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EXALGO™ (hydromorphone HCl) Extended-Release Tablets CII

NDA 21-217

Joint Meeting

Anesthetic and Life Support Drugs Advisory Committee

and

Drug Safety and Risk Management Advisory Committee

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Neuromed Pharmaceuticals, Ltd.
301-2389 Health Sciences Mall
Vancouver BC, V6T1Z3

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ABBREVIATIONS

AAPCC	American Association of Poison Control Centers
AE	adverse event
AERS	Adverse Event Reporting System
AHFS	American Hospital Formulary Service
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ARCI	Addiction Research Center Inventory
ASI-MV	Addiction Severity Index – Multimedia Version
AUC	area under the curve
AUC_t	AUC at time t
AUEC	area under the effect curve
b.i.d.	twice daily
BMI	body mass index
BOCF	baseline observation carried forward
BPI	Brief Pain Inventory
BRM	Benefit Risk Management
CAC	Compliance Assessment Committee
CCDS	Company Core Data Sheet
C_{max}	maximum plasma concentration
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum plasma concentration
C_{maxss}	maximum measured plasma concentration over the last 24-hour dosing interval
C_{minss}	measured plasma concentration at the end of the dosing interval
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
COWS	Clinical Opioid Withdrawal Scale
CSR	Clinical Study Report
C_{ssav}	the ratio of $AUC_(0\text{-}\tau)$ to the dosing interval τ
CV%	coefficient of variation percentage
CYP450	cytochrome P450
DAWN	Drug Abuse Warning Network
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DEA	Drug Enforcement Administration
ECG	electrocardiogram
EU-RMP	European Risk Management Plan
F_{abs}	absolute bioavailability
FDA	Food and Drug Administration

GI	gastrointestinal
h	hour
HCl	hydrochloride
HCP	healthcare professional
IA	intra-arterial
IDI	Individual Depth Interviews
IM	intramuscular
IND	Investigational New Drug Application
IR	immediate release
IV	intravenous
J&J	Johnson & Johnson
KAB	Knowledge, attitude, and behavior
LBP	low back pain
LSM	least squares mean
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
Min	minute
NA	not applicable
NDA	New Drug Application
NOAEL	no-observed-adverse-effect-level
NPDS	National Poison Data System
NRS	Numeric Rating Scale
NSAID	non-steroidal anti-inflammatory drugs
OA	osteoarthritis
pCO_2	partial pressure of carbon dioxide
pO_2	partial pressure of oxygen
ORT	Opioid Risk Tool
PDR	Physician's Desk Reference
PGA	Patient Global Assessment
PI	Prescribing Information
PIN	Patient Identification Number
PK	pharmacokinetics
PO	oral (per os)
PPMA	Prescriber-Patient Medication Agreement
PRD	Pharmaceutical Research and Development
prn	as needed
PSUR	Periodic Safety Update Report
PT	preferred term
PV	paravenous
q.d.	once daily
q.i.d.	four times a day

RADARS	Denver Health's Researched Abuse, Diversion and Addiction-Related Surveillance
REMS	Risk Evaluation and Mitigation Strategy
RDQ	Roland-Morris Disability Questionnaire
RiskMAP	Risk Minimization Action Plan
ROC	REMS Oversight Committee
RSMB	REMS Safety Monitoring Board
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SOAPP	Screener and Opioid Assessment for Patients with Pain
SOC	system organ class
SOCF	screen observation carried forward
SOWS	Subjective Opioid Withdrawal Scale
SPA	Special Protocol Assessment
SR	sustained-release
$t_{1/2}$	apparent terminal half-life
TESS	Toxic Exposure Surveillance System
T_{max}	time to maximum observed plasma concentration
T_{maxss}	time of the maximum measured plasma concentration over the 24-hour dosing interval
US	United States
VAS	visual analog scale
WIS	Web Informed Services
WHO	World Health Organization
WOMAC	Western Ontario and McMaster Osteoarthritis Index

DEFINITION OF TERMS

Abstinence Syndrome	The characteristic signs and symptoms that appear when a drug that causes physical/psychological dependence is regularly used for an extended period of time and then suddenly discontinued or decreased in dosage (may also be referred to as withdrawal syndrome). Acute opioid withdrawal is characterized by diaphoresis, nausea or vomiting, muscle aches, lacrimation, rhinorrhea, papillary dilation, diarrhea, yawning, fever, and/or insomnia.
Abuse	Use of any substance for non-therapeutic purposes or the use of medication for purposes other than those for which the agent is prescribed.
Abuse Liability	The potential for a drug to be abused, misused or diverted.
Addiction	Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving (AAPM, 2001).
Diversion	Unlawful channeling of regulated pharmaceuticals from legal sources to illicit marketplace.
Misuse	Use of any medication by a person for whom it was not prescribed, or for purposes other than those for which it was prescribed.
Opioid Tolerant	Patients considered to be opioid tolerant were those who were taking at least 60 mg oral morphine/day, or at least 30 mg of oxycodone/day, or at least 12 mg of hydromorphone/day, or an equianalgesic dose of another opioid, for a week or longer.
Opioid Naïve	A subject who has not received an opioid in the last 30 days.
Physical Dependence	Physical dependence is a state of adaptation that is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist (AAPM, 2001).
Tolerance	Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time (AAPM, 2001).
Withdrawal Syndrome	See abstinence syndrome, above.

EXECUTIVE SUMMARY

Introduction

EXALGO™ (hydromorphone HCl) Extended-Release Tablets CII (hereafter referred to in this document as EXALGO) are a novel, long-acting formulation of hydromorphone hydrochloride (HCl) developed by Neuromed. Hydromorphone, the active ingredient of EXALGO, is a semisynthetic 5-ring morphinan derivative opioid analgesic with qualitative effects similar to those of morphine. In the United States (US), hydromorphone is currently only available as an immediate release (IR) oral formulation, which requires that it be administered at least every 4 to 6 hours. To support treatment of patients with chronic pain, EXALGO tablets were designed with the OROS® Push-Pull™ technology to release hydromorphone at a relatively constant rate and achieve stable plasma levels over a 24-hour period allowing for once daily administration of hydromorphone.

EXALGO has been shown to be effective and well-tolerated in an adequate and well-controlled clinical study in patients with chronic pain. Because the risks associated with the use of long acting opioids are well-known, Neuromed has designed a Risk Evaluation and Mitigation Strategy (REMS) program to minimize the primary risks of overdose, abuse, and diversion of EXALGO. The clinical benefits and safety of EXALGO, as well as the potential risks associated with its use, are addressed in this Briefing Document.

Disease Burden of Chronic Pain and Medical Need for Opioid Treatment

More than 50 million Americans experience chronic pain from a wide variety of sources, most commonly back pain, joint pain, cancer pain and headache. Chronic pain, the nations' leading cause of disability, exacts a huge toll on individual patients including not just physical distress but profound psychosocial and economic distress as well as functional losses and vocational dysfunction.

The efficacy of opioids for chronic pain treatment is well-established, and their use is known to be safe and effective in a broad range of pain states, including cancer, postoperative pain, and non-cancer pain. The number of people in the US who take prescription opioids for pain is growing. While numerous treatment options exist, there is a significant body of evidence suggesting that pain (both acute and chronic) remains undertreated. There is a growing focus on inadequate treatment of pain from a wide range of stakeholders. Numerous guidelines and policies exist to reinforce the need for effective treatment and to provide instruction on appropriate patient selection and pain management.

There are currently a variety of long-acting opioid products available in the US. While each of these products has demonstrated efficacy for the treatment of chronic pain, there remains a significant number of patients that do not achieve adequate symptom relief from their initially prescribed opioid analgesic. Ordinarily, dose titration should be pursued as a first means of improving pain relief when needed; however, dose escalation is often limited by poor tolerability. In cases where patients cannot reach functional

goals with their assigned opioid analgesic regimen, opioid rotation should be considered. Many patients require trials on multiple opioids to find the one they respond optimally to. Opioid rotation has been shown to improve responses in patients with both cancer-pain and non-cancer pain.

Hydromorphone is a well-characterized potent opioid analgesic that has been used in the United States for over 80 years. Immediate release formulations of hydromorphone are available for treatment of both acute and chronic pain conditions, but the short duration of action of these formulations requires dosing at least every 4 to 6 hours. For patients with chronic pain, availability of a long-acting formulation whose duration extends through the hours of sleep will improve convenience and perhaps compliance. EXALGO was developed to provide a once daily formulation of hydromorphone to existing opioid tolerant, chronic pain patients. EXALGO would provide an additional treatment option to the armamentarium of available pain therapeutics for patients who are not well-managed on their current long- or short-acting opioid.

EXALGO Clinical Development and Post-marketing Experience

Clinical studies have been conducted in a total of 3,777 patients and healthy subjects, including 15 pharmacokinetic/clinical pharmacology trials, and 13 controlled and un-controlled Phase 2 or 3 studies conducted in 2,335 EXALGO-treated patients with chronic cancer pain or non-cancer pain.

Results from the pharmacokinetic/clinical pharmacology trials demonstrated that the EXALGO formulation provided relatively stable blood levels of hydromorphone with less frequent dosing. The same total daily dose of the EXALGO formulation administered once daily resulted in the same exposure to that of the IR hydromorphone formulation administered 4 times a day. The concomitant use of alcohol and EXALGO was evaluated for dose dumping, and the extended release characteristics of the OROS formulation were maintained in the presence of alcohol. There was no food effect on the release of hydromorphone. Furthermore, an abuse liability study demonstrated generally lower drug liking with EXALGO than with IR hydromorphone.

While 13 controlled and uncontrolled clinical studies were conducted, only Study NMT 1077-301 met the US Food and Drug Administration's (FDA's) current requirements for an adequate and well-controlled trial. Neuromed conducted this study in patients with chronic LBP who were opioid tolerant and being treated with opioid analgesics for at least 2 months prior to screening. For the primary efficacy variable, EXALGO demonstrated significant reductions in pain intensity at all doses. EXALGO was also effective across a variety of secondary subjective, behavioral, and disability measures, and demonstrated an expected safety profile. Study NMT 1077-301, therefore, satisfied the FDA request for establishing the safety and efficacy of EXALGO in a setting of moderate to severe pain.

An identical formulation of EXALGO, submitted under the trade name of JURNISTA® by the international subsidiaries of Johnson and Johnson (J&J), was first approved in Denmark in December 2004. The product was first marketed in Germany in 2006 and is

now approved in 26 countries and marketed in 9 countries for the treatment of moderate to severe pain. Post-marketing experience is based on just under 17 million patient days from the time of first approval in December 2004 through December 2008. During this reporting period, 171 spontaneously reported serious adverse events (SAEs) were received by J&J's Benefit Risk Management (BRM) department. Presentation of the post-marketing safety of JURNISTA is provided in Section 5 of this document. Overall, the post-marketing experience with JURNISTA suggests a safety profile that is consistent with other strong opioid analgesics.

Risk Evaluation and Mitigation Strategy (REMS): Exalgo Alliance Program

The primary risks of EXALGO are overdose, abuse and diversion. These risks can be associated with inappropriate prescribing, dispensing, use, and handling. Neuromed has developed a REMS, termed Exalgo Alliance. Exalgo Alliance is a controlled access program for prescribing, dispensing and use of EXALGO under safe use conditions. Exalgo Alliance is designed to ensure that prescribers, pharmacists, and patients understand the benefit-risk profile and responsible use and handling of EXALGO as well as agree to follow Exalgo Alliance program requirements.

Key components of the Exalgo Alliance program are:

- Professional labeling to educate healthcare providers on the risks and responsible use of EXALGO as well as Exalgo Alliance program requirements;
- A Medication Guide to educate patients about risks and safe use and handling of EXALGO as well as Exalgo Alliance program requirements;
- A communication plan to educate all stakeholders about the risks and safe use and handling of EXALGO;
- Elements to assure safe use, to ensure that EXALGO is prescribed, dispensed and used under safe use conditions through enrollment, acknowledgement of risks and responsible prescribing, dispensing and use, as well as agreement to follow Exalgo Alliance program requirements;
- An implementation system to establish the infrastructure of the elements to assure safe use; and
- Regular assessments to evaluate the performance and effectiveness of the Exalgo Alliance program.

EXALGO will only be available through the Exalgo Alliance program. Prescribers who are authorized to prescribe Schedule II drugs can only prescribe EXALGO after they have enrolled in Exalgo Alliance by acknowledging their understanding of EXALGO risks and agreeing to follow responsible EXALGO prescribing practices and other program requirements.

EXALGO can only be dispensed by enrolled pharmacies and other healthcare settings that are authorized to dispense Schedule II drugs. To become enrolled, a pharmacy representative must acknowledge understanding of EXALGO risks. They must agree to responsible dispensing and use, as well as to follow the requirements of Exalgo Alliance. Wholesalers and distributors must agree to sell EXALGO only to enrolled pharmacies and healthcare settings.

EXALGO can only be used to treat patients who are enrolled in Exalgo Alliance. They must sign an agreement with their prescriber acknowledging they understand the risks and will adhere to responsible use and handling, as well as the requirements of Exalgo Alliance. Safe use conditions will be verified every time a prescription is presented. The pharmacist must verify that both the prescriber and the patient are enrolled in Exalgo Alliance, indicating they are following the program requirements. The implementation system will be monitored for program performance and stakeholder compliance. Upon approval of the New Drug Application (NDA), the commercialization of EXALGO and the implementation of the REMS will be the responsibility of Covidien. Covidien will employ comprehensive monitoring and surveillance processes to evaluate the program and take corrective actions as appropriate

The overall goal of the Exalgo Alliance program is to optimize the benefit-risk balance of EXALGO. Implementation of the Exalgo Alliance program will not impede the ability of appropriate patients to have access to EXALGO, but is necessary to ensure that the benefits of EXALGO outweigh its associated risks.

Benefit / Risk Profile

The beneficial use of opioids is well-established for the treatment of a broad range of states associated with chronic pain. Commonly, long-acting opioids are used to provide a stable level of pain relief when around-the-clock relief is needed, while short-acting opioids are used for breakthrough and more transient pain. Opioid rotation is a well accepted clinical practice, and studies of patient opioid use have shown that it is common for patients to move through multiple opioids until they find one that is optimal.

Because opioids are known to have significant potential adverse events (AEs) and a pattern of known very common AEs, a benefit versus risk assessment and decision has to be made for each patient at the time that opioids are prescribed, and has to be kept in mind as the patient's condition progresses. In addition to AEs in individual patients and the risk of abuse or addiction in any patient, the abuse liability of opioids, a known public health problem for decades, extends both to patients and non-patients. The significant clinical benefit of opioids for the patients must be considered in context and balanced relative to the potential risks of addiction and abuse both by patients and non-patients, and in the context of programmatic controls to detect and minimize the risks to both patients and non-patients.

Hydromorphone has been in use for the treatment of pain for decades, and remains widely used today. The chief clinical limitation of available formulations of hydromorphone is that its rapid absorption and short half-life have led to the requirement for very frequent dosing, the risk of significant pain on awakening, and to a blood level pattern of high peaks and low troughs. Hydromorphone is currently available in both IR and a long-acting formulation in 9 countries globally, but is only available in an IR formulation in the US at this time. EXALGO, marketed in those 9 countries under the brand name JURNISTA, was developed as an extended release formulation of hydromorphone intended to provide clinical benefit, including improved continuity of analgesia, to the subset of patients who respond well to hydromorphone and require

around-the-clock therapy. The unique pharmacokinetic characteristics of EXALGO produce relatively stable and effective blood levels of hydromorphone with convenient once-daily dosing. EXALGO does not have an IR component, and is intended and effective for chronic pain but not acute pain. EXALGO bioavailability is not affected by food, and its extended-release properties are maintained in the presence of alcohol with no acute dose dumping of hydromorphone.

Efficacy of EXALGO (used together with rescue medication) over 12 weeks of treatment was demonstrated relative to placebo (supplemented with rescue medication) in the pivotal study NMT 1077-301 in opioid-tolerant patients with chronic pain. The EXALGO treatment response was also reflected in a variety of secondary outcome measures detecting subjective, behavioral and disability-related improvements. Pooled safety data from over 3000 patients in 13 controlled and uncontrolled studies of EXALGO in patients with chronic pain, as well as post-marketing surveillance data from worldwide experience, showed a safety profile that was characteristic of that seen with other strong opioids and revealed no unexpected safety concerns.

Like other opioids, EXALGO has the risk of overdose, misuse and abuse, which must be considered when the product is prescribed, administered and dispensed. To minimize these risks, EXALGO should be prescribed to the appropriate opioid-tolerant patient population. The initiation of dosage, appropriate conversion from other pain medication, and subsequent dose titration should be individualized for each patient being prescribed EXALGO. Patients being considered for EXALGO should be assessed for their clinical risks for opioid addiction or abuse, and should be monitored for signs of misuse, abuse, and addiction.

In conclusion, the data presented in this Briefing Document demonstrate that EXALGO is effective in controlling pain over a 12-week period in opioid-tolerant patients with moderate to severe chronic pain. The safety profile across the EXALGO clinical development program is well understood and is similar to other strong opioids. The primary risks of overdose, misuse, and abuse will be addressed through a comprehensive REMS program. EXALGO will provide an option for clinicians who treat opioid-tolerant patients whose chronic pain is not adequately or optimally controlled by their current opioid therapy. Overall the benefits of EXALGO for patients exceed the risks associated with this new formulation. The risks of EXALGO can be reduced, detected and managed through the comprehensive EXALGO REMS.

1 INTRODUCTION

EXALGO (hydromorphone HCl) Extended-Release Tablets CII (hereafter referred to in this document as EXALGO) is a once daily formulation of hydromorphone hydrochloride (HCl) intended for the treatment of moderate to severe pain in patients requiring opioid analgesics over an extended period of time. Hydromorphone is currently only available in the United States (US) as an immediate release (IR) oral formulation for management of acute pain and chronic pain, and must be administered every 4 to 6 hours.

Neuromed has evaluated EXALGO through an extensive clinical development program, and is seeking Food and Drug Administration (FDA) approval of EXALGO under New Drug Application (NDA) 21-217. This Briefing Document outlines the regulatory history and formulation technology behind EXALGO, and summarizes the clinical safety and efficacy profile of EXALGO in patients with chronic pain. Post-marketing safety experience from JURNISTA (ex-US trade name) use world-wide is also provided. To address the primary risks of abuse, misuse and diversion of EXALGO, a Risk Evaluation and Mitigation Strategy (REMS) developed specifically for EXALGO is outlined in Section 7 of this document.

1.1 Background for Development

1.1.1 Disease Burden of Chronic Pain and Medical Need for Opioid Treatment

More than 50 million Americans experience chronic pain from a wide variety of sources, most commonly back pain, joint pain, cancer pain and headache (Hale 2005; Ruoff 2002; Vo et al. 2008). Chronic pain, the nations' leading cause of disability, exacts a huge toll on individual patients including not just physical distress but profound psychosocial and economic distress as well as functional losses and vocational dysfunction.

The efficacy of opioids for chronic pain treatment is well-established, and their use is known to be safe and effective in a broad range of pain states, including cancer, postoperative pain, and non-cancer pain. The number of people in the United States (US) who take prescription opioids for pain is growing. Between 2000 and 2005, Sullivan and colleagues (2008) reported a 19% increase in the number of patients who received prescriptions for opioids to manage chronic non-cancer pain conditions. Based on a survey conducted from 1998 to 2006 with more than 19,000 subjects, Parsells et al. (2008) reported that 2% of the US population ≥18 years of age legally used opioids as analgesics at least 5 days per week for 4 or more weeks, and another 2.9% used these drugs less frequently.

While numerous treatment options exist, there is a significant body of evidence suggesting that pain (both acute and chronic) remains undertreated. There is a growing focus on inadequate treatment of pain from a wide range of stakeholders, including patients and advocacy groups, healthcare providers and government agencies. Numerous guidelines and policies exist to reinforce the need for effective treatment and to provide instruction on appropriate patient selection and pain management.

The classical model for pain treatment is captured in the 1986 World Health Organization (WHO) analgesic ladder (Breivik 1990). While this guidance focuses on treatment of cancer pain, many of those same criteria have been applied to patients suffering from chronic noncancer pain to ease their suffering. The WHO ladder includes a complete and comprehensive assessment based on the needs of the patient, disease targeted remediation of causes, multi-modal therapy with an escalation of therapeutic modalities through a variety of non-opioid therapies up to weak and then strong opioid therapy when appropriate together with continual reappraisal of the patient's adherence to treatment.

There are a wide range of barriers to effective pain management. These include poor knowledge of clinical guidelines for pain management, concern that prescribing controlled substances will elicit scrutiny by regulatory or legal authorities, and misunderstanding about the risk of abuse and dependence. To address some of these barriers, the Federation of State Medical Boards issued their Model Policy for the Use of Controlled Substances for the Treatment of Pain in May 2004 (FSMB 2004). While the document focuses primarily on general principles (patient evaluation, development of a treatment plan, need to discuss risks and benefits of controlled substances, periodic review of response), it emphasizes that undertreatment of pain will be considered a "departure from acceptable medical practices".

