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RESEARCH**

APPLICATION NUMBER:
21-217s000

MEDICAL REVIEW(S)

Clinical Review
Elizabeth Kilgore, MD
NDA 21-217 (Complete Response)
Exalgo (Hydromorphone ER)

CLINICAL REVIEW

Application Type	New Drug Application
Application Number(s)	NDA 21-217
Priority or Standard	(Complete Response)
Submit Date(s)	May 22, 2009
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Division / Office	Anesthesia, Analgesia and Rheumatology (DAARP)
Reviewer Name	Elizabeth Kilgore, M.D.
Review Completion Date	October 28, 2009
Established Name	Hydromorphone HCl Extended Release
(Proposed) Trade Name	Exalgo™
Therapeutic Class	Opioid Analgesic

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Applicant	Neuromed Pharmaceuticals
Formulation(s)	Oral (Oral Osmotic)
Dosing Regimen	Once Daily
Indication(s)	Persistent, Moderate-to- Severe Pain
Intended Population(s)	Opioid-tolerant patients requiring continuous, opioid therapy for an extended period of time

Template Version: [March 6, 2009](#)

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Throughout this review, the terms Hydromorphone extended-release (ER), OROS, OROS hydromorphone HCL, and Exalgo will be used interchangeably.

Approval is recommended for Exalgo (Hydromorphone extended release) 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 pending the Risk Evaluation and Mitigation Strategy (REMS) approval.

Efficacy was supported by the findings of pain improvement in Exalgo-treated patients compared to placebo-treated patients. There were an adequate number of patients exposed during clinical trials and the adverse event profile appeared acceptable across the intended to-be-marketed dosage range of 8 to 32 mg. The profile of adverse events was consistent with a mu-opioid agonist.

The dosing recommendations are acceptable based on the data from Phase 2 and 3 studies. The label will contain information that the drug is contraindicated in any situations where opioids are contraindicated, those with known hypersensitivity to any of its components, paralytic ileus and those who have had surgical procedures and/or underlying disease that would result in narrowing of the gastrointestinal tract, or have “blind loops” of the gastrointestinal tract or gastrointestinal obstruction.

1.2 Risk Benefit Assessment

The efficacy of Exalgo (Hydromorphone extended release) was demonstrated with a single, adequate and well-controlled study that had been the subject of a Special Protocol Assessment agreement. This key efficacy clinical trial was conducted as a 12 week, multicenter, double-blind, placebo-controlled study with a randomized withdrawal design in patients with chronic low back pain at dosage strengths of 8 to 64 mg once daily. The primary endpoint was change from Baseline to Week 12/Final Visit in weekly mean pain intensity scores. Statistical significance of the primary endpoint was shown ($p < 0.001$) using acceptable imputation methods that included the reason for discontinuation. Baseline Observation Carried Forward (BOCF) was used for discontinuation due to opioid withdrawal syndrome, Screening Observation Carried Forward (SOCF) for discontinuation due to AEs, and Last Observation Carried Forward (LOCF) for discontinuation due to other reasons. All of the secondary endpoints except

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Rescue Medication Use supported the primary endpoint. Therefore, Exalgo was found to be efficacious in the population studied.

From the perspective of risk, the safety data submitted were generally consistent with those of the opioid class of drugs. There were no deaths definitely or probably attributable to Exalgo and no unexpected or unusual adverse events of interest. The use of the OROS technology formulation appeared to result in similar risks in terms of gastrointestinal obstruction and bezoar formation as other marketed OROS formulation products.

All opioids pose the risk of abuse and misuse. The findings of the review by Dr. JianPing Gong, from the Agency's Controlled Substances Staff (CSS), summarized the following points regarding Exalgo's risk of abuse and misuse:

- Hydromorphone has a high abuse potential at least comparable or slightly higher than oxycodone.
- The PK/PD profile of altered Exalgo (8 mg dosage) is similar to that of hydromorphone immediate release (8 mg dosage).
- Exalgo has a high abuse potential as indicated by the intensity and duration of the positive subjective effects as measured by the Applicant's Abuse Liability study C-2004-022.
- Exalgo would be predicted to have high levels of abuse and diversion.

The reader is referred to Dr. Gong's review for further discussion regarding abuse and misuse potential of this product

The risks (including overdose, misuse and abuse) associated with this potent extended-release opioid appear similar to other opioids in this class. These risks, however, appear to be manageable with appropriate risk-management strategies and should not preclude approval.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The Applicant submitted a Risk Evaluation and Mitigation Strategy (REMS) proposal, referred to as the *Exalgo Alliance™ Program*. The final REMS to be adopted for Exalgo is currently under review by the Agency. The review team has determined that an "interim REMS" consisting of a MedGuide and a Communication Plan is appropriate at this time pending the approval of class-wide opioid REMS.

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1.4 Recommendations for Postmarket Requirements and Commitments

In order to comply with the Pediatric Research Equity Act (PREA), the Applicant submitted a pediatric plan.

The Applicant initially requested a Pediatric Waiver for children aged 0 to ≤ 6 years of age. The Applicant was notified by the Agency that a pediatric waiver could be granted for children aged 0 to less than 2 years of age because the population of patients with chronic pain requiring around the clock opioid treatment is small and studies would be impractical. They were informed that an age-appropriate dosage form would be needed for children between the ages 2-7 years since the OROS dosage form requires that the tablet be swallowed intact in order to maintain the extended-release delivery of hydromorphone. The Applicant agreed to evaluate the feasibility of developing an age-appropriate formulation using the OROS technology.

A Pediatric Deferral was requested by the Applicant for children aged 7 to 17 years old. The Applicant was informed that PK, efficacy and safety studies must be conducted in patients aged 2-17 years of age.

The timeline for the Applicant’s proposed pediatric studies is shown in Table 1.

Table 1. Timeline for Proposed Pediatric Studies

Study Title	Protocol Submission Date	Study Start Date	Completion Date	Final Study Submission Date
A Phase 1, PK Study in Children (Ages 7-17) who are Opioid Tolerant with Chronic Pain	6 mths after NDA approval	6 mths after protocol is submitted	12 mths after start date	3 mths after study completion (b) (4)
(b) (4)				
A Phase 1, PK Study in Children (Ages 2-<7) who are Opioid Tolerant with Chronic Pain	3 mths after formulation feasibility	6 mths after protocol is submitted	12 mths after start	3 mths after study completion (b) (4)
(b) (4)				

(Source: Table prepared by reviewer based upon Applicant’s submitted data)

The pediatric plan and deferral request were reviewed by the Pediatric Review Committee (PERC) on 10/14/09.

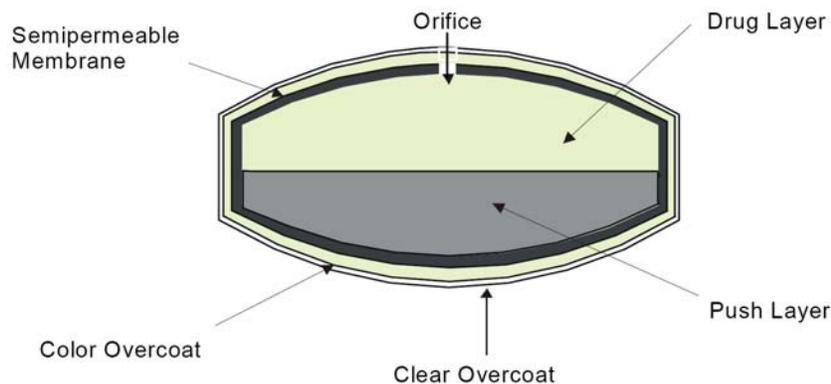
2 Introduction and Regulatory Background

2.1 Product Information

Exalgo is an extended-release hydromorphone tablet which uses the OROS® Push-Pull™ technology to deliver the hydromorphone HCl drug substance in a controlled manner over a 24-hour period to provide once-a-day treatment for the management of moderate-to-severe chronic pain.

As seen in Figure 1, the core of the tablet consists of a drug layer and push layer. As described verbatim from the Applicant's submission, "The drug layer contains a drug-suspending polymer to assist in the delivery of hydromorphone HCl in a controlled manner over 24 hours. Additionally, the expansion of the hydrated polymeric excipients in the push layer contributes to the drug delivery. A semi-permeable membrane, also referred to as the rate-controlling membrane, surrounds the core. This membrane provides rate control and adds mechanical durability to the tablet. An orifice is drilled on the drug layer dome of the tablet to provide an exit port for the drug solution." The drug is delivered when the volumetric expansion of the osmotic push layer begins to push the drug solution through the orifice. The Applicant maintains that this technology allows the drug to be continuously released from the core as the tablet travels along the gastrointestinal tract. The biologically inert core of the tablet remains intact during GI transit and is eliminated in the feces as an insoluble shell. The tablets are to be swallowed whole.

. **Figure 1. OROS Hydromorphone HCL Tablet Diagram**



(Source: Applicant's Submission, Section 3.2.P.1, Description and Composition of Drug Product, p.1)

According to an AERS database search conducted by the Agency's Office of Surveillance and Epidemiology (OSE), there are currently seven marketed, FDA-approved drugs which are delivered via the OROS technology. The drug trade

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names are Concerta, Covera HS, Ditropan XL, DynaCirc, Glucotrol XL, Procardia XL and Sudafed 24. Procardia XL was the first US-marketed drug using OROS technology in 1989.

The active ingredient in Exalgo is hydromorphone, a semi-synthetic, hydrogenated ketone of morphine which acts on the μ -opioid receptors. The Exalgo product is summarized as follows:

- Drug description: Extended-release oral tablet
- Dosage strengths: 8, 12, 16 and 32 mg
- Dosing regimen: Daily
- Established name: Hydromorphone extended release
- Tradename: Exalgo
- Pharmacologic class: Opioid analgesic
- Proposed indication: Management of moderate-to-severe pain in opioid-tolerant patients requiring continuous, around-the-clock opioid analgesia for an extended period of time

2.2 Tables of Currently Available Treatments for Proposed Indications

Multiple products are available for the treatment of moderate-to-severe pain, including immediate and extended-release opioids, prescription strength NSAIDs, and tramadol.

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient in this product is hydromorphone. Immediate-release hydromorphone is presently marketed as Dilaudid® and generic immediate-release hydromorphone products. Dilaudid is available as an injectable, oral solution, oral tablets (2, 4 and 8 mg) and suppository. There currently is no extended-release hydromorphone product marketed in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

Opioids: The risks associated with the use of Exalgo hydromorphone extended release appear similar to the risks of other immediate-release and extended-release opioids. These risks include death, respiratory depression, withdrawal, physical dependence, misuse, abuse, diversion and overdose (intended or accidental). Exalgo is to be used in opioid-tolerant patients only. The class of opioids, in general, carry label warnings regarding concomitant use with CNS depressants such as alcohol, other opioids, anesthetic agents, sedative-hypnotics and skeletal muscle relaxants which can potentiate respiratory-depressant effects and increase the risk of adverse outcome.

Alcohol interaction: Palladone (NDA 21-044) approved in September, 2004 for the indication of management of moderate-to-severe pain in opioid-tolerant patients requiring continuous opioid analgesic for an extended period of time, was the first FDA-approved Hydromorphone extended-release product. An Advisory Committee meeting was held in September, 2003 to discuss the Abuse/Misuse Risk Management strategy. Palladone was voluntarily withdrawn from the market in July, 2005 after an in vivo alcohol interaction study revealed that the integrity of the extended-release profile of Palladone was defeated in the presence of alcohol resulting in a potential for dose dumping. The average peak hydromorphone concentration was up to approximately six times greater with 40% alcohol than water.

OROS technology: There have been literature reports of the formation of medication bezoars (with associated GI obstruction and other GI complications) in some OROS products ^(1,2,3). A bezoar is defined as a mass or concretion of partly or wholly undigested material found in the GI tract ⁽¹⁾. Consideration and precautions should, therefore, be used when Exalgo is prescribed to patients who are taking other medications which may increase the risk of constipation and/or are using other OROS technology products.

2.5 Summary of Key Presubmission Regulatory Activity Related to Submission

- December 28, 1999
 - NDA 21-217 was originally submitted under the Tradename of Dilaudid CR® (Hydromorphone HCL 8, 16, 32 and 64 mg) by Knoll Pharmaceutical Company for the indication of analgesia for moderate to severe pain
- October 27, 2000
 - Approvable letter was issued with deficiencies in the following areas:
 - Chemistry – Data would be needed to support the Drug Substance, Product and Drug Product specifications
 - Nonclinical – carcinogenicity studies would be required
 - Clinical – one adequate and well-controlled (AWC) study with multiple dosing of the to-be-marketed formulation in the setting of moderate to severe pain to establish efficacy would be required

1 Prisant, LM, et al. Archives Internal Medicine, Vol. 151, Sept. 1991, p. 1868-69

2 Taylor, JR, et al. The Annals of Pharmacotherapy, Vol. 32, Sept. 1998, p. 940-46

3 Stack, PE, et al. Journal Clin Gastroenterology, Vol. 19 (3), 1994, pages 264-5

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- May 10, 2001
 - Knoll transferred the NDA to Abbott laboratories
- July 16, 2004
 - NDA was transferred to Alza corporation
- August 15, 2007
 - SPA for Protocol NMT-1077-301 in low back pain was accepted
- October 5, 2007
 - NDA 21-217 was transferred to Neuromed
- November 16, 2007
 - SPA for Protocol NMT-1077-302 in osteoarthritis was accepted (Study 302 is ongoing at the time of this submission)
 - Neuromed requested a meeting with the Division of Anesthesia, Analgesia and Rheumatology Products (DAARP) which was denied.
- January 22, 2008
 - Written responses from the Agency to the Sponsor's questions from 9/7/07 were provided
- August 8, 2008 - A pre-submission meeting was held and the Sponsor was informed of the following:
 - Carcinogenicity studies could be conducted as a post-approval requirement. Studies must be started at the time of submission
 - Comments on the plans for the Risk Evaluation and Mitigation Strategy were provided from the Agency to the Sponsor
 - For in vitro and in vivo tamper resistance evaluation studies, the Sponsor was advised to include complete protocols and study results. The sponsor would also need to provide data to assess the effects of biting and chewing on the release of hydromorphone from intact tablets presoaked in artificial saliva or water
 - The Sponsor would need to provide in vitro studies to assess various solvents, temperatures, agitation, and grinding conditions
- May 22, 2009
 - Complete Response was submitted by Neuromed

2.6 Other Relevant Background Information

This product, under the Tradename Jurnista, was approved in Denmark in 2004, and first marketed in Germany on 7/31/2006 for the treatment of moderate-to-severe pain. Jurnista has been approved in 26 countries and marketed in 9 countries. The formulation of Jurnista is identical to that in Exalgo but is available in dosage strengths of 4, 8, 16, 32 and 64 mg.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission appeared to be of good quality. It was well organized and easily navigated. A number of clinical information requests were sent to the Applicant for tables and clarifications. Additional datasets were requested by the statistics reviewer.

3.2 Compliance with Good Clinical Practices

The Applicant reported that all clinical studies in this application were conducted in the US, Canada, and Europe in accordance with applicable regulatory guidances and relevant sections of the International Conference on Harmonization guidelines.

The Division of Scientific Investigations (DSI) conducted routine inspections of 2 specific sites. The study sites were selected based on the number of enrolled study subjects. The DSI audits at the 2 sites were able to validate the primary endpoint and determine that there was no under reporting of adverse events. However, the audit found systemic clinical trial conduct issues concerning lack of adequate urine drug screens for tramadol and fentanyl and reporting of only abnormal drug screens to each clinical site by the central laboratory.

As a result of this finding by DSI, an information request was sent to the Applicant requesting additional information regarding these sites and number of patients who would have been affected. At the time of this review, the Applicant's response is pending.

3.3 Financial Disclosures

The Applicant's submission included the completed Certification: Financial Interests and Arrangements of Clinical Investigators in compliance with 21 CFR part 54. This certified that the Applicant had not entered into any financial arrangement with the listed clinical investigators, that each clinical investigator had no financial interests to disclose and that no investigator was the recipient of any other sorts of payments from the Applicant.

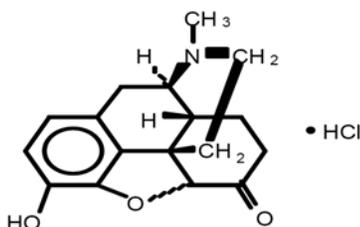
4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Hydromorphone HCL drug substance is a white to almost white crystalline powder with a molecular weight of 321.80 and a molecular formula of $C_{17}H_{19}NO_3 \cdot HCl$. Hydromorphone hydrochloride, USP is 4,5 α -epoxy-3-hydroxy-17-methylmorphinan-6-one hydrochloride. (b) (4)

(b) (4) Figure 2 below depicts the structural formula of hydromorphone hydrochloride.

Figure 2. Structural Formula of Hydromorphone Hydrochloride



(Source: Applicant's submission, Annotated Label, p. 28)

The reader is referred to the review by Yong Hu, Ph.D. for the complete CMC discussion. Dr. Hu reported that the Applicant's resubmission addressed the CMC deficiencies in the Approvable letter. Approval is recommended by CMC pending the resolution of drug substance DMF (b) (4) deficiency (b) (4) specification) and acceptable recommendation from the Office of Compliance on manufacturing facilities.

The CMC review notes that the inactive ingredients of OROS hydromorphone HCL tablets are conventional pharmaceutical excipients and are acceptable. The tablet core (drug layer and push layer) and coat contain the following excipients:

- (b) (4) Polyethylene oxide (b) (4), Povidone (b) (4) Magnesium stearate, butylated hydroxytoluene (b) (4)
- (b) (4) Polyethylene oxide (b) (4), Sodium chloride, Hypromellose (b) (4) Magnesium stearate, Butylated hydroxytoluene, and (b) (4) black iron oxide and lactose (b) (4)
- (b) (4) (b) (4) cellulose acetate (b) (4), Polyethylene glycol (b) (4)

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4.2 Clinical Microbiology

This product is not an antimicrobial.

4.3 Preclinical Pharmacology/Toxicology

The Applicant relied on results from formal studies which they conducted, as well as information from the published literature, to characterize the primary and secondary pharmacological activities and safety pharmacology profile of hydromorphone. The reader is referred to Dr. Belinda Hayes's review for the full preclinical pharmacology/toxicology discussion. There were no specific safety issues identified in the preclinical studies performed. Respiratory depression, a known extension of the pharmacological action of hydromorphone, is the most prominent adverse effect of hydromorphone which would be relevant to the proposed clinical use. Dr. Hayes noted that there were no pharmacology/toxicology issues which would preclude approval.

Primary Pharmacodynamics: Hydromorphone appeared to show similar pharmacodynamic properties to those produced by morphine (although more potent). Hydromorphone is an opioid agonist with activity at the mu opioid receptor. Activation of mu-opioid receptors is associated with analgesia, respiratory depression, sedation, decreased gastrointestinal motility, euphoria and physical dependence.

Safety Pharmacology: The Applicant conducted formal safety pharmacology studies to characterize the hydromorphone safety profile. Results from these studies demonstrated that hydromorphone had a good safety profile when evaluated for potential central nervous system and cardiovascular toxicity. In rodents, it did not produce neurobehavioral toxicity. Hydromorphone had no effects on cardiac action potential and the in vitro hERG assay showed that it did not possess potassium channel blocking properties at a concentration of 10 µM.

Toxicology: In support of the chronic indication, the systemic toxicity of hydromorphone was studied in mice, rats and dogs. Animal studies have shown that the major toxicological effects appear to target the central nervous system and gastrointestinal tract (as may be expected with opioids). Genetic toxicology studies performed with hydromorphone demonstrated that, under the condition of the Ames and chromosomal aberrations assays, hydromorphone was considered to be non-mutagenic and non-clastogenic, respectively.

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4.4 Clinical Pharmacology

Dr. Wei Qiu performed the Agency's Clinical Pharmacology review. Aside from a biopharmaceutics proposal regarding specific language to be used in the package insert, there were no issues identified related to Biopharmaceutics that would affect the approvability of Exalgo. At the time of this review, the status of the proposed language change is pending.

4.4.1 Mechanism of Action

Hydromorphone binds more specifically to μ receptors than structurally related morphine. The principal therapeutic action is analgesia. The exact mechanism of action of opioid analgesics is not fully known but the effects are thought to be mediated through opioid-specific receptors located predominantly in the central nervous system (CNS).

4.4.2 Pharmacodynamics

It is known that hydromorphone exerts its primary pharmacological effects on the CNS and smooth muscle, as do other opioid analgesics. It is estimated that hydromorphone is 5 to 8 times more potent than morphine by weight.

Opioids are known to produce dose-related respiratory depression; adverse events of nausea and vomiting; reduction in motility of the GI tract (constipation) and other smooth muscles; cardiovascular effects of peripheral vasodilation (orthostatic hypotension) and release of histamine with or without peripheral vasodilation (pruritus, flushing, etc). Opioid agonists have also been shown to variably affect the endocrine system (inhibiting some hormones and stimulating others).

4.4.3 Pharmacokinetics

According to the Agency's Clinical pharmacology review performed by Dr. Wei Qiu, "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. They reported that plasma concentrations of hydromorphone were proportional to dose for 8, 16, 32 and 64 mg tablets in healthy subjects. C_{max} and AUC increased in a linear, dose-proportional manner but T_{max} and terminal half-life (t_{1/2}) were independent of dose".

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

Single dose: Single oral dose of the 16 mg Exalgo tablet provided equivalent AUC_t or AUC_{inf} of hydromorphone as the 4 mg IR tablet every 6 hours (q6h) under fasting conditions. On average, the C_{max} value of Exalgo tablet and the reference IR tablet were 1.89 and 3.57 ng/mL, respectively.

Multiple dose: Multiple oral doses of the once daily (qd) 16 mg Exalgo tablet provided equivalent exposure (AUC_{0-τ}) of hydromorphone as the 4 mg IR tablet q6h at steady state under fasting condition. 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 were 2.15 ng/mL and 1.47 ng/mL, respectively.

Exalgo Hydromorphone HCL reached approximately 50% of peak concentrations (C_{max}) by 6 hours after a single dose and was sustained for 18-24 hours. In a single dose, the mean half life ranged from 8-15 hours, with the mean approximately 11 hours as shown below in Table 2.

Table 2. Mean (±SD) Exalgo PK Parameters

Regimen	Dosage	T _{max} (hrs)	C _{max} (ng/mL)	AUC (ng · hr/mL)	T _½ (hr)
Single Dose	8 mg	16.0 (7.2)	0.93 (1.01)	18.1 (5.8)	10.6 (4.3)
	16 mg	16.8 (5.4)	1.69 (0.78)	36.5 (11.3)	10.3 (2.4)
	32 mg	15.7 (5.4)	3.25 (1.37)	72.2 (24.3)	11.0 (3.2)
	64 mg	17.4 (5.7)	6.61 (1.75)	156.0 (30.6)	10.9 (3.8)
Multiple Dose ^a	16 mg q24h	12.3 (5.4)	3.54 (0.96) ^b	57.6 (16.3)	NA
	IR 4 mg q6h	8.4 (4.6)	5.28 (1.37) ^c	54.8 (14.8)	NA

NA = not applicable

a. Steady-state results on Day 5 (0-24 hours)

b. C_{min} 2.15 (0.87) ng/ml

c. C_{min} 1.47 (0.42) ng/ml

(Source: Applicant's submission, Annotated Label, p. 32 from Summary of Clinical Pharmacology Studies pages 29-32)

Absorption

As can be seen in Table 3 below, steady-state plasma concentrations for hydromorphone were reached after approximately 48 hours (2 doses) and sustained throughout the 24-hour dosage interval.

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Table 3: Mean Steady State (Day 4) Hydromorphone Pharmacokinetic Parameters

Pharmacokinetic Parameter	IR Hydromorphone (4 mg every 6 hours for 4 days)	OROS[®] Hydromorphone (16 mg QD for 4 days)
C _{max} (ng/mL)	3.4	2.6
T _{max} (hr)	1.12	14.7
C _{min} (ng/mL)	0.9	1.2
T _{min} (hr)	4.1	6.4
AUC ₀₋₂₄ (ng-hr/mL)	41.7	45.6

(Source: Final Study Report DO-109, p. 23)

Metabolism and Elimination

After oral administration of Hydromorphone immediate release (IR), there is extensive first-pass metabolism primarily in the liver. After oral administration of the immediate release formulation, approximately 75% of the administered hydromorphone dose is excreted in urine as metabolites.

Food effect

The PK of Exalgo was not affected by food.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The Applicant reported that they have conducted thirty-two studies in a total of 3,777 patients and healthy subjects and provided a Table of studies which was reviewed.

The original NDA 21-217 (filed by Knoll Pharmaceuticals) included clinical data from the following 12 studies:

- Complete final reports of six Phase 1 single dose Clinical Pharmacology PK safety studies (D-101;D-102; D-103; DO-123; DO-124; DO-129)
- Complete final reports of two multiple-dose Phase 1 Studies (C-96-054-01 and DO-108)
- Complete final report of Phase 3 safety/efficacy study DO-119
- Phase 2 safety/efficacy interim report Study DO-104
- Phase 2 safety/efficacy final report Study DO-105
- Preliminary safety report of Phase 3 Study DO-109. (Study DO-109 missed the cutoff date for the 120-day Safety Update)

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Data from the following studies were not previously submitted to the Agency and are included in this Complete Response submission:

- Eleven Phase 1 Clinical Pharmacology studies
 - C-2005-013 (PK: in vitro/in vivo)
 - C-94-014; C-2005-020; C-2005-032; 42801-PAI-1008/1009;
 - DO 113; DO-114; DO-121; DO-122 (PK gender, age, renal impairment, hepatic impairment respectively)
 - C-2004-022 (PD: abuse liability)
- Nine completed Phase 2/3 safety/efficacy studies: MO3-644-05, DO-118/118X, DO-132, DO127/127X, DO-130, OROS-ANA-3001, and NMT 1077-301
- Safety update of ongoing Studies NMT 1077-302 and 42801-PAI-3001

It should be noted that Phase 1 studies C-2005-020 (alcohol-interaction study) and C-2004-022 (abuse/liability study) were reviewed and are discussed in further detail later in this review.

The Phase 2, 3 and 4 completed and ongoing studies are briefly summarized in Table 4 below. (Study DO-108 was a Phase 1 repeat-dose study included in the pooled Phase 2/3 safety data and, therefore, is included in the Table. The other Phase 1 studies are not included in this Table).

Table 4. Phase 2, 3 and 4 Completed and Ongoing Studies

Study	Brief Description
Phase 1	
DO-108	Phase 1, repeat-dose, Multicenter, open-label, no control. 22 adults chronic pain patients (non malignant or cancer)
Phase 2	
DO-104	Multicenter, open-label, single-blind (with respect to dose), repeated-dose study. 127 patients with chronic cancer pain
DO-105	Multicenter, open-label, single-blind (with respect to dose) repeated-dose study. 336 patients with chronic non-cancer pain
DO-127	Multicenter, Open-label, non-randomized, non-comparative, repeated-dose study. 207 patients with chronic low back pain
DO-127X	Multicenter, open-label extension study for patients from study DO-127. No control. 113 patients who completed study 127
Phase 3	
DO-118	Multicenter, randomized, double-blind, multiple-ascending-dose, parallel-group study. Active control. Immediate-release HM Phase included 99 patients who received HMIR and 101 Morphine. Sustained release HM Phase included 77 patients who received HMSR and 86 morphine. Cancer patients requiring 60-540 mg oral morphine or ME/day
M03-644-05	Multicenter, randomized, double-blind, fixed-dose, parallel-group study. Placebo controlled. 319 patients received 8 mg OROS HM; 330 patients received 16 mg OROS HM; 332 patients received placebo. Osteoarthritis pain of the knee or hip

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	unable to be controlled with non-opioid medications or had received an opioid for pain but non-controlled pain
NMT 1077-301	Multicenter, open-label conversion and titration phase followed by double-blind, randomized maintenance phase. Placebo control. 134 patients in OROS HM and 134 patients in placebo with chronic, low-back pain. Opioid tolerant
DO-109	Multicenter, open-label extension study for patients from studies DO-104, DO-105 or DO-119. Total of 388 patients with chronic nonmalignant or cancer pain
DO-119	Randomized, double-blind, repeated-dose, parallel-group comparison of the efficacy and tolerability of Dilaudid CR Tablets and Immediate Release Dilaudid Tablets in patients with chronic pain. Key AWC study in original NDA 21-217 submission. 74 treated patients. Failed efficacy study
DO-118X	Multicenter, open-label extension study for patients from study DO-118. 68 patients with cancer pain who successfully completed DO-118 and required ≥ 8 mg/day OROS HM
OROS-ANA-3001	Multicenter, randomized, open-label, parallel group study with Titration and Maintenance Phases. 504 patients with chronic, non-malignant pain
DO-130	Multicenter, randomized, open-label, single-dose, pilot study for acute post-operative pain after total knee replacement surgery. Treated 50 total (18 at 8 mg OROS, 18 at 16 mg OROS and 14 at 32 mg OROS)
DO-132	Multicenter, open-label, randomized, dose-titration, repeated-dose, 2-1rm, parallel-group study. Active control. 71 patient treated with OROS HM and 67 patients treated with Oxycontin. Chronic primary OA of the knee or hip.
Phase 4	
OROS-ANA-4001	Multicenter, noncomparative open-label study. No control. 218 patients with severe chronic pain due to osteoporosis (Germany). Postmarketing safety data.
OROS-ANA-4002	Multicenter, noncomparative open-label study. No control. 207 patients with severe chronic pain due to osteoarthritis (Germany). Postmarketing safety data.

Ongoing Studies

Phase 3	
NMT-1077-302	Multicenter, open-label conversion and titration phase followed by double-blind randomized phase. Placebo control. Planned 240 patients with OA of the knee or hip, opioid tolerant
Phase 3b	
42801-PAI-3001	Multicenter, randomized, double-blind, parallel group study with Titration and Maintenance Phases. 270 patients planned with moderate to severe pain due to OA of the hip or knee (Europe)
Phase 4	
HYD-KOR-4001	Multicenter, open-label, prospective study. 120 patients planned with cancer pain and prior opioid analgesics (South Korea)
HYD-KOR-4002	Multicenter, open-label, prospective study. 134 patients planned with cancer pain and sleep disturbance (South Korea)
OROS-ANA-4003	Multicenter, non-comparative, open-label study. No control. 200 patients with severe chronic pain due to osteoporosis or osteoarthritis planned. (Germany)

Study Terminated early

Phase 3	
42801-PAI-3008	Multicenter, randomized, open-label study. Active control. 110 patients with cancer pain planned (Taiwan)

(Source: Table prepared by reviewer from Applicant's submitted data)

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5.2 Review Strategy

The Phase I studies from the original NDA and current submission were not individually reviewed by this reviewer except as needed for pertinent sections of the safety review. The full protocol and final report for the key efficacy study in this submission as well as synopses of all Phase 2/3 studies (except for Study 42801-PAI-3008) were reviewed. Any studies which the Applicant purported to support claims of efficacy or were used in the Applicant's pooled or unpooled safety analysis were reviewed. The Medical Officer review of the original NDA was also reviewed and pertinent sections of the original NDA 21-217 submission.

Study 42801-PAI-3008 was a study conducted in Taiwan which terminated early (December, 2008) due to slow enrollment and expiration of clinical trial supplies in January, 2009). There were only two patients enrolled (one received OROS hydromorphone and one received morphine SR).

The Applicant reported that in addition to the key efficacy study (NMT 1077-301), there were 11 additional studies supportive of the proposed indication (five controlled studies [M03-644-05, DO-118, DO-119, OROS-ANA-3001 and DO-132], three uncontrolled studies [DO-104, DO-105, and DO-127] and three open-label extension studies [DO-109, DO-118X, and DO-127X]).

The key efficacy study is discussed in detail below, followed by brief summaries of the Applicant's purported supportive efficacy studies included in this submission, then summaries of studies reviewed in the original NDA (DO-104, DO-105, DO-119 and DO-109).

5.3 Discussion of Individual Studies/Clinical Trials

Protocol Number: NMT 1077-301 (Key Efficacy Study)

Title: A Phase III, Variable-Dose Titration Followed by a Randomized Double-Blind Study of Controlled-Release OROS® Hydromorphone HCL (NMED-1077) Compared to Placebo in Patients with Chronic Low Back Pain

Date Issued: The original protocol for NDA 21-217 was opened under IND (b) (4) After 3 failed Special Protocol Assessment agreements, a new IND 78,223 was opened on July 20, 2007 under a SPA which was agreed to by the Agency on 8/15/07. Amendments were submitted on July 13, 2007; August 29, 2007; September 20, 2007; and January 28, 2008. The first patient was enrolled on October 15, 2007.

Objective: The primary objective of this study was to evaluate the efficacy of

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Hydromorphone extended release (ER) in the treatment of chronic low back pain.

Population: Approximately 272 patients were to have entered the double-blind phase of the study. It was expected that approximately 400 adult patients with stable, chronic low back pain (LBP) who were currently being treated with opioid analgesic around-the-clock were to have been enrolled.

Duration: There was to have been a 14-day Screening period. The total treatment time in the study was to have been up to 16 weeks with 4 weeks in the Conversion and Titration phase and 12 weeks in the double-blind phase.

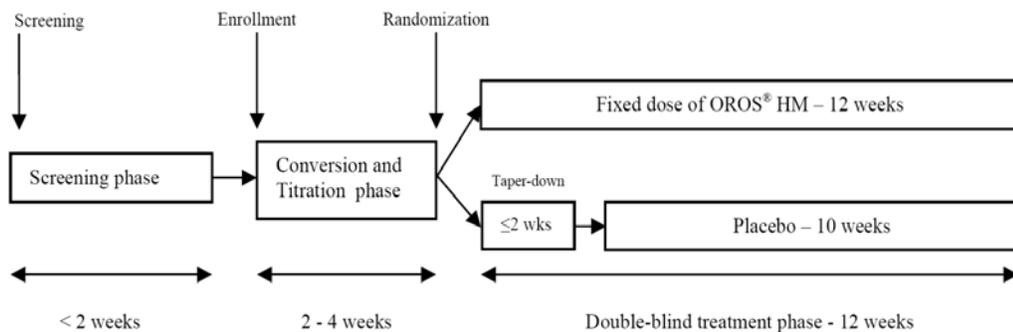
Study Design: This was to have been a multi-center, randomized, placebo-controlled, double-blind study with a Conversion and Titration phase (2 to 4 weeks) and a Double-blind phase (12 weeks). Patients who were randomized to placebo were to have been gradually tapered from the titrated dose to placebo during the first 14 days of double-blind treatment.

Study Drugs:

- Hydromorphone extended release (ER) at 4, 8, 16, and 32 mg tablets (Hydromorphone ER starting dosages were 12, 16, 24, 32, 40 or 48 mg/day not to exceed 64 mg/day)
- Matching placebo tablets
- Dilaudid® at 2 mg, 4 mg, or 8 mg for breakthrough pain during the open-label Conversion and Titration and Double-blind phases of the study

Study Conduct: The study was to have consisted of the following three phases: 1) Screening 2) Open-Label Conversion and Titration and 3) Double-blind. The Study Flow Chart is shown in Table 5 below.

Table 5. Study NMT 1077-301 Flow Chart



(Source: Clinical Study Report NMT 1077-301, p. 24)

- **Screening Phase Conduct**
 - Within 14 days prior to conversion and titration with written informed consent
 - Prior to visit 1, all non-opioid analgesics (e.g., COX-2 inhibitors and NSAIDs) or drugs with anticipated analgesic effect (e.g., Neurontin) were to have been discontinued with the exception of aspirin 325 mg for cardiovascular prophylaxis.
 - The washout period for the non-allowed medicines was to have been at least 1 day, or 5x PK half-life of the medicines, whichever was longer.

- **Conversion and Titration Phase Conduct (Open Label)**
 - Duration between 2 and 4 weeks
 - Conversion to a dosage of hydromorphone ER that was approximately 75% of the equianalgesic dosage of their previous opioid dosage using a morphine conversion table and assuming a hydromorphone HCl: morphine potency ratio of 5:1. (The conversion table and rescue medication schedule is discussed under the Study Procedures section of this review).
 - Hydromorphone ER tablets administered orally once daily in total daily doses of 12, 16, 24, 32, 40, 48, or 64 mg (titrated to response and tolerability for each patient)
 - Rescue medication was allowed

- **Double - Blind Phase Conduct**
 - Duration of 12 weeks
 - Patients were to have been randomized in a 1:1 ratio to continue receiving either the same dosage of hydromorphone ER or matching placebo.
 - During the first 14 days, patients randomized to placebo received hydromorphone ER in dosages tapering from their assigned dosage with gradual reduction over a maximum 14-day period
 - Rescue medication was allowed

- **Study Completion**
 - Upon completion of the Double-blind phase (or early discontinuation), patients returned to the clinic for a final visit and study termination procedures
 - Patients were converted to another opioid at the discretion of the investigator (with conversion dosages at approximately 25% of the patient's stable blinded dosage with unlimited rescue dosages allowed).

Key Inclusion Criteria:

1. Male and female patients aged 18-75 years, inclusive.
2. Documented diagnosis of moderate to severe chronic low back pain that must have been present (by history) for at least:
 - ≥ 20 days /month, and
 - ≥ 3 hrs/day, and
 - ≥ 6 months
3. Classified as non-neuropathic (Class 1 and 2) or neuropathic Class 3, 4, 5 and 6) of LBP based on the Quebec Task Force Classification of Spinal Disorders
4. Required daily scheduled opioid analgesics for low back pain for at least 2 months prior to the screening visit
5. Required daily opioid usage of ≥ 60 mg oral morphine equivalent (≥ 12 mg hydromorphone), but ≤ 320 mg morphine (≤ 64 mg hydromorphone) per day within the 2 months prior to the screening visit
6. Were on a stable dose (≥ 2 weeks) of all prior analgesics (both opioid and non-opioid) prior to the screening visit
7. Women must be postmenopausal, surgically sterile, or practicing or agree to practice an effective method of birth control or male partner sterilization
8. Willing and able to use a paper diary during the study

Key Exclusion Criteria:

1. Active diagnosis of fibromyalgia, complex regional pain syndrome (including reflex sympathetic dystrophy or causalgia), acute spinal cord compression, severe or progressive lower extremity weakness or numbness, bowel or bladder dysfunction as a result of cauda equina compression, diabetic amyotrophy, meningitis, diskitis, back pain because of secondary infection or tumor, or pain caused by a confirmed or suspected neoplasm.
2. Have undergone a surgical procedure for back pain within 6 months prior to the screening visit.
3. Have undergone nerve or plexus block, including epidural steroid injections or facet blocks, within 1 month prior to the screening visit.
4. Any other chronic pain condition that, in the investigator's opinion, would have interfered with the assessment of low back pain (e.g., osteoarthritis, rheumatoid arthritis, postherpetic neuralgia, pain associated with diabetic neuropathy, migraine headaches requiring opioid therapy)
6. History of any illicit drugs of abuse, opioid abuse or drug seeking behavior within 5 years prior to the screening visit.
7. History of prescription medication or alcohol abuse within 5 years prior to the screening visit
8. Positive alcohol or drugs of abuse test at screening visit or conversion and titration visit 1. Patients with positive urine test for medications that were

- not prescribed to the patients or were not medically explainable after conversion and titration visit 1 were to have be discontinued from the study.
9. Women who were pregnant (as indicated by a positive result in a serum pregnancy test administered at screening visit), or breast feeding, or planning to breast feed within 30 days prior to the screening visit.
 10. No bowel movement within three days, or bowel obstruction within 60 days, prior to the screening visit
 11. Pre-existing severe narrowing of the gastrointestinal tract secondary to:
 - a. prior gastrointestinal surgery (e.g., vagotomy, antrectomy, pyroloplasty, gastroplasty, gastrojejunostomy) or
 - b. gastrointestinal disease resulting in impaired gastrointestinal function (e.g., paralytic ileus, gastroparesis, inflammatory bowel disease, "short gut" syndrome due to adhesions or decreased transit time, past history of peritonitis, cystic fibrosis, chronic intestinal pseudobstruction, or Meckel diverticulum)
 12. Major psychiatric condition or clinically significant anxiety or depression
 13. Clinically significant abnormal laboratory results in clinical chemistry, hematology or urinalysis, (normal values provided) including serum glutamic-oxaloacetic transaminase/aspartate aminotransferase (AST) or serum glutamic-pyruvic transaminase/alanine aminotransferase (ALT) \geq 3.0 times the upper limit of the reference range or a serum creatinine \geq 2.0 mg/dL at screening.
 14. Serious or unstable intercurrent illness (uncontrolled seizure disorder, increased intracranial pressure, severe pulmonary diseases)

Treatments Administered:

- Open-label Conversion and Titration phase: Hydromorphone ER tablets once daily in total daily doses of 12, 16, 24, 32, 40, 48, or 64 mg (titrated to response and tolerability for each patient).
- Double-blind phase: Hydromorphone ER tablets administered orally once daily in same dosages as above (the dose administered was based on the stable dose obtained in the Conversion and Titration phase) or matching placebo tablets orally once daily (number and dosage of tablets to match the number and dosage of the stable dose of hydromorphone ER obtained in the Conversion and Titration phase).
 - In order to maintain blinding during the 2-week taper down period, the tablets for both placebo and active drug were over-encapsulated
 - Patients were given "taper cards", which contained the appropriate combination of hydromorphone ER and placebo, over the 2- week period during which they were tapered from their stabilized dosage to placebo

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Procedures: Study procedures are summarized in Table 6 below.

Table 6. Time and Events Schedule (Procedures)

	Screen Visit 1	Conversion and Titration Phase ^a (2-4 weeks) +/- 1 day		Double-Blind Phase ^c (12 weeks) +/- 3 days except DB visits 1-5										DB Visit 11 Day 85 (Week 12: Early Term ^b)			
		CT Visit 1	CT Visits 2 & 3 (4 & 5 if applicable)	DB Visit 1 Day 1	DB Visit 2 Day 4 +/- 1 day	DB Visit 3 Day 8 (Week 1) +/- 1 day	DB Visit 4 Day 11 +/- 1 day	DB Visit 5 Day 15 (Week 2) +/- 2 days	DB Visit 6 Day 22 (Week 3)	DB Visit 7 Day 29 (Week 4)	DB Visit 8 Day 43 (Week 6)	DB Visit 9 Day 57 (Week 8)	DB Visit 10 Day 71 (Week 10)				
Informed Consent ^d	X																
Medical History including Alcohol Abuse	X																
Inclusion / exclusion Criteria	X	X		X													
HADS Anxiety and Depression	X																
Quebec Task Force Classification	X																
Physical Examination ^e	X	X															X
12-lead ECG	X																X
Urine Drug and Alcohol Tests ^f	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Pregnancy Test	X																X
Clinical Laboratory Tests	X																X
Vital Signs ^g	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Reporting ^h	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Monitor Treatment Compliance		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
11-point Likert NRS (clinic visit)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Roland-Morris Disability Questionnaire (RDQ)	X	X		X		X		X	X	X	X	X	X	X	X		X
Subjective Opiate Withdrawal Scale (SOWS)		X	X	X	X	X	X	X									X
Clinical Opiate Withdrawal Scale (COWS)		X	X	X	X	X	X	X									X
Patient Global Assessment (PGA)		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Study Drug Titration Assessment		X	X														
Randomization				X													
Dispense Study Drug		X	X	X	X ^h	X ^h	X ^h	X	X	X	X	X	X	X	X		
Collect and Inventory Study Drug			X	X	X ^h	X ^h	X ^h	X	X	X	X	X	X	X	X		X
Patient Diary	<i>Beginning at Screening. Recording study medicine use, rescue medication use and 11-Point NRS Pain Intensity every evening from 7 PM to 11.59 PM.</i>																
a. Telephone contact with patient regularly during titration phase	f. Oral temperature and weight measured at screening, baseline, and final visits only and premature discontinuation (if applicable)																
b. Perform as soon as possible after discontinuation and/or within 3 days after the last dose of study drug	g. Collect SAEs until 30 days following study drug discontinuation.																
c. Obtain prior to performing screening procedures	h. Rescue medication only.																
d. Height recorded only at screening visit	i. Required urine drug and alcohol tests at screening, CT visit 1 and final visits; collection at 2 DB visits for random testing																
e. Phone contacts every other day for 2 Wks, 1 Wk at Wks 3, 4 and Wks 5, 7, 9 and 11.																	

(Source: Protocol NMT 1077-301, Amendment 4, p. 73, Appendix 2)

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Screening Phase Procedures:

- Physical examination (including respiratory rate, pulse, blood pressure, height and weight)
- Laboratory assessments (including blood and urine for standard laboratory assessments), urine test for the presence of drugs of abuse and alcohol, and a serum pregnancy test for women of child-bearing potential
- Three 12-lead ECGs
- Quebec Task Force low-back pain classification, Hospital Anxiety and Depression Scale (HADS), Roland-Morris Disability Questionnaire (RDQ), and 11-point Likert NRS pain intensity scale

Conversion and Titration Phase Procedures:

Details of the individual office visit procedures are shown in Table 6 (Time and Events Schedule) above.

Conversion was to have been accomplished by first establishing the morphine equivalents of prior opioids using the opioid to morphine conversion table as shown in Table 7 below. The Applicant reported that they developed this Table based upon other similar opioid conversion tables and what is known about hydromorphone in other clinical trials and reported literature.

Table 7. Equianalgesic Potency Conversion

Equianalgesic Potency Conversion Table

Name	Equianalgesic Dose (mg) ^a	
	IM ^{b, c}	PO
Morphine	10	60
Hydromorphone (Dilaudid®)	1.5	7.5
Methadone (Dolophine®)	10	20
Oxycodone	15	30
Levorphanol (Levo-Dromoran®)	2	4
Oxymorphone (Numorphan®)	1	20
Meperidine (Demerol®)	75	300
Codeine	130	200
Hydrocodone	-----	30
Fentanyl (transdermal) (Duragesic®)	(transdermal) 25 micrograms per 8 mg OROS	
Nalbuphine (Nubain)	10	-
Butorphanol (Stadol)	2	-
Pentazocine (Talwin)	30	50
Buprenorphine (Buprenex)	0.4	-
Tramadol (Ultram)	-	250

^a All IM and PO doses in this chart are considered equivalent to 10 mg of IM morphine in analgesic effect. IM denotes intramuscular, PO oral, and PR rectal.

^b Based on single-dose studies in which an intramuscular dose of each drug listed was compared with morphine to establish the relative potency. Oral doses are those recommended when changing from parenteral to an oral route. Reference: Fotey, K.M. (1985) The treatment of cancer pain. NEJM 313(2): 84-95

^c Although controlled studies are not available, in clinical practice it is customary to consider the doses of opioid given IM, IV or subcutaneously to be equivalent. There may be some differences in pharmacokinetic parameters such as C_{max} and T_{max}.

(Source: Protocol NMT 1077-301, Amendment 4, p. 83)

Assuming a hydromorphone: morphine potency ratio of 5:1, patients were to have been converted to a dose of hydromorphone approximately 25% less than the equianalgesic dose of hydromorphone ER, as shown in Table 8 below.

Table 8. Dose Conversion from Oral Morphine Equivalents to Hydromorphone ER Using 5:1 (Hydromorphone: Morphine) Potency Ratio

Total Daily Morphine Equivalent Range (mg)		Starting OROS [®] Hydromorphone Dose (mg)
Low	High	
60	80	12
81	130	16
131	180	24
181	230	32
231	280	40
281	320	48

(Source: Protocol NMT 1077-301, Amendment 4, p. 24)

- Patients taking less than 80 mg of morphine equivalents a day were to have been initiated on hydromorphone ER 12 mg for the first week. The dose of hydromorphone ER could have been increased as frequently as every 3 days according to the next available dose (12 mg, 16 mg, 24 mg, 32 mg, 40mg, 48 mg, and 64 mg). Only one change was to have been made *via* telephone between any 2 clinic visits.
- Patients could not exceed 64 mg during the titration and conversion phase. During this phase, patients were to have been allowed to decrease their dose of hydromorphone only once as needed, and not below 12 mg.

- Rescue Medication
 - Unlimited rescue medication of Dilaudid® IR permitted for the first 3 days
 - The frequency of rescue medication reduced to less than 2 tablets per day by Day 4
 - Clinicians were allowed to increase or decrease the rescue medication dose as clinically required.
 - The rescue medication dose was 5-15% of daily opioid dose. Patients were to have been provided with 2 mg, 4 mg, or 8 mg Dilaudid® Immediate release (IR) tablets as follows:
 - Dilaudid® 2 mg for patients on 12 or 16 mg of hydromorphone ER
 - Dilaudid® 4 mg for patients on 24, 32 or 40 mg of hydromorphone ER
 - Dilaudid® 8 mg for patients on 48 or 64 mg of hydromorphone ER
- Pain Intensity Ratings
 - Patients rated average pain intensity during the past 24 hours using a paper diary every evening
 - Pain intensity measurements recorded at each regularly scheduled clinic visit
- COWS/SOWS
 - Visits 1, 2, 3 (4 and 5 if applicable)
- Monitoring
 - Telephone calls performed every 2 to 3 days as medically indicated between visits
 - Weekly Office visits
- Patients were to have continued into the double-blind phase if they met the following stability criteria:
 - Were taking ≥ 12 mg and < 64 mg hydromorphone ER by the end of the conversion and titration phase
 - Remained on same dose of hydromorphone ER without change for at least 7 consecutive days
 - Took an average of < 2 tablets of rescue Dilaudid®/day during the stable dose period
 - Achieved adequate pain control as indicated by a Pain Intensity score ≤ 4 on the 11-point NRS during the stable dose period
 - Indicated “yes” to the question: “Has this medication (OROS® hydromorphone) helped your (low back) pain enough so that you would continue to take the medication?”
 - Had no intolerable side effects or side effects which may impact the patient’s ability to complete the study

Double - Blind Phase Procedures

- See Table 6 (Time and Events Schedule) for details of visits
- Patients who completed the conversion and titration phase were to have been randomized 1:1 to continue receiving the same dose of hydromorphone ER or matching placebo during a double-blind treatment phase lasting 12 weeks.
- For the first two weeks of the double-blind phase, patients who were randomized to placebo were to receive, in a blinded manner, hydromorphone in doses tapering from their assigned dose to achieve a gradual taper over a maximum of 14 days.
- No other dose adjustments were permitted during this phase
- Rescue Medication
 - Patients were provided with 2 mg, 4 mg, or 8 mg Dilaudid® Immediate release (IR) tablets with use as follows:
 - Mean of ≤ 7 tablets per day during Week 1
 - Mean of ≤ 4 tablets per day during Week 2
 - Mean of 2 tablets per day after Day 14
 - Mean of > 2 tablets per day during any continuous 7-day period was considered treatment failure and patient was discontinued from the study
- Monitoring
 - Telephone calls performed every other day between visits during the first 2 weeks and once per week during Weeks 3 and 4; once per week on the weeks with no scheduled clinic visit (Weeks 5, 7, 9 and 11) and as needed
 - Visits Summary
 - Eleven (11) study visits total
 - Days 1, 4, 8, 11 and Weeks 2, 3, 4, 6, 8, 10 and 12
 - Vital signs, urine for drugs of abuse/alcohol, concomitant medications and AEs were assessed at each visit
 - PI (NRS), Patient Global Assessment (PGA), were assessed at each visit
 - COWS, SOWS were assessed at Visits 1, 2, 3-5 (which is the first 2 weeks of Double-blind phase) and Visit 11 (which is Week 12 or final visit)
 - Roland-Morris Disability Questionnaire (RDQ) was assessed at all visits except Visit 4
 - Visit 11 (final visit) or Study termination included all of the above as well as blood and urine for standard laboratory assessments and 12-lead EKG

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Reviewer's comment: The placebo taper schedule and opioid conversion table appear appropriate.

Concomitant Therapy

- Prohibitions and restrictions:
 - Topical analgesics
 - All other analgesics (oral NSAIDs, oral corticosteroids, tramadol, opioids, COX-2 inhibitors)
 - Monoamine oxidase inhibitors (MAOIs)
- Rescue Medication – discussed above in Procedures section
- Other Concomitant Therapy
 - Osmotic laxatives (lactulose, sorbitol)
 - Peristalsis increasing agents (senna, bisacodyl)
 - Antiemetics as needed
 - Muscle relaxants, selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, and/or benzodiazepines if patient had been taking for at least 2 weeks prior to Screening
 - Inhaled and topical corticosteroids for specific chronic medical conditions
 - Aspirin for cardiovascular prophylaxis (≤ 325 mg per day); acetaminophen; over the counter NSAIDs within approved doses for short-term treatment of acute LBP, fever, or other acute medical needs

Outcome Measures Assessments (all data collected according to Time and Events as per Table 6 above)

- Efficacy Assessments: Pain intensity (PI) measured by Numeric Rating Score at each visit from Screening to End of Study
- Safety Assessments:
 - AEs ongoing at each visit during study
 - SAEs until 30 days following study discontinuation
 - ECGs, physical examinations, vital signs, serology, urine drug screen
 - Clinical Opiate Withdrawal Scale (COWS) and Subjective Opiate Withdrawal Scale (SOWS)
 - Pregnancy tests

Pharmacokinetic Assessments: none performed

Pharmacogenomics: none performed

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Other evaluations: Abuse and Diversion was monitored by collecting and performing inventory on study drug dispensed and returned through use of individual and overall drug accountability forms.

Efficacy endpoints:

- **Primary** - The primary efficacy endpoint was the change from Baseline to Double-blind Week 12 or final visit in weekly mean pain intensity (PI) scores recorded in the patient diaries.
- **Secondary** – There were multiple secondary endpoints which included the following:
 - Change from baseline to the entire 12-week Double-blind phase in weighted mean patient diary pain intensity NRS scores versus time curve (AUC)
 - Change from baseline to each office visit in pain intensity during the 12-week Double-blind phase
 - Time to treatment failure (TTF) between drug and placebo groups as defined by the following:
 - Study discontinuation due to lack of analgesic efficacy
 - Study discontinuation due to AEs
 - If, after Day 14 in the Double-blind phase, the patient took a mean of more than two tablets of rescue medication per day within any 7-day period
 - Change in baseline from Patient Global Assessment (PGA) scores
 - Change in baseline from Roland-Morris Disability Questionnaire (RDQ) total scores
 - Proportion of patients requiring rescue medication in each group
 - Cumulative total number of rescue medication tablets taken
 - Mean number of rescue medication tablets used per day
 - Proportion of patients who discontinued from the study for any reason in each treatment group

Subject completion/withdrawal: Subjects could withdraw from the study at any time. The Investigator could discontinue a patient for necessary reasons determined by the Investigator. Protocol-driven reasons for discontinuation included the following:

- Positive urine drug screen for alcohol and/or drugs of abuse
- Investigator determined AEs
- Sponsor discretion or Investigator determined failure to return appropriate amount of study drug

Statistical methods:

- Sample size determination - The Applicant reported that one study in their clinical development showed a mean difference of 23.0 (SD 35.1) between placebo and oxymorphone in the change in mean pain intensity using a VAS during the 12 week Double-blind treatment phase, indicating an effect size of 0.655 in the patient population studied. The Applicant estimated that a sample size of approximately 115 patients per group would have 99% power to detect a 20-unit difference on VAS between placebo and study drug at a significant level of $p < 0.05$ using a two-sided test. However, because of some differences between study NMT 1077-301 and the other study, the Applicant determined that approximately 272 patients (136 per group) could be randomized to ensure adequate patient numbers.
- Patient Disposition – the Applicant analyzed the number of patients who completed and discontinued the study, the primary reason for discontinuation in premature withdrawal from the Conversion and Titration phase and Double-blind phase summarized by treatment group and hydromorphone ER dose.
- Populations analyzed
 - Intent-to-treat (ITT) was the population used for efficacy analyses and defined as all patients randomized to the Double-blind phase who received at least one dose of randomized study medication.
 - Safety population included all patients who were enrolled and took at least one dose of study drug.
 - Dropouts during titration were all patients who took at least one dose of study drug in the Conversion and Titration phase, but did not meet the established stability criteria to be randomized into the Double-blind phase.
 - Modified intent-to-treat (mITT) was defined as the population identified to evaluate the effect of hydromorphone ER treatment in a subset of patients in the ITT population who most closely adhered to the protocol
- Patient characteristics - Demographic characteristics evaluated included age, age group (18 - 64 years and 65-75 years), gender, race, weight, height, and body mass index (BMI). Patient data was also analyzed for drug exposure and compliance as well as prior and concomitant medications.

- Primary Efficacy Analyses
 - The primary population for the efficacy analysis was the intent-to-treat (ITT) population which was defined as all patients randomized to the Double-blind phase who received at least one dose of randomized study medication. The Baseline value was defined as the mean of the patient diary measurement in the week prior to randomization. The Cochran-Mantel-Haenszel (CMH) chi-square test was used to test the difference between drug-treated and placebo-treated groups.
 - Final visit scores for patients who discontinued before Week 12 were imputed based on the reason for discontinuation:
 - Discontinuation due to opioid withdrawal - Baseline observation carried forward (BOCF)
 - Discontinuation due to AEs – screening observation carried forward (SOCF)
 - Discontinuation due to other reasons – last observation carried forward (LOCF)
- Secondary Efficacy Analyses
 - Change from baseline to the entire 12-week Double-blind phase in weighted mean patient diary pain intensity NRS scores were summarized using an AUC calculation using the trapezoidal rule
 - Change from baseline to each office visit in pain intensity during the 12-week Double-blind phase used ANCOVA or the CMH chi-square test
 - Time to treatment failure (TTF) between drug and placebo groups was analyzed using Kaplan-Meier methods and the proportional hazard assumption
 - Change in baseline for Patient Global Assessment (PGA) scores and change in baseline for Roland-Morris Disability Questionnaire (RDQ) total scores used data collected at Baseline and each subsequent visit and changes from Baseline to Week 12 (or final visit) using the CMH chi-square test
 - Proportion of patients requiring rescue medication in each group was analyzed as follows
 - Cumulative total number of rescue medication tablets taken used non-parametric estimation calculated with 95% confidence limits
 - Mean number of rescue medication tablets used per day used Wilcoxon rank-sum tests (or t-test)

Proportion of patients who discontinued from the study for any reason in each treatment group used a continuity corrected chi-square test

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Interim Analyses: none

AdHoc Analysis: An ad hoc analysis of the primary efficacy variable in a subset of the efficacy population was performed.

