No increase in micronucleated PCEs were observed. Cyclophosphamide produced a statistically significant increase in micronucleated polychromatic erythrocyte cells.

2.6.6.5 Carcinogenicity

No new studies were submitted for review.

2.6.6.6 Reproductive and developmental toxicology

No new studies were submitted for review.

2.6.6.7 Local tolerance

No new studies were submitted for review.

2.6.6.8 Special toxicology studies

No new studies were submitted for review.

2.6.6.9 Discussion and Conclusions

To improve the solubility of morphinone in the assays it was converted to morphinone besylate (also known as morphinone benzenesulfonate). The conversion could have had an impact on the results as benzenesulfonates are also considered potential mutagenic agents. However, as one can see the addition of besylate did not appear to directly impact the results of the genotoxicity assay. The results indicate that morphinone besylate was clastogenic in the Chinese Hamster Ovary chromosomal aberration assay –S9 (metabolic nonactivation) at concentrations ≥3.75 µg/mL and +S9 (metabolic activation) at 25 µg/mL only. It was not mutagenic in the *in vitro* Ames reverse bacterial assay or *in vivo* mouse micronucleus assay.

2.6.6.10 Tables and Figures: Not applicable.

2.6.7 TOXICOLOGY TABULATED SUMMARY: Not applicable.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

The Sponsor was informed of the need to decrease the morphinone impurity level (i.e., establish a manufacturing specification) to — or qualify morphinone by conducting a standard genotoxicity battery. These requests were based on the ICH-S3A guidance. The Sponsor established a [ ] specification for morphinone and decided to qualify morphinone at this specification by conducting a genotoxicity battery. The results indicate that morphinone as a besylate salt was not mutagenic in the *in vitro* Ames bacterial reversion assay or clastogenic in the *in vivo* mouse micronucleus assay. However, morphinone besylate was clastogenic in the Chinese Hamster Ovary chromosomal aberration assay -S9 (metabolic nonactivation) at concentrations ≥3.75 µg/mL and +S9 (metabolic activation) at 25 µg/mL following a 20 hr treatment period.

The Sponsor's specification is currently set at [ ] which they believe is equivalent to — ng of morphinone/mg hydromorphone. The Sponsor believes that the maximum human dose will be — mg (—mg, Q4D) which would be equivalent to 64 µg/day of morphinone. If the assumption of 100% bioavailability and equal blood distribution in — µL blood volume then blood concentrations of — ng morphinone/mL (in 70 kg person) would be achieved. While this appears a reasonable explanation, if one examines the amount that would be achieved in assuming the — ppm or —mg/day amount

using their proposed — mg/day maximum human daily dose it that would lead to — mg/day or — ppm/day or — of morphinone/day. This level is significantly higher than the [ ] level requested.

The Sponsor contends that the positive finding in the chromosomal aberration assay is a class-related effect of opioids as similar findings are observed for hydromorphone, morphine, hydrocodone, meperidine, and codeine. While many opioids have tested positive in one or another genotoxicity assay, the specification for the morphinone impurity does not provide adequate qualification for safety.

Based on the positive result in one assay of the genotoxicity battery, morphinone has not been adequately qualified per ICH-S3A in the drug substance or per ICH-S3B in the drug product. Further, in light of the positive genotoxicity finding, the current manufacturing specification needs to be lowered to [ ] as previously conveyed to the Sponsor. Tim McGovern, the previous reviewer, noted that an acceptable specification could be ( ) Regardless of the specification of [ ] morphinone has not been adequately qualified and the specification should be lowered to an acceptable level. As previously agreed with the Sponsor, the decrease in the specification to ( ) or whichever appropriate specification is established can be conducted as a Phase 4 post-marketing commitment.

Unresolved toxicology issues: None at this time.

Recommendations: None at this time.

Suggested labeling:
CLINICAL PHARMACOLOGY

Hydromorphone is a pure opioid agonist whose principal therapeutic action is pain relief. Pharmacological effects of opioid agonists include anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis, and cough suppression, and analgesia. No defined maximum dose is limited as pain relief increases with dose, however effective pain relief and increase in dose is limited by side effects, primarily somnolence, respiratory depression, nausea, and vomiting.

Central Nervous System

Opioid receptors for naturally occurring compounds that produce opioid activity have been identified throughout the central nervous system and thought to play a role in the pain relieving effects of hydromorphone.

Hydromorphone produces respiratory depression by direct activation of the brain stem respiratory centers. The respiratory depression reduces responsiveness of the brain stem to increases in carbon dioxide and to electrical stimulation.

Hydromorphone depresses the cough reflex by direct activation of the medullary center, even at doses that would not produce analgesia. In the setting of deliberate or accidental overdose, hydromorphone is associated with sedation and increased risk of aspiration. (See OVERDOSAGE section)

Hydromorphone causes miosis (pinpoint pupils), even in total darkness. Miosis is a sign of opioid overdose but is not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen due to hypoxia in the setting of Palladone™ Capsule overdose (see **OVERDOSAGE section**).

Gastrointestinal System

Hydromorphone causes a reduction in motility in the gastric antrum and duodenum as a result of an increase in smooth muscle tone. Digestion of food is delayed in the small intestine and propulsive contractions in the small intestine and colon are decreased. Intestinal tone may be increased resulting in spasm and constipation. Hydromorphone may cause a reduction in gastric, biliary and pancreatic secretions, spasm of the sphincter of Oddi, and transient elevations in serum amylase.

Cardiovascular System

Hydromorphone may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity studies have been conducted in animals. Hydromorphone was negative (not mutagenic) in the *in vitro* bacterial reverse mutation assay and negative (not clastogenic) in the *in vivo* mouse micronucleus assay. Hydromorphone was negative (not mutagenic) in the mouse lymphoma assay in the absence of metabolic activation, but was positive (clastogenic) in the mouse lymphoma assay in the presence of metabolic activation. Morphinone, an impurity, as a besylate salt was negative (not mutagenic) in the *in vitro* bacterial reverse mutation assay and negative (not clastogenic) in the *in vivo* mouse micronucleus assay. Morphinone was positive (clastogenic) in the mouse lymphoma assay in the absence and presence of metabolic activation.

Hydromorphone did not affect fertility in rats at oral doses up to 5 mg/kg which is equivalent to the 32 mg human daily oral dose on a body surface area basis.

Pregnancy - Pregnancy Category C

Hydromorphone was not teratogenic in female rats given oral doses up to 10 mg/kg or female rabbits given oral doses up to 50 mg/kg during the major period of organ development. Estimated exposures ($AUC_{0\text{-}24h}$) in the female rat and rabbit were approximately 2.7-fold and 6-fold higher than the 32 mg human daily oral dose. Hydromorphone had no effect on pup development when female rats where given oral doses up to 0.5 mg/kg during neonatal and postnatal development which is approximately <1-fold lower than the 32 mg human daily oral dose on a body surface area basis.

Hydromorphone administration to pregnant Syrian hamsters and CF-1 mice during major organ development revealed teratogenicity as a result of maternal toxicity associated with sedation and severe hypoxia In Syrian hamsters given subcutaneous doses up to 20 mg/kg

during the peak of organogenesis (gestation days 8-9) hydromorphone produced skull malformations (exencephaly and cranioschisis). Continuous infusion of hydromorphone (5 mg/kg, s.c.) via implanted osmotic minipumps during peak organogenesis (gestation days 7-10) produced soft tissue malformations (cryptorchidism, cleft palate, malformed ventricles and retina), and skeletal variations (supraoccipital, checkerboard and split sternebrae, delayed ossification of the paws and ectopic ossification sites). The malformations and variations observed in the hamsters and mice were at doses approximately 3-fold higher and <1-fold lower than the 32 mg human daily oral dose on a body surface area basis. There are no adequate and well-controlled studies in pregnant women. Hydromorphone crosses the placenta, resulting in fetal exposures. Palladone™ Capsules should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (see Labor and Delivery).

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/s/

Suzanne Thornton-Jones
6/10/04 05:17:35 PM
PHARMACOLOGIST

R. Daniel Mellon
6/10/04 05:25:49 PM
PHARMACOLOGIST
I concur

Memo to File

NDA#: 21-044
Drug: Palladone (hydromorphone HCl extended release)
Sponsor: Purdue Pharma L.P.

Reviewer: Timothy J. McGovern, Ph.D., Supervisory Pharmacologist
Date: May 29, 2003

The sponsor submitted a "Response to Approvable Letter" for this NDA on October 4, 2002 (submission N-000-BZ). An Approvable letter was sent to the sponsor on September 13, 2002. This response included a revised package insert and Patient Package Insert, a revised drug substance specification sheet and a description and proposed timeline for the initiation and completion of the studies to examine the genotoxic potential of the impurity morphinone, for which a structural alert has been identified. This memo addresses the sponsor's proposal to address the lattermost issue.

The Approvable letter of September 13, 2002 contained the following comment:

> Provide adequate qualification of the genotoxic potential of the drug substance impurity morphinone (one point mutation assay and one cytogenetic assay with the isolated impurity tested up to the limit doses for each assay). Alternatively, provide a specification (test, method, and acceptance criteria) and validation for this impurity with a limit of [redacted].

In response to this comment, the sponsor plans to conduct an Ames bacterial reverse mutation assay and a chromosomal aberrations assay in CHO cells. The sponsor states that both assays will follow ICH Guidelines and both studies will be performed according to GLP regulations. Protocols are currently being prepared. The sponsor states that it will take [redacted] from the date of the correspondence to synthesize adequate quantities of the impurity and that, once sufficient quantities have been synthesized, the studies will be conducted and final reports prepared within [redacted] Based upon this timeline, the sponsor requests that if qualification of the morphinone impurity is the only outstanding issue, that approval be granted with the study reports required as a post-approval commitment.

Following an internal meeting of the review team for this NDA, it was decided that the qualification studies proposed by the sponsor for the morphinone impurity could be submitted as a post-approval commitment if this issue is the only outstanding issue at the time of product approval.

It is also noted that the sponsor has committed to perform carcinogenicity studies in rats and mice as a Phase 4 commitment and has provided a timeline in which the studies will be conducted and submitted (see Pharmacology/Toxicology Review #5, dated September 3, 2002). Due to a recent evaluation of studies required under a 505(b)(2) NDA

submission by the Office of New Drugs, carcinogenicity studies will no longer be required for this NDA. The sponsor will, however, be encouraged to conduct these studies in the interest of public health and should at the least conduct a review of the published literature and include any relevant information in the product label.

External comments to sponsor:

Your proposal to submit qualification studies for the morphinone impurity (Ames bacterial reverse mutation assay and a chromosomal aberrations assay in CHO cells) as a post-approval commitment if this is the only outstanding issue at the time of product approval is acceptable.

Due to a recent evaluation of requirements to support a 505(b)(2) NDA submission by the Office of New Drugs, carcinogenicity studies are no longer a requirement for this NDA. The Agency notes that you have previously committed to perform carcinogenicity studies in rats and mice as a Phase 4 commitment and have provided a timeline in which the studies will be conducted and submitted. You are encouraged to conduct these studies in the interest of public health and should at the least conduct a review of the published literature and include any relevant information in the product label.

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/s/

Timothy McGovern
5/29/03 03:49:04 PM
PHARMACOLOGIST

PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: 21-044
Review number: 5
Sequence number/date/type of submission: March 12, 2002/AZ
Information to sponsor: Yes (X) No ( )
Sponsor and/or agent: Purdue Pharma LP, Norwalk, CT
Manufacturer for drug substance: [redacted]

Reviewer name: Timothy J. McGovern, Ph.D.
Division name: Anesthetic, Critical Care and Addiction Drug Products
HFD #: 170
Review completion date: September 3, 2002

Drug:

Trade name: Palladone Controlled Release Capsules
Generic name (list alphabetically): hydromorphone HCl
Code name: NA
Chemical name: 4,5α-epoxy-3-hydroxyl-17-methylmorphinan-6-one-hycrochloride
CAS registry number: 71-68-1
Mole file number: NA
Molecular formula/molecular weight: 321.81
Structure: see previous NDA reviews

Relevant INDs/NDAs/DMFs: IND 38,424

Drug class: Opioid analgesic, semi-synthetic congener of morphine

Indication: Management of moderate to severe pain in patients requiring continuous around-the-clock opioid analgesia for an extended period of time.

Clinical Formulation:

Ingredient	Function	Unit Dosage Strength (mg/capsule)			
Pellets		**12**	**16**	**24**	**32**
Hydromorphone HCl,	USP Active Ingredient	12.0	16.0	24.0	32.0
Ethylcellulose					
Steryl alcohol, NF	Retardant				
Weight of Multi-Dose Pellets (mg/capsule)					
Capsules					
No. 2 Gelatin Capsule					
No. 2 Gelatin Capsule					
No. 1 Gelatin Capsule	Blue	---			
No. 0 Gelatin Capsule (White					
Total Filled Capsule Weight					

Route of administration: Oral

Proposed use: Palladone™ Capsules are appropriate if the patient is opioid-exposed, requires a minimum total daily dose of opioids equivalent to 12 mg of oral hydromorphone, and around-the-clock therapy with an opioid is indicated. The extended-release nature of the formulation allows it to be administered once every 24 hours. Palladone™ 24 mg and 32 mg Capsules are for use in opioid-tolerant patients only.

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

Executive Summary

I. Recommendations

A. Recommendation on Approvability: These applications are approvable from a non-clinical perspective with the suggested label modifications (see section IX).

B. Recommendation for Nonclinical Studies: Carcinogenicity studies should be performed by the sponsor as a Phase 4 commitment. The sponsor has submitted an acceptable timeline for the initiation of the studies and the submission of the study reports (see section VI).

C. Recommendations on Labeling: The sponsor's proposed labeling related to non-clinical information is acceptable with the proposed modifications in the "Carcinogenesis, mutagenesis, impairment of fertility" and "Pregnancy" section. See section IX for specific details.

II. Summary of Nonclinical Findings

A. Brief Overview of Nonclinical Findings: Acute toxicology studies identified doses producing 50% lethality as 55-104 mg/kg IV and 84-120 mg/kg SC in mice, and 51 mg/kg SC in rats. The lowest lethal dose was 2.5 mg/kg IV in rabbits and 3 mg/kg IV in cats. Hydromorphone was 3-9X more potent than morphine and toxicities included reduced activity, incoordination, increased heart rate, increased heart rate, salivation, increased muscle tone, focused gaze, ptosis, absent feces, dehydration, respiratory depression, excitation, and convulsions and death at high doses. Repeat dose toxicology studies in rats, rabbits and dogs resulted in reduced body weight gains, clinical signs associated with opioids, discoloration of kidney and urinary bladder (rat), and collapsed and discolored lungs (rabbits). Hydromorphone hydrochloride was negative in an in vitro bacterial mutation assay (Ames) and an in vivo mouse micronucleus assay. The compound was positive in an in vitro mouse lymphoma assay in the presence of S9 metabolic activation; results were negative in the absence of S9 metabolic activation. No drug-related effects on mating and fertility parameters were observed in rats at oral doses up to 5 mg/kg. Hydromorphone produced no developmental effects in previously conducted embryo-fetal development studies in rats and rabbits other than reduced fetal weight in high-dose rabbits (50 mg/kg). Literature reports note minor skeletal defects in mice and cranioschisis and exencephaly in hamsters. In a pre- and post-natal development study in rats increased pup mortality and reduced pup weights were observed. No effects were noted on pup growth, development, learning memory or reproductive performance.

B. Pharmacologic Activity: Hydromorphone is a selective mu-opioid receptor agonist with binding potency of 10-30 X greater than morphine, and pharmacological potency for analgesia for 4-10 X greater than that of morphine. The hydromoprhone affinity for the mu-opioid receptor (Ki =0.26) was approximately 60 X that of oxycodone and 400 X and 700 X the binding potencies for the kappa and delta opioid receptors,

respectively. The metabolites also showed affinity for the mu receptor with potencies in the order of dihydroisomorphine (0.39 nM) > hydromorphone-N-oxide (1.5 nM) > dihydroisomorphine-6-glucoside (Ki 4.7 nM) > dihydroisomorphine-6-glucuronide (Ki 10 nM) > hydromorphone-3-glucoside (Ki 51 nM). The metabolite dihydroisomorphine also showed considerable affinity for the kappa receptor subtype (Ki 38 nM).

In a study of antinociceptive effects, hydromorphone metabolites 7,8-dihydro-6-beta-hydroxymorphine and 7,8-dihydromorphone-N-oxide monohydrate were as potent as hydromorphone, and the metabolites 7,8-dihydro-6-beta-hydroxymorphine-6-glucuronide, 7,8-dihydro-6-beta-hydroxymorphine-6-glucoside and 7,8-dihydromorphone-3-glucoside were significantly less potent than the parent drug in antagonizing the stretching response to p-phenylquinone than the pain induced by thermal stimulation.

Secondary pharmacological actions of hydromorphone, related to opioid agonist activity are somnolence, respiratory depression, neuroendocrine inhibition, nausea and emesis, depression of cough reflex, and convulsions. Hydromorphone decreases motility and increases resting tone in the gastrointestinal tract, decreases uterine tone and inhibits urinary voiding reflex. Hydromorphone induces arterial and venous dilatation, decreases myocardial oxygen consumption by decreasing heart rate, left ventricular end-diastolic pressure and decreasing cardiac work. Immunoinhibitory effects have been observed.

C. Nonclinical Safety Issues Relevant to Clinical Use: There are no non-clinical safety issues relevant to clinical use.

III. Administrative

A. Reviewer signature: Timothy J. McGovern, Ph.D.

B. Supervisor signature: Concurrence - Timothy J. McGovern, Ph.D.

C. cc: list:

TABLE OF CONTENTS - PHARMACOLOGY/TOXICOLOGY REVIEW

PHARMACOLOGY/TOXICOLOGY REVIEW

I. PHARMACOLOGY:

See original NDA review by Dr. Kathleen Haberny, finalized on December 22, 1999.

II. SAFETY PHARMACOLOGY:

See original NDA review by Dr. Kathleen Haberny, finalized on December 22, 1999.

III. PHARMACOKINETICS/TOXICOKINETICS:

See original NDA review by Dr. Kathleen Haberny, finalized on December 22, 1999.

IV. GENERAL TOXICOLOGY:

See original NDA review by Dr. Kathleen Haberny, finalized on December 22, 1999.

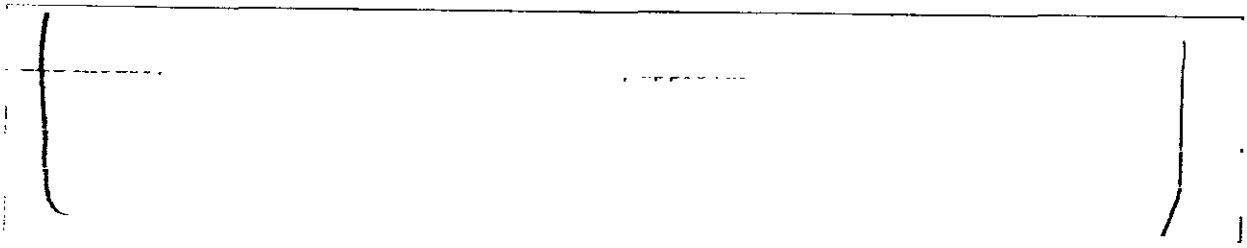
V. GENETIC TOXICOLOGY:

Genetic toxicology conclusions: Hydromorphone hydrochloride was negative in an in vitro bacterial mutation assay (Ames) and an in vivo mouse micronucleus assay. The compound was positive in an in vitro mouse lymphoma assay in the presence of S9 metabolic activation; results were negative in the absence of S9 metabolic activation. See original NDA review by Dr. Kathleen Haberny, finalized on December 22, 1999.

Labeling recommendations: The product label should reflect the results of the genetic toxicology studies summarized above.

VI. CARCINOGENICITY:

Carcinogenicity summary: As requested in the Not Approvable letter of October 2001, the sponsor will be performing carcinogenicity studies in rats and mice as a Phase 4 commitment. The sponsor, as requested, has committed to the following timelines:



Carcinogenicity conclusions: The sponsor's proposed timeline to assess the carcinogenic potential of hydromorphone HCl is acceptable. Conclusions concerning the carcinogenic potential await receipt of the study reports.