Specific treatment guidelines also exist for use of opioids in the treatment of noncancer pain. In early 2009, the American Academy of Pain Medicine (AAPM 2009) issued the Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain. In their report, the expert panel concluded that opioid therapy can be a safe and effective treatment option for patients with chronic noncancer pain provided that patients are appropriately selected and monitored. The AAPM Guidelines provides comprehensive recommendations related to topics such as proper patient selection, informed consent, appropriate therapy initiation and titration, treatment of high-risk patients, management of opioid adverse events, management of breakthrough pain, and awareness of federal and state laws. Such guidelines are important tools to educate clinicians about appropriately balancing the benefits of opioid therapy with the risks of abuse, addiction and diversion.

There are currently a variety of long-acting opioid products available in the United States. While each of these products has demonstrated efficacy for the treatment of chronic pain, there remains a significant number of patients that do not achieve adequate symptom relief from their prescribed opioid analgesic. Ordinarily, dose titration should be pursued as a means of improving pain relief when needed. However, dose escalation is often limited by poor GI and/or CNS tolerability. In cases where patients cannot reach functional goals with their assigned opioid analgesic regimen, opioid rotation should be considered. This practice has been described widely in the literature, including a recent publication by Fine (2008):

"Opioid rotation is the practice of switching to a different opioid analgesic when adequate effectiveness is not achieved during a trial of reasonable duration, or when side effects become intolerable. This approach to managing lack of efficacy or intolerable side effects is supported both by empirical clinical evidence as well as current research.

Clinically significant inter-patient variability in response to opioids has been observed for decades, in terms of both efficacy and side effects."

Opioid rotation has been shown to improve responses in patients with both cancer-pain and non-cancer pain. In a prospective study evaluating the frequency, indications, outcomes and predictive factors associated with opioid switching in cancer patients, Mercadante et al. (2009) reported that "opioid switching was an effective method to improve the balance between analgesia and adverse effects in more than 80% of cancer patients with a poor response to an opioid." Similarly, Quang-Cantagrel et al. (2000) et al. considered opioid rotation for a population with chronic non-cancer pain by a retrospective chart review. They found that the first opioid prescribed was effective for only 36% of patients, was stopped due to side effects for 30% and stopped for lack of efficacy in the other 34%. The remaining patients who still had uncontrolled pain or side effects were given a different opioid and the second opioid was effective in 31% of those treated. Further rotation led to effectiveness of the third opioid tried in 40%, the fourth in 56%, and the fifth in 14%.

Hydromorphone is a well-characterized potent opioid analgesic that has been used in the United States for over 80 years. Immediate release formulations of hydromorphone are approved and available for treatment of both acute and chronic pain conditions. However, the short duration of action of these formulations necessitate taking these products at least every 4 to 6 hours. For patients with chronic pain, availability of a long-acting formulation will improve convenience and perhaps compliance. In comparison to other potent opioids, hydromorphone has the additional advantages of having a low likelihood of pharmacokinetic drug-drug interactions. This can be particularly important since many patients with chronic pain are on multiple concomitant medications. EXALGO was developed to provide a once daily formulation of hydromorphone to existing opioid-tolerant, chronic pain patients. EXALGO would provide healthcare professionals with another extended release formulation option for the treatment of chronic pain; many of the existing extended release formulations are only approved for twice daily administration. Once daily administration would reduce the total number of tablets needed for therapeutic effect, thereby improving patient convenience and, perhaps, patient compliance. Additionally, an extended-release hydromorphone would provide an additional treatment option to the armamentarium of available pain therapeutics for patients who are not well-managed on their current long- or short-acting opioid.

Given the large number of patients who have an inadequate response to a given opioid, availability of another treatment option for chronic treatment is important for both patients and their healthcare providers. Furthermore, given the common practice of opioid rotation, EXALGO provides an important once daily option for patients suffering from chronic pain.

1.2 EXALGO Product Profile

1.2.1 OROS (Hydromorphone HCl) Advantages

Hydromorphone is a Schedule II prescription opioid with analgesic potency that is approximately 5 times stronger than morphine. It has been available for use in the US for at least 80 years. Hydromorphone has been shown to be effective and well-tolerated. In the clinic setting, it has been extensively used in the treatment of moderate to severe pain, and is the only strong opioid analgesic not available in a long-acting oral formulation in the US. In its IR form, hydromorphone has an onset of effect (peak plasma concentrations occurring 30-60 minutes after administration) and a relatively short initial elimination half-life (2-3 hours) that necessitates dosing every 4 to 6 hours. While these pharmacokinetic (PK) characteristics may be ideal for treating acute pain, for chronic pain patients the frequent dosing requirements may be associated with poor adherence and, possibly, inadequate analgesia.

EXALGO's dosage form was designed using the ALZA Corporation's OROS® (oral osmotic drug delivery system) technology (see Section 2.1), which has been used in 13 marketed prescription and nonprescription products since 1989, including Procardia XL® (nifedipine) Extended Release Tablets, and another CII product, Concerta® (methyphenidate HCl). The advantage of this delivery system is that plasma concentrations of EXALGO reach a broad, relatively flat plateau within 6 to 8 hours after dosing (with steady-state reached within 3-4 days), and are sustained for approximately 24 hours, a profile that indicates continued and consistent drug absorption throughout the gastrointestinal (GI) tract.

1.2.2 Proposed Indication, Dosage and Administration

1.2.2.1 Proposed Indications and Usage

EXALGO is indicated 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. Patients considered to be opioid tolerant are those who are taking at least 60 mg oral morphine/day, or at least 30 mg of oral oxycodone/day, or at least 12 mg hydromorphone/day, or an equianalgesic dose of another opioid, for a week or longer.

EXALGO must only be used in opioid-tolerant patients because fatal respiratory depression could occur in patients who are not already receiving and tolerant to opioid therapy.

Since the risks of EXALGO and its potential to be abused, misused, or diverted are similar to those of all Schedule II long-acting opioids, the proposed labeling for EXALGO contains opioid class labeling, particularly in the Black Box Warning, Warnings and Precautions, and Drug Abuse and Dependence sections.

1.2.2.2 Proposed Dosage and Administration

The proposed dose of EXALGO is 12 mg to 64 mg administered once daily. As with other opioid analgesics used to treat chronic pain, the dose of EXALGO should be titrated in each patient to achieve the best balance between analgesia and side effects. The extended-release nature of the formulation allows EXALGO to be administered every 24 hours with or without food. It is usually appropriate to treat a patient with only one extended-release opioid for around-the-clock therapy.

1.2.2.3 Initiation of Therapy

It is critical that prescribers initiate the dosing regimen individually for each patient. Overestimating the EXALGO dose when converting patients from another opioid medication can result in a fatal overdose with the first dose. The following dosing recommendations can be considered as suggested approaches to what is actually a series of clinical decisions over time in management of the chronic pain of each individual patient.

In selecting the initial dose of EXALGO, attention should be given to the following:

1. The daily dose, potency, and specific characteristics of the opioid the patient has been taking previously;
2. The reliability of the relative potency estimate used to calculate the equivalent hydromorphone dose needed;
3. The patient's degree of opioid tolerance;
4. The age, general condition, and medical status of the patient;
5. Concurrent non-opioid analgesics and other medications, such as those with central nervous system (CNS) activity
6. The type and severity of the patient's pain;
7. The balance between pain control and adverse effects;
8. The patient's risk factors for abuse, addiction, or diversion, including a prior history of abuse, addiction, or diversion.

1.2.2.4 Conversion to EXALGO in Opioid-Tolerant Patients

Patients receiving oral hydromorphone may be converted to EXALGO by administering a starting dose equivalent to the patient's total daily oral hydromorphone dose. The dose of EXALGO can be titrated every 3 to 4 days until adequate pain relief and acceptable side effects have been achieved.

For conversion from other oral opioids to EXALGO, physicians and other healthcare professionals (HCPs) are advised to refer to published relative potency information (also provided in the proposed Prescribing Information), keeping in mind that conversion ratios are only approximate. In general, EXALGO therapy should be started by administering 50% to 75% of the calculated total daily dose of EXALGO once daily every 24 hours. The initial dose of EXALGO can be titrated until adequate pain relief and acceptable side effects have been achieved.

For conversion from transdermal fentanyl patch, EXALGO treatment can be initiated 18 hours following the removal of the patch. For each 25 µg/hour fentanyl transdermal dose, the equianalgesic dose of EXALGO is 12 mg every 24 hours. Due to the slow onset (6-8 hours) of EXALGO, which makes it unsuitable for the treatment of acute pain, the Prescribing Information (PI) advises that patients should be instructed to use supplemental analgesia (IR preparations) with special attention paid to the first dose. Educational materials for the patient and physician on this topic are also included in the labeling.

1.2.2.5 Dosage Forms and Strengths

EXALGO Tablets will be available in 8, 12, 16, or 32 mg dosage strengths.

1.3 Regulatory History

1.3.1 Development Program

NDA 21-217 was originally submitted to the FDA on 28 December 1999 by Knoll Pharmaceuticals under the trade name Dilaudid CR®. Knoll received an Approvable Letter from the FDA on 27 October 2000. The NDA was subsequently transferred to the ALZA Corporation, a subsidiary of Johnson & Johnson (J&J), who changed the product name to OROS® hydromorphone HCl. ALZA continued discussions with the FDA up to 2005, and additional clinical and nonclinical studies were conducted throughout this time for registration of OROS hydromorphone in countries outside the US. Neuromed acquired the US rights to OROS® hydromorphone HCl from the ALZA Corporation in April 2007, and opened an Investigational New Drug Application (IND) on 19 July 2007 to continue development. Neuromed established the company code of NMED-1077 and the trade name of EXALGO to refer to the OROS® hydromorphone formulation.

J&J has retained ex-US rights to the product. It was first approved by the regulatory authorities in Denmark in December 2004, and first marketed in Germany in 2006 under the brand name JURNISTA® (OROS hydromorphone). To date, OROS hydromorphone is marketed in 9 countries for the treatment of moderate to severe pain.

The original NDA 21-217 for EXALGO was transferred to Neuromed on 05 October 2007. Upon FDA approve of the NDA, Covidien will assume ownership for the application and will have sole responsibility for the regulatory, commercial, marketing and risk management activities of EXALGO in the US.

1.3.2 Approvable Letter

The Approvable Letter outlined 5 deficiencies in the chemistry, nonclinical, and clinical sections of the application.

The first item in the Approvable Letter addressed the need for one adequate and well-controlled study, with multiple dosing of the to-be-marketed formulation, in the setting of moderate to severe pain, to establish the efficacy of the product. Protocol NMT 1077-301 was conducted by Neuromed under a Special Protocol Assessment (SPA) in which

the study's design, clinical endpoints, and statistical analyses were agreed with the FDA. The results of this study are summarized in Section 4.3.1 of this document.

Questions 2, 3, and 4 of the Approvable Letter were related to the Chemistry, Manufacturing and Controls of the Drug Substance and Drug Product. Responses to these questions and supportive data have been submitted to the NDA.

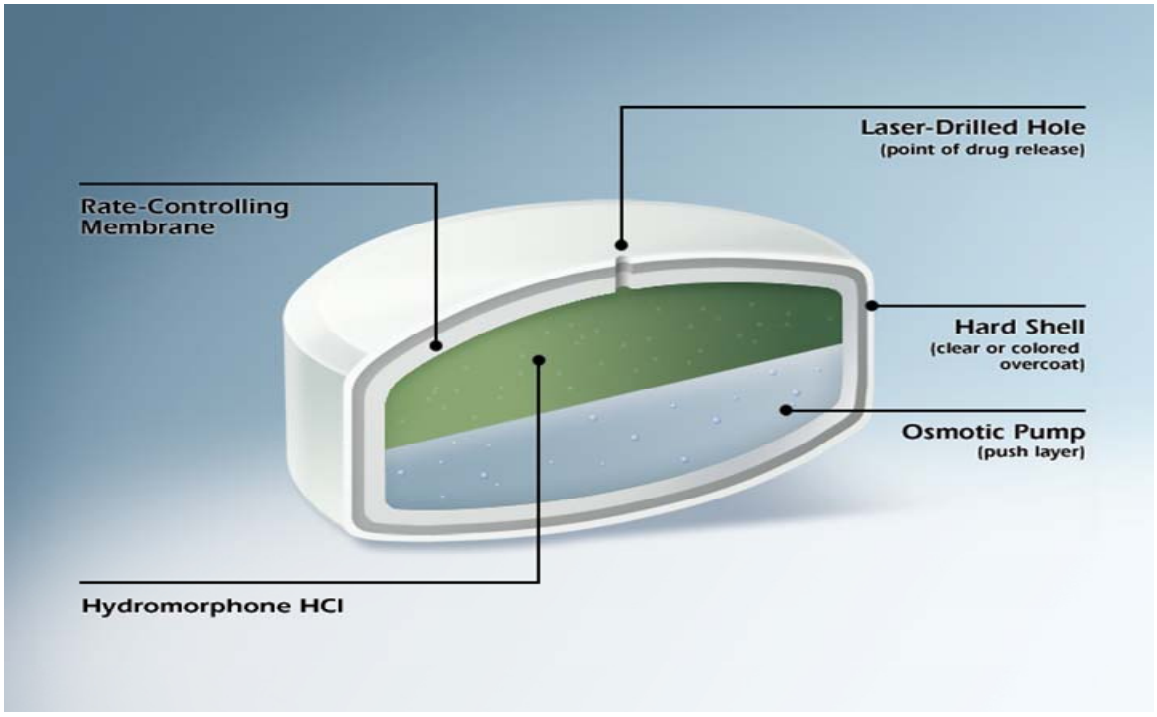
Question 5 of the Approvable Letter was related to the conduct of carcinogenicity studies. In response, carcinogenicity studies in rats and mice were initiated on 18 March 2009 and 24 March 2009, respectively (see Section 3.2), and SPA agreements were reached for both studies, including agreement that the final study reports would be submitted to the NDA as post approval requirements.

2 EXALGO FORMULATION DEVELOPMENT

2.1 Overview of OROS Technology

The extended-release formulation of EXALGO utilizes an osmotic delivery system (OROS® Push-Pull™) developed by the ALZA Corporation. Using the OROS® Push-Pull™ system, hydromorphone is delivered at a controlled rate and for an extended period of time to achieve once daily dosing. The Push-Pull™ tablet system is a small, round tablet, composed of a bilayer tablet core surrounded by a semi-permeable membrane and a hard outer shell with color and clear overcoating (Figure 1). One layer of the core, the "pull" (or drug) layer, contains the drug substance, hydromorphone HCl, along with hydrophilic, osmotically active polymers and other standard tablet excipients. The second layer, the "push" layer, contains an osmotically active expansion polymer of high molecular weight, an adjunct osmotic agent (sodium chloride), a colorant (ferric [or iron] oxide) for layer discrimination during laser drilling, and other typical tablet excipients. The excipients and the mixtures used for the push layer colorant, color overcoat, clear overcoat, and print are comprised of compendial ingredients. The excipient levels used are typical for oral formulations.

Figure 1 Diagram of EXALGO Controlled Release Tablet (System)



In the GI tract, the drug layer hydrates, and a gel-like solution/suspension of hydromorphone HCl is formed in situ. Water is imbibed through the semipermeable membrane and into the core as a result of the osmotic activity gradient established across the membrane by the osmotic excipients in the bilayer tablet core. As the push layer similarly imbibes water, the polymeric and osmotic excipients hydrate and the push layer begins to expand to a greater extent than the drug layer excipients. Drug is expelled from

the core continuously as the system travels along the GI tract until the gradient across the membrane can no longer drive the release. The resulting emptied inert membrane shell is excreted in the feces unchanged.

3 NONCLINICAL DEVELOPMENT PROGRAM

3.1 Nonclinical Studies

As is typical for development of an oral tablet dosage formulation, the non-clinical program was conducted primarily using hydromorphone drug substance. Only one study (1 month oral study in dogs) was conducted using the EXALGO formulation. An extensive non-clinical program on hydromorphone was conducted to support global registration. An outline of the overall safety pharmacology and toxicology studies conducted for the EXALGO NDA is shown in Table 1.

Table 1 Overview of Safety Pharmacology and Toxicology Studies Conducted with Hydromorphone

Study Type and Duration	Route of Administration	Species/Model
Safety Pharmacology Studies		
Effects on cardiac ionic currents (hERG channels)	in vitro	Human embryonic kidney cells
Effects on electro-physiologic properties, compared to morphine	in vitro	Guinea pig papillary muscle
Cardiovascular and respiratory effects in normotensive dogs after single oral dose	PO	Dog
Neurobehavioral evaluation after oral dosing	PO	Rats
Toxicology Studies		
Single-dose toxicity		
Acute toxicity	PO and IV	Mouse, rat
	PO	Dog
Repeat-dose toxicity		
Dose-ranging studies		
1 week	PO	Dog
2 weeks	PO	Mouse, rat, dog
1 month	PO	Rat
3 months	PO	Mouse, rat
Repeat-dose toxicity		
EXALGO[a] 1 month	PO	Dog
Hydromorphone		
1 month	PO	Rat, dog
3 months	PO	Rat
6 months	PO	Rat
9 months	PO	Dog
Developmental and reproductive toxicity		
Fertility and early embryonic development to implantation (Segment I)	PO	Rat
Effects of embryo-fetal development (Segment II)	PO	Rat, rabbit
Effects of pre- and postnatal development, incl. maternal function (Segment III)	PO	Rat
Genotoxicity		
Ames test	in vitro	*S. typhimurium*
Chromosome aberration test	in vitro	Human lymphocytes
Micronucleus test	PO	Mouse
Local tolerance		
Local tolerance	IV, IM, IA, PV, SC	Dog
Dermal irritation	Dermal, IV	Rabbit
Allergic contact sensitization	Dermal	Guinea pig
Other toxicity studies		
Oculotoxicity	IV	Rat

[a] EXALGO tablets administered

IA=intra-arterial; IM=intramuscular; IV=intravenous; PO=oral (per os); PV=paravenous; SC=subcutaneous.

In general, the safety pharmacology characteristics of hydromorphone were similar to those of morphine. In the nonclinical safety pharmacology studies for the EXALGO NDA, the effects of hydromorphone could be summarized as follows: depression (sedation) of the CNS at low doses, and stimulation (convulsions) at high doses; suppression of respiratory function resulting in decreased pO_2 and increased pCO_2; decreases in mean arterial blood pressure, with compensatory increase in heart rate, but no adverse effects on electrocardiogram parameters (QT); inhibition of guinea pig ileum longitudinal muscle contraction, and reduced rate of propulsion of charcoal in the mouse GI system; and reduced urine volume. These same effects have been noted in nonclinical studies with other opiates, and are considered to be class effects; they do not represent any safety concern unique to hydromorphone.

Hydromorphone was tested under repeat-dosing conditions in dogs and demonstrated no target organ toxicity. Overall, the animal data demonstrated that hydromorphone had a toxicity profile characterized by exaggerated pharmacologic activity.

3.2 Status of Carcinogenicity Studies

Carcinogenicity studies in rats and mice were initiated (18 March 2009 and 24 March 2009, respectively) following agreed SPAs on the design and doses used in the studies. The results of these studies will be submitted to the FDA as a post-approval requirement.

4 CLINICAL DEVELOPMENT PROGRAM

This summary of the clinical development program provides an overview of the biopharmaceutics and clinical pharmacology studies that characterize the unique drug delivery system of EXALGO. Safety and efficacy data from controlled and uncontrolled trials of EXALGO in patients with chronic pain are summarized, with specific focus on results of the pivotal Study NMT 1077-301.

4.1 Overview

Clinical studies have been conducted in a total of 3,777 patients and healthy subjects. These studies included 13 controlled and uncontrolled Phase 2 or 3 studies conducted in 2,335 EXALGO-treated patients with chronic cancer pain or non-cancer pain (Table 2) and 15 clinical pharmacology studies (Table 3).

In the Approvable Letter (see Section 1.3.2), the agency identified one clinical deficiency, which was that data presented in the original NDA did not demonstrate efficacy for the intended indication due to both the lack of placebo controlled data and the overall duration of exposure. The FDA therefore requested that an adequate and well-controlled study be conducted to establish efficacy with the to-be-marketed formulation of EXALGO in patients with moderate to severe pain.

Study NMT 1077-301 provided the primary evidence of efficacy in the EXALGO NDA as it was the only adequate and well-controlled trial that met both its primary endpoint and was designed in compliance with current FDA requirements for a pivotal study in chronic pain. These require a study to be a placebo-controlled, 12-week duration trial in a chronic pain model such as LBP or osteoarthritis, with landmark analysis of pain intensity as the primary endpoint, and the use of a conservative imputation method such as Baseline Observation Carried Forward (BOCF).

Twelve (12) additional Phase 2 or 3 studies were conducted by other sponsors as part of a global registration program, or were Phase 4 studies conducted outside the US. Of these, only one approached the current US standard, Study MO3-644-05 conducted by the ALZA Corporation. This trial was designed as a fixed-dose, placebo-controlled, parallel-design study; the study did not meet its primary endpoint by BOCF. Of the remaining studies, 4 were active controlled and thus useful for international registration and marketing support, and 7 were open or open-label extension studies used to generate additional safety data for long-term use. None of the additional 12 studies were considered by FDA to be pivotal to the NDA, and a listing of all the studies can be found in Table 12.

