

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-217s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

NDA: 21-217	Submission Date(s): May 22, 2009
Brand Name	EXALGO
Generic Name	hydromorphone
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OCP Division	DCPII
OND division	DARRP
Sponsor	Premier Research Group for Neuromed
Relevant IND(s)	78,223
Submission Type	Resubmission; 505(b)(1)
Formulation; Strength(s)	Extended Release Tablets, 8, 12, 16, and 32 mg
Indication	Management of moderate to severe pain in opioid tolerant patients requiring continuous, around-the-clock opioid analgesia for an extended period of time.

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1 Executive Summary

Neuromed submitted a resubmission to the Approvable Letter for NDA 21-217 issued on October 27, 2000, and is seeking approval of EXALGO (hydromorphone) Extended-Release (ER) Tablets for once daily administration for the management of moderate to severe pain in opioid tolerant patients requiring continuous, around-the-clock opioid analgesia for an extended period of time. The Approvable letter contains five deficiencies related to CMC, Nonclinical and Clinical. There is

no clinical pharmacology associated deficiency. Neuromed conducted Study NMT 1077-301 to address the clinical deficiency of “adequate and well-controlled study with multiple dosing of the to-be-marketed formulation, in the setting of moderate to severe pain, to establish the efficacy of the product”. Study NMT 1077-301 was a double-blind, placebo-controlled, 12-week, randomized withdrawal design in opioid-tolerant Low Back Pain patients.

A total of 19 clinical pharmacology studies were included in this current submission. Thirteen (13) of them were either submitted in the original NDA 21-217 or included in the NDAs for Dilaudid (hydromorphone hydrochloride Oral Liquid) (NDA 19-891), Dilaudid (hydromorphone hydrochloride 8 mg Tablets) (NDA 18-892), or Dilaudid HP (hydromorphone hydrochloride Injection (NDA 19-034). Six new studies were submitted. This review focuses on the following in vivo studies: dosage form equivalence study (C-2005-032), single dose relative BA and food effect study (42801-PAI-1008), multiple dose relative BA study (42801-PAI-1009), alcohol interaction study (C-2005-020), and abuse potential study (C-2004-022). In addition, in vitro inhibition study, in vitro alcohol interaction study, and pediatric plan are also reviewed.

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed this resubmission dated May 22, 2009 and finds it acceptable provided that a satisfactory agreement can be reached between the sponsor and the Agency regarding the language in the package insert.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Dosage Form Equivalence (2 x 4 mg Exalgo v.s. 1 x 8 mg Exalgo ER tablets): Two of the 4 mg tablets are bioequivalent to one 8 mg tablet. The least squares estimate of the ratios (2 x 4 mg / 1 x 8 mg) for the AUC_{inf}, AUC_t, and C_{max} are 101%, 103%, and 101%, respectively, and the corresponding 90% Confidence Intervals (CIs) are 96 -106%, 98 – 108%, and 96 – 106%. All of the 90% CIs are within the range of 80 to 125%. It should be noted that sponsor is not proposing to market 4 mg strength at this time.

Relative Bioavailability (Exalgo ER tablet vs Immediate Release (IR) Tablet):

Single dose: Single oral dose of the 16 mg Exalgo tablet provides equivalent AUC_t or AUC_{inf} of hydromorphone as the 4 mg IR tablet every 6 hours (q6h) under fasting condition. The point estimate of the geometric mean ratio (Exalgo ER tablet/IR tablet) for AUC_{inf} and AUC_t are 107% and 104%, respectively. The corresponding 90% CIs are 97 - 118% and 95 - 115%. On average, the C_{max} value of Exalgo tablet and the reference IR tablet are 1.89 and 3.57 ng/mL, respectively.

Multiple dose: Multiple oral doses of the once daily (qd) 16 mg Exalgo tablet provides equivalent exposure (AUC_{0-τ}) of hydromorphone as the 4 mg IR tablet q6h at steady state under fasting condition. The point estimate of the geometric mean ratios (Exalgo tablet/IR tablet) for AUC_{0-τ} is 105% with 90% confidence interval of 100 to 111%. The plasma concentration fluctuation based on C_{max} and C_{min} values are significant less for Exalgo tablet than the IR tablet. On average, the steady state C_{max} values of Exalgo 16 mg tablet qd and 4 mg IR tablet q6h are 3.54 ng/mL and 5.28 ng/mL, respectively. The steady state C_{min} values of Exalgo 16 mg qd and 4 mg IR tablet q6h are 2.15 ng/mL and 1.47 ng/mL, respectively.

Food Effect: Food does not affect the PK of Exalgo tablet. The point estimates of the geometric means ratios (fed/fasting) for AUC_{last}, AUC_{inf}, and C_{max} are 100%, 100%, and 94%,

respectively. The corresponding 90% confidence intervals are 91 – 110%, 90 – 110%, and 85 – 104%, respectively. All of the 90% confidence intervals fell within the range of 80-125%.

Alcohol Effect: The controlled-release property of Exalgo tablet is maintained in the presence of alcohol and that there is no ‘dose dumping’ of hydromorphone. With various concentrations of alcohol (4%, 20% and 40%) the median Tmax is 12 to 16 hours with the range of 4 to 27 hours, which are similar to 0% alcohol. The Cmax values in the 3 alcohol treatments in the fasted state are higher than that in the 0% alcohol treatment, with mean geometric ratios of 117%, 131%, and 128% for the 4%, 20%, and 40% alcohol treatments, respectively. In the fed state, the mean geometric ratios are 114%, 114%, and 110%, for the 4%, 20%, and 40% alcohol treatments, respectively. The maximal increase in Cmax observed in any individual subject is 2.5-fold in fasting condition and 2-fold under fed condition in the comparison of the 40% vs 0% alcohol treatments. Although the in vitro release rate is slightly increased in the presence of 40% alcohol, the release characteristics were maintained.

Abuse Potential: Because the Abuse Potential study (C-2004-022) contains both PK and PD data, this study is briefly reviewed. For comprehensive review, please refer to the review conducted by Control Substance Staff (CSS). Generally, the pharmacodynamic response profiles for all treatments reflected the pharmacokinetic profiles. The numerical trends for Cmax and maximum response for Drug Liking and Cole/ARCI subscales are in similar order.

2 Question Based Review

2.1 General Attributes of the Drug

1. *What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?*

Hydromorphone hydrochloride, a hydrogenated ketone of morphine, is a potent opioid analgesic first synthesized from morphine in 1921 and brought to market several years later. Several dosage forms are currently available for hydromorphone administration including immediate-release (IR) tablet (NDA 18-892), oral liquid (NDA 19-891), and solutions for injection (NDA 19-034).

Knoll Pharmaceuticals submitted the original NDA 21-217 under the trade name of Dilaudid CR® 8, 16, 32, and 64 mg strengths on December 28, 1999. The Agency issued an Approvable Letter on October 27, 2000 which contained five deficiencies in the Chemistry, Nonclinical and Clinical areas. No clinical pharmacology related deficiency was identified. This NDA was transferred to ALZA Corporation, a subsidiary of Johnson and Johnson, who changed the product name to OROS® Hydromorphone HCl. Neuromed acquired the US rights to the product from the ALZA Corporation in April 2007, and NDA 21-217 was transferred to Neuromed on October 5, 2007. The sponsor is now seeking approval of 8, 12, 16, and 32 mg strengths, not the 64 mg strength. In this review, both OROS and Exalgo are used interchangeably..

Among all the 19 clinical pharmacology studies included in this current submission, 10 studies (D-101, DO-123, DO-124, DO-129, D-102, D-103, C94-014-00, C-96-054-01, D-108, and D-109) were included in the original submission and were reviewed in the first review cycle (please find Dr. Albert Chen’s review in Appendix 1). Some of the studies were submitted to the NDAs for Dilaudid® products including NDA 19-891, NDA 19-892, and NDA 19-034. This review will focus on the following new studies: a dosage form equivalence study (C-2005-032), single dose relative BA and food effect study (42801-PAI-1008), multiple dose relative BA study (42801-PAI-1009), alcohol interaction study (C-2005-020) and abuse potential study (C-2004-022).

2. *What are the proposed mechanism(s) of action and therapeutic indication(s)?*

The precise mechanism of action of hydromorphone is not known, although it is believed to exert its primary effects on opioid receptors in the central nervous system. Hydromorphone is generally considered four to eight times more potent than morphine on a milligram-for-milligram basis.

The proposed indication is for the management of moderate to severe pain in opioid tolerant patients requiring continuous, around-the-clock opioid analgesia for an extended period of time.

3. *What are the proposed dosage(s) and route(s) of administration?*

The proposed dose range of Exalgo is 12 mg to 64 mg once daily following oral administration. This controlled release dosage form, which utilized OROS technology, is developed in 4 strengths containing 8 mg, 12 mg, 16 mg, and 32 mg of hydromorphone. This technology has been used in other prescription and nonprescription products.

2.2 General Clinical Pharmacology

1. *What is the protein binding of hydromorphone?*

The protein binding is low in human. Using a DIANORM equilibrium dialyser, the protein binding in human plasma is 27% at hydromorphone concentrations of 10, 50, and 100 ng/mL. This is consistent with previously published literature data which showed a binding of $19\% \pm 9\%$ (Parab et al., 1988; Reidenberg et al., 1988). The extent of binding is mainly mediated by albumin, with minimal contribution from α 1-acid glycoprotein.

2. *What is the abuse potential of the Exalgo ER tablets?*

Abuse Potential study (C-2004-022) is briefly reviewed here. For comprehensive review, please refer to the review conducted by Control Substance Staff (CSS).

Generally, the pharmacodynamic profiles for all treatments reflected the pharmacokinetic profiles. The numerical trends for C_{max} and maximum response for Drug Liking and Cole/ARCI subscales: stimulation - Euphoria are in the similar order.

Study C-2004-022 is a single-center, single-dose, double-blind, double-dummy, placebo-controlled, randomized, crossover study in healthy subjects who had a history of polydrug use and moderate opiate use, but were not dependent on opiates. It consists of two phases, Phase A and Phase B. In phase A, each subject received single doses of Exalgo hydromorphone 16 mg, Exalgo hydromorphone 32 mg, Exalgo hydromorphone 8 mg crushed, hydromorphone 8 mg IR tablet (active control), and placebo. If all treatments were well tolerated, subjects entered Phase B. In Phase B, subjects received single doses of Exalgo hydromorphone 64 mg and hydromorphone 8 mg IR tablet (active control). Sixty-four subjects were screened, 38 subjects were treated in and 30 completed Phase A, and 29 subjects were treated in and 28 completed Phase B of the study.

Figure 1 shows the PK profiles for subjects who completed Phase A. Table 1 summarizes the PK parameters for subjects who completed Phase A and Phase B. In Phase A, the PK profile of crushed Exalgo 8 mg was similar to that of 8 mg IR tablet, with T_{max} values around 1.4 to 1.7 hours. The T_{max} values of different strengths of Exalgo intact tablets were 16 to 18 hours. The numerical trend of C_{max} values is 8 mg IR tablet > Exalgo 8 mg crushed > Exalgo 32 mg intact > Exalgo 16 mg intact. The PK profiles of IR 8 mg tablet is similar between Phase A and Phase B. In Phase B, the Exalgo 64 mg intact tablet has similar C_{max} as the 8 mg IR tablet.

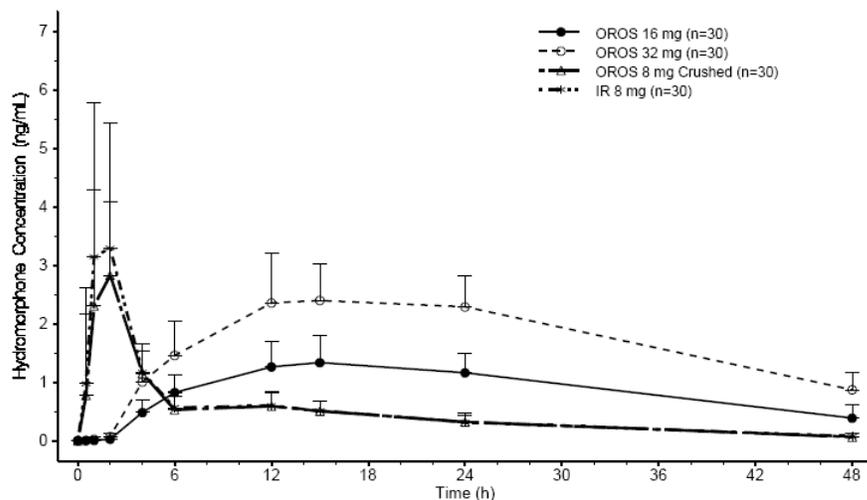


Figure 1 Mean (SD) Plasma Hydromorphone concentration Profiles (all subjects who completed Phase A)

Table 1 Mean (SD) Plasma Hydromorphone Pharmacokinetic Parameters

Parameter	Phase A (n = 30)				Phase B (n = 28)	
	8 mg IR tablet	Exalgo 32 mg	Exalgo 16 mg	Exalgo 8 mg crushed	8 mg IR Tablet	Exalgo 64 mg
C _{max} (ng/mL)	4.86 (2.3)	2.79 (0.66)	1.50 (0.41)	3.67 (1.5)	5.00 (2.6)	4.43 (1.6)
T _{max} (h)	1.43 (0.75)	17.0 (5.7)	16.0 (4.7)	1.74 (0.93)	1.49 (1.0)	18.3 (7.1)
T _{1/2} (h)	12.1 (4.0)	16.5 (2.9)	16.9 (5.3)	12.4 (3.4)	13.9 (6.1)	Not estimable
AUC _t (ng.h/mL)	23.5 (7.5)	81.1 (15)	41.1 (11)	21.4 (6.9)	21.9 (6.6)	140 (46)
AUC _{inf} (ng.h/mL)	25.7 (7.7)	101 (18)	50.9 (14)	24.0 (6.5)	24.5 (6.3)	Not estimable

To illustrate the PD effects, the data for Drug Liking and Cole/ARCI subscales: stimulation – Euphoria are shown in Figures 2 and 3, and Tables 2 and 3. The time course of Drug Liking for Exalgo crushed 8 mg is similar to 8 mg IR tablet, with the time to maximal response at approximately 2 hours. The time to maximal response for different strengths of Exalgo tablets were 6 to 12 hours. The numerically trend for the maximal scores is similar to C_{max} values. In comparing to 8 mg IR tablet, Exalgo 64 mg tablet has a higher maximum score (79.7 vs 70.1), although the C_{max} values were comparable. Similar trend is observed for Euphoria.

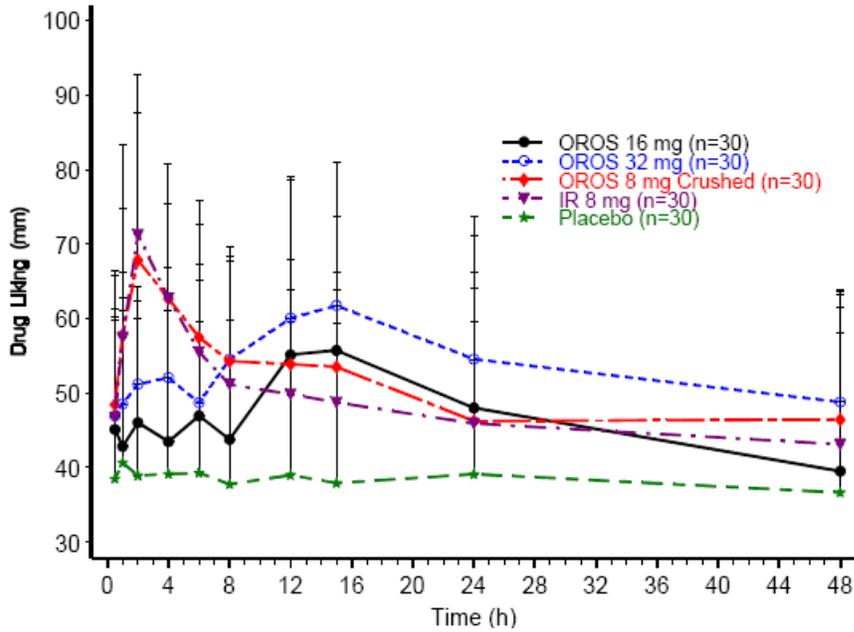


Figure 2 Mean (SD) Profile of Subjective Effect Visual Analog Scale – Drug Liking by Treatment in Subjects Who Completed Phase A.