Recommendations for further analysis: None at this time

Labeling Recommendations: The label should state [ ]. The label should be updated once the studies are submitted and reviewed.

Addendum/appendix listing: Not applicable

VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:

Four new reproductive toxicity studies have been completed to assess the effects of hydromorphone hydrochloride on fertility and general reproductive toxicity (Segment I) as well as pre- and postnatal developmental toxicity (Segment III). The dose range-finding Segment I and III rat studies (NDSE-501 and NDSE-502) were conducted prior to the definitive Segment I and III rat studies (NDSE-503-GLP and NDSE-504-GLP). Only the definitive studies are reviewed below.

Study title: An oral (gavage) fertility and general reproduction toxicity study in rats with hydromorphone hydrochloride

Key study findings:

- Adverse clinical signs were observed at all doses
- Reduced body weight gain was noted at the two highest doses and reduced food consumption at the highest dose.
- No drug-related effects on mating or fertility parameters were observed.
- The NOAEL for paternal and maternal toxicity is less than 0.5 mg/kg
- The NOAEL for reproductive effects is 5 mg/kg.

Study no.: NDSE-503
Volume #, and page #: NA, electronic submission
Conducting laboratory and location: [ ]
Date of study initiation: January, 2001
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, radiolabel, and % purity: hydromorphone hydrochloride USP, /0009057/NA/ —
Formulation/vehicle: reverse osmosis deionized water

Methods:

Species/strain: Rat/ — CD(SD)IGS BR VAF/Plus

Doses employed: 0. 0.3, 2 and 5 mg/kg/day; 0, 0.05, 0.2, 0.5 mg/ml; 10 ml/kg. Doses were selected based on a previous oral (gavage) dose range-finding toxicity study (Study NDSE-501). Rats (10/sex/group) were dosed at 0, 1, 5, 20 or 50 mg/kg/d. Adverse findings included clinical signs, reduced body weight gain or net body weight loss (5 mg/kg or greater) and reduced food consumption (5 mg/kg or greater).

Route of administration: oral gavage

Study design: Rats were individually housed in stainless steel wire-bottom cages except during the cohabitation period. During cohabitation, each pair of male and female rats was housed in the male rat's cage. Male rats were administered the test article or vehicle beginning 28 days before cohabitation (maximum 15 days) and continuing through the day before sacrifice; males were administered test substance for at least 10 weeks prior to sacrifice. Females were administered test article or vehicle once daily beginning 15 days before cohabitation and continuing through DG 7.

Cohabitation period consisted of 21 days; females with spermatozoa observed in a smear of the vaginal contents and/or a copulatory plug in situ were considered DG 0 and assigned to individual housing. Females that did not mate with a male in the first 14 days were assigned an alternate male rat and remained in cohabitation for a maximum of seven additional days.

Number/sex/group: 25/sex/group

Parameters and endpoints evaluated:

Mortality: 2 x per day

Clinical signs: 2 x per day

Body weight: weekly and DGs 0, 3, 6, 7, 8, 10 and 13 (females only), sacrifice

Food consumption: weekly, DGs 0, 3, 6, 7, 8, 10 and 13 (females only), sacrifice

Estrus cycling: examination of vaginal cytology for 14 days prior to dosing initiation, for 14 days beginning with day after first administration and then until spermatozoa were observed in vaginal smear.

Gross necropsy:

Males: after cohabitation period; thoracic, abdominal and pelvic viscera; reproductive organs weighed and retained; sperm evaluation conducted; testes, epididymis, seminal vesicles and prostate weighed; sperm motility and concentration evaluated using computer assisted sperm analysis; histology sections from control and HD groups were prepared and examined. Male rat that died was examined for cause of death.

Females: sacrificed on DG 13. Caesarean section and gross necropsy of thoracic, abdominal and pelvic viscera; Uteri of apparently non-pregnant rats were examined to confirm absence of implantation sites. Number of corpora lutea in each ovary recorded; uterus examined for pregnancy, number and distribution of implantation sites and viable and non-viable embryos. Female 17458 escaped during cohabitation; when found was sacrificed and examined for gross lesions and for pregnancy status.

Results:

Mortality: One mid-dose male died on day 42 (~ 58 minutes after dosing). Clinical observations included excessive chewing (days 30 and 37), chromorhinorrhea (days 32, 33, 39), hyperactivity (day 37), chromodacryorrhea (days 39 to 42), and misaligned incisors (days 39 to 42). The rat gained weight until week 5 after which weight loss occurred from weeks five to six. All tissues were normal at necropsy except for slight degree of autolysis. No females died during the course of the study.

Clinical signs: Observations typical of hydromorphone administration were observed and included excessive chewing, hyperactivity, chromorinorrhea.

Observation	Males				Females			
N=25	0	0.5	2	5	0	0.5	2	5
Found dead	0	0	1	0	0	0	0	0
Excessive chewing	0/0	181/25	570/25	657/25	0/0	8/7	52/20	75/22
Hyperactivity	0/0	34/15	240/23	444/25	0/0	6/5	61/20	71/22
Chromorhinorrhea	21/9	50/18	130/22	122/22	0/0	0/0	0/0	1/1
Incisors: total	4/1	9/2	49/4	44/2	0/0	0/0	0/0	0/0
missing broken	4/1	9/2	24/3	44/2	0/0	0/0	0/0	0/0
Twitches	0/0	0/0	0/0	2/2	0/0	0/0	0/0	0/0
Right forepaw: swollen digits	0/0	0/0	0/0	2/1	0/0	0/0	0/0	1/1

Body weight:
Male: Mean body weight was reduced by 3, 11 and 12% respectively in the LD, MD and HD groups compared to control animals. Significant response noted at MD and HD. Body weight gain was dose-dependently reduced from week 1 of dosing onward during the 4-week pre-cohabitation period (13-37%). Although values were reduced in the weeks following the cohabitation period, the changes were not statistically significant.
Females: Body weight gain was significantly reduced (17 and 43% at the MD and HD) during the gestation period in which rats were dosed; body weight gain was significantly increased in the second week of gestation. Overall, body weight gain was reduced by 12% at the end of the dosing period at the highest dose.

Food consumption: Food consumption was reduced in all male dose groups from the first week of dosing onward. The level of reduction was comparable between week 1 and week 10. In females, reduced consumption (14%) was observed in HD females during the first week of gestation but was comparable to control animals during the second week after dosing was halted.

	Males			Females		
	0.5	2	5	0.5	2	5
BW gain (% Δ from control)						
Week 1-28	-13	-34	-37			
Days 1-77	-9	-30	-32			
Gestation days 0-8				-2	-17	-43
Gestation days 8-13				7	30	24
Gestation days 0-13				2	5	-12
Food consumption, g/day (% Δ from control)						
Week 1-28	-3	-8	-12			
Days 1-77	-2	-8	-10			
Gestation days 0-8				-2	--	-14
Gestation days 8-13				-1	-2	-3
Gestation days 0-13				-1	-1	-9

Toxicokinetics: not performed

Terminal and necroscopic evaluations:

Males:

Gross: Slight dilatation of the kidney pelvis was noted in one rat each from the MD and HD groups.

Organ weight: Slight reductions in absolute organ weights were noted in the epididymis (6-7%), testes (2-3%), seminal vesicle (6-12%) and prostate (13%) weight.

Histopathology: Microscopic assessment of the left testes from control and HD males revealed no drug-related findings.

Females:

Gross: One HD female exhibited diverticulum of the ileum.

Mating and fertility:

Males: No drug-related effects on number of days in cohabitation, number of rats that mated, number of pregnancies per number of rats in cohabitation and rats that mated, or rats with confirmed mating dates.

Spermiogenic parameters: No drug related effects on sperm motility, count and density were observed.

Females: The number of estrous stages per 14 days were comparable among the four dosage groups. No drug-related effects on number of days in cohabitation, number of rats that mated, fertility index, number of pregnancies per number of rats in cohabitation and rats that mated, rats with confirmed mating dates.

Caesarean sectioning: Caesarean sectioning and litter parameters (corpora lutea, implnatations, litter sizes, live fetuses, early and late resorptions, dams with only nonviable embryos, dams with viable embryos, and percent nonviable embryos/litters) were comparable among the four dose groups. There were no dead fetuses and all placentae appeared normal.

Summary of individual study findings: Administration of hydromorphone hydrochloride resulted in adverse clinical signs at all doses, reduced body weight gain at the two highest doses and reduced food consumption at the highest dose. No drug-related effects on mating and fertility parameters were observed. The NOAEL for paternal and maternal toxicity is less than 0.5 mg/kg while the NOAEL for reproductive effects is 5 mg/kg. This conclusion is in concurrence with that of the sponsor.

Study title: An Oral (Gavage) Pre- and Post-Natal Development Study in Rats with Hydromorphone Hydrochloride

Key study findings:

- Findings in the Fo dams included clinical signs and reduced body weight at the mid- and high-doses.
- Increased pup mortality and reduced pup weights were observed in the mid- and high-dose groups.
- No effects noted on pup growth, development, learning memory or reproductive performance.
- NOAEL for maternal toxicity is 0.5 mg/kg.
- NOAEL for developmental parameters is 0.5 mg/kg.

Study no.: NDSE-504-GLP
Volume #, and page #: NA, electronic submission
Conducting laboratory and location: [ ]
Date of study initiation: December 2000
GLP compliance: Yes
QA reports: yes (X) no ( )
Drug, lot #, radiolabel, and % purity: hydromorphone hydrochloride USP, /0009057/NA/
Formulation/vehicle: reverse osmosis deionized water

Methods:

Species/strain: Rat – CD(SD)IGS BR VAF/Plus
Doses employed: 0. 0.5, 2 and 5 mg/kg/day; 0, 0.05, 0.2, 0.5 mg/ml; 10 ml/kg. Doses were selected based on a previous oral (gavage) dosage range-finding toxicity study (Study NDSE-502). Female rats (10/sex/group) were dosed at 0, 1, 5, 10 or 20 mg/kg/d. Adverse findings included clinical signs, reduced body weight gain or net body weight loss and reduced food consumption (5 mg/kg or greater). At the two highest doses, one and two litters, respectively, had total litter loss during postpartum days 1 through 4. Pup weights in these groups were also lower than controls.
Route of administration: oral gavage
Study design: Fo generation rats were individually housed in stainless steel wire-bottom cages except during the cohabitation and postpartum period. During cohabitation, each pair of male and female rats was housed in the male rat's cage. No later than gestation day (DG) 20, Fo female rats were individually housed in nesting boxes. Each dam and delivered litter were housed in a common nesting box during the postpartum period. Female rats were administered the test article or vehicle once daily on DG7 through DG24 (rats that did not deliver a litter) or lactation day (DL) 20 (rats that did deliver a litter).
Cohabitation period consisted of a maximum 5 days; females with spermatozoa observed in a smear of the vaginal contents and/or a copulatory plug in situ were considered DG 0 and assigned to individual housing.

F1 generation rats were at least 70 days of age prior to cohabitation assignment, one male per one female with exclusion of sibling mates. Cohabitation period lasted 14 days. Female rats with spermatozoa observed in a smear of the vaginal contents and/or a copulatory plug observed in situ considered to be at DG 0 and assigned individual housing.

Number/sex/group: 25/females/group; males were used for breeding only and were not part of the test system

Parameters and endpoints evaluated:

In-life observations:

Dams: Mortality: 2 x per day

Clinical signs: 2 x per day

Body weight: DGs 0, 7, 10, 13, 15, 18, 21 and 25 and DLs 1, 4, 7, 10, 14 and 21

Food consumption: weekly and DGs 0, 7, 10, 13, 15, 18, 21 and DLs 1, 4, 7, 10, and 14

Reproductive parameters: duration of gestation, delivered litter size (all pups), live litter size, and pup viability at birth. Maternal behavior evaluated on days 1, 4, 7, 14 and 21.

Offspring: preweaning: pup weights taken on day 1 of lactation, viability evaluated 2X daily, clinical observation 1X daily, body weights on DLs 1, 4, 7, 14 and 21

Postweaning: observed for viability 2X daily, clinical observations and general appearance weekly. Body weights for males evaluated on weekly during postweaning period and at sacrifice. Female rats weighed weekly during postweaning period and on DGs 0, 7, 10, 14, 17 and 21. Food consumption measured weekly for males except during cohabitation; measure in females weekly during postweaning period and on DGs 0, 7, 10, 14, 17 and 21.

Females evaluated for age of vaginal patency on day 28 postpartum; males evaluated for preputial separation on day 39 postpartum.

Beginning day 24, one male and one female from each litter, where possible, were evaluated in a passive avoidance test for learning, and short- and long-term retention. Beginning at approximately day 60 postpartum, one male and one female from each litter, where possible, were evaluated in a water-filled M-maze for overt coordination, swimming ability, learning and memory.

Terminal and necroscopic evaluations:

Dams: Females sacrificed after 21-day postpartum period. Gross necropsy of thoracic, abdominal and pelvic viscera. Number and distribution of implantation sites recorded. Rats that did not deliver were sacrificed on DG 25 and examined for gross lesions and examined to confirm absence of implantation sites. The dam with no surviving pups was sacrificed after last pup was found dead or missing and presumed cannibalized. Gross necropsy was performed.

Offspring: Pups that died before initial examination were evaluated for vital status at birth. Lung immersion test performed to assess stillborn vs liveborn. Gross examination was performed. Pups found dead or sacrificed due to moribundity examined for gross lesions and for cause of death or moribundity. Gross lesions found days 2-4 postpartum preserved in Bouin's solution; lesions found days 5-21 preserved in neutral buffered 10% formalin. Pups not selected for further evaluation sacrificed of DL 2 and examined for gross lesions; included single cut at

suture of the frontal and parietal bones of the skull, and cross-sectioned brain was examined for hydrocephaly.

F1 generation rats: males sacrificed, gross necropsy performed after Caesarean sectioning of females. Testes and epididymis excised and paired organ weight recorded and preserved. All surviving females sacrificed DG 21. Uteri of apparently nonpregnant rats examined to confirm absence of absence of implantation sites. Rats examined for number and distribution of corpora lutea, implantation sites, live and dead fetuses, early and late resorption. Each fetus weighed and examined for sex and gross external alterations.

Rats that died or were sacrificed due to moribund condition were examined cause of death or moribundity on day that observation was made; rats were examined for gross lesions. Testes and epididymis excised and paired organ weight recorded and preserved. Pregnancy status and uterine contents of female rats was recorded.

Results:

In-life observations:

Dams:

Mortality: All animals survived to terminal sacrifice.

Clinical signs: During gestation, the incidence of alopecia increased at the highest dose. One or two of these rats also had a scab and/or ulceration on the forepaw or forelimb. The incidence of alopecia increased during the lactation period and was noted at all doses (significant at the two highest doses). The incidences of excessive chewing, swollen forepaws and excessive grooming were significantly increased at the highest dose while excessive licking, scabbing on forepaw or chest, abrasion of forepaw, red substance on forepaw, ptosis, excess salivation and a swollen forepaw digit occurred in one or two rats in the mid or high dose groups.

Observation N=25		Females 0	0.5	2	5
Gestation:					
Alopecia	Total	0/0	0/0	13/1	73/8
	Limbs	0/0	0/0	12/1	73/8
	Underside	0/0	0/0	11/1	13/2
Lactation:					
Alopecia	Total	2/1	42/3	80/6	125/8
	Limbs	2/1	42/3	70/5	125/8
	Underside	0/0	0/0	36/2	42/2
	Back	0/0	0/0	0/0	12/1
Excessive chewing		0/0	0/0	0/0	21/7
Swollen forepaws		0/0	0/0	0/0	15/3
Excessive grooming		0/0	0/0	0/0	5/3

Body weight: Body weight gain was reduced on days 7-10 of gestation at the mid- and high-doses and at the high dose only on days 10-13 and 15-18. Body weight gain was not significantly affected during the lactation period.

Food consumption: Absolute and relative food consumption was reduced in mid and high-dose animals during the gestation period. Food consumption was also reduced in

mid- and high-dose animals (15-19%) during days 1-4 of the lactation period but no significant changes were observed thereafter.

	Females		
	0.5	2	5
BW gain (% ch from control)			
Gestation days 7-21	-7	-9	-21
Gestation days 0-21	-7	-7	-18
Absolute food consumption, g/day (% ch from control)			
Gestation days 7-21	-4	-8	-18
Gestation days 0-21	-4	-6	-13

Toxicokinetics: not performed

Offspring:
Mortality: The total number of pups that were stillborn or found dead increased in mid- and high-dose animals.

	0	0.5	2	5
Total pups stillborn, found dead or sacrificed	8	6	18	17
Stillborn	1	5	6	5
Found dead	6	1	12	12

* number of live

Pup pre-/post-partum mortality was significantly increased on days 2-4 in the mid- and high-dose groups and on days 8-14 in the high-dose group. One dam (15054) in the mid-dose group had no surviving pups on lactation day 2. Thus, the viability index in the mid- and high-dose groups was reduced. Other parameters were not significantly affected.

	Females			
	0	0.5	2	5
Dams with stillborn pups	1 (4.3)	5 (20.8)	4 (19)	4 (19)
Dams with all pups dying				
Days 1-4 postpartum	0 (0)	0 (0)	1 (4.8)	0 (0)
Pups fond dead or presumed cannibalized (%)				
Day 1	1.2	0.3	2.3	1.6
Days 2-4	1.5	1.4	4.4	3.2
Days 5-7	0.6	0	1.1	0.7
Days 8-14	0	0.3	0.7	2
Days 15-21	0.3	0	0	0
Viability index*	97.4	98.2	93.4	95.2

* number of live pups on day 4 postpartum/number of liveborn pups on day 1 postpartum

During the postweaning period, no drug related deaths occurred in males; one high-dose female died on day 12 postweaning. The only clinical sign was excessive salivation and death was considered to be due to a failure to thrive postweaning.

Clinical signs: No drug related effects occurred.

Body weight: Body weight gain in males was unaffected by drug-treatment through day 91 postweaning. In females, no significant changes in body weight gain were noted over the course of the postweaning period (73-77 days) although BW gain was reduced by 5-7% in the mid-and high-dose groups. This decrease was significant in the period of days 1 through 50 (6-8%). No effects on BW gain were noted during the gestation period following cohabitation.
Food consumption: No drug related effects occurred.
Toxicokinetics: Not assessed

Sexual maturity: No effects noted on preputial separation in males and vaginal patency.

Developmental assays: No significant drug-related effects were observed in a passive avoidance paradigm or in watermaze performance.

Mating and fertility: No effects on the fertility or mating of the F1 generation rats were observed.

Terminal and necroscopic evaluations:

Dams: Gross observations in dams resulted in only two masses in the inguinal area containing a green caseous material in one HD dam. The relationship to study drug is unclear.

Offspring:
Gross evaluation: One of 24 high dose males exhibited small bilateral epididymides. One high-dose female exhibited a left uterine horn that was reduced to a ligament. A definitive relationship to drug-treatment cannot be determined for these findings.
Organ weight: No effects were observed on testes and epididymides weights in the F1 generation males.
Caesarean section: No drug-related effects were noted on the number of corpora lutea, implantations, litter sizes, resorptions, dams with any resorptions, dams with all conceptuses dead or resorbed, dams with viable fetuses or normal placentae. There was one dead fetus in the high-dose maternal group; the relationship to drug treatment is unclear.
F2 litter observations: No drug-related effects were observed on implantations, live fetuses, gender distribution, fetal body weights, or % dead or resorbed conceptus/litter.
Fetal gross external alterations of F2 generation litters: No drug-related effects were observed.

Summary of individual study findings: Findings in the Fo dams included clinical signs and reduced body weight at the mid- and high-doses. Increased pup mortality and reduced pup weights were observed in the mid- and high-dose groups. No effects were noted on pup growth, development, learning memory or reproductive performance. The NOAEL for maternal toxicity

is 0.5 mg/kg while the NOAEL for developmental parameters is 0.5 mg/kg, in concurrence with the sponsor's conclusions.