Table 2 EXALGO Controlled and Uncontrolled Phase 2 or 3 Studies

Study	Patient population	Total Treated	Total Treated with EXALGO
CONTROLLED STUDIES IN PATIENTS WITH CHRONIC PAIN			
DO-118	Cancer	200	77
DO-119	Non-cancer	113	74
DO-132	OA	138	71
M03-644-05	OA	981	649
NMT 1077-301	LBP	447	447
OROS-ANA-3001	Non-cancer	504	254
UNCONTROLLED STUDIES IN PATIENTS WITH CHRONIC PAIN			
DO-104	Cancer	127	127
DO-105	Non-cancer	336	336
DO-108	Non-cancer	22	22
DO-109	104/105/119 Extension	388	388 (38) [a]
DO-118X	118 Extension	68	68 (33)
DO-127	LBP	207	207
DO-127X	127 Extension	113	113 (0)
POOLED ANALYSIS SAMPLE POPULATIONS			
Total, Primary Studies		3075	2264
Patients not treated with EXALGO during primary studies but treated with EXALGO during extension studies		(Not applicable)	71
Total, Extension Studies		569	569 (71)
Total Controlled plus Uncontrolled in Patients with Chronic Pain		3075	2335 [b]

[a] The number in parentheses indicates the subtotal of patients who received EXALGO for the first time during an extension study (having received a different treatment in a primary study).
[b] Unique patient number
LBP=low back pain; OA=osteoarthritis.

4.2 Overview of Biopharmaceutics and Clinical Pharmacology

Fifteen clinical pharmacology studies were conducted to characterize the bioavailability, PK and pharmacodynamics of EXALGO (see Table 3). The results of the key studies are described in this overview of biopharmaceutics and clinical pharmacology.

Overall, the data demonstrated that the EXALGO formulation provided relatively stable blood levels of hydromorphone compared to IR hydromorphone over a 24-hour dosing interval with less frequent dosing. The same total daily dose of the EXALGO formulation administered once a day resulted in the same total hydromorphone exposure to that of the IR formulation administered 4 times a day. The concomitant use of alcohol and EXALGO, as well as the intake of food, did not alter the extended release profile or result in significantly different total exposure. Furthermore, results from an abuse liability study demonstrated generally lower drug liking for the EXALGO

formulation within the first 4 hours after a single dose, when compared to the IR hydromorphone formulation.

Table 3 EXALGO Clinical Pharmacology Studies (Phase 1)

SINGLE-DOSE STUDIES	
Bioavailability/Bioequivalence	
C-94-014	Bioavailability of 32 mg EXALGO and 4 x 5 mg IR formulation doses in 12 healthy volunteers
D-102	Bioavailability of 16 mg EXALGO formulation with food and naltrexone blockade in 29 healthy volunteers
DO-123	Bioequivalence of 8 mg and 64 mg EXALGO clinical trial and commercial formulations in 36 healthy volunteers
DO-124	Bioequivalence of 32 mg EXALGO clinical trial and commercial formulations in 52 healthy volunteers
DO-129	Bioequivalence and intra-subject variability of 64 mg EXALGO clinical trial and commercial formulations in 56 healthy volunteers
C-2005-032	Bioequivalence of 4 mg and 8 mg EXALGO formulations in 52 healthy volunteers
42801-PAI-1008	Bioequivalence of 16 mg EXALGO formulation administered with and without food in 30 healthy volunteers
Pharmacokinetic	
D-101	Pharmacokinetics and pharmacodynamics of IV, IR, and EXALGO formulation in experimental pain model in 12 healthy volunteers
D-103	Pharmacokinetic dose proportionality of 8 to 64 mg in 32 healthy volunteers
C-2005-013	Pharmacokinetics of different 16 mg EXALGO formulations for in vitro in vivo correlation in 52 healthy volunteers
C-2005-022	Pharmacokinetics of 16 mg EXALGO formulation with 0%, 4%. 20%, 40% alcohol in 48 healthy volunteers
Pharmacokinetic/Pharmacodynamic	
C-2004-020	Abuse liability of EXALGO (16-64 mg) and IR (8 mg) formulations in 38 opiate-experienced, non-dependent subjects
MULTIPLE-DOSE STUDIES	
Pharmacokinetic	
C-96-054	Multiple-dose pharmacokinetics of EXALGO (16 mg q.d.) and IR (4 mg q.i.d.) formulations in 22 healthy volunteers
DO-108	Multiple-dose pharmacokinetics of EXALGO formulation in 22 patients with chronic pain
42801-PAI-1009	Multiple-dose pharmacokinetics of EXALGO (16 mg q.d.) and IR (4 mg q.i.d.) formulations in 29 healthy volunteers

IR=immediate release; IV=intravenous; q.d.=once daily; q.i.d.=four times a day

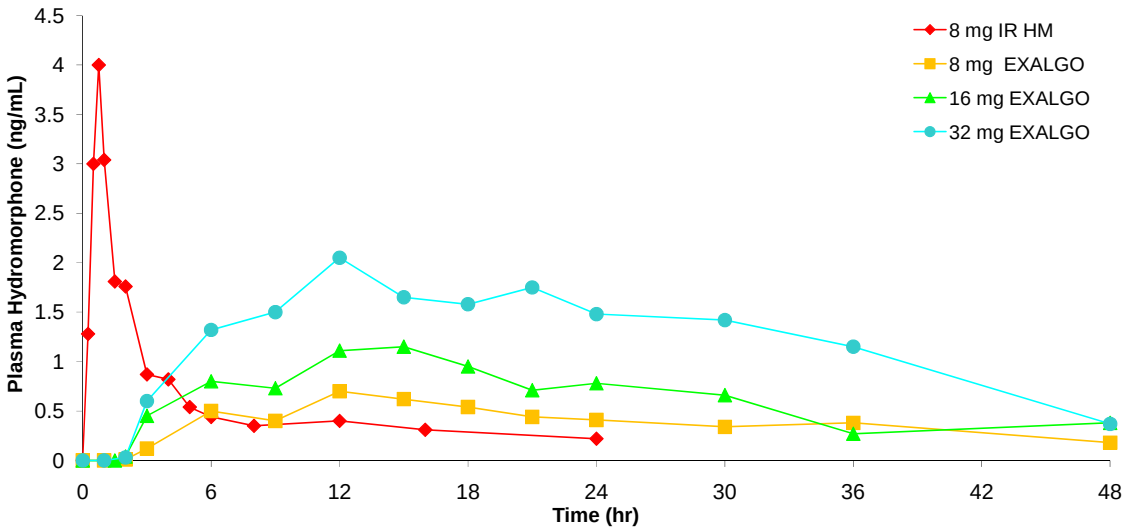
4.2.1 Biopharmaceutics

In single-dose studies evaluating the extended release pharmacokinetics of EXALGO, there was a prolonged release of hydromorphone from the EXALGO tablet relative to the IR hydromorphone formulation. As expected, the rate of absorption of hydromorphone from EXALGO was slower than from the IR hydromorphone tablet, indicating that drug absorption was controlled by the release of hydromorphone from the dosage form. Plasma concentrations reached a broad, relatively flat plateau region within 6 to 8 hours postdose, and remained in this plateau region until approximately 30 hours postdose. Hence, as intended, drug absorption continued for approximately 18-24 hours, suggesting that hydromorphone was released at a constant rate from the dosage form, and was absorbed throughout the GI tract.

The bioavailability of EXALGO was compared to 2 hydromorphone formulations (intravenous [IV] and IR). The linearity of the pharmacokinetics of 3 dose levels of EXALGO was assessed in a Phase 1, randomized, double-blind, 3-phase study (Study D-101). Twelve healthy adult subjects were enrolled in the study, and each subject took part in all 3 phases of the study. Phase 1 of this 3-phase study was a single-period, open-label examination of the pharmacokinetics of 8 mg IV hydromorphone, given as a 10-minute infusion. Serial blood samples were obtained at specified times over 24 hours post-infusion. Phase 2 was a single-period, open-label examination of the pharmacokinetics of 8 mg IR hydromorphone. Serial blood samples were obtained at specified times over 24 hours postdose. Phase 3 was a nested, 4-period, randomized, double-blind, placebo-controlled, crossover substudy in which placebo and 3 single oral doses (8, 16, and 32 mg) of EXALGO were administered. Serial blood samples were obtained at specified times up to 48 hours postdose.

The mean concentration-time profiles following the 8 mg IR hydromorphone oral tablet and the EXALGO doses of 8, 16, and 32 mg are displayed in Figure 2. PK parameters are presented in Table 4.

Figure 2 Mean Hydromorphone Plasma Concentrations Following an 8 mg Immediate Release Oral Tablet and 8, 16, or 32 mg EXALGO Tablets



hr=hour; IR HM=immediate release hydromorphone.

Table 4 Mean (SD) Hydromorphone Pharmacokinetic Parameters Following Administration of 8 mg Intravenous HM, 8 mg Immediate Release HM, and EXALGO (8, 16, or 32 mg Tablets)

Pharmacokinetic Parameter	IV HM 8 mg/10 min	IR HM 8 mg	EXALGO 8 mg	EXALGO 16 mg	EXALGO 32 mg
C_{max} (ng/mL)	186 (35)	4.74 (1.76)	0.77 (0.33)	1.45 (0.43)	2.41 (0.85)
T_{max} (h)	0.15 (0.02)	0.94 (0.53)	13.3 (8.0)	15.8 (6.3)	16.5 (5.0)
AUC_t (ng*h/mL)	72.6 (10.2)	13.7 (4.7)	18.2 (6.0)	34.5 (9.9)	61.0 (16.4)
$t_{1/2}$ (h)	NE	13.8 (8.4)	18.1 (4.3)	16.7 (4.3)	17.8 (6.7)
F_{abs} (%)	NA	19 (5)	24 (6)	23 (6)	22 (8)

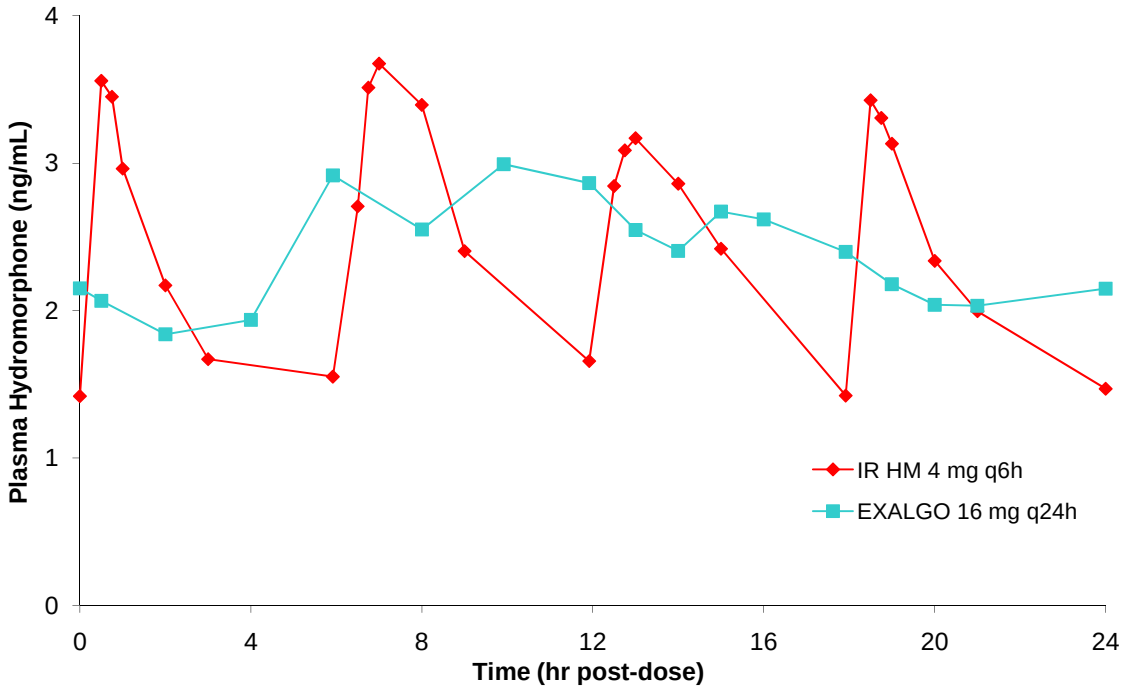
AUC=area under the curve; AUC_t=AUC at time t; C_{max}=maximum observed plasma concentration; F_{abs}=absolute bioavailability; h=hour; HM=hydromorphone; IR=immediate release; IV=intravenous; min=minute; NE=not estimable for IV; NA=not applicable; SD=standard deviation; $t_{1/2}$=apparent terminal half-life; T_{max}=time to maximum observed plasma concentration.

The mean absolute bioavailability of hydromorphone from EXALGO ranged from 22% to 24%, and appeared to be marginally greater than the absolute bioavailability of 19% seen with the IR hydromorphone formulation (Table 4). However, at steady-state following multiple dosing for 5 days, the hydromorphone area under the curve (AUC) for the EXALGO formulation was observed to be equivalent to that of the IR hydromorphone formulation (meeting the 80% to 125% bioequivalence criteria [Schuirmann, 1987]).

In a study to determine the steady-state characteristics of EXALGO, a randomized, open-label, single-center, multiple-dose, 2-period crossover study in healthy adult

subjects was conducted. Each subject was randomly assigned to 1 of 2 treatment sequences on Day 1 of Period 1, prior to the first dose of study medication. Subjects who received the EXALGO formulation during a treatment period received 1 dose every 24 hours, following a 12-hour fast, for a total of 5 days. Subjects randomized to receive the IR formulation of hydromorphone received 1 dose every 6 hours for a total of 20 doses over a 5-day period. The first dose of the IR hydromorphone formulation each day was administered after a 12-hour fast, while each subsequent dose was given after a 2-hour fast. Figure 3 graphically summarizes the mean plasma concentration-time profiles of hydromorphone during this study once steady-state was achieved.

Figure 3 **Mean Steady-State Plasma Concentration-Time Profiles of Hydromorphone Following Multiple Oral Doses of 16 mg EXALGO Once a Day and 4 mg Immediate Release Hydromorphone Administered Every 6 Hours Under Fasted Conditions in Healthy Subjects**



hr=hour; IR HM=immediate release-hydromorphone; q6h=every 6 hours; q24h=every 24 hours

Table 5 summarizes the mean (standard deviation; SD) steady-state PK parameters for hydromorphone administered as multiple oral doses of one 16-mg EXALGO tablet per day, and the 4 mg IR hydromorphone tablet administered every 6 hours, under fasted conditions.

Table 5 Mean (SD) Steady-State Plasma Pharmacokinetic Parameters of Hydromorphone Following Multiple Oral Doses of a 16 mg EXALGO Once a Day and 4 mg IR Hydromorphone Administered Every 6 Hours Under Fasted Conditions in Healthy Subjects

Parameter	IR HM N=29	EXALGO N=29
$AUC_{(0-\tau)}$ (ng.h/mL) [a]	54.8 (14.8)	57.6 (16.3)
C_{maxss} (ng/mL)	5.28 (1.37)	3.54 (0.959)
C_{minss} (ng/mL)	1.47 (0.417)	2.15 (0.872)
C_{ssav} (ng/mL)	2.28 (0.618)	2.40 (0.678)
T_{maxss} (h) [b]	7.00 (0.500 - 18.8)	11.9 (5.92 - 24.2)
Flux 1 (%) [c]	172 (57.6)	60.5 (41.1)

$AUC_{(0-\tau)}$=area under the plasma concentration-time curve from time zero to time τ; C_{maxss}=maximum measured plasma concentration over the last 24-hour dosing interval; C_{minss}=measured plasma concentration at the end of the dosing interval; C_{ssav}=the ratio of $AUC_(0-\tau)$ to the dosing interval τ; h=hour; IR HM=immediate release HM (Dilaudid®); SD=standard deviation; T_{maxss}=time of the maximum measured plasma concentration over the 24-hour dosing interval.

[a] τ=24 hours.

[b] T_{maxss} reported as median (minimum-maximum)

[c] Percent fluctuation calculated, $[(C_{maxss} - C_{minss})/C_{ssav}] \times 100$

Multiple oral doses of the once daily 16 mg EXALGO formulation provided the same exposure (area under the plasma concentration-time curve from time zero to time τ [$AUC_{(0-\tau)}$] of hydromorphone as the 4-times daily 4 mg IR hydromorphone formulation: 57.6 versus 54.8 ng·h/mL, respectively, with a smaller degree of fluctuation between peak and trough concentrations (60.5% versus 172%, respectively). The observed median time of the maximum measured plasma concentration over the 24-hour dosing interval (T_{maxss}) of the EXALGO formulation (11.9 h) occurred approximately 5 hours later than for the IR hydromorphone formulation administered every 6 hours (7.0 hours - which occurred 1 hour after administration of the second dose). In addition, steady-state was achieved by Day 4.

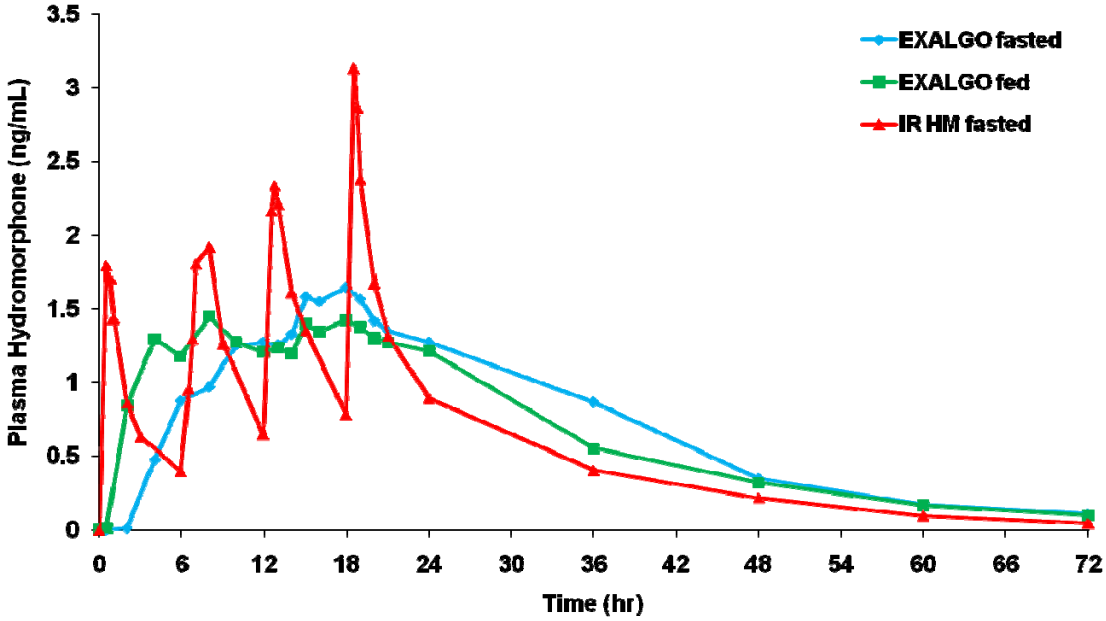
These results suggest that the same total daily dose of hydromorphone may be administered as a once-daily dose of EXALGO compared to 4 times a day administration of the IR hydromorphone formulation. This further suggests that the formulation is well-suited to the proposed indication.

4.2.1.1 Effect of Food (Study 42801-PAI-1008)

EXALGO may be administered with or without food. Results from Study 42801-PAI-1008 revealed that the ratio of the geometric means and corresponding 90% confidence intervals (CIs) between EXALGO under fasted and fed conditions for maximum observed plasma concentration (C_{max}) and AUC_{∞} were contained within the acceptance criteria of 80% to 125%. The hydromorphone concentration profiles for the fed and fasted EXALGO treatments from this study are displayed graphically in Figure 4, and the PK parameters are shown in Table 6. A

third treatment of the IR tablet at a dose of 4 mg every 6 hours for a total of 4 doses was also included in this study as a reference for comparing total exposure to hydromorphone. A comparison of the AUC_{∞} for the fasted EXALGO and the fasted IR hydromorphone treatments indicated no significant differences. Therefore, dosing with EXALGO is not restricted by the timing of meals.

Figure 4 Plasma Concentration-Time Profiles of Hydromorphone Following Single Oral Dose Administration of a 16 mg EXALGO Formulation Under Fed and Fasted Conditions and 4 mg IR Hydromorphone Administered Every 6 Hours Under Fasted Conditions in Healthy Subjects



hr=hour; IR HM=immediate release hydromorphone

Table 6 Mean Ratios and 90% Confidence Intervals for the EXALGO 16 mg Under Fed and Fasted Conditions

	Geometric LSM				
Parameter	Treatment C EXALGO Fed	Treatment A EXALGO Fasted	Ratio C/A (%)	90% CI	Intrasubject CV%
AUC_{∞} (ng.h/mL)	47.332	47.578	99.5	90.1 - 109.9	23.1
C_{max} (ng/mL)	1.722	1.823	94.5	85.4 - 104.4	22.8

AUC_{∞}=area under the plasma concentration-time curve from zero to infinity; CI=confidence intervals
C_{max}=maximum observed plasma concentration; CV%=coefficient of variation percentage; h=hour; LSM=least squares mean.