Protocol Amendments: The original protocol was submitted as IND 78,223 on 7/23/07. Amendments were as follows:

- Amendment 1 (7/13/07; prior to patient enrollments)
 - The primary efficacy endpoint was changed to “mean change from Baseline to Week 12 average pain score of Double-blind treatment phase based on the weekly NRS scores obtained from patient diary entry.”
 - “Time to treatment failure” was changed from the primary efficacy endpoint to a secondary efficacy endpoint.
 - Portion of treatment failures was removed as a secondary efficacy variable
 - The allowed rescue medication use during the first 2 weeks of the Double-blind phase was changed from unlimited to a mean of ≤ 6 tablets daily during Week 1, mean of ≤ 4 tablets daily during Week 2 and starting with Day 15, a mean ≤ 2 tablets daily during any 7-day period.
 - COWS and SOWS were collected at Double-blind Visits 1 through 5 and at discontinuation.
 - Opiates were added to the urine drug test to verify previous opioid use and to monitor study drug administration. Hydromorphone results remained blinded throughout the Double-blind phase.
- Amendment 2 (issued 8/29/07; prior to patient enrollments)
 - Primarily administrative changes except for the following:
 - Over-the-counter NSAIDs were allowed with approved doses and durations
 - LBP patients with spinal stenosis based on radiographic evidence (but not neurogenic claudication (Class 7) and LBP patients with asymptomatic post-surgical status (> 6 months after intervention) (Class 9.1) were also enrolled
- Amendment 3 (issued 9/20/07; prior to patient enrollments)
 - COWS and SOWS were included in CRF
 - Opioid conversion table was updated to include more opioids
 - Detailed instructions about the urine drug and alcohol tests were added
- Amendment 4 (issued 1/28/08; 82 patients had been enrolled). These amendments were permitted by the Agency
 - The sentence “Patients who require a mean of 2 tablets of rescue medication per day during any 7-day period starting on Day 4 of the

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Conversion and Titration phase will be discontinued from the study”
was deleted.

- “Patients with positive urine test for medications that are not prescribed to the patients or are not medically explainable after Conversion and Titration Visit 1 will be discontinued from the study”
- Administrative changes

Reviewer’s comment: The first 3 Amendments were issued prior to patient enrollment. Amendment 4 changes occurred after 82 patients were enrolled. The first changes in Amendment 4 (rescue medication) applied to the Conversion/Titration phase and did not affect the double-blind phase. The second change (positive urine tests) would be applicable to all treatment sites and both treatment groups. Therefore, this amendment should not have affected the efficacy analysis.

The results from Study NMT 1077-301 are discussed in Section 7 of this review.

Additional Studies (Synopsis)

The Applicant’s supportive efficacy studies (M03-644-05, DO-118, DO-132, OROS-ANA-3001, DO-118X, and DO 127/127X) which were included in this complete response submission are discussed following Table 9 (which summarizes the primary features of five of the studies and their efficacy measures). Following the discussion of these 7 studies is a brief discussion of the supportive efficacy studies included in the original NDA 21-217 submission and reviewed in that submission but included here for completeness.

Table 9. Supportive Efficacy Studies (Key Features and Efficacy Measures)

Features of the study	NMT 1077-3 01	M03-644 -05	DO-1 18	DO-1 32	OROS-ANA -3001	DO-11 8X
Randomized and double-blind study	+	+	+	+		
Placebo-controlled study	+	+				
Active-controlled study			+	+	+	
12-week treatment duration	+	+			+	+
Titration to efficacy before randomization	+		+	+	+	+
Enrolled opioid-tolerant patients only ^a	+		+			+
Efficacy Measures:						
Pain Intensity assessed with NRS, BPI WOMAC, etc.	+	+	+	+	+	+
Time to treatment failure	+	+			+	+
Patient or clinician global assessment	+	+	+		+	+
Disability assessments	+	+	+			
Rescue medication use	+	+	+			
Total drop-out for any reasons	+		+			
Pain relief			+			
MOS sleep quality		+	+	+	+	
Quality of life (SF-36)		+		+	+	
Change of study medication			+	+		
Time to efficacious dose		+	+	+		
Equianalgesic dose					+	
Number/ percentage of responders		+				

^aPatients in these studies may have been previously treated with opioids but not necessarily opioid-tolerant (Studies DO-118, DO-132, and the open-label extension studies). In Studies MOS-644-05 approximately 66% of enrolled patients were opioid-naïve; in Study DO-132 approximately 63% were opioid-naïve, and in Study OROS-ANA-3001, approximately 30% of enrolled patients were opioid-naïve; the remainder had been treated with weak opioids or non-opioid analgesics. BPI= Brief Pain Inventory; MOS=Medical Outcomes Study; NRS=Numeric Rating Scale; SF=Short Form; WOMAC=Western Ontario and McMaster Osteoarthritis Index

(Source: Summary of Clinical Efficacy, p. 67)

Study 1) Protocol M03-644-05

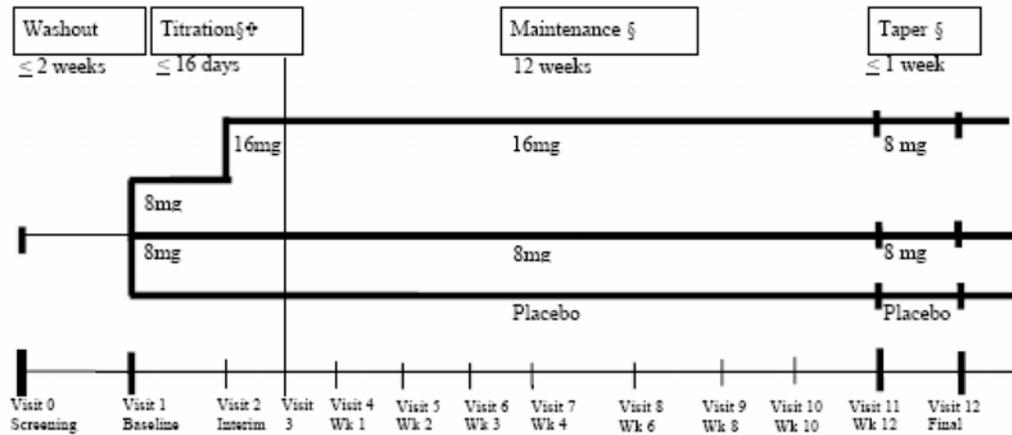
Title: A Phase 3, Randomized, Double-Blind, Fixed-Dose, Parallel-group Comparison of Controlled-Release Hydromorphone HCl vs. Placebo in Patients with Osteoarthritis

Objective: To compare the analgesic efficacy and safety of OROS hydromorphone 8 and 16 mg to placebo in the treatment of OA

Design: Randomized, double-blind, placebo-controlled, fixed dose, parallel-group, multi-center study in adult patients ≥21 years old with osteoarthritis (OA) of the hip or knee with uncontrolled pain on non-opioid medications or who had received an opioid for treatment of pain.

Study Methods: Analgesic taper and washout period (≤ 2 weeks), a Titration Phase (≤ 16 days) for 16 mg group, a Maintenance Phase (12 weeks), and a Study Drug Taper period (≤ 1 week). The key features of each study phase are shown in Figure 3 below.

Figure 3: Study M03-644-05 Schematic: Key Features



(Source: Summary of Clinical Efficacy, p. 31)

Primary endpoint: AUC for pain through Week 12

Secondary efficacy variables:

- Western Ontario and McMaster osteoarthritis Index (WOMAC) OA Index
- PGA
- Analysis of treatment responders (defined as patients who achieved $\geq 30\%$, $\geq 40\%$, or $\geq 50\%$ improvement in the change from Baseline to the final evaluation using the office visit pain intensity score)
- Weekly pain intensity via the interactive voice response system (IVRS) (using a 4-point categorical scale)
- Rescue medication use
- Medical Outcomes Study (MOS) sleep scale

Missing data were imputed, per the protocol-specified analysis, by substituting the Baseline observation for all missing values or Baseline Observation Carried Forward (BOCF)

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Results: Nine hundred ninety (990) patients were randomized and 981 received at least one dosage of study drug. Table 10 summarizes the endpoints' results.

Table 10. Primary and Key Secondary Endpoint Results at Maintenance Week 12 for All Treated Patients (BOCF and LOCF) in Study M03-644-05

Efficacy Measure/Imputation Method	OROS [®] HM 8 mg	OROS [®] HM 16 mg	Placebo	Results at Maintenance Week 12	Results at Maintenance Week 12
	Mean (SD)	Mean (SD)	Mean (SD)	Placebo vs. 8 mg	Placebo vs. 16 mg
(1) AUC ratio of office visit pain intensity					
BOCF imputation	0.18 (0.265)	0.19 (0.254)	0.20 (0.266)	Results significant through Titration Week 2; At Maintenance Week 12, p=0.3636	Results significant through Maintenance Week 4; At Maintenance Week 12, p=0.5535
LOCF imputation	0.25 (0.327)	0.30 (0.322)	0.22 (0.305)	Results significant through Maintenance Week 3; At Maintenance Week 12, p=0.3257	Results significant through Maintenance Week 12; At Maintenance Week 12, p=0.0009
(2) WOMAC pain subscale AUC ratio					
BOCF imputation	0.19 (0.251)	0.17 (0.235)	0.16 (0.271)	Results significant through Maintenance Week 10; At Maintenance Week 12, p=0.0807	Results significant through Maintenance Week 6; At Maintenance Week 12, p=0.5782
LOCF imputation	0.24 (0.326)	0.27 (0.293)	0.18 (0.309)	Results significant through Maintenance Week 12; At Maintenance Week 12, p=0.0077	Results significant through Maintenance Week 12; At Maintenance Week 12, p=0.0001

AUC=area under the curve; BOCF=Baseline observation carried forward; HM=hydromorphone; LOCF=last observation carried forward; OROS[®]=oral osmotic; SD=standard deviation; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index

(Source: Summary of Clinical efficacy, p. 33)

Reviewer's comments: This was considered a failed study as, using the planned analysis of BOCF, neither hydromorphone dose was found to be superior to placebo.

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Study 2) Protocol DO-118

Title: A Randomized, Double-Blind, Controlled Trial of Hydromorphone (Immediate and Sustained-release) vs. Morphine (Immediate and Sustained-release) in Cancer Pain

Primary Objective: To demonstrate the clinical equivalence of hydromorphone and morphine using the “worse pain the past 24 hours” item of the Brief Pain Inventory (BPI)

Secondary Objectives: To compare hydromorphone and morphine for the following variables:

- Other BPI Pain Measures
- Investigator Global Assessment
- Patient Global Assessment (PGA)
- Number of breakthrough-pain medication doses taken
- Time to dose stabilization
- Number of discontinuations
- Numbers of patients who changed dosage levels
- Mean number of dosage level changes
- Safety and tolerability variables

Design: Double-blind, randomized, active-controlled (morphine), parallel-group study in patients with chronic cancer pain

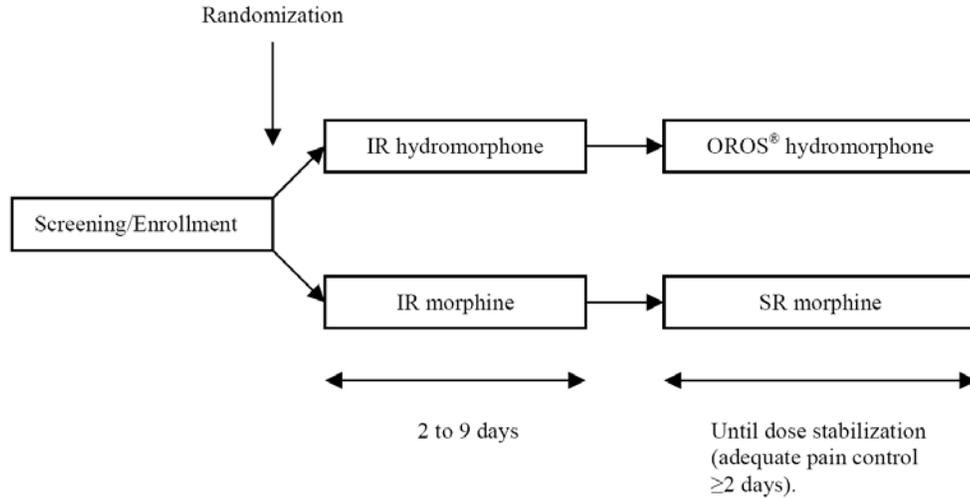
Study Methods: Study DO-118 consisted of 2 phases: an initial IR phase and a subsequent SR phase. Eligible patients were randomized 1:1 to receive either hydromorphone HCl or morphine sulfate (IR formulation in the IR phase, SR formulation in the SR phase). In the IR phase (2-9 days), patients were started on the appropriate initial dose of IR medication q4h (6 doses/day) using a 5:1 conversion ratio (morphine equivalents:hydromorphone dosage).

When the patient achieved dose-stable pain control, the SR phase could be entered. The patient was given an equivalent dosage of a SR formulation of the same drug (OROS hydromorphone daily or morphine sulfate SR bid).

After 2-9 days they were converted to either hydromorphone ER or sustained released (SR) morphine and maintained on that treatment until dose stabilization had been achieved.

Figure 4 summarizes the key features of Study DO-118.

Figure 4. Key Features Study DO-118



IR=immediate release; OROS[®]=oral osmotic; SR=sustained release

(Source: Summary of Clinical Efficacy, p. 36)

Efficacy Variables: The primary efficacy analysis was the BPI worst pain in the past 24 hours (the mean of the last two post-baseline recorded values or last value if only one value was available) in each phase (IR and SR) for hydromorphone versus morphine.

Results: There were no significant treatment differences in any of the efficacy measures. The Applicant noted that there was a lower “pain now” score for OROS treated patients in the p.m. compared to SR morphine. The summary of efficacy analysis results is shown in Table 11 below.

Table 11. Primary Efficacy Analysis Results in All Treated Patients in Study DO-118

BPI worst pain in the past 24 hours ^a	IR Phase		SR Phase	
	HM IR n=99	Morphine IR n=101	OROS [®] HM n=77	Morphine SR n=86
Observed mean (end of phase)	5.0	4.8	3.5	4.1
SD	2.72	2.41	2.47	2.69
Range	0.0, 10.0	0.0, 9.0	0.0, 10.0	0.0, 9.5
LS (adjusted) mean ^b	5.0	4.8	3.5	4.3
LS mean of the treatment difference ^c (SEM)	0.21 (0.33)		-0.80 (0.40)	
95% CI for treatment difference	(-0.44, 0.86)		(-1.59, -0.01)	
Treatment difference p-value	0.5230		0.0463	

^aMeasured on an 11-point scale (0=no pain; 10=pain as bad as you can imagine)

^bAdjusted for Baseline (initial value in IR phase)

^cA negative difference favors hydromorphone.

BPI=Brief Pain Inventory; CI=confidence interval; HM=hydromorphone; IR=immediate release; LS=least squares; n=number of patients; OROS[®]=oral osmotic; SD=standard deviation; SEM=standard error of the mean; SR=sustained release

(Source: Summary of Clinical Efficacy, p. 38)

Reviewer's comment. This study does not support a clinical or statistically significant finding of efficacy of OROS compared to the other drugs studied in this trial when using the Applicant's analysis of the primary and secondary efficacy endpoints.

Study 3) Protocol DO-132

Title: A Randomized, Repeated-Dose, Parallel-Group Comparison of Safety, Efficacy, and Quality of Life Measures with Dilaudid CR (Hydromorphone HCl) or Oxycontin (Oxycodone HCL) in Patients with Chronic Osteoarthritis. (Dilaudid CR refers to OROS hydromorphone in this title).

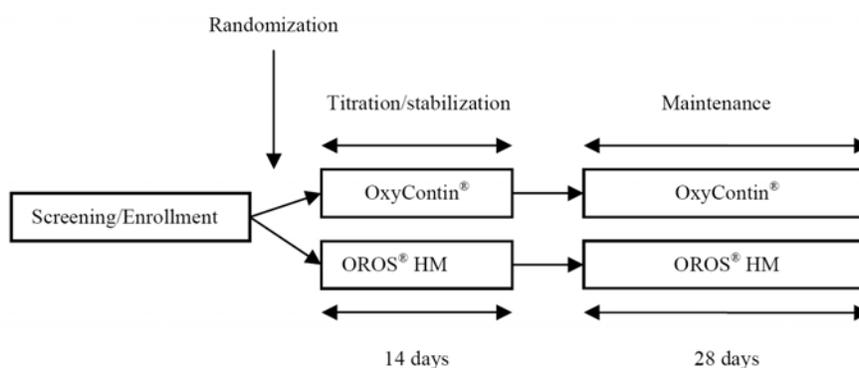
Objective: To characterize the efficacy and safety of OROS hydromorphone and Oxycontin (oxymorphone) in patients with OA

Design: Multi-center, open-label, parallel-group, active-controlled study consisted of a 14-day randomization, dose-titration, and stabilization period, followed by a 28-day Maintenance phase.

Study Methods: Male and female patients ≥ 18 years of age with OA of the hip or knee for at least 3 months before enrollment with moderate-to-severe chronic pain inadequately controlled with non-opioids were enrolled. Patients were

randomized equally to begin therapy with either OROS hydromorphone 8 mg once daily or Oxycontin 10 mg twice daily with upward dose titration. After 14 days, if therapeutic efficacy with dose stabilization had been documented, the patient was allowed to begin the 4-week Maintenance phase. Dosages of OROS hydromorphone and Oxycontin ranged from 8 to 64 mg and 10 to 160 mg, respectively. The key features of the study are shown in Figure 5.

Figure 5: Key Features Study DO-132



(Source: Summary of Clinical Efficacy, p. 40)

Primary Efficacy Variables: Primary variables were the mean pain relief score (5 point scale) at endpoint and time from study medication initiation to the third day of moderate to complete pain relief on the patient's final titrated dosage.

Secondary efficacy variables:

- Change from Baseline to Endpoint for the following
 - Mean pain relief score
 - Mean pain intensity score
 - Mean total daily dosage of study medication
 - Mean daily number of tablets of study medication

- Change from Baseline to subsequent visits for the following
 - MOS sleep assessment
 - Investigator global assessment
 - PGA
 - WOMAC OA Index

Results: The data revealed that the mean pain relief scores at Endpoint were identical for both treatments. The 95% confidence interval demonstrated the non-inferiority of OROS hydromorphone relative to Oxycontin. The Applicant

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maintained that there was less sleep disturbance and daytime drowsiness in the OROS treated group than the Oxycontin arm.

Reviewer's comments: This study was open-label with no placebo-control. No claims can be made regarding efficacy, sleep disturbance or daytime drowsiness.

Study 4) Protocol OROS-ANA-3001

Title: Randomized, Open-label, Comparative Parallel Group Study to Assess Efficacy and Safety of Flexible Dosages of OROS Hydromorphone once-daily Compared to Sustained Release (SR) Oxycodone twice-daily in Subjects with Chronic, Non-Malignant Pain Severe Enough to Require Continuous Opioid Therapy

Design: Randomized, open label, comparative parallel group study to assess efficacy and safety of flexible dosages of OROS hydromorphone once-daily compared to sustained release oxycodone twice-daily in subjects with chronic non-malignant pain severe enough to require continuous opioid therapy

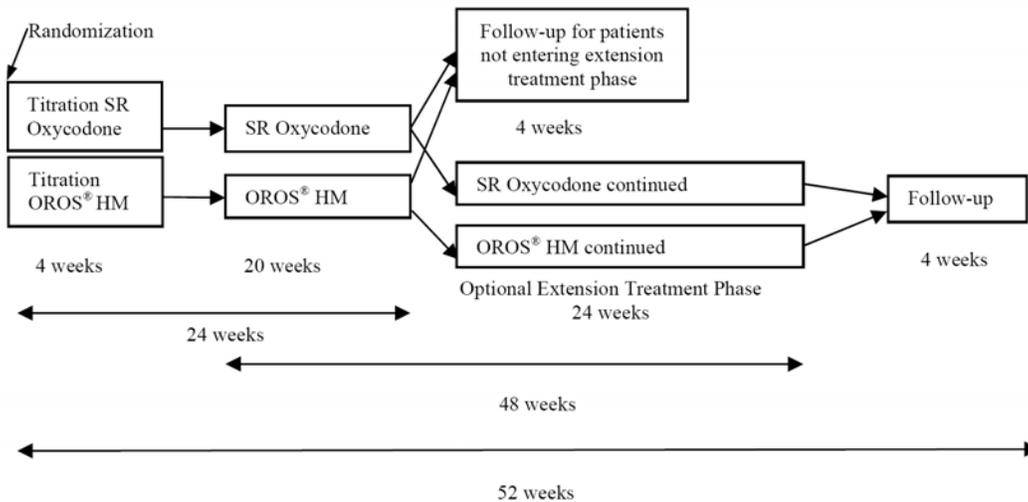
Primary Objective: To demonstrate non-inferiority of OROS hydromorphone compared to SR oxycodone with regard to pain control and to determine the equi-analgesic dosage of OROS hydromorphone once-daily and SR oxycodone twice-daily

Population: Chronic, non-malignant pain patients. N=504 ITT; 277/504 completed the Core Phase (Weeks 0 to 24) and 97/112 completed the Extension Phase (Weeks 24-52)

Study Methods: Weeks 0-24 consisted of a 4-week titration phase followed by 20 weeks maintenance phase. An Extension phase (Weeks 24-52) was of 28 weeks' duration.

Figure 6, below, displays the schematic of the study.

Figure 6. Study OROS-ANA-3001



(Source: Summary of Clinical Efficacy, p. 44)

Treatment A:

- OROS hydromorphone (8, 16, and 32 mg tablets)
- Oral administration: once daily (mandatory)
- Initial dose and minimal dose: 8 mg
- Maximal daily dosage: 32 mg

Treatment B:

- SR oxycodone (Oxycontin; 10, 20, and 40 mg tablets)
- Oral administration: twice daily (mandatory)
- Initial dose and minimal dose: 10 mg twice daily
- Maximal daily dosage: 80 mg

Primary endpoints

- Pain control, defined as change in BPI pain severity sub-score “pain right now” (BPI item 6) from baseline to endpoint of the core (first) study phase.
- Equi-analgesic dosage of OROS hydromorphone once-daily and SR oxycodone twice-daily with regard to pain control, defined as average dose used at endpoint of core (first) study phase under the condition that non-inferiority with respect to pain control has been established.

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Secondary endpoints

Main Secondary Endpoints in Hierarchical Order:

1. Change in BPI pain severity sub-score “pain at its worst” (BPI item 3) from baseline to endpoint of core phase
2. Change in sleep quality, i.e. MOS sleep scale index 1, from baseline to endpoint of the core phase (Week 4, Week 24, and Endpoint compared with Baseline)
3. Change in subject diary evening mean pain score “pain right now” from baseline to endpoint of the core phase
4. Change in Subject Diary Morning Mean Pain Score “Pain Right Now” from BL to Endpoint of Core Phase
5. Proportion of subjects with Dose Escalation

Results:

Statistical efficacy results of the study are summarized in Table 12 below with discussion following the Table.

Table 12. Study OROS-ANA-3001 - Pain Control (Change in BPI Pain Severity Sub-Score “Pain Right Now” from Baseline to Endpoint of Core Phase in ITT Population)

	OROS [®] Hydromorphone (N=254)	SR Oxycodone (N=250)	Total (N=504)	Difference Between Groups
Pain right now				
Baseline				
N	247	237	484	
Mean (SD)	6.6 (1.59)	6.8 (1.72)	6.7 (1.66)	
Median	7.0	7.0	7.0	
Range	2.0 – 10.0	1.0 – 10.0	1.0 – 10.0	
Endpoint of Core phase				
N	234	225	459	
Mean (SD)	4.5 (2.31)	4.7 (2.41)	4.6 (2.36)	
Median	4.0	4.0	4.0	
Range	0.0 – 10.0	0.0 – 10.0	0.0 – 10.0	
	233	223	456	456
Change from Baseline to Endpoint of Core phase	-2.1 (2.43)	-2.1 (2.41)	-2.1 (2.42)	
N	-2.0	-2.0	-2.0	
Mean (SD)	-10.0 – 4.0	-9.0 – 4.0	-10.0 – 4.0	
Median				-0.12
Range				-0.53; 0.29
Difference between LS means				<0.001
95% Confidence interval	247	237	484	
p-value	6.6 (1.59)	6.8 (1.72)	6.7 (1.66)	

Note: The presented p-value tests the null hypothesis of inferiority versus the alternative hypothesis of non-inferiority.

BPI=Brief Pain Inventory; LS=least square means; SD=standard deviation

(Source: Summary of Clinical Efficacy, p. 47)

Reviewer’s comments: The Applicant maintained that OROS hydromorphone proved to be non-inferior to SR oxycodone with respect to the change in BPI pain severity sub-score “pain right now” after 24 weeks of treatment. However, there are study limitations since this was not an AWC study (open-label with no placebo for comparison). In addition, multiple non-validated endpoints were assessed without correction for multiplicity. Therefore, this study can not support claims regarding efficacy or secondary endpoint claims.

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Study 5) Protocol DO-118X

Title: Safety and Tolerability of Long-term Administration of Dilaudid SR (Hydromorphone HCL) in Cancer Pain

This was an open-label extension study for patients who completed Study DO-118 who received OROS hydromorphone and SR morphine. The patients received study medication for up to one year. Only 10/68 (14.7%) of the patients who entered the study completed the full year.

Reviewer's comment: Although the Applicant purports that the results support the claim that OROS hydromorphone is an effective long-term analgesic for the treatment of chronic pain, no efficacy conclusions could be drawn from this study since this was an open-label study.

Studies 6 and 7) Protocol DO-127 and DO- 127X

These studies are discussed together as DO-127X as an extension study of DO-127.

Title (DO-127): An Open-Label, Repeated-Dose Trial to Characterize the Efficacy and Safety, and Impact on Quality of Life Measures of Dilaudid CR (Hydromorphone HCl) in Patients with Chronic Low Back Pain

Title (DO-127X): Safety, Efficacy, and Impact on Quality of Life of Long-Term Administration of Dilaudid CR (Hydromorphone HCl) in Patients with Chronic Low Back Pain

Primary Objective: To characterize the safety, efficacy, and impact on quality of life (QOL) measures of Dilaudid CR (hereafter referred to as OROS hydromorphone) in patients with chronic low back pain.

Methods: Study DO-127 was a short-term, non-randomized, non-comparative, open-label, repeated-dose study of OROS hydromorphone consisting of 3 phases:

- Phase 1: prior opioid stabilization phase (2-7 days)
- Phase 2: OROS hydromorphone conversion, titration, and stabilization phase (3-14 days)
- Phase 3: OROS hydromorphone maintenance therapy phase (28 days)

Methods: Study DO-127X was a long-term (6 months), open-label, extension study. Patients enrolled in Study DO-127X were to continue their therapy with OROS hydromorphone at the stable dose previously identified in the short-term

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study. Adjustments to dose could be performed as needed, at the discretion of the Investigator and rescue medication was allowed. Patients were evaluated monthly

Primary efficacy parameters: Pain relief score ratings (mean pain relief score from the last 2 days of therapy, derived from daily pain relief ratings in weekly diaries (DO-127) or monthly visits (DO-127X))

Secondary parameters

- Investigator and patient Global Evaluations
- Brief Pain Inventory (BPI)
- QOL measurement (SF-36)
- Sleep assessment (Medical Outcomes Study Questionnaire [MOS])

Applicant's Conclusions:

- Results of the primary efficacy analyses indicated that OROS hydromorphone treatment was efficacious during the first 4 weeks of treatment (DO-127), and that efficacy was sustained over the following 6 months (DO-127X)
- Regarding the secondary outcomes, the Applicant concluded that efficacy results were consistent across each of the secondary parameters (Patient and Investigator Global Evaluations, BPI, SF-36, and MOS). During short-term treatment with OROS hydromorphone, the overall global evaluation of study drug, as assessed by both patients and Investigators, increased (improved) over the course of Study DO-127 (4 weeks). These increases were sustained over the course of Study DO-127X (6 months). Mean results for the BPI, SF-36, and MOS assessments were consistent in that an improvement was noted during short-term treatment with OROS hydromorphone (DO-127) and sustained during long-term treatment (DO-127X).

Reviewer's comments: While the data reviewed does appear to support the Applicant's conclusions, no labeling claims regarding these endpoints can be made as Study DO-127 was not a placebo-controlled study and Study DO-127X was a open-label, uncontrolled study.

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The following 4 studies were cited by the Applicant as supportive of the proposed indication and have been previously reviewed in the original NDA.

Study 1) DO-104/DO-105

Title: A Repeated-Dose Evaluation of Analgesic Use and Safety of OROS Hydromorphone HC in Patient with Chronic Cancer (DO-104) and Non-Malignant (DO-105) Pain

Objectives: To develop recommended dosing information for initiation of therapy in patients with chronic pain converting from other strong oral or transdermal opioids; safety, titration

Methods: Patients receiving chronic opioid therapy were converted to once daily OROS hydromorphone using oral morphine equivalents. Immediate-release hydromorphone was allowed for rescue medication. The dose of OROS hydromorphone was increased after every 2 days of therapy unto no more than 3 doses of IR hydromorphone were required in a 24-hour period. Once a patient could be maintained on a stable dose of OROS for 3 consecutive days, the patient entered a 2-week maintenance phase. Patients who completed the study were eligible for participation in an OROS hydromorphone long-term extension study (Study DO-109). There was a combined total of 463 patients with chronic pain.

Design: Multicenter, open-label, single-blind (with respect to dose), repeated-dose with no control.

Results: The efficacy outcome results are summarized in Table 13. Information is presented for the combined DO-104/105 group.

Table 13. Efficacy Results Study DO-104 and DO-105

	End of prior Opioid Stabilization	Start of Titration	End of Dilaudid CR Titration	End of Dilaudid CR Maintenance
% of Patients Requiring Rescue Medication	33.9%	99.2%	97.5%	97.0%
Average Total Daily Dose Of Rescue Medication (mg)	NA	14.1	12.7	11.5
Average Pain Relief	1.9	1.6	2.2	2.3
Mean Pain Intensity Difference ^a	3.0		2.8	2.5
Global Evaluation, Ratings of Good to Excellent				
Patient	49.1%		62.1%	79.3%
Investigator	47.8%		63.6%	84.7%

^a The difference between the worst pain and the least pain over the past 24 hours
 (Source: Medical Officer Review, original NDA 21-217 submission, p. 41)

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Reviewer's comments: This study was reviewed in the original NDA. The reviewer, Dr. Sharon Hertz, noted that "there was a marked increase in the number of patients requiring rescue medication after conversion from prior opioids to Dilaudid CR". There were various explanations as to why this may have been the case. The Applicant maintained that this result was noted primarily due to study design (use of Dilaudid IR was specified during the titration and maintenance phases). However, the Reviewer noted that "the percentage of patients requiring rescue did not appreciably decrease after titration was completed and lack of efficacy of the Dilaudid CR may have been a plausible explanation". It was further noted by the Reviewer that "the improvement in pain relief and decrease in difference in pain intensity were modest". The overall satisfaction with treatment (as based on the Global Evaluation) did improve.

Study 2) Protocol DO- 119

Title: A Randomized, Double-Blind, Repeated-Dose, Parallel-Group Comparison of the Efficacy and Tolerability of Dilaudid CR Tablets and Immediate Release Dilaudid Tablets in Patients with Chronic Pain

Objectives:

- To characterize a safe and effective means of conversion and titration to an appropriate dose of Dilaudid
- To demonstrate significant differences in the amount of breakthrough-pain medication taken in comparison between the full-dose Dilaudid CR group and the ½ dose Dilaudid CR group. If the ½ dose Dilaudid CR group did not require more rescue medication, then it was anticipated that the full-dose Dilaudid CR would demonstrate superior efficacy
- To demonstrate comparable efficacy of Dilaudid CR and Dilaudid IR

Methods: Study was designed to evaluate the ability of Dilaudid CR (OROS) to control pain in a dose-controlled design comparing Dilaudid IR, ½ dose Dilaudid CR, and full-dose Dilaudid CR.

Primary Efficacy Variable: Change in daily doses of breakthrough-pain medication across days 3 through 7 of the double-blind phase of the study

Secondary Efficacy Variables:

- Pain intensity
- Pain relief
- Sleep interference
- Ratings on the Brief Pain Inventory
- Normalized breakthrough-pain medication

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- Global Evaluation Ratings
- Proportion of patients dropping out due to lack of efficacy

Results: As shown in Tables 14 and 15 below.

Table 14. Baseline Breakthrough Pain Medication use by Treatment Group (Study DO-119)

Baseline ^a Parameter	Dilaudid SR (N=34) ^b	1/2 Dilaudid SR (N=40)	Dilaudid IR (N=39)	All Groups (N=113)
Total Daily Dose (mg)				
n ^b	34	40	39	113
Mean±STD	16.4±16.3	10.7±9.9	14.3±16.4	13.7±14.5
Median	9.0	8.0	6.0	8.0
Range	0-64	0-36	0-52	0-64
p-Value	N/A ^c	N/A	N/A	0.2520 ^d
Normalized Dose (%)^e				
n	34	40	39	113
Mean±STD	43.0±33.3	28.2±22.7	32.5±29.9	34.2±29.1
Median	33.5	25.8	25.0	30.0
Range	0-160	0-90	0-100	0-160
p-Value	N/A	N/A	N/A	0.1329 ^d
Number of Times/Day of Breakthrough Pain Medication Use				
n	34	40	39	113
Mean±STD	2.1±0.9	1.8±1.1	1.7±1.2	1.8±1.1
Median	2.0	2.0	2.0	2.0
Range	0-3	0-4	0-3	0-4
p-Value	N/A	N/A	N/A	0.3441 ^d
Source: Section 9, Table 10.0.				
^a Baseline was the last 2 days on the stable dose during the open-label dose conversion and titration between Visits 2 and 3.				
^b N = Number of patients randomized; n = Number of patients evaluated				
^c N/A = Not applicable.				
^d Kruskal-Wallis test.				
^e The total amount of breakthrough pain medication converted to a percentage of the final titrated dose of Dilaudid IR.				

(Source, Original NDA 21-217 submission, Vol. 67, p. 69)

Table 15. Breakthrough Pain Medication: Total Daily Dose at Endpoint and Change from Baseline to Endpoint by Treatment Group (Study DO-119)

Parameter	Dilaudid SR (N=34) ^a n ^a (%)	1/2 Dilaudid SR (N=40) n (%)	Dilaudid IR (N=39) n (%)	All Groups (N=113) n (%)
<u>Total Daily Dose (mg)</u>				
<u>Endpoint^b</u>				
n	33	38	39	110
Mean±STD	23.2±19.8	19.1±17.5	21.4±23.8	21.1±20.5
Median	18.0	11.4	16	14.4
Range	0-80.0	0-76.8	0-108.8	0-108.8
p-Value	N/A ^c	0.5681 ^d	0.3717 ^e	f
<u>Change From Baseline</u>				
n	33	38	39	110
Mean Change±STD	6.6±16.0	9.2±12.0	7.1±14.5	7.7±14.1
Median	2.0	7.4	4.4	5.1
Range	-24.0-64.0	-8.2-52.8	-23.2-60.8	-24.0-64.0
p-Value				
Within treatment ^g	0.027	<0.001	0.001	N/A
Between treatment	N/A	0.159 ^d	0.760 ^e	f
Source. Section 9, Tables 14.0 and 18.0.				
^a N = Number of patients randomized, n = Number of patients evaluated				
^b Endpoint is the mean of Days 3 to 7 of the double-blind phase based on non-missing diary days				
^c N/A = Not applicable.				
^d Dilaudid SR vs. 1/2 Dilaudid SR. Wilcoxon Rank-Sum test				
^e Dilaudid SR vs. Dilaudid IR. Wilcoxon Rank-Sum test.				
^f Overall p-value: Kruskal-Wallis test: Endpoint, p=0.6927; Change from baseline, p=0.238				
^g Wilcoxon Signed Rank test.				

(Source, Original NDA 21-217 submission, Vol. 67, p.71)

Reviewer's comments: This study was submitted and reviewed in the original NDA as the key, AWC study to demonstrate efficacy. The primary medical reviewer determined the following (taken verbatim from the original NDA review):

“Analysis of the primary efficacy variable revealed a small increase in the amount of breakthrough-pain medication used by all three treatment groups across days 3 through 7 of the double-blind phase, which did not reach statistical significance in between-group analyses. The within-treatment differences, however, were significant for all three treatments. There were no statistically significant between-group differences for the secondary efficacy variables of pain intensity, pain relief or sleep interference. Pain relief was slightly worse for all three groups, but only

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reached a within-group, statistically significant difference for the 1/2-dose Dilaudid CR.

Pain intensity was unchanged for Dilaudid CR, slightly worse for Dilaudid IR and had the greatest increase for the 1/2-dose Dilaudid group, reaching a within-group, statistically significant difference. The difference in normalized dose of breakthrough-pain medication did not reach statistical significance between treatment groups. The dose of breakthrough-pain medication increased over the treatment period reaching a statistically significant difference from baseline within each treatment group.

The results of this study not only fail to demonstrate that Dilaudid CR is more effective than ½ Dilaudid CR or Dilaudid IR, but suggest that pain control on full-dose Dilaudid CR, ½ dose Dilaudid CR, and Dilaudid IR was not sustained throughout the duration of this study and may have been inferior to the treatment used prior to the study. An additional minor problem is that the 64 mg tablet was not studied in this protocol. Thus, data is only available for the 8, 16, and 32 mg tablets.”

3) Protocol DO-109

Title: Safety and Tolerability of Long-term Administration of Dilaudid CR (Hydromorphone HCL)

Objective: To characterize the safety and tolerability of long-termed, repeated dosing of Dilaudid CR (8, 16, 32 and 64 mg tablets) in patients with chronic cancer or chronic non-malignant pain

Methods: Patients who completed studies DO-104, DO-105 or DO-119 continued to receive the dose of OROS HM that they had been receiving in the short-term study, with dose adjustments needed to control pain and adverse events.

Primary Efficacy Variable: Change in Pain intensity and Pain Relief Scores from Brief Pain Inventory

Results: This study was ongoing at the time of the submission of the original NDA. The safety results are discussed in Section with the pooled safety data. Efficacy results, according to the Applicant, showed that the effectiveness of OROS hydromorphone was maintained throughout the long-term extension study.

Reviewer's comments: The final study report (Applicant's Tables J and K, Final Report Protocol DO-109, pages 58-63) was reviewed and appeared to support the Applicant's conclusion that the effectiveness of OROS hydromorphone in controlling pain was maintained throughout the study. However, this study was an extension study of DO-104/105 (which were open-label studies) and DO-119 (which was a failed efficacy study). Therefore, no efficacy claims can be supported from findings of this study.

6. Review of Efficacy

Efficacy Summary

6.1 Indication

Hydromorphone extended release tablets are to be marketed in the US in once daily oral dosage strengths of 8, 12, 16 and 32 mg. The proposed indication is for the management of moderate-to-severe pain in patients requiring continuous, around-the-clock opioid therapy for an extended period of time. A 64 mg dosage is available and was studied in clinical trials. However, the Applicant reports that, currently, the 64 mg strength is not to be marketed in the US.

6.1.1 Methods

The Applicant has conducted one Phase 3 study (NMT-107-301) to be used as the pivotal efficacy study to assess the safety and efficacy of hydromorphone extended release (ER) in the relief of moderate-to-severe pain. Study NMT-1077-301 evaluated the use of hydromorphone ER with repeated dosing for up to 12 weeks in opioid-tolerant patients with low back pain (LBP).

This review will report the findings of the pivotal efficacy study NMT-1077-301 in detail in this section. The other studies have been briefly summarized in Section 5.3.

Study NMT 1077-301 was a double-blind, placebo-controlled, 12-week enriched study with a randomized withdrawal (for placebo-treated patients) design after a flexible dose titration phase in opioid-tolerant LBP patients conducted under an FDA-approved Special Protocol Assessment (SPA). The Applicant maintains that this study provides evidence for the efficacy and safety of hydromorphone ER in dosages of 12 to 64 mg per day in the treatment of chronic pain in opioid-tolerant LBP patients.

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This study consisted of a Screening Phase (< 2weeks), a Conversion and Titration Phase (2- 4 weeks) and a Double-blind Treatment Phase (12 weeks). Subjects who completed the OL Conversion and Titration Phase and who attained a daily stable dosage of Hydromorphone ER (at starting dosages of 12, 16, 24, 32, 40 and 48 mg) orally were randomized in a 1:1 ratio to either Hydromorphone ER at their stable dosage or to a matching placebo. The placebo treated patients underwent a 2 week taper-down period from their stabilized dosage. Criteria for stabilization were defined. Patients who were unable to stabilize on an adequate dosage of study drug during the Conversion and Titration phase were discontinued.

6.1.2 Demographics

The Applicant's data, as shown in Table 16 below, denotes the demographic and baseline characteristics of the ITT population.

The treatment arms were generally well balanced. Most subjects were white (84.6%). There were more males in the hydromorphone group (54.1%) but more females (54.9%) in the placebo group. The majority (94.0%) were under the age of 65. Most of the patients in the ITT population had non-neuropathic low back pain (64.3%). The baseline mean pain intensity NRS scores were 3.2 in the hydromorphone ER group and 3.1 in the placebo group.

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Table 16. Demographic and Baseline Characteristics (ITT Population)

Characteristic	OROS [®] Hydromorphone N=133	Placebo N=133	Total N=266
Age, years			
Mean (SD)	47.8 (10.53)	49.4 (10.57)	48.6 (10.56)
Median	49.0	49.0	49.0
Range (min, max)	24, 75	23, 72	23, 75
Age Group, n (%)			
18 to 64	128 (96.2)	122 (91.7)	250 (94.0)
65 to 75	5 (3.8)	11 (8.3)	16 (6.0)
Gender, n (%)			
Male	72 (54.1)	60 (45.1)	132 (49.6)
Female	61 (45.9)	73 (54.9)	134 (50.4)
Race, n (%)			
American Indian	0	1 (0.8)	1 (0.4)
Black	14 (10.5)	9 (6.8)	23 (8.6)
Caucasian	108 (81.2)	117 (88.0)	225 (84.6)
Hispanic	9 (6.8)	5 (3.8)	14 (5.3)
Oriental	1 (0.8)	1 (0.8)	2 (0.8)
Other	1 (0.8)	0	1 (0.4)
Weight, kg			
Mean (SD)	90.43 (24.598)	93.10 (23.731)	91.77 (24.160)
Median	85.40	89.30	88.50
Range (min, max)	44.0, 164.3	56.7, 168.0	44.0, 168.0
Height, cm			
Mean (SD)	172.50 (11.178)	169.93 (10.486)	171.21 (10.893)
Median	171.50	170.20	170.70
Range (min, max)	142.2, 198.1	127.0, 194.3	127.0, 198.1
BMI, kg/m ²			
Mean (SD)	30.16 (6.925)	32.16 (7.289)	31.16 (7.167)
Median	28.90	30.20	29.60
Range (min, max)	18.6, 62.1	21.5, 54.1	18.6, 62.1
NRS Pain Score ^a			
Mean ^b (SD)	3.2 (0.99)	3.1 (1.07)	3.2 (1.03)
Median	3.3	3.3	3.3
Range (min, max)	0, 6	0, 6	0, 6
Stable Daily OROS [®] Hydromorphone Dose, mg per day ^c			
Mean (SD)	37.3 (17.17)	38.3 (17.69)	37.8 (17.41)
Median	32.0	32.0	32.0
Range (min, max)	12, 64	12, 64	12, 64
Etiology, n (%)			
Non-Neuropathic LBP ^d	90 (67.7)	81 (60.9)	171 (64.3)
Neuropathic LBP ^e	43 (32.3)	51 (38.3)	94 (35.3)
Missing	0	1 (0.8)	1 (0.4)

^aAverage of the patient diary NRS Pain Intensity measurements in the week prior to randomization.

^bMean NRS Pain score ≤ 4 is one of six criteria for entering the Double-Blind phase.

^cStable Dose achieved in Conversion and Titration phase.

^dClass 1 or 2 based on the Quebec Task Force Classification of Spinal Disorders.

^eClass 3, 4, 5, or 6 based on the Quebec Task Force Classification of Spinal Disorders.

LBP=lower back pain; max=maximum; min=minimum; SD=standard deviation

(Source: Clinical Study Report NMT 1077-301, pages 81 and 82)

Medical histories and abnormal physical examination findings: These findings at screening were generally balanced across the treatment groups.

Prior and Concomitant Therapies

- Prior to Randomization – The most common category of prior opioids taken by patients in both groups were opium alkaloid derivatives and combinations (126 patients in the hydromorphone ER group and 122 in the placebo group). This category was further subdivided with the most common drugs being hydrocodone and oxycodone either alone or in combination with acetaminophen.
- OL and Double-blind Period – Benzodiazepine derivatives and related drugs were taken by approximately 35% of patients receiving hydromorphone ER and 31% of those in the placebo group. There were no significant differences noted between the groups.

Rescue Medication Usage: There appeared to have been essentially equal percentage of patients using rescue medication in both the hydromorphone ER and Placebo groups.

The Applicant reported that the mean number of rescue medication tablets per day by patient was 2.7 over the first 3 days of Conversion and Titration, and less than one tablet per day when stable dose was achieved. In the hydromorphone ER group, 96.2% (128/133) of patients used rescue medication at least once during the double-blind phase, compared to 97.0% (129/133) patients in the placebo group as shown in Table 17.

Table 17. Proportion of Patients Requiring any Rescue Medication in the Double-blind Phase (ITT Population)

Status	OROS Hydromorphone N=133	Placebo N=133	P-value
Use of Rescue Medication ^a , n (%)	128 (96.2)	129 (97.0)	
No Use of Rescue Medication, n (%)	5 (3.8)	4 (3.0)	
Comparison of usage rates ^b			>0.999

^a Patients using any rescue medication during the 12-week double-blind phase.
^b P-value for comparison of treatment groups using a continuity corrected chi-square test.

(Source: Clinical Study Report NMT 1077-301, p. 407)

The Applicant’s submission also included a complete Table showing the number of tablets used per day by treatment group. Upon review of the table, it is noted

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that the trend was a decrease in the number of rescue tablets used from Day 4 to Week 12 or final visit in both groups. However, the proportion of patients requiring rescue medication and amount of medication was similar in both groups, being ≤ 2 tablets per day during any 7 day period after Day 14 of the Double-blind phase.

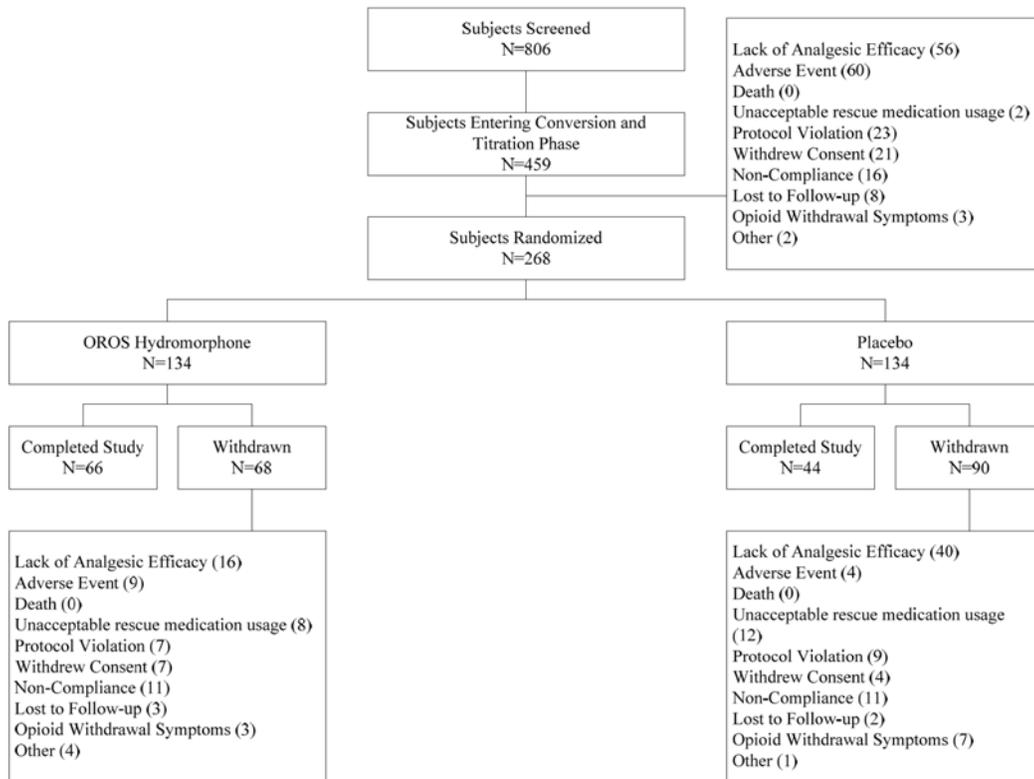
Reviewer's Comments: Overall, the demographic characteristics appear relatively equally distributed and do not appear to affect the efficacy outcome. However, the nearly equal number of rescue medications can not be fully explained. The Applicant reports that patients who took more than the allowed amount of rescue medication were discontinued from the study and therefore, the restrictions may have provided a ceiling effect which would explain why there were not considerable differences between the groups. This may be a plausible explanation from a clinical standpoint.

6.1.3 Subject Disposition

Four hundred and fifty-nine (459) patients were enrolled in the Conversion and Titration Phase, 268 patients were randomized to the Double-blind phase (134 patients to hydromorphone ER arm and 134 to the placebo arm). One patient randomized to receive hydromorphone ER did not report taking any study medication. Another patient, randomized to receive placebo, did not have Baseline values for the primary efficacy variable. Both of these patients were excluded from the ITT population. Therefore, the ITT population had 266 patients. A total of 110 patients completed the study (66 patients in the hydromorphone arm and 44 in the placebo arm).

The disposition of patients is summarized in the Applicant's submitted Figure 7 below.

Figure 7: Patient Disposition Study NMT 1077-301



(Source: Clinical Study Report NMT 1077-301, p. 74)

The final efficacy analysis was based upon a total of 179 patients who dropped out during titration; 268 patients randomized, 266 ITT, and 206 modified ITT. The discussion of patient disposition follows:

OL Conversion and Titration: A total of 191 (41.6%) patients dropped out during the OL phase. However, of the 459 patients who entered the Conversion and titration phase, 12 (2.6%) did not receive study drug. Therefore, an actual total of 179 patients (39.0%) discontinued from the Conversion and Titration phase after receiving study drug. Adverse events (13.1%) and lack of analgesic efficacy (12.2%) were the most common reasons for discontinuation from the OL Phase.

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Double Blind: The percentage of subjects who completed the double-blind treatment period was highest in the hydromorphone ER group at 66 (49.2%) compared to 44 (32.8%) in the placebo group. A total of 158 patients dropped out during the Double-blind phase, 68 (50.7%) in the hydromorphone group and 90 (67.2%) in the placebo group.

The most common reason for discontinuation in both groups was lack of analgesic efficacy (11.9% in the hydromorphone ER and 29.9% in the placebo group). The second most common reason for discontinuation in the placebo group was unacceptable rescue medication at 9.0%.

The Applicant reported that the majority of discontinuations (70.4%) were among patients receiving 64 mg of hydromorphone ER per day. The most common reasons for discontinuation in this dose group were AEs and non-compliance at 18.5% each.

There were five patients who experienced AEs at 64 mg, which was considerably more than those at any other dosage (with zero at 12 and 16 mg and 1 each at the other dosages of 24, 32, 40, and 48 mg).

Noncompliance with protocol or treatment regimen was seen equally in both the placebo and hydromorphone ER groups at 8.2%. Compliance was calculated as the number of days a patient took study medication in the Double-blind phase divided by the number of days the patient was instructed to take study drug.

At the request of the FDA, the Applicant provided narratives for 58 patients who discontinued due to AEs during the OL Conversion and Titration phase; 13 patients who discontinued during the double-blind phase, 3 subjects who experienced opioid withdrawal during the conversion and titration phase; 10 subjects who experienced withdrawal during the double-blind phase and 85 patients of interest. A person of interest was defined as a patient who had study medication accountability discrepancies.

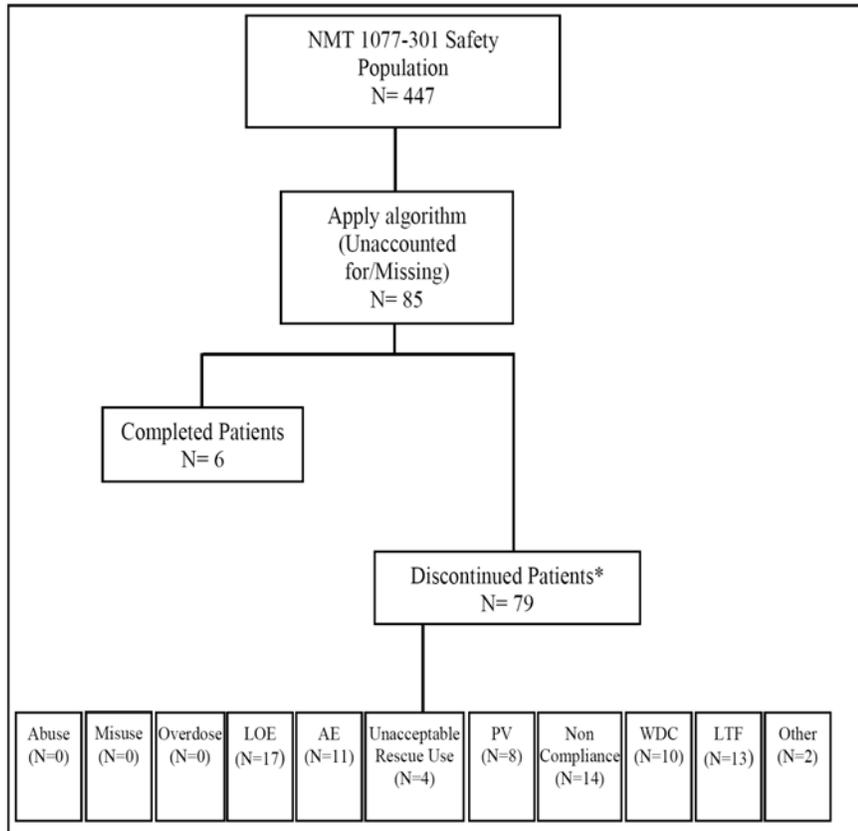
The Applicant developed an Algorithm for abuse, misuse or diversion to identify patients with potentially aberrant behavior. Eighty-five patients (79 who had discontinued from the study and 6 who had completed) were identified using the algorithm as shown:

- review the database for patients with a discrepancy in their medication records as defined by $\geq 5\%$ of their total study medication and $\geq 5\%$ total tablets;
- review daily diary entries to determine if there were missing tablets;

- identify patients who met these criteria and who received hydromorphone ER).

Figure 8 below depicts the flow chart used to identify patients with potentially aberrant behavior using the above algorithm.

Figure 8: Flow Chart for Identifying Patients with Potentially Aberrant Behavior



* Lost Drug: 8 patients of those who discontinued reported losing study medication.
 Stolen Drug: 1 patient was discontinued due to Non compliance and reported stolen study medication.
 Diversion: 2 patients were discontinued due to Protocol Violation and both were noted as possibly diverting medication.
 LOE=lack of efficacy; AE=adverse event; PV=protocol violation; WDC=withdrew consent; LTF=lost to followup

(Source: Clinical Study Report NMT 1077-301, p. 72)

The narratives for these patients were reviewed. The data provided appeared to be consistent with the reasons for discontinuation assigned by the Applicant.

Adverse events, lack of efficacy, opioid withdrawal symptoms and rescue medication overuse were classified by the Applicant as clinical reasons for drop outs. The other causes were classified by the Applicant as administrative reasons. Among the 158 patients who dropped out during the Double-blind

phase in both treatment groups, 99 of them were due to clinical reasons and 59 for administrative reasons. Reasons for withdrawal are shown in Table 18 below.

Table 18. Patient Disposition in the Conversion and Titration Phase and Double-blind Phase (Study NMT 1077- 301)

Reason for Withdrawal ^a	Conversion and Titration Phase	Double-blind Phase		
	OROS [®] Hydromorphone N=459 n (%)	OROS [®] Hydromorphone N=134 n (%) ^b	Placebo N=134 n (%) ^b	All Patients N=268 n (%)
	Lack of Analgesic Efficacy	56 (12.2)	16 (11.9)	40 (29.9)
Adverse Event	60 (13.1)	9 (6.7)	4 (3.0)	13 (4.9)
Unacceptable Rescue Medication Usage	2 (0.4)	8 (6.0)	12 (9.0)	20 (7.5)
Opioid Withdrawal Symptoms	3 (0.7)	3 (2.2)	7 (5.2)	10 (3.7)
Death	0	0	0	0
Protocol Violation	23 (5.0)	7 (5.2)	9 (6.7)	16 (6.0)
Withdrew Consent	21 (4.6)	7 (5.2)	4 (3.0)	11 (4.1)
Non-Compliance	16 (3.5)	11 (8.2)	11 (8.2)	22 (8.2)
Lost to Follow-up	8 (1.7)	3 (2.2)	2 (1.5)	5 (1.9)
Other	2 (0.4)	4 (3.0)	1 (0.7)	5 (1.9)
Total Withdrawn	191 (41.6)	68 (50.7)	90 (67.2)	158 (59.0)

^aPatients were counted once, under their primary reason for withdrawal.

^bPercentages based upon the number of patients randomized to each treatment group.

(Source: Clinical Study Report NMT 1077-301, p 75)

Protocol violations

A definition for a major protocol deviations or violations was not provided by the Applicant. However, review of the reasons for assigning patients to this category appeared appropriate.

A total of 63 protocol violations were found in 60 randomized patients. Of those, 36 patients had a Baseline NRS score > 4.0 at randomization and 24 patients either did not meet inclusion/extension criteria or violated the protocol during the Double-blind phase. Those 60 patients were excluded from the mITT population.

The number of patients who experienced protocol violations during the OL conversion and Titration Phase and the Double Blind (Randomized) phase is shown in Tables 19 and 20, respectively.

Table 19. Patients with Protocol Violations during Titration Phase (Study NMT-1077-301)

Category ^a	OROS Hydromorphone
	N=179 n (%) ^b
Inclusion Criteria Not Met	5 (2.8)
Exclusion Criteria Met	26 (14.5)
Prohibited Medication	7 (3.9)
Suspected Diversion	2 (1.1)
Newly Found History	3 (1.7)
Other	10 (5.6)

^aPatients may be included in multiple categories.