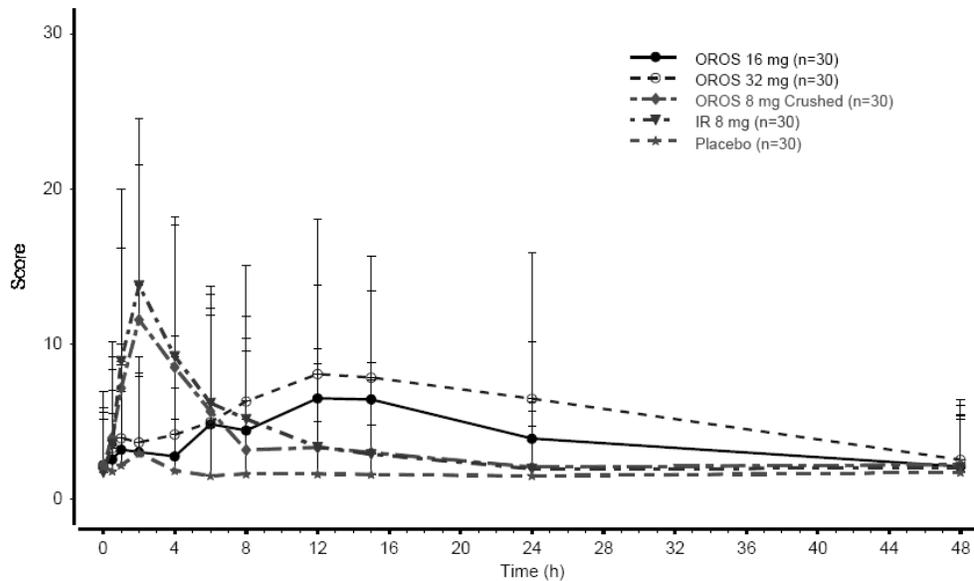


Figure 3 Mean (SD) Profile of Cole/ARCI Subscales: Stimulation – Euphoria by Treatment in Subjects Who Completed Phase A

Table 2 Maximum Scores on the Subjective Effects VAS – Drug Liking by Treatment

Treatment	Mean (SE)	Median	Min, Max	
Phase A n = 30	8 mg IR tablet	78.3 (2.8)	77.0	50, 100
	Exalgo 32 mg	73.6 (2.8)*	72.0	50, 100
	Exalgo 16 mg	65.0 (3.8)	65.0	0, 100
	Exalgo 8 mg	75.8 (2.8)	76.0	50, 100

	crushed			
	Placebo	42.8 (3.8)	50.0	0, 66
Phase B n = 28	8 mg IR	70.1 (4.8)	75.5	0, 100
	Exalgo 64 mg	79.7 (3.4)	85.0	35, 100

Table 3 Maximum Scores for Cole/ARCI Subscales: Stimulation – Euphoria

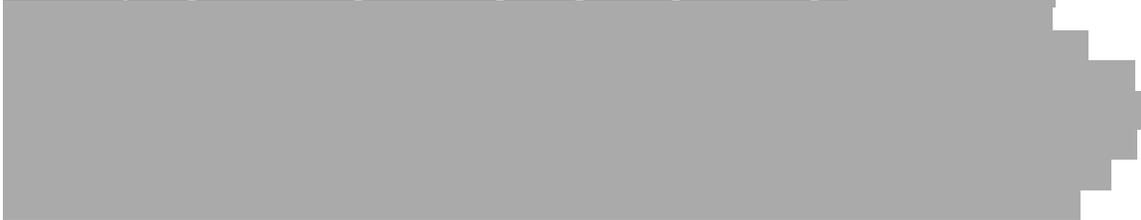
Treatment		Mean (SE)	Median	Min, Max
Phase A n = 30	8 mg IR Tablet	16.9 (1.8)	15.5	0, 42
	Exalgo 32 mg	13.2 (1.9)	11.5	0, 39
	Exalgo 16 mg	9.9 (1.5)	7.0	0, 28
	Exalgo 8 mg crushed	14.7 (1.8)	15.5	0, 34
	Placebo	4.4 (1.0)	2.0	0, 20
Phase B n = 28	8 mg IR Tablet	12.8 (1.5)	12.5	0, 26
	Exalgo 64 mg	16.6 (2.0)	17.0	0, 42

2.3 Intrinsic Factors

1. What is the pediatric plan?

Under the Pediatric Research Equity Act (PREA), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new route of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indications in pediatric patients unless this requirement is waived, deferred, or inapplicable. This application represents a new indication, new dosage form and new dosing regimens.

To fulfill the PREA requirement, sponsor requested waiver for ages 0 to 2 and submitted a pediatric plan for deferred studies for ages 2 to 17. Sponsor plans to submit a protocol to conduct a PK study in age 7 – 17 using the existing dosage strengths of Exalgo. (b) (4)



Proposed studies:

1. A Phase 1, Pharmacokinetic Study in Children (Ages 7 – 17) who are opioid Tolerant with Chronic Pain
2. (b) (4)
3. A Phase 1, Pharmacokinetic Study in Children (Ages 2 - < 7) who are Opioid Tolerant with Chronic Pain
4. (b) (4)

PeRC meeting was held on October 14, 2009, it was concluded that agency is waiving the pediatric study requirement for ages 0 through 2 years for this application because necessary studies are impossible or highly impracticable. Agency is deferring submission of pediatric studies for ages 2 through 17 years for this application in a defined timeline. Since chewing tablet may defeat the extended release characteristics, the children should be taught not to chew the tablets.

2.4 Extrinsic Factors

1. Does alcohol affect the PK of EXALGO?

In the presence of alcohol (up to 240 mL of 40%), the extended release profile of Exalgo is maintained and there is no significant potential for “dose dumping”.

The effect of various concentrations of alcohol (240 mL of 0%, 4%, 20%, and 40% alcohol in orange juice) on the PK of EXALGO was assessed in Protocol C-2005-020-01. Protocol C-2005-020-01 is a single center, open-label, randomized, 4-treatment, 4-period, 4-sequence, crossover study in 2 groups (fasting and high-fat fed conditions) of healthy subjects. Subjects also received oral naltrexone 50 mg as an opioid antagonist 14 hours and 2 hours before each dose of study treatment and twice daily during the 48 hours after each dose. Forty-eight subjects were enrolled (24 in each group) and 39 subjects completed the study (20 in Group 1 and 19 in Group 2).

Study results (Tables 4 and 5) demonstrated that the overall pharmacokinetic profiles were similar for all treatments. Median Tmax values were 16 hours with range of 6 to 27 hours for 0% alcohol. With various concentration of alcohol (4%, 20% and 40%) the median Tmax was 12 to 16 hours with the range of 4 to 27 hours. The AUC values were not affected by alcohol. The geometric mean Cmax values were increased by 17%, 31% and 28% with 4%, 20%, and 40% alcohol, respectively, under fasting condition. Under fed condition, the geometric mean Cmax values were increased by 10% to 14% with 4%, 20%, and 40% alcohol. The maximal increase in Cmax observed in one individual was 2.5-fold under fasted condition and 2-fold under fed condition in the comparison of the 40% vs 0% alcohol treatments.

Table 4 Plasma Hydromorphone Pharmacokinetic Parameters Available Data Minus Outliers (Dataset #3) under Fasting Condition (Protocol C-2005-020-01)

Mean (SD)	Treatment A 0% Alcohol N = 20	Treatment B 4% Alcohol N = 22	Treatment C 20% Alcohol N = 19	Treatment D 40% Alcohol N = 17
Cmax (ng/mL)	1.37 (0.32)	1.56 (0.39)	1.90 (0.66)	1.89 (0.85)
Tmax (h) [Median (Range)]	16 (6-27)	12 (6-27)	12 (4-16)	12 (6- 24)
T1/2 (h)	12.4 (5.1) ^a	12.6 (6.5) ^b	12.4 (7.2) ^c	11.1 (3.0) ^d
AUCinf	40.6 (11.0)	39.9 (14.1)	43.7 (12.1)	42.2 (13.2)
Arithmetic Ratio: Mean (Range)				
Cmax	--	1.19 (0.8 – 1.7)	1.35 (0.7 – 2.4)	1.37 (0.7 – 2.5)
AUCinf	--	1.01 (0.4 – 1.5)	1.05 (0.6 – 1.3)	1.03 (0.6 – 1.7)
Geometric Ratio: Mean (90% CI)				
Cmax	--	116.70 (104.48 – 130.36)	131.16 (117.01- 147.02)	128.31 (114.18 – 144.17)
AUCinf	--	96.83 (87.48- 107.17)	103.21 (92.93- 114.62)	101.65 (91.32- 113.13)

^a n=19, ^b n=20, ^c n=18, ^d n=16

Table 5 Plasma Hydromorphone Pharmacokinetic Parameters Available Data Minus Outliers (Dataset #3) under Fed Condition (Protocol C-2005-020-01)

Mean (SD)	Treatment E 0% Alcohol N = 18	Treatment F 4% Alcohol N = 20	Treatment G 20% Alcohol N = 16	Treatment H 40% Alcohol N = 20
Cmax (ng/mL)	1.42 (0.50)	1.64 (0.60)	1.52 (0.32)	1.56 (0.56)
Tmax (h) [Median (Range)]	16 (6-27)	12 (8-24)	12 (6-24)	16 (6-27)
T1/2 (h)	11.6 (5.1) ^a	11.6 (4.9) ^b	10.4 (3.9) ^c	10.8 (4.8)
AUCinf	37.1 (8.6)	36.7 (10.5)	36.6 (9.7)	34.8 (11.9)

Arithmetic Ratio: Mean (Range)				
Cmax	--	1.20 (0.7-1.8)a	1.20 (0.8-1.9)c	1.14 (0.6-2.0)a
AUCinf	--	0.97 (0.6 -1.3)a	1.09 (0.8-1.7)c	0.96 (0.5-1.4)a
Geometric Ratio: Mean (90% CI)				
Cmax	--	113.72 (99.97-129.36)	114.36 (100.14-130.61)	110.34 (97.08-125.41)
AUCinf	--	94.72 (86.44-103.79)	106.21 (96.63-116.73)	94.09 (85.91-103.04)

^a n=17, ^b n=18, ^c n=15

In vitro dissolution study results (Figure 4 and Table 6) showed a slight increase in release rate at early time points but the overall dissolution profiles were not affected by various concentrations of ethanol (up to 40%).

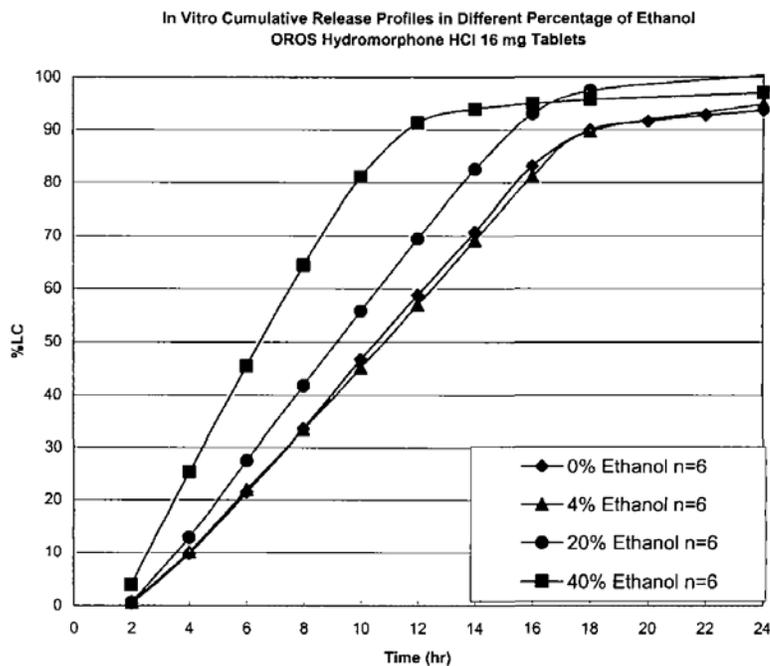


Figure 4 In vitro Cumulative Release Profiles of Exalgo Hydromorphone 16 mg Tablets in Different Percentage of Ethanol

Table 6 Cumulative Release Profiles of Exalgo Hydromorphone 16 mg Tablets in Different Percentages of Ethanol using USP Type VII

Time Hour	0% Ethanol N = 6 % Label Claim	4% Ethanol N = 6 % Label Claim	20% Ethanol N = 6 % Label Claim	40% Ethanol N = 6 % Label Claim
2	0.47	0.72	0.65	4.02
4	9.82	10.08	12.84	25.34
6	21.48	22.04	27.55	45.39
8	33.61	33.48	41.79	64.44
10	46.64	45.08	55.79	81.13
12	58.79	56.92	69.45	91.37
14	70.72	69.18	82.55	94.03
16	83.17	81.14	93.08	95.06
18	90.00	89.70	97.51	95.83

20	91.65			
22	92.82			
24	93.75	94.99	100.36	97.14
Residual	9.56	10.10	6.28	3.12
Mass Balance	103.31	105.10	106.65	100.26

2. Is hydromorphone an inhibitor of CYP enzymes?

The inhibition study in pooled human liver microsomes suggested that hydromorphone would not significantly inhibit CYP1A2 (phenacetin), 2C9 (tolbutamide), 2C19 (S-mephenytoin), 2D6 (dextromethorphan), 3A4 (testosterone), or 4A11 (lauric acid) at therapeutic concentrations.

Table 7 Activities of CYPs in the presence of various concentrations of Hydromorphone

Hydromorphone (μ M)	CYP					
	1A2	2C9	2C19	2D6	3A4	4A11
0 (control)	100	100	100	100	100	100
10	139.4	87.4	103.2	96.3	108.0	112.0
50	122.4	93.4	122.8	56.5	112.6	96.6
100	132.9	83.9	120.0	25.4	87.0	88.0
1000	119.0	87.0	127.2	13.7	106.1	96.4
5000	107.5	87.9	104.0	ND	60.4	88.3
10000	65.0	85.6	44.0	ND	41.1	107.9

ND : Not detectable.

Results are expressed as % metabolite (presence of hydromorphone)/% metabolite (control).

2.5 General Biopharmaceutics

1. Is the bioavailability of Exalgo tablet similar to immediate release hydromorphone (Dilaudid) tablet following single dose administration?

A single oral dose of 16 mg Exalgo hydromorphone tablet provides similar exposure (AUC_{last} and AUC_{inf}) as compared to 16 mg IR tablets (4 mg q6h) (Study 42801-PAI-1008). Study 42801-PAI-1008 was a randomized, open-label, single-center, three-period, crossover study conducted in healthy subjects. The administration of the first of the four doses of the IR tablet of hydromorphone, on Day 1, occurred after at least a 12-hour fast (Treatment B). Subjects fasted again for approximately 2 hours prior to and after each subsequent IR dose. Administration of Exalgo hydromorphone formulation occurred after a 12-hr fast (Treatment A) and under high-fat fed condition (Treatment C). Subjects were dosed with naltrexone at 14 hours and 2 hours prior to the initiation of dosing, and continued at 12-hour intervals up to 58 hours post dose. Thirty (30) (23 males and 7 females) were enrolled and 29 subjects completed the study.

Figure 5 shows the PK profiles. The statistical results for the assessment of relative bioavailability between Exalgo hydromorphone and IR hydromorphone (Dilaudid) tablet are presented in the Table 8. Results showed that the ratio of the geometric means for log transformed AUC values as well as its corresponding confidence intervals fell within the range of 80% to 125%. On average, the C_{max} values of Exalgo 16 mg tablet were 47% lower than 4 mg IR q6h.