An important consideration in the development of a modified-release formulation is adequate and reproducible delivery of the drug from the formulation. The hard outer shell of the OROS® delivery system was designed to not completely disintegrate during passage through the GI tract; the defecated shell may be recovered and analyzed for residual drug content as an assessment of drug delivery. The amount of unreleased hydromorphone contained in EXALGO recovered from the stools of subjects was minimal (approximately 4.1% of the label claim), indicating good performance of the dosage form (Study C-2005-013).

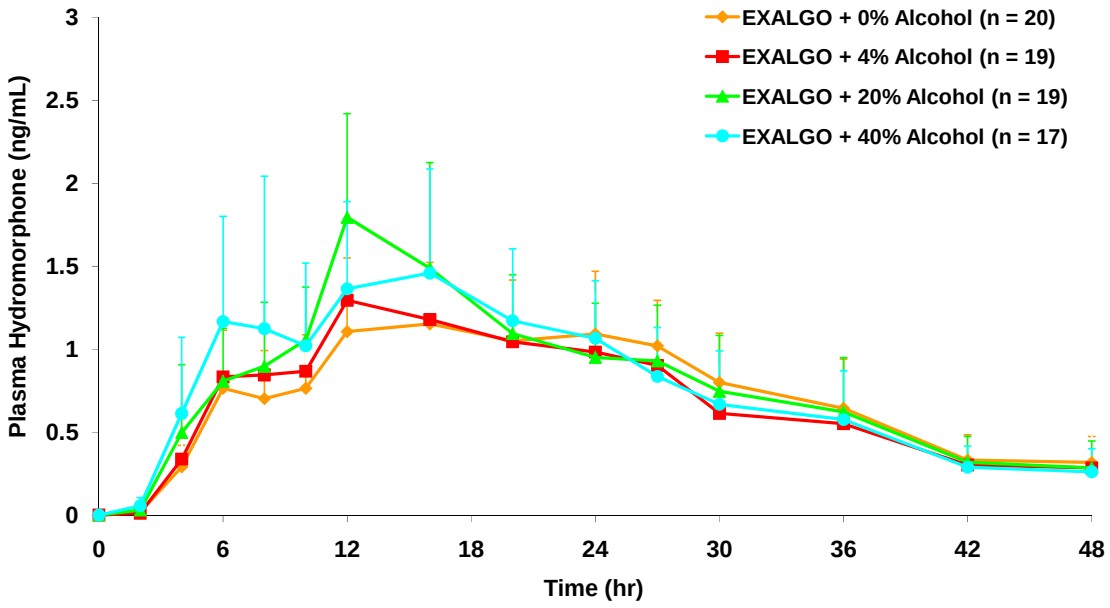
4.2.2 Clinical Pharmacology

4.2.2.1 Pharmacokinetics

4.2.2.1.1 Effect of Alcohol (Study C-2005-020)

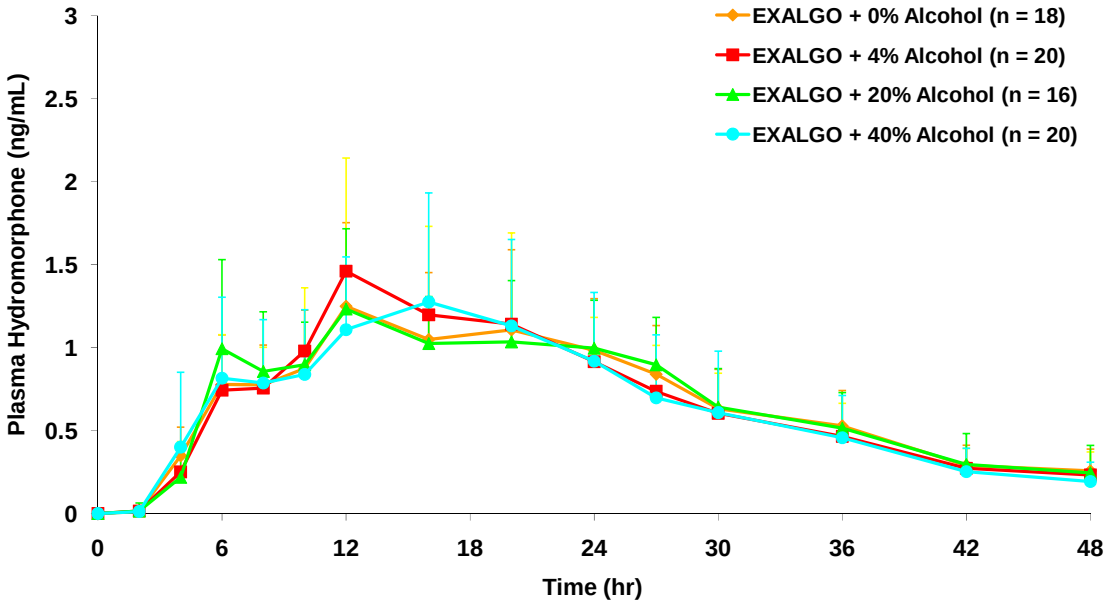
The effect of alcohol on the extended-release mechanism of another once daily sustained-release (SR) hydromorphone product (Palladone™) led to its withdrawal from the market because of the potential fatal effects of dose dumping when taken with alcohol. The effect of alcohol on the pharmacokinetics of EXALGO under fasted and fed conditions was assessed in a 4-treatment crossover study (Study C-2005-020). Subjects were treated with 16 mg EXALGO with 240 mL orange juice and 4%, 20%, and 40% alcohol, with a 6 to 14 day washout period between treatments. Blood samples were collected over 48 hours for analysis of hydromorphone concentrations. Figure 5 and Table 6 present the mean concentration profiles following all 4 treatments in the fasted and fed state, respectively.

Figure 5 Mean (SD) Hydromorphone Plasma Concentration Profiles (Fasted) Following 16 mg EXALGO Dosed with 0%, 4%, 20%, and 40% Alcohol in Healthy Volunteers



hr=hour; SD=standard deviation

Figure 6 Mean (SD) Hydromorphone Plasma Concentration Profiles (Fed) Following 16 mg EXALGO Dosed with 0%, 4%, 20%, and 40% Alcohol in Healthy Volunteers



hr=hour; SD=standard deviation

Plasma hydromorphone PK parameter values for patients in both the fed and fasted state are presented in Table 7.

Table 7 Mean (SD) Hydromorphone Pharmacokinetic Parameters For 16 mg EXALGO Dosed with 0%, 4%, 20%, and 40% Alcohol in Healthy Volunteers

Fasted State				
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 (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}, ng*hr/mL	40.6 (11.0)	39.9 (14.1)	43.7 (12.1)	42.2 (13.2)
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}, ng*hr/mL	Ref	96.83 (87.48-107.19)	103.21 (92.93-114.62)	101.65 (91.32-113.13)
Fed State				
Mean (SD)	**0% Alcohol N=18**	**4% Alcohol N=20**	**20% Alcohol N=16**	**40% Alcohol N=20**
C_{max}, ng/mL	1.42 (0.50)	1.64 (0.60)	1.52 (0.32)	1.56 (0.56)
T_{max}, h (Range)	16 (6-27)	12 (8-24)	12 (6-24)	16 (6-27)
$t_{1/2}$, h	11.6 (5.1)[e]	11.6 (4.9) [c]	10.4 (3.9) [f]	10.8 (4.8)
AUC_{inf}, ng*hr/mL	37.1 (8.6)	36.7 (10.5)	36.6 (9.7)	34.8 (11.9)
Geometric Ratio: Mean (90% CI)				
C_{max}, ng/mL	Ref	113.72 (99.97-129.36)	114.36 (100.14-130.61)	110.34 (97.08-125.41)
AUC_{inf}, ng*hr/mL	Ref	94.72 (86.44-103.79)	106.21 (96.63-116.73)	94.09 (85.91-103.04)

AUC_{inf}=area under the plasma concentration-time curve at infinity; CI=confidence interval; C_{max}=peak plasma concentration; h=hour; SD=standard deviation; $t_{1/2}$=half-life; T_{max}=time to peak plasma concentration.
Note: median values are presented for T_{max}.
[a] N=19, [b] N=20, [c] N=18, [d] N=16, [e] N=17, [f] N=15

Data from the in vivo alcohol-interaction study indicated that concomitant use of alcohol and EXALGO did not result in any significant differences in total exposure (AUC), the extended release profile was maintained for all treatments, and there was no evidence of dose dumping. However, there were alcohol concentration-dependent increases observed in both the fasted and fed states, in hydromorphone absorption resulting in 10% to 31% increases in geometric mean C_{max}. In the fed state, plasma hydromorphone concentration profiles were similar for the 4 treatments, and log-transformed mean C_{max} ratios were slightly lower than those seen in the fasted state. Median time to maximum plasma concentration (T_{max}) with 4%, 20%, and 40% alcohol was 12 to 16 hours, and was 16 hours with 0% alcohol. The minimum T_{max} value was 4 hours in the fasted 20% alcohol treatment, and was 6 hours with 0% alcohol. The maximum increase in C_{max} observed with any individual was 2.5-fold, which occurred in 1 subject in the fasted group, with 40% alcohol treatment compared to 0% alcohol treatment. In this subject, the T_{max} occurred at 6 hours after the EXALGO dose taken with 40% alcohol, indicating that the increased C_{max} was not the result of dose dumping.

By comparison, a pharmacokinetic study for Palladone in healthy subjects showed that co-ingestion of a 12-mg Palladone capsule with 240 mL (8 ounces) of 40% (80 proof) alcohol resulted in an average peak hydromorphone concentration approximately 6 times greater than when taken with water. One subject in this study experienced a 16-fold increase when the drug was ingested with 40% alcohol compared with water. In certain subjects, 8 ounces of 4% alcohol (equivalent to 2/3 of a typical serving of beer) resulted in almost twice the peak plasma hydromorphone concentration than when the drug was ingested with water.

The labeling for EXALGO indicates that the concomitant use of EXALGO with alcohol, or other CNS depressants, increases the risk of respiratory depression, hypotension, and profound sedation, potentially resulting in coma or death.

4.2.2.1.2 Effect of Other Factors on Pharmacokinetics

At clinically relevant concentrations, the mean extent of protein binding of hydromorphone was found to be 27% in human plasma. This low level of protein binding of hydromorphone makes it unlikely to result in protein-displacement drug-drug interactions. In vitro and in vivo data suggest that hydromorphone concentrations observed in clinical practice will have minimal effect on induction or inhibition of human hepatic cytochrome P450 (CYP450) enzymes. The metabolism of hydromorphone in humans is dominated by Phase 2 metabolism (conjugation with glucuronic acid) with a significant first-pass effect, and little potential for PK drug-drug interactions. Therefore, EXALGO can be administered with other drugs, with a low likelihood of PK drug interactions resulting in increased concentrations of hydromorphone or the concomitantly administered drugs. However, the well-known PK drug interactions with monoamine oxidase inhibitors and CNS depressants including but not limited to other opioids, sedatives, hypnotics, tranquilizers (e.g., benzodiazepines), general anesthetics, phenothiazines, skeletal muscle relaxants, and alcohol should be considered in patients treated with EXALGO.

In a population PK analysis of the hydromorphone concentration data collected in clinical study M03-644-05, the covariates of sex, race, age, weight, height, body mass index, target joint, sedation medication use, prior opioid use in the previous 13 weeks, and radiographic osteoarthritis index were evaluated to determine any effect on EXALGO pharmacokinetics. The analysis indicated that body weight and age appeared to have an impact on the clearance of EXALGO with values generally higher in patients with increased body weight and reduced oral clearance in older patients. Based on the median age of 58.5 years for the PK population, every 10 kg increase in weight is predicted to increase clearance (CL/F) by 5%. Based on the median weight of 98 kg of the PK population, every 10 year increase in age is predicted to decrease clearance (CL/F) by 9%. The medical setting of the elderly is often complex; therefore, treatment with hydromorphone in the elderly should be initiated with caution, and the initial dose should be at the low end of the dosing range.

In clinical pharmacology studies conducted with IR hydromorphone, relevant findings were seen for patients with hepatic and renal impairment. Hepatic impairment affected the first-pass metabolism of hydromorphone such that higher plasma concentrations of hydromorphone and the four-fold increase in C_{max} and AUC of hydromorphone were seen in subjects with moderate hepatic dysfunction. Following a single dose, there were substantial changes in hydromorphone 3-glucuronide elimination kinetics in patients with severe hepatic impairment, although hemodialysis was effective at reducing plasma levels of both hydromorphone and hydromorphone 3-glucuronide. There was a 2-fold and 4-fold increase in hydromorphone exposure (AUC) in moderate and severe impairment, respectively.

Patients with moderate hepatic and renal impairment should receive a reduced dose of EXALGO and for patients with severe renal impairment a longer dosing interval should be considered.

4.2.2.2 Pharmacodynamics

4.2.2.2.1 Experimental Pain Model in Healthy Volunteers (Study D-101)

In a study designed to evaluate the relationship between hydromorphone pharmacokinetics and the pharmacodynamic measures in an experimentally induced pain model (nociceptive electrical stimulation of the skin of the right lateral upper arm), 12 healthy volunteers received single doses of 8 mg IR hydromorphone and 8, 16, and 32 mg of EXALGO (Study D-101). For the EXALGO treatments, concentrations were at 50% of the peak concentration after 5 hours, and remained above this level until after 30 hours or for greater than 21 hours after the dose. The placebo and 8 mg IR hydromorphone treatments did not produce statistically significant changes in pain tolerance in this pain model. Compared to baseline, pain tolerance was significantly increased for the 16 and 32 mg EXALGO treatments at 6, 9, 12, and 30 hours after the dose, consistent with the hydromorphone concentration profile.

4.2.2.2.2 Abuse Liability Study (Study C-2004-022)

A study was conducted to evaluate the abuse potential of EXALGO using the methodology of the Addiction Research Center of the United States Public Health Service by comparing acute effects of test drug to placebo (negative control) and IR hydromorphone (positive control), a drug of known abuse potential.

The abuse potential was evaluated for EXALGO (intact and altered), IR hydromorphone, and placebo in opiate-experienced, nondependent, recreational drug users. The study also evaluated the pharmacokinetic/pharmacodynamic relationship of the EXALGO and IR hydromorphone formulations on measures of abuse potential.

The study was conducted in 2 phases. In Phase A (5-period, 5-sequence, randomized, crossover, single-dose design), each subject received single oral doses of EXALGO

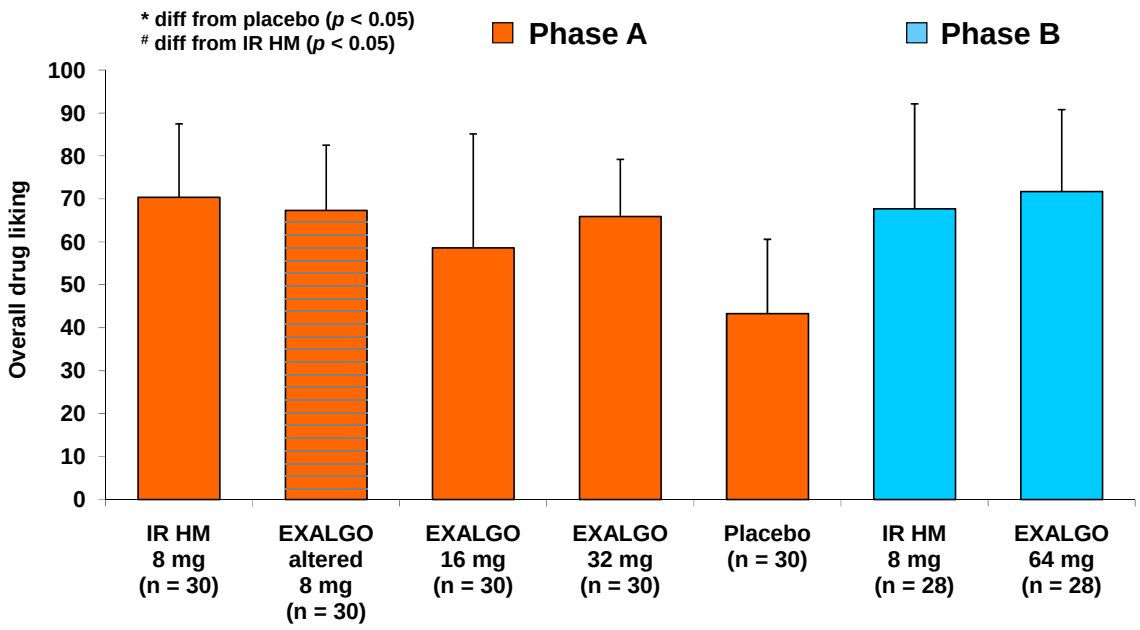
16 mg (intact), EXALGO 32 mg (intact), EXALGO 8 mg (altered, encapsulated), IR hydromorphone 8 mg (intact, encapsulated), and placebo. If all the treatments were well-tolerated by a subject (defined as having University of Wisconsin Hospital and Clinic sedation scores ≤3, respiratory rate ≥8 breaths per minute, and ≤2 vomiting episodes), the subject entered Phase B. In Phase B (2-period, 2-sequence, randomized, crossover, single-dose design), each subject received single oral doses of IR hydromorphone 8 mg (intact, encapsulated) and EXALGO 64 mg (intact), with a 7- to 14-day washout period between treatments.

The primary end point measure of abuse potential, Overall Drug Liking, was assessed at 10 and 48 hours after dosing using a mixed-effects analysis of variance (ANOVA) model to evaluate the average response to any of the pharmacodynamic parameters. For IR hydromorphone, subjects were expected to make the most reliable assessment 10 hours postdose, as this time point was approximately 2 half-lives ($t_{1/2}$=5 hours) after T_{max}; similarly, for EXALGO, subjects were expected to make the most reliable assessment at 48 hours postdose, as this time point was also approximately 2 half-lives ($t_{1/2}$=16 hours) after T_{max}. The responses at these 2 time points were examined separately. In addition, the higher of the 2 values assessed at 10 and 48 hours postdose (defined as the maximum score) was compared between treatments to provide a more conservative analysis.

Other end points included Subjective Drug Value, Subjective Effects Visual Analog Scale (VAS) - any drug effect, good drug effects, bad drug effects, high, take drug again, and drug liking), Observer-rated Single-dose Questionnaire, Subject-rated Opioid Agonist Subscale, and Addiction Research Center Inventory (Cole/ARCI version; selected subscales). These measurements were administered at various time points postdose, and the peak effect and the total area under the effect curve (AUEC) were the primary parameters compared between treatments. For PK analysis, blood samples for measurement of hydromorphone concentrations were collected from each subject at predose, and 0.5, 1, 2, 4, 6, 12, 15, 24, and 48 hours after dosing during each of the 7 treatment periods. Safety measures included adverse events (AEs), vital signs, O_2 saturation, physical exam, laboratory tests, drug and alcohol screening, pregnancy test, and 12-lead electrocardiogram (ECG).

Mean maximum Overall Drug Liking scores by treatment for Phases A and B are presented in Figure 7. The mean pharmacodynamic parameters for all treatments in Phases A and B are presented in Table 8.

Figure 7 Mean Maximum Overall Drug Liking Scores (All subjects who Completed Phase A and B)



IR HM=immediate release hydromorphone

Table 8 Mean (SD) Pharmacodynamic Parameters for Subject Effects VAS: Drug Liking for Subjects Treated in Phase A (N=30) and Phase B (N=28)

		Phase A				Phase B	
Pharmacodynamic Parameter	**Placebo N=30**	**IR HM 8 mg N=30**	**Altered 8 mg N=30**	**EXALGO 16 mg N=30**	**EXALGO 32 mg N=30**	**IR HM 8 mg N=28**	**EXALGO 64 mg N=28**
Max effect[a]	42.8 (21.1)	78.3 (16.3)*	75.8 (15.3)*	65.0 (20.5)*†§	73.6 (15.6)*‡	70.1 (25.3)	79.7 (17.7)**
Time to max[b]	2.59 (5.04)	3.14 (4.54)	5.96 (11.57)	7.54 (5.34)	10.35 (5.84)	2.63 (4.39)	13.59 (11.09)
AUEC[c]	1816.1 (946.7)	2293.1 (692.6)*	2389.9 (543.9)*	2217.6 (912.0)*	2555.2 (467.6)*‡	2199.1 (908.4)	2441.1 (805.5)

*=p <0.05 compared to placebo; †=p <0.05 compared to IR 8 mg (Phase A); ‡=p <0.05 compared to EXALGO 16 mg; §=p <0.05 compared to Altered 8 mg; **=p <0.05 compared to IR 8 mg (Phase B).
AUEC=area under the effect curve; IR HM=immediate release hydromorphone; SD=standard deviation
[a] Mean maximum score
[b] Mean time to maximum score. Not tested statistically.
[c] Mean area under the effect curve

The Maximum Overall Drug Liking scores for all of the hydromorphone treatments (8 mg IR, 8 mg altered EXALGO, 16 and 32 mg intact EXALGO) administered in Phase A were significantly greater than placebo. The 16 mg intact EXALGO

treatment was significantly lower than the 8 mg intact and altered EXALGO treatments. There were no significant differences between the 8 mg IR, 8 mg altered EXALGO and the 32 mg intact EXALGO treatments in Phase A. In Phase B, the difference between the 8 mg IR and the 8-fold greater 64-mg dose of the intact EXALGO was not statistically significant.