^bPercentages based upon the number of patients randomized to each treatment group.

(Source: Clinical Study Report NMT 1077-301, p. 77)

Table 20. Patients with Protocol Violations during Double-blind (Randomized) Phase (Study 301)

Category ^a	OROS Hydromorphone	Placebo
	N=134 n (%) ^b	N=134 n (%) ^b
Inclusion Criteria Not Met	0	2 (1.5)
Exclusion Criteria Met	4 (3.0)	3 (2.2)
Double-blind Inclusion Criteria Not Met	19 (14.2)	18 (13.4)
Prohibited Medication	4 (3.0)	7 (5.2)
Suspected Diversion	0	0
Newly Found History	0	0
Other	3 (2.2)	3 (2.2)

^aPatients may be included in multiple categories.

^bPercentages based upon the number of patients randomized to each treatment group.

(Source Clinical Study Report NMT 1077-301, p. 77)

Extent of Exposure

Extent of exposure in the Safety Population will be discussed under the Safety section of this review.

The duration of exposure for randomized patients during the Conversion and Titration phase reveals that the mean duration of exposure was 23.4 (7.84) days; the range was from 8-47 days as shown in Table 21.

Table 21. Duration of Exposure in the Conversion and Titration Phase; Randomized Population (Study NMT 1077-301)

Duration of Exposure	OROS Hydromorphone N=268 n (%)
Duration in days ^a	
N	268
Mean (SD)	23.4 (7.84)
Median	23.0
Range (min, max)	8, 47
By Range of Weeks ^b , n (%)	
<1 week	0 (0.0)
1 to <2 weeks	18 (6.7)
2 to <3 weeks	66 (24.6)
3 to <4 weeks	80 (29.9)
≥ 4 weeks	104 (38.8)

^a Duration in days calculated as the difference between the first date medication was dispensed and the date of the last dose in the conversion and titration phase.

^b Duration in weeks calculated as the difference between the first date medication was dispensed and the date of the last dose in the conversion titration phase divided by 7.

SD = standard deviation
 (Source: Clinical Study Report NMT 1077-301, p. 421)

The mean duration of exposure to hydromorphone ER during the Double-blind phase was 52.6 days compared to 38.6 days in the placebo group. The most frequent duration of exposure in both groups was 12 to 14 weeks. The total duration of exposure in the Double-blind phase is summarized in Table 22.

Table 22. Duration of Exposure in Double-blind Phase by Dose and Treatment Group (ITT Population)

Duration of Exposure	All OROS [®] Hydromorphone N=133	Placebo N=133
Duration in days ^a		
N	133	133
Mean (SD)	52.6 (33.77)	38.6 (33.63)
Median	56.0	22.0
Range (min, max)	2, 91	2, 90
By Range of Weeks ^b , n (%)		
<1 week	8 (6.0)	17 (12.8)
1 to <2 weeks	18 (13.5)	27 (20.3)
2 to <3 weeks	12 (9.0)	21 (15.8)
3 to <4 weeks	10 (7.5)	11 (8.3)
4 to <5 weeks	5 (3.8)	7 (5.3)
5 to <6 weeks	6 (4.5)	1 (0.8)
6 to <7 weeks	6 (4.5)	2 (1.5)
7 to <8 weeks	1 (0.8)	1 (0.8)
8 to <9 weeks	1 (0.8)	0
9 to <10 weeks	0	3 (2.3)
10 to <11 weeks	0	0
11 to <12 weeks	6 (4.5)	10 (7.5)
12-14 weeks	60 (45.1)	33 (24.8)

^aDuration in days calculated as the difference between the first date medication was dispensed and the date of the last dose.

^bDuration in weeks calculated as the difference between the first date medication was dispensed and the date of the last dose divided by 7.

max=maximum; min=minimum; SD=standard deviation

(Source: Clinical Study Report NMT 1077-301 p. 85)

Dosage: Most patients started the Conversion and Titration phase (42.5%) at a 12 mg dose. The most common final dose for all patients during the Conversion and Titration phase was 64 mg per day (21.8%). During the Double-blind phase, slightly more patients received 64 mg of hydromorphone ER than any other single dose level as the stable dose dispensed at the first visit (with 26 patients or 19.5% compared to 25 patients or 18.8% who received 32 mg).

The Applicant's submission provided a table summarizing the number and percent of patients dispensed each dose in the Double-blind phase by visit (ITT population). There was an increasing trend toward the lower dose levels until Visit 10, where the largest percentage of patients received 32 mg of hydromorphone ER compared to 24 mg placebo.

Reviewer’s Comments: No trends are noted regarding duration of exposure or dosage with regard to efficacy.

6.1.4 Analysis of Primary Endpoint

The primary efficacy endpoint was the change from Baseline to Double-blind Week 12 (or last visit) in weekly mean pain intensity scores (based on the previous week’s mean daily pain intensity Numeric Rating Scale (NRS) scores recorded in patient diaries. The baseline pain score was defined as the average of the diary pain intensity (PI) NRS scores in the week prior to randomization. The analysis was conducted at each visit and at the end of the study.

Primary Efficacy Results: The Applicant reports that the primary efficacy endpoint was found to be significant ($p < .001$) between hydromorphone ER and placebo patients. They reported that the mean change from baseline in the hydromorphone treated group was 0.6 compared to the mean change from baseline for the placebo group at 1.7. Higher scores indicate more severe pain. The median change from baseline was 0.2 and 1.6, respectively.

Table 23 below summarizes the Applicant’s analysis of the primary efficacy endpoint.

Table 23. Numeric Rating Scale (NRS) Pain Intensity Change from Baseline to Week 12 (or final visit) in Double-blind Phase (ITT Population) (Study 301)

Statistic ^a	OROS ^b Hydromorphone	Placebo	P-value ^b
Baseline ^c			
N	133	133	
Mean	3.2	3.1	
Median	3.3	3.3	
Range (min, max)	0, 6	0, 6	
Visit 11/final visit (Week 12) ^d			
N	133	133	
Mean	3.8	4.8	
Median	3.6	4.8	
Range (min, max)	0, 9	0, 9	
Change from Baseline			
N	133	133	0.000007
Mean	0.6	1.7	
Median	0.2	1.6	
Range (min, max)	-5, 5	-3, 7	

^aThis is an 11-point scale ranging from 0 (no pain) to 10 (worst possible pain).

^bP-value from test for significant treatment difference using Cochran-Mantel-Haenszel chi-square test comparing change from Baseline after adjusting for Baseline value using ranks.

^cMean of the patient diary measurements in the week prior to randomization.

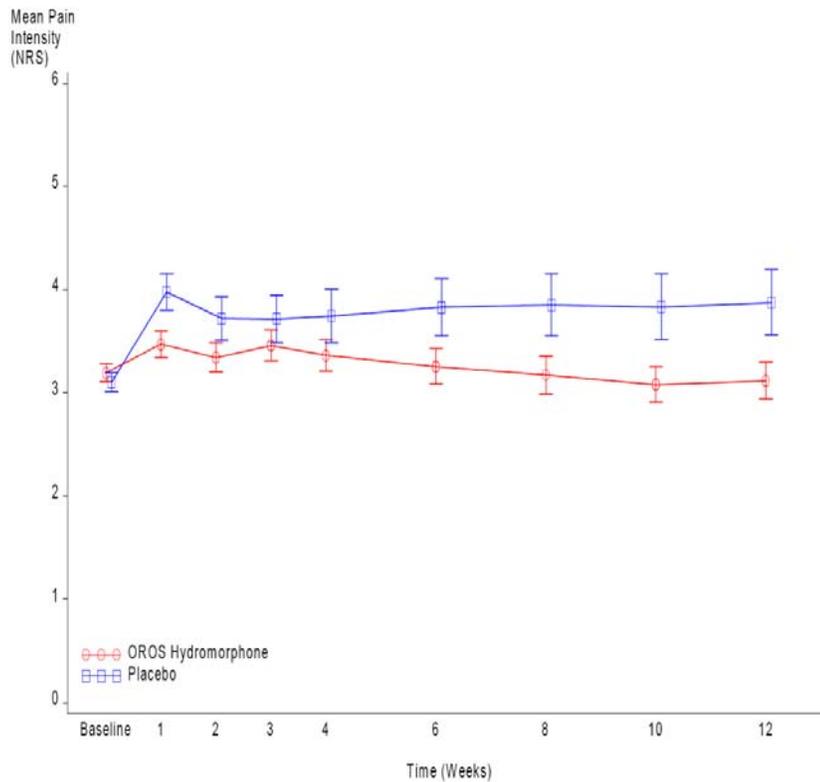
^dPatients with missing weekly patient diary data due to premature withdrawal had their value at final visit imputed based on the reason for discontinuation.

ITT=intent-to-treat; max=maximum; min=minimum

(Source: Clinical Study Report NMT 1077-301, p. 89)

The mean NRS pain intensity data is shown graphically for the Double-blind phase in Figure 9 below:

Figure 9. Mean Observed NRS Pain Intensity in Double-blind Phase (ITT Population)



(Source: Clinical Study Report NMT 1077-301, p. 90)

As can be seen in Table 24 and Figure 10 below, the number of patients reporting $\geq 30\%$ or $\geq 50\%$ reduction in NRS pain score from Screening to Week 12 or final visit was greater in the hydromorphone ER group with reports of 30% or greater ($p < 0.01$) or 50% or greater ($p < 0.005$) reduction in pain intensity in the hydromorphone ER group compared to placebo.

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Table 24. Proportion of Responders from Screening to Week 12 (or final visit) of the Double-blind Phase (ITT Population)

Status	OROS Hydromorphone N=132	Placebo N=133	P-value
30% Reduction in Pain^a			
Responder, n (%)	80 (60.6)	57 (42.9)	
Non-Responder, n (%)	52 (.4)	76 (57.1)	
Comparison of response rates ^b			0.006
50% Reduction in Pain^c			
Responder, n (%)	56 (42.4)	32 (24.1)	
Non-Responder, n (%)	76 (57.6)	101 (75.9)	
Comparison of response rates ^b			0.002

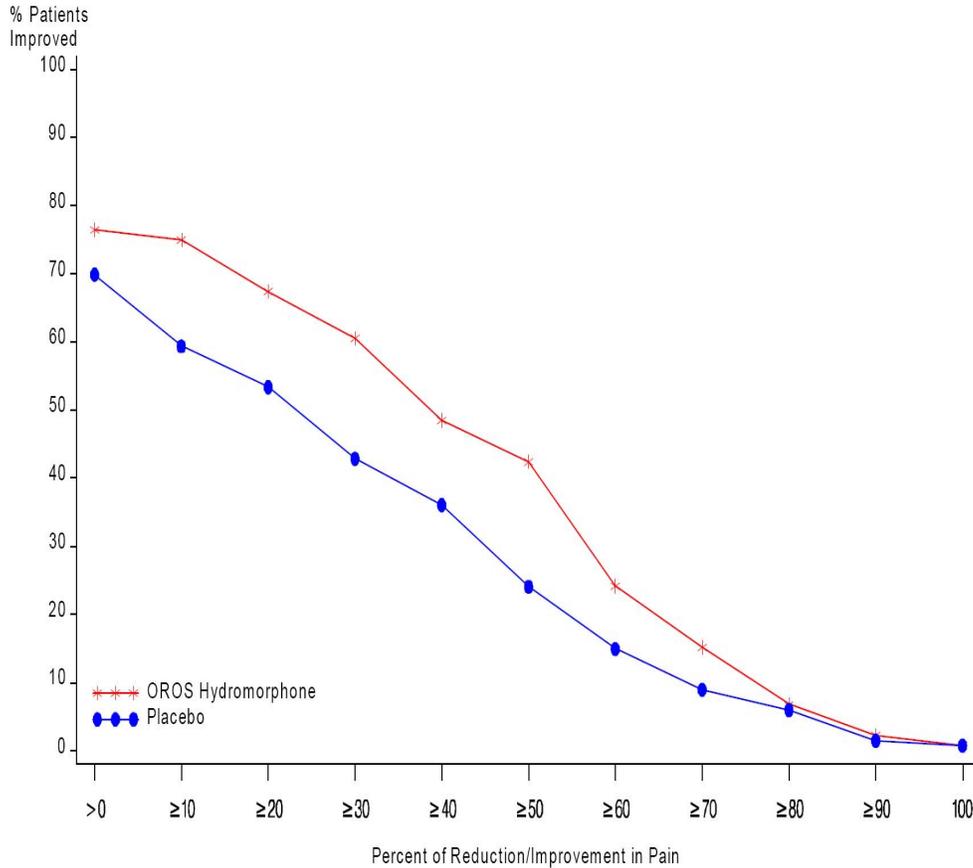
^aA responder is a patient who had at least 30% improvement in pain intensity from Screening Visit to Week 12/final visit.

^bP-value for comparison of treatment groups using a continuity-corrected chi-square test.

^cA responder is a patient who had at least 50% improvement in pain intensity from Screening Visit to Week 12/final visit.

(Source: Clinical Study Report NMT 1077-301, p. 105)

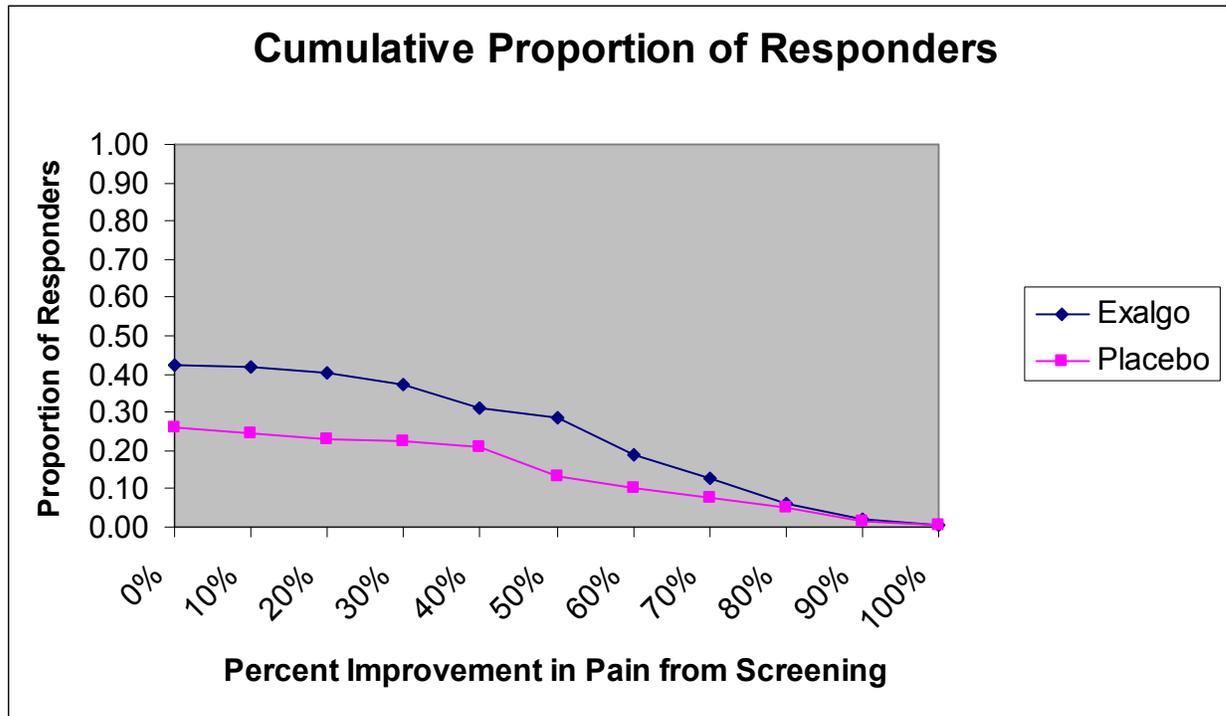
**Figure 10. Responder Analysis from Screening to Week 12 (final visit)
Double-blind Phase (ITT Population)**



(Source: Clinical Study Report NMT 1077-301, p. 104)

Figure 11 below illustrates the proportion of responders for each treatment arm. This graph was compiled by the Agency statistics reviewers and differs somewhat from the Figure provided by the Applicant as, in this graph, responders were calculated based on the change from screening baseline to the end of the study. Patients dropping out were considered non-responders. It is further noted that this represents the randomized population (not the ITT population). For further discussion regarding this analysis, the reader is referred to the FDA statistical review of Dr. Jonathan Norton.

Figure 11. Cumulative Proportion of Responders Graph



(Source: Graph compiled from Agency Statistics Team from Submission Data)

Ad hoc analysis results: An ad hoc analysis of response rates showed 80 Ors-treated patients (60.6%) compared to 57 (42.9%) of placebo-treated patients showed a 30% or greater reduction in pain ($p < 0.01$) and 56 (42.4%) hydromorphone ER compared to 32 (24.2%) placebo showed a 50% reduction in pain ($p < 0.005$).

6.1.5 Analysis of Secondary Endpoints(s)

There were seven secondary endpoints evaluated. The endpoints and brief summary of results are summarized in Table 25 below. All of the secondary endpoints except Rescue Medication Use supported the primary endpoint.

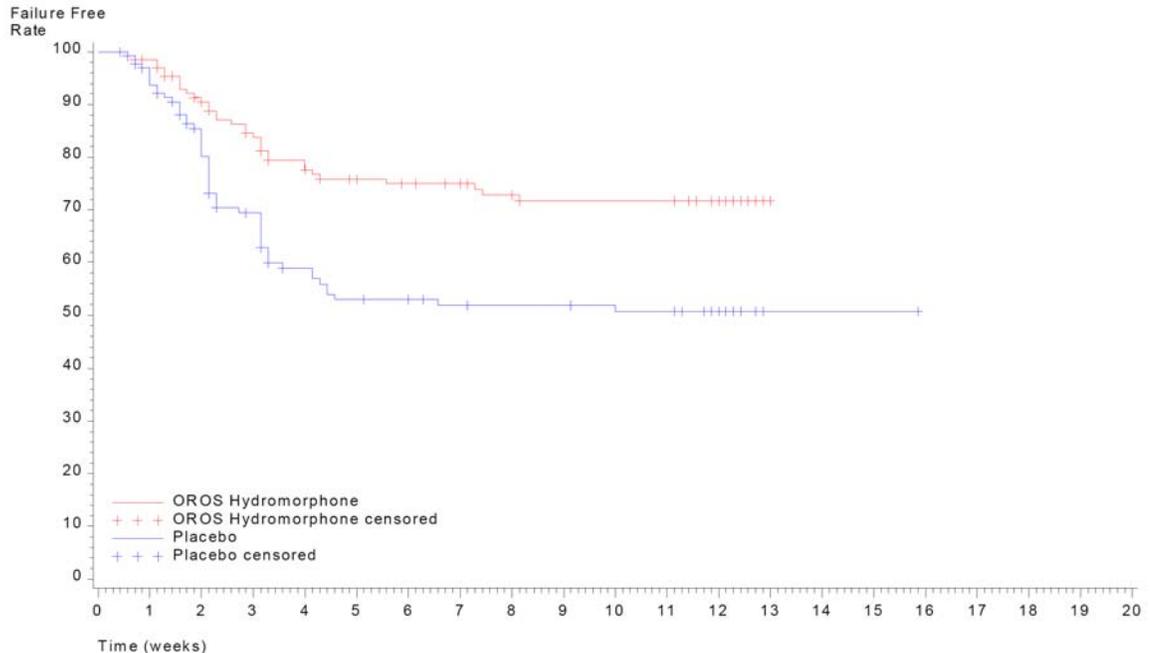
Table 25. Secondary Endpoints and Outcomes

Endpoint	Outcome
Δ PI over Entire 12 week DB Phase	Mean PI scores in placebo group was 1.2 vs 0.4 in Hydromorphone ER (p<0.001)
Office PI Score by Visit	Mean PI score in placebo group was 2.0 vs 0.9 in Hydromorphone ER (p<0.05) except Week 3
Time to Treatment Failure	Percent treatment failures in Placebo group was 41.4 compared to 24.8 in Hydromorphone ER
Patient Global Assessment (PGA)	<p>Mean Δ from BL for placebo group was 0.7 vs 0.1 in Hydromorphone ER.</p> <p>All differences were considered significant except at Weeks 2 and 10.</p> <p>At final visit 80.5% Hydromorphone ER patients rated PGA “good”, “very good” or “excellent” compared to 62.4% Placebo who reported similar ratings</p>
Roland-Morris Disability Questionnaire	OROS hydromorphone at dosages of 12 to 64 mg once daily was superior to placebo in allowing patients to perform routine tasks during their day.
Discontinuations for any reason	Discontinuation percentage in the placebo group was 66.9% vs 50.4% in Hydromorphone ER (p<0.01)
Rescue Medication Use	Nearly equal with 96.2% Hydromorphone ER patients vs 97.0% placebo taking rescue medication

(Source: Table prepared by reviewer from data submitted by Applicant’s Clinical Study Report NMT 1077-301)

The secondary endpoint of Time to Treatment Failure is represented in Figure 12 below.

Figure 12. Time to Treatment Failure



(Source: NMT 1077-301 Final Study Report, p. 170)

Applicant's Efficacy Conclusions:

- OROS hydromorphone at dosages of 12 to 64 mg once daily was superior to placebo in reducing pain intensity at Week 12 or final visit, and over the course of the 12-week treatment period.

Reviewer's Comments: The analysis for the primary endpoint appears appropriate. This primary endpoint incorporates the measurement of pain intensity, which is a fundamental measure that defines the efficacy of an analgesic, and is supported by Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) Recommendations for Core Outcome Measures in Chronic Pain Trials. The Agency's primary statistics reviewer noted that the Applicant proposed different versions of the primary efficacy analysis at different times. The Division granted a Special Protocol Assessment (SPA) agreement for the version in which the primary analysis was analysis of covariance (ANCOVA). The independent variables were to be treatment, site, and baseline pain score.

However, the final SAP included a different primary analysis that the version granted the SPA in that the effect of treatment center was removed from the ANCOVA model and the analysis method used was to depend on whether the data violated certain assumptions. The results of that analysis were included in the clinical study report but the results of the original ANCOVA analysis were not. In response to an information request by the Statistics reviewer, the Applicant performed the ANCOVA analysis specified in the SPA and submitted the results. Both the SPA version and the final version of the SAP state that the baseline pain score will be computed as the average of the diary scores in the week prior to randomization. The final result was that the study showed a positive result on the primary endpoint using both the original and revised analysis plans.

The reader is referred to the Statistics review of Dr. Jonathan Norton for further analysis of the SAP.

This reviewer is in agreement with the efficacy findings reported by the Applicant.

- The treatment failure rate was significantly lower among patients treated with OROS hydromorphone at dosages of 12 to 64 mg once daily than among patients treated with placebo.

Reviewer's Comments: The Applicant's findings appear to support this conclusion.

- In the Roland-Morris Disability Questionnaire, OROS hydromorphone at dosages of 12 to 64 mg once daily was superior to placebo in allowing patients to perform routine tasks during their day.

Reviewer's Comments: A general statement of "better performance of routine daily tasks" may not be accurate as it has not been determined that the Roland Morris Disability Questionnaire is a validated tool to measure "performance of routine daily tasks".

- Patients with chronic LBP treated with OROS hydromorphone at doses of 12 to 64 mg once daily reported better perception of their overall status as measured by the PGA than placebo-treated patients.

Reviewer's Comments: The PGA did show a mean change of 0.1 in the hydromorphone ER compared to 0.7 in the placebo group. However, a general statement of "better perception of **overall** status" may not be

accurate as it has not been determined that the PGA is validated tool to measure “overall status”

- Patients with chronic LBP treated with OROS hydromorphone at dosages of 12 to 64 mg once daily were less likely to discontinue from the study for any reason than patients treated with placebo.

Reviewer’s Comments: The Applicant’s findings support this conclusion.

6.1.6 Other Endpoints: none

6.1.7 Subpopulation

Analysis by subgroup is summarized in Table 26 below.

Table 26. Subgroup Analysis of Primary Endpoint

Subgroup	Exalgo Mean (SD, N)	Placebo Mean (SD, N)	
Age			
	Under 55	0.6 (1.8, 99)	1.8 (1.9, 92)
	55 or Older	0.8 (1.9, 34)	1.3 (1.8, 41)
Gender			
	Female	0.8 (1.9, 61)	1.7 (1.9, 73)
	Male	0.4 (1.7, 72)	1.6 (1.9, 60)
Race			
	Black	0.7 (1.7, 14)	1.1 (1.4, 9)
	Caucasian	0.6 (1.6, 108)	1.7 (1.9, 117)
	Other	0.8 (3.2, 11)	1.4 (1.9, 7)

(Source: Agency Statistics Reviewer, Dr. Jon Norton)

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The recommended dosing regimen for hydromorphone ER is once daily. It is noted that rescue medication was required daily to maintain efficacy. No conclusions can be made at this time regarding those findings. There was no analysis by the applicant of time to rescue following doses of drug. Dosing was based on the patients’ requirements for analgesics with no ceiling for opioids due to tolerance.

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6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The pivotal efficacy study was a 12-week study design. Patients appeared to maintain efficacy of the primary endpoint throughout the 12 week period. The mechanism of action of opioids is well known.

6.1.10 Additional Efficacy Issues/Analyses

Refer to Section 3 for issues related to study conduct, good clinical practices and submission integrity. There were no issues identified that affect the analysis of efficacy in this submission.

7 Review of Safety

7.1 Methods

The Applicant reported that data from a total of 32 studies were used to evaluate safety, as shown in Table 27 below.

Table 27. All Studies Used in Safety Analysis

Type of Study	Number of Studies	Total number treated	Total number treated with OROS HM
Controlled (Chronic Pain)	6	2383	1572
Uncontrolled (Chronic Pain)	7	1261	863*
Controlled (Acute Pain)	1	50	50
Pharmacology (PK)	13	463	460
Pharmacology (PK) Special Groups	4	125	0 (HMIR)**
Pharmacology (PD) Abuse Liability	1	64	38

* Of these 863 patients, 100 were also in the total of 1572 OROS patients exposed in the controlled studies due to participation a controlled primary study prior to an uncontrolled extended study (1572+763)=2335

** HMIR = Hydromorphone Immediate Release

(Source: Table compiled by Reviewer from Applicant's submission)

The Integrated Summary of Safety (ISS) contained safety information from a pool of seven uncontrolled studies (DO-104, DO-105, DO-108, DO-109, DO-118X, DO-127, DO-127X); pool of these uncontrolled studies plus six controlled studies (DO-118, DO-119, DO-132, M03-644-05, NMT-077-301, OROS-ANA-3001), and pool of 13 pharmacokinetic (PK) studies in healthy volunteers (D-101, D-102, D-103, DO-123, DO-124, DO-129, C-2005-020, C2005-032, C-94-014, 42801-PAI-1008, 42801-PAI-1009, C-96-054, and C-2005-013).

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In addition, the ISS contained safety data from non-pooled clinical pharmacology studies of immediate release hydromorphone in special groups (DO-113, DO-114, DO-121, DO-122); one non-pooled pharmacodynamic abuse liability study (C-2004-022), and one non-pooled acute pain study (DO-130). The Applicant is not seeking a claim for acute pain indication.

The controlled study pool contained patients who were opioid-tolerant, opioid-treated but not tolerant, and opioid-naïve.

The primary sources for the safety review were pertinent sections of the submission, the Integrated Summary of Safety (ISS), final study reports, pertinent narratives, line listings, the 120-day Safety Update, the original NDA medical officer review dated October 2, 2000, and pertinent sections of the original NDA 21-217.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Refer to Section 5 (Sources of Clinical Data) for a listing and brief description of the Phase 2/3 studies included in this submission.

A total of 32 studies were used in the safety analysis and included the following:

- Seven Phase Clinical Pharmacology studies submitted in original NDA or Dilaudid NDAs (D-101, D-102, D-103, DO-123, DO-124, DO-129, C-96-054)
- Eleven Phase 1 Clinical Pharmacology studies submitted with this submission
 - C-2005-013 (PK: in vitro/in vivo)
 - C-94-014; C-2005-020; C-2005-032; 42801-PAI-1008/1009;
 - DO 113; DO-114; DO-121; DO-122 (PK gender, age, renal impairment, hepatic impairment respectively)
 - C-2004-022 (PD: abuse liability)
- Thirteen completed Phase 2/3 safety/efficacy studies: MO3-644-05, DO-118/118X, DO-119, DO-132, DO127/127X, DO-130, OROS-ANA-3001, and NMT 1077-301; DO-104/105; DO-109
- Completed Study 108 (Repeat dose Phase 1 study included in pooled Safety Analysis)
- 4-month safety update of Study 42801-PAI-3001
- SAEs of ongoing Study NMT 1077-302

The 120 day Safety Update included integrated safety data from study 42801-PAI-3001. This study was conducted in Europe in patients with OA of the hip or knee. A total of 288 patients were treated (139 with OROS HM and 149 with placebo).

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Table 28, below, summarizes the studies and number of patients treated in each category.

Table 28. Studies and Number of Treated Patients/Subjects in Safety Analysis

Study	Study Classification	Total Treated	Total Treated with OROS [®] HM
CONTROLLED STUDIES IN PATIENTS WITH CHRONIC PAIN			
DO-118	Primary	200 ^a	77
DO-119	Primary	113 ^b	74
DO-132	Primary	138 ^c	71
M03-644-05	Primary	981 ^d	649
NMT 1077-301	Primary	447	447
OROS-ANA-3001	Primary	504 ^e	254
UNCONTROLLED STUDIES IN PATIENTS WITH CHRONIC PAIN (ISS ONLY)			
DO-104	Primary	127	127
DO-105	Primary	336	336
DO-108	Primary	22	22
DO-109	Extended	388	388 (38) ^f
DO-118X	Extended	68	68 (33) ^f
DO-127	Primary	207	207
DO-127X	Extended	113	113 (0) ^f
STUDY IN PATIENTS WITH ACUTE PAIN (ISS ONLY)			
DO-130	Acute pain	50	50
POOLED ANALYSIS SAMPLE POPULATIONS			
Total Controlled plus Uncontrolled in Patients with Chronic Pain		3075 ^g	2335 ^{g,h}
Total, Primary Studies		3075	2264
Patients not treated with OROS [®] HM during primary studies but treated with OROS [®] HM during extended studies		(Not applicable)	71
Total, Extended Studies		569	569 (71) ^f
Total Controlled in Patients with Chronic Pain		2383	1572
Total, Primary Studies		2383	1572
Total, Extended Studies		0	0
Total Uncontrolled in Patients with Chronic Pain		1261 ^g	863 ^g (100) ⁱ
Total, Primary Studies		692	692
Total, Extended Studies		569	569 (71) ^f

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Table 28. Studies and Number of Treated Patients/Subjects in Safety Analysis (cont'd)

POOLED CLINICAL PHARMACOLOGY STUDIES (ISS ONLY)			
D-101	PK: dose linearity	12	12
D-102	PK: food and naltrexone effect	29	29
D-103	PK: dose proportionality	32	32
DO-123	PK: bioequivalence	36	36
DO-124	PK: bioequivalence	52	52
DO-129	PK: bioequivalence	56	56
C-96-054	PK: comparative PK	22	20
C-2005-013	PK: in vitro/in vivo	52	52
C-94-014	PK: comparative PK	12	12
C-2005-020	PK: alcohol effect	48	48
C-2005-032	PK: bioequivalence	52	52
42801-PAI-1008	PK: bioavailability/ food effect	30	30
42801-PAI-1009	PK: bioavailability	30	29
Total Pooled PK		463	460
NON-POOLED CLINICAL PHARMACOLOGY STUDIES OF IR HM IN SPECIAL GROUPS			
DO-113	PK: gender	36	0
DO-114	PK: age	36	0
DO-121	PK: renal impairment	29	0
DO-122	PK: hepatic impairment	24	0
ABUSE LIABILITY STUDY			
C-2004-022	PD: abuse liability	64	38

^a In Study DO-118, patients were randomized to HM or morphine treatment, and received IR drug in a stabilization phase, and extended-release drug in a Maintenance phase. During IR treatment, 99 patients received HM and 101 patients received morphine. During extended-release treatment, 77 patients received HM (OROS[®] HM), and 86 received morphine.

^b In Study DO-119, 39 patients received the active comparator IR HM.

^c In Study DO-132, 67 patients received the active comparator OxyContin[®] (oxycodone).

^d In Study M03-644-05, 332 patients received the placebo comparator.

^e In Study OROS-ANA-3001, 250 patients received the active comparator SR oxycodone.

^f The number in parentheses indicates the subtotal of patients who received OROS[®] HM for the first time during an extended study (having received a different treatment in a primary study).

^g Totals count patients who participated in multiple studies only once.

^h This total contains 71 more patients than the Primary total because 38 patients randomized to receive IR hydromorphone in DO-119 were administered OROS[®] HM in DO-109 and 33 patients randomized to receive morphine in DO-118 were administered OROS[®] HM in DO-118X.

ⁱ One hundred (100) of these patients (who participated in extended studies) were also treated with OROS[®] HM during their prior, primary studies (DO-118 and DO-119).

HM=hydromorphone; IR=immediate-release; ISS=Integrated Summary of Safety; OROS[®]=oral osmotic drug delivery system; PD=pharmacodynamic; PK=pharmacokinetic; SR=sustained-release

(Source: Summary of Clinical Safety, p. 15-16)

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7.1.2 Categorization of Adverse Events

The Applicant reported that deaths and other SAEs were analyzed overall and by study medication dose at onset.

Adverse events (AEs) were recorded either from the time of patient consent or from the first dose of study medication through the end of the study. Four studies collected AEs beyond the end of the study to include the following:

- Study DO-118 collected AEs through 3 days after last dose
- Studies DO-132, M03-644-05, and OROS-ANA-3001 collected AEs through 30 days after discontinuation of study drug

Key efficacy study NMT 1077-301 collected SAEs through 30 days after discontinuation of study drug and Study C-2005-032 instructed patients to follow up by phone for 30 days after discontinuation of study drug for any AEs and pregnancy reporting for up to 3 months post study drug.

AEs and treatment were recorded on the appropriate case report form (CRF).

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Data for deaths, SAEs, and AEs of special interest available within the clinical data base were integrated (where appropriate) and analyzed programmatically. The Applicant noted that due to the diverse study designs, most but not all safety data were integrated for analysis.

Dosing (initiation and conversion), vital signs, and clinical laboratory data and information relating to possible abuse, misuse, and diversion of study drugs were not integrated by the Applicant but was summarized from the individual CSRs.

The Applicant reported that data was tabulated or summarized using descriptive statistics by treatment. No statistical comparisons were performed for any of the safety measures.

Phase I Studies: Eleven of 13 clinical pharmacology studies evaluated hydromorphone PK after a single dose of the study treatments and included IR hydromorphone (8 mg), intravenous hydromorphone (8mg), OROS hydromorphone (8, 16, 32, and 64 mg per day) and placebo.

Studies C-96-054 and 42801-PAI-1009, evaluated repeated dosing with patients in Study 42801-PAI-1009 receiving naltrexone. Study C-94-014 was single dose OROS and repeat dose IR Hydromorphone.

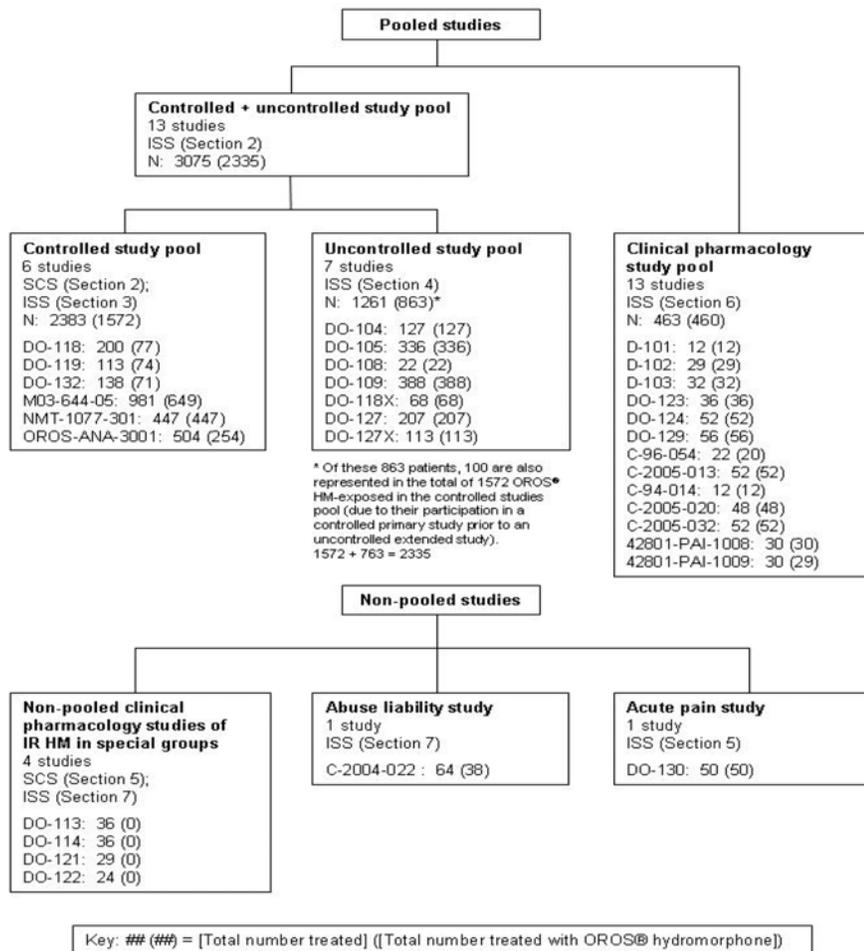
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Phase 1 AEs were categorized separately for the 10 studies that did and the 3 studies (Studies D-101, C-96-054, and C-2005-013) that did not incorporate concomitant naltrexone dosing to block opioid effects in healthy volunteers.

Phase 2/3 Studies: The Phase 2/3 studies were pooled with controlled and uncontrolled safety data.

Figure 13, below, displays the pooled (and non-pooled) studies used for safety analysis.

Figure 13. Hydromorphone ER Safety Analysis Studies Population Flow Chart



HM=hydromorphone; IR=immediate release, ISS=Integrated Summary of Safety, SCS=Summary of Clinical Safety
 (Source: ISS, p. 20)

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The 4 month Safety Update included safety data from Study 42801-PAI-3001 which provided an additional 139 patients treated with OROS, therefore increasing the total from 2,335 to 2,474 as shown in Table 29 below.

Table 29. OROS Hydromorphone Safety Analysis Sample Populations (4-month Safety Update)

Population	ISS	42801PAI3001	SUR
STUDY 42801PAI3001			
Total treated		288	
HM-treated		139	
Placebo-treated		149	
CONTROLLED + UNCONTROLLED STUDY POOL			
Total treated	3075	288	3363
HM-treated	2335	139	2474
Exposure: HM-treated, primary studies	2264	139	2403
Exposure: HM-treated, extended studies	569	0	569
Disposition: HM-treated, primary studies ^a	2130	139	2269
Disposition: HM-treated, extended studies	569	0	569
Demographics: HM-treated	2335	139	2474
Adverse events: HM-treated	2335	139	2474
Adverse events: placebo-treated	466	149	615
CONTROLLED STUDY POOL			
Total treated	2383	288	2671
HM-treated	1572	139	1711
Exposure: HM-treated, primary studies	1572	139	1711
Disposition: HM-treated, primary studies ^a	1438	139	1577
Demographics: HM-treated	1572	139	1711
Adverse events: HM-treated	1572	139	1711
Adverse events: placebo-treated	466	149	615

^a The 134 patients from Study NMT 1077-301 who were treated with OROS[®] hydromorphone during the Conversion and Titration phase but were then randomized to placebo in the Double-blind phase are represented in both the HM-treated and placebo-treated denominators everywhere except in the disposition denominators.

Note: Primary studies included DO-104, DO-105, DO-108, DO-118, DO-119, DO-127, DO-132, M03-644-05, NMT 1077-301, OROS-ANA-3001, and 42801PAI3001. Extended studies included DO-109, DO-118X, and DO-127X

(Source: Safety Update Report, p. 11)

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Exposure

As reported by the Applicant, there were 3,075 patients included in the pooled analysis population for controlled and uncontrolled studies in patients with chronic pain. A total of 2,335 patients received at least one dose of hydromorphone in the primary and extended controlled and uncontrolled clinical studies (2,264 primary and 569 extended). The total for the extended studies included 71 patients who received only comparator treatments in the primary studies but went on to receive hydromorphone ER in the extended studies. Therefore, in regard to the Applicant's proposed indication, an adequate number of subjects have been exposed to hydromorphone ER.

In the primary studies, the duration of treatment ranged from one day to approximately 65 weeks. The median daily dose was 16.0 mg (range: 0.2 to 895.7 mg)

The duration of treatment in the extended studies ranged from 2.0 days to approximately 20 months. The median daily dose was 41.4 mg (ranging from 6 mg to 1,984 mg).

There were 420 patients exposed > 6 months and 141 patients exposed >12 months. The mean (\pm standard deviation) duration of exposure to hydromorphone ER in the 10 primary studies was 53.0 (\pm 68.9) days.

Table 30 summarizes the duration of exposure in the primary and extended studies.

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Table 30. Duration of Exposure for Patients Treated with OROS Hydromorphone: Controlled and Uncontrolled Primary and Extended Clinical Studies in Patients with Chronic Pain

	OROS [®] Hydromorphone Treatment	
	Primary Studies N=2264	Extended Studies N=569
Duration of exposure (days)		
n	2263	568
Mean (SD)	53.0 (68.9)	220.0 (152.1)
Median	28.0	191.5
Range (min, max)	(1.0, 456.0)	(2.0, 623.0)
Missing	1	1
Average daily dose (mg)		
n	2258	568
Mean (SD)	28.2 (37.0)	65.9 (111.6)
Median	16.0	41.4
Range (min, max)	(0.2 ^a , 895.7)	(6.0, 1984.0)
Missing	6	1

^a The minimum value in this range (average daily dose of 0.2 mg per day) is from Patient 59107 in Study OROS-ANA-3001, who took one 8 mg dose of OROS[®] hydromorphone in a 38-day period.

Note: Primary studies included DO-104, DO-105, DO-108, DO-118, DO-119, DO-127, DO-132, M03-644-05, NMT 1077-301, and OROS-ANA-3001. Extended studies included DO-109, DO-118X, and DO-127X.

ISS=Integrated Summary of Safety; Max=maximum; Min=minimum; OROS[®]=oral osmotic drug delivery system; SD=standard deviation

(Source: ISS, p. 62)

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Table 31, below, summarizes the dose exposure in healthy volunteers from PK Studies. As can be seen, the majority (30%) of healthy volunteers received 16 mg dosage, followed by 8 mg dosage (15.5%).

Table 31. Dose exposure in healthy volunteers from PK Studies

Dose	N	(%)
Placebo	12	(1.4 %)
8 mg IV	12	(1.4 %)
8 mg IR	59	(7.0 %)
8 mg	130	(15.5 %)
64 mg	123	(14.7 %)
5 mg IR	12	(1.4 %)
4 mg IR	80	(9.6 %)
4 mg	51	(6.1 %)
32 mg	107	(12.8 %)
16 mg	251	(30.0 %)

(Source: ISS, p. 6659)

Reviewer's comment: There was adequate dose exposure of the study drug at appropriate dosing ranges.

Demographics

In the combined controlled and uncontrolled studies, there were more females (55.5%) compared to males (44.5%), the majority of patients (65.3%) were 40- <65 years of age with 90.9% being Caucasian. This data is shown in Table 32.

Table 32: Demographics (All Patients with Chronic Pain Treated with Hydromorphone in Controlled and Uncontrolled Studies)

	OROS [®] Hydromorphone N=2335
Sex	
n (%)	2335 (100%)
Male	1040 (44.5%)
Female	1295 (55.5%)
Age (years)	
n (%)	2335 (100%)
18-<40	299 (12.8%)
40-<65	1525 (65.3%)
65-<75	378 (16.2%)
≥75	133 (5.7%)
n	2335
Mean (SD)	54.0 (12.67)
Median	54.0
(Min, Max)	(20, 91)
Race	
n (%)	2335 (100%)
Caucasian	2123 (90.9%)
Black	147 (6.3%)
Asian	14 (0.6%)
Other	51 (2.2%)
BMI (kg/m²)	
n (%)	2064 (100%)
<25	535 (25.9%)
25-<30	598 (29.0%)
30-<39	641 (31.1%)
≥39	290 (14.1%)
Missing	271
n	2064
Mean (SD)	30.5 (7.87)
Median	29.1
(Min, Max)	(14, 63)

Note: Controlled and uncontrolled studies included: DO-104, DO-105, DO-108, DO-109, DO-118, DO-118X, DO-119, DO-127, DO-127X, DO-132, M03-644-05, NMT 1077-301, and OROS-ANA-3001.

Note: Patients from DO-118 are counted once in the total column.

BMI=body mass index; ISS=Integrated Summary of Safety; Max=maximum; Min=minimum; OROS[®]=oral osmotic drug delivery system; SD=standard deviation

(Source: ISS p 75)

Of the 2,335 patients treated with OROS, 2097 (89.8%) were treated for non-malignant pain and 238 (10.2%) were treated for cancer pain.

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In the Phase 1 Clinical Pharmacology demographics, again, most were Caucasian. However, these healthy subjects differed from the chronic pain patients in that most of these were males (69%) and younger (with age range of 18-54). These findings are summarized in Table 33.

Table 33. Demographics Clinical Pharmacology Study Pool

	All Enrolled Subjects ^a	Completed Subjects with Naltrexone Block	Completed Subjects without Naltrexone Block
Sex			
n (%)	465 (100%)	352 (100%)	77 (100%)
Male	321 (69%)	242 (68.8%)	56 (72.7%)
Female	144 (31%)	110 (31.3%)	21 (27.3%)
Age (years)			
n	465	352	77
Mean (SD)	31.6 (9.6)	32.3 (9.9)	28.6 (6.9)
(Min, Max)	(18, 54)	(18, 54)	(19, 43)
Race			
n (%)	465 (100%)	352 (100%)	77 (100%)
American Indian	2 (0.4%)	1 (0.3%)	0
Asian	9 (1.9%)	7 (2.0%)	2 (2.6%)
Black	60 (12.9%)	28 (8.0%)	27 (35.1%)
Caucasian	336 (72.3%)	282 (80.1%)	31 (40.3%)
Hispanic	49 (10.5%)	32 (9.1%)	10 (13.0%)
Other	9 (1.9%)	2 (0.6%)	7 (9.1%)

^a All enrolled subjects includes subjects who completed the study and all who discontinued prematurely.

(Source: ISS, p. 163)

Reviewer's comments: There was an appropriate age range of subjects and patients studied in a chronic pain population representing cancer and non-cancer diagnoses.

Disposition

There were 1023/2130 (48%) treated patients in the primary (non-extension) studies who discontinued early. The primary reason for early discontinuation was an adverse event which occurred in 22.1% of patients in the controlled and uncontrolled studies. In the extended studies, the most frequent reason for discontinuation was administrative reasons (33.2%). Table 34 provides a more detailed summary of the patient disposition in the studies.

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Table 34. Patient Disposition in Primary and Extended Controlled and Uncontrolled Studies (All Patients with Chronic Pain treated with Hydromorphone ER)

	OROS® Hydromorphone n (%)
Primary Studies ^a	
Treated	2130 (100%)
Completed	1107 (52.0%)
Discontinued early	1023 (48.0%)
Primary reason for early discontinuation	
Death	4 (0.2%)
Adverse event	471 (22.1%)
Lack of efficacy	244 (11.5%)
Administrative reasons	16 (0.8%)
Lost to follow-up	24 (1.1%)
Recovery	0
Hospital discharge	0
Protocol violation	54 (2.5%)
Withdrew consent	99 (4.6%)
Progression of study disease	4 (0.2%)
Noncompliance	40 (1.9%)
Opioid withdrawal	6 (0.3%)
Unacceptable rescue medication	10 (0.5%)
Other	51 (2.4%)
Missing	0
Extended Studies ^b	
Treated	569 (100%)
Completed	93 (16.3%)
Discontinued early	476 (83.7%)
Primary reason for early discontinuation	
Death	29 (5.1%)
Adverse event	77 (13.5%)
Lack of efficacy	49 (8.6%)
Administrative reasons	189 (33.2%)
Lost to follow-up	16 (2.8%)
Recovery	4 (0.7%)
Hospital discharge	0
Protocol violation	24 (4.2%)
Withdrew consent	53 (9.3%)
Progression of study disease	34 (6.0%)
Noncompliance	0
Opioid withdrawal	0
Unacceptable rescue medication	0
Other	0
Missing	1 (0.2%)

^a Primary studies included DO-104, DO-105, DO-108, DO-118, DO-119, DO-127, DO-132, M03-644-05, NMT 1077-301, and OROS-ANA-3001.

^b Extended studies included DO-109, DO-118X, and DO-127X.

ISS=Integrated Summary of Safety; OROS®=oral osmotic drug delivery system

(Source: ISS, p. 73 and 74)

7.2.2 Explorations for Dose Response

There was one Phase 3 active-controlled study (DO-119) with a secondary objective of demonstrating a dose-response relationship between OROS hydromorphone and one-half dose of OROS hydromorphone (defined as a dose approximately half that of the titrated dose in the study). A total of 113 patients were randomized (39 IR HM, 34 OROS HM, 40 one half dose OROS HM) with chronic non-malignant or cancer pain. This study was reviewed fully in the original NDA. There were no particular safety issues identified in that study with regard to the dosages as noted.

In the Phase 1 PK studies, 10 studies used naltrexone to block opioid effect in healthy volunteers and 3 studies did not use naltrexone blocking. The naltrexone-blocked subjects had higher incidence rates of nausea, headache and vomiting at higher doses. The subjects without naltrexone did not show this effect (however, the Applicant reported that this could have been due to the small number of subjects receiving each dose).

Abuse liability study C-2004-022 showed a dose-response effect for observed AEs with those receiving a higher dose (64 mg) reporting more AEs than those who received immediate-release hydromorphone (8 mg).

7.2.3 Special Animal and/or In Vitro Testing

There was no Phase 2 or 3 special animal or In vitro testing performed.

7.2.4 Routine Clinical Testing

The routine clinical testing performed during the development of Exalgo (hydromorphone extended release) appears adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

The reader is referred to Section 4.4 and the Clinical Pharmacology Review of Dr. Wei Qui for information regarding the metabolic, clearance and interaction workup.

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7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Exalgo hydromorphone HCl extended release is a mu-opioid receptor agonist. Expected adverse events include those related to the central nervous system (i.e. sedation, dizziness, somnolence, headache, and respiratory depression), the gastrointestinal system (i.e. nausea, vomiting, and constipation) and other AEs such as pruritus and fatigue.

The Applicant monitored AEs by eliciting responses to specific questions, observation during examination, or spontaneous reporting by the subjects. Laboratory data, vital signs, and ECGs were collected throughout trials per protocol. The data collected allowed for adequate evaluation of the potential adverse events for similar drug class.

Withdrawal symptoms were evaluated during Study NMT 1077-301. Drug accountability and compliance with study drug treatment was assessed during this study also. Results of these evaluations are discussed in the review by Dr. Jon Gong (CSS).

7.3 Major Safety Results

7.3.1 Deaths

There were 64 deaths in the total 2,335 patients (2.7%) who participated in the 13 controlled and uncontrolled studies. The majority of deaths (58/64) occurred in patients with chronic pain of malignant origin and appeared to be causally related to cancer disease progression. No other patterns could be established by this reviewer.

Two deaths occurred in the controlled studies and 62 in the uncontrolled studies as summarized in Table 35 below. No deaths occurred in the placebo group controlled studies. There were no deaths in the key efficacy study NMT 1077-301. There were no deaths in the 13 pooled Clinical Pharmacology studies.

Table 35. Deaths in Controlled and Uncontrolled Studies – Hydromorphone Extended Release (HMER)

Controlled Study	# deaths
DO-118	2
Uncontrolled Studies	
DO-104/105	12
DO-109	31
DO 118X	19
Total	64

(Source: Table developed by reviewer from Applicant's data)

One death was reported in ongoing Study NMT 1077-302. The final study report was not included in this submission and, therefore, not included in this review.

The 4-month Safety Update reported one death in study 42801-PAI-3001 which occurred in a patient in the placebo group. The cut-off date for the 4-month SU was May 22, 2009.

There were no deaths in terminated Study 42801-PAI-3008.

The Applicant maintains that all of the deaths were either unrelated to study drug or unlikely to be causally related. After review of the narrative summaries provided, this reviewer is in agreement with the Applicant's findings that no deaths appeared definitely related or probably related to study drug. However, there was 1 death in an uncontrolled study, which, in the opinion of this reviewer, could be considered possibly related (Patient DO 105-9405001).

All death narratives were reviewed by this reviewer. Eleven death narrative summaries are provided in this review. The narrative summaries include the following:

- Controlled Study Patient Deaths (2)
- Uncontrolled Study Patient Deaths (9)
 - Possible causality
 - Unlikely related causality
 - Unrelated causality but occurred either in a patient without malignancy or in a cancer patient with a non-cancer disease progression as cause of death
 - Insufficient information to determine causality

Tables 36 and 37, below, summarize the death findings as related to Treatment Diagnosis, Cause of Death Diagnosis and Causality in the Controlled and

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Uncontrolled Studies as determined by this reviewer. Patients with underlying treatment diagnosis of cancer (6) are in bold font.

Table 36. Controlled Studies – Death Narratives Summarized in Review

Study/Patient ID	Treatment Diagnosis	Cause of Death	Related Causality
DO-118-81	Lung Cancer	Respiratory Failure	Unrelated
DO-118-363	Cancer (unknown origin)	Disease Progression	Unrelated

(Source: Table prepared by Reviewer based on Applicant's submission)

Table 37. Uncontrolled Studies - Death Narratives Summarized in Review

Study/Patient ID	Treatment Diagnosis	Cause of Death	Related Causality
DO-105-9405001	Abdominal pain	Intra-abdominal sepsis with subphrenic abscess	Possible
DO-109-1595001	Cervical Radiculopathy	Cardiac arrest	Unlikely
DO-109-1795002	Psoriatic arthritis	Myocardial Infarct	Unlikely
DO-118X-150	Pancreatic Cancer	Cardiac Arrest	Unlikely
DO-109-0394001	Lung Cancer	Respiratory Failure	Unrelated
DO-109-2195004	Low Back Pain	Congestive Heart Failure	Unrelated
DO-109-9795001	Hip Pain	Cardiac Arrest	Unrelated
DO-118X-332	Breast Cancer	None given	Insufficient Info
DO-104-3604001	Ovarian Cancer	Tumor Progression	Insufficient Info

(Source: Table prepared by Reviewer based on Applicant's submission)

Description of Controlled Study with Patients Resulting in Death

Controlled clinical studies included DO-118, DO-119, DO-132, M03-644-05, NMT 1077-301, and OROS-ANA-3001. A total of 1,572 patients received hydromorphone ER treatment in the controlled studies.

Table 38 below lists the two patients (0.1%) who experienced AEs leading to death in the controlled study. No deaths occurred in the placebo group.

Table 38. Deaths in Controlled Study Pool

System Organ Class ^a MedDRA ^b Preferred Term	OROS [®] Hydromorphone N=1572 n (%)	Placebo N=466 n (%)
General disorders and administration site conditions		
Asthenia	1 (0.1%)	0
Respiratory, thoracic, and mediastinal disorders		
Respiratory failure	1 (0.1%)	0

^a A patient may be reported in more than one MedDRA version 11.1 System Organ Class.

^b MedDRA version 11.1

Note: Controlled clinical studies included DO-118, DO-119, DO-132, M03-644-05, NMT 1077-301, and OROS-ANA-3001.

ISS=Integrated Summary of Safety; MedDRA=Medical Dictionary for Regulatory Activities;
 OROS[®]=oral osmotic drug delivery system

(Source: Summary of Clinical Safety, p. 48)

Study DO-118

This study was conducted in cancer patients and was the only controlled study in which there were deaths in patients who received hydromorphone ER. As shown in Table 39, a total of eight patients died in this study (three during the study and five after study completion). Six of the eight deaths occurred in the morphine therapy arm and two occurred in the hydromorphone arm.

Table 39. Deaths in Study DO-118 During or After Study

Patient No.	Age	Sex	Cancer Type	AE (MedDRA® Term)	Relationship to therapy	Study Phase of Death
Hydromorphone Treatment Group						
81	68	Male	Lung	Respiratory failure	Unrelated	Post-treatment
363	70	Male	Other	Asthenia	Unrelated	Withdrawn (SR)
Morphine Treatment Group						
6	62	Male	Lung	Disease progression	Unrelated	Post-treatment
78	68	Female	Breast	Cerebrovascular accident	Unlikely	IR
79	34	Female	Breast	Brain cancer metastatic	Unlikely	Withdrawn (SR)
94	52	Male	Genito-urinary	Dyspnea	Possible	SR
				Fall	Possible	
				General physical health deterioration	Unlikely	
				Mental impairment	Unlikely	
171	19	Male	Other	Disease progression	Unrelated	IR
212	45	Female	Lung	Metastatic neoplasm	Unrelated	Withdrawn (SR)

Severity of each of these AEs was "severe".

Patients 363, 79, and 212 had discontinued early from the study at the time of death. Patients 6 and 81 had completed the study at the time of death. Patients 78, 94, and 171 were enrolled in the study at the time of death.

Source: Appendixes 12.2-3, 12.2-4, 12.2-7, 12.2-17, and 12.3.1

(Source: Final Study Report, p 98)

The Applicant reported that both of the deaths in the hydromorphone treatment group had unrelated causality to study drug. This reviewer is in agreement with the Applicant's causality findings. The Narratives for Patient numbers 81 and 363 are summarized below.

Controlled Study Death Narratives (Unrelated causality)

**Patient No. 81 (OROS hydromorphone 24 mg daily); Respiratory failure;
Unrelated causality**

Patient No. 81 was a 68-year-old man enrolled in the DO-118 study. On 1/18/2000 he began the blinded study drug treatment with IR hydromorphone 24 mg daily for pain due to squamous cell lung carcinoma. On 1/24/ 2000 the patient was switched to OROS hydromorphone 24 mg daily. His relevant medical history included lung cancer with metastasis to bone, surgical repair of groin hernia, cigarette smoking, chronic obstructive pulmonary disease, dyspnea, right lower lobe pneumonia, pulmonary infection, and a possible allergy to penicillin. Baseline medications included furoxime, alprazolam, fluoxetine, indomethacin, megestrol, prednisone, ranitidine, furosemide, as well as other medications. Prior to study entry, the patient was taking morphine, 90 mg orally daily, for pain relief.