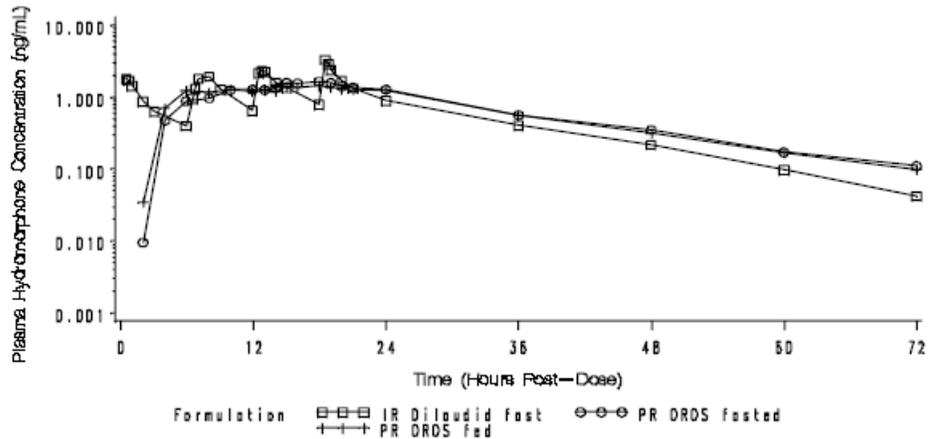


Figure 5 Mean Plasma Concentration-Time Profiles of Hydromorphone Following Single Oral Dose Administration of 16 mg Exalgo Formulation Under Fed and Fasted Conditions and 4 mg Dilaudid tablet Administered q6h Under Fasted Conditions in Healthy Subjects (Study 42801-PAI-1008)

Table 8 Mean (SD) PK parameter of hydromorphone following single oral administration of a 16 mg Exalgo hydromorphone formulation under fasted condition and 4 mg IR hydromorphone tablet administered every 6 hours under fasted condition in healthy adults subjects (Study 42801-PAI-1008)

Parameter	Exalgo Tablet Fasted (Treatment A, N = 30)	IR Tablet Fasted (Treatment B, N = 30)
AUClast (ng.h/ml)	46.9 (13.8)	43.9 (10.4)
AUCinf (ng.h/mL)	50.2 (16.2)	45.5 (10.3)
Cmax (ng/mL)	1.89 (0.48)	3.57 (1.46)
T1/2 (h)	14.4 (6.04)	12.7 (3.43)
Tmax (h) ^a	17.9 (6.01 – 24.2)	0.5 (0.5 – 2.0)
Geometric Mean Ratio (Exalgo/IR) % (90% CI)		
AUClast	104.3 (94.9 – 114.7)	
AUCinf	107.1 (97.0 – 118.1)	

^a tmax reported as median (range)

2. *Is the bioavailability of Exalgo Hydromorphone similar to immediate release hydromorphone (Dilaudid) tablet following multiple dose administration?*

Multiple doses of the once-daily 16 mg Exalgo tablets provided the same exposure (AUC_{0-τ}) of hydromorphone as the 4-times daily 4 mg IR hydromorphone (Dilaudid) tablets. At steady state, the plasma concentration fluctuation based on C_{max} and C_{min} values were significant less for Exalgo formulation than the IR tablet. Study results are consistent with the findings from Study C-96-054, which was submitted in the original NDA.

Study 42801-PAI-1009 was a randomized, open-label, single-center, multiple-dose, two period crossover study conducted in healthy adults subjects. Subjects received the Exalgo hydromorphone formulation one dose every 24 hours, following a 12 hour fast for a total of 5 days (Treatment A). IR tablet 4 mg was given every 6 hours for a total of 20 doses over a 5-day period (Treatment B). Subjects received a concomitant dosing regimen of naltrexone 50 mg, in order to block the opioid effects of hydromorphone. Subjects were dosed with naltrexone at 14 hours and 2 hours prior to the initiation of dosing on Day 1, and thus dosing continued at 12-hour intervals up to 130 hours postdose on Day 1. A total of 30 subjects (15 males and 15 females) were enrolled and 29 subjects completed the study.

Study results are presented in Figure 6 and Table 9. Multiple oral doses of the once-daily 16 mg Exalgo formulation provided the same exposure (AUC_{0-τ}) of hydromorphone as the 4-times daily 4 mg IR hydromorphone (Dilaudid) tablet. At steady state, the C_{max} values of Exalgo formulation is less than the IR tablet. The C_{min} values of Exalgo formulation is greater than the IR tablet.

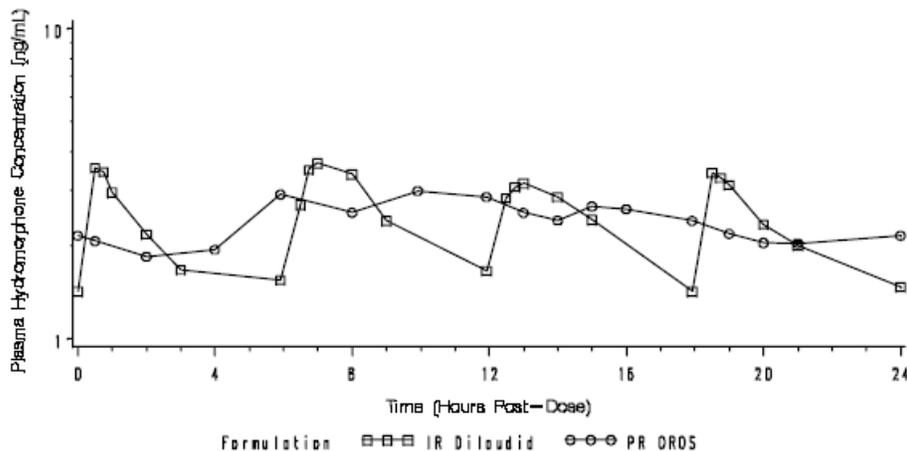


Figure 6 Mean Plasma Concentration-Time Profiles of Hydromorphone on Day 5 Following Multiple Oral Doses of 16 mg Exalgo Tablets and 4 mg Dilaudid Tablet Administered q6h Under Fasted Conditions in Healthy Subjects (Study 42801-PAI-1009).

Table 9 Mean (SD) PK parameter of hydromorphone following multiple oral doses of a 16 mg Exalgo tablet and 4 mg IR hydromorphone tablet administered every 6 hours under fasted conditions in healthy adult subjects on Day 5 (Study 42801-PAI-1009)

PK Parameter	Exalgo Tablet N = 29	IR Tablet N = 29
AUC(0-τ) (ng.h/mL) ^a	57.6 (16.3)	54.8 (14.8)
C _{max,ss} (ng/mL)	3.54 (0.959)	5.28 (1.37)
C _{min,ss} (ng/mL)	2.15 (0.872)	1.47 (0.417)
C _{ssav} (ng/mL)	2.40 (0.678)	2.28 (0.618)
T _{max,ss} (h) ^b	11.9 (5.92-24.2)	0.75 (0.5-2)
Flux (%) ^c	97.1 (144)	277 (115)
Geometric Mean Ratio (Exalgo/IR) % (90% CI)		
AUC _{0-τ}	105.2 (99.9 – 110.8)	--

^a τ = 24 hours ^b median (range) ^c Flux is defined as (C_{max,ss} – C_{min,ss})/C_{min,ss} x 100

Based on the pre-dose concentrations collected on Days 2, 3, 4, 5, and trough levels on Day 6, it was concluded that steady state was attained by Day 4 (Table 10).

Table 10 Pre-dose Concentrations Geometric Means (%CV) per Treatment and Time Point

Day	OROS [®] (A)	IR Dilaudid [®] (B)
2	1.4575 (30.8%)	0.9713 (33.6%)
3	1.5605 (68.9%)	1.2092 (33.7%)
4	2.0247 (38.7%)	1.3859 (34.9%)
5	1.9751 (44.8%)	1.3471 (35.0%)
6	1.9613 (48.8%)	1.4114 (30.0%)

3. Does food affect the bioavailability of hydromorphone from the dosage form?

High fat meal does not affect the bioavailability of Exalgo tablets as shown in Study 42801-PAI-1008. Study 42801-PAI-1008 was a randomized, open-label, single-center, three-period crossover study. Naltrexone 50 mg oral tablet was given to block the opioid effect. High-fat meal consists of 2 strips of fried bacon, 2 eggs fried in butter, 4 ounces (120 gm) hash brown potatoes fried in butter, 2 buttered pieces of white toast and 240 mL whole milk. The meal were served 30 minutes before study drug administration and completely eaten within 30 minutes. The PK results for single dose of 16 mg Exalgo tablet under fasting and high-fat fed conditions are presented in the Table 11.

The 90% confidence intervals for the ratios of geometric means between Exalgo under fasted and fed conditions for C_{max} and all AUC values were contained within the 80-125%. Based on these results, food does not affect the PK of Exalgo tablet.

Table 11 Mean (SD) Plasma Pharmacokinetic Parameters of Hydromorphone following single oral administration of a 16 mg Exalgo tablet under fasted and fed conditions in healthy adults subjects (Study 42801-PAI-1008)

Parameter	Exalgo Fasted (Treatment A, N = 30)	Exalgo High-Fat Fed (Treatment C, N = 29)
AUC _{last} (ng.h/ml)	46.9 (13.8)	45.9 (12.2)
AUC _{inf} (ng.h/mL)	50.2 (16.2)	48.4 (11.6)
C _{max} (ng/mL)	1.89 (0.48)	1.78 (0.50)
T _{1/2} (h)	14.4 (6.04)	14.4 (4.14)
T _{max} ^a (h)	17.9 (6.01 – 24.2)	16.0 (5.92 – 24.2)
Geometric Mean Ratio (Fed/Fasted) (%) (90% CI)		
AUC _{last}	100.3 (91.1 – 110.3)	
AUC _{inf}	99.5 (90.1 – 109.9)	
C _{max}	94.5 (85.4 – 104.4)	

^a Median (Range)

4. *Is the dosage form equivalence established for the 4 mg tablet compared to 8 mg strength tablet?*

The dosage form equivalence between 2 x 4 mg and 1 x 8 mg Exalgo tablets were established because the point estimate of geometric mean ratios and its corresponding 90% confidence intervals for AUC_{inf}, AUC_t, and C_{max} were within the range of 80 – 125%.

Study C-2005-032-02 compared 2 x 4 mg and 1 x 8 mg in healthy subjects. This was a single-centre, single-dose, open-label, 2-treatment, 2-period, 2-sequence, crossover study. Each subject received 2 x 4 mg (Treatment A) and 1 x 8 mg (Treatment B) under fasting condition. For each treatment, subjects received naltrexone 50 mg as the opioid antagonist 14 hours and 2 hours before dosing, and twice daily during dosing through 46 hours post-dose. There are a total of 52 subjects enrolled and 50 subjects completed the study.

Results of the PK parameters and the statistical analysis are summarized in Table 12. The point estimate of the ratios for the log-transformed AUC_{inf}, AUC_t, and C_{max} were 101.14%, 102.69%, and 100.97%, respectively, and the 90% confidence intervals were within the range of 80% to 125%, indicating that the 2 x 4 mg and 1 x 8 mg were bioequivalent.

Table 12 Mean (SD) Plasma Pharmacokinetic Parameters of Hydromorphone following single oral administration of 2 x 4 mg and 1 x 8 mg Exalgo tablets under fast condition in healthy adults subjects (Study C-2005-032)

PK Parameter	Treatment A Exalgo 2 x 4 mg n = 50	Treatment B Exalgo 1 x 8 mg n = 50
Cmax (ng/mL)	0.92 (0.25)	0.92 (0.29)
Tmax (h)	15.0 (5.83)	15.8 (6.82)
T1/2 (h)	12.5 (4.4)^a	13.3 (5.3) ^b
AUCt (ng.h/mL) ^c	23.3 (7.0)^a	22.8 (7.3) ^b
AUCinf (ng.h/mL)	25.2 (7.2)	25.1 (7.5)
Geometric Mean Ratio (2 x 4 mg/1 x 8 mg) % (90% CI)		
AUCinf	101.14 (96.30 – 106.22)	--
AUCt	102.69 (97.92 – 107.69)	
Cmax	100.97 (96.37 – 105.80)	

^a n=47 ^b n= 48 ^c AUCt was based on a sampling duration of 56 hours.

2.6 Analytical Section

1. What bioanalytical methods are used to assess concentrations?

LC/MS/MS method ATM-862 was used in all the studies including Studies 42801-PAI-1008, 42801-PAI-1009, C2004-022, C-2005-020, and C-2005-032. The minimum quantifiable hydromorphone concentration is 0.05 ng/mL. The calibration curve was linear in the range of 0.05 to 10.0 ng/mL. Precision and accuracy were determined by replicate analyses of human plasma quality-control pools spiked with hydromorphone prepared at 0.05 ng/mL and 3 QCs (0.150, 2.00, and 8.00 ng/mL). Precision was measured as the percent coefficient of variation (%CV) of the values determined for each pool. Accuracy was expressed as the percent difference between the mean value for each pool and the theoretical concentration. The interassay precision and accuracy ranges spanning the lower limit of quantitation (LLOQ), low, middle, and high hydromorphone quality control (QC) sample concentrations used during the sample analysis are summarized in Table 13.

Table 13 Summary of the Assay Performance: Precision and Accuracy of Standards and Quality Controls

Study #	Inter-assay accuracy (% Bias)	Inter-assay precision (%CV)
42801-PAI-1008	-6.8 – -0.7	3.2 – 6.0
42801-PAI-1009	-4.8 – -1.1	2.8 – 6.2
C-2004-022	-5.3 – 5.8	4.7 – 9.2
C-2005-020	-5.3 – 1.6	4.2 – 8.5
C-2005-032	-5.0 – 1.0	4.4 – 13.2

3 Detailed Labeling Recommendations

The following labeling comments are proposed by this reviewer. (Deletion is shown by **Red Strike through**, addition is shown by **blue underline**)

6 Page(s) of Draft Labeling have been Withheld in Full immediately following this page as B4 (CCI/TS)

4 Appendix

4.1 Clinical Pharmacology Filing Memo

Office of Clinical Pharmacology New Drug Application Filing and Review Form				
General Information About the Submission				
	Information		Information	
NDA/BLA Number	21-217	Brand Name	Exalgo	
OCP Division (I, II, III, IV, V)	II	Generic Name	Hydromorphone	
Medical Division	DARRP	Drug Class	Opioid	
OCP Reviewer	Wei Qiu, Ph.D.	Indication(s)	Moderate to severe pain in opioid tolerant patients	
OCP Team Leader	Suresh Doddapaneni, Ph.D.	Dosage Form	Tablet	
Pharmacometrics Reviewer	N/A	Dosing Regimen	QD	
Date of Submission	May 22, 2009	Route of Administration	Oral	
Estimated Due Date of OCP Review	October 21, 2009	Sponsor	Neuromed	
Medical Division Due Date	October 23, 2009	Priority Classification	Standard resubmission	
PDUFA Due Date	November 22, 2009			
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	1	1	
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:	x	1	1	
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:	x	1	1	
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				

Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	x	3	3	42801-PAI-1008, 42801-PAI-1009, and C-2005-032
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	x			Part of study 42801-PAI-1008
Bio-waiver request based on BCS				
BCS class				
Alcohol induced dose-dumping	x	2	2	One in vivo (C-2005-020) and one in vitro dissolution study
Abuse potential	x	1	1	C-2004-022
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan	x	1	1	Deferred studies in children aged 2 to 17 years
Literature References				
Total Number of Studies		10	10	

4.2 Clinical Pharmacology Review of Original NDA

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

<u>NDA:</u> 21-217 Hydromorphone HCl 8, 16, 32, 64 mg	<u>SUBMISSION DATE:</u> 12/29/99 (Serial No. 000) 02/16/00 (Serial No. BZ) 05/04/00 (Serial No. BZ)
<u>BRAND NAME:</u> Dilaudid Controlled-Release (CR) Tablets	
<u>SPONSOR:</u> Knoll Pharmaceuticals	<u>REVIEWER:</u> Tien-Mien Chen, Ph.D.
<u>TYPE OF SUBMISSION:</u> Original NDA Submission	Code: 3S

TITLE: "Review of Item 6: Human Pharmacokinetics and Bioavailability Section of An NDA"

SYNOPSIS:

Hydromorphone HCl (HM), a hydrogenated ketone of morphine, is a potent opioid analgesic (Schedule II) which was first introduced in the early 1920's. HM is a pure μ receptor agonist and is currently marketed in the US in various dosage forms. The 1, 2, 3, and 4 mg immediately release (IR) HM tablets (Dilaudid) do not hold NDAs. NDA 19-892 for Dilaudid IR 8 mg tablet was submitted to the Agency and approved on 12/07/92.

On 12/29/99, Knoll Pharmaceuticals submitted NDA 21-217 (Serial No. 000) to the Agency seeking approval for hydromorphone (HM) 8, 16, 32, and 64 mg Dilaudid controlled-release (CR) tablets for oral administration. The CR tablets resemble ordinary tablets in appearance and are composed of a bilayer core (containing a drug layer and a push layer) which in turn is coated with an insoluble cellulosic rate-controlling membrane. An orifice is drilled on the membrane for drug delivery. It utilizes ALZA's Push-Pull technology to provide HM release in a controlled manner over approximately 24 hr. Therefore, Dilaudid CR tablet is to be recommended for QD dosing.