Reproductive and developmental toxicology summary: The sponsor performed a rat fertility and pre- and post-natal development study to complete the reproductive toxicity battery for hydromorphone hydrochloride. In the fertility study, administration of hydromorphone hydrochloride (doses of 0, 0.5, 2 and 5 mg/kg, oral gavage) resulted in adverse clinical signs at all doses, reduced body weight gain at the two highest doses and reduced food consumption at the highest dose. No drug-related effects on mating and fertility parameters were observed. The NOAEL for paternal and maternal toxicity is less than 0.5 mg/kg while the NOAEL for reproductive effects is 5 mg/kg. In the pre- and post-natal development study at identical doses, findings in the Fo dams included clinical signs and reduced body weight at the mid- and high-doses. Increased pup mortality and reduced pup weights were observed in the mid- and high-dose groups. No effects were noted on pup growth, development, learning memory or reproductive performance. The NOAEL for maternal toxicity is 0.5 mg/kg while the NOAEL for developmental parameters is 0.5 mg/kg. Hydromorphone produced no developmental effects in previously conducted embryo-fetal development studies in rats and rabbits other than reduced fetal weight in high-dose rabbits (50 mg/kg). Literature reports note minor skeletal defects in mice and cranioschisis and exencephaly in hamsters. See the Original NDA review by Dr. Kathy Haberny, finalized on December 22, 1999.

Reproductive and developmental toxicology conclusions: Hydromorphone hydrochloride produced no effects on fertility in rats at doses up to 5 mg/kg. No teratogenic effects were observed in rats or rabbits at doses up to 10 and 50 mg/kg, respectively. However, increased pup mortality in rats and reduced rat pup and rabbit fetus weights were noted. No developmental effects were observed.

Labeling recommendations: The above noted findings should be included in the label with reference to dose and appropriate exposure comparisons. The Pregnancy Category should be a "C".

VIII. SPECIAL TOXICOLOGY STUDIES:

No studies have been performed.

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:

Conclusions: NDA 21-044 was considered to be approvable from a non-clinical viewpoint following the initial review of the original NDA submission dated December 22, 1999. A letter indicating that the NDA was approvable was sent to the sponsor dated December 29, 1999. A subsequent letter dated October 4, 2001 informed the sponsor that the NDA was not approvable. The sponsor was asked to provide a post-marketing study commitment to evaluate the carcinogenic potential of hydromorphone hydrochloride, and studies to assess the potential effects of hydromorphone hydrochloride on fertility and on pre- and post-natal development.

Hydromorphone hydrochloride has analgesic properties that are similar to, but more potent than, morphine, with similar side effects and toxicity profile. The oral bioavailability is ~ 60% in humans with drug distribution to the brain, skeletal muscle, kidneys, intestinal tract, liver, spleen and lungs. Metabolism occurs by hepatic oxidation and conjugation to hydromorphone-3-glucuronide, dihydromorphine-6-glucuronide, hydromorphone-3-glucoside and dihydromorphine-6-glucoside. Hydromorphone hydrochloride was positive in an in vitro mouse lymphoma assay in the presence of metabolic activation but was negative in the remainder of the battery performed. The carcinogenic potential has not yet been evaluated but will be a Phase 4 commitment. Hydromorphone hydrochloride produced no effects on fertility in rats at doses up to 5 mg/kg. No teratogenic effects were observed in rats or rabbits at doses up to 10 and 50 mg/kg, respectively. However, increased pup mortality in rats and reduced rat pup and rabbit fetus weights were noted. No developmental effects were observed in rats.

General Toxicology Issues: Carcinogenicity studies will be performed as a Phase 4 commitment as per a previous agreement with the Agency. The sponsor has submitted an acceptable timetable for the initiation of the studies and submission of the study reports (see Section VI of this review).

Recommendations: This application is approvable from a non-clinical perspective with the inclusion of the proposed modifications to the product label described below.

Labeling with basis for findings:

2 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

X. APPENDIX/ATTACHMENTS:

Addendum to review: Label worksheet.
Drug: **Palladone**

	age	mg/dose	# daily doses	mg/day	kg	mg/kg	factor	mg/m²
Pediatric	[redacted]			0	3	0.00	25	0.00
Adult	>12	[redacted]		32	50	0.64	37	23.68

	route	mg/kg/d	conv. factor	mg/m²	Dose Ratio Adults	Dose Ratio Children	Rounded Dose Ratio Adults	Rounded Dose Ratio Children
Carcinogenicity:								
rat	[redacted]		6	0	---	---	---	---
mouse			3	0	---	---	---	---
extra			---	---	---	---	---	---
extra			---	---	---	---	---	---
extra			---	---	---	---	---	---
Reproduction and Fertility:								
rat	[redacted]	5	6	30	1.3	N/A	#NAME?	N/A
rat			6	0	---	N/A	---	N/A
rabbit			12	0	---	N/A	---	N/A
rabbit			12	0	---	N/A	---	N/A
Teratogenicity:								
rat	[redacted]	10	6	60	2.5	N/A	#NAME?	N/A
rat		2	6	12	0.5	N/A	1/2	N/A
rat		0.5	6	3	0.1	N/A	1/8	N/A
rat			6	0	---	N/A	---	N/A
rabbit		50	12	600	25.3	N/A	#NAME?	N/A
Overdosage:								
mouse	[redacted]		3	0	---	---	---	---
rat			6	0	---	---	---	---
dog			20	0	---	---	---	---
rabbit			12	0	---	---	---	---
Other:	Teratogenicity							
mouse	[redacted]	5	3	15	0.6	---	1/2	---
hamster		20	4	80	3.4	---	#NAME?	---
extra			---	---	---	---	---	---
extra			---	---	---	---	---	---
extra			---	---	---	---	---	---

Other relevant materials (Studies not reviewed, appended consults, etc.): None.

Any compliance issues: None.

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/s/

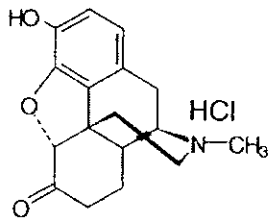
Timothy McGovern
9/3/02 10:09:26 AM
PHARMACOLOGIST

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA

KEY WORDS: Labeling
Reviewer Name: Kathleen Haberny
Division Name: Division of Anesthetic, Critical Care & Addiction Drug Products
HFD # 170
Review Completion Date: June 15, 2001
NDA 21-044
Serial number BZ / March 30, 2001 / Amendment to Pending Application
Information to sponsor: Yes (x) No ( )
Sponsor: Purdue Pharma L.P., One Stamford Forum, Stanford, CT 06901-3431
Manufacturer for drug substance: [ ]

Drug:

Code Name: HHER
Generic Name: Hydromorphone Hydrochloride
Trade Name: Palladone™ Extended-Release Capsules 12, 16, 24 and 32 mg
Chemical Name: 4,5α-epoxy—3-hydroxyl-17-methylmorphinan-6-one-hydrochloride
CAS Registry Number: CAS-71-68-1
Molecular Weight: 321.81
Structure:



Relevant INDs/NDAs/DMFs: IND 38,424; DMFs #s [ ] (Amendment 92)

Pharmacologic Class: Opioid analgesic, semi-synthetic congener of morphine

Proposed Clinical Indication: [ ]

Clinical Formulation (and components):

Ingredient	Function	Unit Dosage Strength (mg/capsule)			
Pellets		**12**	**16**	**24**	**32**
Hydromorphone HCl, USP	Active Ingredient	12.0	16.0	24.0	32.0
Ethylcellulose					
Steryl alcohol, NF					
Weight of Multi-Dose Pellets (mg/capsule)					
Capsules					
No. 2 Gelatin Capsule					
No. 2 Gelatin Capsule					
No. 1 Gelatin Capsule	Blue				
No. 0 Gelatin Capsule (White					
Total Filled Capsule Weight[3]					

Route of administration: Oral

Introduction and drug history: Hydromorphone is approved and has been used successfully in the treatment of moderate to severe pain since 1926. Hydromorphone hydrochloride is currently available in cough syrup (Dilaudid Cough Syrup, Knoll Labs), injection (Knoll Labs, Astra, Elkins-Sinn), oral liquid (Knoll Labs), powder (Knoll Labs), tablets (Knoll Labs, Roxane, Endo) and suppository (Knoll Labs) forms. Palladone was developed to provide a convenient once per day treatment schedule, and to provide more predictable and steady blood concentrations and pain relief than was achievable using immediate-release hydromorphone formulations. Controlled-release hydromorphone hydrochloride capsules using this formulation have not been marketed in any country.

Previous clinical experience: Hydromorphone hydrochloride controlled-release was evaluated in 17 single dose and multiple dose pharmacokinetics studies, with comparisons to immediate-release hydromorphone hydrochloride. Bioequivalence and dose-proportionality were assessed with comparison to Dilaudid® at doses up to 84 mg, and the effects of food, renal and hepatic impairment, gender, race and age on human pharmacokinetic parameters were evaluated. The proposed drug product was studied for potential interactions with drugs that could modify gastrointestinal release rates and absorption (e.g., H2 blockers cimetidine and ranitidine). Efficacy was evaluated in 554 patients with cancer-related pain and non-cancer, or post-operative pain at 12-84 mg/d. One thousand one hundred and eighty five patients were enrolled in Phase I, II and III studies to establish safety. For detailed reviews of the clinical studies on hydromorphone hydrochloride controlled-release, refer to the clinical pharmacokineticist and medical officer reviews.

Note: Portions of this review were excerpted directly from the sponsor's submission.

Studies reviewed within this submission: None

Studies not reviewed within this submission: None

LABELING REVIEW

The following changes to the proposed label are recommended (deletions are denoted by strikethrough, and recommended additions to the proposed labeling are underlined):

Mutagenicity/Carcinogenicity/Impairment of Fertility

Studies of hydromorphone evaluating the carcinogenic potential or effects on fertility in animals have not been conducted.

Pregnancy – Pregnancy Category C

CONCLUSIONS

Based on the known pharmacology and toxicology of hydromorphone hydrochloride, and on the results of the studies conducted by the sponsor and submitted in the original NDA submission, Palladone™ (Hydromorphone Hydrochloride Extended-Release Capsules) is approvable from a pharmacology and toxicology point of view. Revisions to the Label and additional studies needed as Phase 4 commitment are described under RECOMMENDATIONS below.

RECOMMENDATIONS

External Recommendations to Sponsor:

1. The proposed product label should be revised as described under LABELING REVIEW above.

2. Studies to evaluate the carcinogenic potential of hydromorphone hydrochloride will be needed as a Phase 4 commitment.

3. Studies to evaluate the potential effects of hydromorphone hydrochloride on fertility (Segment I) and pre- and post-natal development (Segment III) will be needed as a Phase 4 commitment.

Kathleen A. Haberny, Ph.D.
Pharmacologist

Thomas Papoian, Ph.D.
Supervisory Pharmacologist
(Concurrence/Non-concurrence)

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/s/

Kathy Haberny
6/28/01 08:40:45 AM
PHARMACOLOGIST

Thomas Papoian
6/28/01 09:38:12 AM
PHARMACOLOGIST

DEC 21 1999

Review and Evaluation of Pharmacology/Toxicology Data: Historical Data
Addendum to the NDA Review
Division of Anesthetic, Critical Care & Addiction Drug Products
HFD-170/Kathleen Haberny

NDA 21-044

Submission Date July 23, 1999

Review Date: December 17, 1999

Information to Sponsor Yes ( ) No (x)

Sponsor: Purdue Pharma L.P.
100 Connecticut Avenue
Norwalk, CT 06850-3590

Drug Name: Palladone [ ] Controlled-Release Capsules (hydromorphone hydrochloride), 12, 16, 24 and 32 mg

Chemical Name: 4,5α-epoxy—3-hydroxyl-17-methylmorphinan-6-one-hydrochloride

CAS Number: CAS-71-68-1

Indication: [
]

Route of Administration: Oral

COMMENTS

Historical data on major malformations (Segment II Reproductive toxicology) in the New Zealand white rabbit by hydromorphone hydrochloride over the last 10-15 years was submitted for review, as requested by the Agency on June 20, 1999 in a telephone contact to the sponsor. This data adequately addresses the concerns of the reviewing pharmacologist.

Kathleen A. Haberny 12/17/99
Kathleen A. Haberny, Ph.D.

D.H. (Lin) Jean 12/17/99
Team Leader: Dou H. Jean, Ph.D.

DEC 2 2 1999

Review and Evaluation of Pharmacology/Toxicology Data: Labeling Review
Addendum to the NDA Review
Division of Anesthetic, Critical Care & Addiction Drug Products
HFD-170/Kathleen Haberny

NDA 21-044

Submission Date December 28, 1998

Review Date: October 1, 1999, Revised November 19, 1999

Information to Sponsor **Yes (x) No ( )**

Sponsor: Purdue Pharma L.P.
100 Connecticut Avenue
Norwalk, CT 06850-3590

Drug Name: Palladone [ ] Controlled-Release Capsules (hydromorphone hydrochloride), 12, 16, 24 and 32 mg

Chemical Name: 4,5α-epoxy—3-hydroxyl-17-methylmorphinan-6-one-hydrochloride

CAS Number: CAS-71-68-1

Indication: [

]

Route of Administration: Oral

LABELING REVIEW

The following *Mutagenicity/Carcinogenicity/Impairment of Fertility* and *Pregnancy* sections of the Package Insert were submitted by the sponsor:

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1 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

Kathleen A. Haberny, Ph.D. 11/19/99

Team Leader: Dou H. Jean, Ph.D. 11/19/99

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Review and Evaluation of Pharmacology/Toxicology Data
Division of Anesthetic, Critical Care & Addiction Drug Products
HFD-170/Kathleen Haberny

NDA 21-044

Submission Date December 28, 1998

Review Date: May 21, 1999

Information to Sponsor Yes (x) No ( )

Sponsor: Purdue Pharma L.P.
100 Connecticut Avenue
Norwalk, CT 06850-3590

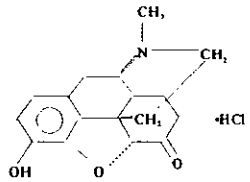
Manufacturer: [redacted]

Drug Name: Palladone [redacted] Controlled-Release Capsules (hydromorphone hydrochloride), 12, 16, 24 and 32 mg

Chemical Name: 4,5α-epoxy—3-hydroxyl-17-methylmorphinan-6-one-hydrochloride

CAS Number: CAS-71-68-1

Structure:



Molecular Weight: 321.81

Relevant INDs/NDAs/DMFs: IND 38,424; DMFs #s [redacted] (Amendment 92)

Drug Class: Opioid analgesic, semi-synthetic congener of morphine

Indication: [redacted]

Note: ***Portions of this review were excerpted directly from the sponsor's submission.***

Clinical Formulation (and components):

Ingredient	Function	Unit Dosage Strength (mg/capsule)			
Pellets		12	16	24	32
Hydromorphone HCl, USP	Active Ingredient	12.0	16.0	24.0	32.0
Ethylcellulose NF	[redacted]				
Steryl alcohol, NF					
Weight of Multi-Dose Pellets (mg/capsule)					
Capsules					
No. 2 Gelatin Capsule (	---				
No. 2 Gelatin Capsule (	—				
No. 1 Gelatin Capsule Blue	---				
No. 0 Gelatin Capsule (White	—				
Total Filled Capsule Weight[3]					

Route of Administration: Oral

Studies Reviewed within this Submission:

Receptor Binding of Hydromorphone and Several Metabolites (includes oxycodone binding study) (BSDR-98-0918 / Vol. 15, p. 1)

Antinociceptive Effects of Hydromorphone and Several Metabolites in p-Phenylquinone Stretching Test in Mice (BSFR-98-0923 / Vol. 15, p. 257)

Pharmaceutical Analysis Report: Hydromorphone Hydrochloride CR 12 mg Capsules and Dilaudid Tablets. Comparison of the Related Substances Content of the Two Drug Products (Vol. 15, p. 290)

Hydromorphone Metabolites Identified by — Analysis from Different Biological Samples (PKDM HD0998-Metab.001 / Vol. 15, p. 300)

A Preliminary Acute and 12-Day Oral Gavage Range Finding Toxicity Study of Hydromorphone Hydrochloride in the Female Albino Rat (DSE-173/ Vol. 12, p. 2)

A Preliminary Acute and 13-Day Range Finding Oral Gavage Toxicity Study of Hydromorphone Hydrochloride in the Female Albino Rabbit (DSE-174/ Vol. 12, p. 112)

An Oral Range-Finding Teratology (Reproduction Segment II) Study of Hydromorphone Hydrochloride in the Rat (DSE-175/Vol. 12, p. 220)

An Oral Teratology (Reproduction Segment II) Study of Hydromorphone Hydrochloride in the Rat (DSE-176-GLP/Vol. 13, p. 1)

Toxicokinetic Aspects of An Oral Teratology (Reproduction Segment II) Study of Hydromorphone in the Rat (DSE-176-GLP PKDM / Vol. 13, p. 388)

An Oral Range Finding Teratology Study of Hydromorphone Hydrochloride in the Rabbit (DSE-177/Vol. 14, p. 1)

An Oral Teratology (reproduction Segment II) Study of Hydromorphone Hydrochloride in the Rabbit (DSE-178-GLP/Vol. 14, p. 135)

Toxicokinetic Aspects of An Oral Teratology (Reproduction Segment II) Study of Hydromorphone in the Rabbit (DSE-178-GLP PKDM / Vol. 14, p. 425)

Mutagenicity Test with Hydromorphone Hydrochloride in the Salmonella-escherichia coli/Mammalian-Microsome Reverse Mutation Assay with a Confirmatory Assay (DSE-333-GLP / Amendment BP, Vol. 1, p. 8)

Mutagenicity Test on Hydromorphone Hydrochloride in the In Vivo Mouse Micronucleus Assay (DSE-334-GLP / Amendment BP, Vol. 1, p. 67)

Mutagenicity Test on Hydromorphone Hydrochloride in the L5178Y $TK^{+/-}$ Mouse Lymphoma Forward Mutation Assay (DSE-335-GLP / Amendment BP, Vol. 1, p. 109)

Studies Not Reviewed within this Submission: The remaining pharmacology and toxicology portion of the NDA is supported by a review of the available literature on hydromorphone HCl.

Introduction/drug History: Hydromorphone is approved and has been used successfully in the treatment of moderate to severe pain since 1926. Hydromorphone hydrochloride is currently available in cough syrup (Dilaudid Cough Syrup, Knoll Labs), injection (Knoll Labs, Astra, Elkins-Sinn), oral liquid (Knoll Labs), powder (Knoll Labs), tablets (Knoll Labs, Roxane, Endo) and suppository (Knoll Labs) forms. One of the disadvantages of using the conventional immediate-release dosage forms is the need to repeat dosing frequently due to the short four- to six-hour half life of the drug. Palladone — was developed to provide a convenient once per day treatment schedule, and to provide more predictable and steady blood concentrations and pain relief than was achievable using immediate-release hydromorphone formulations. Controlled-release hydromorphone hydrochloride capsules using this formulation have not been marketed in any country

Previous Clinical Experience: Hydromorphone hydrochloride controlled-release was evaluated in 17 single dose and multiple dose pharmacokinetics studies, with comparisons to immediate-release hydromorphone hydrochloride. Bioequivalence and dose-proportionality were assessed with comparison to Dilaudid® at doses up to 84 mg, and the effects of food, renal and hepatic impairment, gender, race and age on human pharmacokinetic parameters were evaluated. The proposed drug product was studied for potential interactions with drugs that could modify gastrointestinal release rates and absorption (e.g., H2 blockers cimetidine and ranitidine). Efficacy was evaluated in 554 patients with cancer-related pain and non-cancer, or post-operative pain at 12-84 mg/d. One thousand one hundred and eighty five patients were enrolled in Phase I, II and III studies to establish safety. For detailed reviews of the clinical studies on hydromorphone hydrochloride controlled-release, refer to the clinical pharmacokineticist and medical officer reviews.