Following enrollment in the DO-118 study, the patient developed a respiratory infection on 1/31/ 2000, which was treated with ciprofloxacin. The patient took his last dose of OROS hydromorphone (24 mg) on 2/6/2000 (completed 13 days of treatment with OROS).

On (b) (6) days after starting IR hydromorphone 24 mg daily, and (b) (6) after switching to OROS hydromorphone 24 mg daily, the patient presented with dyspneic crisis and a diagnosis of respiratory failure was established. He was admitted to the hospital, where pulmonary testing showed no signs of infection or bronchospasm. He was diagnosed with **acute respiratory failure**. Due to irreversibility of this patient's neoplasm, palliative support was given.

The patient expired on (b) (6). The event was ongoing at the time of the patient's death. There was no report of an autopsy.

The investigator assessed the event as severe in intensity and unrelated to study drug.

Reviewer's comment: This patient had an underlying diagnosis of squamous cell lung carcinoma and cause of death was reportedly due to respiratory failure. While the causality related to the use of hydromorphone ER can not be fully excluded, it would appear that the underlying causality is more likely related to cancer disease progression. In addition, the death occurred four days after study drug was discontinued.

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Patient No. 363 (OROS 16 mg daily); Disease progression; Unrelated causality

Patient No. 363, a 70-year-old Caucasian man, was enrolled in the DO-118 study and on 3/6/2001, the patient began blinded study drug treatment with IR hydromorphone 12 mg daily for pain due to carcinoma of unknown origin, with metastases to the bone, pleura, and liver. On 3/15/ 2001, the patient began taking OROS hydromorphone 16 mg daily. His relevant medical history included pulmonary tuberculosis, left costal fracture, testicular cyst, depression, smoking, alcoholism, asthenia, anorexia, weight loss, radiotherapy, and chemotherapy.

Baseline concomitant medications included omeprazole, ibuprofen, and Sennosides. Increased asthenia began on 3/13/ 2001 (8 days after starting IR hydromorphone) and was ongoing at the time of the patient's death on (b) (6). The investigator assessed the asthenia event as severe in intensity and unrelated to study drug.

On (b) (6), the patient had an onset of adverse events of dysphagia, sleepiness, and confusion. His family asked that he be hospitalized as they had difficulty caring for him at home, and on (b) (6) the patient was hospitalized. Delirium began on (b) (6) days after starting IR hydromorphone and (b) (6) days after starting OROS hydromorphone).

On (b) (6), the patient discontinued study drug (OROS hydromorphone 16 mg daily) and was discontinued early from the study due to delirium. The patient was treated with haloperidol, midazolam, thioridazine, paroxetine and zolpidem.

Death occurred on (b) (6). The investigator assessed the event as unrelated to study drug. The primary cause of death was reported as metastases of unknown origin, and the secondary cause was **disease progression**. No autopsy report was available. No clinically relevant laboratory values were reported.

Reviewer's comments: This patient was on multiple medications and had metastatic cancer. Although impossible to conclude that study drug had no causality, it can also not be reasonably determined that study drug was a causal factor in this patient who was critically ill. Death occurred (b) (6) days after study drug was discontinued. Therefore, an assignment of unrelated causality is given for this patient.

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Description of Uncontrolled Studies with Patients Resulting in Death

Uncontrolled studies included DO-104, DO-105, DO-108, DO-109, DO-118X, DO-127 and DO-127X. Deaths occurred in studies DO-104/105, DO-109 and DO-118.

The Applicant initially reported that in the uncontrolled trials, 38 deaths were identified among the 863 patients who received OROS hydromorphone ER treatment (4.4%). However, the Applicant amended that report to include an additional 24 deaths that were not reflected in the clinical database for Studies DO-104, DO-105, DO-109, and DO-118 and were identified after the studies ended based on manual review of study documents during preparation of the CSRs. In Study DO 104/105 there were 12 deaths (4 in clinical data base and 8 during CSR preparation); DO 109 had 31 deaths (16 in clinical data and 15 during CSR preparation); and DO 118X experienced 19 deaths (18 in clinical database and 1 during CSR preparation).

Therefore, a total of 62 deaths occurred either during or after hydromorphone ER treatment in the seven uncontrolled studies. All of these deaths were considered unrelated to study treatment by the Investigator except for Patient DO-105-940500 in Study DO-105 whose death the Investigators considered unlikely related to study drug. This reviewer, however, assigned a causality of possibly related in this patient. Causality for the other 8 narratives in the uncontrolled studies is as follows: three patients who were assigned causality as unlikely related to study drug (DO-109-1595001, DO-109-1795002 and DO-118X-150); three assigned as unrelated (DO-109-0394001, DO-109-2195004, and DO-109-9795001) and two insufficient information to assign causality (DO-118X-332 and DO-104-3604001).

The Applicant's individual studies and reported deaths are discussed in detail below with narratives following.

Study DO-104/105

These were two open-label, repeat-dose studies that evaluated a combined total of 463 patients with chronic pain conducted from 1997 to 1999. The 2 studies were identical in design with the exception of the diagnostic entry criteria. Study DO-104 was designed for patients with chronic cancer pain and Study DO-105 was designed for patients with chronic non-cancer pain. The results of Studies DO-104 and DO-105 were presented as a single report.

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An interim report was submitted in the original NDA submitted in 1999. The Medical Officer review at that time included safety data for the 120-day Safety Update to December 1, 1999 and original NDA submission for February 15, 1999. The Medical Officer review from the original NDA submission was reviewed. This review incorporates the Final Study Report for Study DO-104/105 included in this submission dated November 2, 2005.

There were 127 subjects treated with study drug in Study DO-104 and 336 in Study DO-105. There were a total of 12 deaths in the combined studies (11 in study DO-104 and 1 in study DO-105). Five patients died while receiving study medication, 1 patient before receiving study medication, and 6 patients during follow up after receiving their last dose of study medication. The Applicant reported that four of the 12 deaths were reflected in the clinical database and 8 were identified during CSR preparation.

Table 40 below, provided by the Applicant, summarized deaths during Studies DO-104/105 and their proposed relationship to study medication as assigned by the Investigators. This reviewer is in agreement that the 11 deaths in the DO-104 study all appeared to be due to late-stage, metastatic cancer progression effects and not due to study drug. Their narratives will not be summarized in this review. Patient DO-105-9405001 was assigned causality of unlikely related to study drug by Investigators. This patient's narrative summary is provided in the Narratives' section and assigned a possibly related causality by this reviewer.

Table 40. Summary of Deaths During Study DO-104/105 (All Treated Patients)

Summary of Deaths During Study DO-104/105 (All Treated Patients)

Patient Number	Sex/Age (yrs)	Cause of Death	Relationship to Study Medication
DO-104-0204002 ^a	F/63	Progression of non-small cell lung cancer	Unrelated
DO-104-1804001 ^b	M/68	Progression of metastatic cancer	Unrelated
DO-104-2404002 ^a	M/58	Progression of metastatic cancer	Unrelated
DO-104-2404004 ^a	F/38	Progression of metastatic cancer	Unrelated
DO-104-3004020 ^a	F/60	Cardiopulmonary arrest and progression of metastatic cancer	Unrelated
DO-104-3604001 ^a	F/74	Progression of metastatic cancer	Unrelated
DO-104-3604003 ^a	F/48	Progression of metastatic cancer	Unrelated
DO-104-3704005	M/60	Pseudomonas aeruginosa bacteremia, sepsis, advanced pharynx cancer, and pancytopenia	Unrelated
DO-104-3704013	F/67	Progression of metastatic cancer	Unrelated
DO-104-4604004	F/50	Progression of metastatic cancer/liver failure	Unrelated
DO-104-9204002	M/73	Progression of metastatic cancer	Unrelated
DO-105-9405001	F/40	Intra-abdominal sepsis with subphrenic abscess and acute feculent peritonitis following perforation of cecum due to multifocal necrotizing pseudomembranous colitis	Unlikely

Source: Listing 12.2.5-6, patient hospitalization records, and/or SAE files.

^a Patient died during follow-up after patient received last dose of study medication. Death identified on hospitalization records and/or SAE files.

^b Patient died before receiving study medication.

(Source: Final Study Report DO-104/105, p. 103)

Study DO-109

The safety data from this study was reviewed in the original NDA for Dilaudid CR. That review, however, was of an interim study report (dated October 12, 1999) and contained data for 260 patients through February 15, 1999. A full final report for Study DO-109 (dated March 8, 2001) was later available and presented data for all 388 enrolled patients. This review incorporates all findings.

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There were 31 deaths in Study DO-109 (16 identified in the clinical database and 15 identified during CSR preparation). Sixteen deaths occurred while on study drug and 15 deaths occurred after discontinuation from study drug.

All 31 deaths were considered by the Investigators to be unrelated to study treatment. Twenty six deaths were attributed to cancer progression, and five were associated with other conditions (2 cardiac arrests, and 1 patient each with respiratory failure/dehydration, myocardial infarction, and congestive heart failure).

After review of the narratives, this reviewer is in agreement that the deaths appeared unrelated to study drug with the exception of Patient DO-109-1595001 who experienced cardiac arrest and Patient DO-109-1795002 who experienced a myocardial infarct. Both of these narratives suggested an unlikely (rather than unrelated) causality. The narratives of the other three patients with diagnoses other than disease progression are summarized under the narrative section. Four of these five patients were non-cancer patients.

The Applicant's table of Deaths which occurred during and after Study DO-109 is provided below in Tables 41 and 42.

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Table 41. Deaths During Study DO-109

Patient Number	Sex	Age (yrs)	Cause
0394001	Female	70	Respiratory failure and dehydration
1595001	Male	67	Cardiac arrest
1694003	Female	79	Lung neoplasm malignant
1795002	Female	54	Myocardial infarction
2195004	Male	74	Cardiac failure congestive
2195009	Male	53	Adenocarcinoma and pneumonia aspiration
2594001	Female	66	Malignant neoplasm progression
2994003	Female	48	Malignant neoplasm progression
2994004	Male	28	Malignant neoplasm progression
3094014	Male	74	Multiple myeloma
3294002	Female	63	Colorectal cancer
3994001	Male	53	Salivary gland neoplasm
3994004	Female	53	Breast cancer metastatic
4694006	Female	69	Non-small cell lung cancer
4794001	Male	78	Lung neoplasm malignant and chest wall mass
9795001	Female	65	Cardiac arrest

(Source: Final DO-109 Study Report, p. 83)

Table 42. Deaths After Discontinuation from Study DO-109

Deaths After Discontinuation from Study DO-109

Patient Number	Sex	Age (yrs)	Cause
0194001	Female	56	Lung cancer
2094001	Male	91	Colon cancer
3094008	Male	90	Metastatic colon cancer
3594001	Male	58	Colon cancer
3794002	Male	75	Metastatic colon cancer
3794008	Male	74	Lung cancer
3794010	Male	65	Lung cancer
3794011	Female	52	Metastatic esophageal cancer
3994007	Male	53	Multiple myeloma
9194002	Female	34	Metastatic breast cancer
9194003	Female	59	Metastatic breast cancer
9194004	Male	37	Metastatic kidney cancer
9294003	Male	65	Metastatic colon cancer
9294004	Female	50	Metastatic rectal cancer
9795004	Female	79	Lung neoplasm malignant

(Source: Study report DO-109)

Study DO-118X

As can be seen in Table 43 below, there were 19 deaths in Study DO-118X. All of these patients had underlying cancer and the Investigators reported all deaths as unrelated to study drug except for two (Patients 150 and 332), who were assigned causality as unlikely related. This reviewer is in agreement with the Investigators' assignments except for Patient DO-118X-332. It is this reviewer's opinion that there was insufficient information on this patient to determine causality. The narrative summaries for Patients 150 and 132 are provided in the narrative section of this review.

Table 43. Study DO-118X Deaths

Patient No.	Age/ Gender	Cancer Type	Study Onset Day	MedDRA® Term	Relationship to Study Drug
3	70/M	Genitourinary	162	Disease progression	Unrelated
20	32/M	Other	16	Hypercalcemia	Unrelated
83	53/M	Other	109	Cognitive disorder	Unrelated
			113	Septic shock ^a	Unrelated
113	61/M	Lung	Day 1 of Study DO-118	Malignant neoplasm progression	Unrelated
114	48/F	Lung	107	Death	Unrelated
150	63/F	Gastrointestinal	83	Ascites Back pain Constipation	Unlikely Unlikely Unlikely
207	27/F	Genitourinary	85	Renal impairment	Unrelated
221	64/F	Breast	168	Disease progression	Unrelated
224	79/F	Breast	144	Disease progression	Unrelated
225	75/F	Lung	22	Malignant neoplasm progression	Unrelated
226	46/F	Breast	246	Disease progression	Unrelated
249 ^b	64/M	Genitourinary	Approx. 7 months	Asthenia	Unrelated
266	57/F	Gastrointestinal	33	Rectal hemorrhage	Unrelated
282	41/M	Other	16	Disease progression	Unrelated
284	41/M	Lung	36	Dyspnea	Unrelated
321	52/F	Breast	162	Terminal state	Unrelated
332	29/F	Breast	345	Terminal state	Unlikely
362	74/M	Other	36	Hepatic encephalopathy	Unrelated
390	66/M	Gastrointestinal	103	Neoplasm malignant	Unrelated

M = male; F = female

a Adverse event led to premature discontinuation.

b Patient died 70 days after the end of the study.

(Source: Final Study report, p. 36)

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Death Narratives (Possibly related causality)

Patient DO-105-9405001 (OROS hydromorphone 24 mg); Perforated ulcer-cecum/Large intestine perforation; multifocal necrotizing pseudomembranous colitis with intra-abdominal sepsis; Possibly related causality

Patient DO-105-9405001, a 40-year-old Caucasian female, was enrolled into the DO-105 study on 3/5/1998. The patient entered the titration phase of the study on 3/11/1998 and initiated treatment with OROS hydromorphone 24 mg daily for abdominal pain secondary to intra-abdominal adhesions. The patient's relevant medical history included diabetes, asthma, arthritis, headaches, obesity (baseline height/weight = 177.8 cm/163.3 lbs), and stomach ulcer. Due to her obesity, she had undergone an apronectomy. She had a motor vehicle accident, which injured her abdomen and reopened her surgical incision. After this event she had multiple plastic surgeries to her abdomen and her abdominal pain came from abdominal adhesions.

Significant concomitant medications included Amitriptyline, Prednisone, Metformin, Glyburide, Senokot, and Naproxen.

On 3/20/1998, the patient was reportedly doing fine when contacted by the site. On [REDACTED] ^{(b) (6)} days after starting OROS hydromorphone treatment), the patient died. The cause of death appeared to have been a gastro-intestinal emergency described by the investigator as a perforated ulcer that resulted in her death on arrival despite CPR attempts en route. The patient's husband reportedly later indicated that she had increased her prednisone dose, and that she continued to self-medicate with naproxen as needed. An autopsy report indicated that the cause of death was the result of **intra-abdominal sepsis with subphrenic abscess and acute feculent peritonitis** following perforation of cecum due to multifocal necrotizing pseudomembranous colitis.

The investigator assessed the event as severe in intensity and unlikely to be related to study drug.

Reviewer's Comments: This patient had multiple risk factors for GI perforation to include extensive prior abdominal surgeries with abdominal adhesions, obesity and stomach ulcer. She was taking NSAIDs and prednisone which further increased her risk. Although study drug is unlikely to have contributed to a necrotizing, pseudomembranous colitis, the study drug (opioid) may have increased the risk of constipation contributing to intestinal perforation.

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The patient died (b) (6) after starting study drug and was receiving study drug when the death occurred. Given this fact, a more conservative assignment of possible causality to study drug was given by this reviewer.

Death Narratives (Unlikely Related Causality)

Patient DO-109-1595001; (OROS 32 mg); Cardiac Arrest; Unlikely related

Patient DO-109-1595001, a 67-year-old Caucasian male, completed the DO-105 study (DO-105-1505001) and was enrolled into the DO-109 extension study on 7/24/1998. The patient continued treatment with OROS hydromorphone 32 mg daily for pain due to cervical radiculopathy. The patient's relevant medical history included obesity, hypertension, osteoarthritis, constipation, prostatitis, inactive focal seizure disorder, lumbosacral radiculopathy, mood disorder and a history of falls. No significant findings were found during the baseline physical examination.

Relevant concomitant medications included Dulcolax, Calan XL, Dilantin, Prozac, Relafen, Inderal SR, Valium, and Dilaudid IR.

Prior to entering the rollover study DO-109, the patient experienced an episode of falling once on 7/21/1998, during the DO-105 study. This event was considered possibly related to the study drug by the Investigators. No further events were reported.

The patient was reportedly well per phone contact on 8/27/1998, but did not attend an office appointment on 8/31/1998. On (b) (6) days after starting study drug), the patient was found dead in his apartment. The cause of death was determined to be **cardiopulmonary arrest** secondary to myocardial infarction. The date of the last dose of study drug taken is unknown.

Reviewer's Comments: Although it is impossible to determine that study drug was not causally related, given the relative occurrence of cardiac arrests in the general population and this patient's risk factors of obesity and hypertension, it is this reviewer's opinion that study drug was unlikely related as a cause of death in this patient. No autopsy was performed.

Patient DO-109-1795002 (OROS hydromorphone 32 mg); Myocardial infarction; Unlikely related

Patient DO-109-1795002, a 54-year-old Caucasian female, completed the DO-105 study (DO-105-1705002) and was enrolled into the DO-109 extension study on 2/17/1998. The patient continued treatment with OROS hydromorphone 24 mg daily for pain, due to psoriatic arthritis. On 3/18/1998, OROS hydromorphone

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was increased to 32 mg daily. The patient's relevant medical history included diabetes, esophagitis, previous angioplasty, kidney surgery, spinal laminectomy, insulin coma, psoriatic arthritis, and gall bladder removal. No significant findings were found during the baseline physical examination. Concomitant medications were Prednisone, Levaquin, Dilaudid IR, and various other medications.

On (b) (6) days after starting study drug), the subject presented with chest pain. Later that same day she reportedly died of a heart attack while asleep. The Applicant reports that the stated cause of death on the death certificate was **atherosclerotic cardiovascular disease** and insulin dependent diabetes. Her last dose of study drug, 32 mg daily, was taken on (b) (6). No additional information was provided. The investigator assessed the event as severe in intensity and unrelated to study drug.

Reviewer's Comments: Given the relative frequency of myocardial infarction in the general population and this patient's increased risk factor of diabetes, this reviewer agrees that there is unlikely causality. Additionally, a diagnosis of atherosclerotic cardiovascular disease suggests a more chronic etiology rather than more short-term use due to study drug.

Patient No. DO-118X-150 (OROS hydromorphone 48 mg daily); Cardiac arrest; Unlikely related causality

Patient No. 150, a 63-year-old Caucasian woman, completed the DO-118 study and was enrolled into the DO-118X extension study on 3/10/2000. She continued treatment with OROS hydromorphone 48 mg orally daily for pain due to pancreatic cancer pain. Prior to entry in the DO-118 study, the patient's relevant medical history included pancreatic cancer diagnosed in 1999, cholecystectomy, and hysterectomy. Baseline concomitant medications included domperidone manate.

Prior to DO-118 study entry, the patient was taking morphine sulfate 60 mg orally daily and Fentanyl patch, 50 mg daily for pain relief. During participation in the DO-118 study, the patient had onset of nonserious, mild constipation, which was treated with Softene from 3/10/2000 to 3/12/2000. On that same day, her constipation became moderate in intensity, and was treated with Dulcolax 20 mg twice a day from 3/12/2000 to 4/30/2000.

On (b) (6) days after starting OROS hydromorphone), the patient's constipation became severe, and she was hospitalized with fecal impaction. The **fecaloma** was removed manually. At the time of the event, the patient was taking OROS hydromorphone 48 mg daily, which was continued with no dose change. She was discharged on (b) (6). The event resolved on that day. The

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investigator assessed the event as severe in intensity and definitely related to study drug.

On [REDACTED] (b) (6) days after starting OROS hydromorphone), the patient presented with constipation, ascites, and back pain, and was hospitalized. At the time of the event the patient was taking OROS hydromorphone 48 mg daily. Study drug was temporarily withdrawn and replaced with Tramadol and morphine. Concomitant medications included haloperidol, tramadol, Duphalac, and morphine subcutaneous. The investigator assessed the events as severe in intensity and unlikely to be related to study drug.

The physical status of this patient worsened, and she expired on [REDACTED] (b) (6). The patient's last dose of dose of study drug was taken on 6/11/2000. The SAE report form indicated that primary cause of death was **cardiac arrest** and the secondary cause was liver insufficiency. No clinically relevant laboratory values were reported.

The investigator assigned the patient's death as unlikely causally related to study drug.

Reviewer's comments: The SAE of fecaloma was definitely related to study drug (constipation of opioid possibly combined with OROS formulation). The cause of death of cardiac arrest is, in this reviewer's opinion, unlikely related to study drug in this patient with end-stage pancreatic cancer and more chronic liver insufficiency.

Death Narratives (Unrelated causality)

Patient DO-109-0394001 (OROS hydromorphone 32 mg); Respiratory failure; Unrelated

Patient DO-109-0394001, a 70-year-old Caucasian female, completed the DO-104 study, (DO-104-0304001) and was enrolled in the DO-109 extension study on 9/23/1998. The patient continued treatment with OROS hydromorphone 32 mg daily for pain due to lung cancer. The patient's relevant medical history included osteoporosis, compression fractures, headaches, dyspnea, anorexia, tachycardia, depression, cough, and hypertension. There were no significant findings during the baseline physical examination. Concomitant medications included Zolof, Decadron and multiple other medications.

From 9/29/1998 to 10/6/1998, the patient underwent radiation therapy. On [REDACTED] (b) (6) days after starting study drug), the patient was hospitalized after her last chemotherapy on [REDACTED] (b) (6). On admission, initial chest X-ray showed a

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possible right middle lobe infiltrate and moderately sized effusion. The following morning after hospitalization, she appeared to be in acute respiratory distress of unknown etiology. Computed axial tomography (CAT) scan showed a minimal amount of fluid in the pleural space, right middle lobe pneumonia and a considerable amount of tumor and atelectasis in the right lung.

On 10/8/1998, she was taken off of study drug and placed on a morphine infusion for pain management. On (b) (6), the patient went into severe **respiratory failure**. She was ultimately designated a Do Not Resuscitate (DNR) status, and died on the morning of (b) (6). The investigator assessed the events as severe in intensity and unrelated to study drug.

Reviewer's Comment: This patient had an underlying lung cancer and had undergone both chemotherapy and radiation therapy. A CXR showed a probable pleural effusion. Given this extensive history, the causality of death is most likely due to disease progression and unrelated to study drug.

Patient DO-109-2195004: (Oros 16 mg); Cardiac failure congestive; Unrelated

Patient DO-109-2195004, a 74-year-old Caucasian male, completed the DO-105 (DO-105-2105004) study and was enrolled into the DO-109 extension study on 10/22/1998. The patient continued treatment with OROS hydromorphone 16 mg daily for pain due to chronic lower back pain. The patient's relevant medical history included lung cancer, lymphoma, prostatectomy, lung nodule removed in right upper lobe and lip cancer. Pertinent concomitant medications included Bumex Maxzide, furosemide and Coreg.

On 1/28/1999, the patient was diagnosed with a biventricular hypertrophy. Additional cardiac medications were added. On 3/29/1999, congestive heart failure was reported and he was medically treated accordingly. On 5/14/1999, he was diagnosed with cardioamyloidosis and fluid in the lungs.

On (b) (6), he was hospitalized with a 2- to 3-day history of increasing dyspnea. In the emergency room, an electrocardiogram (ECG) showed sinus rhythm with first degree AV block. A chest X-ray showed moderate right pleural effusion. The patient was diagnosed with congestive heart failure exacerbation and was hospitalized.

Discharge date was set for (b) (6), with a poor prognosis at a hospice care. The patient died on (b) (6).

The Death Summary on (b) (6) reported the final diagnosis as end stage

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cardiomyopathy. A follow-up report received on 8/11/2000 reportedly indicated that the patient's cause of death was not solely **congestive heart failure**, but end stage **amyloid cardiomyopathy** secondary to the exacerbation of congestive heart failure.

Reviewer's Comments: This patient's chronic, end-stage cardiomyopathy and congestive heart failure appear unrelated to study drug. The amyloid cardiomyopathy, pre-existing use of diuretics, extent of cardiac disease, and history of lung cancer suggests a more long-term cardiovascular/cardiopulmonary disease process.

Patient DO-109-9795001 (OROS hydromorphone 88 mg); Cardiac arrest; Unrelated

Patient DO-109-9795001, a 65-year-old Caucasian female, completed the DO-105 study (DO-105-9705001) and was enrolled into the DO-109 extension study on 4/21/1998. The patient continued treatment with OROS hydromorphone 48 mg daily for pain due to left hip pain. The patient's hydromorphone dose was up titrated and on 4/7/1999, OROS hydromorphone was increased to 88 mg daily.

The patient's relevant medical history included diabetes, mitral valve disease, atherosclerosis, myocardial infarction, migraine headaches and total hip replacement. She was on multiple diabetic and cardiac medications.

On [REDACTED] (b) (6) days after starting OROS hydromorphone treatment), she reportedly had an insulin reaction that resulted in **cardiac arrest**. The patient collapsed at home, an ambulance was called, and attempts to resuscitate were unsuccessful. The patient arrived dead at the emergency room. No additional information was provided regarding this event. The patient's last dose of OROS hydromorphone, 88 mg daily, was taken on 10/23/1999.

Reviewer's Comments: This patient had a cardiac history and cardiac risk factors of diabetes and atherosclerosis. The cause of death would appear unrelated to study drug.

Death Narratives (Insufficient Information to Assign Causality)

Patient DO-118X- 332 (OROS hydromorphone 32 mg daily and 80 mg daily); Cause of death not given; Insufficient information to assign causality

Patient No. 332, a 29-year-old Caucasian woman, completed the DO-118 study and was enrolled into the DO-118X extension study on 2/15/2001. The patient continued treatment with OROS hydromorphone 32 mg orally daily for pain due to breast cancer. Prior to entry in the DO-118 study, the patient's relevant

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medical history included breast cancer with bone metastases and tympanic drains. Baseline concomitant medications included tamoxifen, diclofenac, paracodeine, paracetamol, naproxen, pamidronate and additional medications.

Myelum compression due to bone metastasis began on 4/3/2001 (66 days after starting study drug) and resolved on (b) (6). The patient was hospitalized and treated with radiotherapy and chemotherapy. The patient was on OROS hydromorphone 32 mg daily when the event occurred but the specific time of last dose prior to the SAE onset is not known. Study drug was continued. No hospital notes were found. No laboratory tests were reported and no information on concomitant medications was available according to the Applicant. The investigator assessed the event as severe in intensity and unrelated to study drug.

Terminal illness started on 1/28/2002 (144 days after starting study drug). The patient was on OROS hydromorphone 80 mg daily when the event occurred but the specific time of last dose prior to the SAE onset is not known. Study drug was continued until the patient's death on (b) (6). The investigator assessed the event as severe in intensity and most likely unrelated to study drug.

Reviewer's Comments: This patient had end stage, metastatic breast cancer. Most likely causality for death was disease progression. However, there is not enough information regarding final diagnosis at death to determine causality. No specific diagnosis other than "terminal illness" is listed as cause of death in the narrative provided by the Applicant.

Patient DO-104-3604001; (OROS hydromorphone 128 mg daily); Tumor Progression; Insufficient information to assign causality

Patient DO-104-3604001, a 74-year-old Caucasian female, was enrolled into study DO-104 on 7/22/1998. The patient entered the titration phase of the study on 7/30/1998 and initiated treatment with OROS hydromorphone 48 mg daily for pain due to ovarian cancer with diffuse intra-pelvic metastases.

The patient's relevant medical history included gall bladder surgery, hysterectomy, hypertension, ovarian cancer, lymphedema, gastrointestinal (GI) ulcer, hypothyroidism, herpes zoster, hiatal hernia, and disc herniation. Concomitant medications included Synthroid, Vasotec, Prilosec, and Zithromax.

On (b) (6) days after starting OROS hydromorphone treatment), the patient was admitted to the hospital with nausea and vomiting which had been unresponsive to medications. She reported no bowel movement in the past 6 days. According to the Applicant, the patient was removed from the study due to the rapid progression of her cancer and unstable pain pattern with new radicular

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pain, making dose titration difficult. The patient's last dose of 128 mg of OROS hydromorphone was taken on 8/27/1998.

Abdominal X-ray revealed possible gastric outlet obstruction; a nasogastric tube was placed and intravenous opiate therapy was initiated. Computed tomography (CT) scan showed multiple hepatic metastases, some loculated ascites, large bilateral pleural effusions, gastric outlet obstruction and mesenteric omental infiltration. A small bowel obstruction was also found. The investigator assessed the event as severe in intensity and unrelated to study drug.

On (b) (6) the patient died due to **progression of tumor**. The gastric outlet obstruction and the small bowel obstruction were ongoing at the time of the patient's death.

Reviewer's Comment: This patient had apparent end-stage cancer and disease progression was, most likely, the cause of death. However, there was associated gastric outlet obstruction and small bowel obstruction which could have been a contributor to death and could, possibly, be related to study drug (OROS formulation). There was insufficient information as to a final cause of death other than progression of tumor. The patient was not on study drug at the time of death, but died within 2 weeks of discontinuing study drug.

7.3.2 Nonfatal Serious Adverse Events

Controlled and Uncontrolled Studies

In the combined 13 controlled and uncontrolled studies, serious adverse events (SAEs) were recorded in 240/2335 patients (10.3%) who received OROS hydromorphone treatment. In addition to these reported SAEs, the Applicant also later found 10 patients who possibly met SAE criteria but were not included in the clinical database in Studies DO-104, DO-118, DO-127, and DO-127X. These SAEs included: pain in extremity and cancer pain in Study DO-104; pleuritic pain (Patient 17), dehydration (Patient 29), disease progression (Patient 212), death due to disease progression (Patient 363), and diarrhea (Patient 370) in Study DO-118 and staphylococcus infection of the right hip in Study DO-127. All of these were assessed as unrelated to study drug per Applicant. Perforated bowel and right-sided weakness was reported in Study DO-127X for which no causality was provided. Furthermore, one patient (Patient 004011) in Study NMT 1077-301 was hospitalized with an SAE of kidney stones, but this event was mistakenly omitted from the database according to the Applicant.

The frequency of occurrence of SAEs by System Organ Classification revealed that the GI system at 49 (2.1%) contained the highest number of patients who experienced an SAE, followed by Infections and infestations at 44 (1.9%), then

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General disorders and administration site conditions at 43 (1.8%) in the combined patients who received OROS Hydromorphone ER in the controlled and uncontrolled studies as can be seen in Table 44 below. A patient may be reported in more than one MedDRA System Organ Classification. Note that the preferred terms under the SOC are not all inclusive and only list the top few most frequently occurring in that SOC.

Table 44. Number of Patients with at Least 1 Serious Adverse Event (Controlled and Uncontrolled Studies)

MedDRA System Organ Classification	OROS HM N = 2335 (%)	Placebo N = 466 (%)
(At least 1 SAE)	239 (10.2)	8 (1.7%)
Gastrointestinal disorders	49 (2.1)	3 (0.6)
Vomiting	14 (0.6)	1 (0.2)
Nausea	14 (0.6)	1 (0.2)
Constipation	4 (0.2)	0
Abdominal pain	3 (0.1)	0
Infections and infestations	44 (1.9)	2 (0.4)
Pneumonia	11 (0.5)	1 (0.2)
Cellulitis	7 (0.3)	0
Sepsis	6 (0.3)	0
Gastroenteritis	4 (0.2)	0
General disorders and administration site conditions	43 (1.8)	1 (0.2)
Chest pain	12 (0.5)	0
Disease progression	7 (0.3)	0
Pain	6 (0.3)	0
Drug withdrawal syndrome	5 (0.2)	1 (0.2)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	31 (1.3)	1 (0.2)
Malignant neoplasm progression	7 (0.3)	0
Nervous system disorders	29 (1.2)	1 (0.2)
Depressed level of consciousness	4 (0.2)	0
Cerebrovascular accident	3 (0.1)	0
Syncope	3 (0.1)	0
Respiratory, thoracic and mediastinal disorders	27 (1.2)	3 (0.6)
Dyspnea		0
Pulmonary embolism	8 (0.3)	0
Pneumonia aspiration	3 (0.1)	0
Respiratory distress	3 (0.1)	0
	2 (0.1)	1 (0.2)
Metabolism and nutrition disorders	24 (1.0)	1(0.2)
Dehydration	18 (0.8)	1(0.2)
Psychiatric disorders	16 (0.7)	0
Confusional state	8 (0.3)	0
Depression	4 (0.2)	0
Hallucination	2 (0.1)	0

(Source: Table compiled by reviewer from Applicant's ISS, Table 2.4.7.1, p. 1924-48)

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Table 45 below summarizes the 4 month Safety Update of Serious Adverse Events. There is no significant change in SAE safety results.

Table 45. Serious Adverse Events Reported in More than One Patient per Group (All Patients with Chronic Pain Treated)

MedDRA Preferred Term	Safety Update Report		Integrated Summary of Safety	
	OROS [®] HM N=2474 n (%)	Placebo N=615 n (%)	OROS [®] HM N=2335 n (%)	Placebo N=466 n (%)
At least one SAE	241 (9.7%)	16 (2.6%)	239 (10.2%)	8 (1.7%)
Dehydration	18 (0.7%)	1 (0.2%)	18 (0.8%)	1 (0.2%)
Nausea	15 (0.6%)	1 (0.2%)	14 (0.6%)	1 (0.2%)
Vomiting	14 (0.6%)	1 (0.2%)	14 (0.6%)	1 (0.2%)
Chest pain	12 (0.5%)	0	12 (0.5%)	0
Pneumonia	11 (0.4%)	1 (0.2%)	11 (0.5%)	1 (0.2%)
Confusional state	8 (0.3%)	0	8 (0.3%)	0
Dyspnoea	8 (0.3%)	0	8 (0.3%)	0
Cellulitis	7 (0.3%)	0	7 (0.3%)	0
Disease progression	7 (0.3%)	0	7 (0.3%)	0
Malignant neoplasm progression	7 (0.3%)	0	7 (0.3%)	0
Overdose	7 (0.3%)	0	7 (0.3%)	0
Pain	6 (0.2%)	0	6 (0.3%)	0
Sepsis	6 (0.2%)	0	6 (0.3%)	0
Anaemia	5 (0.2%)	0	5 (0.2%)	0
Drug withdrawal syndrome	5 (0.2%)	1 (0.2%)	5 (0.2%)	1 (0.2%)
Back pain	4 (0.2%)	0	4 (0.2%)	0
Cerebrovascular accident	4 (0.2%)	1 (0.2%)	3 (0.1%)	0
Constipation	4 (0.2%)	0	4 (0.2%)	0
Depression	4 (0.2%)	0	4 (0.2%)	0
Depressed level of consciousness	4 (0.2%)	0	4 (0.2%)	0
Gastroenteritis	4 (0.2%)	0	4 (0.2%)	0
Hypercalcaemia	4 (0.2%)	0	4 (0.2%)	0
Lung neoplasm malignant	4 (0.2%)	0	4 (0.2%)	0
Abdominal pain	3 (0.1%)	0	3 (0.1%)	0
Abdominal pain upper	3 (0.1%)	0	2 (0.1%)	0
Cardiac failure congestive	3 (0.1%)	1 (0.2%)	3 (0.1%)	1 (0.2%)
Diarrhoea	3 (0.1%)	1 (0.2%)	2 (0.1%)	1 (0.2%)
Diverticulitis	3 (0.1%)	0	3 (0.1%)	0
Pneumonia aspiration	3 (0.1%)	0	3 (0.1%)	0
Pulmonary embolism	3 (0.1%)	0	3 (0.1%)	0
Syncope	3 (0.1%)	0	3 (0.1%)	0
Vertigo	3 (0.1%)	0	3 (0.1%)	0
Ascites	2 (0.1%)	0	2 (0.1%)	0
Asthenia	2 (0.1%)	0	1 (0.0%)	0
Asthma	2 (0.1%)	1 (0.2%)	2 (0.1%)	1 (0.2%)
Atrial fibrillation	2 (0.1%)	1 (0.2%)	2 (0.1%)	0
Breast cancer	2 (0.1%)	0	2 (0.1%)	0
Breast cancer metastatic	2 (0.1%)	0	2 (0.1%)	0

Table 45. Serious Adverse Events Reported in More than One Patient per Group (All Patients with Chronic Pain Treated) (cont'd)

MedDRA Preferred Term	Safety Update		ISS	
	OROS N=2474; n(%)	Placebo N=615; n(%)	OROS N=2335; n(%)	Placebo N=466; n(%)
Bronchospasm	2 (0.1%)	0	2 (0.1%)	0
Cancer pain	2 (0.1%)	0	2 (0.1%)	0
Cardiac arrest	2 (0.1%)	0	2 (0.1%)	0
Deep vein thrombosis	2 (0.1%)	1 (0.2%)	2 (0.1%)	1 (0.2%)
Dizziness	2 (0.1%)	0	2 (0.1%)	0
Dyspepsia	2 (0.1%)	0	0	0
Encephalopathy	2 (0.1%)	0	2 (0.1%)	0
Hallucination	2 (0.1%)	0	2 (0.1%)	0
Hepatic failure	2 (0.1%)	0	2 (0.1%)	0
Hypotension	2 (0.1%)	0	2 (0.1%)	0
Hypoxia	2 (0.1%)	0	2 (0.1%)	0
Intervertebral disc protrusion	2 (0.1%)	0	2 (0.1%)	0
Large intestine perforation	2 (0.1%)	0	2 (0.1%)	0
Metastases to bone	2 (0.1%)	0	2 (0.1%)	0
Metastases to lung	2 (0.1%)	0	2 (0.1%)	0
Myocardial infarction	2 (0.1%)	1 (0.2%)	2 (0.1%)	0
Nephrolithiasis	2 (0.1%)	1 (0.2%)	2 (0.0%)	1 (0.0%)
Non-cardiac chest pain	2 (0.1%)	0	2 (0.1%)	0
Osteoarthritis	2 (0.1%)	0	2 (0.1%)	0
Pancreatitis	2 (0.1%)	0	2 (0.1%)	0
Pyrexia	2 (0.1%)	0	2 (0.1%)	0
Small intestinal obstruction	2 (0.1%)	0	2 (0.1%)	0
Spinal cord compression	2 (0.1%)	0	2 (0.1%)	0
Respiratory distress	2 (0.1%)	1 (0.2%)	2 (0.1%)	1 (0.2%)
Respiratory failure	2 (0.1%)	0	2 (0.1%)	0
Terminal state	2 (0.1%)	0	2 (0.1%)	0

Note: Controlled and uncontrolled studies included: DO-104, DO-105, DO-108, DO-109, DO-118, DO-118X, DO-119, DO-127, DO-127X, DO-132, M03-644-05, NMT 1077-301, and OROS-ANA-3001, and 42801PAI3001.

Note: A patient may have been reported in more than one MedDRA Version 11.1 System Organ Classification.

HM=hydromorphone; ISS=Integrated Summary of Safety; MedDRA=Medical Dictionary for Regulatory Activities; OROS[®]=oral osmotic drug delivery system; SAE=serious adverse event; SUR=Safety Update Report

(Source: 4-month Safety Update Report, p. 47-48)

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Controlled Studies SAEs: Of 1572 patients who received hydromorphone ER in the six controlled studies, 69 (4.4%) experienced at least one SAE compared to a total of 466 patients in the placebo group where eight (1.7%) experienced at least one SAE. The Applicant reported an additional 5 patients in Study DO-118 who possibly met criteria for SAE but was not included in the original clinical data base. The possible SAEs included pleuritic pain (Patient 17), dehydration (Patient 29), disease progression (Patient 212), death due to disease progression (Patient 363), and diarrhea (Patient 370), all assessed by the Investigators as unrelated or of unlikely relationship to treatment.

The MedDRA System Organ classification with the greatest number of SAEs in controlled studies was GI with 15 (1.0%) followed by General disorders and administration site conditions with 11 (0.7%) as shown in Table 46 below.

Table 46. Serious Adverse Events: Controlled Clinical Studies

MedDRA System Organ Classification	OROS HM N = 1572 (%)	Placebo N = 466 (%)
At least 1 SAE	69 (4.4%)	8 (1.7%)
GI	15 (1.0)	3 (0.6)
General disorders and administration site conditions	11 (0.7)	1 (0.2)
Infections and infestations	9 (0.6)	2 (0.4)
Nervous system disorders	7 (0.4)	1 (0.2)

(Source: Table developed by reviewer from ISS, Table 3.4.7.1, p. 4593-4608)

Table 47 below displays the SAEs reported by more than one patient treated with hydromorphone or placebo at the MedDRA preferred term level.

Table 47. Serious Adverse Events Reported by More than One Patient Treated with Hydromorphone or Placebo in the Controlled Study Pool

MedDRA ^a Preferred Term	OROS [®] Hydromorphone N=1572 n (%)	Placebo N=466 n (%)
Drug withdrawal syndrome	3 (0.2%)	1 (0.2%)
Cellulitis	3 (0.2%)	0
Atrial fibrillation	2 (0.1%)	0
Vertigo	3 (0.2%)	0
Vomiting	3 (0.2%)	1 (0.2%)
Nausea	3 (0.2%)	1 (0.2%)
Abdominal pain	2 (0.1%)	0
Constipation	2 (0.1%)	0
Chest pain	2 (0.1%)	0
Diverticulitis	2 (0.1%)	0
Osteoarthritis	2 (0.1%)	0
Deep vein thrombosis	1 (0.1%)	1 (0.2%)

^a MedDRA version 11.1

Note: Controlled clinical studies included DO-118, DO-119, DO-132, M03-644-05, NMT 1077-301, and OROS-ANA-3001.

Note: A patient may be reported in more than one MedDRA version 11.1 System Organ Class.

Note: Patient 023001, a 41-year-old Hispanic male, experienced a non-serious arthralgia of mild intensity while receiving 48 mg per day of OROS[®] hydromorphone in the Double-blind phase; this AE was considered not related to treatment. Since the “serious” box on the CRF was checked in error, this patient was listed as a SAE in the database. However, it was not a SAE, and no MedWatch or SAE reports were generated for this patient. Therefore, this patient is not included in this table.

Note: A patient randomized to placebo in Study NMT 1077-301 whose adverse event started during the Conversion/Titration phase is represented in the OROS[®] Hydromorphone column; an adverse event that started during the Double-blind phase is represented in the placebo column.

AE=adverse event; CRF=case report form; ISS=Integrated Summary of Safety; MedDRA=Medical Dictionary for Regulatory Activities; OROS[®]=oral osmotic drug delivery system; SAE=serious adverse event

(Source: Summary of Clinical Safety, p. 52)

Uncontrolled Studies SAEs: In the seven uncontrolled studies, one or more SAEs were experienced in 173/863 patients (20.0%) who received HMER. In addition, 5 patients had AEs that possibly met SAE criteria that were not included in the clinical database for Studies DO-104, DO-127, and DO-127X. These possible SAEs were identified several years after these studies ended based on manual review of study documents during preparation of the CSRs. The possible SAEs included: pain in extremity and cancer pain, both assessed as unrelated to study medication in Study DO-104; staphylococcus infection of the right hip,

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assessed as unrelated to treatment in Study DO-127; and perforated bowel and right-sided weakness in Study DO-127X, for which no causality was provided.

The MedDRA System Organ with the highest number of SAEs in the uncontrolled studies was the GI system, with 35 (4.1%). Most likely because of the patient population enrolled in these studies (malignant), there was also a high number 35 (4.1%) of Infections and infestations. This category included diagnoses such as pneumonia, sepsis and cellulitis. The next most frequently occurring system organ for SAEs was General Disorders and administration site conditions at 32 (3.7%)

Treatment-Related SAEs: The Applicant identified 17 patients in controlled studies and 27 patients in uncontrolled studies who they determined experienced one or more treatment-related SAEs as displayed in Table 48 below.

Table 48. SAEs Related to Hydromorphone Treatment (All patients with Chronic Pain treated with Hydromorphone ER in Controlled Studies)

Patient No.	Age (y) / Sex/Race	OROS® Dose	MedDRA Preferred Term	Action Taken with Study Treatment
CONTROLLED STUDIES				
NMT 1077-301				
005003	50/F/C	64 mg/d	Drug withdrawal syndrome (Verbatim: headache)	None
134007	59/F/C	24 mg/d	Drug withdrawal syndrome (Verbatim: emesis, renal failure, hypotension, and dehydration)	Drug discontinued
OROS-ANA-3001				
0056345	59/F/C	32 mg/d	Gastrointestinal disorder	Drug discontinued
0044521	87/F/C	8 mg/d	Overdose Somnolence Sedation Fatigue Vertigo	Drug discontinued
0013943	50/F/C	32 mg/d	Drug withdrawal syndrome	None
0103855	71/F/C	8 mg/d	Constipation	None
M03-644-05				
0012402	80/F/C	8 mg/d	Confusional state Hepatic enzyme increased	None
0026001	56/F/C	16 mg/d	Chest pain	Drug discontinued
0033008	74/M/C	16 mg/d	Constipation	Drug discontinued
0041001	59/F/C	8 mg/d	Chest pain	Drug discontinued
0051011	53/F/C	16 mg/d	Diverticulitis Diverticulum	No action reported
0081008	48/F/C	8 mg/d	Fall Forearm fracture	Drug discontinued
DO-118				
0000023	55/M/C	48 mg/d	Cancer pain	Dose increased
0000170	75/F/C	48 mg/d	Dizziness Nausea	None
0000255	77/M/C	48 mg/d	Hypotension Loss of consciousness Pneumonia aspiration Vomiting	Drug discontinued
0000363	70/M/C	16 mg/d	Delirium	Drug discontinued
DO-119				
NONE				
DO-132				
0000113	64/F/C	8 mg/d	Diarrhoea	Drug discontinued
UNCONTROLLED STUDIES				
DO-104				
3204002	63/F/C	24 mg/d	Vomiting	None
9204002	73/M/C	96 mg/d	Confusional state Hallucination	Dose changed, then discontinued

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Table 48. SAEs Related to Hydromorphone Treatment (all patients with Chronic Pain treated with Hydromorphone ER in Controlled Studies) (cont'd)

<u>Patient #</u>	<u>Age(y)/Sex/Race</u>	<u>OROS dose</u>	<u>MedDRA Preferred Term</u>	<u>Action Taken</u>
DO-105				
0705004	53/F/C	24 mg/d	Hypoxia	Drug discontinued
1705006	30/F/C	32 mg/d	Overdose	Drug discontinued
2905002	42/F/C	256 mg/d	Overdose	None
3005001	69/F/C	128 mg/d	Overdose	Drug discontinued
3505005	51/M/C	112 mg/d	Rash	Drug discontinued
DO-108				
NONE				
DO-109				
0595001	43/M/B	88 mg/d	Drug withdrawal syndrome	None
1595003	48/M/C	40 mg/d	Infection	Missing
2194001	79/M/C	32 mg/d	Confusional state	Drug discontinued
3094005	64/M/C	80 mg/d	Overdose	Drug discontinued
3094007	70/M/C	48 mg/d	Encephalopathy	Drug discontinued
8299002	81/M/C	16 mg/d	Encephalopathy	Drug discontinued
8599001	40/F/C	80 mg/d	Constipation	None
		80 mg/d	Headache	None
		160 mg/d	Constipation	None
9995024	42/F/C	40 mg/d ^a	Abdominal pain upper	Drug interrupted
		40 mg/d ^a	Nausea	Drug interrupted
		40 mg/d ^a	Abdominal pain upper	Drug interrupted
		40 mg/d ^a	Nausea	Drug interrupted
DO-118X				
0000121	39/F/C	128 mg/d	Dehydration	None
			Malaise	None
			Nausea	None
			Nausea	Dose reduced
			Vomiting	None
			Vomiting	Dose reduced
			Pain	None
Pain	None			
0000150	63/F/C	48 mg/d	Fecaloma	None
0000170	75/F/C	48 mg/d	Dizziness	Drug discontinued
			Nausea	Drug discontinued
0000175	73/M/C	16 mg/d	Restlessness	None
0000228	52/F/C	40 mg/d	Suicide attempt	None
0000238	60/F/C	192 mg/d	Nausea	Drug discontinued
			Vomiting	Drug discontinued
0000250	54/F/C	56 mg/d	Confusional state	Drug discontinued
			Hallucination	Drug discontinued
			Pain	Drug discontinued
0000274	65/M/C	32 mg/d	Nausea	Drug discontinued
			Vomiting	Drug discontinued

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Table 48. SAEs Related to Hydromorphone Treatment (all patients with Chronic Pain treated with Hydromorphone ER in Controlled Studies) (cont'd)

Patient #	Age(y)/Sex/Race	OROS dose	MedDRA Preferred Term	Action Taken
DO-127/DO-127X				
0000205	40/F/C	56 mg/d	Confusional state	Drug discontinued
0001117	69/F/C	16 mg/d	Small intestinal obstruction	Drug discontinued
0001118	51/F/C	24 mg/d	Diverticulitis	Drug discontinued
			Large intestine perforation	Drug discontinued
0001603	65/M/C	40 mg/d	Drug withdrawal syndrome	Drug discontinued

^a This subject was not receiving OROS[®] hydromorphone at the onset of this event. Her prior dose was OROS[®] hydromorphone 40 mg.

Note: Controlled and uncontrolled studies included: DO-104, DO-105, DO-108, DO-109, DO-118, DO-118X, DO-119, DO-127, DO-127X, DO-132, M03-644-05, NMT 1077-301, and OROS-ANA-3001.

Note: Adverse Events considered related include those definitely related, possibly related, Probable and Probably Related or with Unknown Relationship. "Related" include events evaluated as definitely, probably, possibly related, or with an unknown relationship to OROS[®] hydromorphone.

B=Black; C=Caucasian; d=day(s); F=female; ISS=Integrated Summary of Safety; M=male; MedDRA=Medical Dictionary for Regulatory Activities; OROS[®]=oral osmotic drug delivery system; y=years

(Source: ISS, pages 96-98)

Upon review of the narratives for these patients in the Table above, this reviewer agrees that these are treatment-related SAEs known to be associated with opioids.

The narratives for GI-associated SAEs are discussed under Section 7.3.5 (Submission Specific Primary Safety Concerns).

Other SAEs

In addition to the Treatment-related SAEs identified by the Applicant, the Line Listings of SAEs was also reviewed and a sample of narratives from the patients who experienced SAEs was reviewed. There were no unusual SAEs based upon these narratives which may have been causally related to study drug.

The narratives of four patients with SAE of cerebrovascular accidents and three patients with pulmonary embolism were reviewed. These narratives did not provide evidence that Exalgo hydromorphone HCL extended release was causally related to the development of these events.

SAEs Conclusions:

- The incidence of SAEs increased with each higher dose level being 2.7% incidence at 8 mg per day dose and 24.4% at >128 mg per day dose.
- Most SAEs appeared consistent with those seen in other opioids.

7.3.3 Dropouts and/or Discontinuation

The number of patients who experienced any adverse event which led to discontinuation was 538/2335 (23.0%). The most common reason for AE leading to discontinuation by system was GI disorders (11.7%) in the OROS group. Table 49, below, provides a summary of MedDRA System Organ Classification AEs leading to discontinuation. Note that the MedDRA preferred terms under the SOC are not all inclusive and only lists the top few most frequently occurring in that SOC.

Table 49. Adverse Events Leading to Discontinuation in Controlled Studies

MedDRA System Organ Classification	OROS HM N = 2335 (%)	Placebo N = 466 (%)
(At least 1 Adverse Event)	538 (23.0)	23 (4.9%)
Gastrointestinal disorders	273(11.7)	6 (1.3)
Nausea	140 (6.0)	0
Constipation	85 (3.6)	1 (0.2)
Vomiting	77(3.3)	0
Diarrhea	23 (1.0)	0
Abdominal pain	12 (0.5)	0
Dry mouth	10 (0.4)	0
Nervous system disorders	181 (7.8)	4 (0.9)
Somnolence	59 (2.5)	0
Dizziness	49 (2.1)	2 (0.4)
Headache	40 (1.7)	1 (0.2)
Sedation	10 (0.4)	0
Lethargy	9 (0.4)	0
General disorders and administration site conditions	90 (3.9)	6 (1.3)
Fatigue	32 (1.4)	0
Peripheral edema	13 (0.6)	1 (0.2)
Psychiatric disorders	87(3.7)	4 (0.9)
Confusional state	19(0.8)	0
Anxiety	19 (0.8)	1 (0.2)
Insomnia	16 (0.7)	1 (0.2)
Depression	15 (0.6)	0
Skin and subcutaneous tissue disorders	62 (2.7)	0
Pruritus	28 (1.2)	0
Hyperhidrosis	17 (0.7)	0

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(Source: Table prepared by reviewer based on Applicant's ISS, Table 2.4.6.1, p.1900-1923)

As can be seen in Table 50, the incidence of adverse events that occurred in $\geq 1\%$ for OROS hydromorphone treated patients at termination in patients who discontinued prematurely included the opioid-related events of nausea, constipation, vomiting and somnolence. Table 50 incorporates the integrated 4-month safety update analysis, which shows no major change from the original analysis.

Table 50. Adverse Events at Termination for Patients in $\geq 1\%$ of Patients (All Patients with Chronic Pain Treated with OROS Hydromorphone in Controlled and Uncontrolled Studies)

MedDRA Preferred Term	Safety Update Report		Integrated Summary of Safety	
	OROS [®] HM N=2474 n (%)	Placebo N=615 n (%)	OROS [®] HM N=2335 n (%)	Placebo N=466 n (%)
Any AE	575 (23.2%)	30 (4.9%)	538 (23.0%)	23 (4.9%)
Nausea	154 (6.2%)	0	140 (6.0%)	0
Constipation	93 (3.8%)	1 (0.2%)	85 (3.6%)	1 (0.2%)
Vomiting	80 (3.2%)	0	77 (3.3%)	0
Somnolence	64 (2.6%)	1 (0.2%)	59 (2.5%)	0
Dizziness	53 (2.1%)	2 (0.3%)	49 (2.1%)	2 (0.4%)
Headache	42 (1.7%)	1 (0.2%)	40 (1.7%)	1 (0.2%)
Fatigue	32 (1.3%)	0	32 (1.4%)	0
Pruritus	32 (1.3%)	0	28 (1.2%)	0
Diarrhoea	25 (1.0%)	0	23 (1.0%)	0

Note: Controlled and uncontrolled studies included: DO-104, DO-105, DO-108, DO-109, DO-118, DO-118X, DO-119, DO-127, DO-127X, DO-132, M03-644-05, NMT 1077-301, and OROS-ANA-3001, and 42801PAI3001.

Note: A patient may have been reported in more than one MedDRA version 11.1 System Organ Classification.

AE=adverse event; HM=hydromorphone; ISS=Integrated Summary of Safety;
 MedDRA=Medical Dictionary for Regulatory Activities; OROS[®]=oral osmotic drug delivery system; SUR=Safety Update Report

(Source: 4-Month Safety Update Report, p. 40)

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Reviewer's comments: AEs leading to discontinuation in the Oros Hydromorphone treatment group were most commonly opioid related.

7.3.4 Significant Adverse Events

The Applicant reported that in addition to the common AEs, certain types of AEs were of special interest given the drug class and nature of the Exalgo OROS formulation.

Refer to Section 7.3.5 below for discussion of the Submission Specific Primary Safety Concerns safety concerns related to the OROS formulation.

Refer to Section 7.4.5 for discussion of opioid-related significant adverse events due to alcohol interaction and abuse/liability.

7.3.5 Submission Specific Primary Safety Concerns

OROS Formulation Safety Concerns

As previously noted in this review, OROS formulation has been associated with the formation of bezoars, GI obstruction, perforation, ulcerations, and diverticulitis.

The Exalgo OROS formulation results in the shell of the tablet being excreted in undigested form. The Agency had concerns that the opioid-related increased occurrence of constipation, combined with the OROS formulation (resulting in an undigested, hard, nondeformable outer shell in the GI tract) could lead to increased risk of GI complications.

The Applicant noted that certain types of AEs were considered to be of special interest due to these GI concerns.

They searched the clinical database for MedDRA primary terms and AE verbatim terms that were considered associated with GI-related AEs. These included constipation, obstruction, duodenal obstruction, intestinal obstruction, colonic obstruction, esophageal obstruction, distal obstruction, small intestinal obstruction, colonic pseudo-obstruction, gastric outlet obstruction, distal ileal obstruction, large intestinal obstruction, bezoar and fecaloma.

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The review of GI-related AEs follows and includes discussion of Constipation; Treatment-Related GI Specific SAEs discussion/narratives; GI Obstruction discussion/narratives and GI Perforations discussion/narratives.

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Constipation

The Applicant reported that constipation was seen in 702/2335 patients (30.1%) who received HMER in the controlled and uncontrolled studies. Severe constipation was seen in 75/2335 (3.2%) and resulted in study discontinuation in 85/2335 (3.6%).

GI-related AEs of constipation in controlled studies increased with duration of use greater than seven days. In active comparator studies, constipation was seen more frequently in the hydromorphone group than in any comparator (placebo, SR oxycodone, SR morphine and oxycodone). However, no comparisons can be made due to the variability in the design of studies.

GI Specific SAEs (Controlled and Uncontrolled Studies)

There were four treatment-related GI specific SAEs. Three were related to study drug (OROS ANA Patients 1839-56345 and 0103855; M03-644) with known opioid-related AEs of nausea, vomiting and constipation. One case of diverticulitis (M03-644 Patient 0051022) was unlikely causally related to study drug, but the narrative is included as it may be related to the OROS technology.

In the uncontrolled studies, one narrative was included (DO-109-9995024) as it could be related to the OROS technology.