For the Subjective Effects VAS Drug Liking scores, the mean maximal response with 8 mg IR and the 8 mg altered EXALGO treatments occurred at approximately 3 hours. Mean maximal responses for intact EXALGO treatments occurred later between 6 to 16 hours after the dose.

The plasma hydromorphone concentration profile rose rapidly following the 8 mg IR dose with a mean T_{max} of 1.43 ± 0.75 hours and a mean C_{max} of 4.86 ± 2.3 ng/mL. The PK profile of the 8 mg altered EXALGO was similar to that of the 8 mg IR (mean T_{max} 1.74 ± 0.93 hours, mean C_{max} 3.67 ± 1.5 ng/mL). The mean C_{max} values for the 16 and 32 mg intact EXALGO treatments were lower (1.5 ± 0.41 and 2.79 ± 0.66 ng/mL, respectively), and they occurred later with a mean T_{max} of 16 ± 4.7 and 17.0 ± 5.7 hours, respectively. The mean C_{max} of the 64-mg dose (4.43 ± 1.6 ng/mL) was comparable to the C_{max} of the 8-fold lower dose of the 8 mg IR treatment, but it occurred later with a mean T_{max} was 18.3 ± 7.1 hours. The C_{max} and AUC values for the intact EXALGO 16, 32, and 64 mg treatments were dose proportional.

The following conclusions can be drawn from Study C-2004-022:

- For the reference treatment, IR hydromorphone 8 mg, the maximum Overall Drug Liking was significantly higher than placebo. For the EXALGO 16-mg intact tablet, at double the total IR dose, the maximum Overall Drug Liking was significantly lower than IR hydromorphone 8 mg. For the EXALGO 32- and 64-mg intact tablets, the maximum Overall Drug Liking was not significantly different from IR hydromorphone 8 mg.
- For EXALGO 8 mg altered and the reference treatment, IR hydromorphone 8 mg, maximum Overall Drug Liking was not significantly different.
- Increasing EXALGO doses from 16 to 32 mg and 32 to 64 mg did not significantly increase maximum Overall Drug Liking. The mean Subjective Effects VAS Drug Liking scores were lower for the EXALGO 16, 32, and 64 mg intact treatments compared to the 8 mg IR and 8 mg altered EXALGO treatments for 6 hours after the doses.

The extended release delivery of hydromorphone from the EXALGO formulation delayed effects that led to drug liking. For example, on the Subjective Effects VAS, Drug Liking, the maximum responses were seen approximately 3 hours after dosing with IR hydromorphone 8 mg, compared to approximately 6 to 12 hours after dosing with EXALGO. In addition, doses 4- to 8-fold higher were needed with EXALGO to achieve maximum responses similar to those seen with IR hydromorphone 8 mg.

4.3 Summary of Clinical Efficacy

The clinical efficacy data supporting the use of EXALGO for the management of chronic to severe pain in opioid-tolerant patients is primarily supported by results from Study NMT 1077-301. Additional supportive efficacy data are presented from other controlled studies of EXALGO.

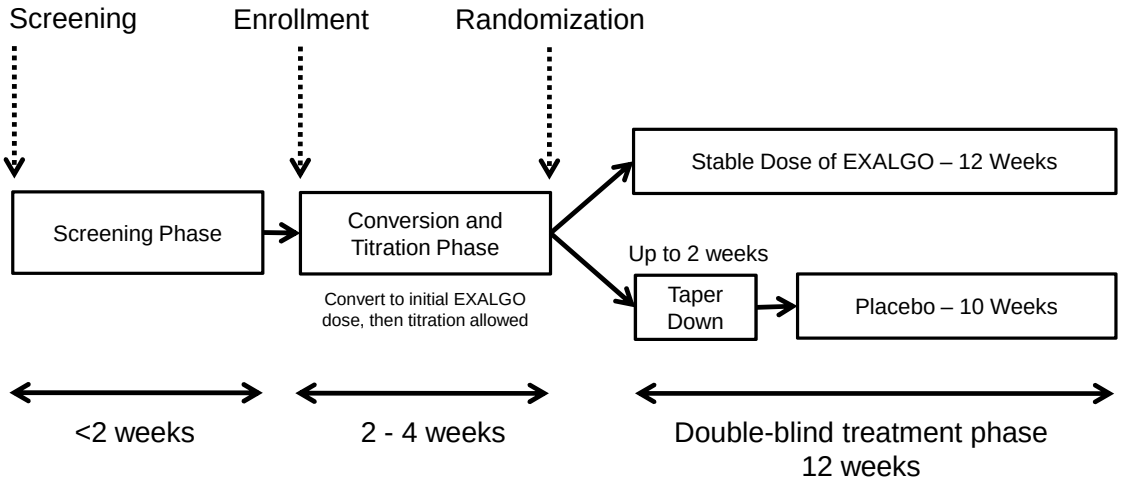
4.3.1 Pivotal Study NMT 1077-301

4.3.1.1 NMT 1077-301 Study Design

Participants in this multi-center, randomized withdrawal study were male and female patients 18 to 75 years of age with stable, chronic LBP (based on the Quebec Task Force Classification of Spinal Disorders) who were opioid tolerant and being treated with opioid analgesics (≥60 mg oral morphine equivalent [≥12 mg hydromorphone], but ≤320 mg oral morphine equivalent [≤64 mg hydromorphone]) for at least 2 months prior to screening.

Study NMT 1077-301 consisted of an open-label conversion and titration phase (up to approximately 4 weeks) followed by a 12-week, double-blind randomized withdrawal phase. During the open-label conversion and titration phase, patients were initially converted to a dosage of EXALGO that was approximately 75% of the equianalgesic dosage of EXALGO calculated based on their prior opioid treatments. This conversion dosage was based on a 5:1 potency ratio between hydromorphone and morphine equivalence. After conversion, if the patient did not achieve satisfactory analgesia with the initial conversion dose, the patient was titrated, in an open-label fashion, to their individual optimal dosage. If adequate pain relief was not achieved up to a maximum total daily dose of 64 mg, or unwanted adverse effects were seen, the patient was discontinued from the conversion and titration phase. Patients who were able to achieve satisfactory analgesia with minimal adverse effects were then randomized at a ratio of 1:1 into the 12- week double-blinded phase. At the time of randomization, the patient was scheduled, in a blinded manner, to continue to receive either their stabilized dosage of EXALGO found during the conversion and titration phase, or the patient was tapered down, according to a pre-defined tapering schedule, over a 2-week period to eventually receive placebo only. During the first 2 weeks of the double-blind phase, tablets for both placebo and EXALGO were over-encapsulated to maintain the blind. See Figure 8 for a summary of key design elements of Study NMT 1077-301.

Figure 8 Study NMT 1077-301 – Key Features of Each Study Phase



A total of 459 opioid-tolerant patients with chronic moderate to severe LBP, requiring daily scheduled opioid analgesics, were enrolled in the open-label conversion and titration phase; 268 patients (58.4%) achieved stable dosage and were randomized to double-blind treatment (134 to EXALGO and 134 to placebo) (Table 9). A total of 110 patients (66 in the EXALGO group and 44 in the placebo group) completed the study, and 158 patients (68 in the EXALGO group and 90 in the placebo group) discontinued prematurely from the study for various reasons during the double-blind phase.

Table 9 Patient Disposition in the Open-label Conversion and Titration Phase and the Double-blind Phase (All Patients)

	Conversion and Titration Phase	Double-blind Phase		
Reason for Withdrawal[a]	EXALGO N=459 n (%)	EXALGO 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)	56 (20.9)
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)

[a] Patients were counted once, under their primary reason for withdrawal.
[b] Percentages based upon the number of patients randomized to each treatment group.

4.3.1.2 Summary of NMT 1077-301 Efficacy

Results from Study NMT 1077-301 demonstrated that EXALGO was superior to placebo in maintaining a reduction in pain intensity through 12 weeks of treatment. Additionally, EXALGO was superior to placebo on subjective, behavioral and disability measures of clinical benefit.

4.3.1.2.1 Primary Efficacy Results

The primary efficacy variable was the change from Baseline (randomization) to double-blind Week 12 (or last visit) in mean pain intensity Numeric Rating Scale (NRS) score based on the weekly mean pain intensity NRS scores calculated from daily patient diaries, compared with placebo. It should be noted that all patients (including those receiving placebo) were allowed to take rescue medication throughout the study and therefore were not completely untreated. In accordance with the SPA, all measurements during the past week(s) were collected, and a weekly mean change from Baseline was calculated for each patient. Missing weekly pain scores due to discontinuation from the study were calculated using the following imputation methods: baseline observation carried forward (BOCF) for patients who discontinued due to opioid withdrawal syndrome; screening observation carried forward (SOCF) for patients who discontinued due to AEs; and last observation carried forward (LOCF) for patients who discontinued

due to other reasons. The Cochran-Mantel-Haenszel (CMH) chi-square test was used to test the difference between drug-treated and placebo treated groups.

The primary efficacy variable was statistically significantly different (p<0.0001; CMH chi-square) between EXALGO-treated and placebo-treated patients (Table 10). The median change from Baseline was 0.2 units on the NRS score for EXALGO-treated patients, and 1.6 for placebo-treated patients (higher scores indicate more severe pain), which demonstrated that patients treated with EXALGO had significantly better pain control than patients treated with placebo.

Table 10 Pain Intensity NRS Scores at Baseline and Week 12 and Change from Baseline in Pain Intensity NRS Scores at Week 12 of the Double-blind Phase from Patient Diary (Intent-to-Treat Population)

Statistic[a]	EXALGO	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			<0.0001
N	133	133	
Mean	0.6	1.7	
Median	0.2	1.6	
Range (min, max)	-5, 5	-3, 7	

Max=maximum; Min=minimum; NRS=Numeric Rating Scale.
[a] This is an 11-point Likert scale ranging from 0 (no pain) to 10 (worst possible pain).
[b] P-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.
[c] Mean of the patient diary measurements in the week prior to randomization.
[d] Patients with missing weekly patient diary data due to premature withdrawal had their value at final visit imputed based on the reason for discontinuation.

4.3.1.2.2 Secondary Efficacy Results

The secondary efficacy variables evaluated in Study NMT 1077-301 are described below. Missing weekly mean pain intensity NRS scores due to discontinuation were handled with the same algorithm used for the primary efficacy variable.

- Change from Baseline to the entire double-blind 12-week treatment phase (diary pain intensity NRS scores), analyzed using an AUC calculation employing the trapezoidal rule;

- Change from Baseline in the pain intensity NRS scores obtained at each office visit, analyzed using either analysis of covariance (ANCOVA) (with baseline NRS pain score as the covariate) or the CMH chi-square test;
- Time from Baseline to treatment failure, analyzed using Kaplan Meier methods and the proportional hazard assumption;
- Change from Baseline in Patient Global Assessment (PGA) score, analyzed using data collected at Baseline and each subsequent visit, as well as the changes from Baseline to Week 12 or final visit;
- Change from Baseline in Roland-Morris Disability Questionnaire (RDQ) score, analyzed using data collected at Baseline and each subsequent visit, as well as the changes from Baseline to Week 12 or final visit;
- The proportion of patients who discontinued from the study for any reason was compared between the treatment groups using a continuity corrected chi-square test;
- Rescue medication use was compared between treatments using a continuity corrected chi-square test, and the mean number of rescue medication tablets used per day was tested using the Wilcoxon rank sum tests (or t test, as appropriate).

Overall, EXALGO demonstrated statistically significant results on multiple secondary efficacy variables as shown in the following summary table (Table 11).

Table 11 Summary of Results of Secondary Efficacy Variables in Study NMT 1077-301

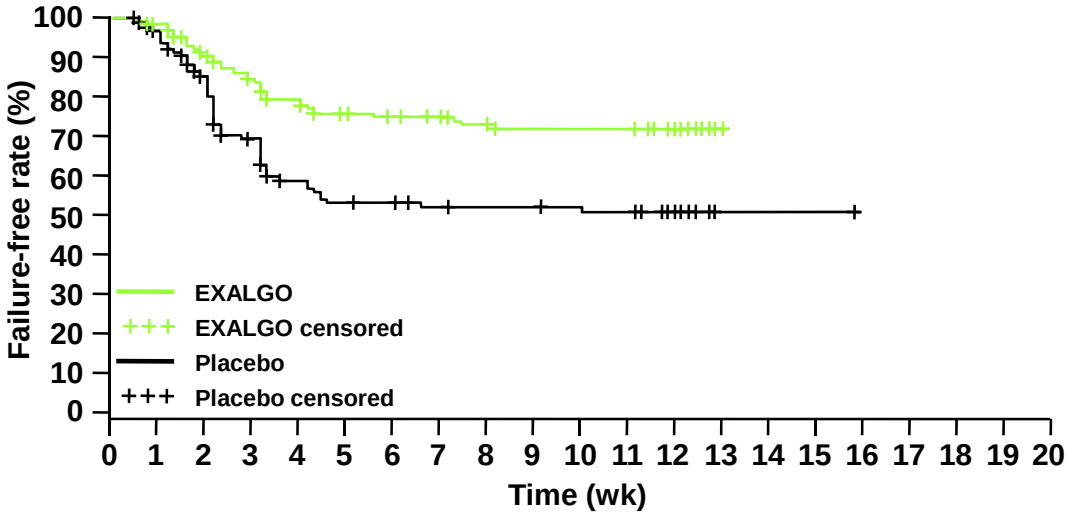
	Placebo (n=133)	EXALGO (n=133)	P Value *
1. Mean change from baseline to entire 12 weeks on diary NRS (AUC analysis)	1.2	0.4	P<0.0001
2. Mean changes from baseline to each office NRS	2.0	0.9	P<0.0001
3. Treatment failure (Drop-out analysis)	55 (41%)	33 (25%)	P<0.0001
4. Total patients dropped out for any reason	89 (67%)	67 (50%)	P=0.009
5. Mean changes on PGA	0.7	0.1	P<0.0001
6. Mean changes on RDQ	2.3	0.3	P=0.0022
7. Rescue medication use (all patients were allowed to take rescue medication at a mean dose of ≤2 tablets/day after taper down period in DB phase)			No difference

* P values were against placebo for Week 12 in most secondary measures except #1 and #7
AUC=area under the curve; DB=double-blind; NRS=numeric rating scale; PGA=Patient Global Assessment; RDQ=Roland-Morris Disability Questionnaire.

Discontinuations due to treatment failure occurred sooner and more frequently among placebo-treated patients than among EXALGO-treated patients. By Week 2, the difference was readily apparent in the Kaplan-Meier plot (Figure 9); the difference in

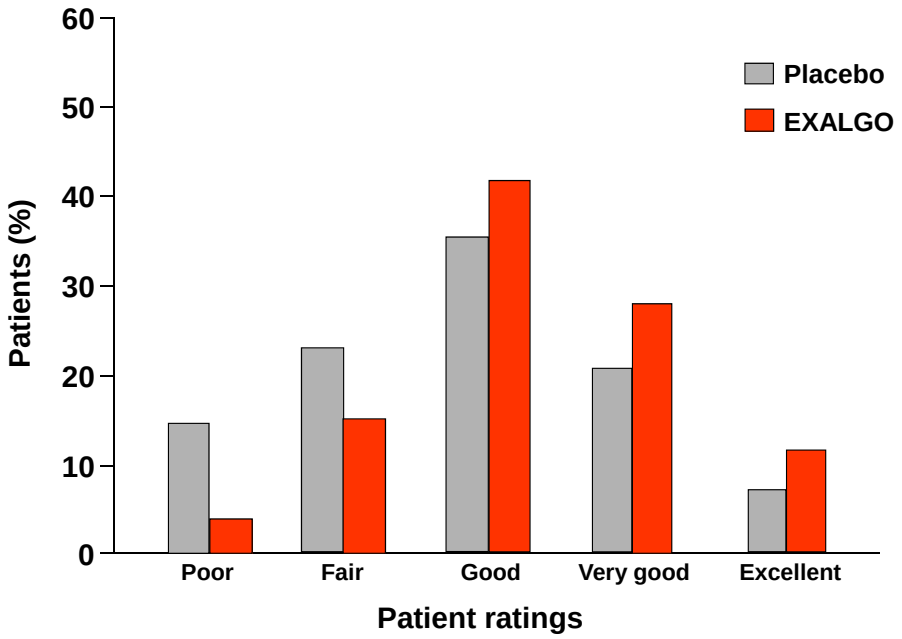
discontinuation rate continued to increase until about Week 5, and was maintained over the entire 12-week double-blind treatment period.

Figure 9 Time to Treatment Failure (Drop-out Analysis) in the Double-blind Phase of Study NMT 1077-301 (Intent-to-Treat Population)



The distribution of patients' PGA scores at the end of the 12-week double-blind treatment phase (broken out by treatment group) is shown in Figure 10. Scores among placebo-treated patients tended to be worse (i.e., lower PGA values) than among EXALGO-treated patients. At the Final Visit, 80.5% of the EXALGO-treated patients rated themselves "good", "very good", or "excellent"; only 62.4% of the placebo-treated patients characterized themselves similarly ($p<0.001$). Therefore, the reduction in pain intensity induced by EXALGO treatment resulted in some improvements on patients' daily functions.

Figure 10 Distribution of Patient PGA Scores at Week 12 or Final Visit of the Double-blind Phase in Study NMT 1077-301 (Intent-to-Treat Population)



PGA=Patient Global Assessment.

No statistically significant differences were seen between groups in rescue medication use, since all the patients were allowed to take a limited amount (on average ≤2 tablets per day during any 7-day period) of rescue medication during the study. Patients who took more than the allowed amount of rescue medication were to have been discontinued from the study; this restriction may have imposed a ceiling effect on rescue medication use that did not allow separation between the treatment groups.

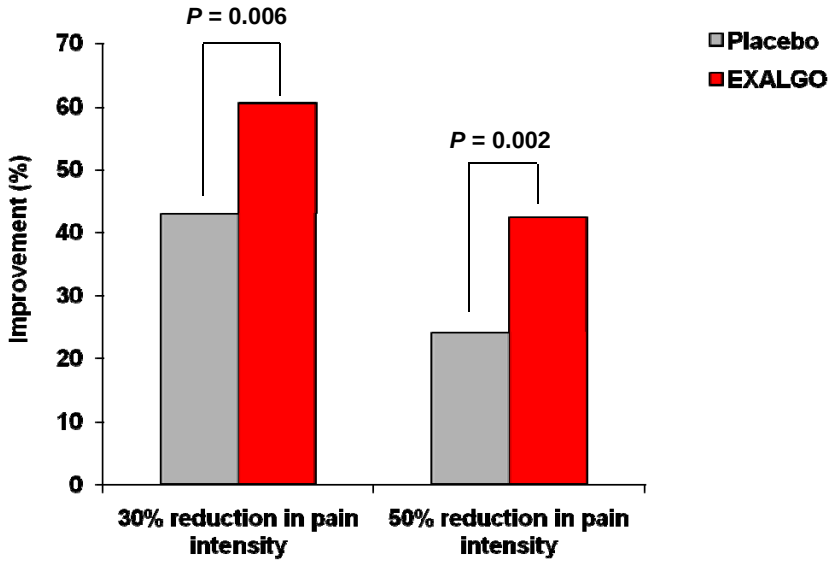
4.3.1.2.3 Post-Hoc Analysis of Response Rates

Neuromed conducted a post-hoc responder analysis to evaluate the effect of EXALGO on pain intensity in the population of patients who adhered closely to the protocol. The percentage of patients who showed varying degrees of responsiveness to EXALGO or placebo (reduction in NRS pain score of 0% to 100%) was evaluated, as was the number of patients who had a ≥30% reduction or a ≥50% reduction in pain intensity from Screening, using a cumulative proportion of responders analysis (Farrar et al. 2006). The same imputation and analysis methods utilized for the primary efficacy variable were applied to this post-hoc analysis.

The number of patients who exhibited a given degree of responsiveness to EXALGO or placebo treatment is summarized in Figure 11. For responses exceeding approximately 10% up to approximately 70%, EXALGO was superior to placebo treatment. Significantly more EXALGO-treated patients reported both a 30% or greater (60.6% in the EXALGO group versus 42.9% in the placebo group, p=0.006) or 50% (42.4% in the

EXALGO group versus 24.1% in the placebo group, p=0.002) reduction in pain intensity compared to placebo-treated patients, which demonstrated the superiority of EXALGO treatment.

Figure 11 Percentage of Patients with Response from Screening to Week 12/Final Visit of the Double-blind Phase (Intent-to-Treat Population)



Overall, Study NMT 1077-301 demonstrated the efficacy of EXALGO for the treatment of moderate-to-severe pain in opioid-tolerant LBP patients:

- EXALGO showed significant results compared to placebo on the primary efficacy endpoint, demonstrating the efficacy of EXALGO in reducing pain intensity in chronic pain patients.
- EXALGO showed significant results compared to placebo across a variety of secondary efficacy endpoints.