Ten pharmacokinetics/bioavailability (PK/Bio) studies were submitted under Item 6, Human PK/Bio section of the NDA. They were conducted in 235 healthy male and female subjects as well as in 29 male and female patients with chronic pain. Additional analyses were also performed for 1) inter-/intra-subject variability, 2) gender differences, (b) (4) (b) (4) and 4) PK/PD (pharmacodynamic) relationships.

Certain human PK parameters for HM are available. Post intravenous (IV) administration of HM, the total clearance of HM was estimated to be 1.5 to 1.9 liters/min. The plasma terminal half-life ($T_{1/2}$) is 2.5 to 3 hr. The protein binding of HM is reported to be ~7%. HM is metabolized primarily in the liver by conjugation to form HM-3-glucuronide (H3G) and by reduction of the C-6 keto group to form 6- α - and 6- β -hydromorphol. It is primarily excreted in urine as H3G (35%) with minor amounts of 6- α - and 6- β -hydromorphol (2%), and unchanged HM (6%).

During the clinical development, 3 to 5 formulations per CR Dilaudid tablet strength were made. Several batches of the 4 strengths (8, 16, 32, and 64 mg) of Dilaudid CR tablets that were employed in the human PK/Bio studies were also employed in the pivotal clinical trial except for the CT 64 mg tablet. Three bioequivalence (BE) studies were conducted to assess the BE between the clinically tested (CT) and the to-be-marketed (TBM) formulations for 8, 32, and 64 mg CR Dilaudid tablets only. With previous consent of FDA, *in vivo* BE assessment for the CR 16 mg tablet was not needed.

In vitro dissolution data for Dilaudid CR tablets were provided and the dissolution specifications were also proposed. HM plasma levels (and those of its metabolite, H3G, in one PK study only) were determined using an LC/MS/MS assay method. The assay results and the validation report were provided for each PK study in the NDA except for one PK study. Finally, a study site inspection was conducted by Division of Scientific Inspection (DSI; HFD-48) for the pivotal BE study (for the 64 mg CR tablet batches) and it has been completed. The report dated 07/25/00 for the study site inspection is also attached.

RECOMMENDATION:

Knoll Pharmaceuticals' NDA 21-217 that was submitted on 12/29/99 for Dilaudid (HM) CR 8, 16, 32, and 64 mg tablets has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE II). OCPB is of the opinion that the human PK/Bio section (Item 6) of the NDA may be considered acceptable provided that the OCPB comments are addressed appropriately. The OCPB General Comments (p. 22) need to be conveyed to the sponsor.

CPB Briefing on 09/14/00: Drs. McCormick, Rapaport, and Hertz (HFD-170), Drs. Lazor, Sahajwalla, Doddapaneni, and Kim (HFD-870), and Dr. Harapanhalli (HFD-160)

09/01/00

Tien-Mien Chen, Ph.D.

Division of Pharmaceutical Evaluation II

RD initialed by John Hunt _____ J. Hunt 09/05/00

FT initialed by John Hunt _____

cc: NDA 21-217, HFD-170 (Hertz, Milstein), HFD-870 (H. Malinowski, J. Hunt, T.M. Chen), CDR (B. Murphy).

<u>TABLE OF CONTENTS:</u>	<u>Page</u>
I. Background	3
II. Summary of PK studies	4
III. Comment to the Reviewing Medical Officer	21
IV. General Comments (Nos. 1-5 need to be sent to the firm)	22
V. Labeling Comments (Need <u>NOT</u> be sent to the firm)	23

Appendix 1:

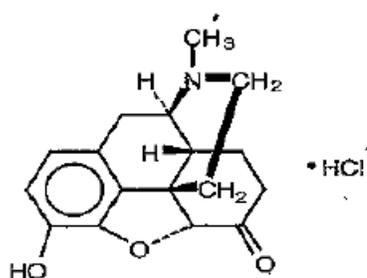
Appendix 1 contains a synopsis for each individual study.

Appendix 2:

Appendix 2 contains additional detailed data/information such as PI, assay validation reports, 07/25/00 report of study site inspection from the Division of Scientific Investigation (DSI; HFD 48), CT and TBM formulations for the 4 CR tablet strengths.

I. BACKGROUND:

HM is highly water-soluble, fine white or almost white odorless crystalline powder. It is moderately lipid soluble (octanol/phosphate buffer partition coefficient being close to 2). The structure of HM is shown below:



II. SUMMARY OF PHARMACOKINETICS, BIOEQUIVALENCE, PHARMACODYNAMICS, ETC.:

Table 1: Summary of 10 PK Studies

Study No.	Study Objectives/Design	Dosage Forms (Formulation Code)	No. of Subjects (M/F)
D-101 (Vol. 1.33)	6-period, SD ^a , IV, oral IR, and nested DB ^b 4x4 (CR 8, 16, 32 mg and placebo) for basic PK in healthy adults	IV 8 mg, IR 8 mg tablet CR 8 (H), 16 (C), 32 (E) mg + Placebo	12 (6M+6F)
DO-123 (Vol. 1.38)	SD, randomized, 4x4 BE in healthy adults	CR 8 mg (J, W*) CR 64 mg (P, Z*)	34 (29M+5F)
DO-124 (Vol. 1.42)	SD, randomized, 2x2 BE in healthy adults	CR 32 mg (L, Y*)	51 (29M+22F)
DO-129 (Vol. 1.46)	SD, randomized, 4-period, 2-sequence replicate BE in healthy adults	CR 64 mg (P, Z*)	50 (38M+12F)
D-102 (Vol. 1.57)	SD, randomized, 3x3 for food effect and DDI ^c with Naltrexone in healthy adults	CR 16 mg (C)	27 (21M+6F)
D-103 (Vol. 1.52)	SD, 4x4, dose proportionality PK in healthy adults	CR 8 (Q), 16 (N), 32 (O), 64 (P) mg	31 (20M+11F)
C94-014-00 (Vol. 1.65)	SD, randomized, 2x2 for one dose CR 32 mg vs. 4 doses of 5 mg IR (q 6hr) in healthy adults	CR 32 mg (A) IR 2 and 3 mg tablets	12M
C-96-054-01 (Vol. 1.61)	MD ^a , randomized, 2x2, CR 16 mg (qd) vs. IR 4 mg (q 6hr) for 4 days in healthy adults	16 CR mg (C) IR 4 mg tablet	18 (14M+4F)
D-108 (Vol. 1.62)	MD PK in patients with chronic pain	CR 8 (Q), 16 (N), 32 (O), 64 (P) mg	22 (18M+4F)
D-109 (Vol. 1.113)	MD PK in patients with chronic pain (high dose; 128 to 1984 mg)	CR 8 (Q), 16 (N), 32 (O), 64 (P) mg	7 (5M+2F)

^a. Single-dose (SD) and multiple-dose (MD).

^b. Double blind (DB).

^c. Drug-drug interaction (DDI).

*. To-be-marketed formulation.

1. SINGLE-DOSE PHARMACOKINETICS:

SUMMARY:

- The absolute bioavailability (F_{abs}) for the oral IR 8 mg tablet was estimated to be 19%. For CR 8, 16, and 32 mg tablets, F_{abs} ranged between 22-26%.
- The higher F_{abs} value for CR tablets than the IR tablet could be due to continuous absorption of CR in the lower GI tract where hepatic first-pass metabolism is less and/or reduced gut-wall metabolism in the distal portions of the GI tract.
-  (b) (4)

The above PK parameters for HM were obtained in Study No. **D-101**. It was a 6-period, single dose study evaluating an intravenous (IV) 8 mg dose, an IR 8 mg dose, and a nested double-blind 4x4 for CR 8, 16, 32 mg and placebo.

Note: A single-dose, pilot PK Study No. **C-94-014-00** was conducted earlier in 1994 to compare Dilaudid CR 32 mg with IR 5 mg q 6 hr. The results obtained from this pilot study show that 1) Dilaudid CR tablet is at least 90% bioavailable as compared to the IR tablet after dose-normalization, and 2) the absorption of HM from Dilaudid CR 32 mg tablet is continuous throughout the GI tract.

2. BIOEQUIVALENCE:

SUMMARY (BE assessment based on the Agency's BE acceptance criteria):

- For the 8 mg CR tablet, the TBM formulation (Test) is bioequivalent to the CT formulation (Reference): $\ln C_{max}$ (80.1-110.3) and $\ln AUC_{0-\infty}$ (90.3-102.8). However, for the 64 mg CR tablet, BE is not demonstrated, $\ln C_{max}$ (98.6-125.1) and $\ln AUC_{0-\infty}$ (100.3-129.7) [Study No. **DO-123**].
- For the 32 mg CR tablet, the TBM formulation is bioequivalent to the CT formulation: $\ln C_{max}$ (91.7-108.2) and $\ln AUC_{0-\infty}$ (81.3-113.8) [Study No. **DO-124**].
- For the 64 mg CR tablet, the TBM formulation is bioequivalent to the CT formulation: $\ln C_{max}$ (92.0-100.0) and $\ln AUC_{0-\infty}$ (90.4-99.0) [Study No. **DO-129**].

The inspection at one of the PK study sites (Study No. **DO-129**) was requested and completed. It is concluded by DSI (HFD-48) on 07/25/00 that the sponsor failed to keep the unused test articles at the study site for verification by the Agency, therefore, the study results are considered not acceptable.

Thus, a question is raised:

Are the above BE studies acceptable to support the approval of the 4 TBM strengths?

The above BE results for both CR 8 and 32 mg TBM and CT tablets did demonstrate bioequivalence. For the CR 64 mg tablet, 1) Study No. DO-123 showed minor deviation in both $\ln C_{max}$ and $\ln AUC_{0-\infty}$ and 2) the PK data obtained from Study No. DO-129 were spot checked and did not show any flaw. Therefore, failing to keep the unused test articles at the study site may be considered minor and the overall BE results are considered less satisfactory but acceptable. For the CR 16 mg tablet, since 1) the formulation differences between the TBM and CT tablets are not considered substantial and 2) dose proportionality between 8 and 64 mg has been demonstrated, a waiver to conduct a BE study is appropriate. Finally, if the NDA is deemed not to be approved due the clinical efficacy and/or safety reasons and new clinical trial(s) need(s) to be conducted, it is recommended that the TBM CR tablet formulations be employed.

Note : It should be noted that since healthy subjects were employed in the above three BE studies, Naltrexone, a synthetic, pure opioid antagonist to block the opioid pharmacodynamic effects, was given BID (12 hr prior to, at, and every 12 hr post Dilaudid CR treatment). The Naltrexone doses used are shown below in Table I:

<u>Dilaudid CR Tablet Dose</u>	<u>Naltrexone Tablet Dose</u>
8 mg	None
16 mg (<u>Not</u> tested for BE)	-----
32 mg	1 x 50 mg tablet BID for 3 doses
64 mg	1 x 50 mg tablet BID for 4 doses

3. INTER-/INTRA-SUBJECT VRIABILITY:

SUMMARY: (Study No. DO-129)

- Inter-subject variability of HM in healthy volunteers was calculated to be 27.1%-29.1% for C_{max} and 25.8-40.0% for AUC.
- Intra-subject variability of HM in healthy volunteers was calculated to be 15.7%-16.3% for C_{max} and 14.2-14.4% for AUC.

The inter/intra-subject variability of HM in healthy volunteers was investigated in BE Study No. DO-129 with a replicate design for 64 mg CR tablets, formulation Nos. P (CT tablet) and Z (TBM tablet). The detailed results of the analysis are shown below:

Table 2: Inter- and Intra-Subject Variability in the PK Parameters of HM after Administration of Single Dose of Dilaudid CR Tablets

Study No.	Dose	Formulation No.	No. of Subjects	Inter-subject CV%		Intra-subject CV%	
				C _{max}	AUC	C _{max}	AUC
DO-129	64 mg	P	46	27.1%	25.8%	16.3%	14.2%
		Z*	48	29.1%	40.0%	15.7%	14.4%

*. To-be-marketed formulation.

4. DOSE PROPORTIONALITY:

SUMMARY: (Study No. D-103)

- HM mean C_{max} and AUC_{0-∞} values increased proportionally as dose increased (8, 16, 32, and 64 mg).
- Mean T_{max} was calculated to be around 15 –17 hr and mean apparent terminal half-life (T_{1/2}) was estimated to be about 10-11 hr.
- Double-peaking was observed for all the CR tablet strengths in all the single-dose PK studies. As reported by the sponsor, this could be due to enterohepatic recycling secondary to HM glucuronide formation, biliary secretion, and subsequent hydrolysis to the parent molecule by gut flora.

The following question is therefore raised:

Are there other possible reasons for the double-peaking where the second peak is greater than the first peak?

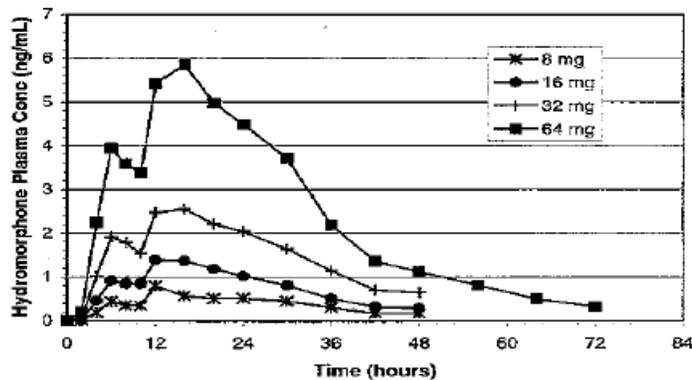
It could be or partially due to continuous and significant absorption of HM from the lower portion of the GI tract, since the mean T_{max} is 15-17 hr post dosing. After a discussion with the reviewing medical officer (MO), the double-peaking phenomenon is, however considered not critical to the efficacy or safety of Dilaudid CR tablet.

The above dose proportionality for the 4 CR tablet strengths, 8, 16, 32, and 64 mg was investigated in Study No. D-103. Naltrexone 50 mg tablet was also given BID similarly (Table 1) to 8 mg, 16, mg and 32 mg treatment arms (3 doses) and for 64 mg treatment arm, a fourth Naltrexone dose was further given. The mean PK parameters are shown below in Table 3 and the mean plasma profiles are shown in Figure 1.

Table 3. Mean (\pm SD) PK Parameters of HM After Single Oral Doses of Dilaudid CR 8, 16, 32, and 64 mg to Healthy Subjects (n=31; Study No. D-103)

PK Parameters/Treatment	TX A: 8 mg CR tablet	TX B: 16 mg CR tablet	TX C: 32 mg CR tablet	TX D: 64 mg CR tablet
C_{max} (ng/ml)	0.929 (1.01)	1.69 (0.78)	3.25 (1.37)	6.61 (1.75)
T_{max} (hr)	16.0 (7.2)	16.8 (5.4)	15.7 (5.4)	17.4 (5.7)
$AUC_{0-\infty}$ (ng-hr/ml)	19.5 (5.9)	40.8 (13.7)	80.3 (29.6)	178.7 (35.2)
$T_{1/2}$ (hr)	10.6 (4.3)	10.3 (2.4)	11.0 (3.2)	10.9 (3.8)

Figure 1: Mean Plasma HM Levels After Single Oral Doses of Dilaudid CR 8, 16, 32, 64 mg Tablets in Healthy Subjects (Study No. D-103)

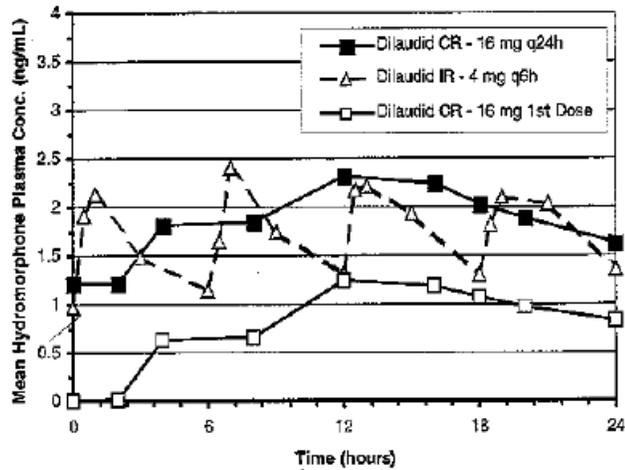


5. MULTIPLE-DOSE PHARMACOKINETICS:

SUMMARY: For HM (Parent Drug; Study No. C96-054-01):

- There is approximately 2-fold accumulation of HM during QD dosing of Dilaudid CR tablet compared to the first dosing (Day 1).
- Seemingly comparable systemic exposure was observed between QD dosing for the Dilaudid CR 16 mg tablet and Q 6hr dosing for the Dilaudid IR 4 mg tablet.
- A significant reduction of peak-to-trough fluctuation of plasma levels was also observed after CR administration when compared to IR administration

Figure 2: Mean Plasma HM Levels Following Administration of Dilaudid CR 16 mg tablet (QD) or IR 4 mg tablet (Q 6 hr)



The following question is raised:

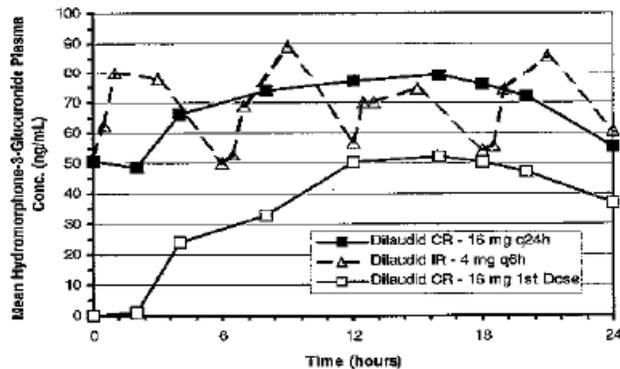
Did double-peaking seen in the single-dose PK study disappear in the multiple-dose study?