Narratives Treatment-Related GI Specific SAEs (Controlled Studies)

1) Study OROS ANA 3001; Patient 1839-56345; (OROS 32 mg); Intensive nausea and vomiting

This 59-year-old female was treated with OROS hydromorphone 8 mg/day from 1/9/2007, then dose was increased to 32 mg/day on 1/12/2007 and the last full dose of study medication was received on 4/10/2007. The underlying disease was musculoskeletal pain. The subject had a drug allergy to acetylsalicylic acid. On 2/2/2007 this subject had a recorded AE of 'dividing the tablet of OROS hydromorphone into two parts'. (Further description or clarification about how it was being divided was not provided). The stop date for the event was 2/12/2007. The Investigator considered this event as 'very likely' related. This subject is also reported to have gradually developed intensive nausea/vomiting during the study (onset 5/1/07), despite adequate intake of anti-emetics. No further information was provided in the narrative or CRF.

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Reviewer's Comment: This SAE was coded by the Investigators as a "GI disorder". After reviewing the narrative, it appears that the primary clinical presentation was **intense nausea and vomiting**. These are known AEs of opioids. It is noted that this patient may not have been taking the medication correctly. It is not clear how the medication was being divided but this could have contributed to GI effects. She did not withdraw from the study as a result of the AE.

2) Study OROS-ANA-3001; Patient 0103855; (OROS 8mg/day); Constipation

This 71-year-old female patient was treated with OROS hydromorphone 8 mg/day initiated on 3/19/2007. The underlying disease was lumbar syndrome. The concurrent conditions included: thyroid nodule, gastritis, helicobacter infection, sigmoid diverticulitis, blindness, vertigo, chronic pain, colon adenoma, fibromyalgia and prolapse of an intervertebral disc.

On (b) (6) the subject was hospitalized due to **severe constipation** which had been ongoing for two weeks. The subject also experienced nausea. A colonoscopy showed several small erythematous lesions and erosions of the sigmoid colon with no evidence of a tumor. The last full dose of study medication was received on 5/3/2007.

Reviewer's comment: Study drug was the likely/probable causality for this patient's severe constipation, a known opioid AE. The role of OROS technology is not definitive.

3) Study M03-644; Patient 0033008 (OROS 16 mg); Constipation; Terminated from study due to this SAE

This patient was a 74 year-old- man who was randomized to the 16 mg treatment arm and began treatment on 9/21/04 at 8 mg of OROS HM.

His significant PMH included kidney stones, CAD, CABG, GERD. His concomitant medications included ASA 81 mg, Aciphex, Colace, Fleet mineral oil, Golytely, Mg citrate, Metoprolol, Senokot and Zocor. He had been on Voltaren for OA pain. He did not have a history of opioid use.

Twenty-three days after starting study drug, he presented to the hospital with a three-day history of "**no bowel movement**" and dehydration. He was medically treated and symptoms improved within 24 hours. He experienced his first episode of constipation on (b) (6) (seven days after starting study drug), treated with laxative. He had "several additional" episodes of constipation in the week

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leading up to his hospitalization. He terminated from the study on 11/2/04 due to this SAE.

Reviewer's Comments: Likely/probable causality for constipation, a known opioid AE. The role of OROS technology in contributing to the constipation can not be excluded.

4) Study M03-644; Patient 0051011; (OROS 16 mg); Diverticulitis

Patient 51011, a 53-year-old Caucasian female, was enrolled in the double-blinded M03-644 study, randomized to OROS hydromorphone 16 mg and began treatment with OROS hydromorphone 8 mg on 12/23/2003 for the treatment of target joint pain from OA Grade II of the knee. The patient's medical history included hysterectomy, gastroesophageal reflux disease, colon cancer, and diverticulitis. In addition, the patient underwent a right hemicolectomy in April 2002 secondary to right colon carcinoma with partial bowel obstruction that revealed 4 positive nodes and was treated with 6 months of chemotherapy. Concomitant medications included Prevacid and Celebrex.

On (b) (6) days after starting OROS hydromorphone treatment), the patient experienced severe diverticulitis and severe constipation. The investigator assessed both events as probably related to study drug. The patient was admitted to the hospital and both events were classified as SAEs. Diverticulitis and constipation resolved on (b) (6). A CT scan of the abdomen/pelvis-KUB was negative. However, the results of the colonoscopy performed on (b) (6) revealed **diverticulosis** without evidence of inflammation, bleeding, or recurrent tumor.

Her final hospital diagnosis was recorded as severe constipation and diverticular disease of the sigmoid colon. On (b) (6), she was discharged home from the hospital.

The patient was withdrawn from the study on 3/8/2004 due to her past medical history of colon cancer found in review of the SAE. The last dose of study medication was also taken on 3/8/2004.

Reviewer's Comment: This patient had an extensive GI history. There is likely/probable causality for **constipation**. The role of study drug in the development of her diverticulosis can not be determined. The diverticulitis is unlikely causally related to study drug given this patient's significant past abdominal surgical history of hemicolectomy and past medical history of diverticulitis.

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Narratives Treatment-Related GI Specific SAEs (Uncontrolled Studies)

1) Patient DO-109-9995024 (OROS hydromorphone 40 mg); Abdominal pain upper, nausea

Patient DO-109-9995024, a 42-year-old Caucasian female, completed the DO-105 study and was enrolled into the DO-109 extension study on 11/10/1998. The patient continued treatment with OROS hydromorphone 32 mg daily for pain due to fibromyalgia. On 12/10/1998 the study drug dose was increased to 40 mg daily. The patient's relevant medical history included labile hypertension, irritable bowel syndrome, obesity (baseline height was 152 cm; weight was 91.9 kg), gastrointestinal (GI) distress with episodes of abdominal pain and nausea, and insomnia.

Concomitant medications included Accupril, Hydrochlorothiazide, and Dilaudid IR.

The patient was hospitalized twice after starting OROS hydromorphone treatment because of **stomach pain and nausea**. During the second hospitalization, an endoscopy revealed early-stage stomach ulcers (gastric ulcer). Barium swallow indicated slow draining bowel. Colonoscopy and computed tomography (CT) scan of the body were normal.

The events of stomach pain and nausea continued after the patient's discharge, but at a lower intensity, and eventually resolved upon discontinuation of the study drug. The patient received her last dose of OROS hydromorphone (40 mg) and completed the study on 11/18/1999.

Reviewer's comments: Multiple chronic GI problems confound the history and causality of study drug to this SAE. However, the fact that the symptoms resolved after discontinuation of study drug increases possibility/probability of causality to study drug.

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GI Obstruction

Table 51, below, shows that intestinal obstruction was reported in 6/2335 patients treated with hydromorphone ER. No patients treated with placebo experienced GI obstruction. All cases of obstruction occurred in the uncontrolled studies.

All of these cases were considered by this reviewer to be possibly causality related to study drug except for two (Patients 3604001 and 0000150). Patient 3604001 in Study DO-104 and Patient 0000150 in Study DO-118X have been discussed under Death Narratives. Patient 3604001 had insufficient information to determine causality of GI obstruction to study drug. Patient 0000150 had a SAE of fecaloma which was felt to be definitely related to study drug. The remaining 4 narratives for possible causality of study drug (OROS formulation) to GI obstruction are discussed below following Table 51.

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Table 51. Treatment-Emergent Gastrointestinal Obstructive Events during OROS Hydromorphone Treatment in Controlled and Uncontrolled Studies in Patients with Chronic Pain

STUDY Patient No. Age (y)/Sex/Race	Verbatim/MedDRA PT	OROS [®] HM Dose (Study Day Onset)	Intensity/ Relationship	Study Drug Action Taken	Relevant Medical History ^a
UNCONTROLLED STUDIES					
DO-104					
3604001 74/F/C	Gastric outlet obstruction/ Gastric outlet obstruction	128 mg/d (29)	Severe/ Unrelated	Terminated study drug and study	Gall bladder surgery, hysterectomy, ovarian cancer, GI ulcer, hiatal hernia.
DO-109					
2695005 44/F/C	Bezoar of stomach/ Bezoar	24 mg/d (19) ^b	Severe/ Possibly related	Dose reduced and tapered off; terminated study	Removal of ovarian cyst, oophorectomy, cholecystectomy, vagotomy, appendectomy, pyloroplasty, oversewing of perforated ulcer, antrectomy; history of alcohol abuse.
1595002 49/F/C	Small bowel obstruction/ Small intestinal obstruction	8 mg/d (34) ^b	Severe/ Not related	Dosing interrupted; completed study	Crohn's disease, chronic nausea, cervical radiculopathy, vomiting, diarrhea, loss of appetite.
2094001 91/M/C	Bowel obstruction/ Intestinal obstruction	40 mg/d (5) ^b	Severe/ Unrelated	Probably discontinued study drug for multiple events	Cholecystectomy, removal of 10 inches of colon, left inguinal hernia repair, lower abdominal tenderness, and urinary frequency. RLQ mass consistent with neoplasm identified on study.
DO-118X					
0000150 63/F/C	Fecal impaction/ Fecaloma	48 mg/d (52)	Severe/ Definitely related	None	Cholecystectomy, hysterectomy, pancreatic carcinoma, worsening constipation on study.
DO-127X					
0001117 69/F/C	Small bowel obstruction/ Small intestinal obstruction	16 mg/d (87)	Severe/ Related	Terminated study drug and study	Hiatal hernia, lower GI bleed, unsuccessful colonoscopy due to colon tortuosity, chronic constipation with chronic laxative abuse, hysterectomy with bilateral salpingo-oophorectomy.

^a Includes medical history and events that occurred on study.

^b For Study DO-109, study day onset reflects treatment duration from the start of the extension study and does not include treatment duration from the prior study.

Note: Controlled and uncontrolled studies included: DO-104, DO-105, DO-108, DO-109, DO-118, -118X, DO-119, DO-127, DO-127X, DO-132, M03-644-05, NMT 1077-301, and OROS-ANA-3001.

Note: No obstructive events were reported in any of the controlled studies.

C=Caucasian; d=day(s); F=female; GI=gastrointestinal; HM=hydromorphone; M=male; MedDRA=Medical Dictionary for Regulatory Activities; OROS[®]=oral osmotic drug delivery system; PT=preferred term; RLQ=right lower quadrant; y=years

Cross-reference: Relevant CSRs and associated narrative summaries

(Source: ISS, pages, 100 and 101)

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Narratives GI Obstruction

1) Study DO-104; Patient 3604001; (OROS hydromorphone 128 mg daily); Tumor Progression; Insufficient information to assign causality

Narrative reviewed under Death Narratives

2) Study DO-109; Patient 2695005; Oros hydromorphone 24 mg/day; Bezoar; Possible causality

This was a 44-year old female who completed Study DO-105 and was enrolled in to the DO-109 extension study.

Prior to enrollment in the DO-109 study, the patient's baseline relevant medical history included removal of a left ovarian cyst, oophorectomy, cholecystectomy, vagotomy, appendectomy, and pyloroplasty, oversewing of perforated ulcer and antrectomy, and insomnia. She also had a past history of alcohol abuse, kidney stones, mild chronic lung disease, and smoking (ongoing). Baseline medications included nortriptyline, Pamelor, Lorabid, and Neomycin eardrops for an ear infection.

On 5/11/1998 (43 days after starting OROS hydromorphone 24 mg/day in Study DO-105), the patient experienced reflux and intermittent vomiting. She was placed on Prilosec, for 3 days (5/11 to 5/14/1998) while receiving OROS hydromorphone 24 mg/day from 4/24/1998 to 5/21/1998.

On 6/12/1998, the patient had an abdominal X-ray performed (results unspecified). The patient went to her local doctor, and on an unspecified date and reportedly had an upper GI series that showed a **bezoar** in her stomach. A computed tomography (CT) scan, done on an unspecified date several weeks later, confirmed a persisting bezoar. The patient was referred to her gastroenterologist, who evaluated her on 6/15/1998, noting a history of a combination of regurgitation and vomiting for the last six months. An upper GI endoscopy was performed on 6/17/1998; findings included a normal esophagus, and a normal small bowel for 30 cm distal to anastomosis. Angulation was noted at the gastroenteric anastomosis; otherwise the anastomosis appeared normal, without mechanical obstruction. There was a large amount of retained food in the stomach, though no one solid piece of food. The endoscopist broke the collection of food into several small pieces. Due to the amount of food present in the stomach, all of the gastric mucosa could not be visualized. The endoscopy report made no mention of any retained fragment or whole OROS systems; no mention

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of a biopsy, or removal of any material from the stomach, and no mention of any specimens sent for pathologic examination.

The patient was tapered off study drug and received her last dose on 8/3/1998. Study drug was withdrawn due to the adverse event of bezoar of the stomach. The bezoar was ongoing at the time of the patient's early termination from the study.

The investigator assessed the bezoar event as severe in intensity and possibly related to study drug.

Reviewer's Comments: Inconclusive information regarding the contents of the bezoar to determine that it was a hydromorphone medication bezoar. However, using a conservative assignment, the role of OROS formulation can not be excluded and may have been a contributor to the bezoar formation.

3) Study DO-109; Patient 1595002; OROS Hydromorphone 8 mg/day; Small intestinal obstruction; Possible causality

This 49-year-old Caucasian female completed the DO-105 study and was enrolled into the DO-109 extension study on 7/30/1998. The patient continued treatment with OROS hydromorphone 8 mg daily for pain due to lumbar radiculopathy. Her relevant medical history included Crohn's disease, hypertension, chronic nausea, sinus headaches, cervical radiculopathy, vomiting, diarrhea, insomnia, loss of appetite and sciatica.

Concomitant medications included Premarin, Asacol, Zofran, Neurontin, Procardia, and Prilosec.

On 6/30/1998, while still enrolled in study DO-105, the patient experienced an exacerbation of nausea with vomiting requiring medical management, and an adjustment of the study drug from 16 to 8 mg daily was made on 7/3/1998. On 7/16/1998, the patient was restarted on OROS hydromorphone 8 mg daily, and nausea did not reoccur until 8/31/1998, when she suddenly developed nausea with projectile vomiting. On [REDACTED] (b) (6) days after starting study drug), she was diagnosed with a **small bowel obstruction**, and hospitalized for gastric decompression and medication adjustment. On [REDACTED] (b) (6), study drug was interrupted. On [REDACTED] (b) (6), the event resolved and she was discharged home. The investigator stated that the event was due to an exacerbation of the patient's pre-existing Crohn's disease and that the patient normally has several exacerbations each year which require hospitalization. On 9/7/1998, study drug was resumed, and on 12/11/1998, the patient took her last dose of study drug, 8 mg daily, due to a substantial pain improvement that no longer required pain medication. The

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investigator assessed the event as severe in intensity and unrelated to study drug.

Reviewer's Comment: Although this subject's medical history predisposes to GI problems, the development of small bowel obstruction while on study drug must be considered as being possibly related to study drug and particularly, the OROS technology.

4) Study DO-109; Patient 2094001 (OROS hydromorphone 40 mg); Bowel obstruction/Intestinal obstruction; Possible causality

Patient DO-109-2094001 had 2 SAEs which included deep vein thrombosis and intestinal obstruction. This patient was a 91-year-old Caucasian male who completed the DO-104 study (DO-104-2004001) and was enrolled into the DO-109 extension study on 1/22/1999. The patient continued treatment with OROS hydromorphone 40 mg daily for pain due to colon cancer. The patient's relevant medical history included hypothyroidism, cholecystectomy, removal of 10 inches of colon, left inguinal hernia repair, glaucoma, urinary frequency, left leg paralysis, and peripheral edema.

Concomitant medications included Synthroid, Lasix, Compazine and multivitamins.

On (b) (6) days after starting study drug), the day of rollover into the DO-109 extension study, the patient was hospitalized and received anticoagulation therapy for a DVT diagnosed on 1/21/1999. On 1/27/1999 (36 days after starting study drug), **bowel obstruction** was diagnosed. Computed tomography (CT) scan of the abdomen and pelvis revealed a small bowel obstruction likely secondary to an enlarging right lower quadrant mass which was consistent with neoplasm.

Reviewer's comment. In this patient with right lower quadrant (RLQ) mass and underlying colon cancer, it is not likely that study drug was the probable or likely cause of bowel obstruction. However, the role of study drug and OROS technology can not be excluded.

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**5) Study DO-118X; Patient 0000150; (Oros Hydromorphone 48 mg/day);
Fecaloma; Definite causality**

Patient 0150 narrative was reviewed under the Death Narratives section.

**6) Study DO-127X; Patient 0001117; (OROS Hydromorphone 16 mg/day);
Small bowel obstruction/Small intestinal obstruction; Possible causality**

Patient 0001117 was a 69-year-old Caucasian female who enrolled in study DO-127X on 8/25/2000. The patient was on OROS hydromorphone 24 mg/day for chronic low back pain secondary to facet arthropathy when she completed study DO-127. The dose was reduced to OROS hydromorphone 16 mg/day when she enrolled in study DO-127X due to adverse events of somnolence and dizziness. The patient's pertinent relevant medical history included hypertension, hyperlipidemia, coronary artery disease, silent heart attack, chronic angina, hiatal hernia, dizziness due to inner ear disturbance, osteoarthritis, lower GI bleed, unsuccessful colonoscopy due to colon tortuosity, chronic constipation with chronic laxative abuse, atopic allergy, hysterectomy with bilateral salpingo-oophorectomy, depression, and insomnia. She was on multiple baseline concomitant medications.

On [REDACTED] (b) (6) days after starting study drug), the patient presented to the emergency room complaining of one day of worsening diffuse constant cramping abdominal pain, nausea, vomiting, and anorexia. Abdominal X-rays revealed air-fluid levels and distended loops of small bowel. The patient was admitted and treated. Abdominal and pelvic computed tomography (CT) scan performed the following morning showed numerous sigmoid diverticula, but no evidence of diverticulitis. The patient was discharged on [REDACTED] (b) (6). No further information is available regarding the hospital course or follow-up after discharge. At the time of the event, the patient was taking OROS hydromorphone 16 mg/day. The investigator assessed **small intestinal obstruction** as severe in intensity and possibly related to study drug. Study drug was permanently withdrawn as a result of this event and the patient discontinued the study on 12/13/ 2000.

Reviewer's Comments: The role of study drug in the causality of intestinal obstruction can not be excluded with possible causality related to the OROS formulation.

II) GI Perforations

In addition to gastrointestinal (GI) obstructive events, bezoar formation has also been associated with GI perforation. Table 52 below summarizes those patients who experienced GI perforation events. As can be seen in the Table, there was one patient in a controlled study who experienced a GI perforation and three in uncontrolled studies. Of these four reported GI perforations, this reviewer determined that one was considered likely or probably related to study drug (Patient DO-1332-0203); two were possibly related (Patient 9405001 and Patient 0001118) and one (Patient 000102) had insufficient information in the narrative to assign causality. One patient (9405001) had an outcome of death due to sepsis and the narrative was discussed under the Death Narratives. Brief narratives for the GI perforation patients follow Table 52 below.

Table 52. Treatment-Emergent Gastrointestinal Perforation Events during OROS Hydromorphone Treatment in Controlled and Uncontrolled Studies in Patients with Chronic Pain

Study Patient No. Age (y)/Sex/Race	Verbatim/ MedDRA PT	OROS [®] HM Dose (Study day Onset)	Intensity/ Relationship	Study Drug Action Taken	Relevant Medical History ^a
CONTROLLED STUDIES					
DO-132					
0203 70/F/C	Severe abdominal pain/Abdominal pain (led to diagnosis of perforated sigmoid colon)	48 mg/d (25)	Severe/ Not related	Terminated study drug and study	Hysterectomy, obesity
UNCONTROLLED STUDIES					
DO-105					
9405001 40/F/C	Perforated ulcer-cecum/ Large intestine perforation (event led to death)	24 mg/d (12)	Severe/ Not related	Unchanged	Multifocal necrotizing pseudomembranous colitis that led to intra-abdominal sepsis
DO-127X					
000102 85/F/C	Perforated bowel/ no MedDRA term ^{b,c}	24 mg/d (207)	Severe/ Unrelated	Unchanged	Constipation, pseudomembranous colitis
0001118 51/F/C	Diverticulitis with perforated sigmoid colon/ large intestine perforation	24 mg/d (82)	Severe/ Related	Terminated study drug	Gastroparesis, rectal neuritis, sphincterotomy (anal) x2, fistula repair, constipation

(Source: ISS, p. 102 and 103)

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Narratives GI Perforation

1) Study DO-105; Patient 9405001; (OROS Hydromorphone 24 mg/day); Perforated ulcer-cecum/Large intestine perforation; Possible causality

Reviewer's Comment: Narrative discussed under Death Narratives

2) Study DO-132; Patient DO 132-0203 (OROS hydromorphone 48 mg/day); Severe abdominal pain/Perforated Sigmoid Colon; Probable causality

Patient DO-132-0203, a 70-year-old Caucasian woman, was enrolled in study DO-132 on 8/29/2000. She began treatment on 9/1/2000 with OROS hydromorphone, 8 mg daily, for pain due to severe right knee osteoarthritis. Her baseline medical history included hysterectomy, right benign breast biopsy, right rotator cuff repair, bilateral cataract surgery, hypertension, hyperlipidemia, migraine headaches, and depression. Her baseline physical examination was significant for a subumbilical scar and obesity (body mass index was 38.2 kg/m²) with height/weight of 154.9 cm /91.6 kg, respectively. Baseline concomitant medications included Rofecoxib, Premarin, Fluoxetine, Diltiazem, Simvastatin, and Sumatriptan.

On (b) (6) days after starting study drug), the patient presented to the emergency room with severe abdominal pain. Chest and abdominal X-rays were performed, and free air was identified in the abdominal cavity. The patient was taken to the operating room, where laparotomy revealed a **perforated sigmoid colon**. A colon resection with temporary colostomy was performed. The investigator assessed the event as severe in intensity and unlikely to be related to study drug. The patient was discontinued from the study prematurely due to the SAE of severe abdominal pain. Her last dose of study drug, 48 mg OROS hydromorphone, was taken on 9/24/2000. As of 9/29/2000, the SAE was assessed by the investigator as resolving but no resolution date was provided. On 10/2/2000, the patient was seen for follow-up, and reportedly was doing well. No additional information or clinically relevant laboratory values were provided.

Reviewer's comment: Likely or probable causality given that the patient was on study drug at the time of the SAE. Aside from a prior hysterectomy, there did not appear to be other significant GI risk factors.

3) Study DO-127X; Patient 11-1118 (OROS hydromorphone 32 mg/day); Diverticulitis with perforated sigmoid colon; Possible causality

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Patient DO-127X-11-1118 was a 51-year-old Caucasian female, who was enrolled in study DO-127X on 9/23/2000. The patient was on OROS hydromorphone 32 mg/day for chronic low back pain due to ankylosing spondylitis when she completed the DO-127 study, and was continued at the same dose when she enrolled in study DO-127X. The patient's relevant medical history included gastroparesis, chronic migraine headaches, rectal neuritis, mitral valve prolapse, sphincterotomy (anal) x 2, fistula repair, stress incontinence, constipation, knee arthritis, and allergies.

Baseline concomitant medications included Cleocin, Dilaudid, Gabitril, Trileptal, Domperidone, and Guaifenes.

On (b) (6) days after starting study drug), the patient was hospitalized for a scheduled coccygectomy for the treatment of coccydynia and chronic rectal neuritis. No information is available regarding the surgical procedure, perioperative hospital course, or postoperative follow-up. At the time of the event, the patient was taking OROS hydromorphone 32 mg/day; however, the specific time/day of her last dose of study drug prior to event onset is not known. Study drug was not changed as a result of this event. On 10/28/2000, the OROS hydromorphone dose was decreased from 32 to 24 mg/day. The reason for the dose reduction was not given.

On (b) (6) days after starting study drug), the patient presented to the emergency room complaining of 1 day of worsening sharp left lower quadrant abdominal pain not relieved with Fleets enema, associated with one episode of vomiting. Abdominal computed tomography (CT) scan confirmed the diagnosis of **perforated viscus**, most probably sigmoid colon.

The patient was admitted and on (b) (6) underwent a sigmoid resection with end-colostomy and Hartmann's pouch procedure. She reportedly recovered well and was discharged on (b) (6). At the time of these events, the patient was taking OROS hydromorphone 24 mg/day; however, the specific time/date of last dose prior to the onset of the event is unknown. Study drug was permanently withdrawn as a result of these events. The patient was discontinued from study on 2/7/2001.

Reviewer's comments: Possible causality to study drug since the patient was taking study drug at the time and the GI events may be related to the OROS formulation.

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4) Study DO-127; Patient 000102; (OROS hydromorphone 32 mg/day); perforated bowel; Insufficient information to assign causality

Patient DO-127-01-0102, an 85-year-old-Caucasian female, was enrolled in study DO-127 on 12/9/1999 and converted directly from her prior Dilaudid regimen to OROS hydromorphone 32 mg/day for chronic low back pain due to spinal stenosis. She was enrolled in study DO-127X on 1/27/2000 with a dose of OROS hydromorphone 24 mg/day. The patient's relevant medical history included diabetes mellitus type II, edema, stomach upset, hypertension, osteoporosis, cramps, sick sinus syndrome, osteoarthritis, rheumatoid arthritis, adrenal insufficiency, depression, constipation and cholecystectomy. Baseline concomitant medications during Study DO-127 included Dilaudid, Neurontin, Lasix, Cardura, Lanoxin, Imdur, Prednisone, Glucotrol, Pepcid, Zoloff, K-Dur, Os-Cal, and a stool softener. In addition, during study DO-127X, the patient's concomitant medications included Augmentin, Cipro, Pepcid, Prilosec, Immodium, and Metamucil.

On (b) (6) days after starting study drug), the patient developed fever and symptoms of respiratory infection (SAE) and presented to the emergency room. No further information is available regarding her hospital course or treatment provided. The respiratory tract infection resolved (b) (6) days later on (b) (6). At the time of the event, the patient was taking OROS hydromorphone 32 mg/day. Study drug dose was not changed as a result of this event.

On (b) (6) days after starting study drug), the patient presented to the emergency room for chest pain (SAE). The event resolved the following day, on 8/4/2000. On 8/5/2000, the investigator noted on the AE CRF that study drug was permanently withdrawn as a result of the SAE of chest pain. However, the study drug administration CRF for Visit 6 indicated that study drug was stopped on (b) (6) (almost (b) (6) month prior to the onset of chest pain). The patient was terminated early from the study due to the SAE of chest pain.

Since the patient did not return for her final visit, it cannot be confirmed that she was switched to another opioid regimen after she discontinued OROS hydromorphone or if any withdrawal symptoms were experienced.

On (b) (6) days after starting study drug and (b) (6) days after discontinuing drug) the patient was readmitted to the hospital for dehydration secondary to intractable diarrhea (SAE). The patient was not on OROS hydromorphone when this SAE occurred. The investigator assessed diarrhea as severe in intensity and unlikely related to study drug. The diarrhea was presumed secondary to pseudomembranous colitis, a complication of recent antibiotic therapy. The

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antibiotic therapy was presumably for perforated bowel (possible SAE, not previously reported). Diarrhea resolved on 8/28/2000.

On an unspecified date, the patient experienced **perforated bowel**. A hospital discharge summary dated [REDACTED] ^{(b) (6)}, which summarizes the inpatient course for diarrhea stated that the patient's pertinent history included perforated bowel that was treated with antibiotics, and the return to the hospital this time was precipitated by pseudomembranous colitis secondary to antibiotics therapy suggesting that there may have been a recent prior hospitalization for perforated bowel treatment. The study sponsor received no reports of perforated bowel as either an adverse event or serious adverse event. No assessment of the possible relationship between study drug and the event of perforated bowel was provided. No further information was available.

Reviewer's comments: The narrative does not provide details regarding the date of onset of perforated bowel and may not have been on study drug at the time of onset. As a result, there is insufficient information in the narrative to assign causality.

OROS Technology Summary:

- The use of the OROS technology formulation appeared to result in similar risks in terms of gastrointestinal obstruction and bezoar formation as other marketed OROS formulation products.
- The patients presented with nonspecific symptoms of nausea, vomiting, early satiety, abdominal pain and weight loss.
- Five of the six patients with GI obstruction had a history of prior abdominal surgery; one of the six had Crohn's disease.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The Applicant reported that the overall AE incidence with hydromorphone ER was 80.5% (1880/2335 patients) in all controlled and uncontrolled studies in patients with chronic pain. Trends were noted as follows:

- Opioid-related AEs were the most common (incidence $\geq 10\%$)
 - GI related (constipation, nausea, and vomiting)
 - CNS related (somnolence, dizziness and headache)
- Most AEs were mild to moderate in severity
- AEs were generally higher in older (≥ 65 years), female and opioid naive

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Table 53 below provides data on the adverse event incidence in $\geq 10\%$ in the OROS hydromorphone group by MedDRA System Organ Class. GI disorders represents the highest percentage at 55.4% of patients who experienced AEs in the controlled and uncontrolled studies.

Table 53. Adverse Events Reported in $\geq 10\%$ of Patients by System Organ Class (All Patients with Chronic Pain Treated with OROS Hydromorphone in Controlled and Uncontrolled Studies)

MedDRA System Organ Class	OROS [®] Hydromorphone N=2335 n (%)
Gastrointestinal disorders	1294 (55.4%)
Nervous system disorders	909 (38.9%)
General disorders and administration site conditions	608 (26.0%)
Infections and infestations	513 (22.0%)
Psychiatric disorders	471 (20.2%)
Skin and subcutaneous tissue disorders	446 (19.1%)
Musculoskeletal and connective tissue disorders	387 (16.6%)
Respiratory, thoracic, and mediastinal disorders	257 (11.0%)

Note: Controlled and uncontrolled studies included: DO-104, DO-105, DO-108, DO-109, DO-118, DO-118X, DO-119, DO-127, DO-127X, DO-132, M03-644-05, NMT 1077-301, and OROS-ANA-3001.

Note: A patient may have been reported in more than one MEDRA version 11.1 System Organ Classification.

(Source: ISS, p. 111)

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Similarly, treatment-related adverse events were also most frequently GI (opioid) related as shown in Table 54 below.

Table 54. Treatment-related Adverse Events Reported in \geq 1% of All Patients with Chronic Pain Treated with Hydromorphone ER in Controlled and Uncontrolled Studies

MedDRA Preferred Term	OROS [®] Hydromorphone N=2335 n (%)
Any related AE	1505 (64.5%)
Constipation	674 (28.9%)
Nausea	529 (22.7%)
Somnolence	303 (13.0%)
Vomiting	215 (9.2%)
Dizziness	201 (8.6%)
Headache	173 (7.4%)
Pruritus	147 (6.3%)
Fatigue	146 (6.3%)
Hyperhidrosis	114 (4.9%)
Dry mouth	98 (4.2%)
Insomnia	86 (3.7%)
Diarrhoea	70 (3.0%)
Anorexia	49 (2.1%)
Drug withdrawal syndrome	47 (2.0%)
Anxiety	42 (1.8%)
Sedation	40 (1.7%)
Decreased appetite	36 (1.5%)
Confusional state	33 (1.4%)
Oedema peripheral	30 (1.3%)
Lethargy	29 (1.2%)
Rash	29 (1.2%)
Tremor	26 (1.1%)
Dyspepsia	26 (1.1%)
Vertigo	24 (1.0%)
Vision blurred	25 (1.1%)
Abdominal pain	24 (1.0%)
Hot flush	24 (1.0%)
Asthenia	24 (1.0%)
Depression	23 (1.0%)
Abdominal pain upper	23 (1.0%)

Note: Controlled and uncontrolled studies included: DO-104, DO-105, DO-108, DO-109, DO-118, DO-118X, DO-119, DO-127, DO-127X, DO-132, M03-644-05, NMT 1077-301, and OROS-ANA-3001.

Note: Adverse events considered related include categories of definite, possible, possibly related, probable, probably related, and unknown relationship.

Note: A patient may have been reported in more than one MedDRA version 11.1 System Organ Classification.

AE=adverse event; ISS=Integrated Summary of Safety; MedDRA=Medical Dictionary for Regulatory Activities; OROS[®]=oral osmotic drug delivery system

(Source: ISS p. 79)

Reviewer's Comments: The common AEs seen in Exalgo-treated patients appear to be consistent with the opioid-class of drug.

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7.4.2 Laboratory Findings

The Applicant reported that Controlled Studies DO-118, M03-644-05 and NMT 1077-301 had clinical laboratory testing (hematology, chemistry and urinalysis) at scheduled intervals per protocol throughout these studies. They further reported that because of the clinical experience with hydromorphone, routine clinical laboratory measures were assessed only at Screening or as required to follow up on AEs in all other studies.

The Applicant provided data on laboratory testing for the studies. Laboratory related AEs included anemia, hypercalcemia, neutropenia and hypokalemia. However, these findings were noted in the cancer study population.

In the 2 placebo controlled studies (NMT 1077-301 and M03-644-05) there were similar changes in laboratory values between the treated and placebo. No trends could be identified and clinical laboratory abnormality as a cause for AE occurred infrequently.

In the Phase I healthy population no trends in laboratory findings could be identified in patients treated with OROS hydromorphone.

7.4.3 Vital Signs

Vital signs (blood pressure, heart rate and respiratory rate) were measured in all studies except DO-118 and DO-118X. Respiratory rate was not collected in Study M03-644-05. Time points for data collection varied. Overall, there was no pattern of clinically significant changes in vital signs seen in patients treated with OROS hydromorphone.

Study C-2004-022 (Abuse Liability) reported 8 patients with decreased oxygen saturation (mild) onset 15-28 hours after dosing.

Study DO-130 (acute postop pain) was stopped prematurely because of the number of patients who experienced adverse events of decreased oxygen saturation (11 patients total with 4 in the 8 mg group; 4 in the 16mg group and 3 in the 32 mg group). None of those patients had an oxygen saturation level less than 91% at any time point after dosing. At the time the study was halted, 50 of the 60 patients had been enrolled. The protocol criteria considered decreased oxygenation as less than 94%. This was a post-op population who were also receiving other medications which could have contributed to hypoxemia.

Reviewer's comment: Opioids are known to cause respiratory depression. The patients who experienced decreased oxygenation is not unexpected.

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7.4.4 Electrocardiograms (ECGs)

The Applicant conducted no special QT studies. T wave abnormality was noted in one patient of all treated patients. There were no patterns in the abnormal ECGs.

Study C-2004-022 reported 2 patients with ventricular tachycardia which resolved; Study DO-130 reported 4 patients with tachycardia.

No trends in ECG abnormalities were noted in the studies reviewed.

7.4.5 Special Safety Studies/Clinical Trials

1) Alcohol Interaction Study (Protocol C-2005-020)

This study is reviewed fully by Dr. Wei Qiu, Clinical Pharmacology. A brief summary of the key features is as follows:

Title: Effect of Alcohol on the Pharmacokinetics of OROS Hydromorphone in Healthy Subjects

Design: 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).

Methods: 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. Subjects received one 16 mg OROS hydromorphone tablet orally.

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.

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)

Results: as shown below in Table 55 with discussion to follow.

Table 55. PK Results of Exalgo-Alcohol Interaction Study, Fasted State

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				

(Source: Final Study Report, p. 6)

Applicant's Alcohol Interaction Safety Results Summary:

- No SAEs or severe AEs were reported, and no subjects discontinued from the study because of AEs.
- In both the fasted and the fed groups, more AEs were reported with the higher dose of alcohol than with the lower doses.
- The most commonly reported AEs were vomiting and nausea. changes in clinical laboratory values, vital sign values, physical examination results, or ECG findings during the study.

Applicant's Alcohol Interaction Conclusions:

- Plasma hydromorphone concentrations rose slowly following dosing in all 4 treatments in both fed and fasted groups.
- Median Tmax values were between 12 and 16 hours, and the ranges of Tmax values generally were similar for all treatments in each group.
- In the fasted state, mean Cmax values in the 3 alcohol treatments were higher than the corresponding value in the 0% alcohol treatment
- In the fed state, plasma hydromorphone concentration profiles were similar for the 4 treatments
- The maximal increase in Cmax 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.

Reviewer's comments: The results of the Exalgo- alcohol interaction study indicate that the controlled-release property of the formulation is maintained in the presence of alcohol and that there is no dose dumping.

II) Abuse Liability Study (Protocol C-2004-022)

This study is reviewed fully by Dr. John Gong (CSS). A brief summary of the key features of the study are as follows:

Title: Study to Evaluate the Abuse Potential of OROS Hydromorphone Compared to Hydromorphone Immediate Release (IR) in Opiate-Experienced Non-dependent Volunteers

Primary Objective: 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.

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Secondary Objective: To evaluate the pharmacokinetic/pharmacodynamic relationship of hydromorphone IR and OROS hydromorphone on measures of abuse potential

Methods: 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

Subjects were screened for their ability to perceive a single dose of hydromorphone IR 8 mg as being active and distinct from placebo. A visual analog scale (VAS) for drug liking was administered at various time points and vital signs and oxygen (O₂) 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:

- *Phase A* subjects received single doses of OROS hydromorphone (16 mg, 32 mg, 8 mg crushed), hydromorphone 8 mg IR (active control), and placebo. If clinically stable, patients moved to Phase B
- *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.

Results: For the Abuse potential subscale on the Cole/ARCI (Stimulation-euphoria and Abuse potential), there were no significant differences between hydromorphone 8 mg IR and all 3 OROS hydromorphone doses. There were also no significant differences between the 3 doses. The safety data from this study is included in the safety review section.

Reviewer's comments: See page 7 of this review

7.4.6 Immunogenicity

This product does not raise concerns regarding immunogenicity

7.5 Other Safety Explorations

Events Related to Histamine Response

Pruritus was reported by 7.8% (183/2335) of the patients treated with OROS hydromorphone and by 1.7% (8/466) of the patients treated with placebo. Pruritus generalized was reported by 0.6% (14/2335) of the patients treated with OROS hydromorphone and none of the patients treated with placebo. Pruritus allergic was reported by 0.04% (1/2335) of the patients treated with OROS hydromorphone and none of the patients treated with placebo.

Urticaria was reported by 0.4% (9/2335) of the patients treated with OROS hydromorphone and none of the patients treated with placebo.

No event of anaphylaxis, anaphylactic reaction, drug rash with eosinophilia and systemic symptoms, or rash pruritic was reported by any patient treated with OROS hydromorphone or placebo in the controlled and uncontrolled study pool

7.5.1 Dose Dependency for Adverse Events

The Applicant reported that the overall incidence of treatment-related AEs (as determined by the Investigators) was 1505/2335 (64.5%) for those receiving study drug.

The incidence of AEs was highest at the >128 mg per day dose level (51/82). Very common opioid-related AEs of moderate-to-severe intensity at the >128 mg per day dose level were vomiting (18 patients), constipation (17 patients), nausea (15 patients), somnolence (10 patients) and headache (9 patients). The 8 mg per day group had the highest incidence of treatment-related constipation (285), nausea (236), and dizziness (87). The >128 mg per day group (n=82 patients) had the highest incidence of treatment-related vomiting (9 patients) somnolence (12 patients) and headache (6 patients). Table 56 presents a summary of the findings.

Table 56. Summary of All AEs by OROS Hydromorphone Dose in the Double-blind Phase (Randomized Population) Study NMT-1077-301

Evaluation ^a	OROS [®] Hydromorphone							All OROS [®]	
	12 mg N=11 ^b	16 mg N=15	24 mg N=18	32 mg N=25	40 mg N=16	48 mg N=22	64 mg N=27	Hydromorphone N=134	Placebo N=134
Patients with adverse events, n (%)	2 (18.2)	6 (40.0)	10 (55.6)	15 (60.0)	7 (43.8)	10 (45.5)	15 (55.6)	64 (47.8)	73 (54.5)
Patients with serious adverse events, n (%)	0	1 (6.7)	1 (5.6)	1 (4.0)	0	2 (9.1)	2 (7.4)	7 (5.2)	3 (2.2)
Patients who discontinued due to adverse events ^c , n (%)	0	0	0	1 (4.0)	0	1 (4.5)	5 (18.5)	7 (5.2)	3 (2.2)
Adverse events, n	6	27	39	73	15	47	58	265	286
Deaths, n (%)	0	0	0	0	0	0	0	0	0

^aAdverse events are counted at the dose of onset of the adverse event or at the dose the adverse event increased in intensity.

^bN is number of patients who were exposed to that dose.

^cEach occurrence of an adverse event is counted, e.g. multiple occurrences of the same adverse event within 1 patient are counted as multiple adverse events.

(Source: Clinical Study Report NMT 1077-301, p. 118)

7.5.2 Time Dependency for Adverse Events

The Applicant reported no relationship between dose at onset and incidence of the most common AEs. There was a general trend that the higher dosages (40 mg/day to > 128 mg/day) had a higher percentage of patients with at least one AE than the lower dosages (8 mg/day to 32 mg/day).

7.5.3 Drug-Demographic Interactions

- **Age:** Patients ≥65 but <75 years of age represented 16.2% of treated patients. The incidence of AEs was higher in patients ≥65 years of age, as shown in Table 57 below.

Table 57. Adverse Events Reported in ≥5% of Patients by Dichotomous Age in Controlled and Uncontrolled Studies

Preferred Term	<65 years N=1824 n (%)	≥65 years N=511 n (%)
Any AE	1455 (79.8%)	454 (88.8%)
Constipation	476 (26.1%)	226 (44.2%)
Nausea	473 (25.9%)	169 (33.1%)
Vomiting	248 (13.6%)	74 (14.5%)
Somnolence	232 (12.7%)	90 (17.6%)
Headache	250 (13.7%)	50 (9.8%)
Dizziness	174 (9.5%)	73 (14.3%)
Diarrhoea	136 (7.5%)	58 (11.4%)
Fatigue	138 (7.6%)	52 (10.2%)
Pruritus	145 (7.9%)	38 (7.4%)
Insomnia	126 (6.9%)	32 (6.3%)
Hyperhidrosis	100 (5.5%)	36 (7.0%)
Oedema peripheral	95 (5.2%)	37 (7.2%)
Dry mouth	84 (4.6%)	26 (5.1%)
Anxiety	68 (3.7%)	27 (5.3%)

Note: Controlled and uncontrolled studies included: DO-104, DO-105, DO-108, DO-109, DO-118, DO-118X, DO-119, DO-127, DO-127X, DO-132, M03-644-05, NMT 1077-301, and OROS-ANA-3001.

(Source: ISS, p. 172)

- **Race:** There were no safety patterns noted. However, there was a small sample size for all races other than Caucasian (Caucasian, n =2123; Black n=147; Asian, n=14, Other, n=51).
- **Gender:** Overall, there was a higher incidence of females than males in the studies. Overall, AEs, occurred more frequently in females (83.8%) than males (76.4%). At the preferred term level of AE of nausea occurred almost twice as frequently in females (34.3%) as in males (19.0%) and vomiting (18.1%) to 8.5% respectively. The only AE which occurred more frequently in males was hyperhidrosis. The clinical significance of this is unclear. Table 58 below denotes the AEs by gender.

Table 58. Adverse Events Reported in ≥5% of Patients by Gender in Controlled and Uncontrolled Studies

Preferred Term	Male Patients N=1040 n (%)	Female Patients N=1295 n (%)
Any AE	795 (76.4%)	1085 (83.8%)
Nausea	198 (19.0%)	444 (34.3%)
Constipation	278 (26.7%)	424 (32.7%)
Vomiting	88 (8.5%)	234 (18.1%)
Somnolence	112 (10.8%)	210 (16.2%)
Headache	108 (10.4%)	192 (14.8%)
Dizziness	86 (8.3%)	161 (12.4%)
Pruritus	54 (5.2%)	129 (10.0%)
Diarrhoea	69 (6.6%)	125 (9.7%)
Fatigue	73 (7.0%)	117 (9.0%)
Insomnia	77 (7.4%)	81 (6.3%)
Hyperhidrosis	61 (5.9%)	75 (5.8%)
Oedema peripheral	39 (3.8%)	93 (7.2%)

Note: Controlled and uncontrolled studies included DO-104, DO-105, DO-108, DO-109, DO-118, DO-118X, DO-119, DO-127, DO-127X, DO-132, M03-644-05, NMT 1077-301, and OROS-ANA-3001.

(Source: ISS, p. 174)

7.5.4 Drug-Disease Interactions

The Applicant reported that of the 2,335 patients who received OROS hydromorphone, renal function was impaired in five and renal function status was unknown in 314. Hepatic function was impaired in 19 and hepatic status unknown in 314.

Studies DO-121 and DO-122 were Phase 1, PK studies of immediate release hydromorphone in normal, moderate and severe renal impairment and normal and moderate hepatic impairment, respectively.

The PK findings in the mild- to-moderate renal and hepatic impaired suggests that dose adjustments may be required. In the severe renal and hepatic impaired, an increased dosing interval should be considered and these patients should be monitored during maintenance therapy for development of opioid-related adverse events.

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7.5.5 Drug-Drug Interactions

The Applicant reported that there were no specific clinical studies performed to specifically address drug-drug interactions. Using what is known about the opioid class of drugs, the Applicant has proposed labeling for precautions and warnings regarding potential drug interactions with monoamine oxidase inhibitors (MAOIs), CNS depressants, and CYP isoenzymes.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

As part of the special protocol assessment agreement for the key efficacy study (NMT 1077-301), the Agency agreed that the carcinogenicity studies needed to be ongoing at the time of submission. The Applicant reported that rat and mouse carcinogenicity studies were initiated on March 18, 2009 and March 24, 2009, respectively.

7.6.2 Human Reproduction and Pregnancy Data

No specific studies were carried out to assess this safety category. The Applicant plans to rely on what is known regarding labeling for opioids as a class.

7.6.3 Pediatrics and Assessment of Effects on Growth

No event of pediatric exposure was reported in the submission.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdosage

There were 8 patients who received OROS hydromorphone who experienced SAEs related to overdosage (8/2335) or 0.3% and none in placebo. No patient in study NMT 301 experienced an overdose. One patient in study NMT 1077-302 experienced a fatal, presumably intentional overdose. That patient is not included in this submission as the study is ongoing. Seven of the patients recovered and one had an outcome as ongoing.

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Drug Abuse Potential

All opioids have the potential for abuse. Refer to CSS review for further discussion.

Adverse Events Related to Opioid Withdrawal and Rebound

In the controlled and uncontrolled study pool, drug withdrawal syndrome was reported by 2.4% (55/2335) of patients treated with OROS hydromorphone and by 3.4% (16/466) of patients treated with placebo. In the controlled studies, drug withdrawal syndrome was reported by 2.5% (40/1572). It is noted that drug withdrawal syndrome was reported by 16/466 (3.4%) of patients receiving study drug during any controlled or uncontrolled study and 27/1108 (2.4%) of patients receiving any other treatments. In controlled studies, 6 patients discontinued due to opioid withdrawal (0.4%). Drug withdrawal syndrome was seen in 35/1572 (2.2%) patients treated with OROS in the controlled studies and determined to be a treatment-related AE.

Study NMT 1077-301 was the only study with a randomized withdrawal design. During the first phase of this study (Conversion and Titration), patients were converted from their prior opioid to OROS hydromorphone and then titrated until they reached a stable dose. Patients were then randomized, in the Double-blind phase, to continue on their stable dose of OROS hydromorphone or to be tapered down until they were taking only placebo for the remaining 10 weeks. Three patients in the Conversion/Titration phase discontinued due to opioid withdrawal symptoms.

During the Double-blind phase, the incidence of AEs classified by the Investigators as drug withdrawal syndrome was 11.9% in the placebo group and 9.7% in the OROS hydromorphone group. Three patients in the OROS hydromorphone group and 7 in the placebo group were discontinued for this reason.

Given the clinical difficulty distinguishing opioid withdrawal syndrome from opioid-related AEs of nausea, vomiting, diarrhea, insomnia and muscle aches, the Investigators were instructed to follow the DSM-IV criteria for the determination of opioid withdrawal syndrome and to evaluate the change on the Clinical Opiate Withdrawal Scale (COWS) and Subjective Opiate Withdrawal Scale (SOWS) scores from Baseline to the onset of the events.

Data regarding the COWS and SOWS was provided by visit and dosage during the OL Conversion and Titration phase and double-blind, randomized phase of Study NMT 1077-301. These were reviewed. During the Conversion and

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Titration phase of the study, the mean (\pm SD) COWS score at the first Conversion and Titration visit was 0.9 (\pm 1.49) and declined to 0.4(\pm 1.24) at Visit 5. The mean SOWS score at the first Conversion and Titration visit was 5.3 (\pm 6.13), and decreased to 2.6 (\pm 3.75) at Visit 5. Similar decreases were seen in patients receiving each of the seven possible starting dosages of OROS hydromorphone.

During the Double-blind phase, placebo-treated patients showed a slightly higher increase in mean (\pm SD) COWS scores, 1.0 (\pm 3.07), than OROS hydromorphone-treated patients, 0.4 (\pm 1.72), over the 12-week treatment period. Similar results were seen on the SOWS; placebo treated patients showed a mean (\pm SD) increase of 2.9 (\pm 6.75) on this scale, and OROS hydromorphone-treated patients showed an increase of 1.1 (\pm 5.36).

7.7 Additional Submissions / Safety Issues

8 Postmarket Experience

The Applicant reported that they performed an analysis of a compilation and assessment of the AE cases received from December 22, 2004 to December 31, 2008 for Jurnesta. The Applicant reported that approximately (b) (4) tablets of OROS hydromorphone were sold or distributed with an estimated exposure of approximately the same number (since this is a daily tablet).

Individual reviews for all cases with a fatal outcome and cases that met the criteria for classification as serious and unlisted were presented in the submission. Non-serious listed AE cases were also included by the Applicant in the submission and were reviewed by this reviewer.

The Applicant conducted a search of the BRM post-marketing safety database from December 22, 2004 through December 31, 2008 showed a total of 147 medically confirmed cases (10 follow-up) reporting 238 serious unlisted, serious listed, or non-serious unlisted AEs.

These cases were received from a variety of sources, and the events were classified as the following: spontaneous/regulatory AEs (182), post-marketing clinical study studies AEs (52), and AEs from solicited cases (4). Five cases had a fatal outcome.

In addition, 192 medically confirmed cases (4 follow-up) reporting 329 non-serious listed AEs were received. Each of these events was classified by the Applicant as spontaneous/regulatory.

Serious Adverse Events

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A total of 170 events met the definition of an SAE. Of the 170 SAEs, 121 were listed according to the reference safety information and 49 were unlisted. The highest proportion of SAEs (20%) was from the Psychiatric Disorders SOC. The majority of the SAEs within this SOC were suicidal ideation and depression (both 18%), followed by hallucination (15%). The second highest proportion of events (15%) was from the Gastrointestinal Disorders SOC and the third highest proportion of events (14%) was from the General Disorders and Administration Site Conditions SOC.

The narratives for the SAEs were reviewed. Most of the cases had confounding medical variables which made it impossible to assign causality to OROS hydromorphone.

Suicide Ideation: There were 3 cases of suicidal ideation. These narratives were reviewed. The information provided in the narratives was incomplete in some cases. The role of study drug could not be excluded but neither was there evidence to support probable causality.

Suicide Attempt : Patient DE-JNJFOC-2007080462 was a reported case in which 20 doses of OROS HM (strength not specified) was taken in a 45 year old male with weight of 75 kg. In addition to the study drug, the patient took hydromorphone IR and a combination of oxycodone and naloxone. The patient experienced sleepiness. Final outcome was not reported.

Drug-Drug Interaction: There were 3 cases in which OROS was probably the cause of SAEs due to drug-drug interaction as follows: Phenprocoumon resulting in fluctuating prothrombin time; Pregabalin resulting in loss of field vision (tunnel vision) and Metamizole/Metoclopramide resulting in nausea and panic attack. Review of these narratives was inconclusive that study drug was the causal factor.

Cases with Fatal Outcome

Of the total number of patients exposed to OROS hydromorphone, 5 experienced a fatal outcome during this reporting period. For these 5 cases, respiratory failure (3) and accidental overdose (2) were the most frequently reported events; 2 patients experienced both events. In addition, 1 patient experienced an intentional overdose of OROS hydromorphone.

The narratives for these patients were reviewed and are consistent with the Applicant's reports. No new safety information pertaining to Exalgo was found.

Non-Serious Listed Adverse Events

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A total of 192 non-serious cases (4 follow-up) reporting 329 non-serious listed AEs (13 follow-up) were recorded in the Applicant's postmarketing safety database.

The highest proportion of events (30%) was from General Disorders and Administrative Site Conditions SOC with the breakdown as follows: drug ineffective (41%); pain (11%) and fatigue (9%). Next most frequently occurring SOC was from the GI disorders (23%) followed by Nervous System Disorder (10%).

Other Significant Adverse Events

Abuse/ Misuse

Two cases of abuse were reported and eleven cases of misuse by tablet manipulation was reported (9 cases in which the tablet was split, crushed or pulverized and 2 cases where the tablet was chewed).

Drug Withdrawal Syndrome

There were 10 medically confirmed and 9 non-medically confirmed spontaneous cases of Withdrawal syndrome involving OROS hydromorphone. In addition, there were 3 non-serious medically confirmed spontaneous cases (all listed) and 4 serious medically confirmed cases (1 spontaneous and 3 study) of Drug withdrawal syndrome (2 listed, 2 unlisted). The narratives were provided for the 10 cases which contained sufficient information for a medical assessment. These narratives were reviewed.

Reviewer's comments: No patterns could be identified with regard to drug withdrawal syndrome development. This is a known risk with opioids. Patients should be educated and monitored for symptoms of withdrawal while on the drug.

Gastrointestinal

Postmarketing data did not report any cases of bezoars (except for the previously discussed case in a clinical study).

There was one case (CA-JNJFOC-20040607109) of a 42 year old female who experienced severe abdominal pain, nausea and vomiting. A barium swallow showed a "slow-draining" bowel. The patient had 1 year history prior to taking OROS of crampy, abdominal pain. The patient recovered when the OROS was discontinued.

9 Appendices

9.1 Literature Review/References

The Applicant provided a data review of 31 publications reporting safety results of OROS hydromorphone from December 22,2004 through December 31,2008. A review of those abstracts by this reviewer revealed no new safety data.

9.2 Labeling Recommendations

The labeling review is still ongoing by the Division. The proprietary name is being reviewed by DMEPA. The warnings and precautions will be consistent with the class of other opioids with the distinction that OROS hydromorphone is to be used in opioid-tolerant patients only.

9.3 Advisory Committee Meeting

On September 23, 2009, a Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee meeting was held to discuss NDA 21-217 with the following specific questions asked of the Committees:

1. Discuss where Exalgo lies in the spectrum of risk for abuse, including abuse-related overdose and death, compared to other opioid drug products.
2. Based on your assessment of the risk associated with abuse of Exalgo, discuss which of the following options would be appropriate for risk management:
 - a. A program similar to Onsolis, including registration for physicians and patients
 - b. An opioid class-like program, including physician education and registration, but no patient registry and, in the short term, an interim REMS pending the larger opioid class program as was done with Embeda
 - c. A unique program

There was considerable discussion with the Committees' overall recommendations as follows:

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1. Exalgo is an abusable drug similar to Oxycontin in its abusability. There was no real consensus as to where Exalgo may lie along a continuum, but it is felt that this drug has a high abuse potential.
2. Exalgo should have a REMS which fits into the opioid-class REMS. The Committee felt that the REMS proposed by the Applicant contained several important features but that it would need to be approved and coordinated through the Agency.
3. The Palladone (Hydromorphone extended release capsule previously approved by the FDA in 2004 but withdrawn in 2005 due to alcohol dose dumping-effects) model of a restricted marketing roll-out was presented to the Committee by the Agency. Many Committee members felt that a restricted marketing roll out may be an effective strategy for OROS hydromorphone (Exalgo).

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

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

/s/

ELIZABETH M KILGORE
10/29/2009

ELLEN W FIELDS
10/29/2009
concur



FDA CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857
Tel:(301)-827-7410

MEMORANDUM

DATE: October 24, 2000

TO: File, NDA 21-217 Dilaudid CR (hydromorphone HCl) Controlled Release Tablets

FROM: Cynthia G. McCormick, M.D., Director *Cynthia G. McCormick M.D.*
Division of Anesthetic, Critical Care and Addiction Drug Products
ODE II, CDER

RE: Memorandum of Action

This memorandum summarizes for the file the basis for the action to be taken on the NDA 21-217 Dilaudid CR (hydromorphone HCl) controlled release tablets, and why, while I concur with the conclusions of the review team I, propose to take an action that is different.

Background:

Hydromorphone is a potent μ -opiate that has been marketed in this country since the early 1920's. In 1984 Dilaudid (hydromorphone HCl) injectable was approved and in 1992 an application was submitted for an immediate release oral formulation in 8-mg strength which was also approved. The NDA, which is the subject of the current action, is for a modified release oral formulation of hydromorphone using the OROS® technology. The development plan for this NDA was discussed with the sponsor in an End of Phase 2 Meeting on October 3, 1997 and a preNDA meeting on August 4, 1999 during which times the sponsor was informed that an adequate and well-controlled study would be used in making the determination of efficacy for this application. The sponsor attempted to craft an argument that the product's pharmacokinetics would allow for the extrapolation of efficacy from the Agency's prior finding of efficacy. This argument was not compelling, however, in that the case for a discrete PK/PD relationship has never been made for this product, and further, by design, the PK profile of this product varies from the approved product. The sponsor's burden, then, as discussed at two Agency-Industry

meetings, was to establish that the efficacy of the new product with its different pharmacokinetic profile is retained. The sponsor was informed at these meetings that an adequate and well-controlled study was needed for this purpose. There was agreement that the safety database of approximately 800 patients would suffice for this new formulation.

The NDA 21-217 for Dilaudid CR was filed after having been submitted on December 29, 1999 with one adequate and well controlled study, which on its face and by design should have been capable of demonstrating the efficacy of hydromorphone in chronic pain, a safety database of sufficient size to be able to evaluate the safety of this new formulation and a full pharmacokinetic characterization of this drug product.

Pharmacokinetics

This product uses Alza's OROS® technology in which there is a bilayer core (drug/push layer) which is coated with an insoluble cellulose coating membrane. An orifice is drilled into the membrane for drug delivery. In the case of this product, hydromorphone is released over the course of 24 hours. The pharmacokinetic profile of this product has been satisfactorily worked out for 8, 16, 32 and 64 mg tablets. There were not significant drug interaction findings, no food effect, and no gender interaction findings. The once-daily dosing regimen is appropriate, and there is adequate dose proportionality across the range of doses.