PHARMACOLOGY

Hydromorphone hydrochloride is a selective mu-opioid receptor agonist (K_D 0.26). The affinity for the delta opioid receptor is approximately 700x less, and for the kappa receptor 400x less than for the mu receptor. The binding potency of hydromorphone hydrochloride is 10x-30x greater, and the pharmacological potency is 4x-10x greater than that of morphine. Hydromorphone pharmacological effects are predominantly in the central nervous system (CNS) and intestines. Hydromorphone receptor (mu-opioid) binding sites are in highest concentration in the limbic system, striatum, thalamus, midbrain, hypothalamus and spinal cord. Hydromorphone-induced analgesia is believed to be mediated by altered perception of pain due to action at the

spinal cord, substantia gelatinosa, spinal trigeminal nucleus, periaqueductal gray, periventricular gray, medullary raphe nuclei and hypothalamus, and by altering the emotional response to pain.

Purdue Research Center Pharmaceutical Analysis Report: Hydromorphone Hydrochloride CR 12 mg Capsules and Dilaudid Tablets, Comparison of the Related Substances Content of the Two Drug Products. (Vol. 15, p. 290).

Note: Performing Laboratory: Purdue Research Center, Yonkers, NY. Report date: September 1, 1998. Non-GLP study.

Methods: Dilaudid Tablets (Lot No. 10900187, 4 mg; and Lot No. 11200047, 8 mg) and hydromorphone HCl (Lot No. 9K, 12 mg capsules) were compared for substances content by HPLC (Assay Method , [ ]) and two Related Substances Methods ([ ]
There was one protocol deviation; Dilaudid was dissolved in [ ] . The specifications for "Related substances" in the elution assays were: no more than — of any individual known related substance, no more than — any individual unknown related substance and no more than — total related substances.

Results:

HPLC Assay Sample	Percent of Label Claim Hydromorphone HCl
Dilaudid Tablet, 4 mg (Lot No. 10900187)	
Dilaudid Tablet, 8 mg (Lot No. 11200047)	
Hydromorphone HCL Controlled Release Capsules, 12 mg (Lot No. 9K; [ ]	

HPLC Assay for Early-Eluting Related Substances Using Method [ ]

Related Substance	Retention Time (minutes)	Relative Retention Time	Percent Found in Sample Analyzed		
			Dilaudid 4 mg	Dilaudid 8 mg	HHCR 12 mg
Dihydromorphine N-oxide	[ ]				
Dihydromorphine					
Morphine Sulfate $5H_2O$					
Hydromorphone N-oxide					
Morphinone					
Hydromorphone HCl					
Unknown 1					
Unknown 2					
Unknown 3					
Total of Related substances			[ ]		

*ND: None detected. HHCR: Hydromorphone HCL Controlled Release 12 mg Capsules.

HPLC Assay for Late-Eluting Related Substances Using Method [ ]

Related Substance	Retention Time (minutes)	Relative Retention Time	Percent Found in Sample Analyzed		
			Dilaudid 4 mg	Dilaudid 8 mg	HHCR 12 mg
Hydromorphone HCl					
Hydrocodone	[ ]				
Benzophenone					
Pseudohydromorphone					
7-(6-dihydromorphinyl) hydromorphone					
7-diphenylhydroxymethyl hydromorphone					
Unknown 1					
Unknown 2					
Total of Related substances					

*ND: None detected. HHCR: Hydromorphone HCL Controlled Release 12 mg Capsules.

Receptor Binding of Hydromorphone and Several Metabolites (includes oxycodone binding study) (BSDR-98-0918 / Vol. 15, p. 1)

Note: Performing laboratory: [ ] Quality Assurance statement signed and present.

Methods: The test articles (see table under Results) were dissolved in binding buffer and subjected to ligand binding in human recombinant expressed in CHO cells. The K_D (binding affinity) values were 0.23 nM, 0.3 nM and 0.26 nM in the mu, delta and kappa binding assays respectively. The Bmax (receptor number) values were 3, 6 and 1.5 pmol/mg protein in the mu, delta and kappa binding assays respectively. To determine interactions with the cloned mu binding sites, the radioligand was [3H]-diprenorphine (30-50 Ci/mmol) and final ligand concentration 0.6 nM. Naloxone [10 mcM] was the non-specific determinant, reference compound and positive control. The reactions were conducted in 50 mM TRIS-HCl (pH 7.4) containing $MgCl_2$ 5 mM for 150 minutes at 25°C, and terminated by rapid vacuum filtration onto glass fiber filters. The radioactivity that was trapped on the filters was measured and compared to the control counts. In the delta opiate receptor binding assay, the radioligand was [^{3}H]-Naltrindole (30-50 Ci/mmol), final ligand concentration 0.5 nM, the non-specific determinant, reference compound and positive control was Naltriben [3.0 mcM], and the reaction was carried out for 60 minutes. In the kappa opiate binding assay, TRIS-HCl contained 10 mM $MgCl_2$ and the reaction was carried out for 60 minutes. The data were interpreted as follows:

-20% to +20% inhibition: Baseline, inactive
<20% inhibition: Result of extraction procedure, warrants retesting at lower concentration
20% to 40% inhibition: marginal activity at the receptor site
χ50% inhibition: active, expect dose-dependent response

Results:

Compound	μ	δ	κ
	Ki (95% confidence limits), nM		
Hydromorphone	0.26 (0.14, 0.48)	172 (72, 412)	99 (42, 238)
Hydromorphone-N-oxide	1.5 (0.90, 2.5)	3766 (1601, 8858)	2476 (724, 8463)
Dihydroisomorphine	0.39 (0.19, 0.81)	212 (91, 495)	38 (20, 73)
Dihydroisomorphine-6-glucuronide	10(4.9, 22)	291 (94, 905)	655 (254, 1689)
Dihydroisomorphine-6-glucoside	4.7 (1.8, 13)	868 (484, 1557)	440 (148, 1312)
Hydromorphone-3-glucoside	51 (18, 148)	4500 (3500, 42050)	2400 (724, 8085)
Oxycodone	15 (7.6, 28)	10320 (1485, 86320)	8229 (1219, 55570)

Compound	μ	δ	κ
	IC50 (M)		
Hydromorphone	8.63E-10	7.49E-08	1.95E-07
Hydromorphone-N-oxide	7.42E-09	6.81E-05	3.46E-06
Dihydroisomorphine	1.48E-09	8.44E-07	5.09E-08
Dihydroisomorphine-6-glucuronide	1.08E-08	2.99E-07	1.93E-06
Dihydroisomorphine-6-glucoside	2.43E-09	1.74E-06	4.46E-07
Hydromorphone-3-glucoside	4.60E-08	3.27E-06	2.37E-06
Oxycodone	1.27E-08	6.56E-05	1.31E-04

Conclusions: Hydromorphone showed selectivity for the mu opioid receptor, with a higher affinity constant value (Ki: 0.26 nM) than for the kappa (Ki 99 nM) and delta (Ki 172 nM) receptor subtypes. In comparison, the Ki values for oxycodone were 15, 8229 and 10320 nM at the mu, kappa and delta receptors respectively, and morphine Ki values are approximately 19, 230 and 220 nM at the mu, kappa and delta receptors respectively in literature reports. The hydromorphone metabolites hydromorphone-N-oxide, dihydroisomorphine,

dihydroisomorphine-6-glucuronide, dihydroisomorphine-6-glucoside and hydromorphone-3-glucoside also showed high affinity for the cloned human mu opioid receptor subtype (Ki values 1.5, 0.39, 10, 4.7, and 51 respectively), and greater affinity for the mu than for the kappa and delta receptors. However, dihydroisomorphine also showed considerable affinity for the kappa opioid receptor subtype (Ki 38 nM)

Antinociceptive Effects of Hydromorphone and Several Metabolites in p-Phenylquinone Stretching Test in Mice. (BSFR-98-0923 / Vol. 15, p. 257)

Note: Performing Laboratory: [ ]

[ ] Study Dates: Started on October 26, 1998. Non-GLP study.

Methods: Male ICR mice ([ ] n=8/drug/dose) were administered hydromorphone, 7,8-dihydro-6-beta-hydroxymorphine, 7,8-dihydromorphone-N-oxide monohydrate, 7,8-dihydro-6-beta-hydroxymorphine-6-glucuronide, 7,8-dihydro-6-beta-hydroxymorphine-6-glucoside (1'–α,β mixture), 7,8-dihydromorphone-3-glucoside (test article sources and lot numbers not provided) or vehicle by oral gavage (in distilled water at 0.1 mg/kg, 0.1 ml/10 g body weight). Five doses/test article were tested to generate dose-response curves. At 30 minutes, p-phenylquinone (PPQ) was injected (2 mg/kg IP) and stretches (writhing movements) were counted for 1 minute at 37 minutes and at 42 minutes. Antinociception was defined as inhibition of stretches and %inhibition = [1-#stretches with drug/#stretches without drug] X 100. The tail-flick response was assessed at baseline and at 43 minutes, using a radiant heat lamp as source of thermal stimulus and measurement of the latency to tail flick to indicate pain perception. Antinociceptive effect was defined as % maximum possible effect (%MPE) where %MPE=(test latency – control latency)/(cutoff – control latency) X 100, with a cutoff time of 10 seconds.

Results:

Test Article, PPQ Test	ED50 (mg/kg)	Range (mg/kg)
Hydromorphone	0.75	[
7,8-dihydro-6-beta-hydroxymorphine	2.45	
7,8-dihydromorphone-N-oxide monohydrate	0.98	
7,8-dihydro-6-beta-hydroxymorphine-6-glucuronide	24.38	
7,8-dihydro-6-beta-hydroxymorphine-6-glucoside (1'-α,β mixture)	4.32	
7,8-dihydromorphone-3-glucoside	23.34	]

Test Article, Tail Flick Test	Dose (mg/kg)	%MPE	ED50 (mg/kg)
Hydromorphone	5 (highest dose tested)	29%	ND*
7,8-dihydro-6-beta-hydroxymorphine	0.1 – 10	<20% in all doses	ND
7,8-dihydromorphone-N-oxide monohydrate	0.1	31%	89.9
	1	9%, 32%	
	2	10%, 8%	
	3	38%	
	5	59%	
	10	42%	
7,8-dihydro-6-beta-hydroxymorphine-6-glucuronide	10	26%	91.5
	15	7%	
	20	14%	
	40	13%	
	50	22%	
	70	77%	
7,8-dihydro-6-beta-hydroxymorphine-6-glucoside (1'-α,β mixture)	20 (highest tested)	21%	ND

7,8-dihydromorphone-3-glucoside	60 (highest tested)	17%	ND

*ND: Not Determined.

The following findings on hydromorphone potency and efficacy were reported in the literature:

Species/Model	Route	Results	Reference
Mouse			
Hot Plate	SC	All doses hydromorphone evaluated (2.5-20 mg/kg) were 100% analgesic; ≥4x more potent than morphine	Sacerdote *et al.*, 1997 Br. J. Pharmacol 121:834-40.
Tail flick	IP	Tolerance beginning on day 1 after administration of 1 mg/kg (80% of analgesic response); maximum by day 8 (25% of response)	Shuster *et al.*, 1963 J Pharmacol Exp Ther 40:149-54.
Rat			
Tail flick	IV	ED50 0.28 mg/kg; 5x more potent than morphine	Hennies *et al*, 1988 Arzneim-Forsch/Drug res 38:877-80.
Hot plate (low intensity and high intensity)	SC	ED50 low intensity 0.11 mg/kg, 2.5x more potent than morphine. ED50 high intensity 0.36 mg/kg; 6 x more potent than morphine.	Abram *et al.*, 1997 Anesthesiology 87:127-34.
Cat			
Tail pinch	SC	0.17 mg/kg minimum effective dose; 4.4 times more potent than morphine	Eddy and Reid. 1934 J Pharmacol Exp Ther 52:468-93.
Dog			
Pinch	PO	4 mg/kg is minimum effective dose; 4x more potent than morphine	King et al., 1935. U.S. Treasury Dept, Public Health Service, Suppl. 113 to the Public Health Reports 1-38.
Pinch, pin prick	IP	Pinch analgesia to 5 mg/kg for 4-5 hours; respond to pin prick	Stanton. 1936. J Pharmacol Exp Ther 56:252-263.

Tolerance developed to a lesser extent to hydromorphone-induced respiratory depression and postural and labyrinthine reflexes compared to morphine in rabbits (King et al., 1935 U.S. Treasury Department, Public Health Service, Supplement 113 to the Public Health Reports, p. 1-38). Tolerance was demonstrated in rhesus monkeys (Ternes *et al.*, 1983 Behav Neurosci 97:327-30) and rats (Stanton 1936 J Pharmacol Exp Ther 56:252-263) and cross tolerance with other mu opioids has been demonstrated in rats (King et al., 1935). Hydromorphone was 10x more potent than morphine in inducing lever-press responding in rats, indicating the drug's reinforcing properties and potential addiction liability (Collins and Weeks 1965 Naunyn-Schmiedebergs Arch Exp Path u Pharmak 249:509-14). Indices of hydromorphone dependence were observed on non-treatment days, including irritability, chattering, hunched posture, apprehension, difficult behavior, trembling, and shivering, in rhesus monkeys given hydromorphone at up to 30 mg/kg SC for 85 days (Ternes *et al.*, 1983 Behav Neurosci 97:327-30). Indices of drug withdrawal in dogs given hydromorphone at 2-5 mg/kg SC for 10 weeks included lethargy, apprehension, weight loss and salivation (Eddy and Reid, 1934).

SAFETY PHARMACOLOGY

Secondary pharmacological actions of hydromorphone, related to opioid agonist activity, were reported in the literature:

Organ System	Pharmacological Action	References
Central nervous system	Somnolence (10x more potent than morphine)	King *et al.*, 1935 U.S. Treasury Dept, Public Health Service, Suppl 113 to the Public Health Reports: 1-38; Stanton 1936 J Pharmacol Exp Ther 56:252-63.
	Respiratory depression (decreased rate,	Eddy and Reid 1934 J Pharmacol Exp

	minute volume and tidal exchange, 10x more potent than morphine)	Ther 52:468-93; King *et al*, 1035; Stanton, 1936; Wright and Barbor 1935 J Pharmacol Exp Ther 53:34-45.
	Neuroendocrine inhibition (inhibit gonadotropin-releasing hormone, corticotropin-releasing hormone, leuteinizing hormone, follicle-stimulating hormone, ACTH, beta-endorphin, prolactin, testosterone and cortisol, causes hyperglycemia)	Panerai *et al.*, 1983 Life Sci 32:1751-6.
	Modification of thermoregulation (acute hypothermia, hyperthermia with chronic dosing)	Eddy and Reid, 1934; Eddy 1933 J Am Med Assoc 100:1032-35.
	Nausea and emesis (direct stimulation of chemoreceptor trigger zone in area postrema, 0.1x as potent as morphine)	Eddy and Reid, 1934; Huggins *et al.*, 1949 J Pharmacol Exp Ther 95:318-21.
	Depression of cough reflex	Hennies *et al.*, 1988.
	Other excitatory effects (e.g., convulsions, similar to morphine)	King *et al.*, 1935.
Gastrointestinal tract	Decreased motility	Harned and Curl 1936 J Pharmacol Exp Ther 57:126-7.
	Increased resting tone	King *et al.*, 1935; Gruber and Brundage 1935 J Pharmacol Exp Ther 53:120-36; 445-53; Gruber *et al.*, 1936 J Pharmacol Exp Ther 57:170-8.
Cardiovascular system	Arteriolar and venous dilation (less potent than morphine), Opioids decrease myocardial oxygen consumption by decreasing heart rate, left ventricular end-diastolic pressure and decreasing cardiac work.	Huggins *et al.*, 1949; Reisine and Pasternak 1996 Goodman and Gilman's The Pharmacological Basis of Therapeutics 9th ed,.NY: McGraw-Hill 521-55.
	Decreased myocardial work	Abram *et al.*, 1934.
Metabolic	Hyperglycemia (similar to morphine)	King *et al.*, 1935.
Urogenital system	Decreased uterine tone, inhibit urinary voiding reflex (activity similar to morphine)	Bruber *et al.*, 1935 J Pharmacol Exp Ther 55:430-34; Reisine and Pasternak 1996
Immune system	Immunoinhibitory effects	Panerai *et al.*, 1983.

Hydromorphone-induced respiratory depression is a result of decreased sensitivity of brain stem respiratory centers to increases in PCO_2 and depression of the pontine and medullary centers regulating respiratory rhythm. Nausea and vomiting results from stimulation of the chemoreceptor trigger zone in the medulla oblongata. Hydromorphone induces nausea, emesis and GI disturbances to a lesser extent than does morphine in the dog (Booth and McDonald, 1982, Veterinary Pharmacology and Therapeutics, 5th ed. Ames, Iowa, Iowa State University Press, p. 284). Hydromorphone also decreases gastric, biliary and pancreatic secretions, and affects smooth muscle tone, resulting in constipation. Increased smooth muscle tone and spasms in the urinary tract may induce urinary urgency or induce difficult urination. Stimulation of vasopressin and epinephrine, and inhibition of corticotropin, gonadotropin and thyrotropin release were demonstrated in animals.

PHARMACOKINETICS/TOXICOKINETICS

Absorption

Oral absorption of hydromorphone hydrochloride is approximately 60% (51.35% ± 29.29%, Ritschel, 1987, J. Clin Pharmacol. 27(9):647-53). The bioavailability of controlled-release hydromorphone was not studied. The results of the toxicokinetics analysis in gravid female rats (see Study DSE-176-GLP under Reproductive Toxicology) administered 1, 5, and 10 mg/kg/d hydromorphone hydrochloride by oral gavage on gestation days 6-17 are presented under Pharmacokinetics/Toxicokinetics below. In summary, increases in the maximum plasma levels were less than dose proportional. The Cmax and AUC values on day 17 were twice as high as on day 6 in the high dose group (10 mg/kg/d), but not in the low and mid dose groups, suggesting potential accumulation at high doses.

In gravid rabbits administered 10, 25 and 50 mg/kg/d hydromorphone hydrochloride on gestation days 7 through 19 (see study DSE-178-GLP under Reproductive Toxicology below), peak plasma levels were proportional to dose on both days 7 and 19 and were similar on both days, suggesting no accumulation with repeated dosing at up to 50 mg/kg/d. In another study in rabbits given 5 mg/kg IV and 20 mg/kg PO hydromorphone, the oral bioavailability was approximately 20%.

Distribution

No reports on hydromorphone distribution in animals were found in the published literature, nor were generated by the sponsor. In humans, hydromorphone is distributed to skeletal muscle, kidneys, intestinal tract, liver, spleen, lungs and the brain, and crosses the placenta (Ellenhorn and Barceloux, 1988, Medical Toxocology – Diagnosis and Treatment of Human Poisoning, New York, NY: Elsevier Science Publishing Co., Inc., p. 749).

Metabolism

Hydromorphone hydrochloride is extensively metabolized by hepatic oxidation and conjugation. Some metabolism also occurs in the CNS, kidneys, lungs, and placenta (American Hospital Formulary Service – Drug Information 89. Bethesda, MD: Amer. Soc . of Hospital Pharmacists, 1989 (Plus Supplements), 1026). The major metabolites in rats, rabbits and humans are hydromorphone-3-glucuronide and dihydromophine-6-glucuronide. Hydromorphone-3-glucoside and dihydromorphine-6-glucoside are also found in human plasma, and in trace amounts in rabbit plasma. No glucosides were found in rat plasma. The metabolic profile of hydromorphone is similar in plasma, urine and human hepatocyte incubate. In urine the major hydromorphone metabolites are hydromorphone-3-glucuronide (22%-51%, Reynolds and Prasad, eds. Martindale – The Extra Pharmacopoeia. 28th ed. London: The Pharmaceutical Press, 1982. 1014), hydromorphone-3-glucoside, dihydromorphine-6-glucuronide and dihydromorphine-6-glucoside, and the minor metabolites are dihydromorphine and dihydroisomorphine.

Hydromorphone Metabolites Identified by [ ] from Different Biological Samples. (PKDM HD0998-metab.001 / Vol. 15, p. 299).