In conclusion, this pivotal study established the treatment benefits of EXALGO for opioid-tolerant patients with chronic moderate-to-severe pain and, therefore, satisfied the regulatory requirement of one adequate and well-controlled study to demonstrate efficacy for a new formulation of an existing product.

4.3.2 Summary of Supportive Efficacy Data

Study NMT 1077-301 provides the primary evidence of efficacy in the EXALGO NDA, as it was the only adequate and well-controlled trial that both met its primary endpoint and was designed in compliance with current FDA requirements for a pivotal study in chronic pain. Five other controlled studies were conducted for global registration and marketing support. A listing of these studies can be found in Table 12. The results of the active-controlled trials are briefly summarized in this section.

Table 12 Synopsis of Supportive Studies

Study Identifier	Primary Objective	Study Design and Type of Control	Test Product(s) Dosage Regimen Route of Administration	Number of Subjects	Healthy Subjects, Diagnosis of Patients Location(s)	Duration of Treatment
Double-Blind Studies						
M03-644-05	Compare the analgesic efficacy and safety of EXALGO 8 and 16 mg to placebo in patients with OA.	Multicenter, randomized, double-blind, fixed-dose, parallel-group study Placebo control	EXALGO 8 mg, EXALGO 16 mg, or placebo q.d. Oral administration	981 EXALGO 8mg: 319 EXALGO 16mg: 330 placebo: 332	Adult men and women with OA in the knee or hip, unable to consistently control/ treat pain with nonopioid medications or had received an opioid for pain US	Titration: ≤16 d Maintenance: 12 wk (Subjects randomized to placebo underwent study drug taper in the first ≤1 wk of maintenance)
DO-118	Demonstrate the clinical equivalence of EXALGO and morphine (IR and SR formulations) using the "worst pain in the past 24 h" item of the BPI.	Multicenter, randomized, double-blind, multiple-ascending-dose, parallel-group study Active control	IR and EXALGO, and IR and SR morphine IR phase: IR HM (q4h) and IR morphine (q4h), titrated to optimal analgesia SR phase: EXALGO q.d. or SR morphine b.i.d. at titrated dose Oral administration	IR phase: 200 HM: 99 morphine: 101 SR phase: 163 HM: 77 morphine: 86	Adult men and women with cancer pain requiring and responsive to strong oral or transdermal analgesics (60-540 mg oral morphine or ME/d) Europe and Canada	IR phase: 2-9 d SR phase: 10-15 d
DO-119	Characterize a safe and effective means of conversion and titration to an appropriate dose of hydromorphone.	Multicenter, randomized, double-blind, repeated-dose, 3-arm parallel study	IR HM, EXALGO, Titration: IR HM 5 doses daily (q4h) titrated to optimal analgesia Randomized treatment: IR HM or EXALGO q.d. (converted at titrated dose or ½ titrated dose) Oral administration	113 randomized IR HM: 39 EXALGO: 34 ½-dose EXALGO: 40	Adult men and women with chronic non-cancer or cancer pain US	14 d on IR HM (Phase 2), 7 d on randomized treatment (Phase 3)

Study Identifier	Primary Objective	Study Design and Type of Control	Test Product(s) Dosage Regimen Route of Administration	Number of Subjects	Healthy Subjects, Diagnosis of Patients Location(s)	Duration of Treatment
Open-Label Studies						
DO-132	Characterize the efficacy, safety, and impact on QOL measures of EXALGO and OxyContin® in patients with chronic OA of the knee or hip who were receiving chronic NSAIDs or other nonsteroidal, nonopioid analgesic treatment.	Multicenter, open-label, randomized, dose-titration, repeated-dose, 2-arm, parallel-group study Active control	EXALGO or OxyContin® q.d. (EXALGO) or b.i.d. (OxyContin®), titrated to best balance between pain relief and side effects Oral administration	138 EXALGO: 71 OxyContin®: 67	Adult men and women with chronic primary OA of the knee or hip US	Titration and stabilization: 14 d Maintenance: 28 d
OROS-ANA-3001	Determine an equianalgesic dosage of EXALGO once daily and SR oxycodone twice daily.	Multicenter, randomized, open-label, parallel group study with a titration phase followed by a maintenance phase Active control	EXALGO q.d. or SR oxycodone b.i.d. Study treatments flexibly titrated to achieve satisfactory pain control Daily dose ranges: EXALGO: 8 to 32 mg SR oxycodone: 10 to 80 mg Oral administration	504 patients 252/group	Adult men and women with chronic non-cancer pain severe enough to require continuous opioid therapy Europe	Titration: 4 wk Maintenance: 20 wk Titration permitted in both phases

b.i.d.=twice daily; d=day; h=hour; IR=immediate release; HN= hydromorphone; NSAID=non-steroidal anti-inflammatory drug; ME=morphine equivalent; OA=osteoarthritis; q.d.=once daily; q.i.d.=four times a day; QOL=quality of life; SR=sustained release; US=United States; wk=week

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Study M03-644-05: This randomized, double-blind study compared the analgesic efficacy and safety of fixed daily doses of EXALGO 8 and 16 mg to placebo in patients with osteoarthritis (OA). Following a 2-week analgesic and washout period, patients randomized to EXALGO all took 8 mg for the first week of the double-blind treatment period. During the second week, the EXALGO dosage was increased to 16 mg in the 16 mg group, while the 8 mg group continued to receive 8 mg, after which the dosage remained fixed with no dosage adjustments permitted during the double-blind maintenance phase. There was no option to increase or decrease the dosage to optimize analgesia or to minimize AEs. Efficacy results for the primary endpoint showed no statistically significant difference between the EXALGO and placebo groups in Office Visit Pain AUC ratio at the end of study (using BOCF). For the secondary efficacy endpoints, which included alternate imputation methods for the primary efficacy variable and analyses of the Western Ontario and McMaster Osteoarthritis Index (WOMAC) pain subscale efficacy endpoint, EXALGO 16 mg was effective through the first 6 weeks of treatment, and EXALGO 8 mg was effective through the first 2 weeks of treatment, regardless of the imputation method used.

Study DO-118: The primary objective of this randomized, double-blind, active-controlled, multiple-ascending dose study in patients with cancer pain was to demonstrate the clinical equivalence of hydromorphone and morphine using the "worst pain in the past 24 hours" item of the Brief Pain Inventory (BPI). Secondary objectives included comparisons of hydromorphone and morphine for the following variables: other BPI pain measures, Investigator 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, and safety and tolerability variables. The study consisted of 2 phases: an IR phase and an extended release phase. In the IR phase, patients were administered IR hydromorphone (2-18 mg) or IR morphine (10-90 mg) orally every 4 hours. In the extended release phase, patients received EXALGO (16-96 mg) orally every 24 hours, or morphine (30-260 mg) orally every 12 hours. Dosage increases were permitted every 2 days if the patient had >3 breakthrough pain episodes in 24 hours. Primary efficacy results demonstrated that hydromorphone and morphine were equivalent within and across both phases of the study. The secondary efficacy endpoint, BPI "pain now" evening scores, was significantly higher for patients treated with extended release morphine than for those taking EXALGO at the end of the extended release phase. Another secondary efficacy endpoint, BPI interference with normal work scores, was significantly lower for hydromorphone IR than for morphine IR at the end of the IR phase. Dosage stabilization occurred significantly sooner with morphine than with hydromorphone in both phases. Results of other secondary efficacy assessments were similar for both treatments in both phases.

Study DO-119: The primary objective of this randomized, double-blind, active-controlled study in patients with chronic non-cancer or cancer pain was to characterize a safe and effective means of conversion and titration to an appropriate dose of hydromorphone HCl (Dilaudid). Patients were titrated to 5 oral doses of Dilaudid IR daily (every 4 hours) to optimal analgesia, and then randomized to oral Dilaudid IR or EXALGO every day (converted at a titrated dose or ½ titrated dose). Results of the study demonstrated that

patients in the ½ dose EXALGO group took more rescue medication and experienced less analgesic effect than those in the full dose EXALGO group. The only 2 patients who discontinued due to lack of efficacy were in the ½ dose EXALGO group. No significant difference between EXALGO and Dilaudid IR was detected for rescue medication use, indicating comparable efficacy between EXALGO and Dilaudid IR at equal total daily doses. In conclusion, this study demonstrated a dose-response relationship with EXALGO, and clinically comparable efficacy between EXALGO and Dilaudid IR at equal total daily doses.

Study DO-132: This randomized, open label, active-controlled study was conducted to characterize the efficacy, safety, and impact on quality of life measures of EXALGO and OxyContin® (oxycodone HCl controlled-release) tablets in patients with chronic OA of the knee or hip who were receiving chronic non-steroidal anti-inflammatory drugs (NSAIDs) or other nonsteroidal, nonopioid analgesic therapy. Patients began treatment with EXALGO 8 mg once daily or OxyContin 10 mg twice daily, with upward dose titration allowed every 2 days, based on pain relief and side effects. After 14 days, if therapeutic efficacy with dose stabilization was achieved, patients began a 4-week maintenance phase, during which time the doses ranged from 8 to 64 mg for EXALGO, and from 10 to 160 mg OxyContin. Primary efficacy results for mean pain relief scores were identical for both treatments at the endpoint, and the associated 95% CI demonstrated the noninferiority of EXALGO (administered every day) relative to the OxyContin (administered twice a day). Secondary efficacy endpoints demonstrated that EXALGO was associated with significantly less sleep disturbance and daytime drowsiness than OxyContin.

Study OROS-ANA-3001: This primary objective of this randomized, open label, active-controlled study in patients with stable, chronic, non-cancer pain was to determine the equianalgesic dosage of EXALGO administered every day and SR oxycodone administered twice a day. Secondary objectives were to: document noninferiority of pain control of EXALGO versus SR oxycodone; compare the side effect profiles; evaluate impact on well-being and functionality in daily living; compare possible dose increases; assess and compare resource utilization of pain management; and assess subject satisfaction with treatment. Initial treatments were EXALGO 8 mg once daily and SR oxycodone 10 mg twice daily, followed by individual titration to optimal analgesia over 4 weeks, with dosage adjustments permitted during the maintenance phase. The maximum allowed daily dosages of EXALGO and SR oxycodone were 32 and 80 mg, respectively. The primary efficacy endpoint of change in pain score demonstrated decreases in both EXALGO and SR oxycodone, and EXALGO was proved to be non-inferior to SR oxycodone. The equianalgesic doses of EXALGO and SR oxycodone were 18.9 and 48.3 mg, respectively. Secondary efficacy variables were similar in patients treated with EXALGO and SR oxycodone.

4.4 Summary of Clinical Safety

Safety data in this section are summarized for Study NMT 1077-301 alone, as well as for all combined controlled and uncontrolled studies of EXALGO in patients with chronic pain.

4.4.1 Summary of NMT 1077-301 Safety

The safety profile and reported AEs of EXALGO in Study NMT 1077-301 were comparable to those of other strong opioids. No unexpected safety issues were revealed during the study.

4.4.1.1 Safety Overview

There were no deaths reported in Study NMT 1077-301. During the double-blind phase, the number of patients with any AE was higher in the placebo group than in the EXALGO treatment group (Table 13). The number of patients with serious adverse events (SAEs) was higher in the EXALGO treatment group than in the placebo group, although no dose-response relationship was established. The number of patients who discontinued due to AEs was higher in the EXALGO group (increasing proportionally to dosage).

Table 13 Summary of All Adverse Events in the Double-blind Phase (Randomized Population)

Evaluation	EXALGO N=134	Placebo N=134
Patients with adverse events, n (%)	64 (47.8)	74 (55.2)[b]
Patients with serious adverse events, n (%)	7 (5.2)	3 (2.2)[b]
Patients who discontinued due to adverse events, n (%)	7 (5.2)	3 (2.2)
Total number of adverse events[a] (n)	265	286
Deaths, n (%)	0	0

[a] Each 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.
[b] The total number of adverse events in the placebo group was increased by 1 to reflect a patient with a serious adverse event of nephrolithiasis.

During the open-label conversion and titration phase, a total of 55.3% of patients reported at least 1 AE, 1.3% of patients reported at least 1 SAE, 13% of patients discontinued due to AEs, and 43.0% of patients had treatment-related AEs. The majority of AEs were mild or moderate in severity. The majority of AEs most frequently reported as severe were also more often considered related to treatment. Constipation was the most commonly occurring AE in both groups, and the highest incidence rate occurred among patients who received 24 mg of EXALGO. There was no apparent relationship between the occurrence of AEs leading to discontinuation and the EXALGO dosage, and most AEs were considered possibly or probably related to treatment.

4.4.1.2 Common Adverse Events

Table 14 presents incidence rates of AEs that occurred in ≥2% of patients in either treatment group in the double-blind phase by system organ class (SOC) and preferred term (PT). Overall, the most commonly occurring AEs in the EXALGO group were: drug withdrawal syndrome (9.7%); nausea (9.0%); constipation (7.5%); vomiting (6.0%);

arthralgia (6.0%); headache (5.2%); and insomnia (5.2%). The most commonly occurring AEs in the placebo group were: drug withdrawal syndrome (11.9%); nausea (7.5%); headache (7.5%); diarrhea (6.7%); and back pain (6.0%).

Table 14 Number and Percent of Patients with Most Commonly Reported (≥2%) Adverse Events by System Organ Class and MedDRA Preferred Term in the Double-blind Phase (Randomized Population)

System Organ Class MedDRA[a] Preferred Term	EXALGO N=134 n (%)	Placebo N=134 n (%)
Any Adverse Event	64 (47.8)	73 (54.5)
Gastrointestinal Disorders	**29 (21.6)**	**30 (22.4)**
Abdominal Pain Upper	2 (1.5)	3 (2.2)
Constipation	10 (7.5)	5 (3.7)
Diarrhoea	5 (3.7)	9 (6.7)
Nausea	12 (9.0)	10 (7.5)
Toothache	3 (2.2)	0
Vomiting	8 (6.0)	6 (4.5)
General Disorders and Administration Site Conditions	**24 (17.9)**	**26 (19.4)**
Chills	2 (1.5)	3 (2.2)
Drug Withdrawal Syndrome	13 (9.7)	16 (11.9)
Fatigue	1 (0.7)	4 (3.0)
Oedema Peripheral	3 (2.2)	1 (0.7)
Pain	1 (0.7)	3 (2.2)
Infections and Infestations	**24 (17.9)**	**12 (9.0)**
Influenza	4 (3.0)	2 (1.5)
Sinusitis	6 (4.5)	1 (0.7)
Upper Respiratory Tract Infection	4 (3.0)	3 (2.2)
Urinary Tract Infection	4 (3.0)	2 (1.5)
Investigations	**5 (3.7)**	**8 (6.0)**
Weight Decreased	4 (3.0)	3 (2.2)
Musculoskeletal and Connective Tissue Disorders	**17 (12.7)**	**19 (14.2)**
Arthralgia	8 (6.0)	3 (2.2)
Back Pain	6 (4.5)	8 (6.0)
Muscle Spasms	3 (2.2)	1 (0.7)
Musculoskeletal Pain	2 (1.5)	3 (2.2)
Nervous System Disorders	**12 (9.0)**	**17 (12.7)**
Dizziness	3 (2.2)	2 (1.5)
Headache	7 (5.2)	10 (7.5)
Tremor	1 (0.7)	3 (2.2)
Psychiatric Disorders	**9 (6.7)**	**10 (7.5)**
Anxiety	0	4 (3.0)
Insomnia	7 (5.2)	5 (3.7)
Respiratory, Thoracic and Mediastinal Disorders	**8 (6.0)**	**5 (3.7)**
Nasal Congestion	3 (2.2)	2 (1.5)

Note: Patients counted at most once in a System Organ Class even if there are multiple events within the System Organ Class.

[a] MedDRA version 11.1.

4.4.1.3 Treatment-related Adverse Events

More patients in the placebo group (32.1% [43/134]) had treatment-related AEs (i.e., AEs rated as 'probably' or 'possibly' related by the Investigator) than patients in the EXALGO group (26.9% [36/134]). The number of treatment-related AEs was higher in the placebo group (137) than in the EXALGO group (90) in the double-blind phase.

The patterns of occurrence of treatment-related AEs in the 2 treatment groups were similar to the patterns of occurrence of all AEs. In the EXALGO group, treatment-related AEs found in more than 2 patients during the double-blind phase were drug withdrawal syndrome (7.5%), constipation (6.0%), and nausea and headache (3.0% each). In the placebo group, treatment-related AEs found in more than 2 patients during the double-blind phase were drug withdrawal syndrome (11.2%), nausea (5.2%), headache (3.7%), and constipation and insomnia (2.2% each).

4.4.1.4 Intensity of Adverse Events

The majority of AEs in both groups were mild or moderate in intensity. The single severe intensity AE occurring in more than 1 patient in the EXALGO group was drug withdrawal syndrome (2.2% [3/134]). The severe intensity AEs occurring in more than 1 patient in the placebo group were drug withdrawal syndrome (3.0% [4/134]) and back pain (2.2% [3/134]).

Events reported as severe in intensity were considered related to treatment in 3.7% (5/134) of patients and not related in 3.0% (4/134) of patients in the EXALGO group, and related in 3.0% (4/134) of patients and not related in 5.2% (7/134) of patients in the placebo group. However, in both treatment groups, the majority of events of severe intensity drug withdrawal syndrome were considered related to treatment.

4.4.1.5 Adverse Events by Dose

Among patients in the EXALGO groups, those treated with 12 mg had the fewest AEs (18.2%); AEs at the higher dosage levels (16, 24, 32, 40, 48, and 64 mg per day) of EXALGO ranged between 40.0% and 60.0% of patients. There were too few SAEs to be able to conclude any dose-response relationship. Discontinuations due to AEs appeared to rise with an increasing dose of EXALGO. In the EXALGO group, 5 of the 7 patients (18.5% of patients at that dose level) who discontinued due to AEs did so while receiving a 64-mg dose of EXALGO. No AE leading to discontinuation occurred in more than 1 patient.

4.4.1.6 Adverse Events Across Demographic Subgroups

The incidence of AEs was higher in women than men in the double-blind phase. In the EXALGO group, 50.8% (31/61) of women experienced any AE, compared to 45.2% (33/73) of men; in the placebo group, 56.2% (41/73) of women experienced any AE, compared to 52.5% (32/61) of men.

The numbers of patients in the racial subgroups and in the elderly were too small to support any conclusions regarding the relationship of incidence of AEs and race and the incidence of AEs and age group, respectively.

4.4.1.7 Adverse Events Leading to Discontinuation

During the double-blind phase, AEs leading to discontinuation occurred more frequently in EXALGO patients (7 patients, 5.2%) than in placebo patients (3 patients, 2.2%). The 7 AEs that led to discontinuation of 1 patient each in the EXALGO group were constipation, gastroenteritis, dehydration, back pain, headache, mania, and suicidal ideation. The 3 AEs that led to discontinuation of 1 patient each in the placebo group were haematochezia, intervertebral disc injury, and anxiety. No AE leading to discontinuation from either treatment group occurred in more than 1 patient.

Dose reduction was not permitted during the double-blind phase. If a patient developed a tolerability problem during the double-blind phase, the patient was to be discontinued from the study. There was no apparent relationship between the occurrence of specific AEs leading to discontinuation and the EXALGO dosage.

4.4.1.8 Deaths and Non-fatal Serious Adverse Events

In the open-label conversion and titration phase, 5 (1.3%) patients reported a total of 10 non-fatal SAEs. All 5 of the patients who experienced an SAE were receiving 24 mg of EXALGO during the event. During the double-blind phase, 6 (5.2%) EXALGO patients reported 12 non-fatal SAEs including vomiting, diarrhea, pulmonary embolism, abdominal pain, external ear infection, and headache. Four (2.2%) placebo patients had 8 non-fatal SAEs including nephrolithiasis, diarrhea, dehydration, deep vein thrombosis, emesis, and renal failure. Most were not considered to be treatment-related. More SAEs occurred at the higher dose levels, suggesting a possible relationship between the occurrence of SAEs and EXLAGO dose.

Both non-fatal SAEs and AEs leading to discontinuation reported in this study were quantitatively and qualitatively similar to previously reported incidences with other opioids. This evidence further confirms that the AE profile of EXALGO is similar to the typical AE profile with most opioids.

4.4.1.9 Significant Adverse Events

No GI obstructive events or altered GI motility were reported during the open-label conversion and titration and double-blind phases. The incidence of constipation was 15.4% (69/447) during the open-label conversion and titration phase, and 7.5% (10/134) in EXALGO patients and 3.7% (5/134) in placebo patients during the double-blind phase.

Respiratory depression was not reported as an AE for any patient who received EXALGO in this study. Dyspnea was reported in 3 (0.7%) patients during the open-label conversion and titration phase, and in no patient during the double-blind phase. However, respiratory failure, hypoventilation, and dyspnea exacerbated were not reported by any patients during any phase of study.

No case of overdose was reported in this study.

4.4.1.10 Clinical Laboratory Test Results, Vital Signs, Physical Exams and 12-Lead ECG Recordings

The small observed changes in clinical laboratory test results, vital signs measurements (including respiratory rate), physical examinations, and 12-lead ECG recordings were not clinically meaningful and were similar between the 2 treatment groups.