Efficacy

Study M019 as reviewed by Dr. Sharon Hertz, and summarized further by Dr. Rappaport does not provide evidence of the efficacy of this product due to failure of the primary and secondary efficacy measures. This was a multicenter, double-blind, double-dummy active and dose controlled study in patients with chronic malignant and nonmalignant pain, already maintained on a stable regimen of opioid therapy. By design, all patients were converted to Dilaudid IR during a stabilization period and then randomized to receive either Dilaudid CR + placebo IR (qid), ½ dose Dilaudid CR + placebo IR (qid), or Dilaudid IR (5 times daily) where the dose of Dilaudid was determined by the stabilization dose. The primary outcome variable in this study was the total daily dose of breakthrough medication averaged over the last four days of the double blind phase as compared to the last two days of titration. The mean changes from baseline were then analyzed using ANOVA. The underlying premise was that if the stable dose was reduced by half in a group of patients, their pain would not be adequately controlled, and that pain would manifest itself by requests for additional rescue medication. This was not the case, however, and the statistical analysis revealed no statistically significant treatment effect.

It is noted that the baseline requirements for rescue medication were not comparable across treatment groups, but more significantly, in all groups the mean requirements for rescue medication were increased over the baseline means, and this increase was greatest in the group for which there was no change in dosage. The sponsor provided several *post hoc* analyses of these data, but none of them were persuasive. These are clearly discussed

in Dr. Rappaport's memorandum of October 11, 2000 and Dr. Permutt's review of June 9, 2000.

It is the conclusion of the review team that this study has failed in its goal of demonstrating the efficacy of Dilaudid CR tablets in the treatment of moderate to severe pain.

Safety—nonclinical

The nonclinical evaluation of safety in this product was based in part on previous literature reports of hydromorphone. This application did include Segments I-III reproductive toxicology in rats and rabbits, genotoxicity in the standard battery and one 30 day toxicity study in dogs. There were no significant findings of concern. Carcinogenicity testing has never been provided for this compound and will be required.

Safety—clinical

No unexpected adverse events were reported in a clinical safety database of nearly 800 subjects and patients. The adverse event profile is similar to that of other products of similar potency in the opiate class. This product does have the distinction of possibly leading to serious GI side effects resulting from bezoar formation by the ghosts of the OROS delivery system, complicated by the reduced GI motility characteristic of this class of drugs. There were 15 serious gastrointestinal adverse events described in the NDA, although no unequivocal cause was described. OPDRA (Office of Post Marketing Drug Risk Assessment) was consulted to aid in the assessment of risk related to the OROS® formulation by evaluating reports from currently marketed products using the OROS® technology. They noted a higher incidence of reports in patients with a preexisting GI problem, such as inflammatory bowel disease, anatomical abnormality, or prior surgery of the GI tract. This will have to be incorporated in the labeling of this product once approved.

The above concern is reflected in the decision to defer the submission of pediatric studies for this formulation under the Pediatric rule (63 FR 66632) until postmarketing data can be obtained from the adult experience.

Safety—abuse liability

Hydromorphone is already in the most restrictive schedule for a marketed drug. No increases in abuse potential are anticipated for this new dosage form to warrant a more restrictive risk management program. Provisions for child resistant packaging have been made.

Data Integrity

There were no inspections of the pivotal clinical trial, because upon review it was determined that there was insufficient evidence of efficacy. It was decided that FDA resources should not be applied to the inspection of a trial that clearly could not be used in the formulation of a decision to approve this product.

The inspection of the pharmacokinetics trial revealed that the samples used for PK analysis were not retained for further verification. Since there were no irregularities or ambiguities in the data to suggest that these data are unreliable, the decision was made to rely upon them. So, regardless of this breach in protocol, the data from this trial will be accepted.

Chemistry, Manufacturing, and Controls

There are a number of chemistry deficiencies in this application that are detailed in Dr. Harapanhali's review. The most important of these relate to the lack of adequate stability data to justify an appropriate shelf life, the existence of certain impurities which may reach levels requiring qualification, and inadequate specifications for both drug substance and drug product to ensure its quality. There was inadequate information about the container closure system, child resistance testing and packaging. These are all potentially correctable problems, but render the application incomplete.

Summary

While I agree with the review team that the sponsor has failed to demonstrate the effectiveness of hydromorphone hydrochloride CR tablets, it is expected that a more rigorous trial may yet demonstrate the efficacy of the product. It is also expected that the CMC deficiencies can be successfully resolved, and qualification of the impurities is within their capability. In short, all of the problems seen in this application are potentially correctable. Therefore the sponsor will be issued an approvable letter for this application. The sponsor must, then, perform an additional adequate and well-controlled study in the context of chronic pain with multiple dosing, demonstrating the superiority of this product over a comparator (placebo or dose control, or both) in order for the FDA to approve this product.

Action:

The sponsor will be issued an approvable letter detailing the deficiencies and corrective actions for this NDA.



FDA CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS

HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857

Tel: (301)443-3741

MEMORANDUM

DATE: October 11, 2000

TO: File, NDA 21-217

FROM: Bob A. Rappaport, M.D.
Deputy Director, DACCADP
Team Leader, Anesthetic Drug Group

RE: Supervisory Review of NDA 21-217, Dilaudid-CR
[Hydromorphone HCl], Controlled-Release Tablets

BACKGROUND:

NDA 21-217 for hydromorphone hydrochloride, controlled-release tablets was submitted by Knoll Pharmaceuticals on December 29, 1999. Hydromorphone is a potent opioid analgesic that was first introduced into the market in the early 1920's. It is a pure mu-receptor agonist that is currently marketed in the US in various approved and unapproved dosage forms. The immediate-release tablets are available in 1, 2, 3, 4, and 8-mg doses. Only the 8-mg tablet was approved by the Agency. NDA 19-892 was approved on December 7, 1992.

The controlled-release product that is the subject of this NDA uses the OROS[®] system and has been formulated as 8, 16, 32 and 64-mg tablets. The OROS[®] system consists of a tablet, which comprises a bilayer core coated with an insoluble cellulosic rate-controlling membrane. An orifice drilled into the membrane allows the "push-pull" technology to release hydromorphone in a controlled manner over approximately 24 hours.

This application contains complete reports for three clinical and eight pharmacokinetic studies. The clinical studies of the safety and effectiveness of this new formulation have been reviewed by Sharon Hertz, M.D. [submitted September 28, 2000]. The application

has also been reviewed by Thomas Permutt, Ph.D. (biostatistics), Tien-Mien Chen, Ph.D. (clinical pharmacology and biopharmaceutics), Kathleen Haberny, Ph.D. (pharmacology/toxicology), and Ravi Harapanhalli, Ph.D. (chemistry). In this memo, I will briefly review the evidence of effectiveness and safety summarized in the primary clinical review.

EFFECTIVENESS:

Three studies were submitted in support of the effectiveness of Dilaudid CR. However, Studies DO-104 and DO-105 were open-label, did not employ a comparator, and were only capable of providing safety data. The sponsor was clearly informed that the Division would not accept these two studies in support of efficacy. This is documented in the meeting minutes from October 3, 1997, as well as those from the pre-NDA meeting held on August 4, 1999. Study DO-119 was an adequate and well-controlled study that failed to show a statistically significant treatment effect for a full dose of Dilaudid CR compared to a half dose of Dilaudid CR and Dilaudid Immediate Release [IR].

Study DO-119:

“A randomized, double-blind, repeated-dose, parallel-group comparison of the efficacy and tolerability of Dilaudid CR™ tablets and immediate-release Dilaudid® tablets (hydromorphone HCl) in patients with chronic pain.”

A total of 169 patients with chronic pain of malignant or nonmalignant origin, who were already receiving oral or transdermal opioid analgesics on a daily basis or who were assessed as needing advancement to opioid therapy, were enrolled from 15 centers. During a Stabilization Period that lasted up to 7 days patients were to be stabilized on their prior opioid. Twenty-one patients discontinued during that phase. The remaining 148 patients each received at least one dose of study medication and comprised the safety population. Thirty-five patients discontinued during the open-label Conversion/Titration Phase. During that phase, patients were converted from their prior opioid medication at a ratio of 5-mg oral morphine equivalents to 1 mg of oral hydromorphone. Titration to adequate pain control was completed within 14 days. Patients were considered stabilized when they experienced no change in total dose and no more than three doses of rescue medication per day for two consecutive days.

Patients who required from 20 to 60 mg of Dilaudid IR before rescue use were randomized into the 7-day, double-blind portion of the study. The patients were randomized to one of three arms:

1. Full dose of Dilaudid CR determined during the Conversion/Titration Phase administered one time per day, with placebo IR doses four times per day

2. One-half dose of Dilaudid CR determined during the Conversion/Titration Phase administered one time per day, with placebo IR doses four times per day
3. Full dose of Dilaudid IR determined during the Conversion/Titration Phase, administered as a five times per day regimen

Of the 113 patients who entered the Double-Blind Phase of the study, 7 discontinued before completion. Two of those discontinuations were due to adverse events, 3 due to withdrawal of consent and 2 to lack of efficacy. The two patients with adverse events were in the full-dose Dilaudid-CR group. Both of the patients who withdrew due to lack of efficacy and two of the three who had consent withdrawn were in the half-dose Dilaudid CR group. The third patient who had consent withdrawn was in the full-dose Dilaudid-CR group.

A single protocol violation occurred during the Double-Blind Phase of the trial. That patient had been receiving a higher than permitted dose of Duragesic. Nevertheless, the patient was included in the effectiveness analyses. Baseline characteristics and demographics were similar across the three treatment groups with the exception of rescue medication use. Patients with the highest baseline rescue medication use were randomized to the Full-Dose Group; and patients with the lowest rescue medication use were disproportionately randomized to the Half-Dose Group.

Primary Outcome Analyses:

The primary efficacy outcome variable in this study was the total daily dose of breakthrough-pain medication, averaged over the last four days of the Double-Blind Phase and compared to the average dose over the last two days of the Titration Phase. The mean changes from baseline for the three treatments were compared by analysis of variance. That analysis revealed no statistically significant treatment effect, with a p-value of 0.42. Dr. Permutt's Table 2, page 3 of his review, summarizes the results for the primary outcome variable, and has been duplicated with modifications below:

Table 1. Average Daily Rescue Dose of Hydromorphone (mg)

	SR/Full	SR/Half	IR
n	34	40	39
Endpoint:			
mean \pm s.d.	23.2 \pm 19.8	19.1 \pm 17.5	21.4 \pm 23.8
median	18.0	11.4	16.0
Baseline:			
mean \pm s.d.	16.4 \pm 16.3	10.7 \pm 9.9	13.7 \pm 14.5
median	9.0	8.0	8.0
Change:			
mean \pm s.d.	6.6 \pm 16.0	9.2 \pm 12.0	7.1 \pm 14.5
median	2.0	7.4	4.4

[derived from sponsor's Tables 24 and 25, volume 119, pp. 69 and 71]

Of note, although the change in rescue medication use from baseline was greater for the Half-Dose Group, the average endpoint rescue medication was actually higher in the Full-Dose Group compared to the Half-Dose Group. This was because there was a greater difference between the two groups at baseline.

The sponsor performed a post-hoc analysis on the percent change from baseline in total daily dose of rescue medication. The results of this analysis showed a statistically significant treatment effect for the Full-Dose compared to the Half-Dose and IR Groups, with mean values of 133, 330 and 386, respectively. A rank-sum test applied to the two SR groups resulted in a two-sided p-value of 0.037. However, extreme percent changes from very low or zero scores to somewhat low scores influenced the resulting means, particularly for the Half-Dose Group.

Another post-hoc analysis compared change in direction in total daily dose of breakthrough medication. More patients in the Half-Dose Group increased their rescue medication use and less decreased rescue use compared to the patients in the Full-Dose Group ($p = 0.026$).

A third post-hoc analysis of the number of doses of breakthrough medication used per day resulted in a statistically significant difference in change from baseline between the Full-Dose and Half-Dose Groups with a p-value of less than 0.001. However, there was no statistically significant difference between the two groups at the endpoint of the study except when analyzed by Poisson Regression. Dr. Permutt concludes that this analysis was performed incorrectly, in that individual days for the same patient were treated as independent observations, whereas they would be expected to be correlated (see Dr. Permutt's discussion on page 5 of his review).

Secondary Outcome Analyses:

Pain Intensity, Pain Relief and Sleep Interference:

There were no statistically significant between-group differences at study endpoint for diary-based pain intensity, pain relief or sleep interference scores, with p-values of 0.17, 0.91 and 0.42, respectively. There were also no statistically significant between-treatment effects for change from baseline in any of the groups. Pain relief was worse for all three treatment groups at the end of the study. Only the change from baseline for the Half-Dose Group was statistically significant, however ($p = 0.002$). See Dr. Hertz's Table 6.8, page 34 of her review for a summary of this data.

Wisconsin Brief Pain Inventory [WBPI]:

There were no statistically significant differences between the treatment groups on any of the subsets of the WBPI at baseline or study endpoint. For the between-group analyses of change in score from baseline to endpoint, only the subset of "Relations with Other People" showed a statistically significant treatment effect for Dilaudid CR compared to IR, with a p-value of 0.035.

Normalized Breakthrough-pain Medication:

For the total daily dose of breakthrough medication converted to a percentage of the final titrated dose of Dilaudid IR, comparing the change from baseline to study endpoint, there were no statistically significant differences in between-group or within-group analyses. See Dr. Hertz's Table 6.9, page 35 of her review, for a summary of this data.

Global Evaluation Ratings:

The overall ratings of effectiveness of study medication worsened during the study. The only statistically significant changes indicated an apparent deterioration in pain control within the Full-Dose ($p = < 0.001$) and Half-Dose ($p = 0.012$) Dilaudid-CR treatment groups.

Studies DO-104/105:

"A repeated-dose evaluation of analgesic use and safety of Dilaudid CR (hydromorphone HCl) in patients with chronic pain."

The stated objective for these two studies was to develop recommended dosing information for initiation of therapy with Dilaudid CR in patients with chronic pain converting from other strong oral or transdermal opioids, to characterize a safe and effective means by which patients can be started on Dilaudid CR and titrated to an appropriate maintenance dose, and to evaluate the safety profile.

DO-104 and 105 were open-label, repeated-dose studies that differed only in diagnostic entry criteria and that were presented by the sponsor in one report. DO-104 enrolled patients with chronic pain of malignant origin and DO-105 enrolled patients with chronic pain of non-malignant origin. A total of 445 patients were enrolled and 404 received at least one dose of study medication. There was a marked increase in the number of patients requiring rescue medication after conversion to Dilaudid CR from prior opioid therapies. There was a modest improvement in pain relief from the start to the end of Dilaudid-CR titration; and there was a modest decrease in the mean pain intensity difference (i.e., the difference between the worst pain and the least pain over 24 hours) at the end of Dilaudid-CR titration. Global Evaluations by patients and investigators showed apparent improvement from the end of prior opioid stabilization to the end of Dilaudid-CR titration. See Dr. Hertz's Table 6.14, page 41 of her review, for a summary of this data.

Study DO-109:

“Safety and tolerability of long-term administration of Dilaudid CR™ (hydromorphone HCl).”

This was an open-label, 1 to 2-year, extension study for patients who completed either Study DO-104/105 or DO-119. This study was ongoing at NDA submission.

SAFETY:

Dr. Hertz's Tables 5.5 and 5.7, pages 20 and 22 of her review, summarize the exposure data for the safety database in the Phase 3 and Phase 1 trials, respectively, and have been reproduced below:

Table 2.Table 5.5 Updated Duration of Exposure ^a to Dilaudid CR in the Phase III Clinical Trials

Dose Range	0-23 mg	24-35 mg	36-63 mg	64+ mg	Total ^b
Total Patients Exposed	136	130	140	163	569
Duration of Treatment with Dilaudid CR (days)					
1-7	23	18	5	12	58
8-14	16	10	14	17	57
15-21	12	11	8	8	39
22-28	13	7	2	7	29
29-56	4	10	19	11	44
57-84	8	4	8	7	27
> 84	60	70	84	101	315
>168	43	35	65	83	242
>364	17	14	20	43	94
Cumulative Data					
N	136	130	140	163	569
Mean (days)	135.7	157.0	184.2	212.5	174.5
SD	164.71	166.86	162.38	187.85	173.66
Median	47.0	101.5	140.5	178.0	120.0
Range	1.0-645.0	1.0-619.0	3.0-604.0	2.0-639.0	1.0-645.0

^a Duration of exposure was calculated and categorized by mean daily dose ranges. Mean daily dose = the average daily dose from the start of titration through the end of the long-term study.

^b Total number of patients exposed to Dilaudid CR includes patients who received Dilaudid CR during Studies DO-104, DO-105, and DO-119 and also includes patients who were randomized to Dilaudid IR in Study DO-119 and subsequently received Dilaudid CR in Study DO-109.

Source: Table 9.8.3b, Vol. 3.1, P. 63, Cross-reference ISS Table 8.12.6 (Vol. 115, P. 127) in the NDA.

Table 3.Table 5.7 Duration of Exposure ^a to Dilaudid CR in Study DO-108

Characteristic	0-23 mg	24-35 mg	36-64 mg	Total
Total Patients Exposed	17	2	3	22
Duration of Exposure to Dilaudid CR (days)				
1-7	0	1	2	3
8-14	7	0	0	7
15-21	9	1	0	10
22-28	1	0	1	2
Duration of Exposure to Dilaudid CR (days)				
N	17	2	3	22
Mean	14.9	11.5	12.0	14.2
SD	4.18	13.44	9.54	5.69
Median	15.0	11.5	7.0	15.0
Range	8.0-23.0	2.0-21.0	6.0-23.0	2.0-23.0

^a Duration of exposure was calculated and categorized by mean daily dose ranges. Mean daily dose = the average daily dose from the start of titration

Source: Table 9.8.14, Vol. 3.1, P. 25.

Patients in Studies D-101, D-102, D-103, DO-123, DO-124, and DO-129 received single doses of Dilaudid CR at the following exposures:

Table 4.

Dilaudid-CR dose (mg)	8	16	32	64
N	118	201	148	142

Deaths:

There were no deaths in the Phase 1 studies. There were 34 deaths reported from Studies DO-104/105 and DO-109. Sixteen of these deaths occurred off study drug, 6 within one week of study-drug discontinuation. One of the 16 deaths occurred in a patient who had not received any study drug. Dr. Hertz's Tables 7.2 and 7.3, pages 45 to 47 of her review, summarize the reported causes of death for these patients. Thirty of the 34 deaths occurred in patients with advanced cancer. Based on her review of these cases, Dr. Hertz concluded that, "...there was no pattern of adverse events or other indication that the study drug contributed directly to the cause of death."

There was no apparent dose effect for the 18 deaths that occurred in patients while being treated with study drug, as can be seen in the following table:

Table 5. Number and Incidence of Deaths Occurring at Increasing Doses of Dilaudid CR

Dose (mg)	16	24	32	48	56	64	88	328
N	4	2	5	3	1	1	1	1
Incidence (%)*	3	2	4	2	<1	<1	<1	<1

*calculated as the number of patients with events at that dose divided by the number of patients in that dose range from the exposure data in Table 2 above

Of the 4 deaths occurring in non-malignant pain patients, 3 were attributed to cardiac arrests. Two of those 3 patients had histories significant for atherosclerotic heart disease and Dr. Hertz's review of the third patient's history provided minimal information that would allow a determination of causality.

The fourth death in a non-malignant pain patient was due to a perforated colonic ulcer in a 40-year old woman with a history of morbid obesity. The patient's chronic pain was due to a history of multiple plastic surgeries to the abdomen after an apronectomy scar dehiscid during a motor vehicle accident; she also suffered from arthritis. Dr. Hertz's review of this case was unsuccessful in precisely determining whether the study drug could have contributed to the adverse event. Although the OROS® delivery system has been associated with gastrointestinal obstruction and perforation, no post-mortem examination was performed.

Discontinuations:

Dr. Hertz has thoroughly reviewed the adverse events leading to discontinuation. She has concluded that the events occurring in this clinical development program were consistent with the known profile of opioid drugs and that there did not appear to be an unusual pattern or increased frequency of these events that might suggest a problem specific to Dilaudid CR. There was one reported event of bezoar; but the original and follow-up information that was provided by the sponsor regarding this patient was inadequate to determine if study drug tablets were located within the bezoar.

There did appear to be an increased incidence of adverse events leading to discontinuation in patients treated with Dilaudid CR compared to those treated with Dilaudid IR during the double-blind phase of Study DO-119. However, the numbers of patients with these events were small, generally 1 or 2 for any particular event, and all of the events were known potential side effects of opiate therapy. Dr. Hertz's Table 7.7, page 53 of her review, summarizes this data.

Serious Adverse Events:

Dr. Hertz has thoroughly reviewed the serious adverse events occurring in the Dilaudid-CR safety database. She has determined that the events were consistent with the known profile of opioid drugs and that there did not appear to be an unusual pattern or increased frequency of these events that might suggest a problem specific to Dilaudid CR. No

serious adverse events occurred during treatment with Dilaudid CR in Study DO-119. For studies initiated subsequent to NDA submission, there have been no serious adverse events during study, although vomiting, abdominal pain and dehydration have been reported for one patient post-study.

Fifteen serious adverse events that might be attributable to the use of the OROS® delivery system are summarized in Dr. Hertz's Table 7.12 on page 59 of her review. Gastric outlet obstruction, abdominal pain, bowel obstruction and protracted nausea and vomiting, could be the result of bezoar formation. However, no clearcut determination of causality has been made regarding these events, and they could also be attributable to underlying disease or chronic opiate consumption. It should be noted that individuals at risk for gastrointestinal complications from the OROS® delivery system were excluded from these studies.

Other Adverse Events:

As Dr. Hertz has concluded, the overall adverse event profile is as expected with use of a potent opioid analgesic and in a patient database that includes a large number of patients with malignancies. Table 7.9 on page 56 of her review summarizes the more frequent adverse events occurring in Study DO-119. Only "pain extremity", infection, "injury accidental", somnolence, anxiety, and pruritis appear to occur more frequently in the Dilaudid-CR group compared to the Dilaudid-IR group. Most of these events occurred in a small number of patients. However, somnolence did occur with an 8.8% incidence (n = 3) in the Full-Dose Dilaudid-CR Group, a 2.5% incidence (n = 1) in the Half-Dose Dilaudid-CR Group, and not at all in the Dilaudid-IR Group; and "Skin/General including Pruritis" had an incidence of 14.7% (n = 5) in the Full-Dose Dilaudid-CR Group, 2.5% (n = 1) in the Half-Dose Dilaudid-CR Group, and 7.7% (n = 3) in the Dilaudid-IR Group.

Vital Signs:

There were no clinically significant and unexpected changes in vital signs attributable to the study drug.

COMMENTS:

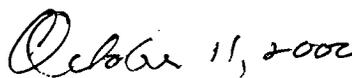
The sponsor has provided no evidence capable of establishing efficacy for their Dilaudid-CR tablets. The safety profile of the product appears to be generally similar to other potent opioid products with the exception of possible serious gastrointestinal adverse events related to bezoar formation by the OROS[®] delivery system tablets.

RECOMMENDATIONS:

The sponsor must perform an adequate and well-controlled trial that demonstrates the effectiveness of their Dilaudid-CR product. Once efficacy has been established, labeling will need to include appropriate warnings regarding the potential for gastrointestinal complications related to the use of this product.



Bob A. Rappaport, M.D.



October 11, 2000

Cc: Original NDA 21-217
HFD-170: Division File
HFD-170:
McCormick
Rappaport
Hertz
Permutt
Chen
Haberny
Harapanhalli
Milstein

MEMORANDUM TO THE FILE

DATE: October 3, 2000

FROM: Judit Milstein, Regulatory Project Manager

JPM 10/3/00

APPLICATION NUMBER: NDA 21-217

Dilaudid CR, hydromorphone hydrochloride

APPLICANT: Knoll Pharmaceuticals, Inc.

SUBJECT: 120 safety update review

120 safety update review : See M.O. review, page 48

CLINICAL REVIEW
Division of Anesthetics, Critical Care and Addiction Drug Products
NDA No. 21-217

Date of Submission:	April 28, 2000
Date of Receipt:	May 1, 2000
Type of Submission:	Original NDA
Drug Product:	Dilaudid CR
Drug Name:	Hydromorphone HCl 8, 16, 32, 64 mg.
Sponsor:	Knoll Pharmaceutical Company
Review Date:	October, 2, 2000
Medical Officer:	Sharon Hertz, M.D.
Project Manager:	Judit Milstein

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Executive Summary

Recommendation:

I recommend non-approval for this NDA for Dilaudid CR. The sponsor has failed to demonstrate the efficacy of Dilaudid CR in the intended indication of analgesia for moderate to severe pain. The clinical development plan for Dilaudid CR was inadequate consisting of one adequate and well-controlled trial which failed on both primary and secondary outcome measures. The sponsor will need to conduct one adequate and well-controlled trial that demonstrates efficacy of this product before approval can be considered.

A. Brief overview of clinical program

The product under investigation and submitted for review in this application is Dilaudid CR. This product consists of hydromorphone hydrochloride, an opioid analgesic, in an oral, controlled release formulation using the OROS® system. The product has been formulated in 8, 16, 32 and 64 mg tablets for once daily administration. A total of 12 trials were submitted in this NDA. A total of 829 subjects were exposed to Dilaudid CR during these trials, including 577 patients who received Dilaudid CR during Phase III clinical trials. The only indication studied during this development plan was analgesia for moderate to severe pain.

B. Efficacy

The sponsor submitted three Phase III clinical trials in support of efficacy, but only Study DO-119, a multicenter, randomized, double-blind, active-controlled, repeated-dose study, could be considered an adequate and well-controlled trial. Studies DO-104 and DO-105 were open-label, non-randomized studies submitted as a single report.

Study DO-119 was designed to evaluate the ability of Dilaudid CR to manage chronic malignant and non-malignant pain in a dose controlled study comparing Dilaudid IR, 1/2-dose Dilaudid CR and full-dose Dilaudid CR. The primary outcome measure was the amount of rescue medication used by patients, the secondary outcome measures were pain relief, pain intensity, sleep interference ratings, Wisconsin Brief Pain Inventory, normalized breakthrough-pain medication, Global Evaluation ratings, and proportion of patients dropping out due to lack of efficacy. Additional post-hoc analyses consisted of the direction of change of the use of breakthrough-pain medication, the number of doses/day using regression analysis, the percent change of total daily dose, and analyses based on special populations.

The full-dose Dilaudid CR treatment arm failed to differentiate from the 1/2-dose Dilaudid CR treatment arm or the Dilaudid IR treatment arm for the primary and all of the secondary efficacy variables. There were differences for within-group comparisons from baseline to the end of the study for some of the outcome measures. There was less pain relief for all three treatment groups, but this only reached a within-group, statistically significant difference for the 1/2-dose Dilaudid CR group. Pain intensity was unchanged for Dilaudid CR. Pain intensity was increased for the Dilaudid IR, but only reached a within-group, statistically significant increase for the 1/2-dose Dilaudid CR group. On the other hand, the difference in normalized dose of breakthrough-pain medication increased over the treatment period reaching statistically significant differences from baseline for within-group comparisons for all three treatment groups.

There were fewer patients who rated the overall effectiveness of study medication as good to excellent at the end of the study than at baseline for all three groups. The only post hoc analyses to reach statistical significance between full-dose and 1/2-dose Dilaudid CR groups were direction of change in amount of breakthrough medication and the percent change in breakthrough medication. These two analyses favored full-dose over 1/2-dose Dilaudid CR but neither measure has significant clinical meaning.

To summarize, patients taking Dilaudid CR, 1/2-dose Dilaudid CR and Dilaudid IR were indistinguishable for the primary and secondary outcome measures. In addition, all three treatment groups required increased amounts of breakthrough medication and reported less pain relief and less satisfaction with the study medication at the end of the study than at baseline.

C. Safety

The safety database established was appropriate to provide adequate safety information. A total of 12 studies were submitted in support of the safety evaluation of Dilaudid CR consisting of 829 subjects who received Dilaudid CR, 613 patients in Phase III studies. A total of 315 patients received Dilaudid CR for at least 84 days, and 94 patients for at least 364 days.

The pattern of serious adverse events, adverse events leading to study discontinuation and adverse events in general observed during the Phase I and Phase III studies of Dilaudid CR was consistent with the known adverse event profile of hydromorphone and comparable to the adverse events associated with opioids in general. Of the 34 deaths in the database, 30 occurred in patients with chronic pain of malignant origin, and three deaths were attributed to cardiac events. One death, which occurred in a patient with non-malignant pain, was due to a perforated colon. A relationship between the study drug and, in particular, the delivery system, while unlikely, cannot be definitively excluded. Nausea (27%), vomiting (24%) and constipation (17%) were among the top five most common adverse events and were the three most common individual adverse events leading to study discontinuation.

Safety concerns for the Dilaudid CR product focus on the delivery system. A risk of gastrointestinal obstruction and/or bezoars has become evident during post-marketing surveillance of other products using the OROS delivery system. In this safety database there was one report of a bezoar, but there was insufficient detail reported to establish the presence of a causal relationship with Dilaudid CR. As noted, there was also one report of a perforated colon resulting in death, but again, not enough detail was available in the narrative or CRF to determine if the study medication played a role. It is important to recognize that patients with greater risk for gastrointestinal narrowing from pre-existing medical or post-surgical conditions were excluded from these clinical trials. Should the development of this product reach the approval stage, clear warnings and recommendations concerning the risk of gastrointestinal obstruction due to the delivery system will need to be established.

D. Dosing

The dosage of Dilaudid CR will be based on the individual patient's requirements for pain control. The formulations available, 8, 16, 32 and 64 mg, will provide adequate flexibility for individual dose adjustment. The pharmacokinetics of the product support the intended regimen of once per day dosing. It can be expected that patients on chronic opioid therapy will develop

physical tolerance and require increased dosages over time. No specific upper limit for Dilaudid CR dosage has been defined.

E. Special Populations

Gender

The Phase III clinical trials were well balanced for enrollment of men and women. There were no gender differences in the primary measure for efficacy, however, adverse events were more common among women (88.8 vs. 74.7%).

Race/Ethnicity

The majority of the subjects studied during this development plan were Caucasian. The number of non-Caucasian study participants was too small for meaningful comparisons.

Elderly

There was a greater incidence of adverse events among patients over 65 and more so among patients over 75 years of age. These findings are consistent with the known increased sensitivity to opioids that occurs in the elderly.

Renal Insufficiency

The exposure of patients with renal insufficiency during the Phase III trials was inadequate to characterize any effects on efficacy or safety.

Hepatic Insufficiency

The exposure of patients with hepatic insufficiency during the Phase III trials was inadequate to characterize any effects on efficacy or safety.

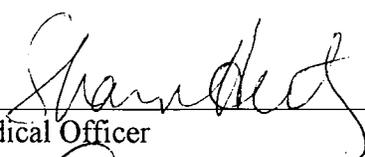
Pediatric Plan

The sponsor has requested deferment of pediatric studies pending completion of the trials in the adult population. It is anticipated that there will be a greater risk of gastrointestinal obstruction among the pediatric population due to the smaller size of the gastrointestinal tract in this population in general, and particularly among those children with additional risk factors for narrowing due to surgery and scarring.

F. Pharmacokinetics and Pharmacodynamics

[Redacted]

(b) (4)



Medical Officer

10/4/00

Date



Team Leader/Deputy Division Director

10/12/00

Date

SECTION 1 INTRODUCTION AND BACKGROUND

SECTION 1.1 INDICATION

The current indication proposed for this NDA is analgesia for moderate to severe pain.

SECTION 1.2 RELATED INDs AND NDAs AND RELATED AGENTS

The active ingredient in Dilaudid is hydromorphone HCl, a hydrogenated ketone of morphine, which has been marketed since the 1920's. As an opioid, in addition to its analgesic property, Dilaudid produces sedation, respiratory depression, nausea and vomiting, cough suppression, reduced GI motility, and increased biliary pressure. Dilaudid is also capable of producing miosis, enhanced parasympathetic activity, elevated cerebrospinal fluid pressure, and a transient hyperglycemia.

Hydromorphone is currently available in the US as an immediate release tablet, oral liquid, rectal suppository, powder, cough syrup, and solution for IV, SQ, and IM injection. A controlled release capsule is available in Canada. The sponsor holds NDAs for Dilaudid 8 mg, 19-891, Dilaudid Oral Liquid, 19-892 and Dilaudid-HP Injection, 19-034. The sponsor also produces 2 mg and 4 mg immediate release Dilaudid tablets and 3 mg Dilaudid Suppositories which were not approved under NDAs.

Approved products marketed in the US using the OROS delivery system include: Covera HS, Ditropan XL, DynaCirc CR, Efidac24, Glucotrol XL, Procardia XL, Sudafed 24 and Volmax.

SECTION 1.3 ADMINISTRATIVE HISTORY

The sponsor has submitted four studies in support of efficacy: D-104, D-105, D-109, and D-119. These were studied under IND (b) (4). Studies D-104 and D-105 were open-label studies without comparator and Study D-109 was an open-label long-term extension study without comparator. The Agency had directly communicated with the sponsor that open-label studies and studies without comparators would not be acceptable for efficacy trials. This was clearly documented in the meeting minutes dated September 2, 1999, from the pre-NDA meeting held on August 4, 1999. In particular, the Division Director of the Division of Anesthetics, Critical Care and Addiction Drug Products stated that the Agency does not rely on open-label studies to demonstrate efficacy, that open-label studies are not sufficient for efficacy, and that studies used for efficacy need a comparator.

In the information packet submitted by the sponsor for a meeting dated October 3, 1997, the sponsor indicated that the objectives for Studies D-104 and D-105 were to, "Develop safe dose initiation and titration recommendations for converting to Dilaudid CR from other opioids. Characterize adverse event profile." In the protocol synopsis from the same meeting package, study objectives are stated as: "Develop recommended dosing information for initiation of therapy by converting from other strong oral or transdermal opioids. Characterize a starting starting (sic) dose and titration recommendation." This is further information indicating that the sponsor did not originally plan these studies as efficacy studies.

In the meeting minutes from the October 3, 1997 meeting, the Agency stated that the sponsor would need at least one well-controlled, double-blind, double-dummy, pivotal trial. A design was suggested, consisting of conversion, titration, and stabilization phase with Dilaudid IR, followed by a double-blind, randomized, three arm efficacy phase. Dilaudid IR, Dilaudid CR at 50% dose and Dilaudid CR at 100% dose were suggested, with inclusion of the use of rescue medication as an endpoint. This became Study D-119. The Agency also communicated that, with this drug product, either a second adequate and well-controlled trial or an adequate PK/PD study would be acceptable for efficacy. If a PK/PD study were to be used for efficacy, the one adequate and well-controlled clinical trial must yield positive results. However, subsequent to this meeting, the Agency informed the sponsor that, for this reformulation, a single adequate and well-controlled trial would be sufficient.

SECTION 1.4 FOREIGN MARKETING

As of the submission date of this NDA, there has been no foreign marketing of this product.

SECTION 1.5 FINANCIAL DISCLOSURE

The sponsor has submitted financial disclosure form 3455 for the Investigator site of (b) (6). This form was submitted to disclose an unrestricted grant payment of \$95,290.00 on June 28, 1999 in support of an educational fellowship program within the (b) (6) at that site.

(b) (6) and the (b) (6) site enrolled (b) (6) patients (4.1%) into Study (b) (6) patients (1.8%) into (b) (6), and (b) (6) patients (2.1%) into (b) (6).

The sponsor submitted certification with a form 3454 for the remainder of the Principle Investigators and their sub-investigators for Studies DO-104, DO-105, DO-109, DO-119, DO-123, D)-124 and DO-129.

Summary

Based on review of the submitted information, the financial disclosure information is complete. Although a large sum of money was provided to one site as an unrestricted educational grant, the number of patients enrolled into studies from that site was not large enough to influence the outcome of those studies.

SECTION 2 CMC/ PRECLINICAL PHARMACOLOGY AND TOXICOLOGY

SECTION 2.1 Preclinical Pharmacology and Toxicology

Segment I reproductive toxicology for fertility was studied in rats. The study revealed no effects of hydromorphone on male and female rat fertility.

Segment II reproductive toxicology studies for teratogenicity was performed in rats and rabbits. There was no teratogenicity demonstrated in fetal rabbits in doses up to 25 mg/kg/d given during gestation days 6-20. There was no teratogenicity demonstrated in rats at doses up to 6.25 mg/kg/d given during gestation days 6-17.

Segment III reproductive toxicology for pre and postnatal development was studied in rats dosed on gestation days 6 through 21. There were no effects on gestation duration or reproduction parameters except a potential parturition effect of severe blood loss in one of 24 high-dose (6.26 mg/kg/d) dams. There was no effect on the number of live pups prior to lactation, but live pups were decreased on day four of lactation with reduced viability and survival indices at the high dose. The NOAEL for developmental toxicity was 1.56 mg/kg/d.

Genotoxicity was assessed using the Ames test, the Mouse Micronucleus test and the Chromosome Aberration Assay in human lymphocytes. There was no evidence of mutagenicity by the Ames test or Chromosome Aberration Assay, nor any clastogenicity in the Mouse Micronucleus test.

Carcinogenicity was not evaluated and will be requested as a Phase IV commitment.

The excipients in Dilaudid CR are all approved and generally recognized as safe.

A GLP toxicity study in dogs submitted to IND 53, 157 demonstrated no deaths or serious adverse events with Dilaudid CR, 64 mg/d, for 30 consecutive days. Drug delivery was incomplete as evidenced by analysis of the drug content of the recovered OROS systems, reaching approximately 75% in the 8 mg system and 45-66% in the 64 mg system. Cmax increased proportionally with increasing dose. The AUC demonstrated dose-proportionality with the 8 and 64 mg systems. The NOAEL was found to be 8 mg/d (approximately 1 mg/kg/d) for the OROS hydromorphone formulation. The MTD was 64 mg/d (approximately 9 mg/kg/d) for the OROS hydromorphone formulation.

SECTION 2.2 CMC

The current application represents the first extended release formulation of hydromorphone to be marketed in the U.S., if approved. A controlled release capsule is available in Canada.

The product studied under this application consists of a controlled release formulation of hydromorphone hydrochloride using the OROS® push-pull osmotic pump delivery system. The OROS system is composed of a semipermeable membrane enclosing a bilayer core, consisting of the hydromorphone and excipients in one layer, and osmotic agents in the other. As water within the GI tract flows through the semipermeable membrane, it causes the osmotic agents to swell pushing the hydromorphone from the drug layer. The rate of delivery is determined by the properties of the membrane and osmolality of the core constituents. The OROS system is excreted intact.

The size of the Dilaudid CR tablets varies by dosage strength. The 8 mg dose has a diameter of $9/32$ ", 16 mg and 32 mg a diameter of $11/32$ ", and 64 mg a diameter of $3/8$ " (0.375 inches).

SECTION 3 PHARMACOKINETICS AND PHARMACODYNAMICS

Summary:

The sponsor has submitted eight studies in support of the PK and PD profile of Dilaudid CR. The results of these studies support a once-daily dosing schedule. Two minor problems were identified in the bioequivalence testing of the studied formulation and the to-be-marketed formulation. First, the 64 mg tablets were found to be bioequivalent in one study but not a second. Second, a DSI inspection found that the lab conducting these bioequivalence studies failed to keep the unused test articles at the study site for Study DO-129, and, in fact, for all of the bioequivalence studies. (b) (4)

The relative bioavailability of the 8, 16 and 32 mg tablets was within acceptable limits, ranging from 104 to 114% of the comparable immediate release Dilaudid dose. There was an increased rate of absorption of hydromorphone following a high fat meal, but total absorption was unchanged. Steady state hydromorphone levels were twice single-dose levels and were achieved after 48 hours. There was no significant gender effect. The half life was shorter for chronic pain patients compared with normal controls.

Findings:

The sponsor submitted eight clinical pharmacology studies and two clinical efficacy trials with pharmacokinetic information. The following review is based on the summary of human pharmacokinetics and biopharmaceutics submitted by the sponsor and the review performed by the Agency's clinical pharmacologist.

Single-Dose Studies

Bioavailability

The relative bioavailability for the 8, 16, and 32 mg CR formulations was 119%, 114%, and 104%, respectively, compared to the IR formulations. The absolute bioavailability for the 8, 16, and 32 mg CR tablets was between 22 and 26%. Plasma concentrations of hydromorphone after single doses of the 8, 16, 32, and 64 mg CR formulations were proportional.

Pharmacokinetic Parameters

C_{max} was achieved at approximately six hours and sustained near maximal levels for approximately 24 hours. A high fat meal increased the rate but not the extent of absorption of hydromorphone. Absorption of hydromorphone was continuous throughout the GI tract for the 32 mg Dilaudid CR tablet. After a single dose of 64 mg CR, the inter-subject variability in C_{max} and AUC was less than 40% and intra-subject variability less than 17%.

There are two peaks in the serum level following single-dose administration at approximately six and 12 hours. Possible explanations for these two peaks include enterohepatic circulation, and ongoing absorption sufficiently distal in the intestine to avoid first pass metabolism. It is unclear if two peaks occur following multiple dosing as the sampling interval during the multi-dose PK study was too long to detect a peak in the 8-12 hour period.

Bioequivalence

The 8, 32, and 64 mg CR formulations of the to-be-marketed product were tested for bioequivalence with the formulations used during the clinical efficacy and safety trials. Bioequivalence was demonstrated for the 8 mg tablets in Study DO-123, for the 32 mg tablets in Study DO-124, and for the 64 mg tablets in DO-129. However, the results for the 64 mg tablets in Study DO-123 were outside the usually accepted range of 80-125%. The DSI inspection found that the lab conducting these bioequivalence studies failed to keep the unused test articles at the study site for Study DO-129, and, in fact, for all of the bioequivalence studies. The Agency reviewer for the Division of Pharmaceutical Evaluation determined that, while the effect of this break in standard protocol was less satisfactory bioequivalence studies, the results would be considered acceptable.

Special Populations

No clinically relevant difference in the PK of hydromorphone was demonstrated between male and female subjects. The Tmax was shorter with chronic pain patients (9.8 hours) compared to healthy subjects (14.7 hours).

Drug Interactions

Co-administration of naloxone increased Cmax by nearly 40% but did not change the AUC.

Repeated-Dose Studies

Steady state plasma concentrations of Dilaudid CR were approximately twice those following the first dose and were reached by the third dose within approximately 48 hours. The average plasma concentration of hydromorphone produced by Dilaudid CR was similar to the same daily dose of the IR tablets over the 24 hour dosing period. Peak to trough fluctuation with Dilaudid CR was less than IR tablets dosed every six hours.

(b) (4)



SECTION 4 REVIEW METHODS

SECTION 4.1 REVIEW METHODOLOGY

The study protocols and study reports were compared for the three studies submitted for efficacy and the results reviewed. The ISS was reviewed, and the data compared with the appendices. Data points from all of the deaths and serious adverse events were followed through from the ISS, appendices, narratives, CRT's, and CRF's. Data points from approximately 10% of the adverse events and background information were followed through the appendices, CRT's, and CRF's. Additional information was requested and reviewed for specific adverse events (see Section 7.3.4.3).

The sponsor's plans for pediatric testing and information on financial disclosure were reviewed.

A consult was requested from OPDRA on the post-marketing experience with the OROS system in other products. The response, dated June 6, 2000, was reviewed and the results were compared to the safety data from the studies of Dilaudid CR.

SECTION 4.2 DETERMINATION OF DATA QUALITY AND INTEGRITY

As it was determined early in the review process that the one adequate and well-controlled trial failed to demonstrate efficacy, a DSI audit was not requested by the Division. A DSI inspection was initiated by Clinical Pharmacology and Biopharmaceutics. The study site for Study DO-129 failed inspection for failing to keep the unused test articles at the study site.

SECTION 5 CLINICAL DATA SOURCES

SECTION 5.1 OVERALL DATA

Volumes 1.1, 1.66-1.117 were reviewed in whole or in part, along with portions of these volumes provided in electronic format. Additional information requested by the Agency, submitted by the sponsor on 2/16/00 and 2/18/00, was reviewed. Volumes 3.1-3.10 of the 120-day Safety were reviewed in whole or in part. Additional information was requested on two patients. One case represented a death and the information was received by fax on 7/27/00. The second represented an adverse event of bezoar and the information was received by fax on 8/9/00. The material reviewed for the efficacy evaluation consisted solely of studies performed in the development of this product. No post marketing data was available as this product is not marketed in any country. The material reviewed for the safety evaluation included the information submitted in the original NDA, the 120-day safety update and the consult requested by the Division to OPDRA as noted in section 4.1.

SECTION 5.2 PRIMARY SOURCE DATA

A total of 12 studies were submitted in support of the safety evaluation of Dilaudid CR, including the three studies submitted in support of efficacy. The number of patients and subjects in these studies are presented in Table 5.1. Of the 875 unique subjects enrolled in these studies, 829 received Dilaudid CR.

Table 5.1 Listing of Studies Comprising the Dilaudid CR Clinical Development Program and the Number of Patients/Subjects Contributing to the Integrated Safety Databases

Study Number	Number of Patients/Subjects Included in Original NDA Submission	Number of Patients/Subjects Enrolled Subsequent to Original Submission	Number of Patients/Subjects Included in the 4-Month Safety Update
Phase I Pharmacokinetic/Biopharmaceutic			
Normal Volunteers			
C-96-054-01	22	---	22
D-101	12	---	12
D-102	30	---	30
D-103	32	---	32
DO-123	36	---	36
DO-124	52	---	52
DO-129 ^a	---	56 ^a	56
Total	184	56	240
Patients			
DO-108 ^a	---	22 ^a	22
Total Phase I	184	78	262
Phase III Short -Term Repeated Dose			
DO-104	73	55	128
DO-105	337	---	337
DO-119	148	---	148
Phase III Long-Term Repeated Dose			
DO-109 ^b	284 ^c	104 ^c	388 ^c
Total Phase III	558^d	55^d	613^d
Total All Phases			875

a Patients/subjects were enrolled concurrently with the preparation of the original submission and data were not available to allow full integration within the ISS.

b Continuation protocol for patients previously completing Protocols DO-104, DO-105, and DO-119.

c Patients enrolled in Protocol DO-109 do not contribute to the Total because they are already accounted for under the respective individual short-term studies (DO-104, DO-105, or DO-119).

d Unique patients enrolled in any one of the four safety and efficacy studies.

SECTION 5.1.1 Description of Studies

Study C-96-054-01 was an open-label, randomized, multiple-dose, 2-way crossover PK study comparing Dilaudid CR to Dilaudid IR. The treatments were Dilaudid CR 16 mg daily for four days and Dilaudid IR 4 mg every six hours for four days with a three day washout between phases.

Study D-101 was a three-phase, 6-way crossover PK and PD study. Each subject received hydromorphone 8 mg IV over 10 minutes in phase 1, Dilaudid IR 8 mg in phase 2, and Dilaudid CR 8, 16, and 32 mg and placebo in phase 3.

Study D-102 was an open-label, randomized, single-dose, 3-way crossover food effect PK study. The effect of Naltrexone blockade on the PK profile of Dilaudid CR was also examined. Patients received the following three treatments: Dilaudid CR 16 mg fasting, Dilaudid CR 16 mg under fed conditions, and Dilaudid CR 16 mg fasting with prior naltrexone administration.

Study D-103 was an open-label, randomized, single-dose, 4-way crossover dose proportionality study. The treatments were Dilaudid CR 8, 16, 32, and 64 mg in naltrexone blocked subjects.

Study D-108 was a repeated-dose PK study in patients with chronic pain. Patients were converted and titrated from their existing opioid analgesic to Dilaudid CR at a conversion ratio of 5:1 oral morphine equivalent to hydromorphone. Following titration, patients received a stable dose of Dilaudid CR for up to 21 days with morphine as rescue.

Study D-123 was an open-label, randomized, single-dose, 4-way crossover bioequivalence study comparing two formulations of Dilaudid CR. The treatments were two formulations each of Dilaudid CR 8 mg and 64 mg in naltrexone blocked subjects.

Study DO-124 was an open-label, randomized, single-dose, 2-way crossover bioequivalence study comparing two formulations of Dilaudid CR 32 mg in naltrexone blocked subjects.

Study DO-129 was an open-label, randomized, single-dose, 2-way crossover bioequivalence study comparing two formulations of Dilaudid CR 64 mg in naltrexone blocked subjects for one to four days.

Studies DO-104 and DO-105 were open-label, repeated-dose studies in patients with chronic cancer pain (DO-104) and chronic non-cancer pain (DO-105). The studies were conducted in three phases: stabilization on prior opioid, conversion to and titration on Dilaudid CR, and maintenance on Dilaudid CR.

Study DO-119 was a randomized, double-blind, repeated-dose, parallel-group comparison of the efficacy of Dilaudid CR and IR in patients with chronic pain. Patients first underwent conversion to and stabilization on Dilaudid IR, followed by double-blinded, randomized administration of Dilaudid IR, Dilaudid CR at full-dose of Dilaudid CR at 1/2 dose.

Study DO-109 was a non-randomized, open-label, extension study for patients completing Study DO-104/5 or DO-119. This study was ongoing as of the cutoff date for the 120-day Safety Update.

SECTION 5.1.2 Demographics and Baseline Characteristics

Section 5.1.2.1 Phase III Trials

The four Phase III clinical trials were: Studies DO-104, DO-105, DO-109 and DO-119. The demographic profiles from the four Phase III trials are presented in Table 5.2. There were more males than females in DO-104 compared to other studies and the integrated population. The mean age in DO-104 was somewhat older and the mean weight somewhat lighter than the other studies. The sponsor used a population of 570 patients in the demographic tables which represents all those patients who received Dilaudid CR except seven patients who were excluded for lack of dosing information (and who did not experience adverse events).

Table 5.2 Summary of Demographics and Baseline Characteristics of Patients Receiving Dilaudid CR in the Phase III Clinical Trials

	Study DO-104	Study DO-105	Study DO-119	Study DO-109 ^a	Updated Integrated CR Population ^b
Characteristic	(N=127)	(N=331)	(N=74)	(N=388)	(N=570)
Gender					
Female	59	182	40	197	297
Male	68	149	34	191	273
Race					
Asian	4	2	0	3	6
Black	10	15	4	20	30
Caucasian	111	307	69	359	524
Other	2	7	1	6	10
Age (yrs)					
N	127	331	74	388	570
Mean	59.9	48.2	46.3	50.1	50.3
SD	12.80	11.70	11.82	12.97	12.88
Median	60.0	46.0	44.0	47.5	48.0
Range	28.0-91.0	20.0-86.0	27.0-81.0	27.0-91.0	20.0-91.0
Height (cm)					
N	124	327	74	384	563
Mean	169.8	170.6	171.6	170.7	170.7
SD	11.47	11.10	8.95	10.72	10.88
Median	170.2	170.2	170.2	170.2	170.2
Range	148.6-195.6	127.0-200.7	142.2-188.0	127.0-200.7	127.0-200.7
Weight (kg)					
N	125	329	74	383	564
Mean	72.8	81.2	83.9	79.9	79.7
SD	18.56	21.98	21.42	20.58	21.32
Median	71.7	77.6	79.4	77.1	77.1
Range	37.2-119.3	39.5-181.4	42.6-153.7	37.2-181.4	37.2-181.4

a Continuation protocol for patients previously completing Protocols DO-104, DO-105, and DO-119.

b The integrated denominator includes patients who received Dilaudid CR during Studies DO-104, DO-105, and DO-119 and also includes patients who were randomized to Dilaudid IR in Study DO-119 and subsequently received Dilaudid CR in Study DO-109.

Source: Table 9.8.2, Vol. 3.1, P. 58, Cross reference ISS Table 8.12.4 (Vol. 115, P.122) in the NDA.

The baseline pain characteristics of the patients in the Phase III studies are summarized in Table 5.3. The majority of patients (442/570, 77.5%) had non-cancer pain, with 52.5% (232/442) of these patients having musculoskeletal pain and 36.2% (176/442) having neuropathic pain. Of the 128 patients with cancer pain, 51.1% (65/128) had pain of somatic origin, and 14.2% (18/128) had pain of neuropathic origin.

Table 5.3 Summary of Baseline Pain Characteristics, Phase III Clinical Trials

	Study DO-104	Study DO-105	Study DO-119	Study DO-109	Updated Integrated CR Population ^a
	(N=127)	(N=331)	(N=74)	(N=388)	(N=570)
Primary Pain Type					
Cancer Pain	127	0	0	79	128
Non-Cancer Pain	0	331	74	309	442
Cancer-Related Pain					
Cancer	0	0	0	1	1
Neuropathic	18	0	0	11	18
Other	7	0	0	5	7
Somatic	65	0	0	44	65
Treatment related	3	0	0	1	3
Visceral	34	0	0	17	34
Non-Cancer Pain					
Musculoskeletal	0	172	40	164	232
Neuropathic	0	132	29	122	176
Other	0	11	1	8	12
Symptom maintain	0	16	4	15	22
Pain Location ^b					
Back	0	192	43	194	261
Limbs	0	176	44	173	240
Face/Head/Neck	0	64	25	62	98
Torso	0	55	10	44	69
Analgesic Requirement					
At Step 3	116	257	74	341	485
Below Step 3	11	74	0	47	85

a The integrated denominator includes patients who received Dilaudid CR during Studies DO-104, DO-105, and DO-119 and also includes patients who were randomized to Dilaudid IR in Study DO-119 and subsequently received Dilaudid CR in Study DO-109.

b Pain location was not collected in Study DO-104. Patients could report pain in multiple locations so categories are not mutually exclusive so these patients are excluded from the calculations.

Source: Table 9.8.2, Vol. 3.1, P. 58, Cross reference ISS Table 8.12.4 (Vol. 115, P.122) in the NDA.

Section 5.1.2.2 Phase I Trials

The Phase I trials consisting of single-dose studies and some crossover designs, which enrolled normal volunteers were: D-101, D-102, D-103, DO-123, DO-124, and Study DO-129. A multiple-dose Study DO-108, enrolled patients with chronic pain.

The demographic characteristics of these studies differed from the Phase III trials, particularly in age. The mean age across the Phase III trials was 50 years. The single-dose studies enrolled normal volunteers with mean age ranging from 27.3 years to 32.4 years, while Study DO-108 enrolled patients with a mean age of 51.2 years. The demographic and baseline characteristics are detailed in Table 5.4.

Table 5.4 Summary of Demographic Data and Baseline Characteristics of Subjects/Patients in the Clinical Pharmacology Studies

	C-96-054 (N=22)	D-101 (N=12)	D-102 (N=30)	D-103 (N=32)	DO-123 (N=36)	DO-124 (N=52)	DO-129 (N=56)	DO-108 (N=22)	Updated Total (N=262)
	N	N	N	N	N	N	N	N	N
Gender									
Female	6	6	9	12	5	23	13	18	92
Male	16	6	21	20	31	29	43	4	170
Race									
Native Amer.	0	0	0	1	1	0	0	0	2
Asian	0	1	0	3	0	0	3	1	8
African-Amer.	3	2	2	1	3	2	5	0	18
Caucasian	19	5	27	26	31	50	48	20	226
Hispanic	0	0	1	1	1	0	0	0	3
Other	0	4	0	0	0	0	0	1	5
Age (yrs)									
Mean	27.5	27.3	33.1	32.7	29.5	32.2	29.7	51.2	32.4
SD	7.0	4.2	10.6	9.2	8.9	10.5	9.5	13.8	11.4
Range	19.0-43.0	21.0-34.0	19.0-49.0	20.0-50.0	19.0-50.0	19.0-50.0	19.0-50.0	25.0-81.0	19.0-81.0
Weight (lbs.)									
Mean	159.3	153.5	169.9	168.2	177.5	166.4	166.0	168.1	167.4
SD	19.7	23.0	19.4	24.0	21.2	21.3	21.2	43.1	24.2
Height ^a (ins)									
Mean	68.9	NA	69.3	69.4	70.4	69.1	70.2	65.7	69.3
SD	3.3	NA	2.9	3.5	3.1	3.7	3.2	3.4	3.5

a Height was not collected in Study DO-101.

Source: Table 9.8.15, Vol. 3.1, P. 177. Cross reference ISS Table 8.12.37 [Volume 116, page 2] in the NDA

SECTION 5.1.3 Extent of Exposure

Section 5.1.3.1 Phase III Trials

The extent of exposure is summarized in Table 5.5. The sponsor used a population of 569 patients for extent of exposure, reflecting the population of 577 patients who received Dilaudid CR and excluding eight patients for whom dosing information was missing. The exposure data was presented by the sponsor in multiples of seven days. There were 315 patients who received Dilaudid CR for at least 84 days, and 94 patients for at least 364 days.

Table 5.5 Updated Duration of Exposure ^a to Dilaudid CR in the Phase III Clinical Trials

Dose Range	0-23 mg	24-35 mg	36-63 mg	64+ mg	Total ^b
Total Patients Exposed	136	130	140	163	569
Duration of Treatment with Dilaudid CR (days)					
1-7	23	18	5	12	58
8-14	16	10	14	17	57
15-21	12	11	8	8	39
22-28	13	7	2	7	29
29-56	4	10	19	11	44
57-84	8	4	8	7	27
> 84	60	70	84	101	315
>168	43	35	65	83	242
>364	17	14	20	43	94
Cumulative Data					
N	136	130	140	163	569
Mean (days)	135.7	157.0	184.2	212.5	174.5
SD	164.71	166.86	162.38	187.85	173.66
Median	47.0	101.5	140.5	178.0	120.0
Range	1.0-645.0	1.0-619.0	3.0-604.0	2.0-639.0	1.0-645.0

a Duration of exposure was calculated and categorized by mean daily dose ranges. Mean daily dose = the average daily dose from the start of titration through the end of the long-term study.

b Total number of patients exposed to Dilaudid CR includes patients who received Dilaudid CR during Studies DO-104, DO-105, and DO-119 and also includes patients who were randomized to Dilaudid IR in Study DO-119 and subsequently received Dilaudid CR in Study DO-109.

Source: Table 9.8.3b, Vol. 3.1, P. 63, Cross reference ISS Table 8.12.6 (Vol. 115, P. 127) in the NDA.

There was no consistent effect of gender on duration of exposure as demonstrated in Table 5.6. There were roughly five times more patients under 65 years old than over 65. The older patients on average spent a smaller duration of time on Dilaudid CR, 155.7 days compared to 178.1 days for patients less than 65 years of age.