Note: Testing Facility: Purdue International R&D, 99-101 Saw Mill River Road, Yonkers, NY. Study Dates: 6 studies conducted between October, 1995 and August 1998. Non-GLP studies.

Methods:
The following studies were conducted to determine the metabolic profile of hydromorphone in the controlled-release product compared to the metabolism of hydromorphone in immediate-release form:

Study Number Protocol Number	Study Title	Dose	Dates
HD98-0505 HD98-0505	A phase I single-dose, crossover study to evaluate the comparative bioavailability of immediate-release hydromorphone and Dilaudid®	6 mg IR hydromorphone	6/24/98-11/6/98
HD 95-0702 HD 95-0702	A multiple dose, two treatment, randomized, crossover, analytically blinded pharmacokinetic/pharmacodynamic comparison study of hydromorphone hydrochloride controlled-release capsules 12 mg once daily (HHCR 12 mg) and hydromorphone hydrochloride immediate-release 3 mg Q6H (HHIR 3 mg)	HHCR 12 mg OD and HHIR 3 mg Q6H	7/9/96-7/26/96
M98-015 M-041798-01	Production of hydromorphone metabolites after *in-vitro* exposure in human hepatocyte suspensions	-	6/8/98-8/3/98
DSE-176-GLP 96060	An Oral teratology (reproduction segment II) study of hydromorphone HCl in the rat	1, 5, and 10 mg/kg/d	2/13/97-8/3/98
DSE-178-GLP 96062	An oral teratology (reproduction segment II) study of hydromorphone HCl in the rabbit	10, 25 and 50 mg/kg/d	1/13/97-8/3/98
014.002	Double-blind, randomized, cross-over, comparison of the dose equivalence, clinical efficacy, safety and steady-state pharmacokinetics of controlled-release oxycodone and controlled-release hydromorphone in chronic cancer pain	36 mg q12h	10/19/95-8/4/98

In study HD98-0505, plasma was sampled at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 18 and 24 hours. In study HD95-0702, steady-state hydromorphone metabolites in human plasma were analyzed. Five plasma samples, collected on day 1 (0 hr), day 2 (0 hr), day 5 (0-6 hr pooled), day 5 (6.25-12 hr pooled) and day 5 (12.25-24 hr pooled) were analyzed for each condition (controlled release 12 mg and immediate release 3 mg Q6H hydromorphone hydrochloride). Hydromorphone metabolites from human patient urine were analyzed in study 014.002. In the in vitro study, suspended human hepatocytes were incubated with hydromorphone (100 mcg/ml) at 37degC for 4 hours. Negative controls were hepatocytes in incubation media alone and incubation media without hepatocytes. Fresh urine was spiked with hydromorphone, alone and combined with various combinations of hydromorphone-3-glucuronide, dihydromorphine, dihydromorphine-6-glucuronide, and hydromorphone-N-oxide to study the stability of hydromorphone in human urine and to determine if hydromorphone-N-oxide is produced in urine.

Hydromorphone metabolites were identified in rat and rabbit plasma. For methods, see studies DSE-176-GLP and DSE-178-GLP under Reproductive Toxicology.

Results:

Hydromorphone Metabolites From fresh Human Plasma (Immediate-Release Formulation, Study HD98-0505)

	Abundance Relative to Parent Drug (at 0.25-2.0 hours[A])	Retention Time (minutes, from samples at 0.25-2.0 hours[A])	[ ]
Hydromorphone	100%		
Hydromorphone-3-glucuronide	3273%		
Dihydromorphine-6-glucuronide	1078%		
Dihydromorphine	1%		
Dihydro-iso-morphine	22%		
Hydromorphone-3-glucoside	110%		
Dihydromorphine-6-glucoside	37%		

[A] Time period of highest concentration.

[B] [ ]

Hydromorphone Metabolites Identified from Human Plasma (Study HD95-0702)

	Abundance Rel. to Parent	Retention Time (minutes)
From Controlled-Release formulation, Fraction CR5, 12.25-24 hr		
Hydromorphone	100%	
Hydromorphone-3-glucuronide	890%	
Dihydromorphine-6-glucuronide	120%	
Dihydromorphine	10%	
Dihydro-iso-morphine	32%	
Hydromorphone-3-glucoside	450%	
Dihydromorphine-6-glucoside	67%	
From Immediate-Release formulation, Fraction IR5, 12.25-24 hr		
Hydromorphone	100%	
Hydromorphone-3-glucuronide	1550%	
Dihydromorphine-6-glucuronide	290%	
Dihydromorphine	1.6%	
Dihydro-iso-morphine	66%	
Hydromorphone-3-glucoside	610%	
Dihydromorphine-6-glucoside	155%	

Hydromorphone Metabolites Identified from Human Urine (Study 014.002)

	Abundance Rel. to Parent	Retention Time (minutes)
Hydromorphone	100%	
Hydromorphone-3-glucuronide	290%	
Dihydromorphine-6-glucuronide	85%	
Dihydromorphine	1.4%	
Dihydro-iso-morphine	17%	
Hydromorphone-3-glucoside	100%	
Dihydromorphine-6-glucoside	47%	

Hydromorphone Metabolites Identified from *in vitro* Human Hepatocyte Supernatant (Study M98-015)

	Retention Time (minutes)
Hydromorphone	
Hydromorphone-3-glucuronide	
Dihydromorphine-6-glucuronide	
Dihydromorphine	
Dihydro-iso-morphine	
Hydromorphone-3-glucoside	
Dihydromorphine-6-glucoside	

The stability study demonstrated the presence of hydromorphone-N-oxide at — in urine spiked with hydromorphone with and without hydromorphone-3-glucuronide, dihydromorphine and dihydromorphine-6-glucuronide, in both fresh urine and in urine that was frozen for 5 weeks. Hydromorphine-3-glucoside and dihydromorphine-6- glucoside were not found in the urine, suggesting that the compounds are metabolites of hydromorphone. No hydromorphone-N-oxide was found in the [ ] extracted reagent blank and extracted urine blank, or in the reference standards, suggesting that the compound be not formed as a result of the sample preparation or from [ ] analysis.

Hydromorphone Metabolites Identified from Rat plasma (DSE-176-GLP)

	Abundant Relative to Parent	Retention Time (minutes)
Hydromorphone	100%	
Hydromorphone-3-glucuronide	1500%	
Dihydromorphine-6-glucuronide	39%	
Dihydromorphine	7.3%	

Hydromorphone Metabolites Identified from Human Plasma (Study HD95-0702)

	Abundance Rel. to Parent	Retention Time (minutes)
From Controlled-Release formulation, Fraction CR5, 12.25-24 hr		
Hydromorphone	100%	
Hydromorphone-3-glucuronide	890%	
Dihydromorphine-6-glucuronide	120%	
Dihydromorphine	10%	
Dihydro-iso-morphine	32%	
Hydromorphone-3-glucoside	450%	
Dihydromorphine-6-glucoside	67%	
From Immediate-Release formulation, Fraction IR5, 12.25-24 hr		
Hydromorphone	100%	
Hydromorphone-3-glucuronide	1550%	
Dihydromorphine-6-glucuronide	290%	
Dihydromorphine	1.6%	
Dihydro-iso-morphine	66%	
Hydromorphone-3-glucoside	610%	
Dihydromorphine-6-glucoside	155%	

Hydromorphone Metabolites Identified from Human Urine (Study 014.002)

	Abundance Rel. to Parent	Retention Time (minutes)
Hydromorphone	100%	
Hydromorphone-3-glucuronide	290%	
Dihydromorphine-6-glucuronide	85%	
Dihydromorphine	1.4%	
Dihydro-iso-morphine	17%	
Hydromorphone-3-glucoside	100%	
Dihydromorphine-6-glucoside	47%	

Hydromorphone Metabolites Identified from *in vitro* Human Hepatocyte Supernatant (Study M98-015)

	Retention Time (minutes)
Hydromorphone	
Hydromorphone-3-glucuronide	
Dihydromorphine-6-glucuronide	
Dihydromorphine	
Dihydro-iso-morphine	
Hydromorphone-3-glucoside	
Dihydromorphine-6-glucoside	

The stability study demonstrated the presence of hydromorphone-N-oxide a' ——— in urine spiked with hydromorphone with and without hydromorphone-3-glucuronide, dihydromorphine and dihydromorphine-6-glucuronide, in both fresh urine and in urine that was frozen for 5 weeks. Hydromorphine-3-glucoside and dihydromorphine-6- glucoside were not found in the urine, suggesting that the compounds are metabolites of hydromorphone. No hydromorphone-N-oxide was found in the [ ] extracted reagent blank and extracted urine blank, or in the reference standards, suggesting that the compound be not formed as a result of the sample preparation or from [ ] analysis.

Hydromorphone Metabolites Identified from Rat plasma (DSE-176-GLP)

	Abundant Relative to Parent	Retention Time (minutes)
Hydromorphone	100%	
Hydromorphone-3-glucuronide	1500%	
Dihydromorphine-6-glucuronide	39%	
Dihydromorphine	7.3%	

Dihydro-iso-morphine	3.4%	[			J
Hydromorphone-3-glucoside	ND*				
Dihydromorphine-6-glucoside	ND*				

*ND: Not Detected.

Hydromorphone Metabolites Identified from Rabbit Plasma (DSE-178-GLP)

	Abundant Relative to Parent	Retention Time (minutes)	[			J
Hydromorphone	100%	[				
Hydromorphone-3-glucuronide	5100%					
Dihydromorphine-6-glucuronide	600%					
Dihydromorphine	42%					
Dihydro-iso-morphine	23%					
Hydromorphone-3-glucoside	6.3%					ND
Dihydromorphine-6-glucoside	0.8%				J	ND

*ND: Not Detected.

Excretion

Hydromorphone excretion is primarily renal. In a metabolism study, guinea pigs, rats and rabbits were administered hydromorphone hydrochloride at 5 mg SC and urine was collected at 24 hour intervals for 2 days for analysis by — The results showed 60%-95% urinary recovery of parent drug, the conjugated metabolites and the 6-hydroxy metabolites dihydromorphine and dihydroisomorphine combined, in the urine.

Pharmacokinetics/Toxicokinetics

Toxicokinetic Aspects of "An Oral Teratology (Reproduction Segment II) Study of Hydromorphone in the Rat (DSE-176-GLP PKDM / Vol. 13, p. 388)

Note: See study DSE-176-GLP under Reproductive Toxicology.

Methods: See study DSE-176-GLP under Reproductive Toxicology. The rats received 1, 5, and 10 mg/kg/d hydromorphone HCl by oral gavage on gestation days 6-17. Plasma samples were collected (n=4/timepoint/dose group) on gestation days 6 and 17 at 0.5, 1, 3 and 6 hours after dosing and were analyzed by [J

Results:

Mean Hydromorphone Plasma Concentration (ng/ml, n=4))

Dose (mg/kg/d PO)	Gestation Day 6				Gestation Day 17			
	0.5 hr	1 hr	3 hr	6 hr	0.5 hr	1 hr	3 hr	6 hr
1	4.50	3.42	1.86	0.97	3.86	2.77	2.00	1.39
5	16.6	12.2	5.64	8.88	16.8	14.5	7.71	5.24
10	20.7	14.7	11.6	9.92	40.1	31.5	19.1	13.6

Hydromorphone Pharmacokinetic Parameters

	Day 6			Day 17		
Dose (mg/kg/d PO)	1 mg/kg/d	5 mg/kg/d	10 mg/kg/d	1 mg/kg/d	5 mg/kg/d	10 mg/kg/d
Cmax (ng/ml)	4.50	16.6	20.7	3.86	16.8	40.1
Tmax (h)	0.5	0.5	0.5	0.5	0.5	0.5
AUC 0-6 (ng.h/ml)	12.6	51.0	72.6	12.5	53.7	128
AUC 0-24 (ng.h/ml)	21.4	131	162	25.0	101	250

Toxicokinetic Aspects of "An Oral Teratology (Reproduction Segment II) Study of Hydromorphone in the Rabbit" (DSE-178-GLP PKDM / Vol. 14, p. 425)

Note: See study DSE-178-GLP under Reproductive Toxicology

Methods: See study DSE-178-GLP under Reproductive Toxicology. The rabbits received 10, 25, and 50 mg/kg/d hydromorphone HCl by oral gavage on gestation days 7-19. Plasma samples were collected (n=4/timepoint/dose group) on gestation days 7 and 19 at 0.25, 0.5, 1, 2, 4 and 8 hours after dosing and were analyzed by [redacted]

Results:

Mean Hydromorphone Plasma Concentration (ng/ml, n=4) in Gravid Rabbits

Dose (mg/kg/d PO)	Gestation Day 7						Gestation Day 19					
	0.25hr	0.5hr	1 hr	2 hr	4 hr	8 hr	0.25hr	0.5hr	1 hr	2 hr	4 hr	8 hr
10	15.3	15.1	16.2	10.2	7.17	1.84	18.0	19.6	22.4	16.0	7.01	1.73
25	38.2	41.1	29.7	21.2	17.3	9.72	358*	110	83.9	44.1	13.5	11.2
50	24.7	30.0	44.1	28.3	87.5	28.5	68.9	50.7	64.9	57.7	44.3	26.7

*Due to extreme high plasma level in one animal ([redacted] ng/ml).

Hydromorphone Pharmacokinetic Parameters in Gravid Rabbits

	Day 7			Day 19		
Dose (mg/kg/d PO)	10 mg/kg/d	25 mg/kg/d	50 mg/kg/d	10 mg/kg/d	25 mg/kg/d	50 mg/kg/d
Cmax (ng/ml)	17.3	49.7	87.5	22.4	487*	85.8
Tmax (h)	0.6	1.7	4.0	1.0	0.9	0.6
AUC 0-6 (ng.h/ml)	61.9	150	431	87.4	430	357
AUC 0-24 (ng.h/ml)	76.6	228	659	101	550	570

*Due to extreme high plasma level in one animal ([redacted] ng/ml).

TOXICOLOGY

Single Dose Toxicology

In acute studies, parenteral hydromorphone was approximately 3x-9x more toxic than morphine. Acute hydromorphone toxicity in rats and/or rabbits included reduced activity, incoordination, increased heart rate, salivation, increased muscle tone, focused gaze, ptosis, absent feces, dehydration, respiratory depression, excitation, convulsions and at high doses, deaths.

Summary of Hydromorphone Acute Toxicity Study Results*

Species	Dosage form	Route	LD_{50} (mg/kg)	LD_{LO} (mg/kg)
Mouse	Hydromorphone base	Intravenous	104	NR
Mouse	Hydromorphone HCl salt	Subcutaneous	84	NR
Mouse	Hydromorphone base	Intravenous	55	NR
Mouse	Hydromorphone HCl salt	Subcutaneous	120	NR
Rat	Hydromorphone base	Subcutaneous	51	NR
Rabbit	Hydromorphone HCl salt	Intravenous	NR	2.5
Cat	Hydromorphone base	Intravenous	NR	3

*Source: Registry of Toxic Effects of Chemical Substances (RTECS), 1995; NR: Not reported.

Repeated Dose Toxicology

A non-GLP 12-day range finding toxicity study (see DSE-173 under Reproductive Toxicology below) in female rats administered 50, 100, 150 or 200 mg/kg/d hydromorphone hydrochloride (n=5) showed 1 death at 50 mg/kg/d (day 5), 2 deaths at 150 mg/kg/d (days 4 and 6) and 1 death at 200 mg/kg/d (day 4). Decreased body weights were observed at all doses, and clinical signs were consistent with opioid drug effects and similar to those observed after single dose administration (reduced activity, incoordination, increased heart rate, shallow breathing, increased muscle tone, rigidity, focused gaze, salivation and unresponsive to external stimuli). Macroscopic observations at necropsy were pale discoloration of the kidneys, dilatation of the ureters, and urinary bladder dilatation, thickening, dark discoloration, pale/dark areas, clots and dark fluid.

A non-GLP subchronic toxicity study was conducted in female rabbits (see DSE-174 under Reproductive Toxicology below), administered 0, 10, 25, 50 or 100 mg/kg/d hydromorphone (n=5) for 13 consecutive days, to determine the dose for the subsequent teratology study. There were 2 deaths at 100 mg/kg/d (day 1). Clinical signs at 50-100 mg/kg/d were reduced activity, decreased muscle tone and dilated or constricted pupils. Treatment-related gross pathology observations were spongy/collapsed lungs, dark areas and pale or dark frothy fluid in the lungs, bronchi or trachea.

In a subchronic toxicity study reported in the literature (Beck et al., 1998, Pharmacokinetics Following Oral Administration of Immediate-Release and Continuous Release Hydromorphone Hydrochloride to Dogs. Toxicological Sciences 42(1S:47): Abstract 231), beagle dogs were given hydromorphone in a controlled-release formulation at 0, 8, or 64 mg/d, or in an immediate-release formulation at 64 mg/d for 30 days. Decreased body weights were observed in both groups administered 64 mg/d, and clinical signs consistent with known effects of opioid drugs were observed at all active doses. Necropsy results were not reported.

There are no literature reports or sponsor toxicology studies on chronic hydromorphone administration.

CARCINOGENICITY

No studies have been conducted to evaluate the carcinogenic potential of hydromorphone hydrochloride.

REPRODUCTIVE TOXICOLOGY

A Preliminary Acute and 12-Day Oral Gavage Range Finding Toxicity Study of Hydromorphone Hydrochloride in the Female Albino Rat (DSE-173/ Vol. 12, p. 2)

Note: Project Number 87524. Performing Laboratory: [redacted] Study Dates: April 3, 1996 – May 8, 1996. Non-GLP study; however, signed GLP statement present.

Methods: Female Sprague-Dawley CD [redacted] CD®(SD)BR) VAF Plus rats ([redacted] ages 70 days, weights 224-291 g, n=1 [groups 1-4], n=2 [groups 5-8], n=5 [groups 9-13]) were administered hydromorphone HCl (Purdue Frederick Co., Norwalk, CN, Lot No. 3245-SPE-135, in deionized water [redacted] 10 ml/kg) by oral gavage according to the following schedule. Phase I animals were given a single dose at **10, 100, 500, or 1000 mg/kg** in groups 1-4, **100, 250, 500 or 750 mg/kg** in groups 5-8. Phase II animals (groups 9-13) received daily test article at **0, 50, 100, 150 or 200 mg/kg/d** for 12 days. Groups 1-4 were observed for 5 days and groups 5-8 were observed for 14 days after

dosing. The observations were mortality, moribundity and clinical signs (2x daily), body weights (baseline and weekly), rectal body temperature (baseline and day 1 at 0, 0.5, 1, 4 and 6 hours after dosing), and gross pathology.

Results:

Phase I	Dose (mg/kg)	Dose Schedule	#Deaths	Day & Type of Death	Related findings
	100	Single Dose	1	Day 1/Found dead	*Gross pathological findings in kidneys, ureters and urinary bladder (dilatation, discoloration)
	500	Single Dose	2	Day 2/Found dead* Day 2/Euthanized*	
	750	Single Dose	2	Day 2/Euthanized* Day 2/Euthanized*	
	1000	Single Dose	1	Day 3/Euthanized*	
Phase II	50	Daily/ 12 days	1	Day 5/Found dead*	
	150	Daily/ 12 days	2	Day 4/Found dead* Day 6/Found dead*	
	200	Daily/12 days	1	Day 4/Found dead	

The treatment-related clinical signs in groups 1-4 were decreased activity and respiratory rate, increased muscle tone, focused gaze and unresponsiveness to external stimuli, observed from 1 hour after dosing and lasting for approximately 6 hours. The high dose female (1000 mg/kg) showed signs of reduced activity and was dazed for up to 3 days and also showed black fur staining (dried blood), absent feces and dehydration. The signs were characteristic of opioid overdose. Groups 5-8 showed treatment-related reduction in activity, loss of coordination, increased heart rate, shallow breathing, increased muscle tone/rigidity, focused gaze and lack of response to external stimuli within 1 hour of dosing. Head bobbing was observed in the animals given 100 mg/kg and greater doses, abdominal/vaginal region bleeding in rats given 250-500 mg/kg, and convulsions or tremors in rats given 1000 mg/kg. The signs in the group 5-8 animals lasted for two days. Phase II rats showed treatment-related signs similar to those observed in the single dose Phase I animals described above. Additionally, blood staining was observed throughout dosing and red vaginal discharge was seen on day 2.