4.4.1.11 Clinical Opioid Withdrawal Scale and Subjective Opioid Withdrawal Scale

Clinical Opioid Withdrawal Scale (COWS) and Subjective Opioid Withdrawal Scale (SOWS) were used in this study as tools, together with the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DMS-IV) Diagnostic Criteria for Opioid Withdrawal Syndrome, to determine whether patients had developed opioid withdrawal syndromes. Higher COWS and SOWS scores indicate more severe withdrawal symptoms. The COWS and SOWS were obtained at all visits beginning with Visit 1 in the conversion and titration phase through and including the double-blind Week 2 visit, and at Week 12 or final visit.

The overall mean COWS and SOWS scores for all EXALGO doses decreased over time. Since study medication was withdrawn in placebo patients, the placebo group showed slightly higher changes on COWS and SOWS scores compared to the EXALGO group, as expected. As per the study design, placebo patients were still allowed rescue medication (IR hydromorphone) over the course of the double-blind treatment phase. However, no clear pattern was apparent for mean COWS and SOWS scores at different doses of EXALGO over time.

4.4.1.12 Safety Conclusions for Study NMT 1077-301

In conclusion, EXALGO was safe and well-tolerated in this patient population. The following safety conclusions were consistent with the profile of other strong opioids and revealed no new safety concerns:

- There were no deaths in this study, and no unexpected safety issues were reported.
- SAEs occurred infrequently, and most were not considered by the investigators to be treatment related.
- The majority of AEs were mild to moderate in severity, included GI and CNS events, and were determined by the investigators to be not related to EXALGO.
- There were no occurrences of GI obstruction, respiratory depression, or other significant AEs related to the study medication.

4.4.2 Summary of Pooled Safety Data from Controlled and Uncontrolled Studies

4.4.2.1 Overall Exposure and Patient Characteristics

Of the 3,075 patients included in the pooled analysis population for 13 controlled and uncontrolled studies in patients with chronic pain, 2,335 received one or more doses of EXALGO. The actual duration of exposure to EXALGO ranged from 2.0 days to approximately 20 months. A total of 420 patients were treated for over 6 months, and 141 patients for over 1 year (see Table 15). The median daily dose of EXALGO was 41.4 mg (range: 6 to 1984 mg). EXALGO has not been studied in the pediatric population; a pediatric plan was submitted to the NDA.

Enrolled patients with chronic pain who received EXALGO (n=2335) were predominantly Caucasian (90.9%), and a majority were female (55.5%). The patients who received EXALGO had a mean age of 54.0 years (range: 20 to 91 years) and a mean body mass index (BMI) of 30.5 kg/m^2 (range: 14 to 63 kg/m^2). Patients ≥65 years of age represented 21.9% of treated patients (511/2335 patients), and patients ≥75 years of age represented 5.7% of treated patients (133/2335 patients).

Of the 2,335 chronic pain patients treated with EXALGO, 2,097 patients (89.8%) were treated for non-cancer pain, of which musculoskeletal pain (pain from OA per protocol enrollment criteria) was the largest portion, representing 80.6% of patients overall (Table 15). The remaining 238 patients who received EXALGO (10.2%) were treated for cancer pain. The majority of patients had chronic non-cancer pain and were opioid tolerant, although the program did include significant numbers of opioid naïve and opioid treated but not tolerant patients.

Table 15 EXALGO Exposure in Chronic Pain Studies

	Patients, n (%) N = 2,335
Disease state	
Non-cancer	2,097 (89.8)
Cancer	238 (10.2)
Prior opioid history	
Opioid tolerant	1251 (53.6)
Opioid treated but not tolerant	521 (22.3)
Opioid naïve	563 (24.1)
Treatment duration (up to 20 months)	
>6 months	420
>12 months	141

4.4.2.2 Common Adverse Events

All AEs that occurred in ≥5% of patients during EXALGO treatment are summarized in Table 16. The most common AEs overall were opioid-related GI events of constipation,

nausea, and vomiting, and opioid-related nervous system events of somnolence, headache, and dizziness.

Table 16 Adverse Events Reported in ≥5% of Patients (All Patients with Chronic Pain Treated with EXALGO in Controlled and Uncontrolled Studies)

MedDRA Preferred Term	EXALGO N=2335 n (%)
Any AE	1880 (80.5%)
Constipation	702 (30.1%)
Nausea	642 (27.5%)
Vomiting	322 (13.8%)
Somnolence	322 (13.8%)
Headache	300 (12.8%)
Dizziness	247 (10.6%)
Diarrhea	194 (8.3%)
Fatigue	190 (8.1%)
Pruritus	183 (7.8%)
Insomnia	158 (6.8%)
Hyperhidrosis	136 (5.8%)
Oedema peripheral	132 (5.7%)

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 11.1 System Organ Classification.
AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities.

The overall incidence of AEs in elderly patients (≥65 years of age) was higher, with a greater than 5% difference in rates for constipation and nausea when compared with younger (<65 years of age) patients. The overall incidence of adverse reactions in female patients was higher, with a greater than 5% difference in rates for nausea, vomiting, constipation and somnolence when compared with male patients.

4.4.2.3 Deaths and Other Serious Adverse Events

Among the 2,335 patients who received EXALGO in the 13 controlled and uncontrolled studies, 64 deaths were identified (2 in controlled studies and 62 in uncontrolled studies); 58 of these deaths were in cancer patients, and 6 were in non-cancer patients. None of the deaths was considered related to study treatment according to the investigators.

In 5 of the 6 controlled studies with EXALGO, no deaths occurred in patients treated with EXALGO during the studies or within 30 days after completion of study treatments. The 2 deaths that occurred in controlled studies were in Study DO-118, but both occurred after completion or discontinuation of EXALGO: one patient died from respiratory

failure (thought to have originated from pulmonary thromboembolism) 4 days after completing the study, and one patient died from cancer metastases and disease progression 13 days after being withdrawn from the study.

Additionally, in a placebo controlled study of patients with OA pain (Study NMT 1077-302), which was ongoing at the time of the EXALGO NDA submission and is not summarized in this Briefing Document, a 56-year-old male patient, with a history of depression and anxiety, experienced an intentional overdose with a fatal outcome. Two hours before being found in cardiopulmonary arrest and asystole, the patient had been noted to be drinking. A suicide note was found in the patient's pocket indicating that he was ending his life because he was facing a jail sentence. Autopsy and toxicology studies revealed the cause of death as severe hydromorphone toxicity.

A total of 62 deaths occurred in the uncontrolled studies, during or after EXALGO treatment. Of these, 56 were attributed to cancer; 2 were associated with cardiac arrest; and one each was associated with sepsis, respiratory failure/dehydration, myocardial infarction, and congestive heart failure

Among the chronic pain patients in the 13 controlled and uncontrolled studies, SAEs were identified in 240/2335 patients (10.3%) who received EXALGO treatment. In addition, 10 patients had AEs that possibly met SAE criteria that were identified after several studies ended, based on manual review of study documents. These SAEs were originally not recorded according to protocol-specified reporting requirements, and were therefore not included in the safety database. In total, a subset of 44 EXALGO-treated patients reported treatment-related SAEs defined as either definitely, probably, possibly related, or with an unknown relationship to EXALGO, and are listed in Table 17.

Table 17 Number of Patients Who Reported ≥1 Treatment-related SAE in the Controlled and Uncontrolled Chronic Pain Studies

SAE	Number of patients*
Drug withdrawal syndrome	5
Overdose	5
Confusional state	4
Constipation	4
Chest pain	2
Dizziness	2
Encephalopathy	2
Nausea	2
Diverticulitis	2
Diarrhea	1
Vomiting	1
Small intestinal obstruction	1
Fecaloma	1
Abdominal pain	1
Dehydration	1
GI disorder	1
Hypoxia	1
Hypotension	1
Delirium	1
Suicide attempt	1
Fall	1
Cancer pain	1
Rash	1
Infection	1
Restlessness	1
Total	44

GI=gastrointestinal; SAE=serious adverse event.
* The patients who reported >1 SAE were counted only once by the first SAE.

The overall incidence of SAEs in the clinical database by EXALGO dose at onset increased with each higher dose level, from 2.7% (32/1,203 patients) at the 8 mg per day dose level to 24.4% (20/82 patients) at the >128 mg per day dose level. There were no clear dose-related patterns in the incidence of specific SAEs. Additionally, no patterns were evident when SAE incidence by dose was analyzed adjusting for patient-years of exposure.

4.4.2.4 Adverse Events of Special Interest

Due to the drug class and nature of the EXALGO dosage form, certain types of AEs were considered to be of special interest in the safety evaluation. These were identified by searching the clinical database for Medical Dictionary for Regulatory Activities

(MedDRA) primary terms and AE verbatim terms that were considered associated with the AE of special interest.

4.4.2.4.1 Gastrointestinal Obstruction

Constipation is a known side effect of opioid drugs. The combination of hydromorphone with the nondeformable hard outer shell EXALGO formulation, therefore, warranted an evaluation of constipation and other GI obstructive AEs. Other terms that were considered to be possibly associated with GI obstruction were the following: obstruction, duodenal obstruction, intestinal obstruction, colonic obstruction, oesophageal obstruction, distal obstruction, small intestinal obstruction, colonic pseudo-obstruction, gastric outlet obstruction, distal ileal obstruction, large intestinal obstruction, bezoar, and fecaloma.

Constipation was recorded for 702/2335 patients (30.1%) in the controlled and uncontrolled studies. The vast majority of these events were considered treatment-related (674/2335 patients, 28.9%). Constipation was rated as severe in 75/2335 patients (3.2%), and led to study discontinuation in 85/2335 patients (3.6%).

The following GI obstruction AEs were reported by patients treated with EXALGO or placebo in the controlled and uncontrolled study pool. Small intestinal obstruction was reported by 0.1% (2/2335) of patients treated with EXALGO and none of the patients treated with placebo. Intestinal obstruction, obstruction gastric, bezoar, and fecaloma were each reported by 0.04% (1/2335) of patients treated with EXALGO and none of the patients treated with placebo. For the bezoar and fecaloma events, there was no evidence of EXALGO shells in the impacted material.

Because of the potential for serious obstructive events with EXALGO, it should not be administered to any patient with pre-existing GI disorders or surgical history that would predispose them to impaired motility or obstruction.

4.4.2.4.2 Respiratory Depression

Respiratory depression is a common side effect of opioid treatment. As such, the EXALGO clinical database was searched for the following terms that were considered to be possibly associated with respiratory depression: respiratory depression, dyspnea, dyspnea exacerbated, hypoxia, respiratory distress, respiratory failure, hypoventilation, and decreased oxygen saturation.

The following respiratory depression events were reported by patients treated with EXALGO or placebo in the controlled and uncontrolled study pool. Respiratory depression was reported by 0.04% (1/2335) of the patients treated with EXALGO and none of the patients treated with placebo. Dyspnea was reported in 2.9% (68/2335) of the patients treated with EXALGO and by 0.2% (1/466) of patients treated with placebo. Dyspnea exacerbated was reported in 0.1% (3/2335) of the patients treated with EXALGO and by none of the patients treated with placebo. Hypoxia was reported by 0.4% (2/466) of patients treated with EXALGO and by 0.2% (1/466) of the patients treated with placebo. Respiratory distress was reported by 0.1% (3/2335) of the patients treated with EXALGO and by 0.2% (1/466) of patients treated with placebo.

Respiratory failure was reported by 0.1% (3/2335) of patients treated with EXALGO and none of the patients treated with placebo. Hypoventilation was reported by 0.1% (2/2335) of patients treated with EXALGO and none of the patients treated with placebo. No decreased oxygen saturation event was reported by any patient treated with EXALGO or placebo in the controlled and uncontrolled study pool. Decreased oxygen saturation was not seen in any patient in the controlled and uncontrolled study pool.

EXALGO should be used with extreme caution and in a carefully monitored environment in patients with chronic obstructive pulmonary disease or cor pulmonale, and in patients with substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression.

4.4.2.4.3 Hypotension

In addition to respiratory depression, another concern with opioid use is its potential to cause or exacerbate hypotension. Therefore, the following terms possibly associated with hypotension were searched in the EXALGO clinical safety database: hypotension, blood pressure decreased, and blood pressure systolic decreased.

The following hypotension-related events were reported by patients treated with EXALGO or placebo in the controlled and uncontrolled study pool. Hypotension was reported by 0.4% (10/2335) of patients treated with EXALGO and by 0.2% (1/466) of patients treated with placebo. Blood pressure decreased was reported by 0.1% (3/2335) of patients treated with EXALGO and by 0.2% (1/466) of patients treated with placebo. Blood pressure systolic decreased was reported by 0.04% (1/2335) of patients treated with EXALGO and none of the patients treated with placebo.

Opioid analgesics, including EXALGO, may cause severe hypotension in an individual whose ability to maintain blood pressure has been compromised by depleted blood volume or by concurrent administration of phenothiazines or general anesthetics. Therefore, EXALGO should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug could further decrease cardiac output and blood pressure.

4.4.2.4.4 Overdose and Withdrawal Syndrome

Overdose is a known risk of all strong opioids. Overdose was reported as an AE for 8/2335 patients (0.3%) who received EXALGO, and for 1 patient receiving oxycodone during the controlled and uncontrolled studies. Of the 8 EXALGO-treated patients, study medication was discontinued in 5 patients, temporarily stopped in 2 patients, and no action was taken in 1 patient. Seven of these patients recovered without sequelae, and 1 patient had a last-reported status of ongoing. No patient in the pivotal Study NMT 1077-301 experienced an overdose. One patient in the ongoing Study NMT 1077-302 experienced a fatal overdose, as described in Section 4.4.2.3.

A serious overdose with hydromorphone is characterized by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and sometimes bradycardia and hypotension. Overdose should

be managed with prompt supportive care and may include administration of an opioid antagonist such as naloxone.

Due to the PK profile of EXALGO coupled with the conversion recommendation per the label, patients may need supplemental IR medication when initiating EXALGO therapy. This will provide the necessary breakthrough pain analgesia until an optimal analgesic dose is reached by the patient. Supplemental IR medication will also reduce the risk of withdrawal symptoms that may occur during the initial conversion to EXALGO.

5 POST-MARKETING DATA

5.1 World-wide Marketing Experience

JURNISTA was first approved in Denmark in December 2004, and first marketed by Johnson & Johnson in Germany on 31 July 2006 for the treatment of moderate to severe pain. To date, JURNISTA has been approved in 26 countries and marketed in 9 countries. The formulation of JURNISTA is identical to that in EXALGO, and it is marketed outside the US in the following dosage strengths: 4, 8, 16, 32, and 64 mg.

5.2 Post-marketing Safety Database (Reporting Period: 22 December 2004 through 31 December 2008)

The objective of the routine safety surveillance program conducted by J&J Benefit Risk Management (BRM), a Division of J&J Pharmaceutical Research and Development (PRD), is to systematically review post-marketing safety data from multiple sources to detect and evaluate changes suggestive of new safety concerns. Routine pharmacovigilance practices included the following:

- Real-time reviews of single cases;
- Scheduled reviews of aggregate data from the BRM Safety Database to identify relevant changes in reporting frequency or pattern of AEs;
- Data mining, at regular intervals, of regulatory databases such as the US FDA Adverse Events Reporting System/Spontaneous Reporting System and the World Health Organization Vigibase, to identify AEs of interest reported disproportionately for the Marketing Authorization Holder's products relative to other products in the databases;
- Aggregate reviews, at pre-specified intervals, of product quality complaint cases with associated AEs and lot numbers from the BRM Safety Database to identify lots with disproportionate reporting of quality associated AEs suggestive of potential product quality issues.

The post-marketing section in this document contains safety data for the reporting period from 22 December 2004 through 31 December 2008. The BRM Safety Database includes AEs received from the spontaneous reporting system. Serious and non-serious unlisted cases from the medical literature, serious cases from clinical studies, cases from local post-marketing studies and registries and cases sent by health/regulatory authorities are part of this pharmacovigilance system.

A literature review of publications during the reporting period that contained safety results from company-sponsored studies identified 26 publications with relevant, but not exclusive, safety information about hydromorphone. A review of this literature did not reveal any significant new risk information.

5.2.1 Post-marketing Exposure/Changes to Reference Safety Information

When providing an estimate of patient exposure in a safety update containing post-marketing surveillance data, it is important to stress the limitations of reporting frequencies for evaluation of adverse drug reactions. Reporting frequencies do not reflect occurrence rates. Numerous factors influence the reporting of spontaneous experiences and, therefore, caution must be emphasized in the analysis and evaluation of spontaneous reports.

During the reporting period, approximately 16,876,578 tablets of JURNISTA were sold or distributed. The estimated exposure for this period is approximately 16,876,578 patient-days, since JURNISTA is supposed to be dosed once daily. During the reporting period, the following changes/revisions were made to the J&J company core data sheet (CCDS), which is the reference safety information used to determine whether newly reported AEs are expected or unexpected.

In August 2006, the adverse drug reaction 'Urinary hesitation' was changed to 'Urinary retention'.

In November 2006, the Posology and Method of Administration was updated to include dosing information for patients not routinely receiving opioids (JURNISTA labeling does not restrict use to opioid-tolerant patients only). Additionally, to the section Undesirable Effects, 'Fits/Convulsions' (0.12%)' and 'Bradycardia (0.06%)' were added as adverse drug reactions.

In January 2007, the following change addition was made to the Special Warnings and Precautions section: "Clinical conditions or medicinal products that cause a sudden and significant shortening of GI transit time may result in decreased hydromorphone absorption with OROS hydromorphone and may potentially lead to withdrawal symptoms in patients with a physical dependence on opioids."

In July 2007, updated verbiage was added to Posology and Method of Administration to consider appropriate prophylaxis for known adverse reactions (e.g., constipation).

5.3 Discussion of Medically Confirmed Cases

The sections below contain a review and analysis of all world-wide post-marketing cases that reported SAEs that are also *unlisted* (as compared to the reference safety information, i.e., the CCDS) with a fatal outcome, those in the SOCs of psychiatric disorders, GI disorders, as well as cases of drug withdrawal syndrome, abuse potential, misuse and maladministration for JURNISTA, that were received by J&J during the reporting period. The methods used to generate the sections below were a review of individual Periodic Safety Update Reports (PSURs) whereby relevant information was extracted. Note that serious cases that occurred during this same reporting period from patients enrolled in a clinical trial may also be reported here for completeness and overall medical assessment (since they were entered in the safety database), but are also

represented in the discussion and presentation of safety data from the clinical database in Section 4.4.

5.3.1 Serious Adverse Events

A total of 171 events during the reporting period met the definition of an SAE. Of the 171 SAEs, 121 were listed according to the reference safety information and 50 were unlisted. Note that for reported fatalities, a cutoff date of 21 August 2009 was used in order to report the most current information.

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.

5.3.1.1 Fatalities

Of the total number of patients exposed to JURNISTA, 6 experienced a fatal outcome during the reporting period through 21 August 2009. For these 6 cases, the reported events were respiratory failure in 3 patients over 80 years of age, overdose in 2 patients, and cardiac failure in 1 patient:

DE-JNJFOC-20070404883 (Respiratory failure, Accidental Overdose, Drug ineffective, Restlessness): An 85-year-old male (weight unknown) with concurrent epidermoid carcinoma of the head and a history of radiotherapy had severe pain, which was treated with the fentanyl transdermal patch 125 μg/hour. On an unspecified date, the patient experienced a lack of efficacy, and the fentanyl patch was discontinued. Twelve hours later, JURNISTA 64 mg/day was initiated. Three hours following the first dose of JURNISTA, the patient fell into a deep sleep; it was difficult to arouse the patient from his sleep the next morning. Nineteen hours following the first dose, he experienced respiratory paralysis and died. No additional analgesics were administered between the last fentanyl dose and the first JURNISTA dose. Follow-up information confirmed that the fatal outcome was due to an accidental overdose of JURNISTA. It also indicated that a joint decision to not administer an antidote had been taken by the treating physician and the patient's relatives considering the patient's poor prognosis due to the underlying disease. The physician assessed the causality between JURNISTA and respiratory paralysis as probably related. An autopsy was not performed.

DE-JNJFOC-20070903315 (Respiratory failure, Disturbance in attention, Accidental overdose): An 82-year-old female (weight 50 kg) with a medical history of dementia experienced a femur fracture. Seven days after the fracture, the patient received JURNISTA 8 mg/day for pain. Over the next 8 days, the patient underwent total hip prosthesis and developed pneumonia. She was concomitantly treated with tramadol injection 200 mg/day beginning 1 day after surgery. Additional concomitant medications included diclofenac, sertraline, pantoprazole, and pancreatin. The tramadol injection was withdrawn after 2 days. The next day, JURNISTA was withdrawn following an

accidental overdose after 8 days of treatment. Following the accidental overdose, the patient experienced respiratory insufficiency; JURNISTA was discontinued permanently. Quantity of drug ingested and additional information regarding the overdose were not provided. Pneumonic infiltrates and pulmonary venous congestion were identified in the intensive care unit; the patient died 10 days following the overdose. It was unknown whether an autopsy was performed. The reporter considered the events to be probably related to JURNISTA.