Table 5.6 Duration of Exposure ^a to Dilaudid CR by Gender and Age, Phase III Clinical Trials

Characteristic	0-23 mg	24-35 mg	36-63 mg	64+ mg	Total ^b
Duration of Treatment with Dilaudid CR (days)					
Male					
N	67	60	65	80	272
Mean	139.2	137.8	179.8	219.5	172.2
SD	166.53	153.32	157.88	182.68	169.39
Median	60.0	82.5	131.0	201.5	112.0
Range	1.0-645.0	3.0-575.0	5.0-602.0	2.0-629.0	1.0-645.0
Female					
N	69	70	75	83	297
Mean	132.3	173.5	188.1	205.8	176.6
SD	164.06	177.06	167.15	193.57	177.73
Median	37.0	131.0	151.0	162.0	126.0
Range	1.0-608.0	1.0-619.0	3.0-604.0	2.0-639.0	1.0-639.0
<65 years old					
N	110	103	123	141	477
Mean	138.0	150.2	191.0	218.6	178.1
SD	171.02	163.12	164.72	187.19	175.29
Median	47.0	100.0	168.0	183.0	126.0
Range	1.0-645.0	1.0-619.0	3.0-604.0	2.0-639.0	1.0-645.0
65+ years old					
N	26	27	17	22	92
Mean	125.7	182.9	135.6	173.5	155.7
SD	137.27	181.32	139.01	191.72	164.56
Median	67.5	121.0	123.0	60.5	100.5
Range	1.0-441.0	1.0-609.0	9.0-442.0	3.0-575.0	1.0-609.0

a Duration of exposure was calculated and categorized by mean daily dose ranges. Mean daily dose = the average daily dose from the start of titration through the end of the long-term study.

b Total number of patients exposed to Dilaudid CR includes patients who received Dilaudid CR during Studies DO-104, DO-105, and DO-119 and also includes patients who were randomized to Dilaudid IR in Study DO-119 and subsequently received Dilaudid CR in Study DO-109.

Source: Tables 9.8.4b, 9.8.5b, Vol. 3.1, P. 66, 67, 70, 71; Cross reference ISS Tables 8.12.7 and 8.12.8 (Vol. 115, pages 128, 130] in the NDA.

Section 5.1.3.2 Phase I Trials

Patients received single doses of Dilaudid CR in crossover designs in Studies D-101, D-102, D-103, DO-123, DO-124 and DO-129. Duration of exposure is not considered further for these studies. Twenty patients received repeated doses of Dilaudid CR 16 mg in Study C-96-054-01. In Study DO-108, patients with chronic non-malignant pain received repeated, daily doses of Dilaudid CR in dosages ranging from 8 to 64 mg, titrated to analgesia and tolerability. Details of the extent of exposure are presented in Table 5.7.

Table 5.7 Duration of Exposure ^a to Dilaudid CR in Study DO-108

Characteristic	0-23 mg	24-35 mg	36-64 mg	Total
Total Patients Exposed	17	2	3	22
Duration of Exposure to Dilaudid CR (days)				
1-7	0	1	2	3
8-14	7	0	0	7
15-21	9	1	0	10
22-28	1	0	1	2
Duration of Exposure to Dilaudid CR (days)				
N	17	2	3	22
Mean	14.9	11.5	12.0	14.2
SD	4.18	13.44	9.54	5.69
Median	15.0	11.5	7.0	15.0
Range	8.0-23.0	2.0-21.0	6.0-23.0	2.0-23.0

^a Duration of exposure was calculated and categorized by mean daily dose ranges. Mean daily dose = the average daily dose from the start of titration

Source: Table 9.8.14, Vol. 3.1, P. 25.

Most of the patients in DO-108 received less than 24 mg/day of Dilaudid CR. The mean duration of treatment was 14.9 days for these patients and 14.2 days for the entire study population.

SECTION 6 REVIEW OF EFFICACY

SECTION 6.1 FINDINGS

The sponsor submitted three Phase III clinical trials in support of efficacy. Study DO-119 was a multicenter, randomized, double-blind, active-controlled repeated-dose study. Studies DO-104 and DO-105 were open-label, non-randomized studies combined into one report.

Study DO-119 was the only study submitted by the sponsor that could be considered an adequate and well-controlled trial. The study was designed to evaluate the ability of Dilaudid CR to control malignant and non-malignant chronic pain, in a dose controlled design comparing Dilaudid IR, 1/2-dose Dilaudid CR, and full-dose Dilaudid CR. The primary outcome measure planned was the change in daily doses of breakthrough-pain medication across days 3 through 7 of the double-blind phase of the study. The secondary measures planned were: pain intensity, pain relief, sleep interference, ratings on the Brief Pain Inventory, normalized breakthrough-pain medication, Global Evaluation ratings, and proportion of patients dropping out due to lack of efficacy.

Post-hoc analyses performed by the sponsor were: the total daily dose of breakthrough-pain medication by categorizing the direction of change, the number of doses/day using regression analysis, percent change of total daily dose, and analyses based on special populations.

The treatment groups were similar in most baseline characteristics. The baseline amounts of around-the-clock hydromorphone were similar for patients in the different treatment groups, but the patients randomized to full-dose Dilaudid CR had a greater amount of breakthrough medication at baseline than patients randomized to the other treatment groups. This did not reach statistical significance.

Analysis of the primary efficacy variable revealed a small increase in the amount of breakthrough-pain medication used by all three treatment groups across days 3 through 7 of the double-blind phase, which did not reach statistical significance in between-group analyses. The within-treatment differences, however, were significant for all three treatments. There were no statistically significant between-group differences for the secondary efficacy variables of pain intensity, pain relief or sleep interference. Pain relief was slightly worse for all three groups, but only reached a within-group, statistically significant difference for the 1/2-dose Dilaudid CR. Pain intensity was unchanged for Dilaudid CR, slightly worse for Dilaudid IR and had the greatest increase for the 1/2-dose Dilaudid group, reaching a within-group, statistically significant difference. The difference in normalized dose of breakthrough-pain medication did not reach statistical significance between treatment groups. The dose of breakthrough-pain medication increased over the treatment period reaching a statistically significant difference from baseline within each treatment group.

The outcomes of the post hoc analyses performed by the sponsor were variable. The direction of change from baseline to endpoint reached statistical significance between Dilaudid CR and 1/2 Dilaudid CR. The percent change in breakthrough-pain medication used between endpoint and baseline reached a statistically significant difference between Dilaudid CR and 1/2 Dilaudid CR.

The change in the number of times/day of breakthrough-pain medication from baseline to endpoint did not reach statistical significance for any between-treatment group comparisons. There were no statistically significance differences between Dilaudid CR and Dilaudid IR for the post hoc analyses.

There are important statistical points to consider regarding these post hoc analyses: 1) There were no corrections in p-value for the multiple comparisons. 2) By evaluating the percent change in breakthrough-pain medication dose, a relatively small change from a lower dose can be equivalent to a larger change from a higher dose without similar clinical relevance. For example, a change in medication from 1 mg to 2 mg represents a 100% increase and from 2 mg to 1 mg a 50% decrease. Both situations represent a small amount of medication and have limited clinical meaning. A change from 30 mg to 60 mg represents a 100 % increase and 60 mg to 30 mg a 50% decrease. These changes are more clinically meaningful.

The actual change in the amount of breakthrough medication, normalized dose of breakthrough medication, and number of times breakthrough medication was used each day, all failed to reach statistical significance. This underscores the lack of clinical importance of the percent change finding.

The patients in all three treatment groups required, on average, more breakthrough-pain medication at endpoint compared to baseline and worsened pain relief. Furthermore, fewer patients in all three groups rated the overall effectiveness of study medication in the Global Evaluation as “good” to “excellent”.

The results of this study not only fail to demonstrate that Dilaudid CR is more effective than 1/2 Dilaudid CR or Dilaudid IR, but suggest that pain control on full-dose Dilaudid CR, 1/2-dose Dilaudid CR, and Dilaudid IR was not sustained throughout the duration of this study and may have been inferior to the treatment used prior to the study. An additional minor problem is that the 64 mg tablet was not studied in this protocol. Thus, data is only available for the 8, 16, and 32 mg tablets.

Studies DO-104 and DO-105 evaluated the ability of Dilaudid CR to reduce the need for rescue medication in patients with chronic malignant and non-malignant pain. These were open-label studies differing only in patient population and were reported in a single report. The results were mixed. While patients had modest improvements in pain control, there was a marked increase in the use of rescue medication. With the open-label, non-comparator study design, there is no way to determine what is responsible for these findings. The improvement in pain relief may be a reflection of efficacy of Dilaudid CR, efficacy of the nearly universal use of Dilaudid IR rescue medication, and/or a placebo effect.

SECTION 6.2 INDIVIDUAL STUDIES CONTRIBUTING TO EFFICACY

SECTION 6.2.1 STUDY D0-119

Section 6.2.1.1 Study Protocol

Title: A Randomized, Double-Blind, Repeated-Dose, Parallel-Group Comparison Of The Efficacy And Tolerability Of Dilaudid CR Tablets And Immediate Release Dilaudid Tablets In Patients With Chronic Pain

Objective: To characterize a safe and effective means of conversion and titration to an appropriate dose of Dilaudid. Demonstrate significant differences in the amount of breakthrough-pain medication taken in comparison between the full-dose Dilaudid CR group and the 1/2-dose Dilaudid CR group. If the 1/2-dose Dilaudid CR group does not require more rescue medication, then it is anticipated that the full-dose Dilaudid CR will demonstrate superior efficacy. Demonstrate comparable efficacy of Dilaudid CR and Dilaudid IR.

Study Design: (Vol. 1.68, P. 4)

Three phases:

- Visit 1: Screening - medical history, primary diagnosis and type of pain, analgesic history, medications, physical exam, labs. Stabilization on prior opioid, for up to 7 days. Stabilization was to be defined as two consecutive days with no change in total dose and no more than three doses of rescue per day.
 - Visit 2: Conversion to open-label Dilaudid IR with titration to optimal analgesia and stabilization. The 24 hour baseline opiate dose exclusive of breakthrough medication was to be converted to hydromorphone at a ratio of 5 mg oral morphine equivalents to 1 mg oral hydromorphone. Titration of Dilaudid IR was to be in 10 mg increments and completed within 14 days. Patients on transdermal patches were to have the patch removed at Visit 2, and after two days, converted to 10 mg of Dilaudid IR for each 25 ug/h of fentanyl.
 - Visit 3: Double-blind administration of either Dilaudid IR or CR (at full or 1/2 of the total daily dose determined during titration) - This was to be a seven day period, using a double dummy design. Patients were to require from 20-60 mg of Dilaudid IR exclusive of breakthrough following phase 2 to qualify for this phase of the study.
-
- Breakthrough-pain medication was to be limited to immediate release Dilaudid, dosed at 15-30% of the total daily Dilaudid dose
 - Concomitant medication permitted: bowel regimen
 - Study medication: Dilaudid IR 2, 4 mg
Dilaudid CR 8, 16, 32 mg
Placebo

Study Schematic:

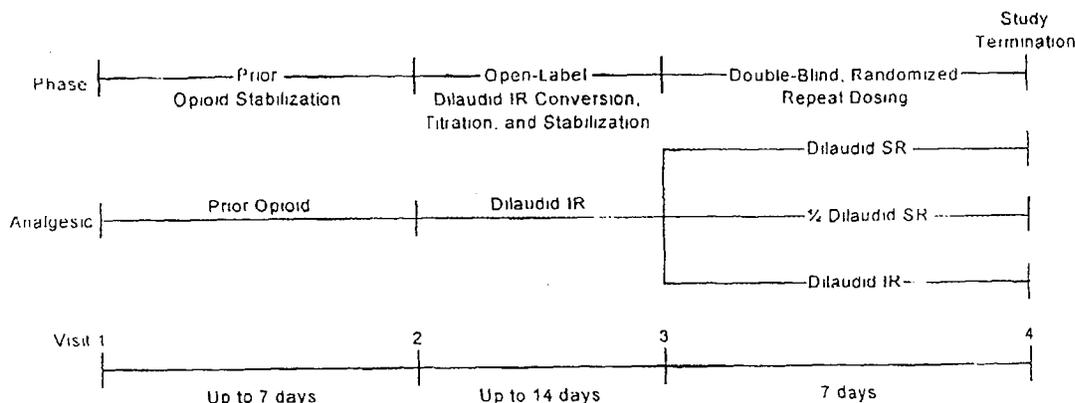


Figure 1. Study Phases

Study Duration: up to 28 days, with option of enrollment in long-term extension at termination

Population: Enrollment of sufficient patients to ensure a total of 75 completed patients, 25 per treatment arm.

Inclusion Criteria:

1. Chronic nonmalignant or cancer pain, currently receiving strong oral or transdermal opioid analgesics on daily bases or suitable for advancement to step 3 on the WHO analgesic ladder
2. Male or female, at least 18 years of age
3. At visit 2, require the equivalent of 80 to 300 mg of oral morphine q 24h or 25-75 ug/h of fentanyl
4. Must be on stable dose of opioid at visit 2- defined as two consecutive days with no change in total daily dose and no more than three opioid rescue doses per day
5. Expectation of reasonably stable opioid requirements during study
6. Medically recognized contraceptive program for female patients and negative pregnancy test prior to administration of study drug

Exclusion Criteria:

1. Hypersensitive or intolerant of hydromorphone or other opioids
2. Dysphagia/unable to swallow tablets
3. Pregnant or breast-feeding
4. Participation in new investigational drug study within 30 days
5. Active blood loss or clinically significant bleeding disorder
6. More than three episodes of vomiting/day within three days of the study, intractable nausea
7. No prior bowel movement or obstruction due to impaction within five days
8. Any GI disorder including GI narrowing that may affect absorption or transit
9. S/p bowel resection
10. Acute abdominal condition that may be obscured by opioids
11. Requirement of radiation therapy during study
12. Known active or h/o drug or alcohol abuse within one year

13. Respiratory compromise/depressed ventilatory function
14. Significant CNS disorder
15. Risk of decreased BP due to opioid administration
16. Clinically significant, impaired hematological function (HCT \leq 25%)
17. Clinically significant renal or hepatic dysfunction, Addison's disease, hypothyroidism
prostatic hypertrophy or urethral stricture

Proposed Analysis Plan:

Sample size determination

The calculations were based on the variance estimate observed in a study in the literature comparing the efficacy and safety of KadianTM/KapanolTM(K) q 24h to Kadian or MS Contin q 12h. The estimate of standard deviation of normalized breakthrough-pain medication at the final day evaluation was 35.7% for the group receiving Kadian q 24h. In addition, a 30% difference was expected in normalized breakthrough-pain medication between the full and half dose Dilaudid CR groups.

Interim Analysis: None planned

Efficacy Variables

Primary efficacy variable - the change from baseline in total daily dose of breakthrough-pain medication for the full-dose Dilaudid CR group vs. 1/2-dose Dilaudid CR group.

Secondary efficacy variables:

- Diary based pain intensity (11 point scale)
- Pain relief
- Sleep interference ratings
- Brief Pain Inventory (BPI)
- Normalized breakthrough-pain medication
- Global Evaluation ratings - Both patient and investigator assess overall effectiveness of study medication on a five point scale from 1 (poor) to 5 (excellent).
- Proportion of patients dropping out due to lack of efficacy

Statistical Methods

1. General plan:
 - No adjustments for multiple comparisons or variables were planned.
 - All statistical analyses were to be 2-sided.
2. The primary outcome measure, daily breakthrough medication, and secondary outcome measures (diary based pain intensity, pain relief, sleep interference ratings, BPI, normalized breakthrough-pain medication) were each to be analyzed using an ANOVA model including treatment-by-center terms, if appropriate.
3. The change from baseline to endpoint was to be calculated for all variables for each patient and the mean of these differences for each treatment group calculated for inferential testing purposes. Baseline was to be defined as the mean responses of the last two days during the open-label conversion and titration with Dilaudid IR. BPI and Global Evaluation baselines were to be done at Visit 3. Endpoint was to be defined as the mean response from days 3-7 of the double-blind phase. BPI and Global Evaluation were to be done at Visit 4 or study termination

4. The Global Evaluation was to be analyzed at Visits 3 and 4 using the Cochran Mantel-Haenzel (CMH) test with row mean scores, controlling for center.
5. The proportion of patients dropping out due to lack of efficacy was to be analyzed using the chi-square test.
6. To compare the efficacy of Dilaudid CR and IR following the administration of comparable doses, 90% confidence intervals were to be constructed around the mean change from baseline for each efficacy variable, but no formal statistical inference was planned.
7. To evaluate the means of conversion and titration to Dilaudid, time to titration to an appropriate Dilaudid dose was to be summarized along with analyses related to daily use of breakthrough medication.

Protocol Amendments:

Amendment 01, 1/19/99

- The range of qualifying doses for patients using transdermal fentanyl as prior opioid was changed from 25-75 ug/h to 25-125 ug/h.
- Administrative changes to correct an error in the description of the patient diary, the pain relief rating was changed from "0 (no relief) to 10 (complete relief) to "0% (no relief) to 100% (complete relief)
- Text was added describing unblinding of study medication in the setting of an emergency.

Section 6.2.1.2 Study Conduct

A number of additional analyses were added post-hoc.

1. Categorization of the change in total daily dose of breakthrough-pain medication, analyzing the number of doses/day of breakthrough-pain medication using a Poisson regression analysis. This included an analysis with effects due to treatment and day.
2. Categorization of change in total daily dose of breakthrough-pain medication using the CMH test
3. Percent change of total daily dose with 0.5 mg imputation for all non-missing values
4. Analyses based on special populations.

Section 6.2.1.2.1 Disposition

A total of 169 patients were enrolled from 15 centers. Only 113 entered the randomized phase. Twenty one patients dropped out while undergoing stabilization on their prior opioid. The remaining 148 patients all received at least one dose of study medication (Dilaudid IR or CR) and were considered to be the safety population by the sponsor, even if they did not receive Dilaudid CR. Of the 148 patients entering the conversion, titration and stabilization on Dilaudid IR phase, 35 dropped out. Of the 113 patients entering the randomized treatment phase, seven dropped out. The details of the disposition of these patients is presented in Table 6.1. The study Appendix 2.9 (Vol. 1.72) contains the listing of all patients treated and those who dropped out of the study. There is no identification of which patients left the study during which of the three study phases. Additional information was requested from the sponsor to delineate the patient identification numbers of those to discontinue study participation prematurely. This information was received by fax on 10/2/00. The sponsor did not define a specific evaluable population, but

based inclusion in the efficacy analyses on the presence or absence of data for the variable and time point of interest. This results in different numbers of patients included in different analyses.

Table 6.1 Disposition of Patients Who Enrolled in Study DO-119

Patient Disposition	All Patients Entered n
Entered into the study	169
Safety Population - Treated with Study Meds ^a	148
Discontinued during Dilaudid IR conversion, titration and stabilization phase	35
Intent-to-Treat Population - All Patients Randomized	113
Discontinued during double-blind, randomized, repeat dosing phase	7
Adverse Event	2
Withdrawal of consent	3
Lack of efficacy	2

^a All patients receiving at least one dose of Dilaudid IR.

Source: Sponsor's Table 11, Vol. 1.67, P. 51.

Table 6.2 further describes the disposition of the 113 patients entering the randomized third phase of the study. Among the seven patients who dropped out, two patients discontinued the study due to adverse events and they had been receiving full-dose Dilaudid CR. The CRFs for the two patients who withdrew due to adverse events were reviewed. Patient 41-19002, had experienced increased pain on study day 2 due to a bus accident which persisted through day 6. On study day 6, the patient did not receive any relief from the first dose of study medication that day and switched back to his prior analgesic, OxyContin® with oxycodone for rescue. Patient 81-19008 discontinued study participation due to general body itching. The two patients who discontinued the study early due to lack of efficacy were receiving half dose Dilaudid CR. Three patients withdrew study consent, one in the Dilaudid CR group and 2 in the 1/2-dose Dilaudid CR group. No details for these three patients were available for review.

Table 6.2 Patient Disposition, Double-Blind, Randomized, Repeat Dosing Phase

Patient Disposition	Dilaudid CR n	1/2 Dilaudid CR n	Dilaudid IR n	All Groups n
Randomized	34	40	39	113
Completed Study	31	36	39	106
Early Discontinuation	3	4	0	7
Primary Reason-				
Adverse Event	2	0	0	2
Consent Withdrawn	1	2	0	3
Lack of Efficacy	0	2	0	2

Source: Sponsor's Table 12 Vol. 1.67, P. 52

Protocol violations

There were 10 patients discontinued from the study prior to randomization due to protocol violations; seven occurred during the prior opioid stabilization phase and three during conversion to Dilaudid IR. Of these patients, five were outside the 80 to 300 mg morphine equivalent range

of analgesic requirement, three were not titrated to a stable dose of either prior opioid or Dilaudid IR, one was noncompliant, and one was identified as having a prior bowel resection.

There was one protocol violation among the 113 patients randomized in phase 3, a patient who had been on a higher Duragesic dose than permitted. This patient received blinded study drug and was included in the efficacy analysis.

Section 6.2.1.2.2 Demographics and Baseline Characteristics

The demographic characteristics were collected at screening. There were more female patients in the 1/2 Dilaudid CR group compared to the other treatment groups, otherwise, demographic characteristics were comparable. No differences reached statistical significance. Baseline was defined as the last two days on a stable dose during the open-label phase between Visits 2 and 3.

Table 6.3 Demographics and Baseline Characteristics at Screening, Randomized Patients by Treatment Group

Baseline Characteristics	Dilaudid CR (N=34) ^a	1/2 Dilaudid CR (N=40)	Dilaudid IR (N=39)	All Groups (N= 113)	p-Value ^b
Sex (n ^a , %)					0.1264
Female	15 (44.1)	25 (62.5)	16 (41.0)	56 (49.6)	
Male	19 (55.9)	15 (37.5)	23 (59.0)	57 (50.4)	
Race (n, %)					0.4381
Black	3 (8.8)	1 (2.5)	1 (2.6)	5 (4.4)	
Caucasian	31 (91.2)	38 (95.0)	38 (97.4)	107 (94.7)	
Other	0 (0.0)	1 (2.5)	0 (0.0)	1 (0.9)	
Age (yrs)					0.6613
N	34	40	39	113	
Mean±STD	46.9±11.8	45.7±12.0	44.6±8.7	45.7±10.8	
Median	46	43.5	45	44	
Range	27-72	28-81	29-60	27-81	
Height (cm)					0.1958
N	34	40	39	113	
Mean±STD	173.5±8.1	169.9±9.4	173.0±10.3	172.1±9.4	
Median	172.7	167.6	175.3	172.7	
Range	160.0-185.4	142.2-188.0	149.9-200.7	142.2-200.7	
Weight (kg)					0.3992
N	34	40	37	111	
Mean±STD	86.9±22.4	81.3±20.6	80.9±19.2	82.9±20.7	
Median	82.8	77.6	77.1	78.9	
Range	57.9-153.8	42.6-133.4	49.0-152.4	42.6-153.8	

a N = Number of patients randomized; n = Number of patients evaluated

b p-value for age, height and weight based on ANOVA , p-value for race and gender based on Fisher's Exact Test

Source: Table 14, Vol. 1.67, P. 58

There were no statistically significant baseline differences in heart rate (p=0.56), systolic blood pressure (p=0.06), diastolic blood pressure (p=0.37) or respiration (p=0.90).

Baseline Pain and Analgesia Characteristics

The baseline pain characteristics were similar across treatment groups with the 1/2 Dilaudid CR group having more musculoskeletal type pain. The patients in the Dilaudid CR group had more pain involving the limbs. All patients were at Step 3 of the WHO Analgesic Ladder. The amount of opioid medication required at baseline in morphine equivalents was not provided. None of the differences reached statistical significance.

Table 6.4 Baseline Pain and Analgesic Characteristics for Patients Entering Double-Blind Phase by Treatment Group

Baseline Characteristic	Dilaudid CR (N=34) ^a n ^a (%)	1/2 Dilaudid CR (N=40) n (%)	Dilaudid IR (N=39) n (%)	All Groups (N=113) n (%)
Pain Type				
Sympathetic	3 (8.8)	1 (2.5)	2 (5.1)	6 (5.3)
Musculoskeletal	16 (47.1)	24 (60.0)	20 (51.3)	60 (53.1)
Neuropathic	15 (44.1)	14 (35.0)	15 (38.5)	44 (38.9)
Cancer	0 (0.0)	0 (0.0)	2 (5.1)	2 (1.8)
Other	0 (0.0)	1 (2.5)	0 (0.0)	1 (0.9)
p-Value ^b	N/A ^c	N/A	N/A	0.5718
Pain Location				
Back	18 (52.9)	25 (62.5)	26 (66.7)	69 (61.1)
Limbs	21 (61.8)	23 (57.5)	20 (51.3)	64 (56.6)
Face/Head/Neck	11 (32.4)	14 (35.0)	9 (23.1)	34 (30.1)
Torso	5 (14.7)	5 (12.5)	5 (12.8)	15 (13.3)
Analgesic Requirement^d				
Step 3	34 (100.0)	40 (100.0)	39 (100.0)	113 (100.0)

a N = Number of patients entered into that study phase, n = Number of patients evaluated

b p-Value based on Fisher's Exact Test

c N/A = Not applicable

d WHO Analgesic Ladder Step 1 = mild to moderate cancer-related pain, to be treated with non-opioid analgesic or combined with adjuvant drugs, Step 2 = limited opioid exposure with moderate to severe pain or failed to achieve adequate relief after a trial of a non-opioid analgesic, Step 3 = severe pain or failed to achieve adequate relief following administration of Step 2 opioids

Source: Table 16, Vol. 1.67, P. 59

Patients entering the randomized phase first had to be stabilized on Dilaudid IR and this was defined as two days on a constant dose of Dilaudid IR with no more than three doses of breakthrough-pain medication per day. There was no statistically significant difference in the time to reach this stabilization between patients subsequently assigned to the different treatment groups (p=0.71).

The total amount of hydromorphone, exclusive of breakthrough medication, at baseline was comparable between the treatment groups. At the endpoint of the study, the hydromorphone doses were unchanged for the Dilaudid CR and IR groups and, as defined by the protocol, half the baseline dose for the 1/2 Dilaudid group. This is summarized in Table 6.5.

Table 6.5 Total Daily Dose of Hydromorphone by Study Time Point by Treatment Group

Study Time Point	Dose at Study Time Point (mg)			
	Dilaudid CR (N=34) ^a	1/2 Dilaudid CR (N=40)	Dilaudid IR (N=39)	All Groups (N= 113)
Baseline (End of Titration Phase) ^b				
n ^a	34	40	39	113
Mean±STD	36.7±14.3	35.0±14.0	37.9±15.0	36.5±14.4
Median	30.0	30.0	40.0	30.0
Range	20-60	18-60	18-60	18-60
Endpoint (Double-Blind Phase) ^c				
n	33	38	39	110
Mean±STD	39.0±14.1	16.6±8.0	37.3±15.0	30.7±16.2
Median	32.0	16.0	40.0	30.0
Range	24-64	8-32	16-60	8-64

a N = Number of patients randomized; n = Number of patients evaluated

b All patients who received Dilaudid IR, assessed as the mean of the last 2 stable days of the titration phase.

c Assessed as the mean of Days 3 to 7 of the double-blind phase

Source: Table 23, Vol. 1.67, P. 67

Section 6.2.1.2.3 Sponsor's Results

Primary Efficacy Variable

The primary efficacy measurement was defined as the total daily dose of breakthrough-pain medication. Although at baseline the 1/2 Dilaudid CR group used less than the other groups, there was no statistically significant difference in the amount of breakthrough medication used between treatment groups. This was also true when the normalized dose and number of times used each day were evaluated. This information is summarized in Table 6.6.

Table 6.6 Baseline Breakthrough-pain Medication Use by Treatment Group

Baseline Parameter	Dilaudid CR (N=34) ^b	1/2 Dilaudid CR (N=40)	Dilaudid IR (N=39)	All Groups (N= 113)
Total Daily Dose (mg)				
n ^a	34	40	39	113
Mean±STD	16.4±16.3	10.7±9.9	14.3±16.4	13.7±14.5
Median	9.0	8.0	6.0	8.0
Range	0-64	0-36	0-52	0-64
p-Value	N/A ^b	N/A	N/A	0.2520 ^b
Normalized Dose (%) ^c				
n	34	40	39	113
Mean±STD	43.0±33.3	28.2±22.7	32.5±29.9	34.2±29.1
Median	33.5	25.8	25.0	30.0
Range	0-160	0-90	0-100	0-160
p-Value	N/A	N/A	N/A	0.1329 ^b
Number of Times/Day of Breakthrough-pain Medication Use				
n	34	40	39	113
Mean±STD	2.1±0.9	1.8±1.1	1.7±1.2	1.8±1.1
Median	2.0	2.0	2.0	2.0
Range	0-3	0-4	0-3	0-4
p-Value	N/A	N/A	N/A	0.3441 ^b

a N = Number of patients randomized; n= Number of patients evaluated

b Kruskal-Wallis test

c The total amount of breakthrough-pain medication converted to a % of the final titrated dose of Dilaudid IR.

At the endpoint for efficacy analyses, the mean of days 3-7, on non-missing diary days, there were no statistically significant differences in the amount of rescue medication used between treatment groups. This was true for the total daily dose of breakthrough medication, as well as for the change in total daily dose from baseline. However, within each group, patients required more breakthrough-pain medication at endpoint than at baseline, reaching statistical significance for all three treatment groups, as summarized in Table 6.7.

Table 6.7 Breakthrough-Pain Medication: Total Daily Dose at Endpoint and Change from Baseline to Endpoint by Treatment Group

Parameter	Dilaudid CR (N=34) n ^a (%)	1/2 Dilaudid CR (N=40) n (%)	Dilaudid IR (N=39) n (%)	All Groups (N=113) n (%)
Total Daily Dose (mg)				
Endpoint ^b				
n	33	38	39	110
Mean±STD	23.2±19.8	19.1±17.5	21.4±23.8	21.1±20.5
Median	18.0	11.4	16	14.4
Range	0-80.0	0-76.8	0-108.8	0-108.8
p-Value	N/A	0.5681 ^c	0.3717 ^d	^e
Change From Baseline				
n	33	38	39	110
Mean Change ±SD	6.6±16.0	9.2±12.0	7.1±14.5	7.7±14.1
Median	2.0	7.4	4.4	5.1
Range	-24.0-64.0	-8.2-52.8	-23.2-60.8	-24.0-64.0
p-Value				
Within treatment ^f	0.027	<0.001	0.001	N/A
Between treatment	N/A	0.159 ^c	0.760 ^c	^e

a N = Number of patients randomized, n = Number of patients evaluated

b Endpoint is the mean of Days 3 to 7 of the double-blind phase based on non-missing diary days

c Dilaudid CR vs. 1/2 Dilaudid CR. Wilcoxon Rank-Sum test

d Dilaudid CR vs. Dilaudid IR. Wilcoxon Rank-Sum test

e Overall p-value Kruskal-Wallis test Endpoint, p=0.6927 Change from baseline, p=0.238

f Wilcoxon Signed Rank test.

Source: Table 25, Vol. 1.67, P. 71

Secondary Efficacy Analyses

Pain Relief/Pain Intensity/Sleep Interference

Pain relief on a scale of 0-100, pain intensity on a scale of 0-10 and sleep interference on a scale of 0-10 were to be recorded daily in the patient diary. In an assessment by the sponsor, comparing baseline diary based analgesia scores by treatment group, there were no statistically significant differences between treatment groups for the baseline values (p= 0.45 for pain relief, 0.61 for pain intensity, and 0.73 for sleep interference). A similar assessment for pain relief, pain intensity, and sleep interference at the study endpoint also failed to demonstrate any statistically significant between group differences (p = 0.17, 0.91, and 0.42 respectively).

When the change from baseline to endpoint for these variables was compared between treatment groups, again, no statistically significant differences were obtained as summarized in Table 6.8. Pain relief was worse for all three treatment groups at the end of the treatment period, although

the amount of decrease in pain relief, when compared between groups, did not reach statistical significance. When pain relief at the study endpoint was compared to pain relief at baseline within each group, there was one group difference that reached statistical significance. This was for the 1/2 Dilaudid CR group.

The change in pain intensity from baseline to study endpoint demonstrated worsened pain for all three treatment groups. The change in pain intensity did not reach statistical significance in between group analyses. The within group comparison of pain intensity from baseline to endpoint demonstrated a statistically significant increase only for the 1/2 Dilaudid CR group.

Sleep interference was slightly worse at study endpoint compared to baseline for the Dilaudid IR group, and slightly improved for the Dilaudid CR and 1/2 Dilaudid CR groups. However, none of the between group or within group comparisons reached statistical significance.

Table 6.8 Change in Diary-Based Analgesia Scores From Baseline to Endpoint by Treatment Group

Endpoint ^a Parameter	Dilaudid CR (N=34) ^b	1/2 Dilaudid CR (N=40)	Dilaudid IR (N=39)	All Groups (N= 113)
Pain Relief ^c				
n ^b	33	38	39	110
Mean Change±STD	-3.6±16.1	-9.0±16.9	-3.6±17.0	-5.5±16.7
Median	-2.0	-7.0	-2.0	-3.0
Range	-37-30	-55-31	-43-32	-55-32
p-Value ^d				
Within treatment	0.2096	0.0023	0.1918	N/A ^e
Between treatment	N/A	0.2014 ^f	0.6707 ^g	^h
Pain Intensity				
n	33	38	39	110
Mean Change±STD	0.1±1.4	0.7±1.7	0.2±1.6	0.3±1.6
Median	0.0	0.7	0.2	0.2
Range	-3-3	-3-7	-3-6	-3-7
p-Value ^d				
Within treatment	0.8467	0.0168	0.4395	N/A
Between treatment	N/A	0.2247 ^f	0.9078 ^g	^j
Sleep Interference ⁱ				
n	33	38	39	110
Mean Change±STD	0.2±2.2	0.4±2.4	-0.2±1.9	0.1±2.2
Median	0.0	0.2	0.0	0.0
Range	-5-7	-6-6	-5-5	-6-7
p-Value ^d				
Within treatment	0.6154	0.3671	0.5309	N/A
Between treatment	N/A	0.9292 ^f	0.2276 ^g	^j

a Endpoint was the mean of Days 3 to 7 of the double-blind phase based on non-missing diary days

b N = Number of patients randomized; n = Number of patients evaluated.

c Pain relief. 0% (no relief) to 100% (complete relief).

d Within treatment comparisons based on paired t-test. Between treatment comparisons based on ANCOVA model

e N/A = Not applicable.

f Dilaudid CR vs. 1/2 Dilaudid CR

g Dilaudid CR vs. Dilaudid IR

h Pain intensity 0 (no pain) to 10 (pain as bad as you can imagine).

i Sleep interference 0 (does not interfere) to 10 (completely interferes).

j Overall p-value. Pain relief, p=0.1857 Pain intensity, p=0.3877 Sleep interference, p=0.3848

Source: Table 32, Vol. 1.67, P. 82

Normalized dose

Normalized dose was defined as the total daily amount of breakthrough medication converted to a percentage of the final titrated dose of Dilaudid IR. This evaluation compared the change from baseline to endpoint where endpoint was defined as Day 3 to Day 7 of the double-blind, randomized phase of the study. There were no differences that reached statistical significance in between group or within group analyses.

Table 6.9 Normalized Dose of Breakthrough-pain Medication at Endpoint and Change From Baseline to Endpoint by Treatment Group

Parameter	Dilaudid CR (N=34) ^a	1/2 Dilaudid CR (N=40)	Dilaudid IR (N=39)	All Groups (N=113)
Normalized Dose (%) ^b				
Endpoint ^c				
n ^a	33	38	39	110
Mean±STD	61.7±48.7	50.5±30.9	49.1±42.6	53.4±41.0
Median	51.2	43.8	48.0	48.0
Range	0-200	0-128	0-181	0-200
p-Value	N/A ^d	0.4890 ^e	0.2929 ^f	g
Change From Baseline				
n	33	38	39	110
Mean Change±STD	18.3±46.0	24.2±28.0	16.5±28.5	19.7±34.4
Median	5.3	18.0	12.0	13.3
Range	-60-160	-41-88	-39-101	-60-160
p-Value				
Within treatment ^h	0.032	<0.001	<0.001	N/A
Between treatment	N/A	0.124 ^e	0.752 ^f	g

a N = Number of patients randomized; n = Number of patients evaluated

b The total amount of breakthrough-pain medication converted to a % of the final titrated dose of Dilaudid IR.

c Endpoint is the mean of Days 3 to 7 of the double-blind phase based on non-missing diary days

d N/A = Not applicable.

e Dilaudid CR vs. 1/2 Dilaudid CR. Wilcoxon Rank-Sum test

f Dilaudid CR vs. Dilaudid IR Wilcoxon Rank-Sum test.

g Overall p-value. Kruskal-Wallis test Endpoint, p= 0.5316 Change from baseline, p=0.207.

h Wilcoxon Signed Rank test.

Source: Table 28, Vol. 1.67, P. 74

Wisconsin Brief Pain Inventory

There were no statistically significant differences between treatment groups at baseline or at endpoint for the subsets of the Wisconsin Brief Pain Inventory. The between group analyses for the change in score from baseline to endpoint reached a statistically significant difference for only one subset, "Relations with Other People". The comparison between Dilaudid CR and IR for this subset reached a statistically significant difference (p=0.0346). The sponsor indicated this isolated finding was likely without clinical significance given the lack of treatment effect found for other measures of social functioning including "Mood" or "Enjoyment of Life" or overall score. There were no statistically significant differences resulting from the between group analyses for: "Pain at Its Worst in the Past 24h", "Pain at Its Least in the Past 24h", "Pain on Average", "Pain Right Now", "Percent Pain Relief Provided in the Past 24h", "General Activity", "Walking Ability", "Normal Work", or "Sleep".

Global Pain Evaluation

The percentage of patients rating the overall effectiveness of study medication as “good” to “excellent” changed from 84% at baseline to 62.9% at study endpoint. There were no differences that reached statistical significance in between-group analyses (Dilaudid CR vs. 1/2-dose Dilaudid CR, $p=0.345$; Dilaudid CR vs. Dilaudid IR, $p=0.230$). However, for within-group analyses, there were statistically significant changes characterized by a lowering of the rating scores for Dilaudid CR ($p=0.002$) and 1/2-dose Dilaudid CR ($p=0.013$), but not Dilaudid IR ($p=0.259$).

Similarly, the percentage of investigators rating the overall effectiveness of study medication as “good” to “excellent” changed from 84% at baseline to 65.5% at study endpoint. There were no differences that reached statistical significance in between-group analyses (Dilaudid CR vs. 1/2-dose Dilaudid CR, $p=0.213$; Dilaudid CR vs. Dilaudid IR, $p=0.072$). However, for within-group analyses, there were statistically significant changes characterized by a lowering of the rating scores for Dilaudid CR ($p=0.0005$) and 1/2-dose Dilaudid CR ($p=0.012$), but not Dilaudid IR ($p=0.369$).

Proportion Of Patients Dropping Out Due To Lack Of Efficacy

Although a planned secondary outcome measure, the proportion of patients dropping out due to lack of efficacy was not discussed or addressed in the results section by the sponsor. Of the 113 patients randomized, two dropped out due to lack of efficacy. Both of these patients were in the 1/2-dose Dilaudid CR group. No inferential statistics were performed on this result. There were three patients who discontinued study participation early with the reason “withdrew consent”. It is possible that these study withdrawals were related to lack of efficacy, but this cannot be conclusively determined.

Table 6.10 Drop-outs, Study DO-119

Patient Disposition	Dilaudid CR n (%)	1/2 Dilaudid CR n (%)	Dilaudid IR n (%)	All Groups n (%)
Randomized	34	40	39	113
Completed Study	31 (91.2)	36 (90.0)	39 (100.0)	106 (93.8)
Early Discontinuation	3 (8.8)	4 (10.0)	0 (0.0)	7 (6.2)
Primary Reason-				
Adverse Event	2 (5.9)	0 (0.0)	0 (0.0)	2 (1.8)
Consent Withdrawn	1 (2.9)	2 (5.0)	0 (0.0)	3 (2.7)
Lack of Efficacy	0 (0.0)	2 (5.0)	0 (0.0)	2 (1.8)

Subgroup Analyses

Race

There were insufficient non-White subjects (6 of 113) for meaningful comparisons.

Gender

There were 57 men and 56 women enrolled in Study DO-119. There were no statistically significant differences between treatment groups by gender for any baseline or endpoint measure of breakthrough-pain medication. There were no statistically significant effects of gender on the

change in total daily dose of breakthrough-pain medication, normalized dose or number of times per day of breakthrough-pain medication use from baseline to endpoint.

There were few statistically significant gender differences among the secondary outcome measures. In women, the difference between the 1/2 Dilaudid CR group and the Dilaudid CR group for the mean change in pain relief score from baseline to endpoint reached statistical significance in the between group analysis (p = 0.0185), but not for men (p=0.4418). This change represented worsened pain relief in women in the 1/2 Dilaudid CR group. Also in women, the difference between the 1/2 Dilaudid CR group and the Dilaudid CR group for the mean change pain intensity score from baseline to endpoint reached statistical significance in the between group analysis (p = 0.032) but not for men (p=0.3154). This change represented greater pain intensity for the women in the 1/2 Dilaudid CR group.

Age

No subgroup analysis by age was performed for efficacy outcomes.

Post Hoc Analyses

Categorical Analysis of Change in Direction of Breakthrough Medication Dosage

As one of the post hoc analyses, a categorical analysis of the change in direction in total daily dose of breakthrough medication was performed. As seen in Table 6.11, there was a greater number of patients in the 1/2 Dilaudid CR group using more breakthrough-pain medication and fewer using less than the Dilaudid CR and IR groups.

Table 6.11 Summary of Direction of Change in Total Daily Dose (mg) of Breakthrough-pain Medication From Baseline to Endpoint by Treatment Group

Direction of Change	Dilaudid CR (N=33) ^a n ^a (%)	1/2 Dilaudid CR (N=38) n (%)	Dilaudid IR (N=39) n (%)	All Groups (N=110) n (%)
Decrease	11 (33)	4 (11)	11 (28)	26 (24)
No Change	2 (6)	3 (8)	4 (10)	9 (8)
Increase	20 (61)	31 (82)	24 (62)	75 (68)
p-Value ^b	N/A ^c	0.0259 ^d	0.7791 ^e	0.0534.

a N = Number of patients randomized; n = Number of patients evaluated

b Based on Cochran-Mantel-Haenszel Test for Non-zero Correlation of Two Ordinal Measures

c N/A = Not applicable

d Dilaudid CR vs. 1/2 Dilaudid CR

e Dilaudid CR vs. Dilaudid IR

Source: Table 26, Vol. 1.67, P. 72

Percent Change Total Daily Dose

The sponsor evaluated the percent change in total daily dose of breakthrough-pain medication adjusting all non-missing values by adding 0.5 mg so that no baseline value would equal 0. This analysis revealed statistically significant differences between Dilaudid CR and the other treatment groups.

Table 6.12 Percent Change From Baseline to Endpoint in Total Daily Dose (mg) of Breakthrough-pain Medication (With 0.5 mg Imputation) by Treatment Group

Parameter	Dilaudid CR (N=34) ^a	1/2 Dilaudid CR (N=40)	Dilaudid IR (N=39)	All Groups (N=113)
Percent Change From Baseline to Endpoint ^b				
n ^a	33	38	39	110
Mean±STD	133.3±309.0	330.3±583.1	386.3±1277.1	291.1±850.5
Median	18.2	93.9	53.3	55.1
Range	-92-1600	-61-2080	-89-7040	-92-7040
p-Value				
Within treatment ^c	0.008	<0.001	<0.001	N/A ^d
Between treatment	N/A	0.037 ^e	0.874 ^f	^g

a N = Number of patients randomized; n = Number of patients evaluated

b Endpoint is the mean of Days 3 to 7 of the double-blind phase based on non-missing diary days

c Wilcoxon Signed Rank test

d N/A = Not applicable

e Dilaudid CR vs. 1/2 Dilaudid CR. Wilcoxon Rank-Sum test

f Dilaudid CR vs. Dilaudid IR. Wilcoxon Rank-Sum test.

g Overall p-value = 0.067 Kruskal-Wallis test.

Source- Table 27, Vol. 1.67, P. 73

Number of Doses of Breakthrough Medication per Day

Although there was no statistically significant difference between treatment groups at endpoint, the change from baseline did show a statistically significant difference between the Dilaudid CR and 1/2 Dilaudid CR. There was no statistically significant difference between Dilaudid IR and Dilaudid CR.

Table 6.13 Number of Times/Day of Breakthrough-pain Medication Use at Endpoint and Change From Baseline to Endpoint by Treatment Group

Parameter	Dilaudid CR (N=34) ^a	1/2 Dilaudid CR (N=40)	Dilaudid IR (N=39)	All Groups (N=113)
Number of Times/Day of Breakthrough-pain Medication Use				
Endpoint ^b				
n ^a	33	38	39	110
Mean±STD	2.9±1.9	3.2±1.5	2.4±1.6	2.8±1.7
Median	2.6	3.0	2.6	2.8
Range	0-10	0-6	0-7	0-10
p-Value				
Non-parametric analysis	N/A ^c	0.1859 ^d	0.7810 ^e	^f
Poisson Regression ^g	N/A	0.0001 ^h	0.8067 ⁱ	^j
Change From Baseline				
n	33	38	39	110
Mean Change±STD	0.8±1.9	1.4±1.6	0.7±1.4	1.0±1.6
Median	0.25	1.05	0.40	0.60
Range	-2-8	-2-5	-1-4	-2-8
p-Value				
Within treatment ^k	0.043	<0.001	0.003	N/A
Between treatment	N/A	0.026 ^d	0.743 ^e	^f

a N = Number of patients randomized, n = Number of patients evaluated

b Endpoint is the mean of Days 3 to 7 of the double-blind phase based on non-missing diary days

c N/A = Not applicable

d Dilaudid CR vs. 1/2 Dilaudid CR Wilcoxon Rank-Sum test.

e Dilaudid CR vs. Dilaudid IR Wilcoxon Rank-Sum test

f Overall p-value. Kruskal-Wallis test Endpoint, p=0.2000 Change from baseline, p=0.041

g Likelihood ratio statistic

h Dilaudid CR vs. 1/2 Dilaudid CR

i Dilaudid CR vs. Dilaudid IR

j Overall P-value = 0.001

k Wilcoxon Rank-Sum test.

Source: Table 29, Vol. 1.67, P. 76

SECTION 6.2.2 STUDY DO-104/105

As discussed, the sponsor was informed during clinical drug development by the Agency that an open-label study without comparator would not be considered acceptable for an efficacy trial. Studies DO-104 and DO-105 are presented here in abbreviated form only.

Section 6.2.2.1 Study protocol

Title: A repeated-dose evaluation of analgesic use and safety of Dilaudid CR (hydromorphone HCl) in patients with chronic pain (DO-104/DO-105)

Objective: To develop recommended dosing information for initiation of therapy with Dilaudid CR in patients with chronic pain converting from other strong oral or transdermal opioids, to characterize a safe and effective means by which patients can be started on Dilaudid CR and titrated to an appropriate maintenance dose, and to evaluate the safety profile.

Study Design: Open-label, repeated-dose study. The two protocols differed only in diagnostic entry criteria and were presented by the sponsor in one report. DO-104 enrolled patients with chronic cancer pain and DO-105 enrolled patients with chronic non-cancer pain.

The studies were to be conducted in three phases

- Stabilization on prior opioid
- Conversion to and titration on Dilaudid CR
- Maintenance on Dilaudid CR

Population: Study DO-104 - patients with chronic cancer pain, Study DO-105 - patients with chronic non-malignant pain; receiving strong opioid analgesics or suitable for advancement to step 3 of the WHO analgesic ladder

Outcome Measures:

Pain relief - five point categorical scale from 0 (no relief) to 4 (complete relief)

Global evaluation - five point categorical scale from 1 (poor) to 5 (excellent)

Wisconsin Brief Pain inventory

The endpoint of the study was mean response from days 10-14 or the last five days of the maintenance phase.

Section 6.2.2.2 Study Conduct

Disposition

A total of 445 patients were enrolled from 48 sites in the US and Canada. A total of 404 patients received at least one dose of Dilaudid CR and were included in the ITT populations. The evaluable population was variable and defined as the number of patients with the data point of interest for that analysis. According to the sponsor, “These were open-label, descriptive, clinical studies that were dependent on patient diary information and, subsequently, case report form entries from study sites.” (Vol. 176, P. 61) Of the 404 patients, 50 dropped out due to adverse events and 38 dropped out due to lack of efficacy. There were three deaths. Eleven patients discontinued early due to protocol violations, but were included in safety and efficacy analyses.

Sponsor’s Results

The sponsor reported that data was analyzed separately for patients converted from oral morphine equivalents to hydromorphone at 8:1 and 5:1, but only one set of results were provided. Patients required an average of 12.1 days to reach a stabilized Dilaudid CR dose (Table 17, Vol. 1.76, P. 57).

The efficacy outcome results are summarized in Table 6.14. Information is presented for the combined DO-104/105 group.

Table 6.14 Results

	End of prior Opioid Stabilization	Start of Titration	End of Dilaudid CR Titration	End of Dilaudid CR Maintenance
% of Patients Requiring Rescue Medication	33.9%	99.2%	97.5%	97.0%
Average Total Daily Dose Of Rescue Medication (mg)	NA	14.1	12.7	11.5
Average Pain Relief	1.9	1.6	2.2	2.3
Mean Pain Intensity Difference ^a	3.0		2.8	2.5
Global Evaluation, Ratings of Good to Excellent				
Patient	49.1%		62.1%	79.3%
Investigator	47.8%		63.6%	84.7%

^a The difference between the worst pain and the least pain over the past 24 hours
 Source: Vol. 1.76, Table 20, P. 60; Table 22, P. 63; Table 25 , P. 67; Table 26, P. 68; Table 29, P. 72.

As can be seen, there was a marked increase in the number of patients requiring rescue medication after conversion from prior opioids to Dilaudid CR. There are many possible explanations for this finding. The sponsor notes that while rescue medication was available at the investigator’s discretion during the prior stabilization phase, the use of Dilaudid IR was specified during the titration and maintenance phases, and, so may have played a role in the increased use during those study phases. Inferior pain control by the Dilaudid CR because of a flaw in the conversion ratio is a possibility, but the percentage of patients requiring rescue did not appreciably decrease after titration was completed. Lack of efficacy of the Dilaudid CR is another possibility. The improvement in pain relief is modest as is the decrease in difference in pain intensity. The overall satisfaction with treatment as evidenced by the Global Evaluation improved.

SECTION 7 SAFETY REVIEW

SECTION 7.1 SAFETY FINDINGS - SUMMARY

The pattern of serious adverse events, adverse events leading to study discontinuation, and adverse events observed during the Phase I and Phase III studies of Dilaudid CR appears consistent with the expected adverse event profile of hydromorphone and is similar to opioids in general. The majority of deaths (30 of 34) occurred in patients with chronic pain of malignant origin. Three of the remaining four deaths appear to have been due to cardiac events. The remaining death occurred in a patient with non-malignant pain and was due to a perforated colon. As discussed below, a relationship between the study drug and the perforated colon cannot be definitively excluded.

Safety concerns for the Dilaudid CR product focus on the delivery system. There is a known risk of gastrointestinal obstruction and/or bezoars identified during use of other products formulated with the OROS delivery system. Among the case reports of OROS system related adverse events identified in a MEDLINE search performed by OPDRA, 19 the 50 cases involved patients with pre-existing gastrointestinal problems including: Crohns disease and ulcerative colitis with resection; diverticulitis; intestinal adhesions and strictures; pyloric stenosis; ischemic bowel; colectomy; and constipation. When patients using this dosage form were diagnosed with gastrointestinal obstruction or bezoars, their presenting symptoms were nonspecific and included nausea, vomiting, early satiety, abdominal pain, and weight loss.

In this safety database, there was one report of a bezoar and one report of a perforated colon. The information provided by the sponsor about the patient with the bezoar was inadequate to determine if there were OROS system tablets within the bezoar. The patient with the colon perforation died as a result of this event. This patient had no risk factors for this adverse event identified in advance. The information provided in the narrative and CRF was too limited to determine if there was a relationship between study drug and the adverse event.

Nausea, vomiting and constipation were the three most common individual adverse events leading to study discontinuation and were among the top five most common adverse events. These are also among the most common adverse events known to occur from opioid medications.

Another potential safety concern is the risk of dose dumping of hydromorphone from the OROS system. The only reports of overdose among the Phase III patients were explained by patients ingesting an incorrect number of tablets and hence a larger dose. There were no reports of unexplained overdose.

It is important to note that the Phase I and Phase III trials contained exclusion criteria that would select patients with the least risk for intestinal obstruction. Patients with a history of any GI disorder including GI narrowing, a history of bowel resection, and a history of obstruction due to impaction within five days of screening were excluded from the study.

SECTION 7.2 ADEQUACY OF SAFETY EXPOSURE AND ASSESSMENT

SECTION 7.3 REVIEW OF THE ISS

This safety evaluation was reviewed from two sources: the 120-day Safety Update and the final study report for DO-119 provided in the original NDA submission. The cutoff date for the 120-day Safety Update was December 1, 1999 and for the original NDA submission February 15, 1999. The 120-day safety update includes information segregated by study and for the entire Dilaudid CR group. None of the studies submitted included a placebo group. To assess the comparative risk of adverse events from Dilaudid CR, the three treatment groups from Study DO-119, full-dose Dilaudid CR, Dilaudid IR and 1/2-dose Dilaudid CR are compared and included in this safety review.

The Phase I and Phase III studies were evaluated separately by the sponsor, even though Study DO-108 was a multiple dose Phase I study in patients with chronic pain. As a result, this reviewer reviewed the safety of the Phase I and III studies separately.

The sponsor converted verbatim terms for adverse events recorded on the CRF to preferred terms and body systems using a customized dictionary developed by Hoechst, Hoechst Adverse Reaction Terminology (C_HART,) which was adapted from the Agency's Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART) dictionary. When an adverse event occurred more than once during a study, it was counted as a single adverse event. More than one adverse event in any given body system was counted only once for that body system, but separately for each AE. AE's occurring in different study phases were counted separately by phase. For patients participating in a short term and then long-term study, AE's from the short term study occurring again in the long-term study were only counted once.

A total of 12 studies were submitted in support of the safety evaluation of Dilaudid CR (see Table 5.1, P. 14). Of the 875 unique subjects enrolled in these studies, 829 received Dilaudid CR and 683 were enrolled in short term Phase III studies, DO-104, DO-105 and DO-119. A total of 613 of these patients entered the conversion and titration phase of their respective studies with 413 patients completing study participation. Three hundred and eighty-eight patients enrolled in the long-term extension study, DO-109. Table 7.1 summarized the reasons for early study discontinuation during the Phase III trials, the most common being adverse events.

Table 7.1 Summary of Patients Discontinued from Dilaudid CR Therapy during the Phase III Trials

	Study DO-104	Study DO-105	Study DO-119	Study DO-109 ^{a, b}	Updated CR Population ^c
Enrolled in Phase III Study	148	366	169	388	683
Received Dilaudid CR	128	337	74 ^d	388 (38) ^e	577
Missing dosing information					
Without AE	1	6	0	0	7
With AE	0	0	0	1	1
Early Discontinuation after receiving Dilaudid CR	43 33.6%	115 34.1%	7 9.5%	292 75.3%	457 79.2%
Reason for Discontinuation					
Admin. Reason	0	7 2.1%	0	109 28.1%	116 20.1%
Adverse Event	16 12.5%	42 12.5%	2 2.7%	48 12.4%	108 18.7%
Death	3 2.3%	1 0.3%	0	14 3.6%	18 3.1%
Lack - Efficacy	13 10.2%	32 9.5%	2 2.7%	38 9.8%	85 14.7%
Lost to Follow-Up	0	6 1.8%	0	11 2.8%	17 2.9%
Disease Progression	3 2.3%	0	0	17 4.4%	20 3.5%
Protocol Violation	1 0.8%	11 3.3%	0	12 3.1%	24 4.2%
Recovery	1 0.8%	0	0	4 1.0%	5 0.9%
Withdraw Consent	6 4.7%	16 4.7%	3 4.1%	39 10.1%	64 11.1%

a Continuation protocol for patients previously completing Protocols DO-104, DO-105, and DO-119.

b Represents data for 79 patients discontinued prior to NDA submission, 54 patients enrolled in and discontinued subsequent to the NDA submission and 159 patients reported in the NDA who subsequently discontinued post NDA cut-off [2/15/99].

c The integrated population includes patients who were dispensed Dilaudid CR during Studies DO-104, DO-105, and DO-109, and also includes patients who were randomized to Dilaudid IR in Study DO-119 and subsequently received Dilaudid CR in DO-109.

d 148 patients initially titrated onto Dilaudid IR, three lacked dosing information, 32 discontinued, of remaining 113, 74 randomized to Dilaudid CR (including full and 1/2 dose), 39 to Dilaudid IR

e 38 patients who received Dilaudid IR in Study DO-119 received Dilaudid CR for the first time in Study DO-109. The remaining 349 patients had received Dilaudid CR in DO-104 and 105 and do not represent unique exposures. Source: Table 9.8.6, Vol. 3.1, P. 72; cross reference ISS Table 8.12.12 [Volume 115, page 135] in the NDA.

There were 165 patients from Studies DO-104, DO-105 and DO-119 who discontinued study participation early, most commonly due to adverse events, followed by lack of efficacy. There were 292 early discontinuations from the long-term study, DO-109. One hundred and nine of these were due to administrative reasons; there was an insufficient supply of Dilaudid CR and patients on the study drug for more than one year were terminated by the sponsor. The next two most common reasons were adverse events and lack of efficacy.

SECTION 7.3.1 DEATHS

Section 7.3.1.1 Phase III Studies

There were a total of 34 deaths reported through the December 1, 1999 cutoff date. These occurred during the Phase III trials DO-104, DO-105 and DO-109. Sixteen deaths occurred following study discontinuation, including one patient who never received study medication. The sponsor and investigators do not consider any of the deaths related to study medication.

There were no deaths during Study DO-119.