There were no treatment-related effects on body weights in the single-dose animals. The Phase II rats showed decreased body weights at days 7 (12% decrease at 150 mg/kg/d compared to 2% increase in controls) and 13 (15%, 17%, 17% and 14% decreases at 50, 100, 150 and 200 mg/kg/d compared to 4.8% decrease in controls). Decreased body temperature was observed at 500-1000 mg/kg lasting up to 6 hours after dosing.

Treatment-related effects were observed in the gross examination at necropsy in animals treated at 500-1000 mg/kg single dose and 50-200 mg/kg/d for 12 days. The gross findings were pale discoloration of the kidneys, unilateral/bilateral dilatation of the kidney pelvis, ureters and urinary bladder, and discoloration, pale/dark areas, clots and dark fluid in the urinary bladder. The NOAEL was not established in the single and repeated dose studies.

A Preliminary Acute and 13-Day Range Finding Oral Gavage Toxicity Study of Hydromorphone Hydrochloride in the Female Albino Rabbit (DSE-174/ Vol. 12, p. 112)

Note: Project Number 87526. Performing Laboratory: [ ] Study Dates: April 3, 1996 – November 25, 1996. Non-GLP study; however, signed GLP statement present.

Methods: New Zealand White rabbits (SPF strain, [ ] ages 19-20 weeks, weights 3.1-4.0 kg, n=1 in groups 1-4, n=2 in groups 5-8 and n=5 in groups 9-13) were given a single dose of hydromorphone HCl (Purdue Frederick Co., Norwalk, CT, Lot No. 3245-SPE-135, in deionized

water [ ] (10 ml/kg) by oral gavage at **10, 100, 500 and 1000 mg/kg** in Phase I groups 1-4 respectively, and at **50, 175, 250 and 360 mg/kg** in Phase I groups 5-8 respectively. The Phase II rabbits received **0, 10, 25, 50 or 100 mg/kg/d** hydromorphone (10 ml/kg) by oral gavage, daily for 13 days. Phase I groups 1-4 rabbits were observed for 5 days after dosing, groups 9-13 were observed for 14 days after dosing, and Phase II rabbits (groups 9-13) were sacrificed at the end of the 13-day dosing period). The observations were mortality, moribundity and clinical signs (2x daily), body weights (baseline and weekly), rectal body temperature (baseline and day 1 at 0, 0.5, 1, 4, and 6 hours after dosing), and gross pathology at sacrifice.

Results: Treatment related deaths were observed at 100 mg/kg (2/6 rabbits, one was a replacement) 175 mg/kg (1/2 rabbits), 250 mg/kg (2/2 rabbits), 350 mg/kg (2/2 rabbits), 500 mg/kg (1/1 rabbit), and 1000 mg/kg (1/1 rabbit), between 24 minutes and 10.5 hours after receiving a single dose. Treatment-related clinical signs in the single dose groups, at ≥ 100 mg/kg were reduced activity, decreased respiratory rate, increased/decreased muscle tone, constricted/dilated pupils, and convulsions/spasms, beginning an hour after dosing and lasting up to 8 hours. Reduced activity was observed at 50 mg/kg. In the repeated dosing groups, treatment-related clinical signs of reduced activity, decreased muscle tone, and dilated/constricted pupils were observed at 50-100 mg/kg/d on days 1-3 beginning an hour after dosing.

There were no effects on body weights and temperature at single oral doses of hydromorphone HCl of up to 1000 mg/kg in the rabbits. In the repeated dosing groups, body weights were reduced slightly at 50 and 100 mg/kg/d in the 7-day evaluation. Treatment-related gross pathology findings were uncollapsed lungs with dark areas, and pale, frothy bronchial and tracheal fluid at 5 days after single doses of 500 and 1000 mg/kg (Groups 3 and 4, all rabbits) and at 14 days after single doses of 50-350 mg/kg (Groups 5-8, all rabbits). Similar gross pathology was observed at 10 (1/5 rabbits) and 100 mg/kg/d (2/5 rabbits) hydromorphone HCl for 13 days (Groups 9-13).

An Oral Range-Finding Teratology (Reproduction Segment II) Study of Hydromorphone Hydrochloride in the Rat (DSE-175/Vol. 12, p. 220)

Note: Project Number 96059. Performing Laboratory: [ ] Study Dates: November 20, 1996 – December 18, 1996. Non-GLP study; however, signed GLP statement present.

Methods: Mated female Sprague-Dawley CD [ ] CD®(SD)BR rats [ ] ages approximately 75 days, weights 231-263 g, n=6/dose group) were administered hydromorphone HCl (Purdue Frederick Co., Norwalk, CN, Lot No. 3245-SPE-135, at **0, 7.5, 15, 30 or 60 mg/kg/d**, in deionized water [ ] at 10 ml/kg/d) once daily by oral gavage on gestation days 6 through 17 inclusively. The observations were mortality, moribundity and clinical signs (2x daily), body weights (baseline and on gestation days 0, 6, 9, 12, 15, 18 and 20), food consumption (during intervals from gestation days 0-6, 6-9, 9-12, 12-15, 15-18 and 18-20), gross pathology including corpora lutea count, weight of gravid uterus, number and position of live and dead fetuses, early, middle and late resorptions, and implantation sites. Fetal observations included external examinations, weights, and sex.

Results: No mortality was observed. Maternal signs at 15, 30 and 60 mg/kg/d PO hydromorphone HCl were reduced activity, shallow breathing, decreased respiration and heart rate, dilated pupils, pale or enlarged eyes, ocular discharge, teeth grinding, muscle rigidity, abnormal gait, self mutilation, and red fur staining, on all dosing days. Decreased muscle tone, weakness, staring and unresponsiveness to external stimuli were observed at 30 and 60 mg/kg/d. Maternal body weight gains were reduced at 7.5 (19% and 28% increase on days 15 and 18 respectively compared to 29% and 44% increases in the control, same days), 15 (7%, 10%, 14%, and 29% increases on days 12, 15, 18 and 20 respectively compared to 24%, 29%, 44% and 58% increase in controls,

same days), 30 (6%, 8%, 16% and 31% increases on days 12, 15, 18 and 20 respectively compared to 24%, 29%, 44% and 58% increases in controls, same days) and 60 (6%, 8%, 9%, and 21% on days 12, 15, 18 and 20 compared to 24%, 29%, 44% and 58% increases in controls, same days) mg/kg/d. Food consumption was reduced in all hydromorphone-treated groups during dosing, and at 60 mg/kg/d after dosing ceased, during the interval from days 18-20. Gross pathology showed depressed or raised areas, capsular adhesion, and dilatation of the kidney pelvis, pale fluid in the kidney pelvis and ureter dilation at 30 and 60 mg/kg/d. At the high dose (60 mg/kg/d) a raised area in the adrenal was seen in one female.

The pregnancy rates (#pregnant rats/#mated rats) were 83.3% in the control and 30 mg/kg/d groups and 100% in all other groups. There were no treatment-related effects on number of implantation sites, live and dead fetuses, early, middle or late resorptions or pre (% preimplantation loss = [#corpora lutea - #implants]x100/#corpora lutea) and post implantation (% post implantation loss = [#implants - #live fetuses]x100/#implants) losses. Total resorption was observed in one high dose female rat. There were no minor abnormalities or major malformations in the fetuses. Fetal weights were slightly decreased (94% of control values) at 60 mg/kg/d.

Based on the results of this study, 10 mg/kg/d was selected as the high dose in the main study (see below).

An Oral Teratology (Reproduction Segment II) Study of Hydromorphone Hydrochloride in the Rat (DSE-176-GLP/Vol. 13, p. 1)

Note: Project Number 96060. Performing Laboratory: [redacted] Study Dates: February 4, 1997 – March 6, 1997. GLP and Quality Assurance statements signed and present.

Methods: Mated female Sprague-Dawley CD – CD®(SD)BR rats [redacted] ages approximately 69-75 days, weights 205-296 g, n=25/dose group in the main study, n=8/dose in the TK Phase) were administered hydromorphone HCl (Purdue Frederick Co., Norwalk, CN, Lot No. 3245-SPE-135, at **0, 1, 5 or 10 mg/kg/d**, in deionized water [redacted] at 10 ml/kg/d) once daily by oral gavage on gestation days 6 through 17 inclusively. The observations were mortality and moribundity (2x daily), clinical examinations (on the days of body weight measurement), clinical signs (2x daily), body weights (baseline and days 0, 6, 9, 1, 15, 18 and 20), food consumption (for the intervals of days 0-6, 6-9, 9-12, 12-15, 15-18 and 18-20), toxicokinetics (1ml blood collected from tail vein at 0.5, 1, 3 and 6 hours after dosing), total number of fetuses in each uterine horn, gross pathology, uterus weight, uterine contents, placentas, number and position of live fetuses, dead fetuses, early, middle and late resorptions and empty implantation sites. Fetal examinations included weights, and external, internal and skeletal examination.

Results: There were no treatment-related deaths or clinical signs in the maternal rats at up to 10 mg/kg/d hydromorphone HCl. Maternal body weight gains were reduced at 5 (20%, 32% and 43% increases at 15, 18 and 20 days gestation compared to 27%, 42% and 54% increases in control rats, same days) and 10 mg/kg/d (13%, 16%, 27% and 33% increases on gestation days 12, 15, 18 and 20, compared to 22%, 27%, 42% and 54% increases in controls, same days). Food consumption was reduced at 5 and 10 mg/kg/d, beginning in the interval of gestation days 6-9 and lasting to the interval of gestation days 18-20. There were no treatment-related gross pathology observations in the maternal rats, except multiple pale areas on the dorsal surface of the left lobe of the liver in one high-dose female.

The pregnancy rates (#pregnant rats/#mated rats) were similar across control and treated groups (≥91%). There were no treatment-related effects on the numbers of corpora lutea, implantation sites, live and dead

fetuses, early, middle and late resorptions, sex ratios and pre (% preimplantation loss = [#corpora lutea - #implants]x100/#corpora lutea) and post implantation (%post implantation loss = ([#implants - #live fetuses]x100/#implants) losses.

There were no treatment-related effects on fetal weights, major malformations, minor external and visceral anomalies, or minor skeletal anomalies. Ossification of the hyoid bone was slightly reduced at 10 mg/kg/d. The percent fetuses with thoracic centrum variants was slightly increased at 10 mg/kg/d.

The results of the toxicokinetics analysis are presented under Pharmacokinetics above. The peak plasma levels, increased with dose, but were not dose proportional on day 6 (4.5, 16.6 and 20.7 ng/ml at 1, 5 and 10 mg/kg/d respectively). The Cmax values in the 1 and 5 mg/kg/d groups on day 17 (3.86 and 16.8 ng/ml respectively) were similar to those on day 6, but the peak plasma level in the high dose group (40.1 ng/ml at 10 mg/kg/d) was 2x higher, suggesting drug accumulation at the high dose. Likewise, exposure (AUC_{0-24}) values were similar after 1 and 5 mg/kg/d doses on day 6 (12.4 and 131 ng.h/ml respectively) and day 17 (25.0 and 101 ng.h/ml respectively), but the AUC after the high dose (10 mg/kg/d) was higher on day 17 (250 ng.h/ml) than on day 6 (162 ng.h/ml). The time to peak plasma level (tmax) was 0.5 h regardless of day and dose.

An Oral Range Finding Teratology Study of Hydromorphone Hydrochloride in the Rabbit (DSE-177/Vol. 14, p. 1)

Note: Project Number 96061. Performing Laboratory: [redacted] Study Dates: November 15, 1996 – December 10, 1996. Non-GLP study; however, signed GLP statement present.

Methods: Timed pregnant New Zealand White rabbits (*Oryctolagus cuniculus*, SPF strain, [redacted] ages approximately 26 weeks, weights 3.3-4.0 kg, n=5/dose group) were administered hydromorphone HCl (Purdue Frederick Co., Norwalk, CN, Lot No. 3245-SPE-135, at **0, 10, 25, 50 or 75 mg/kg/d**, in deionized water [redacted] at 10 ml/kg/d) once daily by oral gavage on gestation days 7 through 19 inclusively. The rabbits were euthanized on gestation day 29. The observations were mortality, moribundity and clinical signs (2x daily), body weights (baseline and on gestation days 0, 7, 9, 12, 15, 18, 21, 24 and 29), food consumption (daily beginning on gestation day 5), gross pathology including corpora lutea count, weight of gravid uterus, number and position of live and dead fetuses, early, middle and late resorptions, and empty implantation sites. Fetal observations included external examinations, weights, and sex.

Results: There were no maternal deaths. The treatment-related clinical signs were decreased defecation, shallow breathing, decreased respiratory rate, dilated pupils, ptosis, lying flat, thin fur on paws/limbs/abdominal region/urogenital region, decreased activity, rigidity or flaccid body, in the animals that received 50 and 75 mg/kg/d hydromorphone HCl. There were occasional observations of decreased defecation at 10 and 25 mg/kg/d. Maternal body weight gains were reduced at 25 (2% and 5% increases on days 21 and 24 respectively compared to 9% and 13% increases in controls, same days), 50 (0% and 2% increases on days 21 and 24 respectively compared to 9% and 13% increases in controls, same days) and 75 (2% increase compared to 13% increase in the controls, day 29) mg/kg/d, and body weights were reduced at 75 mg/kg/d by 4%, 7% and 6% on days 18, 21 and 24 respectively. Body weights remained lower in the high-dose group after the end of treatment, through days 21-29. Maternal food consumption was reduced from gestation days 8 through 22 in the rabbits that received 25, 50 and 75 mg/kg/d. Food consumption was 34%-63% lower than the control level at 25 mg/kg/d, 45%-76% lower at 50 mg/kg/d and 60%-95% at 75 mg/kg/d. The decrease in food consumption was reversible during the recovery period. There were no treatment-related gross pathology findings.

The pregnancy rates were 100% in all groups. There were no treatment-related effects on numbers of corpora lutea, implantation sites, live and dead fetuses, early, middle or late resorptions, or pre (% preimplantation loss = [#corpora lutea - #implants]x100/#corpora lutea) and post implantation (% post implantation loss = [#implants - #live fetuses]x100/#implants) losses.

Fetal weights were reduced at 75 mg/kg/d to 87% of the control fetal weights. There were no treatment-related major fetal malformations or minor fetal anomalies.

Based on the results of this study, 50 mg/kg/d was selected as the high dose for the main study (described below).

An Oral Teratology (Reproduction Segment II) Study of Hydromorphone Hydrochloride in the Rabbit (DSE-178-GLP/ Vol. 14, p. 135)

Note: Project Number 96062. Performing Laboratory: [ ] Study Dates: January 3, 1997 – February 11, 1997. GLP and Quality Assurance statements signed and present.

Methods: Timed mated female New Zealand White rabbits (*Oryctolagus cuniculus*, SPF strain, [ ] ages approximately 23-24 weeks, weights 3.1-4.0 kg, n=10/dose group in the main study and 4/dose group in the Toxicokinetic Phase) were administered hydromorphone HCl (Purdue Frederick Co., Norwalk, CN, Lot No. 3245-SPE-135, at **0, 10, 25, or 50 mg/kg/d**, in deionized water [ ] at 10 ml/kg/d) once daily by oral gavage on gestation days 7 through 19 inclusively. The rabbits were euthanized on gestation day 29. The observations were mortality, moribundity and clinical signs (2x daily), body weights (baseline and on gestation days 7, 9, 12, 15, 18, 21, 24 and 29), food consumption (daily beginning on gestation day 5), gross pathology including corpora lutea count, weight of gravid uterus, number and position of live and dead fetuses, early, middle and late resorptions, and empty implantation sites. Fetal observations included external and internal examinations, skeletal examinations, weights, and sex. Toxicokinetic sampling (1.5 ml, marginal ear vein) was conducted in the satellite groups after the first dose on gestation day 7 and after the last dose on gestation day 19 at 0.25, 0.5, 1, 2, 4 and 8 hours after dosing.

Results: Mortality was observed at 0 mg/kg/d (control, one animal on gestation day 20), 25 mg/kg/d (one animal, day 19) and 50 mg/kg/d (one animal, day 12). Macroscopic examination of the control rabbit that died showed uncollapsed lungs, dark areas/swelling of the thymus, brown fluid in the urinary bladder and dark areas on the vaginal serosa. The rabbit that died at 25 mg/kg/d had convulsions and red liquid in the mouth, dark areas on the jejunum, liver, lung and stomach, dark bronchial and tracheal fluid and dark areas on the vaginal wall. The rabbit that died at 50 mg/kg/d had fur staining, absent urine and feces, reduced activity, incoordination, lying flat, ptosis, and perforated gallbladder. Clinical signs in the animals that survived were occasional decreased/absent feces, difficult breathing, reduced activity, mouth/nares discharge, pupil constriction, ptosis, incoordination and lying flat at the high dose (50 mg/kg/d). There were convulsions in one rabbit at 25 mg/kg/d. Decreased body weights were observed at 50 mg/kg/d (3%, 4%, 5% and 3% decreases on days 15, 18, 21, and 24 respectively compared to weight gains of 6%, 7%, 10% and 11% in controls, same days) and decreased body weight gains at 25 (1%, 2% and 4% increases on days 18, 21 and 24 respectively compared to 7%, 10% and 11% in controls, same doses) and 50 (2% increase on day 29 compared to 15% increase in controls) mg/kg/d. Food consumption was reduced at 25 and 50 mg/kg/d from days 7-22. There were no treatment-related macroscopic findings at necropsy. The pregnancy rates (#pregnant rabbits/#mated rabbits) were ≥87.5% in the treated and control groups. There were no treatment-related effects on numbers of corpora lutea, implantation sites, live and dead fetuses, early, middle and late resorptions and pre (%

preimplantation loss = [#corpora lutea - #implants]x100/#corpora lutea)and post (% post implantation loss = [#implants - #live fetuses]x100/#implants) implantation losses.

Male and female fetal weights were reduced and the incidence of major malformations was slightly, but not significantly increased at 50 mg/kg/d. Common truncus was observed in 1 control fetus and gastroschisis was observed in one fetus at 10 mg/kg/d. The visceral and external observations at 50 mg/kg/d (in a total of 4 fetuses from 3 litters due to multiple abnormalities in some fetuses) were partial cleft palate (1 fetus), hydrocephaly, internal hemorrhage of the lateral ventricles (1 fetus), incompletely formed cochlea (1 fetus), globular heart (1 fetus), interventricular septal defect (1 fetus), common trunctus (1 fetus), absent ductus arteriosus (1 fetus), absent accessory lobe of the lung (1 fetus), abnormal flexure of hindlimb or forelimb (2 fetuses), and were attributed to biological variation by the sponsor. There were no treatment-related minor skeletal, external and visceral anomalies in the fetuses. Extra/rudimentary ossification centers of the bilateral 13th rib (dose-related at 24%-50% above historical range) at 25 and 50 mg/kg/d and total 13th rib (35%-69% above historical control range) at 50 mg/kg/d, were observed in the skeletal examination.

The results of the toxicokinetics analysis are presented under Pharmacokinetics above. The peak plasma levels were similar on gestation days 7 (17.3, 49.7 and 87.5 ng/ml at 10, 25 and 50 mg/kg/d respectively) and 19 (22.4, 487 and 85.8 at 10, 25 and 50 mg/kg/d respectively) except in one animal with an extremely high level on day 19 at 25 mg/kg/d. The results suggest little accumulation of hydromorphone with repeated dosing at 10-50 mg/kg/d. The AUC values were 76.6, 228 and 659 ng.h/ml at 10, 25 and 50 mg/kg/d respectively on day 7, and 101, 550 and 570 ng.h/ml at the same doses on day 19. The increases in Cmax and AUC were dose proportional on both days.