It was noted that in the multiple-dose study, the blood samples were taken less frequently, i.e., no blood sample at 10 hr post dosing, which may contribute to the apparent disappearance/invisibility of the double-peaking phenomenon.

SUMMARY: For H3G (Metabolite; Study No. C96-054-01):

- Single-dose and multiple-dose PK profiles of its metabolite, H3G, post Dilaudid CR administration also show similar and consistent patterns in terms of mean T_{max} (14 to 15 hr) and accumulation ratio (≈ 2).
- Mean AUC of metabolite, H3G (not active), was about 35 to 40-fold higher as compared to that of the parent compound, HM, indicating that HM is extensively metabolized.
- The steady-state AUC ratio of parent/H3G for CR 16 mg tablet QD (0.028) was higher as compared to that obtained from IR 4 mg tablet Q 6hr (0.025) which might imply less GI metabolism of HM post Dilaudid CR administration when compared to Dilaudid IR administration.

Figure 3: Mean Plasma H3G Levels Following Administration of Dilaudid CR 16 mg tablet (QD) or IR 4 mg tablet (Q 6 hr)



The above study, No. C96-054-01, examined the single-dose (Day 1) and steady-state PK profiles of HM and its major metabolite, HM-3-glucuronide (H3G). Dilaudid CR 16 mg QD was compared with IR 4 mg q 6hr for 4 days.

6. HEALTHY SUBJECTS vs. PATIENTS:

Multiple-dose PK of Dilaudid CR tablets was investigated both in healthy subjects and in patients with chronic pain. Therefore, a question is raised:

Did patient and healthy subjects show different PK characteristics?

Comparable PK outcomes were observed, although the mean T_{max} (9.8 hr) obtained from chronic pain patients (Study No. DO-108; n=5) is considerably shorter than that (14.7 hr) observed in healthy subjects (Study No. C96-054-01; n=18). The reason is not known which could be due to sparse patient data.

Table 4. Comparison of Mean (\pm SD) PK Parameters of HM in Healthy Volunteers and Chronic Pain Patients During Multiple-Dosing (Dilaudid CR 16 mg QD)

PK Parameters/Population	Healthy Volunteers (No. C96-054-01)	Chronic Pain Patients (No. DO-108)
No. of Subjects	18	5
C_{max} (ng/ml)	2.62 (0.83)	2.93 (0.60)
T_{max} (hr)	14.7 (5.1)	9.8 (5.8)
C_{min} (ng/ml)	1.16 (0.47)	1.25 (0.31)
AUC_{0-24hr} (ng-hr/ml)	45.6 (16.8)	46.1 (10.6)
Peak-to-Trough Fluctuation (%)	83.1 (31.4)	89.1 (16.4)

Note 1: The used of Naltrexone was also allowed in the protocol for Study No. C96-054-01. However, Naltrexone was given “as needed”. The sponsor indicated that as a result, only one female subject (No. 112) who received Dilaudid IR treatment dosing needed oral Naltrexone for the relief of constipation and other symptoms. Her adverse events were all related to IR treatment. Under these circumstances, the mean C_{max} (2.62 ng/ml) obtained from 16 mg CR tablets should represent and/or should be close to the mean C_{max} value obtained from healthy volunteers receiving 16 mg CR Dilaudid tablet without co-administration of Naltrexone. Therefore, the above comparisons between healthy subjects and patients (both without co-administration of Naltrexone) were considered appropriate.

Note 2: The other study, No. DO-108, investigated the multiple-dose PK of Dilaudid CR tablet in patients (n=22) with chronic pain. However, PK data were obtained from 17 patients only (n=8 for CR 8 mg dose, n=5 for CR 16 mg dose, n=2 for 24 mg dose, n=1 for CR 40 mg dose, and n=1 for 48 mg dose).

- An additional PK study (No. DO-109) was conducted in patients who completed the clinical trial Nos. DO-104, DO-105, and DO-119 (a pivotal one) and were on a stable dose of ≥ 96 mg/day (range: 128-1984 mg).
- The PK data (from one of the study sites, #29 only) also show comparable results; i.e., mean (\pm SD) normalized C_{max} , C_{min} , and AUC values were 2.70 (1.73) ng/ml, 1.19 (0.60) ng/ml, and 49.6 (31.3) ng-hr/ml, respectively (Study No. DO-109).

7. FOOD EFFECT:

SUMMARY:

- A high fat meal did increase the rate of absorption in terms of mean C_{max} (19% ↑), but did not affect the extent of absorption of the CR 16 mg tablet in terms of mean AUC ($\ln C_{max}$: 105.9-133.3 and $\ln AUC_{0-\infty}$: 81.9-99.4).

The following question is then raised:

What is the effect of food and will it influence dosing recommendations since the highest strength 64 mg CR tablet was not tested?

The food effect is to test the possibility of dose dumping. The high fat meal on the PK of the CR 16 mg tablets showed minor deviation from the BE assessment, i.e., an increase in mean C_{max} by 19%. It was concluded internally that since 1) the integrity of the CR tablets is expected to be the same under fed conditions, 2) the formulation differences between the 16 and 64 mg CR tablets are not considered to be substantial, and 3) dose proportionality has been demonstrated for the dose range between 8 and 64 mg, the food is expected to have similar effect on the CR 64 mg tablet, if it is used. Therefore, dose adjustment due to food is not warranted.

The above food effect of a high fat meal on the absorption of Dilaudid CR 16 mg tablet was tested in Study No. **D-102**. In this study, the effect of Naltrexone was also investigated and Naltrexone was given BID similarly (3 oral doses, 12 hr prior to, at, and 12 hr post Dilaudid CR treatment). The study design is shown below:

- TX A: Dilaudid 16 mg CR tablet alone, fasting conditions
- TX B: Dilaudid 16 mg CR tablet alone, fed conditions
- TX C: Dilaudid 16 mg CR tablet with Naltrexone, fasting conditions

Note: The high fat meal consisted of one buttered English muffin, one fried egg, one slice of American cheese, one slice of Canadian bacon, one serving of hash brown, eight fluid oz. (240 ml) of whole milk, and six oz. (180 ml) of orange juice. The above meal was consumed within 30 min and the medication was taken immediately (with water 240 ml) after the meal.

8. DRUG-DRUG INTERACTION (DDI) WITH NALTREXONE:

SUMMARY:

- Naltrexone did affect rate of absorption in terms of mean C_{max} (39% ↑), but did not affect the extent of absorption in terms of mean AUC ($\ln C_{max}$: 123.5-156.1 and $\ln AUC_{0-\infty}$: 85.0-103.0; Study No. **D-102**).
- No other DDI studies were conducted for Dilaudid CR tablet.

The following question is raised:

Is co-administration of Naltrexone critical to the absorption of HM in patients?

After a discussion with the reviewing MO, it was concluded that the above DDI study results for Dilaudid CR tablet with Naltrexone in healthy subjects may be less of a clinical concern for patients since 1) Naltrexone was given only for the purpose of blocking the opioid pharmacodynamic effects in healthy subjects and 2) it is not normally/commonly given to patients with pain receiving Dilaudid CR tablet. (b) (4)

9. GENDER:

SUMMARY:

- Gender differences were analyzed and compared among several studies conducted previously.
- Similar PK data were observed for HM between males and females.
- Females appeared to have marginally higher (~10%) mean systemic exposure in terms of mean C_{max} and AUC values.
- A dose adjustment based on a patient's gender is seemingly not warranted.

10. SPECIAL POPULATIONS:

SUMMARY:

- No other PK studies were conducted in specific populations, e.g., renal/hepatic impairment, elderly, pediatrics.

(b) (4)

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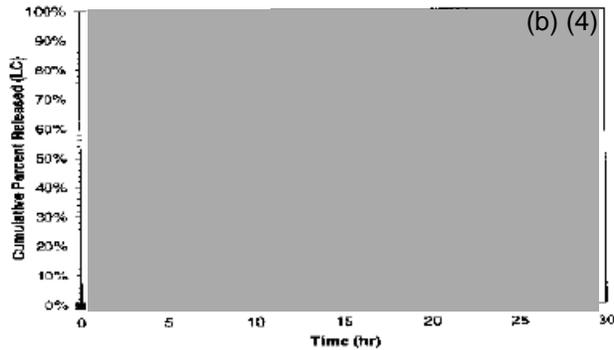
14. FORMULATIONS: (Detailed Formulations Provided in Appendix 2)**SUMMARY:**

- About 3 to 5 different formulations per CR strength were developed and tested clinically (total 20 formulations).
- The drug layers of the CR 8 and 16 mg tablet strengths are compositionally and proportionally the same (in terms of the % of target weight), but that for the CR 16 mg and CR 32 or 64 mg tablet strengths are not. However, the minor differences in the compositions are not considered to be substantial.
- The push layers of all the CR tablet strengths (in terms of the % of target weight) are the same.
- Comparable amounts (% of the 64 mg CT tablet) were obtained (90-97%) from 4 different dissolution media (at 0.1N HCl buffer pH 1.0, phthalate buffer pH 4.5, de-ionized water, and phosphate buffer pH 6.8) indicating that the zero-order drug releasing rate from CR tablet *in vitro* is independent to the media/pHs tested.
- Dissolution data showed similar dissolution pattern among formulations/ strengths tested.

15. CONTENT UNIFORMITY AND DISSOLUTION:**SUMMARY:**

- An overage of (b) (4) was added to Dilaudid CR 8 mg tablet and for Dilaudid CR 16 mg tablet, the overage was (b) (4)%.
- No overage was added to the two higher strengths.
- The dissolution of Dilaudid CR tablets was examined using USP Apparatus 7 (reciprocating holder with agitation 30 cycles/min) in water (50 ml) as a medium at 37 ± 0.5 °C.
- Twelve to 24 CR tablets were used per batch (including CT and TBM) and samples from the dissolution medium were removed at 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24 hr.
- Similar representative cumulative (%) *in vitro* drug release profiles for the 4 strengths of Dilaudid CR tablets were observed.
- Dissolution specifications proposed by the sponsor need minor revision.

Figure 9: Comparison of Representative Cumulative *In Vitro* Drug Release Profiles for the Four Strengths of Dilaudid CR Tablets



The dissolution specifications proposed by the sponsor are revised as interim basis as follows:

<u>Cumulative Release</u>	<u>Time Interval</u>
(b) (4)	0-4 hr
(b) (4)	0-10 hr
(b) (4)	0-24 hr

16. ASSAY: (the summary of assay results provided in Appendix 2).

SUMMARY:

- A sensitive LC/MS/MS analytical method was used for determining plasma levels of HM and/or its metabolite, H3G, at the analytical site, (b) (4) at (b) (4).
- The assay validation report for each individual study was provided except for Study No. C96-054-01.
- The assay results were found to be less than ideal (CV% for QC being > 15% reported in several studies; ranged from 15.5 to 23.2%), but overall it is acceptable.

III. COMMENT TO THE MEDICAL OFFICER:

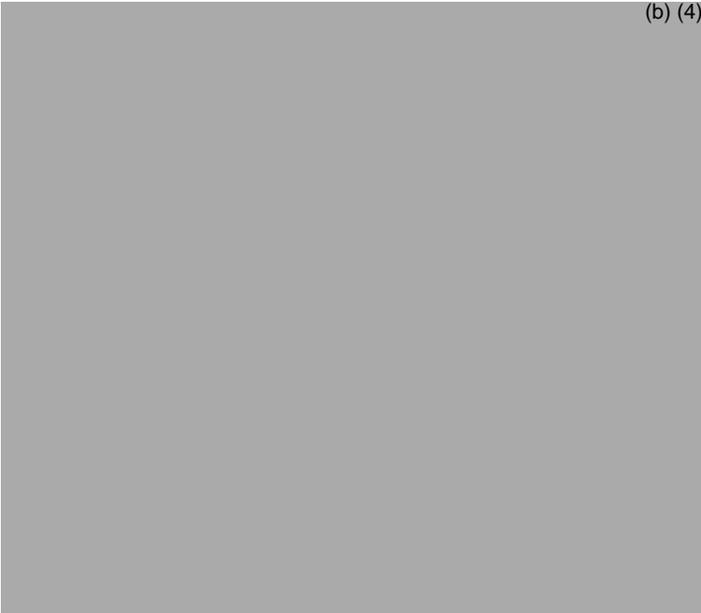
It is recommended that the TBM Dilaudid CR tablet formulations be employed, if this NDA is deemed not to be approved due the clinical efficacy and/or safety reasons and new clinical trial(s) need(s) to be conducted.

IV. GENERAL COMMENTS: (Need to be sent to the sponsor)

1.  (b) (4)

2. In addition to the DDI study No. **D-102**, Naltrexone 50 mg BID was co-administered with the HM dose to healthy subjects in several PK studies, i.e., Study Nos. **DO-123**, **DO-124**, **DO-129**, **D-103**, **C96-054-01**, and **C94-14-00** (except Study No. **D-101**).  (b) (4)

3.  (b) (4)

a.  (b) (4)

b.

c.

(b) (4)

4. It is recommended that the analytical report for Study No. C96-054-01 be submitted for review which was missing from the NDA submission.
5. It is recommended that the Agency's proposed dissolution specifications be implemented as interim basis as follows:

<u>Cumulative Release</u>	<u>Time Interval</u>
(b) (4)	0-4 hr
	0-10 hr
	0-24 hr

V. LABELLING COMMENT: (Need NOT be sent to the sponsor)

Not to be reviewed in this review cycle.

4.3 Individual Study Synopsis

SYNOPSIS

(Page 1 of 7)

Company: ALZA Corporation			
Investigational Product: OROS [®] hydromorphone HCl			
Active ingredient: hydromorphone HCl			
Title: Effect of Alcohol on the Pharmacokinetics of OROS [®] Hydromorphone in Healthy Subjects			
Investigator(s)/Study Center: Lawrence A Galitz, MD, SFBC International, 11190 Biscayne Blvd, Miami, FL			
Publication (reference): none			
Study period: First subject treated: 11 July 2005 Last subject completed: 11 August 2005		Phase of Development: 1	
Objective: To evaluate the effect of alcohol on the pharmacokinetics of OROS [®] hydromorphone under a fasted and a fed state in healthy subjects.			
Methodology: This was a single-center, single-dose, open-label, randomized, 4-treatment, 4-period, 4-sequence, crossover study in 2 groups of healthy subjects (fasted and fed). After screening to ensure subjects met study eligibility criteria, including a naloxone challenge test to identify subjects with opioid withdrawal symptoms, qualified subjects were enrolled and randomized into 1 of 4 sequences of 4 treatments. Treatments A, B, C, and D were used in Group 1 (fasted state), and Treatments E, F, G, and H were used in Group 2 (fed state). Treatments A and E: 16 mg OROS [®] hydromorphone with 240 mL of orange juice Treatments B and F: 16 mg OROS [®] hydromorphone with 4% v/v alcohol in orange juice (total volume 240 mL) Treatments C and G: 16 mg OROS [®] hydromorphone with 20% v/v alcohol in orange juice (total volume 240 mL) Treatments D and H: 16 mg OROS [®] hydromorphone with 40% v/v alcohol in orange juice (total volume 240 mL) Subjects also received oral naltrexone 50 mg as an opioid antagonist 14 hours and 2 hours before each dose of study treatment and twice daily during the 48 hours after each dose. There was a 6- to 14-day washout period between treatments, starting 24 hours after each dose. Blood samples were collected frequently for analysis of hydromorphone concentrations over the 48-hour period following each dose. Safety measures included adverse events, vital signs, physical examinations, clinical laboratory tests, 12-lead electrocardiograms (ECGs), and concomitant medications.			
Number of subjects (planned and analyzed): Planned: n=48 (24 in each group) to ensure that 40 subjects complete the study. Enrolled: n=48, 24 in each group. Completed: n=39, 20 in Group 1 and 19 in Group 2.			