Table 7.2 Summary of Deaths

Study #/ Patient #	Study Phase/ Dose at Onset of SAE ^a	Age ^b /Sex	Adverse Event (HARTS term) and/or Cause of Death	Duration of Treatment at Onset of Event ^c (days)	Duration off study before death
DO-104/ 02-04002	Post-Study	63/ F	Disease Progression - metastatic lung cancer	NA	10 d
DO-104/ 18-04001	Post-Study - No Dilaudid	68/ M	Disease Progression - bladder/prostate cancer	NA	NA
DO-104/ 24-04004	Post-study	38/ F	Disease progression - metastatic breast cancer	NA	24 d
DO-104/ 36-04001	Post-Study	74/ F	Disease Progression - metastatic ovarian cancer	NA	13 d
DO-104/ 37-04005	Titration/ Dilaudid CR 16 mg	60/ M	Metastatic nasopharyngeal cancer Altered level of consciousness (Stupor) Bacteremia/sepsis/Pancytopenia -chemotherapy	4	
DO-104/ 37-04013	Maintenance/ Dilaudid CR 56 mg	67/ F	Vomiting/Nausea, Progression of metastatic pancreatic cancer (Reaction Aggravated)	34	
DO-104/ 46-04004	Titration/ Dilaudid CR 16 mg	50/ F	Metastatic lung cancer Liver Failure	16	
DO-104/ 92-04002	Post-Study	73/ M	Disease Progression - metastatic lung cancer, prostate cancer	NA	20 d
DO-105/ 94-05001	Titration/ Dilaudid CR 24 mg	40/ F	Perforated Ulcer - Cecum (Intestine Large Perforation)	12	
DO-109/ 01-94001	Post-study	56/ F	Disease progression - non-small cell lung cancer	NA	26 d
DO-109/ 03-94001	Dilaudid CR 32 mg	70/ F	Lung cancer, Dehydration Respiratory failure (Apnea)	41 45	
DO-109/ 15-95001	Dilaudid CR 32 mg	67/ M	Cardiac arrest (Heart arrest)	64	
DO-109/ 16-94003	Dilaudid CR 48 mg	79/ F	Progression of lung cancer (Reaction aggravated)	Not avail ^h	
DO-109/ 17-95002	Dilaudid CR 32 mg	54/ F	Heart attack (Infarct Myocardial)	171	
DO-109/ 21-95009	Dilaudid CR 48 mg	53/ M	Aspiration pneumonia LT neck tumor (adenocarcinoma)	297	
DO-109/ 35-94001	Post-Study	58/ M	Disease Progression -metastatic colon cancer	NA	21 d
DO-109/ 37-94002	Post-study	74/ M	Disease progression - colon cancer with pulmonary and hepatic mets	NA	5 d
DO-109/ 37-94010	Post-study	65/ M	Disease progression - lung cancer	NA	2 d
DO-109/ 37-94011	Post-study	52/ F	Disease progression - esophageal cancer with pulmonary metastasis	NA	1 d
DO-109/ 39-94004	Dilaudid CR 64 mg	53/ F	Progression of metastatic breast cancer (Carcinoma Breast)	51	
DO-109/ 46-94006	Dilaudid CR 32 mg	69/ F	Progression of metastatic non-small cell carcinoma (Reaction aggravated)	289	
DO-109/ 91-94004	Post-study	37/ M	Disease progression - renal cell carcinoma with pulmonary metastases	NA	3 d
DO-109/ 92-94004	Post-study	49/ F	Disease progression -rectal carcinoma metastasis of uterus, liver, brain, pelvis, ovaries	NA	28 d

(Table continues)

Table 7.2 continued

Study #/ Patient #	Study Phase/ Dose at Onset of SAE ^a	Age ^b /Sex	Adverse Event (HARTS term) and/or Cause of Death	Duration of Treatment at Onset of Event ^c (days)	Duration off study before death
DO-119/ 21-95004	Dilaudid CR 16 mg	74/ M	Congestive heart failure exacerbation (Heart fail right), h/o lung cancer, chronic LBP	302	
DO-119/ 25-94001	Dilaudid CR 48 mg	66/ F	Progression metastatic esophageal cancer disease (Reaction aggravated)	35	
DO-119/ 29-94004	Dilaudid CR 328 mg	28/ M	Disease progression - Metastatic medullary cancer of the thyroid (Reaction aggravated)	125	
DO-119/ 30-94008	Post-study	90/ M	Disease progression - metastatic colon cancer	NA	19 d
DO-119/ 30-94014	Dilaudid CR 32 mg	74/ M	Disease progression see multiple myeloma (Myeloma)	50	
DO-119/ 32-94002	Dilaudid CR 24 mg	63/ F	Progression of metastatic colorectal cancer (Reaction aggravated)	27	
DO-119/ 39-94001	Post-study	53/ M	Disease progression -adeno-carcinoma of right parotid with pulmonary and hepatic mets	NA	3 d
DO-119/ 47-94001	Dilaudid CR 0 mg (16 mg) ^j 24 mg	78/ M	Chest wall mass (Neoplasm) Progression of metastatic lung cancer (Reaction aggravated)	107 149	
DO-119/ 92-94003	Post-Study	65/ M	Disease Progression - metastatic colon cancer	NA	2 d
DO-119/ 97-95001	Dilaudid CR 88 mg	65/ F	Cardiac arrest (Heart arrest)	576	
DO-119/ 97-95004	Post-study	79/ F	Disease progression - lung cancer	NA	90d +

NA = Not applicable

a Study phase = phase at onset of SAE. Dose = actual dose on day of event or last documented dose if dosing on day of event is missing.

b Age of patient at time of entry into short-term Study DO-104, DO-105 or DO-119.

c Duration of Treatment is calculated as the number of days between the first documented dose of study medication in the short-term study and the onset date of the SAE.

d Duration of Event is calculated as the number of days from the onset date of the SAE to the date of resolution of the SAE [OR] to the date of study discontinuation for ongoing SAEs [OR] to 2/15/99 for SAEs reported in the NDA which were ongoing as of data cut-off for the NDA [OR] to 12/1/99 for SAEs occurring subsequent to the NDA which were ongoing as of data cut-off for the 4-Month Safety Update.

e Event ongoing at study discontinuation.

f Patient subsequently died post-study due to disease progression.

g Incomplete "End of study date" or incomplete SAE stop date does not allow calculation of total duration of the event.

h Incomplete Onset date of SAE does not allow calculation of total duration of the event or duration of treatment at time of the event.

i Data not present in database.

j Dose of 0 mg Dilaudid CR reported on onset date of the SAE. Last reported dose prior to SAE is designated in parenthesis.

Source: Table 9.8.9, Vol. 3.1, P. 101; Cross reference ISS Table 8.12.25 (Volume 115, page 209) in the NDA.

The causes of death for these 34 patients are summarized in Table 7.3. Sixteen deaths occurred off study drug, six within one week of study discontinuation.

Table 7.3 Causes of Death

Cause Of Death	Patients On Study Drug	Patients Off Study Drug
Progression Of Cancer	10	12
Cardiac Arrest	3	
Change In Mental Status		2
Aspiration Pneumonia		
Respiratory Insufficiency		1
Congestive Heart Failure	1	
Liver Failure	1	1
Sepsis	1	
Perforated Colon	1	
Myelodysplasia	1	

The narratives for all of the deaths were reviewed. Review of a sampling of the CRF's revealed little or no detail concerning these deaths. Of the 34 deaths, 30 patients had advanced cancer and in 29 of these patients, death was attributed to complications or progression of the underlying disease. This includes one patient who died during hospitalization for altered level of consciousness (Patient 37-94011) and one patient (Patient 21-95009) who entered the study with chronic non-malignant pain and was diagnosed with and died from cancer while on study drug. The remaining one patient with malignant pain died due to complications of congestive heart failure (Patient 21-95004). Although there was only limited information available concerning the individual circumstances surrounding the deaths of patients with cancer, there was no pattern of adverse events or other indication that the study drug contributed directly to the cause of death in these patients.

Of the four deaths of patients without cancer, three were due to cardiac arrests. Two of these patients had known atherosclerotic heart disease (Patients 17-95002, 97-95001). The third patient had a history of hypertension (Patient 15-95001). Summarized narratives for these three patients follow.

Patient 17-95002 was a 55 year old woman with a history of coronary angioplasty, insulin dependent diabetes and kidney surgery who died while asleep. The patient had complained of chest pain the evening prior to death. Death was attributed to atherosclerotic cardiovascular disease in both the CRF and narrative. Given this patient's medical history and sudden death following the complaint of chest pain, there is no reason to consider that the cause of death was other than atherosclerotic cardiovascular disease as provided by the sponsor. There was no information to suggest a contribution from the study drug.

Patient 97-95001 was a 38 year old women with a history of diabetes, atherosclerotic heart disease, myocardial infarction and left hip replacement. She enrolled in DO-109 on 4/21/98 for left hip and left pain. The patient died on (b) (6) after collapsing at home in cardiac arrest and failed attempts at resuscitation. The CRF states "Apparently patient suffered an insulin reaction and cardiac arrest (b) (6) in morning. Taken by ambulance to Emergency @ hospital- died on arrival." Although this patient was young, she had a remarkable medical history as noted above,

and her sudden death at home was compatible with a cardiac arrest as indicated by the sponsor. There was no information presented to suggest the study drug contributed to the patient's death.

Patient 15-95001 was a 67 year old man with a history of hypertension, seizure and mood disorders. The etiology of the patient's chronic pain was unclear from the narrative and CRF. The patient was found dead and the cause of death attributed to cardiopulmonary arrest due to myocardial infarction. No further medical information was provided. Although it is unlikely that the study drug contributed to what appears to have been a sudden death, the limited amount of information available precludes any further determination of relatedness.

The fourth patient with non-malignant pain, died due to a perforated colonic ulcer. Patient 94-05001 was a 40 year old woman with a history of morbid obesity. Her chronic pain was due to multiple plastic surgeries to her abdomen after an apronectomy scar was reopened in a motor vehicle accident, and arthritis pain. The patient began Dilaudid CR 3/11/98 having been on Dilaudid IR previously. The patient died on (b) (6) due to a perforated colonic ulcer. Of all the deaths described in this safety database, this case is the most uncertain in terms of whether the study drug may have been a contributing factor. The OROS delivery system utilized by the Dilaudid CR formulation has been associated with gastrointestinal obstruction and perforation during experience with other drug preparations. Without a post-mortem examination and report, no clear determination of contribution by study drug to the patient's cause of death can be established.

Section 7.3.1.2 Phase I Studies

There were no deaths during the Phase I studies.

SECTION 7.3.2 SERIOUS ADVERSE EVENTS

Section 7.3.2.1 Phase III Studies

Section 7.3.2.1.1 Serious Adverse Events -120-day Safety Update

There were a total of 208 SAEs in the Phase III population, including 14 SAEs in 10 patients prior to receiving study medication. Of the remaining 194 SAEs, 191 occurred in 120 patients receiving Dilaudid CR and three occurred in three patients receiving Dilaudid IR. Narratives were provided for all SAEs in the original submission, but only for those SAEs considered related to study medication in the safety update. SAEs occurring in 0.9% of patients or greater are summarized in Table 7.4.

Table 7.4 SAE's in $\geq 0.9\%$ of Patients with Onset during Dilaudid CR Therapy, Phase III Trials

	Protocol 104 (N= 127)	Protocol 105 (N=331)	Protocol 119 ^a (N=74)	Combined 104, 105, 119 (N=532)	Protocol 109 ^b (N=388)	Integrated CR Population ^c (N=570)
Any Adverse Event	20 (15.7%)	13 (3.9%)	0 (0.0%)	33 (6.2%)	92 (23.7%)	120 (21.1%)
Body, General Any Event	8 (6.3%)	3 (0.9%)	0 (0.0%)	11 (2.1%)	29 (7.5%)	40 (7.0%)
Respiratory Any Event	2 (1.6%)	4 (1.2%)	0 (0.0%)	6 (1.1%)	22 (5.7%)	27 (4.7%)
Digestive Any Event	5 (3.9%)	1 (0.3%)	0 (0.0%)	6 (1.1%)	20 (5.2%)	26 (4.6%)
Cardiovascular Any Event	0 (0.0%)	1 (0.3%)	0 (0.0%)	1 (0.2%)	22 (5.7%)	23 (4.0%)
Nervous Any Event	2 (1.6%)	2 (0.6%)	0 (0.0%)	4 (0.8%)	15 (3.9%)	19 (3.3%)
Metabolic and Nutritional Any Event	4 (3.1%)	1 (0.3%)	0 (0.0%)	5 (0.9%)	8 (2.1%)	13 (2.3%)
Reaction Aggravated	3 (2.4%)	0 (0.0%)	0 (0.0%)	3 (0.6%)	10 (2.6%)	13 (2.3%)
Dehydration	4 (3.1%)	0 (0.0%)	0 (0.0%)	4 (0.8%)	8 (2.1%)	12 (2.1%)
Pneumonia	1 (0.8%)	2 (0.6%)	0 (0.0%)	3 (0.6%)	9 (2.3%)	11 (1.9%)
Sepsis	1 (0.8%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	4 (1.0%)	5 (0.9%)
Pain Chest	0 (0.0%)	1 (0.3%)	0 (0.0%)	1 (0.2%)	4 (1.0%)	5 (0.9%)
Dyspnea	1 (0.8%)	1 (0.3%)	0 (0.0%)	2 (0.4%)	3 (0.8%)	5 (0.9%)

a Includes patients who received Dilaudid CR and 1/2-dose of Dilaudid CR.

b Continuation protocol for patients previously completing Studies DO-104, DO-105 and DO-119.

c The integrated population denominator includes patients who received Dilaudid CR during Studies DO-104, DO-105, and DO-119 and also includes patients who were randomized to Dilaudid IR in Study DO-119 and subsequently received Dilaudid CR in Study DO-109.

Source: Table 9.8.10, Vol. 3.1, P. 133, Cross reference ISS Table 8.12.26, Volume 115, page 221 in the NDA.

Although there were serious adverse events occurring in more than 1% of patients involving the respiratory, digestive, cardiovascular, nervous, and metabolic/nutritional body systems, there were only three individual SAE's that occurred in $>1\%$ of patients. These were reaction aggravated, dehydration, and pneumonia. Reaction aggravated refers primarily to worsening of the underlying cancer. Three SAE's, sepsis, chest pain, and dyspnea, each occurred in 0.9% of patients. These six most frequent SAE's were not unexpected in the patient populations studied. The patient narratives and CRF's were reviewed for the SAE's. The events of progression of cancer and sepsis occurred primarily in patients with chronic cancer pain. The less common SAE's that occurred in fewer than 0.9% of patients were those expected from an opioid analgesic.

Section 7.3.2.1.2 Serious Averse Events - Study DO-119

The only serious adverse events in Study DO-119 occurred during the prior opioid stabilization and Dilaudid IR titration/stabilization phases. No SAE's took place while on Dilaudid CR during this study.

Table 7.5 Number of Patients With Reported Serious Adverse Events: Onset by Study Phase

	Prior Opioid Stabilization (N=154) ^a	Dilaudid IR Titration/ Stabilization Phase (N=142)	Double-Blind Phase (N=113)	All Phases (N=169)
Serious Adverse Event ^b	n ^a (%)	n (%)	n (%)	n (%)
Patients with any SAE	1 (0.7)	3 (2.1)	0 (0.0)	4 (2.4)
Confusion	0 (0.0)	1 (0.7) ^c	0 (0.0)	1 (0.6)
Drug Abuse	0 (0.0)	1 (0.7) ^d	0 (0.0)	1 (0.6)
Nausea	1 (0.7) ^e	0 (0.0)	0 (0.0)	1 (0.6)
Sweat	1 (0.7) ^e	0 (0.0)	0 (0.0)	1 (0.6)
Pneumonia	0 (0.0)	1 (0.7) ^f	0 (0.0)	1 (0.6)

^a N = Number of patients randomized; n = Number of patients evaluated.

^b Each AE is counted only once per patient.

^c Patient discontinued from study.

^d Patient randomized to 1/2 Dilaudid CR and then discontinued from study.

^e SAEs were reported by one patient, randomized to Dilaudid IR dose group.

^f Patient was randomized to Dilaudid IR dose group

Source: Table 43, Vol. 1.67, P. 110, Cross reference: Section 9, Table 23.6.

Section 7.3.2.2 Phase I Studies

There were no serious adverse events during the Phase I trials.

Section 7.3.2.3 SAEs - Studies Initiated Subsequent to NDA Submission

Three studies were initiated in patients with chronic pain subsequent to the NDA submission cut-off date of February 15, 1999. Study DO-127 is a multicenter open-label short term repeated-dose study in chronic low back pain assessing impact on quality of life. Study DO-127X is a long-term continuation protocol and Study DO-118 is a European, multicenter, double-blind, double-dummy, parallel-group, randomized, multiple ascending dose study comparing hydromorphone and morphine in cancer pain. A total of 35 unique patients have been enrolled into these studies. The databases for these studies are not completed, and only serious adverse events were available for summarization. There were no serious adverse events reported during these studies, but three serious adverse events (vomiting, abdominal pain and dehydration) were reported post-study in one patient.

Summary

Following review of the patient narratives and CRFs, and review of the frequency of occurrence of the serious adverse events reported during the Phase III clinical trials, there was no pattern or frequency of serious adverse events that was unexpected from the use of an opioid analgesic in a population consisting of patients with chronic malignant and non-malignant pain.

SECTION 7.3.3 ADVERSE EVENTS LEADING TO STUDY DISCONTINUATION

Section 7.3.3.1 Phase III Trials

Section 7.3.3.1.1 AEs Leading To Study Discontinuation, 120-day Safety Update

The sponsor compiled the information on discontinuation of study medication due to an adverse event from the CRF End of Study Record and the CRF Adverse Event page. A total of 174

(29.2%) of the 613 patients enrolled in the Phase III studies discontinued due to an adverse event, 159 (25.9%) of these patients had received Dilaudid CR, 15 (2.4%) Dilaudid IR. The AEs leading to study discontinuation which occurred in at least 0.5% of patients are summarized in Table 7.6.

Table 7.6 Adverse Events Leading To Premature Study Discontinuation Occurring In At Least 0.5% Of Patients (Protocols DO-104, 105, 109 and 119)

	Protocol 104 (N=127)	Protocol 105 (N=331)	Protocol 119 ^a (N=74)	Protocols 104, 105, and 119 Combined (N=532)	Protocol 109 ^b (N=388)	Updated Integrated CR Population ^c (N=570)
Any Adverse Event	30 (23.6)	47 (14.2)	5 (6.8)	82 (15.4)	77 (19.8)	159 (27.9)
Nervous, Any Event	14 (11.0)	22 (6.6)	3 (4.1)	39 (7.3)	23 (5.9)	62 (10.9)
Digestive, Any Event	13 (10.2)	20 (6.0)	0 (0.0)	33 (6.2)	26 (6.7)	59 (10.4)
Body, General, Any Event	8 (6.3)	5 (1.5)	3 (4.1)	16 (3.0)	21 (5.4)	37 (6.5)
Nausea	7 (5.5)	14 (4.2)	0 (0.0)	21 (3.9)	9 (2.3)	30 (6.3)
Vomiting	6 (4.7)	4 (1.2)	0 (0.0)	10 (1.9)	5 (1.3)	15 (2.6)
Constipation	1 (0.8)	4 (1.2)	0 (0.0)	5 (0.9)	8 (2.1)	13 (2.3)
Somnolence	2 (1.6)	5 (1.5)	0 (0.0)	7 (1.3)	6 (1.5)	13 (2.3)
Respiratory, Any Event	2 (1.6)	5 (1.5)	0 (0.0)	7 (1.3)	4 (1.0)	11 (1.9)
Headache	3 (2.4)	6 (1.8)	0 (0.0)	9 (1.7)	1 (0.3)	10 (1.8)
Asthenia	1 (0.8)	1 (0.3)	1 (1.4)	3 (0.6)	5 (1.3)	8 (1.4)
Reaction Aggravated	3 (2.4)	0 (0.0)	0 (0.0)	3 (0.6)	5 (1.3)	8 (1.4)
Dizziness	3 (2.4)	3 (0.9)	0 (0.0)	6 (1.1)	2 (0.5)	8 (1.4)
Diarrhea	1 (0.8)	3 (0.9)	0 (0.0)	4 (0.8)	2 (0.5)	6 (1.1)
Confusion	2 (1.6)	1 (0.3)	0 (0.0)	3 (0.6)	3 (0.8)	6 (1.1)
Depression	1 (0.8)	3 (0.9)	1 (1.4)	5 (0.9)	1 (0.3)	6 (1.1)
Dysphagia	2 (1.6)	0 (0.0)	0 (0.0)	2 (0.4)	3 (0.8)	5 (0.9)
Nausea Vomiting	1 (0.8)	2 (0.6)	0 (0.0)	3 (0.6)	2 (0.5)	5 (0.9)
Dyspnea	1 (0.8)	2 (0.6)	0 (0.0)	3 (0.6)	2 (0.5)	5 (0.9)
Pain	1 (0.8)	1 (0.3)	1 (1.4)	3 (0.6)	1 (0.3)	4 (0.7)
Pain Abdomen	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.2)	3 (0.8)	4 (0.7)
Dehydration	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.2)	3 (0.8)	4 (0.7)
Dream Abnormal	0 (0.0)	4 (1.2)	0 (0.0)	4 (0.8)	0 (0.0)	4 (0.7)
Hallucinations	3 (2.4)	1 (0.3)	0 (0.0)	4 (0.8)	0 (0.0)	4 (0.7)
Thinking Abnormal	0 (0.0)	2 (0.6)	0 (0.0)	2 (0.4)	2 (0.5)	4 (0.7)
Pruritus	0 (0.0)	3 (0.9)	1 (1.4)	4 (0.8)	0 (0.0)	4 (0.7)
Rash	1 (0.8)	2 (0.6)	0 (0.0)	3 (0.6)	1 (0.3)	4 (0.7)
Insomnia	0 (0.0)	2 (0.6)	0 (0.0)	2 (0.4)	1 (0.3)	3 (0.5)
Stupor	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.5)	3 (0.5)

The following adverse events were each the cause for two patients (0.4%) to discontinue study medication early: carcinoma, overdose, sepsis, heart failure right, pain chest, edema, hypoxia, myasthenia, pain bone, agitation, anxiety, dry mouth, hypertonia, sedation, sweating, bronchospasm.

The following adverse events were each the cause for one patient (0.2%) to discontinue study medication early: abdomen enlarged, amnesia, anorexia, asthma, ataxia, bezoar, bone fracture, carcinoma breast, carcinoma GI, cellulitis, chills, convulsion, CVA, drug abuse, drug

dependence, dyspepsia, edema peripheral, encephalopathy, fever, flu syndrome, gait abnormal, GI disorder, hostility, hyperkinesia, hypertension, infection, infection upper respiratory, injury accidental, ischemia cerebral, metrorrhagia, myeloma, nervousness, neurosis, obstruction intestinal, pain back, palpitations, pancytopenia, personality disorder, pharyngitis, pleural disorder, pneumonia, sinusitis, skin discolor, sleep disorder, speech disorder, taste perversion, thrombin decreased, tinnitus, urinary tract disorder, urticaria, vasodilation, vertigo, withdrawal syndrome.

The most common body systems involved with early discontinuation were nervous (10.9%), digestive (10.4%), and respiratory (1.9%). The most common adverse events leading to early study termination were nausea (6.3%), vomiting (2.6%), somnolence (2.3%), constipation (2.3%), headache (1.9%), asthenia (1.4%), reaction aggravated (1.4%), and dizziness (1.4%). These adverse events reported leading to early study discontinuation are common to opioids with the exception of reaction aggravated. Reaction aggravated refers to progression of underlying cancer in this study. The narratives and CRFs were reviewed for these patients.

One problem with the manner in which these adverse events were mapped to common terms was that physiologically and symptomatically similar events were mapped to similar but different terms. Sedation (0.4%) was mapped separately from somnolence. Also mapped separately were Confusion (1.1%), thinking abnormal (0.7%) and amnesia (0.2%) most likely reflect the same underlying process and symptoms. In similar fashion agitation (0.4%), anxiety (0.4%), neurosis (0.2%) and nervousness (0.2%) are likely the same events. Mapping similar events to different terms has the effect of diluting the appearance of the common adverse events due to the lower incidence for each individual term. To determine a more accurate accounting of the adverse events, the reported events must be coded and then counted, taking into account that the same adverse event that occurs more than once in an individual subject is only scored once. This remapping was not performed for this safety database.

Section 7.3.3.1.2 AEs Leading To Study Discontinuation, Study DO-119

There were 17 patients in Study DO-119 who discontinued study participation due to an adverse event. Thirteen of these patients discontinued during open-label Dilaudid IR conversion, titration and stabilization. There were four patients who discontinued during the double-blind, randomized phase of the study. One of these four patients had onset of the adverse event during the open-label phase of the study, but the sponsor did not indicate from which treatment group this patient discontinued and the information was not available in the CRF's. The adverse events affecting these four patients are detailed in Table 7.7.

Table 7.7 Reasons for Early Study Discontinuation During Double-blinded Treatment Phase.

	Dilaudid CR (N=34) ^a n ^a (%)	1/2 Dilaudid CR (N=40) n (%)	Dilaudid IR (N=39) n (%)
Preferred Term ^b			
Discontinuing Study Medication Due to AEs	2 (5.9)	2 (5.0)	0 (0.0)
Anxiety	1 (2.9)	0 (0.0)	0 (0.0)
Asthenia	0 (0.0)	1 (2.5)	0 (0.0)
Depression	0 (0.0)	1 (2.5)	0 (0.0)
Dry Mouth	0 (0.0)	1 (2.5)	0 (0.0)
Injury Accidental	1 (2.9)	0 (0.0)	0 (0.0)
Pain	0 (0.0)	1 (2.5)	0 (0.0)
Pruritus	1 (2.9)	0 (0.0)	0 (0.0)
Skin Discolor	1 (2.9)	0 (0.0)	0 (0.0)

^a N = Number of patients randomized; n = Number of patients evaluated.

^b Each AE is counted only once per patient, but each patient may provide more than one AE

Source: Table 45, Vol. 1.67, P. 113. Cross reference: Section 9, Table 23.4

Section 7.3.3.2 Phase I Trials

There were 15 subjects who discontinued prematurely due to an AE, 14 were normal volunteers, one a patient with chronic pain. Eight of the subjects who discontinued after receiving Dilaudid CR did so due to nausea and vomiting. Four of these patients with nausea and vomiting also experienced a combination of some of the following: abdominal pain, anorexia, asthenia, dysphagia, dizziness, hypesthesia, myasthenia, nervousness, pallor, sweating increased, vasodilatation. One patient experienced nausea and impaired urination and the one patient from Study DO-108, vomiting alone. One subject who discontinued after receiving Dilaudid IR, did so due to headache, nausea and vomiting. Three patients discontinued after receiving naltrexone.

In summary, based on the frequencies provided by the sponsor, review of the narratives and CRF's, the adverse events leading to early study discontinuation are consistent with the known adverse events associated with opioids in general and could be attributed to hydromorphone. However, there was no particular pattern or frequency of occurrence that suggested a problem specific to the Dilaudid CR product.

SECTION 7.3.4 ADVERSE EVENTS

Section 7.3.4.1 Phase III Trials

Section 7.3.4.1.1 Adverse Events - 120-day Safety Update

The adverse events that occurred in at least 4.9% of patients are summarized in Table 7.8. Overall, adverse events were common, occurring in 504 (88.4%) of the 570 patients in the group receiving Dilaudid CR with complete dosing information. The most common body systems involved were nervous (62.8%), digestive (62.1%) systems, and respiratory (26.8%). Of the individual adverse events, nausea, constipation, somnolence, headache, vomiting, dizziness, asthenia, accidental injury, diarrhea, sweating, insomnia, pruritus, anorexia, depression dyspepsia, dry mouth, and confusion are all typical of opioid analgesics and have been reported in clinical trials with hydromorphone.

The adverse events of peripheral edema, flu syndrome, upper respiratory infection, infection, and bronchitis are not typically reported with opioids in general or hydromorphone in particular. These events are not unexpected occurrences in a population with a mean age of 50 years, including 128 (22.5%) cancer patients.

The adverse events of pain abdomen, back pain, extremity pain, chest pain most likely reflect the underlying pain syndromes target for treatment in these trials. Pain abdomen may also reflect some opioid related adverse events. The chest pain may also result from coexisting cardiovascular disease as well as some of the occurrences of flu and upper respiratory infection.

The types of adverse events and the frequencies reported are all within what would be expected in a clinical trial of opioids in a patient population consisting of chronic malignant and non-malignant pain patients. There was no pattern of occurrence to suggest a problem specific to the Dilaudid CR formulation

Table 7.8 Adverse Events in $\geq 4.9\%$ of Patients With Onset during Dilaudid CR Therapy by Body System and HARTS Preferred Term; Phase III Trials

HARTS Term	Updated Protocols 104, 105, and 119 Combined (N=532)	Cumulative Protocol 109 (N=388)	Updated Integrated CR Population ^a (N=570)
Any Adverse Event	401 (75.4%)	334 (86.1%)	504 (88.4%)
Nervous, Any Event	262 (49.2%)	194 (50.0%)	358 (62.8%)
Digestive, Any Event	242 (45.5%)	212 (54.6%)	354 (62.1%)
Body, General, Any Event	151 (28.4%)	197 (50.8%)	287 (50.4%)
Nausea	101 (19.0%)	73 (18.8%)	153 (26.8%)
Respiratory, Any Event	64 (12.0%)	109 (28.1%)	153 (26.8%)
Constipation	83 (15.6%)	78 (20.1%)	140 (24.6%)
Metabolic and Nutritional, Any Event	55 (10.3%)	79 (20.4%)	120 (21.1%)
Somnolence	75 (14.1%)	53 (13.7%)	112 (19.6%)
Headache	80 (15.0%)	35 (9.0%)	104 (18.2%)
Skin and Appendages, Any Event	57 (10.7%)	54 (13.9%)	100 (17.5%)
Vomiting	59 (11.1%)	48 (12.4%)	99 (17.4%)
Cardiovascular, Any Event	36 (6.8%)	65 (16.8%)	96 (16.8%)
Dizziness	70 (13.2%)	20 (5.2%)	87 (15.3%)
Asthenia	46 (8.6%)	45 (11.6%)	86 (15.1%)
Urogenital, Any Event	32 (6.0%)	55 (14.2%)	81 (14.2%)
Musculoskeletal, Any Event	20 (3.8%)	64 (16.5%)	79 (13.9%)
Edema Peripheral	36 (6.8%)	39 (10.1%)	69 (12.1%)
Diarrhea	36 (6.8%)	35 (9.0%)	65 (11.4%)
Injury Accidental	17 (3.2%)	47 (12.1%)	60 (10.5%)
Sweat	39 (7.3%)	26 (6.7%)	59 (10.4%)
Special Senses, Any Event	36 (6.8%)	24 (6.2%)	58 (10.2%)
Insomnia	27 (5.1%)	35 (9.0%)	56 (9.8%)
Flu Syndrome	16 (3.0%)	41 (10.6%)	55 (9.6%)
Pain	20 (3.8%)	35 (9.0%)	53 (9.3%)
Pruritus	38 (7.1%)	11 (2.8%)	49 (8.6%)
Pain Abdomen	19 (3.6%)	29 (7.5%)	47 (8.2%)
Anorexia	24 (4.5%)	24 (6.2%)	44 (7.7%)
Infection Upper Respiratory	13 (2.4%)	34 (8.8%)	44 (7.7%)
Depression	15 (2.8%)	28 (7.2%)	42 (7.4%)
Dyspepsia	19 (3.6%)	24 (6.2%)	40 (7.0%)
Infection	7 (1.3%)	32 (8.2%)	38 (6.7%)
Anxiety	12 (2.3%)	26 (6.7%)	38 (6.7%)
Pain Back	13 (2.4%)	28 (7.2%)	37 (6.5%)
Rash	11 (2.1%)	27 (7.0%)	37 (6.5%)
Dyspnea	18 (3.4%)	21 (5.4%)	36 (6.3%)
Hemic and Lymphatic, Any Event	9 (1.7%)	26 (6.7%)	32 (5.6%)
Pain Extremity	12 (2.3%)	19 (4.9%)	31 (5.4%)
Dry Mouth	26 (4.9%)	6 (1.5%)	31 (5.4%)
Nausea Vomiting	15 (2.8%)	14 (3.6%)	29 (5.1%)
Pain Chest	11 (2.1%)	17 (4.4%)	28 (4.9%)
Confusion	15 (2.8%)	13 (3.4%)	28 (4.9%)
Bronchitis	10 (1.9%)	19 (4.9%)	28 (4.9%)

a The integrated population denominator includes patients who received Dilaudid CR during Studies DO-104, DO-105, and DO-119 and also includes patients who were randomized to Dilaudid IR in Study DO-119 and subsequently received Dilaudid CR in Study DO-109.

Source Table 9.8.7, P. 73, Vol. 3.1. Cross reference ISS Table 8.12.14 [Volume 115, page 137] in the NDA.

Section 7.3.4.1.2 Adverse Events - DO-119

There were 60 adverse events reported from the 113 patients randomized in Study DO-119. The adverse events occurring in more than 1% of patients are presented in Table 7.9. The sponsor presented this table with different mapping terms than those used in the 120-day safety update. The larger number of categories for body systems utilized may dilute the appearance of adverse events within a given body system. For example, Nervous system is divided into Parasympathetic, Sympathetic, CNS, and General. Digestive is broken up into Digestive/EC and Digestive/General, and Respiratory into Lung and General.

Table 7.9 Most Frequently Reported ($\geq 1\%$) Adverse Events: Randomized Patients by Treatment Group, Body System, and Preferred Term

Body System/Preferred Term ^b	Dilaudid CR (N=34) ^a		1/2 Dilaudid CR (N=40)		Dilaudid IR (N=39)		All Groups (N=113)	
	n ^a	(%)	n	(%)	n	(%)	n	(%)
Patients With Any AE	19	(55.9)	21	(52.5)	20	(51.3)	60	(53.1)
Body/Abdomen-Pain Abdomen	2	(5.9)	1	(2.5)	0	0.0	3	(2.7)
Body/General	6	(17.7)	7	(17.5)	5	(12.8)	18	(15.9)
Asthenia	1	(2.9)	2	(5.0)	2	(5.1)	5	(4.4)
Pain Extremity	1	(2.9)	2	(5.0)	0	(0.0)	3	(2.7)
Chills	1	(2.9)	0	(0.0)	1	(2.6)	2	(1.8)
Fever	1	(2.9)	0	(0.0)	1	(2.6)	2	(1.8)
Flu Syndrome	1	(2.9)	0	(0.0)	1	(2.6)	2	(1.8)
Infect	1	(2.9)	1	(2.5)	0	(0.0)	2	(1.8)
Injury Accidental	1	(2.9)	1	(2.5)	0	(0.0)	2	(1.8)
Constipation	0	(0.0)	2	(5.0)	1	(2.6)	3	(2.7)
Digestive/General	4	(11.8)	5	(12.5)	6	(15.4)	15	(13.3)
Nausea	2	(5.9)	4	(10.0)	3	(7.7)	9	(8.0)
Dyspepsia	0	(0.0)	1	(2.5)	1	(2.6)	2	(1.8)
Nausea Vomiting	1	(2.9)	0	(0.0)	1	(2.6)	2	(1.8)
Nervous/Parasym including Dry Mouth	2	(5.9)	2	(5.0)	1	(2.6)	5	(4.4)
Nervous/Sympathetic including Sweat	3	(8.8)	4	(10.0)	3	(7.7)	10	(8.9)
Nervous/CNS	4	(11.8)	5	(12.5)	7	(18.0)	16	(14.2)
Insomnia	1	(2.9)	0	(0.0)	4	(10.3)	5	(4.4)
Dizziness	1	(2.9)	0	(0.0)	3	(7.7)	4	(3.5)
Somnolence	3	(8.8)	1	(2.5)	0	(0.0)	4	(3.5)
Anxiety	1	(2.9)	1	(2.5)	0	(0.0)	2	(1.8)
Depression	0	(0.0)	2	(5.0)	0	(0.0)	2	(1.8)
Sedation	0	(0.0)	2	(5.0)	0	(0.0)	2	(1.8)
Nervous/General including Headache	0	(0.0)	5	(12.5)	3	(7.7)	8	(7.1)
Respiratory/ Dyspnea/ URI	0	(0.0)	0	(0.0)	4	(10.3)	4	(3.5)
Respiratory/ Bronchitis/ Pneumonia	1	(2.9)	1	(2.5)	1	(2.6)	3	(2.7)
Skin/Erythema/ Rash	1	(2.9)	0	(0.0)	2	(5.1)	3	(2.7)
Skin/General including Pruritus	5	(14.7)	1	(2.5)	3	(7.7)	9	(8.0)

^a N = Number of patients randomized; n = Number of patients evaluated.

^b Each AE is counted only once per patient. All AEs were included regardless of the phase in which the AE first occurred as long as the AE was still ongoing during the Double-Blind, Randomized, Repeat Dosing Phase.

Source: Table 36, Vol. 1.67, P. 99. Cross reference: Section 9, Table 23.0

The overall distribution of adverse events was comparable among the three treatment groups. More patients in the Dilaudid IR group reported insomnia (10.3%) and dizziness (7.7%) than in 1/2 Dilaudid CR (0 and 0), and Dilaudid CR (2.9% and 2.9%) groups. Pruritus and somnolence were more common in Dilaudid CR (14.7% and 8.8%) treated patients than patients in the 1/2 Dilaudid CR (2.5% and 2.5%) and Dilaudid IR (7.7% and 0.0%) groups. There are no obvious explanations for these findings. The total dose of hydromorphone for patients in the Dilaudid CR and Dilaudid IR groups should have been comparable, so the differences can not be attributed to hydromorphone dose. Given the small number of subjects in each group, these findings could reflect sampling error. There were more headaches in the 1/2 Dilaudid CR group (12.5%) than Dilaudid CR (0) or Dilaudid IR (2.6%). Again, no clear explanation for this finding is apparent.

The most common adverse events reported, those involving the nervous, skin, and digestive systems, are consistent with the known adverse events associated with hydromorphone. The adverse events involving the respiratory system, upper respiratory infection and pneumonia, along with fever, chills, flu syndrome, and infection were present in comparable frequencies among the different treatment arms. These adverse events are likely unrelated to study drug, and more likely reflect spontaneous occurrences in this patient population.

Overall, the adverse events reported were those expected in a clinical trial of an opioid analgesic in a population consisting of patients with chronic malignant and non-malignant pain.

Section 7.3.4.2 Phase I Trials

The normal volunteers in one or more of the treatment arms of Studies D-102, D-103, DO-123, DO-124 and DO-129 received naltrexone which could impact the observed adverse event profile. Nevertheless, adverse events were common in the Phase I trials as summarized in Table 7.10.

Table 7.10 Summary of Adverse Events Reported During Any Treatment in the Phase I Trials

Study Number	Number of Subjects in the Study	Number (%) of Subjects Reporting an AE	Number of AEs Reported ^a
Single-dose Studies			
D-101	12	12 (100%)	154
D-102 ^b	30	24 (80.0%)	172
D-103 ^b	32	21 (65.6%)	117
DO-123 ^b	36	30 (83.3%)	176
DO-124 ^b	52	28 (53.8%)	86
DO-129 ^b	56	35 (62.5%)	246
Multiple-dose Studies			
C-96-054	22	19 (86.3%)	122
DO-108	22	16 (72.7%)	58
Updated Total for 120-Day Safety Update	262	185 (70.6%)	1131

^a Totals include AEs which occurred more than once in a single subject.

^b One or more treatment arms administered with naltrexone blockade.

Source Table 9.8.16, Vol. 3.1, P. 179 Cross reference ISS Table 8.12.38 (Volume 116, page 5) in the NDA.

The adverse events occurring in at least 5% of normal volunteers or patients during the Phase I trials are summarized in Table 7.11. The digestive and nervous systems were most frequently involved as would be expected with hydromorphone. The opioid naïve patients experienced more adverse events overall, than did the opioid tolerant patients. The pattern of adverse events was unremarkable.

Table 7.11 Adverse Events During Phase I Studies Occurring In At Least 5% Of Normal Volunteers Or Patients

	Studies with normal volunteers ^a (N=242)		DO-108 (patients with chronic pain) (N=22)		Total Phase I Population (N=262)	
	Number with AE	%	Number with AE	%	Number with AE	%
Number with AE	169	70.4%	16	72.7%	185	70.6%
General Digestive System	118	49.2%	6	27.3%	124	47.3%
Nausea	107	44.6%	2	9.1%	109	41.6%
General Nervous System	80	33.3%	5	22.7%	85	32.4%
Headache	79	32.9%	5	22.7%	84	32.1%
Central Nervous System	78	32.5%	4	18.2%	81	30.9%
Dizziness	58	24.2%	2	9.1%	60	22.9%
General Body	52	21.7%	4	18.2%	56	21.4%
Vomiting	49	20.4%	3	13.6%	52	19.8%
Asthenia	41	17.1%	1	4.5%	42	16%
Pruritus	22	9.2%	4	18.2%	26	9.9%
Abdominal Pain	23	9.6%	0	0%	23	8.8%
Constipation	10	4.2%	8	36.4%	18	6.9%
Autonomic Nervous System	14	5.8%	2	9.1%	16	6.1%
Sore Throat	12	5.0%	1	4.5%	13	5%
Dyspepsia	9	3.8%	3	13.6%	12	4.6%
Dry Mouth	7	2.9%	2	9.1%	9	3.4%
Insomnia	5	2.1%	2	9.1%	7	2.7%
Injury Accidental	1	0.4%	2	9.1%	3	1.1%

a C96-054, D-101, D-102, D-103, DO-123, DO-124, DO-129

Source: Table 9.8.17, Vol. 3.1, P. 180

Section 7.3.4.3 Adverse Events of Special Interest

Intestinal obstruction/bezoars

The OROS delivery system has been associated with gastrointestinal obstruction and the formation of bezoars in conjunction with other drug products. An evaluation of the occurrence of these events by the Agency, conducted using a search of the Adverse Event Reporting System, identified 50 unduplicated cases. This search reviewed adverse events reported during use of Covera HS, Ditropan XL, DynaCirc CR, Efidac24, Glucotrol XL, Procardia XL, Sudafed 24 and Volmax. Forty four of these events occurred with the use of Procardia XL, the first of these products to be marketed and therefore the product with the longest public exposure time. In addition, there were 14 citations from a MEDLINE search as of May 12, 2000. Nineteen of the 50 cases of GI obstruction or bezoars identified involved patients with pre-existing gastrointestinal problems including Crohn's disease and ulcerative colitis with resection, diverticulitis, intestinal adhesions and strictures, pyloric stenosis, ischemic bowel and colectomy. In two cases, patients had a history of occasional and chronic constipation. Patients using

products formulated with the OROS system who were diagnosed with gastrointestinal obstruction or bezoars presented with symptoms of nausea, vomiting, early satiety, abdominal pain, and weight loss. These symptoms are nonspecific and, in a population using Dilaudid CR, could easily be attributed to hydromorphone.

There were 15 serious adverse events and two deaths among the patients who received Dilaudid CR in Phase III trials that could theoretically be related to the use of the OROS delivery system as summarized in Table 7.12. The available narratives, CRT's, and CRF's were reviewed. Narratives were not provided for eight of these 17 patients. A clear etiology could not be determined based on the information available from the narratives and CRFs. Nine of the patients were enrolled in studies due to chronic malignant pain and the underlying cancer was considered the most likely etiology for the adverse events in those patients.

Table 7.12 Serious Adverse Events and Deaths in Individual Patients from Phase III Trials Possibly Related to The OROS Delivery System

Study #/ Patient #	Dose at Onset of SAE ^a	Age ^b	Adverse Event (HARTS Term) And/ Or Cause Of Death	Duration of Treatment at Onset of Event ^c	Outcome
DO-104/ 37-04013	56 mg	67	Vomiting, Nausea	34 d	Fatal
DO-105/ 94-05001	24 mg	40	Perforated Ulcer - Cecum	12 d	Fatal
DO-104/ 32-04002	24 mg	63	Vomiting	21 d	Resolved
DO-104/ 36-04001	128 mg	74	Gastric Outlet Obstruction	29 d	Ongoing ^d
DO-104/ 46-04009	40 mg	63	Abdominal Pain	4 d	Ongoing
DO-109/ 05-95003	40 mg	48	LLQ Pain	128 d	resolved
DO-109/ 08-95016	64 mg	66	Anorexia	151 d	Resolved
DO-109/ 15-95002	8 mg	49	Small Bowel Obstruction	64 d	Resolved
DO-109/ 97-95002	40 mg	^e	Diarrhea, Vomiting	27 d	Resolved
DO-109/ 99-95018	144 mg	^e	Gastritis	371 d	Resolved
DO-109/ 99-95024	40mg	42	Severe Stomach Pain	112 d	Resolved
DO-109/ 20-94001	40 mg	97	Bowel Obstruction	5 d	NA
DO-109/ 37-94002	32 mg	74	Vomiting	440 d	Ongoing ^d
DO-109/ 39-94002	192 mg	62	Protracted Nausea, Vomiting	38 d	Ongoing
DO-109/ 40-94007	24 mg	52	Intractable Nausea	168 d	Resolved
DO-109/ 91-94003	32 mg	^e	Hematemesis, Nausea, Vomiting	158 d	Ongoing
DO-109/ 85-99002	24 mg	41	Gastroparesis, RUQ Pain	70 d	Ongoing

NA = Not available.

a Dose = actual dose on day of event or last documented dose if dosing on day of event is missing.

b Age of patient at time of entry into short-term Study DO-104, DO-105 or DO-I 19.

c Duration of Treatment is calculated as the number of days between the first documented dose of study medication in the short-term study and the onset date of the SAE.

d Patient subsequently died post-study due to disease progression.

e Data not present in database.

Source: Table 9.8.9, vol. 3.1, P. 101. Cross reference ISS Table 8.12.25 (Volume 115, page 209) in the NDA.

Among the patients who discontinued study participation from Phase III studies due to an adverse event, there was one report of a bezoar. The CRF was reviewed. Patient 26-95005 entered Study 109 from Study 105 on 4/23/98 and was taking Dilaudid CR 16 mg. The patient underwent endoscopy on 6/17/98. The endoscopy report dated 6/17/98 states, "There was a large amount of retained food, but there was no one solid piece of food I was able to break it up into several pieces." There is no comment on the presence of "ghost" pills in the bezoar. The final

impression from the report was “1. Bezoar of the stomach. 2. Normal appearing anastomosis with esophagogastroduodenoscopy.”

There were no reports of gastrointestinal obstruction or bezoars from the Phase I studies. There was no information provided to suggest that the reports of nausea, vomiting or abdominal pain were related to this type of problem.

In summary, the OROS delivery system is associated with an increased risk of bezoar formation and gastrointestinal obstruction. The patients enrolled in the clinical trials for Dilaudid CR were screened to exclude patients with greater risk for gastrointestinal obstruction. There were cases within the safety database that were within the spectrum of adverse events associated with this system. These include one death in a patient with perforated colonic ulcer, an adverse event of bezoar, and several reports of gastrointestinal obstruction, protracted vomiting and abdominal pain. However, there were no cases of bezoar or gastrointestinal obstruction that could be definitively attributed to the drug delivery system.

Section 7.3.4.4 Clinical Laboratory Data

In the Phase III studies, laboratory tests were not considered necessary in assessing the safety of Dilaudid CR because of the existing clinical experience with hydromorphone. Therefore, labs were obtained prior to treatment and then only as necessary. The only clinical laboratory abnormalities recorded were hypercholesteremia, hyperglycemia and hypokalemia in two patients each, and in one patient each were creatinine increased, electrolyte depletion, hyperkalemia, hyperlipemia, and hypomagnesemia.

There were no individual clinically significant laboratory abnormalities or patterns of abnormal findings that could be attributed to Dilaudid CR.

Section 7.3.4.5 Vital Sign Data

The ranges of vital sign measurements defining abnormalities were established as follows:

Systolic BP: $\leq 90, \geq 180$ mmHg

Diastolic BP: $\leq 50, \geq 105$ mmHg

Pulse: $\leq 50, \geq 120$ bpm

Respiratory Rate: $<10, >20$ respirations/minute

Of the 51 patients in Phase III trials with an abnormal result, 33 had treatment emergent vital sign abnormalities. These were reviewed (Table 8.12.35, Vol. 115, P. 231). No pattern of vital sign abnormality was detected that could be attributed to study medication.

The vital sign abnormalities for the Phase I studies were plotted using box and whisker plots. There was one patient with a diastolic BP of 13 mm Hg, but this subject was reported to have no symptoms. Four subjects had heart rates more than 40 bpm below baseline, occurring from hour 3.75 to hour 44, and one each at hour 68 and hour 11.75. One subject in Study D-102 had a decrease in respiratory rate from 24 to 12 at hour 3.75, from 22 to 10 at hour 35.75, and from 20 to 8 at hour 28, while receiving Dilaudid CR with naltrexone blockade. Three subjects in Study

DO-123 and one subject in Study DO-124 had respiratory rate decreases by ≥ 12 rpm on one or more occasion, but all returned to higher rates at the following measurement.

The few vital sign abnormalities reported presented no pattern to suggest an adverse event profile specific to Dilaudid CR or different than expected with opioids in general.

Section 7.3.4.6 Interactions

Section 7.3.4.6.1 Drug-Demographic Interactions

Age

Adverse events were assessed by dividing the safety population into two groups by age. This analysis was performed on the original NDA population with 488 subjects. There were 410 subjects less than 65 years of age and 78 subjects aged 65 and over. There were only six adverse events that occurred more frequently (a difference of $\geq 5\%$) in patients 65 and over compared to patients less than 65: chest pain (7.7 vs. 2.4%), diarrhea (16.7 vs. 5.9%), anorexia (12.8 vs. 4.4%), peripheral edema (14.1 vs. 9.0%), dizziness (19.2 vs. 12.7%) and anxiety (12.8 vs. 2.9%). Only one adverse event, flu syndrome, occurred more frequently among patients less than 65 years of age (8.0 vs. 1.3%).

A subgroup of 21 patients 75 years of age and over was compared with patients less than 65 years (n = 410) and patients 65 to 74 years (n = 57). There were 24 adverse events with a $\geq 5\%$ difference between at least two of these three groups as presented in Table 7.13. In particular, back pain, somnolence, confusion, ataxia, pneumonia, dyspnea, and UTI were more common among patients over 75 compared with patients less than 65 years of age. The elderly are known to be more susceptible to the adverse events associated with opioids and this could account for the different frequencies of somnolence, ataxia, and confusion. There is no apparent explanation for the difference in back pain, pneumonia or UTI. The small number of subjects in the 65 to 74 and ≥ 75 year age groups may have resulted in some degree of sampling error.

Table 7.13 Adverse Events Which Differed by >5% Between Age Subgroups

	C-HARTs	<65 years (N=410)		65 to 74 years (N=57)		≥75 years (N=21)	
		N	%	N	%	N	%
Body System	Adverse Event						
Body, general	Pain back	16	3.9	2	3.5	4	19.0
	Asthenia	42	10.2	9	15.8	2	9.5
	Flu syndrome	33	8.0	0	0.0	1	4.8
	Infection	19	4.6	4	7.0	0	0.0
Cardiovascular	Pain chest	10	2.4	4	7.0	2	9.5
Digestive	Nausea	99	24.1	11	19.3	6	28.6
	Constipation	84	20.5	11	19.3	2	9.5
	Diarrhea	24	5.9	11	19.3	2	9.5
	Anorexia	18	4.4	8	14.0	2	9.5
	Dyspepsia	25	6.1	3	5.3	0	0.0
Metabolic and Nutritional	Edema peripheral	37	9.0	8	14.0	3	14.3
	Weight decrease	5	1.2	3	5.3	0	0.0
	Dehydration	4	1.0	3	5.3	0	0.0
Nervous	Somnolence	68	16.6	7	12.3	5	23.8
	Dizziness	52	12.7	11	19.3	4	19.0
	Confusion	8	2.0	2	3.5	3	14.3
	Anxiety	12	2.9	8	14.0	2	9.5
	Depression	18	4.4	4	7.0	2	9.5
	Ataxia	3	0.7	1	1.8	2	9.5
	Sweating	37	9.0	7	12.3	1	4.8
	Dry mouth	22	5.4	3	5.3	0	0.0
	Hallucination	4	1.0	3	5.3	0	0.0
		UTI	6	1.5	2	3.5	3

Source: Table 23, Vol. 1.115, P. 73

Gender

The number of male and female patients was fairly balanced within the clinical studies. There were 229 men and 259 women enrolled and pooled in the safety population. Adverse events were more common among women, (88.8 vs. 74.7%), and there were nine individual events that occurred ≥ 5% more frequently among female patients as demonstrated in Table 7.14.

Table 7.14 Adverse Events With a ≥ 5% Frequency of Occurrence Between Males and Females

	C-HARTs Adverse	Male (N=229)		Female (N=259)	
		N	%	N	%
Body System	Event				
Digestive	Nausea	42	18.3	74	28.6
	Vomit	25	10.9	51	19.7
Metabolic/ Nutritional	Edema peripheral	15	6.6	33	12.7
Nervous	Headache	29	12.7	55	21.2
	Somnolence	31	13.5	49	18.9
	Dizziness	25	10.9	42	16.2
	Sweat	15	6.6	30	11.6
Respiratory	URI	5	2.2	19	7.3
Skin and Appendages	Pruritus	12	5.2	2	12.4

Source: Table 24, Vol. 1.115, P. 74

The difference in frequency of adverse events between men and women is difficult to explain. Based on the PK studies, women demonstrated a higher mean Cmax and AUC than men, but only approximately 10% higher. This degree of difference is generally not considered clinically significant or of great enough magnitude to warrant a dose adjustment based on gender.

Race

Of the 488 patients in the original NDA safety database, 451 (92.4%) were Caucasian. Only 24 (4.9%) patients were African American, five (1.0%) Asian and eight (1.6%) other races. The small number of patients that were races other than Caucasian limits the usefulness of comparisons. The sponsor compared Caucasian and African American sub-groups and found variable results that are difficult to interpret. These results are presented in Table 7.15.

Table 7.15 Adverse Events for Which the Frequency of Occurrence Differed by $\geq 5\%$ Between Caucasian and Black Patients

C-HARTs Adverse	Race Subgroups			
	Caucasian (N=451)		Black (N=24)	
	N	%	N	%
Flu syndrome	34	7.5	0	0.0
Pain abdomen	32	7.1	0	0.0
Injury accidental	24	5.3	0	0.0
Infection	20	4.4	3	12.5
Vomit	71	15.7	2	8.3
Dyspepsia	23	5.1	3	12.5
Pain throat	8	1.8	2	8.3
Edema peripheral	45	10.0	1	4.2
Headache	82	18.2	0	0.0
Dizziness	60	13.3	2	8.3
Sweat	45	10.0	0	0.0
Dry mouth	24	5.3	0	0.0
Sinusitis	12	2.7	2	8.3
Pruritus	35	7.8	6	25.0
Infect urinary tract	7	1.6	3	12.5

Source: Table 25, Vol. 1.115, P. 75

Section 7.3.4.6.2 Drug Disease Interactions

The sponsor performed a comparison of adverse events in patients with cancer pain (n = 73) compared to patients with non-cancer pain.(n = 415). Adverse events were more common among the patients with cancer related pain, 93.2%, compared to patients with non-cancer related pain, 80.2%. The patients with cancer pain exhibited a greater frequency of asthenia (16.4 vs. 9.9%), diarrhea (12.3 v. 6.7%), peripheral edema (19.2 vs. 8.2%), dehydration (6.8 vs. 0.5%), confusion (9.6 vs. 1.4%), hallucinations (6.8 vs. 0.5%), dyspnea (12.3 vs. 2.9%) and cough (6.8 vs. 1.4%) than patients with non-cancer pain. The non-cancer pain patients exhibited more headache (18.1 vs. 12.3%), dizziness (14.7 vs. 8.2%) and flu (8.0 vs. 1.4%) than the patients with cancer pain. There is no comparison of the Dilaudid dose for these two groups. It may be that patients with cancer related pain required a greater amount of Dilaudid. The higher frequency of dyspnea and cough in the patients with cancer pain could represent greater susceptibility to infection or a result of cancer directed therapy. The higher frequency of headache, dizziness and flu in the non-cancer pain patients has no apparent explanation. Overall, there were no clinically significant findings in the analysis of adverse events based underlying pain etiology.

Renal Insufficiency

There were nine patients in the Phase III trials with mild or moderate renal insufficiency, and four of these entered the study with abnormal creatinine levels. Of the remaining five patients, four had a history of renal insufficiency or kidney disease on entering the study. The AEs experienced by this subgroup were similar to the population as a whole.

Hepatic Insufficiency

There were 14 patients with mild liver disease in the Phase III trials characterized by a history of liver dysfunction, baseline ALT or AST more than twice normal, or an AE suggesting loss of liver function. The adverse events exhibited by these patients were comparable to the study population as a whole.

Section 7.3.4.6.3 Drug-Drug Interactions

There was no systematic evaluation of Dilaudid CR with drugs other than naltrexone. In Study DO-102, 30 normal subjects were administered naltrexone 50 mg every 12 hours for three doses, beginning 12 hours after receiving Dilaudid CR 16 mg. The mean AUC for hydromorphone was not effected. However, the mean Cmax was increased by approximately 40%.

SECTION 7.4 ABUSE POTENTIAL, OVERDOSE AND WITHDRAWAL

There was one patient exhibiting drug seeking behavior reported as an adverse event. He was randomized to 1/2-dose Dilaudid CR and requested removal from the study due to lack of efficacy. This patients had consumed all of his medication and provided records to the study site that were felt to contain discrepancies.

In the Phase III studies, there were eight reports of withdrawal, seven following treatment with Dilaudid CR, one following treatment with Dilaudid IR. The Dilaudid doses during these symptoms ranged from 16 to 96 128 mg of hydromorphone per day, and duration of treatment with Dilaudid from 1 to 96 days. All patients recovered with investigator managed treatment.

In the Phase I studies, one patient exhibited withdrawal symptoms after four days of Dilaudid CR 16 mg.

There were four cases of overdose, three reported as serious adverse events, all due to patients taking an incorrectly large dose of medication. One patient required treatment with naloxone; the others recovered without intervention other than dosage reduction or discontinuation of hydromorphone.

SECTION 8 USE IN SPECIAL POPULATIONS

SECTION 8.1 PEDIATRIC USE

The sponsor has requested deferment of pediatric studies pending completion of the trials in the adult population. In this way safety and efficacy could be assessed in adults prior to pediatric exposure. The sponsor provided brief plans anticipating trials in 200 pediatric patients to characterize the PK and safety of Dilaudid CR in the pediatric population.