Reproductive Toxicity Reported in the Literature

Non-dose related minor skeletal defects were observed in the offspring of mice (Behm et al., 1985, Res. Commun. In Substances of Abuse 6:15-77) given hydromorphone in a continuous infusion at 31x-62x the human dose, and cranioschisis and exencephaly were observed in offspring of hamsters administered hydromorphone in a single dose at 40x-540x the human dose during gestation (Geber, 1970, Pharmacologist 12: 296; Geber and Schramm, 1975, Am. J. Obstet. Gynecol. 123: 705-713). The contribution of maternal toxicity (e.g., decreased food and water intake) to the resulting abnormalities was not addressed in those studies.

GENOTOXICOLOGY

Mutagenicity Test with Hydromorphone Hydrochloride in the Salmonella-Escherichia coli/Mammalian-Microsome Reverse Mutation Assay with a Confirmatory Assay (DSE-333-GLP/Amendment BP,Vol.1,p.8)

Note: Performing Laboratory: [redacted] Study Dates: September 8, 1998 – November 18, 1998. Assay Number 19893-0-4090ECD. Protocol Number 4090ECD, Edition 1. Quality Assurance and GLP statements present, not signed.

Methods: The assay was conducted according to the methods described by Ames et al. (1975). In the dose range finding study, tester strains TA100 and WP2*uvr*A were incubated with hydromorphone hydrochloride (10 doses with range 6.67-5000 mcg/plate) with and without metabolic activation with S9 homogenate [redacted] Batch Nos. 0835, 0856, 0874 and 0883, from Aroclor™ 1254 injected Sprague-Dawley rats). Tester strain genotypes were confirmed by demonstration of the presence of *rfa* wall mutation by sensitivity to crystal violet. The presence of the pKM101 plasmid was demonstrated by resistance to ampicillin and

spontaneous revertants were assessed using vehicle. The acceptable ranges for spontaneous revertants were 8-60 for TA98, 60-240 for TA100, 4-45 for TA1535, 2-25 for TA1537 and 5-40 for WP2*uvr*A. Culture densities were demonstrated at 0.5 x 10^9 bacteria per ml.

In the mutagenicity study, *Salmonella typhimurium* histidine auxotrophs TA98, TA100, TA1535 and TA1537 [ ] and *Escherichia coli* strain WP2*uvr*A [ ] were exposed to hydromorphone hydrochloride (Purdue Pharma, L.P., Lot #B1060-970301, PN#3210, PRC#0497012), vehicle, or positive controls (described below) at 37°C for 52±4 hours, using the plate incorporation method. A positive response was defined as a 2-fold increase in the mean revertants per plate compared to the vehicle control values for strains TA98, TA100 and WP2*uvr*A, a 3-fold increase in revertants for strains TA1535 and TA3537, and the presence of a dose response relationship in numbers of revertants. Mutagenicity of the positive control articles was demonstrated by a 3-fold increase in revertants over control values.

Tester Strain	S9 Mix	Positive Control	Concentration (per plate)
TA98	+	Benzo(a)pyrene (CAS#50-32-8,	2.5 mcg
TA98	-	2-nitrofluorene (CAS#607-57-8,	1.0 mcg
TA100	+	2-aminoanthracene (CAS#613-13-8,	2.5 mcg
TA100	-	Sodium azide (CAS#26628-22-8,	2.0 mcg
TA1535	+	2-aminoanthracene (CAS#613-13-8,	2.5 mcg
TA1535	-	Sodium azide (CAS#26628-22-8,	2.0 mcg
TA1537	+	2-aminoanthracene (CAS#613-13-8,	2.5 mcg
TA1537	-	ICR-191 (CAS#1707-45-0,	2.0 mcg
WP2*uvr*A	+	2-aminoanthracene (CAS#613-13-8,	25 mcg
WP2*uvr*A	-	4-nitroquinoline-N-oxide (CAS#56-57-5,	1.0 mcg

The mutagenicity assay was repeated in a confirmatory assay.

The HPLC method was validated and hydromorphone concentrations verified in the Analytical Chemistry analysis.

Results: In the dose range finding study, no cytotoxicity (increase in number of revertant colonies or thinning/disappearance of bacterial background lawn) was observed in tester strains TA100 and WP2*uvr*A exposed to hydromorphone hydrochloride at up to 5000 mcg/plate. Therefore, the high dose selected for the mutagenicity assay was 5000 mcg/plate. In the mutagenicity assays (initial, confirmatory and repeat confirmatory assays), there were no significant increases in the mean number of revertants per plate.

The results of the mutagenicity assays are presented in the following table:

Mutagenicity Assay			Mean Revertants per Plate				
Test Article	Dose (mcg/plate)		TA98	TA100	TA1535	TA1537	WP2*uvr*A*
Vehicle	0	+S9	27	98	11	11	13 (18)*
Hydromorphone	100	+S9	23	102	8	7	11 (18)*
	333	+S9	25	97	14	8	14 (17)*
	1000	+S9	26	102	12	8	15 (19)*
	3330	+S9	23	107	9	8	12 (12)*
	5000	+S9	26	97	10	8	14 (14)*
Positive Control	See Methods	+S9	460	627	98	90	10 (359)*
Vehicle	0	-S9	12	98	10	4	17
Hydromorphone	100	-S9	10	94	12	5	11
	333	-S9	17	92	11	5	13

	1000	-S9	16	99	12	5	11
	3330	-S9	16	88	10	3	15
	5000	-S9	14	92	9	6	11
Positive Control	See Methods	-S9	178	560	559	433	279
Confirmatory Assay			**Mean Revertants per Plate**				
Test Article	**Dose (mcg/plate)**		**TA98**	**TA100**	**TA1535**	**TA1537**	**WP2*uvrA***
Vehicle	0	+S9	24	113	11	9	15
Hydromorphone	100	+S9	32	95	11	6	19
	333	+S9	25	103	14	5	14
	1000	+S9	28	105	8	8	15
	3330	+S9	23	106	13	6	15
	5000	+S9	21	114	12	6	11
Positive Control	See Methods	+S9	425	1122	129	208	416
Vehicle	0	-S9	15	94	10	9	16
Hydromorphone	100	-S9	15	103	12	8	16
	333	-S9	13	92	11	5	17
	1000	-S9	9	93	10	3	15
	3330	-S9	17	83	9	5	16
	5000	-S9	14	91	10	9	14
Positive Control	See Methods	-S9	189	570	554	334	319

*Unacceptable mean positive control value. Retest value in parenthesis.

Mutagenicity Test on Hydromorphone Hydrochloride in the In Vivo Mouse Micronucleus Assay (DSE-334-GLP / Amendment BP, Vol. 1, p. 67)

Note: Performing Laboratory: [redacted] Study Completion Date: January 28, 1999. Project Number 20996. Assay 19893. Protocol Number 4550ECD. Quality Assurance and GLP statements present, not signed.

Methods: In the dose-range finding study, male and female mice — CD-1®(ICR)BR, [redacted] weights 29.7-33.6 g males and 23.3-25.6 g females, n=3/sex/dose) were administered hydromorphone HCl ([redacted] — Lot B1060-970301, at 200, 500, 800, 1500, and 2000 mg/kg PO in cell culture grade water [redacted] Lot #707267), 10 ml/kg) by oral gavage. The mice were observed for 2 days for clinical signs and mortality. To screen for clastogenicity (chromosome breaks) and interference with mitotic division, male mice (n=6/dose/timepoint) were administered hydromorphone HCl at 50, 100 and 200 mg/kg (10 ml/kg in water) by gavage. The negative control was water vehicle (cell culture grade, PO) and positive control was cyclophosphamide ([redacted] Batch No. 29, in sterile deionized water, 80 mg/kg, 8 mg/ml, 10 ml/kg PO). The mice were observed for clinical signs and mortality until sacrifice. After euthanasia, the bone marrow was removed from the hind limb tibia or femur and mounted on slides for analysis. The marrow cells were scored for micronuclei (historical background frequency 0.0-0.4%) and the PCE (polychromatic erythrocyte) to NCE (normochromatic erythrocyte) cell ratio. The HPLC method was validated and hydromorphone concentrations verified in the Analytical Chemistry analysis.

Results: In the dose range-finding study, hyperactivity and straub tail were observed at all doses immediately after dosing. At one hour after dosing, hyperactivity and straub tail were observed at 200 mg/kg and convulsions at 2000 mg/kg. All mice that received 500 mg/kg and higher died at 1 hour. The MTD was determined to be 200 mg/kg.

In the micronucleus test, one animal died at 100 mg/kg and one at 200 mg/kg hydromorphone HCl. Hunched posture and hypoactivity were observed in all groups at 1 hour after dosing. There were no clinical signs at 1

day after dosing. There was no significant decrease in the PCE to NCE ratio and no increase in micronucleated PCEs compared to the vehicle treated controls. Cyclophosphamide increased micronucleated PCEs (mean 2.92%) compared to the vehicle control value.

Treatment	Dose	Harvest time	%Micronucleated PCEs (mean of 2000/animal ± S.E.)	Ratio PCR:NCE (mean ± S.E.)
Control Vehicle	Water	24 hr 48 hr	0.12 ± 0.05 0.22 ± 0.03	0.56 ± 0.08 1.10 ± 0.25
Positive Control	CP 80 mg/kg	24 hr	2.92 ±0.56	0.48 ± 0.05
Test Article	50 mg/kg 100 mg/kg 200 mg/kg	24 hr 24 hr 24 hr 48 hr	0.19 ± 0.04 0.14 ± 0.05 0.16 ± 0.04 0.13 ± 0.05	0.96 ± 0.09 0.78 ± 0.09 0.77 ± 0.05 0.72 ± 0.12

Mutagenicity Test on Hydromorphone Hydrochloride in the L5178Y TK$^{+/-}$ Mouse Lymphoma Forward Mutation Assay (DSE-335-GLP / Amendment BP, Vol. 1, p. 109)

Note: Performing Laboratory: [ ] Study Dates: September 4, 1998 – December 24, 1998. Project Number 20989. Assay 19893. Protocol Number 431 ICH Edition 1. Quality Assurance and GLP statements signed and present.

Methods: Mouse lymphoma L5178Y cells from stock cultures, previously exposed to conditions that inhibit the TK$^{-/-}$ phenotype, were incubated with hydromorphone hydrochloride (Lot # B1060-970301, up to 3250 mcg/ml [10 mM]) in the dose range finding assay, at 50, 100, 200, 300, 600, 800 and 1000 mcg/ml in the mutation assays, and at 25, 50, 100, 200, 300, 400 and 500 mcg/ml without metabolic activation and 300-1400 mcg/ml with metabolic activation in the confirmatory assays, in Cell Culture Grade Water [ ] Lot #s 706395 and 707267) or vehicle alone at 37°C. Metabolic activation was achieved with the S9 fraction of rat liver homogenate [ ] Lot # 0800, 9000xg supernatant from homogenized livers of aroclor 1254-induced adult male Sprague Dawley rats) and cofactors. The incubation duration was 4 hours in the mutation assays and 24 hours in the confirmatory assays. The positive control articles were methyl methanesulfonate [ ] Lot # 09419LR, 6.5 and 13.0 mcg/ml) for the assays without S9 metabolic activation, and methylcholanthrene [ ] Lot # 75H2510, 2.0 and 4.0 mcg/ml) for the assays with S9 metabolic activation. Criteria for acceptable controls included average absolute cloning efficiency of the vehicle controls of 60%-130%, average suspension growth of vehicle controls for two days of 8x increase, background mutant frequency of $30x10^{-6}$ to $120x10^{-6}$, and mutant frequency for positive control cultures of $200x10^{-6}$. The criteria for mutagenicity was defined as mutation frequency greater than 87.9 x 10^{-6} (2x vehicle control) without metabolic activation and 87.5 x 10^{-6} with activation in the mutation assays, and 134.4 x 10^{-6} without S9 activation and 175.8 x 10^{-6} with activation in the confirmatory assays. The HPLC method was validated and hydromorphone concentrations verified in the Analytical Chemistry analysis.

Results: In the dose range finding assay conducted for 4 hours, hydromorphone was weakly cytotoxic at 6.4-204 mcg/ml without S9 metabolic activation (63.5%-79.4% vehicle control cell density) and at 6.4-408 mcg/ml with metabolic activation (71.8%-98.4% control), moderately cytotoxic at 408-815 mcg/ml without activation (17.9%-38.9% control) and 815 mcg/ml with activation (46.3% control), and excessively cytotoxic at doses higher than 815 mcg/ml in both non-activated (1.6%-2.0% control) and activated (0.0%-5.3% control) systems. After 24 hours incubation, hydromorphone was noncytotoxic or weakly cytotoxic at 6.4-408 mcg/ml (53.4%-112% control) and excessively cytotoxic at doses higher than 408 mcg/ml (0.0% control) in both activated and non-activated systems.

The results of the mutagenicity and confirmatory assays are presented in the following table:

	Without Metabolic Activation		With Metabolic Activation	
Condition	Relative Growth (%)	Mutant Frequency (10E-6 Units)	Relative Growth (%)	Mutant Frequency (10E-6 Units)
Initial Mutation Assay				
Vehicle Control	116.2	47.5	104.7	48.5
Vehicle Control	95.3	44.4	74.9	47.3
Vehicle Control	86.4	39.9	122.5	35.5
MMS (6.5mcg/ml)	21.9	353.6	ND	ND
MMS (13 mcg/ml)	17.8	547.1	ND	ND
MCA (2 mcg/ml)	ND	ND	62.8	355.9
MCA (4 mcg/ml)	ND	ND	63.2	367.7
Hydromorphone (50 mcg/ml)	75.5	37.8	71.3	58.6
Hydromorphone (100 mcg/ml)	75.2	60.3	72.8	75.6
Hydromorphone (200mcg/ml)	83.1	48.9	69.3	97.1
Hydromorphone (300 mcg/ml)	91.6	61.1	69.1	132.8
Hydromorphone (600 mcg/ml)	40.4	64.8	49.0	282.0
Hydromorphone (800 mcg/ml)	29.2	46.6	51.2	254.0
Hydromorphone (1000 mcg/ml)	13.9	64.0	25.3	290.0
	Without Metabolic Activation		**With Metabolic Activation**	
Confirmatory Mutation Assay	**Relative Growth (%)**	**Mutant Frequency (10E-6 Units)**	**Relative Growth (%)**	**Mutant Frequency (10E-6 Units)**
Vehicle Control	106.7	54.2	95.8	87.0
Vehicle Control	96.9	76.0	104.0	86.8
Vehicle Control	94.0	71.4	100.1	90.0
MMS (6.5mcg/ml)	25.8	865.1	ND	ND
MMS (13 mcg/ml)	4.8	1218.6	ND	ND
MCA (2 mcg/ml)	ND	ND	58.4	475.3
MCA (4 mcg/ml)	ND	ND	66.4	467.4
Hydromorphone (25 mcg/ml)	102.4	64.8	ND	ND
Hydromorphone (50 mcg/ml)	105.0	66.1	ND	ND
Hydromorphone (100mcg/ml)	71.6	74.6	ND	ND
Hydromorphone (200 mcg/ml)	69.5	74.3	114.8	167.9
Hydromorphone (300 mcg/ml)	52.8	75.0	111.4	212.6
Hydromorphone (400 mcg/ml)	65.5	71.7	ND	ND
Hydromorphone (500 mcg/ml)	26.3	95.6	ND	ND
Hydromorphone (600 mcg/ml)	ND	ND	68.8	360.9
Hydromorphone (800 mcg/ml)	ND	ND	58.6	355.4
Hydromorphone (900 mcg/ml)	ND	ND	47.7	356.0
Hydromorphone (1000 mcg/ml)	ND	ND	30.1	474.7
Hydromorphone (1200 mcg/ml)	ND	ND	21.0	327.5
Hydromorphone (1400 mcg/ml)	ND	ND	15.9	367.8

ND: Not Done.

OVERALL SUMMARY and DISCUSSION

This submission is for a once-per-day, controlled-release formulation of hydromorphone hydrochloride (Palladone) at 12-32 mg/capsule, for the treatment of moderate to severe pain in opioid exposed patients. Hydromorphone is currently approved and marketed in oral syrup, liquid, injection, immediate-release tablet and suppository forms. The controlled-release formulation was developed to provide more predictable and steady blood concentrations and pain relief than could be achieved using the immediate-release hydromorphone formulations. Non-clinical studies were conducted on receptor binding, antinociceptive effects, pharmaceutical analysis of substances content, metabolic profile, teratology (reproductive toxicology segment II) and mutagenicity for the NDA.

Hydromorphone is a selective mu-opioid receptor agonist with binding potency of 10x-30x greater, and pharmacological potency for analgesia of 4x-10x greater than that of morphine. In a receptor binding study conducted by the sponsor, the hydromorphone affinity for the mu-opioid receptor (Ki 0.26) was approximately 60x that of oxycodone (Ki 15), and 400x and 700x the binding potencies for the kappa (Ki 99) and delta (Ki 172) opioid receptors respectively. The metabolites also showed affinity for the mu receptor with potencies in the order of dihydroisomorphine (0.39) > hydromorphone-N-oxide (1.5) > dihydroisomorphine-6-glucoside (Ki 4.7) > dihydroisomorphine-6-glucuronide (Ki 10) > hydromorphone-3-glucoside (Ki 51). The metabolite dihydroisomorphine also showed considerable affinity for the kappa receptor subtype (Ki 38 nM).

The antinociceptive effects of hydromorphone and several metabolites were studied in the p-phenylquinone stretching test in mice. Based on the results of this study, the hydromorphone metabolites 7,8-dihydro-6-beta-hydroxymorphine and 7,8-dihydromorphone-N-oxide monohydrate were as potent as hydromorphone, and the metabolites 7,8-dihydro-6-beta-hydroxymorphine-6-glucuronide, 7,8-dihydro-6-beta-hydroxymorphine-6-glucoside (1'-α,β mixture) and 7,8-dihydromorphone-3-glucoside were significantly less potent than the parent drug in antagonizing the stretching response to PPQ in mice. The metabolites 7,8-dihydromorphone-N-oxide monohydrate and 7,8-dihydro-6-beta-hydroxymorphine-6-glucuronide were most efficacious in the tail-flick test, but the effects were not dose-related. Hydromorphone and the metabolites tested were more efficacious in blocking the pain induced by PPQ than the pain induced by thermal stimulation. The sponsor justified testing of all metabolites at 30 minutes because the peak effect for hydromorphone was previously found to occur at 30 minutes. However, peak plasma levels of the metabolites may not have been reached at that time. The doses tested were not high enough in the tail-flick test. The sponsor did not describe why 2 MPE values were given for the 1 mg/kg and 2 mg/kg dose levels of 7,8-dihydromorphone-N-oxide monohydrate in the tail flick test.

Secondary pharmacological actions of hydromorphone, related to opioid agonist activity are somnolence, respiratory depression, neuroendocrine inhibition (gonadotropin-releasing hormone, corticotropin-releasing hormone, leuteinizing hormone, follicle-stimulating hormone, ACTH, beta-endorphin, prolactin, testosterone and cortisol), nausea and emesis, depression of the cough reflex, and at high doses convulsions. Hydromorphone decreases motility and increases resting tone in the gastrointestinal tract, decreases uterine tone and inhibits urinary voiding reflex. In the cardiovascular system, hydromorphone induces arteriolar and venous dilation, decreases myocardial oxygen consumption by decreasing heart rate, left ventricular end-diastolic pressure and decreasing cardiac work. Immunoinhibitory effects have been observed.

The ADME and pharmacokinetic profile of hydromorphone hydrochloride are well known. The oral bioavailability of hydromorphone is approximately 60%, and distribution in humans includes skeletal muscle, kidneys, intestinal tract, liver, spleen, lungs and brain. Hydromorphone crosses the placenta. Hydromorphone is extensively metabolized by hepatic oxidation and conjugation., and additional metabolism occurrs in the CNS, kidneys, lungs and placenta. In the [ ] analyses conducted by the sponsor, the major hydromorphone metabolites detected in human plasma and urine were hydromorphone-3-glucuronide, dihydromorphine-6-glucuronide, hydromorphone-3-glucoside and dihydromorphine-6-glucoside. The minor metabolites were dihydro-iso-morphine and dihydromorphine. The metabolites were detected in similar profiles after both immediate-release and controlled-release formulations. There were no differences in the profile of metabolites after administration of the immediate-release and controlled-release formulations, no differences between the metabolites in urine, plasma, and in the supernatant of human hepatocytes incubated with hydromorphone, and no differences in fresh and 5-week aged plasma. In rats and rabbits, the major hydromorphone metabolites were hydromorphone-3-glucuronide and dihydromorphine-6-glucuronide and the minor metabolites were dihydromorphine and dihydro-iso-morphine. Trace levels of the human glycoside metabolites hydromorphone-3-glucoside and dihydromorphine-6-glucoside were found in rabbits but not in rat plasma. The results of the stability study suggested that hydromorphone-N-oxide, found in human urine but not in plasma, may be a degradation product rather than a metabolite of hydromorphone. Excretion is primarily renal.