SYNOPSIS

(Page 2 of 7)

Company: ALZA Corporation		
Investigational Product: OROS [®] hydromorphone HCl		
Active ingredient: hydromorphone HCl		
<p>Diagnosis and main criteria for inclusion: Healthy adult subjects 21-45 years of age who provided written consent and met the inclusion/exclusion criteria were included in the study. Subjects had to weigh at least 70 kg, be within 25% of the normal weight for height and body build, with no clinically significant abnormalities, and with screening blood pressure (BP) values in the range of 100 to 140 mmHg systolic and 60 to 90 mmHg diastolic. Subjects had to consent to use a medically acceptable method of contraception throughout the study, including the washout periods, and for 1 week (women) or 90 days (men) after completion of the study. Subjects had to have a history of social ingestion of alcohol and an ability to tolerate alcohol.</p>		
<p>Test product, dose and mode of administration, batch number:</p>		
<p>Dose: OROS[®] hydromorphone 16 mg tablet – Lot Number: 0516721</p>		
<p>Mode of administration: Oral</p>		
<p>Duration of trial: 1 month</p>		
<p>Duration of individual participation: Approximately 25-49 days</p>		
<p>Reference therapy: N/A</p>		
<p>Criteria for evaluation:</p> <p><i>Pharmacokinetics:</i> Blood samples for measurement of plasma hydromorphone concentrations were collected from each subject at predose, and 2, 4, 6, 8, 10, 12, 16, 20, 24, 27, 30, 36, 42, and 48 hours after dosing.</p> <p><i>Safety:</i> Adverse events (AEs), vital signs, physical examinations, clinical laboratory tests, 12-lead ECG, and concomitant medication usage.</p>		
<p>Statistical methods:</p> <p><i>Pharmacokinetics:</i> Descriptive statistics were calculated for pharmacokinetic (PK) parameters (C_{max}, T_{max}, $t_{1/2}$, AUC_t, and AUC_{inf}).</p> <p>A mixed-effect analysis of variance (ANOVA) model was used for the analysis of log-transformed hydromorphone pharmacokinetic (PK) parameters. This model included treatment, sequence, and period as fixed effects and subject-within-sequence as a random effect. The least-square estimates of the treatment ratios (B/A, C/A, D/A and F/E, G/E, and H/E) of PK parameters (log-transformed AUC_{inf} and C_{max}) and the 90% confidence intervals were computed.</p> <p>The PK data were analyzed in 3 datasets:</p> <ul style="list-style-type: none"> • Dataset #1: All available data in each period. • Dataset #2: The planned dataset containing data from those subjects who completed all 4 treatment periods (completers) and who had evaluable data. • Dataset #3: All available data minus data from any subject who had values considered outliers in any period (those subjects' data were only excluded from the treatment period in which the outlier occurred). 		

SYNOPSIS

(Page 3 of 7)

Company: ALZA Corporation		
Investigational Product: OROS [®] hydromorphone HCl		
Active ingredient: hydromorphone HCl		

Statistical methods, continued:

Seven subjects vomited following study treatment but provided complete data for the treatment period and had area-under-the-concentration-time curve (AUC) data similar to those during the other treatments; their data were included in the analyses in order to obtain the maximal amount of C_{max} and T_{max} data.

Four subjects in Group 1 (fasted state) and 4 subjects in Group 2 (fed state) had unusually low concentration values (considered outliers) in 1 of the treatments. There was no clinical explanation for the low values in these subjects. These 8 subjects' data were excluded from the third dataset.

Summary statistics and statistical analyses are provided for all 3 datasets, however the main focus in this report, and the basis for the pharmacokinetic conclusions, is the third dataset (available data minus outliers), which includes the maximal amount of data collected in the study, while omitting inexplicable outlier data (low hydromorphone concentrations).

Safety: Data were summarized and, where applicable, descriptive statistics were calculated.

SYNOPSIS

(Page 4 of 7)

Company: ALZA Corporation Investigational Product: OROS [®] hydromorphone HCl Active ingredient: hydromorphone HCl		
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Pharmacokinetic Results Summary:

Plasma hydromorphone concentrations were close to the limit of quantification at the first measurement 2 hours after dosing; thereafter plasma hydromorphone concentrations rose slowly in all 4 treatments in both fed and fasted groups. Median T_{max} values were between 12 and 16 hours, and the ranges of T_{max} values generally were similar for all treatments in each group.

Group 1 (Fasted State): Plasma Hydromorphone Pharmacokinetic Parameters Available Data Minus Outliers (Dataset #3)

Mean (SD)	0% Alcohol n=20	4% Alcohol n=22	20% Alcohol n=19	40% Alcohol n=17
C _{max} (ng/mL)	1.37 (0.32)	1.56 (0.39)	1.90 (0.66)	1.89 (0.85)
T _{max} (h) [Median (Range)]	16 (6-27)	12 (6-27)	12 (4-16)	12 (6-24)
T _{1/2} (h)	12.4 (5.1) ^a	12.6 (6.5) ^b	12.4 (7.2) ^c	11.1 (3.0) ^d
AUC _{inf}	40.6 (11.0)	39.9 (14.1)	43.7 (12.1)	42.2 (13.2)
Arithmetic Ratio: Mean (Range)				
C _{max}	Ref	1.19 (0.8-1.7)	1.35 (0.7-2.4)	1.37 (0.7-2.5)
AUC _{inf}	Ref	1.01 (0.4-1.5)	1.05 (0.6-1.3)	1.03 (0.6-1.7)
Geometric Ratio: Mean (90% CI)				
C _{max}	Ref	116.70 (104.48-130.36)	131.16 (117.01-147.02)	128.31 (114.18-144.17)
AUC _{inf}	Ref	96.83 (87.48-107.19)	103.21 (92.93-114.62)	101.65 (91.32-113.13)

^a n=19, ^b n=20, ^c n=18, ^d n=16

SYNOPSIS

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Company: ALZA Corporation Investigational Product: OROS [®] hydromorphone HCl Active ingredient: hydromorphone HCl		
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Pharmacokinetic Results Summary, continued:

The C_{max} values in the 3 alcohol treatments in the fasted state were higher than that seen in the 0% alcohol treatment, with mean geometric ratios of 117%, 131%, and 128% in the 4%, 20%, and 40% alcohol treatments, respectively. In the fed state, plasma hydromorphone concentration profiles were similar for the 4 treatments, and C_{max} ratios were lower than those seen in the fasted state (114%, 114%, and 110% in the 4%, 20%, and 40% alcohol treatments, respectively, versus 0% alcohol treatment). The maximal increase in C_{max} observed in any individual subject was 2.5-fold in Group 1 (fasted state) and 2-fold in Group 2 (fed state); these occurred in the comparison of the 40% vs 0% alcohol treatments.

Group 2 (Fed State): Plasma Hydromorphone Pharmacokinetic Parameters Available Data Minus Outliers Dataset (Dataset #3)

Mean (SD)	0% Alcohol n=18	4% Alcohol n=20	20% Alcohol n=16	40% Alcohol n=20
C _{max} (ng/mL)	1.42 (0.50)	1.64 (0.60)	1.52 (0.32)	1.56 (0.56)
T _{max} (h) [Median (Range)]	16 (6-27)	12 (8-24)	12 (6-24)	16 (6-27)
T _{1/2} (h)	11.6 (5.1) ^a	11.6 (4.9) ^b	10.4 (3.9) ^c	10.8 (4.8)
AUC _{inf}	37.1 (8.6)	36.7 (10.5)	36.6 (9.7)	34.8 (11.9)
Arithmetic Ratio: Mean (Range)				
C _{max}	Ref	1.20 (0.7-1.8) ^a	1.20 (0.8-1.9) ^c	1.14 (0.6-2.0) ^a
AUC _{inf}	Ref	0.97 (0.6-1.3) ^a	1.09 (0.8-1.7) ^c	0.96 (0.5-1.4) ^a
Geometric Ratio: Mean (90% CI)				
C _{max}	Ref	113.72 (99.97-129.36)	114.36 (100.14-130.61)	110.34 (97.08-125.41)
AUC _{inf}	Ref	94.72 (86.44-103.79)	106.21 (96.63-116.73)	94.09 (85.91-103.04)

^a n=17

^b n=18

^c n=15

The 90% confidence intervals for the AUC ratios of each of the 3 alcohol treatments relative to the 0% alcohol treatment met the 80% to 125% bioequivalence criteria in both the fed and fasted states.

SYNOPSIS

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Company: ALZA Corporation Investigational Product: OROS [®] hydromorphone HCl Active ingredient: hydromorphone HCl		
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Safety Results Summary:

No SAEs or severe AEs were reported, and no subjects discontinued from the study because of AEs. The majority of AEs were of mild severity. Numbers of AEs reported were low in all treatments. In both the fasted and the fed groups, more AEs were reported with the highest dose of alcohol than with the lower doses. There were no clear differences in the incidences of AEs in the fasted vs fed groups except in the highest alcohol dose treatment (OROS[®] hydromorphone with 40% alcohol), where more subjects reported AEs in the fasted state (52.4%) than in the fed state (19.0%). The most commonly reported AEs were vomiting and nausea. These AEs are known to be associated with hydromorphone and were considered by the investigator to be probably related to study treatment. There were no clinically significant changes in clinical laboratory values, vital sign values, physical examination results, or ECG findings during the study.

Conclusions:

- Plasma hydromorphone concentrations rose slowly following dosing in all 4 treatments in both fed and fasted groups.
- Median T_{max} values were between 12 and 16 hours, and the ranges of T_{max} values generally were similar for all treatments in each group.
- In the fasted state, mean C_{max} values in the 3 alcohol treatments were higher than the corresponding value in the 0% alcohol treatment, with log-transformed mean C_{max} ratios of 117%, 131%, and 128% in the 4%, 20%, and 40% alcohol treatments, respectively.
- In the fed state, plasma hydromorphone concentration profiles were similar for the 4 treatments, and log-transformed mean C_{max} ratios were slightly lower than those seen in the fasted state (114%, 114%, and 110% in the 4%, 20%, and 40% alcohol treatments, respectively, versus 0% alcohol treatment).
- The maximal increase in C_{max} observed in any individual was 2.5-fold in Group 1 (fasted state) and 2-fold in Group 2 (fed state).
- In both the fed and fasted states, OROS[®] hydromorphone AUC with each of the 3 alcohol treatments (4%, 20%, and 40% alcohol) met the bioequivalence criteria relative to OROS[®] hydromorphone with the 0% alcohol treatment.
- These results indicate that the controlled-release property of the formulation is maintained in the presence of alcohol and that there is no 'dose dumping' of hydromorphone.

SYNOPSIS
(Page 7 of 7)

Company: ALZA Corporation Investigational Product: OROS [®] hydromorphone HCl Active ingredient: hydromorphone HCl		
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Conclusions, continued: <ul style="list-style-type: none">• No SAEs or severe AEs were reported, and no subjects discontinued from the study because of AEs. The majority of AEs were of mild severity. Numbers of AEs reported were low in all treatments. In both the fasted and the fed groups, more AEs were reported with the highest dose of alcohol than with the lower doses. There were no clear differences in the incidences of AEs in the fasted vs fed groups except in the highest alcohol dose treatment (OROS[®] hydromorphone with 40% alcohol), where more subjects reported AEs in the fasted state (52.4%) than in the fed state (19.0%). The most commonly reported AEs were vomiting and nausea.• There were no clinically significant changes in clinical laboratory values, vital sign values, physical examination results, or ECG findings during the study.
Date of the report: 20 Oct 2005

SYNOPSIS

(Page 1 of 7)

Company: ALZA Corporation		
Investigational Product: OROS [®] hydromorphone HCl		
Active ingredient: hydromorphone HCl		
Title: Study to Evaluate the Abuse Potential of OROS [®] Hydromorphone Compared to Hydromorphone Immediate Release (IR) in Opiate-Experienced Non-dependent Volunteers		
Investigator(s)/Study Center: Edward M Sellers, MD, PhD, FRCPC/Ventana Clinical Research Corporation; 720 King Street West, Suite 700; Toronto, Ontario, Canada		
Publication (reference): none		
Study period: First subject treated: 20 January 2005 Last subject completed: 05 May 2005	Phase of Development: 1	
Objectives: Primary – To evaluate the abuse potential of single-doses of OROS [®] hydromorphone (controlled-release formulation, intact and crushed), hydromorphone IR (Dilaudid [®] , immediate-release formulation), and placebo in opiate-experienced, non-dependent recreational drug users. Secondary – To evaluate the pharmacokinetic/pharmacodynamic relationship of hydromorphone IR and OROS [®] hydromorphone on measures of abuse potential.		
Methodology: This was a single-center, single-dose, double-blind, double-dummy, placebo-controlled, randomized, crossover study in healthy subjects who had a history of polydrug use and moderate opiate use, but were not dependent on opiates (DSM-IV-TR). After prescreening to ensure subjects met study eligibility criteria, subjects were screened for their ability to perceive a single dose of hydromorphone IR 8 mg as being active and distinct from placebo. During this screening period, a visual analog scale (VAS) for drug liking was administered at various time points and vital signs and oxygen (O ₂) saturation were monitored. There was a 24-hour washout period between doses. Subjects that tolerated the hydromorphone IR 8 mg treatment well and were able to discriminate the hydromorphone 8 mg IR dose from placebo (≥15-mm difference in peak score on a 100-mm drug-liking VAS) were enrolled in the study as follows: <ul style="list-style-type: none"> • In Phase A, each subject received single doses of OROS[®] hydromorphone 16 mg, OROS[®] hydromorphone 32 mg, OROS[®] hydromorphone 8 mg crushed, hydromorphone 8 mg IR (active control), and placebo. If all treatments were well tolerated (University of Wisconsin Hospital and Clinic [UWHC] sedation score ≤3, respiratory rate ≥8 breaths/minute, vomiting ≤2 episodes), subjects entered Phase B. • In Phase B, subjects received single doses of OROS[®] hydromorphone 64 mg and hydromorphone 8 mg IR (active control). The washout period (7-14 days) began immediately after each treatment was administered. Subjects remained at the study site during each treatment period. In the event of a clinically significant overdose, intravenous (IV) or subcutaneous (SC) naloxone was given. If >8 subjects in Phase A or >4 subjects in Phase B needed rescue with naloxone for respiratory depression, dosing was to be suspended immediately pending review.		