Toxicokinetics analyses were performed in the teratology studies in rats and rabbits. In the study in gravid rats given 1, 5 and10 mg/kg/d hydromorphone by oral gavage on gestation days 6-17, the increase in Cmax was not dose-proportional. The AUC values were similar for the 1 and 5 mg/kg/d groups on gestation days 6 and 17, but the AUC was significantly higher on day 17 than on day 6 in the rats that received 10 mg/kg/d, suggesting drug accumulation. In pregnant rabbits administered 10, 25 and 50 mg/kg/d hydromorphone by oral gavage on gestation days 7-19, the peak plasma levels and AUC levels were similar on gestation days 7 and 19, except in one animal with an extremely high level on day 19 at 25 mg/kg/d. This suggests little accumulation of hydromorphone in gravid rabbits with repeated dosing at 10-50 mg/kg/d. The increases in Cmax and AUC were dose-proportional on both days. The time to peak plasma level increased with dose on day 7 but decreased with dose on day 19.

In acute toxicology studies, the LD50 values were 55-104 mg/kg IV and 84-120 mg/kg SC in mice, and 51 mg/kg SC in rats. The lowest lethal dose was 2.5 mg/kg IV in rabbits and 3 mg/kg IV in cats. Hydromorphone was 3x-9x times more toxic than morphine in parenteral form, and toxic effects included reduced activity, incoordination, increased heart rate, salivation, increased muscle tone, focused gaze, ptosis, absent feces, dehydration, respiratory depression, excitation, and at high doses convulsions and deaths.

Repeated dose toxicology was assessed in the range finding toxicity studies in gravid rats and rabbits. Pregnant rats given 50, 100, 150 and 200 mg/kg/d hydromorphone hydrochloride by oral gavage for 12 days on gestation days 6-17 showed 20%-40% deaths in each group, decreased body weights and clinical signs consistent with opioid drug effects (reduced activity, incoordination, increased heart rate, shallow breathing, increased muscle tone, rigidity, focused gaze, salivation and unresponsive to external stimuli. Treatment-related macroscopic observations in the necropsy were pale discoloration of the kidneys, dilatation of the ureters and dilatation, thickening, dark discoloration, pale or dark area clots and dark fluid in the urinary bladder. The NOAEL was not established.

In pregnant rabbits administered 10, 25, 50 or 100 mg/kg/d hydromorphone on gestation days 7-19, there were 40% deaths at 100 mg/kg/d and clinical signs (reduced activity, decreased muscle tone and dilated or constricted pupils) at 50 and 100 mg/kg/d. Gross pathology showed spongy or collapsed lungs, dark areas and pale or dark frothy fluid in the lungs, bronchi or trachea in all groups. The NOAEL was not established in this study.

Beagle dogs given oral hydromorphone in immediate-release and controlled-release formulations at up to 64 mg/kg/d for 30 days showed decreased body weights at the high dose, and clinical signs consistent with known opioid effects at all doses (8-64 mg/kg/d). The necropsy results were not reported. There were no studies by the sponsor or literature reports on the effects of chronic hydromorphone administration.

No studies were conducted to evaluate the carcinogenic potential of hydromorphone hydrochloride.

Teratogenicity (Reproductive toxicology Segment II) studies were conducted on hydromorphone in rats and rabbits. In the preliminary dose-range finding study in non-pregnant female rats, the adverse effects of hydromorphone HCl at 100-1000 mg/kg PO single dose and 50-200 mg/kg/d PO for 12 days were deaths, clinical signs of opioid overdose, decreased body weights and body temperatures and pathology in the kidneys, ureters and urinary bladder. Therefore, the maximum tolerated dose (MTD) selected for the dose-range-finding teratology study was less than 50 mg/kg/d PO. In female rabbits, adverse effects were deaths at single doses ≥ 100 mg/kg PO, clinical signs of reduced activity (50 mg/kg single and multiple doses) and altered muscle tone and constricted or dilated pupils (100-1000 mg/kg PO single dose and 50 mg/kg repeated doses), and gross pathology in the lungs, bronchi and trachea at 50-1000 mg/kg single doses and 100 mg/kg/d repeated dosing for 13 days (except for one rabbit at 10 mg/kg/d). The maximum dose selected for the dose-range-finding teratology study in rabbits was also 50 mg/kg/d PO hydromorphone HCl.

Pregnant female rats were given hydromorphone HCl at 7.5-60 mg/kg/d by oral gavage on gestation days 6-17, and evaluated for maternal and fetal toxicity up to gestation day 20: Based on observations of treatment-related maternal toxicity (opioid related clinical signs, decreased body weight gain and food consumption, and gross pathology in the kidney and ureter) in this study, a high dose of < 15 mg/kg/d hydromorphone HCl was selected for the teratology study in rats. Mean weight gain values were 29%, 31% and 21% at 15, 30 and 60 mg/kg/d respectively compared to 58% in the control group, measured on day 20. There was no evidence of hydromorphone-induced teratogenicity at up to 60 mg/kg/d (gestation days 6-17) in the external examination in this study. Fetal weights were slightly reduced compared to controls, at 60 mg/kg/d.

In the main teratogenicity study in rats, hydromorphone HCl at 1, 5 and 10 mg/kg/d by oral gavage on gestation days 6-17 produced no fetal toxicity, teratogenicity or embryolethality at maternally toxic doses (5 mg/kg/d PO [approximately 2x the high human dose on an AUC basis] to10 mg/kg/d [4x the human dose on an AUC basis]) given on gestation days 6-17. Maternal toxicity was demonstrated by reduced food consumption and body weight gain (43% and 33% at 5 and 10 mg/kg/d respectively on day 20, compared to 54% in the control group). There was a slight, non-significant increase in the incidence of reduced ossification of the hyoid bone and thoracic centrum variants at 10 mg/kg/d. The peak plasma levels at 10 mg/kg/d were 20.7 and 40.1 ng/ml on days 6 and 17 respectively. The AUC_{0-6} at the NOEL for reproductive toxicity (10 mg/kg/d) was 128 ng.h/ml on day 17. In comparison, the AUC in humans at steady state at 36 mg/d hydromorphone, was 29.2 ng.h/ml.

Based on the maternal toxicity in the oral range finding study in non-pregnant female rabbits, the maximum dose selected for dose-range finding teratogenicity study in rabbits was 50 mg/kg/d hydromorphone HCl. Maternal toxicity was indicated by clinical signs that were consistent with known opioid effects (e.g., respiratory depression, decreased defecation, reduced body weight gains and reduced food consumption). Body weight gains were 5% and 2% at 25 and 50 mg/kg/d respectively compared to 13% in the controls on day 24, and 2% at 75 mg/kg/d compared to 13% in the controls on day 29. Hydromorphone HCl was fetotoxic at 75 mg/kg/d PO, shown by slightly decreased fetal weights, but there was no evidence of hydromorphone-induced embryolethality or teratogenicity in this study.

In the main teratogenicity study in rabbits given 10, 25 and 50 mg/kg/d hydromorphone HCl by oral gavage on gestation days 7-19 inclusively, maternal toxicity was shown by clinical signs characteristic of opioid effects, including decreased defecation, respiratory difficulty, and pupil constriction, decreased body weights and weight gains and decreased food consumption. Fetotoxicity was shown by decreased fetal weights in both males and females at the high dose (50 mg/kg/d). Although there was no evidence of hydromorphone-induced teratogenicity or embryolethality at maternally toxic doses (up to 50 mg/kg/d, Cmax 85.8 ng/ml, AUC_{0-8} 357 ng.h/ml, 10x the human exposure [AUC_{0-6} 29.2] at 32 mg/d at steady state), visceral and external malformations were observed in greater frequency in the high dose group (4 fetuses) compared to the controls (1 fetus), low dose (1 fetus) and mid dose (no abnormalities) groups. There was one observation of common truncus in a control fetus. Gastroschisis was observed in one low dose fetus. The malformations in the high dose group included partial cleft palate (1 fetus), hydrocephaly, internal hemorrhage of the lateral ventricles (1 fetus), incompletely formed cochlea (1 fetus), globular heart (1 fetus), interventricular septal defect (1 fetus), common trunctus (1 fetus), absent ductus arteriosus (1 fetus), absent accessory lobe of the lung (1 fetus), abnormal flexure of hindlimb or forelimb (2 fetuses). Increases in extra/rudimentary ossification centers of the bilateral 13^{th} rib (25 and 50 mg/kg/d, dose-related) and total 13^{th} rib (50 mg/kg/d) were considered minor differences in normal variants. The malformations in the high dose group fetuses are considered to be due to biological variation and/or maternal toxicity (including respiratory depression, decreased food consumption and weight loss). The peak plasma levels (Cmax) were 17.3, 49.7 and 87.5 ng/ml on gestation day 7 and 22.4, 487 and 85.8 ng/ml on day 19 at 1, 5 and 10 mg/kg/d respectively in the rabbits. Overall exposure (AUC_{0-24}) in the rabbits were 76.6, 228 and 659 ng.h/ml on day 7 and 101, 550 and 570 ng.h/ml on day 19 at 10, 25 and 50 mg/kg/d PO respectively. The NOEL for reproductive toxicity can be considered 25 mg/kg/d (approximately 7x

the human exposure at 32 mg/d on an AUC basis) and the LOEL (reproductive toxicity) 50 mg/kg/d (approximately 19x the human exposure of 32 mg/d on an AUC basis).

The bioanalytical methods [ ], for quantitation of hydromorphone in rat and rabbit plasma were validated in the range of [ ] ng/ml, using plasma containing known concentrations of the drug. The stability of hydromorphone in rat and rabbit plasma was assessed for intervals of [ ] and [ ] and found to be stable for up to [ ]

Studies to evaluate the genotoxic potential of hydromorphone were conducted by the sponsor during the review period. Hydromorphone was non-mutagenic in the Ames test with *Salmonella typhimurium* histidine auxotrophs TA98, TA100, TA1535 and TA1537 and *Escherichia coli* strain WP2*uvr*A at up to 5000 mcg/ml in the presence and absence of metabolic activation with aroclor 1254-induced S9 fraction of rat liver homogenate. In the *in vivo* mouse micronucleus assay, hydromorphone hydrochloride was not cytotoxic to bone marrow (no decrease in PCE:NCE ratio) and was negative for clastogenesis (no increase in bone marrow polychromatic erythrocyte micronuclei) at clinically toxic doses (up to 200 mg/kg PO). Hydromorphone hydrochloride was negative in the absence of S9 metabolic activation, but showed a positive genotoxic response at 200-1000 mcg/ml in the presence of S9 metabolic activation in the Mouse Lymphoma Forward Mutation Assay. Mutation frequencies were 2.2x-6.6x higher than control values in that study. The study was replicated and results confirmed.

The hydromorphone hydrochloride CR 12 mg capsules and Dilaudid tablets were compared for related substances content by HPLC [ ] and two related substances methods [ ]. The percent of label claim for hydromorphone HCL was [ ] in the controlled release capsules after [ ] at 30 degrees C and 60% relative humidity. This value was greater than in the Dilaudid Tablets for both 4 mg and 8 mg strengths. The total early and late eluting related substances found in the hydromorphone HCl controlled release capsules were [ ] respectively. The related substances in the controlled release capsules were dihydromorphine N-oxide and hydromorphone N-oxide in the early-eluting assay and hydrocodone, pseudohydromorphone, and 7-(6-dihydromorphinyl) hydromorphone in the late-eluting assay. In comparison, the substances in the Dilaudid tablets at 4 mg and 8 mg totaled [ ], in the early-eluting assay respectively, and [ ] in the late-eluting assay respectively. Dihydromorphine N-oxide, dihydromorphine, morphine sulfate $5H_2O$, hydromorphone N-oxide, and an unknown substance were found in greater concentrations in the Dilaudid tablets than in the controlled release capsules in the early-elution assay, and hydrocodone, pseudohydromorphone, and two unknown substances were found in greater concentrations in the tablets in the late-eluting assay. The Dilaudid 4 mg tablets and the hydromorphone HCl CR capsules passed the specifications for related substances as defined by the sponsor.

Based on the known pharmacology and toxicology of hydromorphone hydrochloride and on the results of the studies conducted by the sponsor, this NDA is approvable from a pharmacology and toxicology point of view, with changes to the proposed label, described below.

CONCLUSIONS

- Hydromorphone analgesic properties similar to, but more potent than those of morphine, with similar side effect and toxicity profiles, TI (LD50 SC/ED50 SC; 51 mg/kg/0.36 mg/kg – 51 mg/kg/0.11 mg/kg) approximately 142-464 in the rat.
- Impurity profile similar to Dialudid, but with lower levels of impurities
- Oral bioavailability approximately 60% in humans, distribution to brain, skeletal muscle, kidneys, intestinal tract, liver, spleen and lungs

- Metabolism by hepatic oxidation and conjugation to hydromorphone-3-glucuronide, dihydromorphine-6-glucuronide, hydromorphone-3-glucoside and dyhydromorphine-6-clugoside, also dihydro-iso-morphine and dihydromorphine. Similar metabolic profile in immediate-release and controlled-release, and in rats, rabbits and humans. Similar in urine, plasma and hepatocytes
- Excretion primarily renal
- Acute toxicity in animals included reduced activity, incoordination, increased heart rate, salivation, increased muscle tone, focused gaze, ptosis, absent feces, dehydration, respiratory depression, excitation, and at high doses convulsions and deaths. LD50 55-104 mg/kg IV and 84-120 mg/kg SC in mice and 51 mg/kg SC in rats. LDLo 2.5 mg/kg IV in rabbits and 3 mg/kg IV in cats.
- Repeated dose toxicology in gravid rats (50-200 mg/kg/d PO, gestation days 6-17) and rabbits (10-100 mg/kg/d PO, gestation days 7-19) showed treatment-related decreased body weights and clinical signs consistent with known opioid drug effects. Macroscopic observations at necropsy included discoloration in the kidneys, dilation of the ureters and urinary bladder with discoloration, clots and dark fluid in rats, and spongy or collapsed lungs, dark or pale areas and frothy fluid in the lungs, bronchi or trachea in rabbits. NOAEL not established in rats. NOAEL, aside from opioid signs, 10 mg/kg/d in rabbits.
- 30-day studies in dogs showed decreased body weights at 64 mg/kg/d PO and clinical signs consistent with known opioid effects at 8-64 mg/kg/d. No necropsy report.
- No studies on carcinogenicity were conducted
- No fetal toxicity, teratogenicity or embryolethality of hydromorphone HCL (1-10 mg/kg/d PO, gestation days 7-17) in fetal rats at maternally toxic doses (5-10 mg/kg/d PO, 2x-4x the human exposure at 32 mg/d in a 60 kg patient at steady state on an AUC basis); Slight increase in incidence of reduced ossification of hyoid bone and thoracic centrum variants at 10 mg/kg/d PO in fetal rats
- Hydromorphone HCl not teratogenic at 50 mg/kg/d PO (10x the human exposure at steady state in a 60 kg patient on an AUC basis) given on gestation days 7-19 in rabbits, but fetal weights were slightly decreased (mean 84% of control) and maternal toxicity. Increase in frequency of minor skeletal variations such as cleft palate, internal hemorrhage of lateral ventricles, incompletely formed cochlea, globular heart, interventricular septal defect, abnormal flexure of hindlimb or forelimb in 1 or 2 fetuses at 25-50 mg/kg/d.
- Hydromorphone was negative in the Ames test and in the Mouse Micronucleus Assay with, and without metabolic activation, and in the mouse lymphoma forward mutation Assay without activation. Hydromorphone was positive in the presence of metabolic activation in the Mouse Lymphoma Forward Mutation Assay.
- Palladone — Controlled-Release Capsules approvable from a pharmacology and toxicology viewpoint with changes to the proposed label to reflect the results of the reproductive toxicology and genotoxicology studies

RECOMMENDATIONS

Recommendations to the Sponsor:

The Quality Assurance and GLP statements for the studies entitled "Mutagenicity Test with Hydromorphone Hydrochloride in the Salmonella-escherichia coli/Mammalian-Microsome Reverse Mutation Assay with a Confirmatory Assay" (DSE-333-GLP / Amendment BP, Vol. 1, p. 8) and "Mutagenicity Test on Hydromorphone Hydrochloride in the In Vivo Mouse Micronucleus Assay" (DSE-334-GLP / Amendment BP, Vol. 1, p. 67) should be signed.

It is recommended that the results of the Segment II teratogenicity studies on hydromorphone HCl in rats and rabbits be included in the product label, as described under the Labeling Review, using exposure data for comparison between animals and humans. Please provide the historical control data for the rabbits.

LABELING REVIEW

The proposed *Mutagenicity/Carcinogenicity/Impairment of Fertility* and *Pregnancy* sections of the Package Insert are presented below.

[redacted]

The following changes to the proposed Package Insert are recommended.

1. The section on Mutagenicity/Carcinogenicity/Impairment of Fertility should be revised to include the results of the mutagenicity studies, and should state:

[redacted]

2. The third paragraph under Pregnancy should define the drug administration routes and the teratogenic effects observed in the hamsters and mice. Multiples of the human drug exposure comparing subcutaneous infusion in mice and oral administration in humans should not be used.

3. Recommended wording for the Pregnancy section follows:

Pregnancy – Pregnancy Category C

Kathleen A. Habermy 8/9/99
Kathleen A. Habermy, Ph.D.

D.H. Lou Jean August 9, 1999
Team Leader: Dou H. Jean, Ph.D.

Review and Evaluation of Pharmacology/Toxicology Data
Division of Anesthetic, Critical Care & Addiction Drug Products
HFD-170/Kathleen Haberny

MAY 24 1999

NDA 21-044 Amendment BP (Amendment to Pending Application: Mutagenicity Study Reports)

Submission Date April 16, 1999

Review Date: May 18, 1999

Information to Sponsor **Yes (x) No (x)**

Sponsor: Purdue Pharma L.P.
100 Connecticut Avenue
Norwalk, CT 06850-3590

Drug Name: Palladone ™ Controlled-Release Capsules (hydromorphone hydrochloride), 12, 16, 24 & 32 mg

Chemical Name: 4,5α-epoxy—3-hydroxyl-17-methylmorphinan-6-one-hydrochloride

Relevant INDs/NDAs/DMFs: IND 38,424; DMFs #s [redacted]
(Amendment 92)

Drug Class: Opioid analgesic, semi-synthetic congener of morphine

Indication: [redacted]

Route of Administration: Oral

GENOTOXICOLOGY

The following studies, submitted in this amendment, were reviewed (May 21, 1999) under NDA 21-044 (Palladone

Mutagenicity Test with Hydromorphone Hydrochloride in the *Salmonella-Escherichia coli*/Mammalian-Microsome Reverse Mutation Assay with a Confirmatory Assay (DSE-333-GLP)

Mutagenicity Test on Hydromorphone Hydrochloride in the *In Vivo* Mouse Micronucleus Assay (DSE-334-GLP)

Mutagenicity Test on Hydromorphone Hydrochloride in the L5178Y TK+/- Mouse Lymphoma Forward Mutation Assay (DSE-335-GLP)

Kathleen G. Haberny 5/24/99
Kathleen Haberny, Ph.D.

D.H. Jean, Jr. 5/24/99
Team Leader: Dou H. Jean, Ph.D.

Cc: NDA 21-044 Arch
HFD 170/Division File
HFD 170/K Haberny
HFD 170/N Chamberlin