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<p>Company: ALZA Corporation Investigational Product: OROS® hydromorphone HCl Active ingredient: hydromorphone HCl</p>		
<p>Methodology (continued): At specified times, measures of abuse potential were administered, blood samples were collected for determination of plasma hydromorphone concentrations, and vital signs were recorded. Subjects were monitored for AEs throughout the study from prescreening through follow-up. Hydromorphone 8 mg IR, the reference treatment, was included in Phase B of the study to allow comparison between the 2 study phases.</p>		
<p>Number of subjects (planned and analyzed): Screening: Treated n=64 Phase A: Planned n=50; Treated n=38; Evaluable n=38; Completed n=30 Phase B: Treated n=29; Evaluable n=29; Completed n=28</p>		
<p>Diagnosis and main criteria for inclusion: Healthy adult subjects 18-50 years of age with a history of polydrug use and moderate opiate use (defined as nontherapeutic use ≥10 times in a lifetime and ≥1 time in the 12 weeks before screening), but not dependent on opiates (DSM-IV-TR), who provided written consent and met the inclusion/exclusion criteria were included in the study. Subjects could not be attempting to stop their recreational drug use nor could they have been in a drug rehabilitation program in the year before screening.</p>		
<p>Test product, dose and mode of administration, batch number: Dose: OROS® hydromorphone 16 mg tablet, intact – 0413750 OROS® hydromorphone 32 mg tablet, intact – 0311223 OROS® hydromorphone 64 mg tablet, intact – 0311237 OROS® hydromorphone 8 mg tablet, crushed, encapsulated – 0413738 (crushed and encapsulated at site) Mode of administration: Oral</p>		
<p>Duration of trial: 15 weeks</p>		
<p>Duration of individual participation: Screening: approximately 10 days Treatment (Phases A and B): approximately 3 months</p>		
<p>Reference therapy: Placebo that matched: OROS® hydromorphone 16 mg tablet, intact – 0413757 OROS® hydromorphone 32 mg tablet, intact – 0311228 OROS® hydromorphone 64 mg tablet, intact – 0327669 Hydromorphone IR 8 mg tablet intact, encapsulated – Commercial product obtained by site and encapsulated at site Placebo capsule – prepared at site</p>		

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<p>Company: ALZA Corporation Investigational Product: OROS[®] hydromorphone HCl Active ingredient: hydromorphone HCl</p>		
<p>Criteria for evaluation: <i>Pharmacodynamics:</i> Overall Drug Liking, Subjective Drug Value, Subjective Effects VAS (Any drug effect, Good drug effect, Bad drug effect, High, Take drug again, Drug liking), Observer-rated Single-dose Questionnaire, Subject-rated Opiate Agonist Scale, and Addiction Research Center Inventory (Cole/ARCI) were administered at scheduled time points before and/or after dosing. <i>Pharmacokinetics:</i> During each of the 7 treatment periods, blood samples for measurement of hydromorphone concentrations were collected from each subject at predose, and 0.5, 1, 2, 4, 6, 12, 15, 24, and 48 hours after dosing. <i>Safety:</i> Adverse events (AEs), vital signs, O₂ saturation, physical exam, laboratory tests, drug and alcohol screening, pregnancy test, and 12-lead electrocardiogram (ECG).</p>		
<p>Statistical methods: <i>Pharmacodynamics:</i> To evaluate if average response to any of the pharmacodynamic (PD) parameters was different between single doses of OROS[®] hydromorphone (controlled-release formulation, intact and crushed), hydromorphone IR, and placebo, a mixed-effects analysis of variance (ANOVA) model was used. This ANOVA model included the fixed-effect factors of treatment, sequence, and period, and the random effects of intersubject and intrasubject factors. Provided an overall treatment difference was found, the protected least square difference (LSD) approach was used to assess pairwise comparisons. The 2 pairwise comparisons of particular interest for all PD measures were (1) OROS[®] hydromorphone 32 mg and hydromorphone 8 mg IR, and (2) OROS[®] hydromorphone 8 mg crushed and hydromorphone 8 mg IR. In order for the differences between the active treatments and the active control (hydromorphone 8 mg IR) to have been accepted, the comparison between the active control and placebo must have been significant. The assessments for Overall Drug Liking collected 10 hours and 48 hours after dosing were analyzed using the ANOVA model. Subjects should have been able to make the most reliable assessment 10 hours postdose (~2 half-lives [$t_{1/2} = 5$ hours] after T_{max}) for hydromorphone IR and 48 hours postdose for the OROS[®] treatments (~2 half-lives [$t_{1/2} = 16$ hours] after T_{max}). The assessments at these 2 time points were compared to determine the difference in average Overall Drug Liking. It was assumed that at 2 half-lives after T_{max}, subjects were unlikely to be intoxicated and would have experienced the effects of the test drug recently enough to have made a reliable assessment. In addition, the higher of the 2 values assessed at 10 and 48 hours postdose (defined as the maximum score) was compared between treatments to provide a more conservative analysis. For the Subjective Effects VAS, Observer-rated Single-dose Questionnaire, Subject-rated Opiate Agonist Scale, and Cole/ARCI, the peak effect and the total area under the effect curve (AUEC) were the primary parameters compared between treatments.</p>		

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<p>Company: ALZA Corporation Investigational Product: OROS[®] hydromorphone HCl Active ingredient: hydromorphone HCl</p>		
<p>Statistical methods (continued): Endpoints at each time point were summarized for each treatment period. Descriptive statistics for each of the 4 active treatments in Phase A are displayed with the placebo treatment over time. An exploratory analysis of the data collected in both phases of the study was used to evaluate the dose-response relationship between OROS[®] hydromorphone 64 mg, 32 mg, and 16 mg using the last Overall Drug Liking score. This comparison required that the responses for the 2 administrations of hydromorphone 8 mg IR were similar. <i>Pharmacokinetics:</i> Descriptive statistics were calculated for pharmacokinetic (PK) parameters (C_{max}, T_{max}, AUC_t). If appropriate, k, $t_{1/2}$, and AUC_{inf} were estimated. Descriptive statistics for the PK parameters for the reference treatment, hydromorphone 8 mg IR (Treatments 4 in Phase A and Treatment 6 in Phase B), were compared. An exploratory analysis of the dose linearity of OROS[®] hydromorphone 64 mg, 32 mg, and 16 mg was performed. <i>Safety:</i> Data were summarized and, where applicable, descriptive statistics were calculated.</p>		
<p>Pharmacodynamic Results Summary: In general, the pharmacodynamic results for all treatments reflected the pharmacokinetic profiles, ie, maximum pharmacodynamic scores were generally lower after OROS[®] hydromorphone treatments than after hydromorphone IR. Based on 10-hour postdose, 48-hour postdose, and maximum scores for Overall Drug Liking (the primary endpoint), the following conclusions could be drawn:</p> <ul style="list-style-type: none"> • The reference treatment, hydromorphone 8 mg IR, was significantly higher than placebo, supporting the study design. • OROS[®] hydromorphone 16 mg intact tablet, at double the total dose, was significantly lower than hydromorphone 8 mg IR. • OROS[®] hydromorphone 32 mg and 64 mg intact tablets, at 4 and 8 times the total dose, respectively, were not significantly different from, but were generally lower than, hydromorphone 8 mg IR. • OROS[®] hydromorphone 8 mg crushed and the reference treatment, hydromorphone 8 mg IR, were not significantly different. • Hydromorphone 8 mg IR treatments in Phase A and Phase B were not significantly different, which allowed comparison across the 3 OROS[®] hydromorphone doses (16 mg, 32 mg, and 64 mg). This further supported the study design in that mean responses were similar each time hydromorphone 8 mg IR was administered. • Increasing OROS[®] hydromorphone doses from 16 mg to 32 mg and 32 mg to 64 mg did not significantly increase Overall Drug Liking. 		

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<p>Company: ALZA Corporation Investigational Product: OROS[®] hydromorphone HCl Active ingredient: hydromorphone HCl</p>		
<p>Pharmacodynamic Results Summary (continued): Results for Overall Drug Liking, the primary endpoint, were generally supported by the secondary endpoints – Subjective Drug Value (10-hour postdose, 48-hour postdose, and maximum scores), and the Subjective Effects VAS, Subject-rated Opioid Agonist Subscale, and the Cole/ARCI Scale (maximum scores). Listed below are the key observations related to the secondary endpoints:</p> <ul style="list-style-type: none"> • The secondary endpoints of Subjective Effects VAS (Any effects, Good effects, High, Take drug again, and Drug liking) and the Cole/ARCI (Stimulation-euphoria and Abuse potential) were significantly lower for OROS[®] hydromorphone 16 mg intact tablet than hydromorphone 8 mg IR. • The secondary endpoints were collected at serial time points. For the High and Drug liking items on the Subjective Effects VAS, the maximal response with hydromorphone 8 mg IR was seen at approximately 2 hours, at which time the responses for the 3 intact OROS[®] hydromorphone treatments (16 mg, 32 mg, and 64 mg) were lower. Maximal responses for the 3 intact OROS[®] hydromorphone treatments were seen later (median T_{max}, 6 to 12 hours). Other items on the VAS and the Cole/ARCI (Stimulation-euphoria and Abuse potential) generally paralleled these results. • AUEC values were estimated for the secondary endpoints collected at serial time points (Subjective Effects VAS, Subject-rated Opioid Agonist Subscale, and the Cole/ARCI Scale). For the pairwise comparisons (hydromorphone 8 mg IR vs placebo, OROS[®] hydromorphone 8 mg crushed vs hydromorphone 8 mg IR, and hydromorphone 8 mg IR in Phase A vs hydromorphone 8 mg IR in Phase B), AUEC values were generally consistent with results for Overall Drug Liking (10-hour postdose, 48-hour postdose, and maximum scores). As expected for the intact dosage forms, AUEC values followed the general order of hydromorphone 8 mg IR < OROS[®] hydromorphone 16 mg < OROS[®] hydromorphone 32 mg < OROS[®] hydromorphone 64 mg. Other observations related to AUEC values for these assessments included: <ul style="list-style-type: none"> • Although the OROS[®] 16 mg had double the total dose of hydromorphone, its effects were generally not significantly different from hydromorphone 8 mg IR. • Hydromorphone 8 mg IR and OROS[®] hydromorphone 32 mg were not significantly different on the Take drug again and Drug liking items of the Subjective Effects VAS. • For the Abuse potential subscale on the Cole/ARCI, there were no significant differences between hydromorphone 8 mg IR and all 3 OROS[®] hydromorphone doses (16 mg, 32 mg, and 64 mg), nor were there any significant differences among the 3 OROS[®] hydromorphone doses. <p>In Phase A, observer ratings were not consistent with subject-rated assessments for the crushed OROS[®] hydromorphone 8 mg dose; this dose was rated lowest among the 4 active treatments by observers. In Phase B, observer ratings and subject-rated assessments (Subjective Effects VAS, Subject-rated Opioid Agonist Subscale, and the Cole/ARCI Scale) were generally consistent.</p>		

SYNOPSIS

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<p>Company: ALZA Corporation Investigational Product: OROS[®] hydromorphone HCl Active ingredient: hydromorphone HCl</p>		
<p>Pharmacokinetic Results Summary: In this double-blind study, the concentration profiles corresponded to the treatments given, confirming that the randomization schedule was followed at the site and the study was conducted as specified in the protocol. The pharmacokinetic profile (C_{max} and AUC) of crushed OROS[®] hydromorphone 8 mg was similar to that of hydromorphone 8 mg IR. Dose-normalized C_{max} values for the 3 intact OROS[®] treatments (16 mg, 32 mg, and 64 mg) were statistically significantly lower than the C_{max} for hydromorphone 8 mg IR. C_{max} and AUC_t values for OROS[®] hydromorphone 16 mg, 32 mg, and 64 mg were dose proportional.</p>		
<p>Safety Results Summary: No SAEs and no severe AEs were reported. The majority of AEs were of mild severity. During Screening, AEs were reported in 13 (34.2%) subjects receiving hydromorphone 8 mg IR and 3 (7.9%) subjects receiving placebo. In Phase A, AEs were reported in 22 (64.7%), 24 (72.7%), and 13 (38.2%) subjects receiving OROS[®] hydromorphone 16 mg, 32 mg, and 8 mg crushed, respectively, and in 20 (60.6%) subjects receiving hydromorphone 8 mg IR and 13 (35.1%) subjects receiving placebo. In Phase B, AEs were reported in 12 (41.4%) subjects receiving hydromorphone 8 mg IR and 27 (96.4%) subjects receiving OROS[®] hydromorphone 64 mg. The most frequently reported AEs (reported in ≥5% of subjects during any treatment) were headache, pruritus, nausea, insomnia, vomiting, generalized pruritus, O₂ saturation decreased, dizziness, urinary hesitation, tachycardia, constipation, contact dermatitis, somnolence, abnormal dreams, ventricular tachycardia, anorexia, back pain, skin lesion, and hypertension. Most of these AEs are known to be associated with hydromorphone and were considered treatment related by the investigator, with the exceptions of contact dermatitis, back pain, ventricular tachycardia, and skin lesion. Six subjects discontinued the study because of AEs: 1 after hydromorphone 8 mg IR (mild, treatment-related hypertension), 1 after placebo (moderate, treatment-related urticaria); 3 after OROS[®] hydromorphone 16 mg (mild, treatment-related irritability, and mild ventricular tachycardia not treatment related in 1 subject and treatment related in another); and 1 after OROS[®] hydromorphone 32 mg (moderate epigastric discomfort, not treatment related). All doses, including OROS[®] hydromorphone 64 mg, were generally well tolerated. No abnormal laboratory values were reported as treatment-related AEs. Several minor laboratory abnormalities (elevations in eosinophils and changes in liver function tests) were noted, but none were considered clinically significant. Overall, changes in vital signs were commensurate with effects associated with opiates. There were no clinically significant changes in physical examination findings, and no changes from prestudy values were noted on ECG findings at termination.</p>		

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<p>Company: ALZA Corporation Investigational Product: OROS[®] hydromorphone HCl Active ingredient: hydromorphone HCl</p>		
<p>Conclusions: Preference for OROS[®] hydromorphone 16 mg was significantly lower than hydromorphone 8 mg IR based on all analyses of the primary endpoint, Overall Drug Liking, and maximum scores on the Subjective Effects VAS (Any effects, Good effects, High, Take drug again, and Drug liking) and the Cole/ARCI (Stimulation-euphoria and Abuse potential). When crushed, OROS[®] hydromorphone behaved similarly to hydromorphone 8 mg IR. OROS[®] hydromorphone 32 mg and 64 mg were not significantly different from, but were generally lower than, hydromorphone 8 mg IR, based on the primary endpoint, Overall Drug Liking. Results demonstrated a generally lower drug liking with OROS[®] hydromorphone than with the IR formulation. The controlled-release delivery of hydromorphone from the OROS[®] formulation delays effects leading to drug liking: with hydromorphone 8 mg IR, the maximum responses on items such as High and Drug liking were seen approximately 2 hours after dosing. With OROS[®] hydromorphone, however, maximum responses occurred approximately 6 to 12 hours after dosing – which has the potential to lessen the appeal of this product to an abuser seeking a rapid high. In addition, doses 4- to 8-fold higher were needed with the OROS[®] formulation to achieve maximum responses similar to those seen with the 8 mg IR formulation.</p> <p>The pharmacokinetic profiles (C_{max} and AUC) of crushed OROS[®] hydromorphone 8 mg and hydromorphone 8 mg IR were similar. Dose-normalized C_{max} values for the 3 intact OROS[®] treatments were statistically significantly lower than the C_{max} for hydromorphone 8 mg IR. C_{max} and AUC_t values for OROS[®] hydromorphone 16 mg, 32 mg, and 64 mg were dose proportional.</p> <p>No SAEs and no severe AEs were reported. Most AEs were of mild severity and were considered treatment related. No new safety issues were identified during this study.</p>		
<p>Date of the report: 17 October 2005</p>		

SYNOPSIS

Company: ALZA Corporation Investigational Product: OROS® (hydromorphone HCl) 4 mg Active ingredient: Hydromorphone HCl	
Title: A Pharmacokinetic Study to Evaluate the Bioequivalence of OROS® Hydromorphone 2 × 4 mg to OROS® Hydromorphone 1 × 8 mg in Healthy Subjects	
Investigator: C James Kissling, MD Study Center: MDS Pharma Services; Lincoln, NE	
Publication (reference): none	
Study period: First subject treated: 11 March 2006 Last subject completed: 9 April 2006	Phase of Development: 1
Objective: To evaluate the bioequivalence of OROS® hydromorphone 2 × 4 mg to OROS® hydromorphone 1 × 8 mg in healthy subjects. A new dosage strength, OROS® hydromorphone 4 mg, was studied for the first time in humans.	
Methodology: This was a single-center, single-dose, open-label, 2-treatment, 2-period, 2-sequence, crossover study in healthy adult subjects. After screening and the naloxone challenge test, subjects were randomized to 1 of 2 treatment sequences. Each subject received the following 2 treatments in the fasted state: Treatment A: 2 × 4 mg OROS® hydromorphone Treatment B: 1 × 8 mg OROS® hydromorphone For each treatment, subjects received naltrexone 50 mg as the opioid antagonist 14 hours and 2 hours before dosing, and twice daily during dosing through 46 hours postdose. Subjects remained in the clinical study unit during dosing and the follow-up study procedures of each treatment period. The washout period between treatments was a minimum of 6 days and not more than 16 days. The washout period started 24 hours after dosing. In the event of a clinically significant overdose, intravenous (IV) or subcutaneous (SC) naloxone was to be given, according to the discretion and under the supervision of the principal investigator (PI). Alternatively, a naloxone infusion could be started. Stools were collected from 24 hours postdose until the OROS® systems were retrieved or until 72 hours postdose, whichever occurred first. Recovered systems were analyzed for residual drug content. At specified times, blood samples were collected to determine plasma hydromorphone concentrations, and vital signs were measured. Subjects were monitored for adverse events (AEs) throughout the study, including the washout period. Subjects who vomited within 24 hours after dosing and had an OROS® system in the vomitus were to be monitored for AEs and vital signs as long as deemed necessary by the PI. No additional pharmacokinetic blood samples were to be collected, and the subject was to be withdrawn from the study.	
Number of subjects (planned and analyzed): Planned n=52; Enrolled n=52; Completed n=50	
Diagnosis and main criteria for inclusion: Healthy adult males and females, 18 to 45 years of age (inclusive), who provided written consent and who met inclusion/exclusion criteria were included in the study.	

SYNOPSIS

Company: ALZA Corporation		
Investigational Product: OROS [®] (hydromorphone HCl) 4 mg		
Active ingredient: Hydromorphone HCl		
Test product, dose and mode of administration, batch number:		
	Treatment A	Treatment B
Dose	OROS [®] hydromorphone 2 × 4 mg	OROS [®] hydromorphone 1 × 8 mg
Mode of administration	Oral	Oral
Lot number	0540620	0524291
Duration of treatment	Single dose	Single dose
Duration of individual participation	10 to 20 days (excluding screening)	
Duration of trial	1.5 months	
Reference therapy: Not applicable		
Criteria for evaluation:		
<i>Pharmacokinetics:</i> Blood samples for measurement of hydromorphone concentrations were collected from each subject predose and 2, 4, 6, 8, 10, 12, 16, 20, 24, 27, 30, 36, 42, 48, and 56 hours postdose.		
<i>System functionality:</i> Stools were collected from 24 hours postdose until the OROS [®] systems were retrieved or until 72 hours postdose, whichever occurred first. Recovered systems were analyzed for residual drug content.		
<i>Safety:</i> Adverse events were monitored. Clinical laboratory tests (blood chemistry, complete blood count, and urinalysis), physical examinations, and electrocardiograms (ECGs) were performed at screening and at study termination (or early withdrawal). A serum pregnancy test (female subjects), urine drug screen, and alcohol test were performed at screening and before the start of each treatment period. Vital signs (blood pressure, heart rate, respiratory rate, and temperature) were measured at screening, during each treatment period (at predose and 0.5, 1, 2, 4, 6, 8, 10, 12, 14, 24, 30, 36, 48, and 56 hours postdose), and at study termination.		
Statistical Methods:		
<i>Pharmacokinetics:</i> Descriptive statistics were calculated for the pharmacokinetic (PK) parameters (C_{max} , T_{max} , k , $t_{1/2}$, AUC_t , AUC_{0-56} , and AUC_{inf}).		
A mixed-effects analysis of variance (ANOVA) model, which included treatment, period, and sequence as fixed factors, and subject-within-sequence as a random effect, was used for the analysis of the log-transformed hydromorphone PK parameters, AUC and C_{max} . The least square estimate of the treatment ratio (A/B) and the 90% confidence interval (CI) were computed.		
<i>System functionality:</i> The percent drug remaining in the recovered systems was tabulated and summarized.		
<i>Safety:</i> Data were summarized and, where applicable, descriptive statistics were calculated.		

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Company: ALZA Corporation Investigational Product: OROS [®] (hydromorphone HCl) 4 mg Active ingredient: Hydromorphone HCl		
Pharmacokinetic Results Summary: The mean hydromorphone plasma concentration time profiles following the 1 x 8 mg OROS [®] hydromorphone and 2 x 4 mg OROS [®] hydromorphone treatments were comparable, indicating similar pharmacokinetics (PK) for the 2 treatments. Area under the time-concentration curve was calculated up to the last measurable concentration (AUC _t) and extrapolated to infinity (AUC _{inf}). The degree of extrapolation was low (ie, less than 15% on average). As shown in the table below, all PK parameters were comparable between the 2 OROS [®] treatments.		
Mean (SD) Values for Plasma Hydromorphone Pharmacokinetic Parameters n=50^a		
Parameter	Treatment	
	Treatment A OROS[®] hydromorphone 2 x 4 mg	Treatment B OROS[®] hydromorphone 1 x 8 mg
C _{max} (ng/mL)	0.92 (0.25)	0.92 (0.29)
T _{max} (h)	15.0 (5.83)	15.9 (6.82)
t _{1/2} (h)	12.5 (4.4) ^b	13.3 (5.3) ^c
k (h ⁻¹)	0.062(0.02) ^b	0.059(0.021) ^c
AUC _t (ng.h/mL) ^d	23.2 (7.0)	22.8 (7.3)
AUC _{inf} (ng.h/mL)	25.2 (7.2)	25.1 (7.5)
^a Subjects who received both treatments and had no OROS [®] found in the vomitus and reported no signs of diarrhea within 24 hours of dosing. ^b n=47 (t _{1/2} was not estimable for the remaining 3 subjects.) ^c n=48 (t _{1/2} was not estimable for the remaining 2 subjects.) ^d AUC _t was based on a sampling duration of 56 hours for the OROS [®] treatments.		

Company: ALZA Corporation Investigational Product: OROS [®] (hydromorphone HCl) 4 mg Active ingredient: Hydromorphone HCl				
<p>Pharmacokinetic Results Summary (continued): Results of the statistical analysis of log-transformed hydromorphone PK parameters (AUC_{inf}, AUC_t, and C_{max}) are summarized in the following table for the 50 subjects who received both treatments and met the protocol-specified rule regarding vomiting and diarrhea. The least square estimate of the OROS[®] hydromorphone ratios for the log-transformed AUC_{inf} (2 x 4 mg/1 x 8 mg) and log-transformed C_{max} (2 x 4 mg/1 x 8 mg) were 101.14 and 100.97, respectively, and the 90% confidence intervals (CIs) were within the range of 80% to 125%, indicating that the 2 x 4 mg and 1 x 8 mg OROS[®] hydromorphone formulations were bioequivalent. The power for all comparisons in this model was >99%.</p>				
Statistical Analysis of Log-transformed Pharmacokinetic Parameters for Hydromorphone Following OROS[®] hydromorphone Treatments (n=50)				
Parameter	Ratio (%)	Power ^b (%)	90% CI	
			Lower (%)	Upper (%)
Bioequivalence of 2 x 4 mg OROS[®] hydromorphone and 1 x 8 mg OROS[®] hydromorphone, n=50^a				
$\ln AUC_{inf}$	101.14	>99	96.30	106.22
$\ln AUC_t$	102.69	>99	97.92	107.69
$\ln C_{max}$	100.97	>99	96.37	105.80
^a Subjects who received both treatments and had no OROS [®] found in the vomitus and reported no signs of diarrhea within 24 hours of dosing				
^b Power to detect a difference equal to 20% of the reference mean, at a significance level of 0.05, expressed as a percentage of the reference mean (1 x 8 mg OROS [®] hydromorphone).				

SYNOPSIS

<p>Company: ALZA Corporation Investigational Product: OROS[®] (hydromorphone HCl) 4 mg Active ingredient: Hydromorphone HCl</p>	
<p>Pharmacokinetic Results Summary (continued): <i>OROS[®] System Recovery:</i> Mean residual hydromorphone was 0.52 mg (range, 0.30-0.83 mg) for the 4-mg OROS[®] hydromorphone system, and 1.05 mg (range, 0.55-1.84 mg) for the 8-mg OROS[®] hydromorphone system. The OROS[®] hydromorphone system includes an overage of (b) (4) of the label claim for both the 4-mg and 8-mg systems that is not intended to be released. The median transit time (time from dosing to time of stool collection when system was recovered) was similar for the 2 treatments, 46.14 hours (range, 25.15 to 62.02 hours) and 50.58 hours (range, 24.83 to 61.92 hours) for 4-mg OROS[®] hydromorphone system and 8-mg OROS[®] hydromorphone system, respectively. These values are consistent with what is expected for OROS[®] hydromorphone.</p>	
<p>System Functionality: Stools were collected from 24 hours postdose until the OROS[®] systems were retrieved or until 72 hours postdose, whichever occurred first. All stool samples were refrigerated until searched; OROS[®] systems were frozen after they had been retrieved from the stool samples. The recovered OROS[®] systems were analyzed for residual drug content. The percent drug remaining in the system was tabulated and summarized.</p>	
<p>Safety Results: No SAEs were reported, and no subject discontinued the study because of an AE. No severe AEs were reported. Adverse events were reported in 17 (33.3%) subjects receiving 2 x 4 mg OROS[®] hydromorphone, and in 15 (29.4%) subjects receiving 1 x 8 mg OROS[®] hydromorphone. The most frequently reported AEs (reported in ≥5% of subjects during any treatment) were dizziness, nausea, headache, vomiting, and abdominal pain. These AEs are known to be associated with hydromorphone. For AEs occurring during treatment, 7/11 instances of dizziness, 6/10 instances of nausea, 10/15 instances of headache, 1/4 instances of vomiting, and 3/5 instances of abdominal pain were considered possibly or probably treatment related by the investigator. No abnormal laboratory values were reported as AEs. Mean vital signs were similar for the 2 treatment groups and generally remained stable throughout the study. There were no clinically significant changes in physical examination or ECG findings at termination.</p>	

<p>Company: ALZA Corporation Investigational Product: OROS[®] (hydromorphone HCl) 4 mg Active ingredient: Hydromorphone HCl</p>	
<p>Conclusions:</p> <ul style="list-style-type: none"> • Mean C_{max}, $t_{1/2}$, and AUC_{inf} were comparable between the 2 OROS[®] formulations. • The 90% CIs of the treatment ratios (2 x 4 mg OROS[®] hydromorphone versus 1 x 8 mg OROS[®] hydromorphone) for log-transformed AUC_{inf}, AUC_t, and C_{max} were within the 80% to 125% range, indicating that the 2 x 4 mg OROS[®] formulation was bioequivalent to 1 x 8 mg OROS[®]. • For the 2 x 4 mg OROS[®] system, mean residual hydromorphone was 0.52 mg; and for the 1 x 8 mg OROS[®] system, 1.05 mg. The OROS[®] hydromorphone system includes an overage of (b) (4) of the label claim that is not intended to be released. The median transit time was similar for the 2 treatments, 46.14 hours and 50.58 hours for 2 x 4 mg OROS[®] system and 1 x 8 mg OROS[®] system, respectively. These values are consistent with what is expected for OROS[®] hydromorphone. • No SAEs were reported, and no subject discontinued the study because of an AE. No new safety issues were identified during this study. 	
<p>Date of the report: 10 October 2006</p>	

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21217	ORIG-1	NEUROMED PHARMACEUTICA LS LTD	DILAUDID CR (HYDROMORPHONE HCL)8/16/32/6

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/s/

WEI QIU
10/21/2009

SURESH DODDAPANENI
10/21/2009

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	21-217
Submission Date:	5/22/2009
Generic Name:	OROS Hydromorphone HCl
Formulation:	SR Tablets
Strength:	8, 16, 32 and 64 mg
Sponsor:	Neuromed Pharmaceuticals
Reviewer:	John Duan, Ph.D.
Submission Type:	Complete response

BACKGROUND

Oros Hydromorphone HCl is proposed to be indicated for moderate to severe pain. It is an orally administered extended release formulation using OROS Push-Pull technology to deliver hydromorphone HCl in a controlled manner over 24 hours.

NDA 21-217 was originally submitted on December 28, 1999 by Knoll Pharmaceuticals under the trade name of Dilaudid CR[®]. Knoll received an Approvable Letter from the FDA on October 27, 2000 which contained five deficiencies in the Chemistry, Nonclinical and Clinical areas. The NDA was subsequently transferred to the ALZA Corporation, a subsidiary of Johnson and Johnson, who changed the name to OROS[®] Hydromorphone HCl. ALZA continued discussions with the Division up to 2007 in order to reach agreement on addressing the deficiencies in the Approvable Letter. Neuromed acquired the U.S. rights to the product from the ALZA Corporation in April 2007, and NDA 21-217 was transferred to Neuromed on October 5, 2007. Neuromed established the company code of NMED-I077 to refer to the OROS Hydromorphone formulation. Johnson and Johnson has maintained ex-U.S. rights to the product; OROS hydromorphone is now approved in 26 countries and is currently being marketed internationally under the trademark of JURNISTA[®].

Neuromed opened IND 78,223 on July 19, 2007 to continue development of EXALGO (hydromorphone HCl) Extended-Release Tablets. A 12 mg dosage strength has been developed to complement the dosage strengths (8, 16, 32 and 64 mg) that were originally submitted. A submission dated June 12, 2008 requested waiver for an in vivo bioavailability study for the 12 mg dosage strength. To support the biowaiver, a dose proportionality study report was submitted along with the rationale for the waiver request. However, although a biowaiver for lower strength 12 mg is possible based on the establishment of the dose proportionality study reviewed previously, the supportive information is not adequate in the following regards.

- The exact weight of each excipient in each strength and the percent excipient (w/w) out of total target dosage form weight should be provided.
- Dissolution comparisons should be performed in at least three media (e.g., pH 1.2, 4.5, and 6.8 buffer). The raw data, dissolution conditions and detailed profile comparisons should be submitted.

The above information was requested and the current submission is an NDA resubmission including the responses to the request.

THE COMPOSITIONS OF DIFFERENT STRENGTHS

Table 1 and Table 2 show the quantitative compositions for all strengths. As can be seen, the major components have similar percentages in each strength. However, the weights of the tablet layers are different. Considering the confirmed dose proportionality study, the weights of the tablet layer do not play a significant role in the bioavailability. The strength of 12 mg, which is the subject of current biowaiver, is bracketed between 8 mg and 16 mg.

Table 1: Quantitative Formulation (Wt %) for Each Tablet Layer Present in Each OROS® Hydromorphone HCl Dosage Strength

Excipients	Excipient/Active Loadings for Each Layer (Weight %)				
	8 mg	12 mg	16 mg	32 mg	64 mg
(b) (4)					
Hydromorphone Hydrochloride					(b) (4)
Polyethylene Oxide (b) (4)					(b) (4)
Povidone (b) (4)					
Magnesium Stearate					
Yellow Ferric Oxide					
Butylated Hydroxytoluene					
(b) (4)	b	b	b	b	b
(b) (4)					
Polyethylene Oxide					(b) (4)
Sodium Chloride					(b) (4)
Hypromellose (b) (4)					
Iron Oxide Black (b) (4)					
Magnesium Stearate					
Butylated Hydroxytoluene					
(b) (4)	b	b	b	b	b
(b) (4)					
Cellulose Acetate (b) (4)					(b) (4)
Polyethylene Glycol (b) (4)					
(b) (4)	b	b	b	b	b
(b) (4)	b	b	b	b	b
(b) (4)					
(b) (4)					(b) (4)
(b) (4)	b	b	b	b	b
(b) (4)					
(b) (4)					(b) (4)
(b) (4)	b	b	b	b	b
(D) (4)					
(b) (4)					(b) (4)
(b) (4)	b	b	b	b	b

NP = Not present

(b) (4)

Table 2. Quantitative formulation (mg) for each tablet layer present in each OROS hydromorphone HCl Dosage strength

Excipients	Excipient/Active Loadings for Each Layer (mg)				
	8 mg	12 mg	16 mg	32 mg	64 mg
(b) (4)					
					(b) (4)
Hydromorphone Hydrochloride					(b) (4)
Polyethylene Oxide (b) (4)					(b) (4)
Povidone (b) (4)					
Magnesium Stearate					
Yellow Ferric Oxide					
Butylated Hydroxytoluene					
(b) (4)	b	b	b	b	b
(b) (4)					
					(b) (4)
Polyethylene Oxide (b) (4)					(b) (4)
Sodium Chloride					
Hypromellose (b) (4)					
Iron Oxide Black/ (b) (4)					
Magnesium Stearate					
Butylated Hydroxytoluene					
(b) (4)	b	b	b	b	b
(b) (4)					
Cellulose Acetate (b) (4)					(b) (4)
Polyethylene Glycol (b) (4)					
(b) (4)	b	b	b	b	b
(b) (4)	b	b	b	b	b
(b) (4)					(b) (4)
(b) (4)	b	b	b	b	b
(b) (4)					(b) (4)
(b) (4)	b	b	b	b	b
(b) (4)					(b) (4)
(b) (4)	b	b	b	b	b

NP = Not present

(b) (4)

(b) (4)

John Duan, Ph.D.
Reviewer
Biopharmaceutics Review Staff

Date

Angelica Doranates, Ph.D.
Team Leader
Biopharmaceutics Review Staff

Date

Patrick Marrooum, Ph.D.
Biopharmaceutics Review Staff

Date

cc: NDA 21-217
Patrick Marrooum, Angelica Doranates, John Duan