DE-JNJFOC-20070602396 (Cerebral infarction, Depressed level of consciousness, Respiratory failure): An 82-year-old male (weight 74 kg) with a medical history and concurrent conditions of arrhythmia absoluta (including atrial fibrillation), hypertension, reflux esophagitis, arterial embolism, Billroth's operation II, chronic ischemic cardiac disease, colon diverticulosis, cor pulmonale (due to lung tuberculosis), and right therapeutic pneumothorax received JURNISTA 8 mg/day for general pain. Two days after initiation of JURNISTA, the patient was hospitalized due to respiratory insufficiency following a cerebral infarction. He required ventilation. Concomitant medications included esomeprazole, metoprolol, digitoxin, verapamil, and sulbactam/ampicillin. Five days later, the patient's condition worsened; he died from cerebral infarction on an unspecified date. It was unknown whether an autopsy was performed. According to the reporter, JURNISTA had a partial effect on the respiratory insufficiency.

US-JNJFOC-20081106318 (Overdose): This case was received from an ongoing EXALGO clinical study 1077-302. A 56-year-old patient was treated with EXALGO 24 mg for arthralgia. The patient's medical history and concurrent conditions included anxiety, bilateral knee pain, recurring bronchitis, chronic right wrist pain, deformity of right distal radius, depression, fracture right hand, gastroesophageal reflux disease, hypertension, left hip pain, mild chronic obstructive pulmonary disease, osteoarthritis, and periodontal disease. Co-suspect drug was hydromorphone hydrochloride. Concomitant medications included ibuprofen, mirtazapine, quetiapine, hydrochlorothiazide, lisinopril, ranitidine, and atenolol. Five days after initiation of treatment with EXALGO, the patient experienced a possible drug overdose and died on the same day. Upon examination, empty cards of the EXALGO 24 and 4 mg rescue (IR hydromorphone) medications were found, while the EXALGO 32 mg card and a 4 mg rescue medication card were missing. The subject was in the conversion-titration phase of the trial at the time of the event. An autopsy report was received at follow-up, and confirmed the cause of death to be due to hydromorphone toxicity. It was also reported that the patient left a suicide note, thereby confirming that the overdose in this case was intentional.

CA-JNJFOC-20040606862 (Malignant neoplasm progression, Hallucination, Confusional state): This case was received from a clinical study. A 73-year-old male patient with extensive medical history including hallucination, dyspnea, small lung cancer, and prostate cancer with metastases (liver, bone, and soft tissue) was hospitalized due to hallucinations and confusion, which had occurred 7 days after beginning treatment with JURNISTA 96 mg/day. These 2 events were reported as related to JURNISTA. After JURNISTA was tempered and finally stopped, there was only some decrease of

events. The patient became more jaundiced and hepatomegaly became more pronounced. The patient died a month after the onset of hallucination and confusional state due to progression of cancer, which was not considered related to JURNISTA.

DE-JNJFOC-20090706963 (Cardiac failure, disorientation, wrong technique in drug usage process). This case involved a 40-year-old male with metastatic cancer of the liver and small pelvis, and final stage testicular cancer (with "death expected within 36 hours"). The patient died 4 hours after receiving morphine SC and 1 JURNISTA 64 mg tablet; it was reported that the patient "cracked the tablet in his mouth" and "swallowed the tablet." The physician reported cause of death as cardiovascular failure due to tumor progression, and determined that the death was not related to JURNISTA.

Medical Assessment: Three cases with a fatal outcome reported respiratory failure in patients over 80 years of age. For 2 of the cases, the reporter assessed the causality as probably related (DE-JNJFOC-20070404883, DE-JNJFOC-20070903315). For the other case (DE-JNJFOC-20070602396), JURNISTA was considered to have had a partial effect on the respiratory failure. Case DE-JNJFOC-20070404883 involved administration of a JURNISTA dose considered appropriate via tables for conversion from transdermal fentanyl, but in an elderly cancer patient who may have had a reduced fentanyl clearance. The patient with overdose of JURNISTA had experienced respiratory failure. He did not receive an opioid antagonist following the overdose based on a joint decision by the treating physician and family, which may have contributed to the fatal outcome. Case DE-JNJFOC-20070602396 involved a male patient who had a medical history of cor pulmonale following tuberculosis, in addition to cardiac disease. Two days after initiating JURNISTA treatment, he experienced respiratory failure in the context of cerebral infarction, for which he had several risk factors, including hypertension, ischemic heart disease, and a history of arterial embolism. The remaining case (DE-JNJFOC-20070903315) described a female patient who experienced respiratory failure following an accidental overdose. She was at additional risk due to her dementia and concurrent lung infiltrates and pulmonary congestion following pneumonia. Furthermore, she had been treated with an additional weak opioid agonist (tramadol) 2 days prior to the day of the JURNISTA overdose.

For case US-JNJFOC-20081106318, the reported cause of death was hydromorphone toxicity due to intentional overdose.

The final case (CA-JNJFOC-20040606862 from Study DO-104) involved a 73-year-old male patient with extensive medical history who experienced hallucination and confusion in the context of cancer progression. The events of hallucination and confusion were reported as related to JURNISTA; however, the progression of cancer resulting in death was not related to JURNISTA.

Taking these fatalities into consideration, it is important to note that the proposed PI for EXALGO contains specific language in the Warnings and Precautions section regarding respiratory depression, which is the most important hazard of strong opioids including hydromorphone, and occurs most frequently in the elderly and in overdose and debilitated situations.

5.3.1.2 Psychiatric Disorders

5.3.1.2.1 Acute Psychosis

DE-JNJFOC-20081001946 (Acute psychosis): A 75-year-old male was treated with JURNISTA (indication of therapy and dose not reported). Medical history and concomitant medications were not reported. On an unspecified date after the initiation of JURNISTA, he experienced acute psychosis. The action taken with JURNISTA and the event outcome were not reported.

5.3.1.2.2 Confusional State / Hallucination

CA-JNJFOC-20040606862, a case with a fatal outcome that involved the events of confusional state and hallucination, is discussed fully in Section 5.3.1.1.

DE-JNJFOC-20080302286 (Hallucination): A 91-year-old female received treatment with JURNISTA 8 mg (indication of therapy not reported). Medical history and concomitant medications were not reported. It was reported that the patient was taking two 8-mg tablets/day for an undetermined amount of time. On an unspecified date after the initiation of JURNISTA, she experienced hallucination. Treatment with JURNISTA was discontinued after 21 days. The event resolved and the patient recovered (duration not reported).

5.3.1.2.3 Restlessness

GB-JNJFOC-20040605833 (Anxiety, Abdominal pain, Restlessness, Nausea, Vomiting): This case was received from a clinical study. A 73-year-old male cancer patient developed anxiety, abdominal discomfort, retching, and restlessness requiring hospitalization. Concomitant medications included diethylstilbestrol, dexamethasone, anti-inflammatory therapy, lansoprazole, dorbanex, sodium fluoride, temazepam, and Mag-Lax. A recent CT scan had shown progressive liver metastases, enlarged adrenal glands bilaterally, retroperitoneal metastases, and bilateral pleural effusion. Corrective treatment included diamorphine, metoclopramide, and lorazepam. On an unspecified date after the initiation of JURNISTA 16 mg/day, the patient experienced abdominal pain, nausea, and vomiting. Also at an unspecified time, the patient experienced anxiety and restlessness concomitantly. The events were ongoing following discontinuation of JURNISTA (duration of treatment not reported).

5.3.1.2.4 Suicidal Ideation

DE-JNJFOC-20070902045 (Suicidal ideation, Depression): A 37-year-old female (weight 110 kg) with a medical history or concurrent conditions of underlying disease of chronic pain, different length of extremities, intervertebral disc translocation, migraine, radiculopathy, tension headache, depressive episode, diabetes mellitus, eating disorder, enzyme deficiency, hypertension, fibromyalgia, osteochondrosis of vertebral column, and post-traumatic stress disorder received JURNISTA 8 mg/day for chronic pain. On an unknown date, the patient experienced suicidal ideation and worsening of depression.

JURNISTA was withdrawn within 6 weeks of initiation, and the patient recovered from both events. Concomitant medications were not reported.

DE-JNJFOC-20070904462 (Suicidal ideation, Depression): A 39-year-old female (weight 65 kg) with a medical history and concurrent conditions of chronic pain, depression "associated with a wish to die", endometriosis, unspecified muscle disorder, other enduring personality changes, sacroiliitis, somatization disorder, and spondylopathy was treated with JURNISTA 24 mg/day for chronic pain. On an unknown date, she experienced depressive mood swings, and 9.5 months following initiation of JURNISTA, severe depression and suicidal ideation. Treatment with JURNISTA was withdrawn and unspecified antidepressants were started. The outcomes for severe depression, suicidal ideation, and depressive mood swings were not known. It was reported that the patient suffered from psychiatric comorbidities.

DE-JNJFOC-20071107227 (Suicidal ideation, Anxiety, Restlessness, Fatigue, Pruritus, Dysuria, Drug ineffective): A 46-year-old male with a medical history of chronic pain, compartment syndrome, renal infarction, and suicidal ideation who began treatment with JURNISTA for chronic pain. The dose was initially 16 mg/day for 4 days and then increased to 32 mg/day for 2 days. Seven days after commencing JURNISTA treatment, the patient experienced insufficient efficacy; consequently, the dose was increased to 64 mg/day. Two days later, he experienced restlessness, severe tiredness, state of anxiety, pruritus, micturition difficulties, and suicidal thoughts. Five days after the initiation of 64 mg, JURNISTA was discontinued. The following day, the patient recovered from all events. Concomitant medications included metamizole and amitriptyline hydrochloride for pain, and phenprocoumon for renal infarction. The causality between all events and JURNISTA was reported as very likely/certain.

5.3.1.2.5 Suicide Attempt

DE-JNJFOC-20070804642 (Suicide attempt, Intentional overdose, Somnolence): A 45-year-old male patient (weight 75 kg) ingested 20 doses of JURNISTA (strength not specified) in 1 day in an attempted suicide. He also took unknown doses of co-suspect medications hydromorphone IR and a combination of oxycodone and naloxone. No concomitant medications were reported. The patient experienced sleepiness. Outcomes of the events were not reported.

5.3.1.2.6 Transient Psychosis

DE-JNJFOC-20071110299 (Transient psychosis): A patient (sex and age not provided) began treatment with JURNISTA 16 mg/day (indication and duration of treatment not provided). The patient experienced transient psychosis (time to onset not provided) and treatment with JURNISTA was stopped (duration of treatment not provided). The patient recovered from transient psychosis (duration of event not provided).

Medical assessment: All cases received on or before 07 July 2008 reporting any PT from the Depression and Suicide/Self-Injury MedDRA Standardised Medical Query and the Suicide/Self-Injury sub-Standardised Medical Query were subject to a recent cumulative

review. The report concluded that there was insufficient evidence to conclude that suicide, suicidal behavior, and suicidal ideation are adverse drug reactions associated with the use of JURNISTA. Additionally, based on the review of the post-marketing data and medical literature, it was concluded that there was insufficient evidence to support additional warnings in the JURNISTA CCDS regarding the risk for development of suicidal ideation or related events in specific populations at risk.

Of the 3 cases of suicidal ideation, 2 (DE-JNJFOC-20070904462, DE-JNJFOC-20071107227) involved patients with a history of suicidal ideation. For DE-JNJFOC-20070904462, the reporter also stated that the patient had psychiatric comorbidities and the onset of the severe depression and suicidal ideation occurred 9.5 months after initiation of JURNISTA. Case DE-JNJFOC-20070902045 involved a patient with a history of depression who reported progression of depression associated with suicidal ideation on an unknown date after initiation of JURNISTA. The reporter cited the pre-existing depression before JURNISTA was started as a possible contributing factor. Case DE-JNJFOC-20070804642 reported a suicide attempt with a JURNISTA overdose and co-suspect medications of hydromorphone IR and oxycodone/naloxone, resulting in somnolence (non-serious).

Suicide and suicidal ideation are not listed adverse drug reactions for the hydromorphone active ingredient, morphine, or other morphine derivatives. The population being treated with JURNISTA, particularly patients with chronic pain, may be predisposed to the development of suicidal behavior since it has been reported that individuals suffering chronic pain are at increased risk for suicidal behavior. Anxiety and depression are listed events in the JURNISTA CCDS and the EXALGO PI.

The case of acute psychosis (DE-JNJFOC-20081001946) lacked information necessary to make an assessment, including medical history, dose, indication, concomitant medications, and outcome. The case of hallucination (DE-JNJFOC-20080302286) also lacked information necessary to make an assessment regarding the onset date of the hallucination event, including medical history, indication, and concomitant medications. In addition, the patient was reported to have taken two 8 mg tablets/day for an undefined amount of time. Case GB-JNJFOC-20040605833 described a patient who experienced restlessness concomitantly with anxiety (listed). Restlessness is an unlisted event for JURNISTA; however, agitation and nervousness are listed events. The event of restlessness was considered associated with JURNISTA.

Case DE-JNJFOC-20071110299, which reported transient psychosis, provided insufficient information for a medical assessment.

5.3.1.3 Gastrointestinal Disorders

CA-JNJFOC-20040607109 (Gastric ulcer, Abdominal pain upper, Gastrointestinal hypomotility, Nausea): This case was received from a clinical study. A 42-year-old female patient with fibromyalgia and a medical history including "crampy" abdominal pain (duration of 1 year) associated with nausea, irritable bowel syndrome, and obesity. The patient started treatment with JURNISTA 32 mg/day; the dose was increased to 40

mg/day 1 month later. She was hospitalized with severe stomach pain, nausea, and vomiting and readmitted 2 days later with the same symptoms. Investigations included a barium swallow, which showed a slow-draining bowel. The patient recovered on discontinuation of JURNISTA.

20080103788 (Gingival recession, Loose tooth, Dental caries, Tooth fracture): A 54-year-old male with a history of hypertension, chronic vertebral column syndrome, and spinal canal stenosis was treated with JURNISTA (tablet, oral) 96 mg/day for chronic spinal column syndrome. Concomitant medications included candesartan, amitriptyline, meloxicam, omeprazole, and metoclopramide. On an unknown date, the patient developed gingival recession and reported his teeth becoming loose. It was reported that the incisor teeth were affected by severe caries. For this reason, all of the patient's teeth were extracted approximately 9 months after initiation of JURNISTA treatment. At the time of this case, the patient had recovered with sequelae from loosening of teeth, and the outcome was not reported for gingival recession. The dose of JURNISTA was not changed, and treatment was ongoing.

Medical assessment: For case CA-JNJFOC-20040607109, the patient had a 1-year history of "crampy" abdominal pain and vomiting, so a pre-existing condition cannot be excluded. For case 20080103788, the patient reported severe caries and loose teeth. The patient was using amitriptyline[1] as a concomitant medication, which is reported to cause dental caries and xerostomia. Dry mouth, though not reported in this case, is also listed in the JURNISTA CCDS. Xerostomia, itself, is also associated with increased risk for dental caries, inflammation of the oral cavity, and gum shrinkage.

5.3.2 Other Significant Adverse Events (Serious and Non-serious)

5.3.2.1 Drug Withdrawal Syndrome

During the reporting period, there were 10 medically confirmed (3 serious, 7 non-serious) and 9 non-medically confirmed (5 serious, 4 non-serious) spontaneous cases of withdrawal syndrome involving EXALGO. 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 (all listed).

Of the 17 medically confirmed cases involving the events of drug withdrawal syndrome or withdrawal syndrome, 7 contained insufficient information for a medical assessment. Among the remaining 10 cases, most patients' doses were not titrated down as recommended in the J&J CCDS. Therefore, the proposed PI for EXALGO states that if cessation of therapy is indicated, the dose of EXALGO should be reduced by 25% to 50% every 2-3 days until the lowest possible dose is reached, at which time therapy may be safely discontinued. If symptoms of withdrawal appear, tapering should be stopped. The dose should be slightly increased until the signs and symptoms of opioid withdrawal disappear. Tapering should then begin again but with longer periods of time between each EXALGO dose reduction, or before converting to an equianalgesic dose of another opioid to continue tapering.

5.3.2.2 Cases of Potential Abuse

During the reporting period, only 2 cases of JURNISTA abuse were reported, 1 of which was accidental. In the first case, which was coded as intentional drug misuse, a 55-year-old male initiated treatment with JURNISTA 8 mg on an unknown date for vertebral disk prolapse. The patient took JURNISTA 16 mg instead of the prescribed 8 mg (no details of the abuse were reported). Co-suspect medications included pregabalin and amitriptyline. Additional concomitant medications were not reported. The next day, the patient experienced sleepiness, tiredness, and hypertension (160 to 170 mmHg systolic). On an unknown date, the patient recovered.

In the second case, which was coded as accidental overdose and inappropriate schedule of drug administration, a female (age unknown) with a medical history of pain (cause unknown), received JURNISTA 16 mg/day for pain. Concomitant medications were not reported. On an unknown date, acting on her own authority, the patient increased the dose to 48 mg/day due to sudden pain increase. She experienced an accidental overdose (no clinical symptoms were specified), which led to hospitalization. The patient recovered from accidental overdose 2 to 3 days after the onset of the event. Action taken with JURNISTA 16 mg was unknown.

5.3.2.3 Medication Error/Maladministration

During the reporting period (22 December 2004 through 21 December 2008), 9 cases described situations in which JURNISTA tablets were split or crushed prior to administration (maladministration). Two cases involved health care professionals who either split or recommended that the patient split JURNISTA tablets prior to administration, while another case involved a patient, who was a physician, who divided half of a tablet and ingested half of the crumbs. None of the patients in these cases reported SAEs, and all of the AEs reported in association with the medication error/ maladministration are listed in the JURNISTA CCDS. In reviewing additional fatal cases that occurred after 21 December 2008 (and up through 21 August 2009), one additional case of a patient chewing a tablet was reported. This patient was a 40-year-old male with metastatic cancer of the liver and small pelvis, and final stage testicular cancer. This case is discussed in Section 5.3.1.1. Five cases reporting inappropriate schedule of drug administration: all involved patients who were prescribed or who took JURNISTA more than once daily, and are described below. Both in the Dosage and Administration section of the J&J CCDS, as well as in various sections throughout the proposed EXALGO label, it is indicated that EXALGO should be given once every 24 hours or once daily.

In 2 cases reporting an inappropriate administration schedule, no AEs were experienced. One case additionally reported insufficient efficacy, which is listed in the JURNISTA CCDS along with inappropriate schedule of drug administration. One case involved drug exposure during pregnancy, and reported an AE of diabetes mellitus in a patient with a family history of diabetes. Intrauterine growth retardation was also reported. This event may also have been due to the patient's diabetes, or to concomitant use of confounding medication (anti-epileptic therapy). The final case of 'inappropriate schedule of drug administration' reported decreased respiratory rate, sopor, and miosis, which may have

also been due to the administration of melperone hydrochloride following the second dose of JURNISTA.

Another case involved a patient who took more than 1 daily dose of JURNISTA; however, it was classified as a general medication error, (i.e., the event 'inappropriate schedule of drug administration' was not used). The patient ingested 3 doses instead of 1, but did not experience any additional events.

The single case of accidental exposure reported opioid-related events, which could have been possibly due to the concomitant use of oxycodone/naloxone and hydromorphone hydrochloride.

These cases highlight the importance of following the proposed product labeling, which states that EXALGO tablets should be swallowed whole and are not to be broken, chewed, dissolved, crushed or injected.

5.3.3 Comparison with Clinical Safety Profile

The JURISTA post-marketing safety data did not identify any new safety signal or issue, other than the changes that were made to the CCDS described in Section 5.2. The post-marketing safety profile for JURNISTA is similar to the safety profile observed during clinical research. As with all opioids, patients with pre-existing conditions such as decreased pulmonary function, GI disorders, and seizure activity, should be monitored carefully since EXALGO might exacerbate these pre-existing conditions.

5.4 Evidence of Abuse/Diversion in Any Country

A European Risk Management Plan (EU-RMP) for JURNISTA was developed by ALZA Corporation, J&J PRD, and its European subsidiary, Janssen-Cilag. This RMP includes a Pharmacovigilance Plan, as well as the following Risk Minimization Action Plan (RiskMAP) activities: Supply Chain Integrity, Manufacturing Quality Controls, Launch Activities, and an Educational Program.

In accordance with this EU-RMP, various safety monitoring activities have been implemented as of the date of the launch of the product in the first EU country (Germany, August 2006). The pharmacovigilance plan is comprised of routine surveillance using the safety database, which identified no interval changes in the reporting frequency of individual AEs during any of the 6-monthly review periods since the implementation of the EU-RMP pharmacovigilance plan in August 2006. Additionally, no spontaneous reports involving JURNISTA were found in queries of the WHO Vigibase during the same period. Based on review of data from pharmacovigilance and RiskMAP activities described in the EU-RMP, no new safety concerns were identified with the use of JURNISTA during the review period.

There were 26 publications (other than those reporting results from company-sponsored studies) which contained relevant, but not exclusive, safety information about hydromorphone, and were published during this reporting period. A review of this

literature did not reveal any meaningful evidence of abuse or deterrence in any country where JURNISTA is marketed.

6 ABUSE/MISUSE/DIVERSION

As with any other opioid analgesic, when prescribing EXALGO, care should be taken with regard to the potential for abuse and diversion. EXALGO contains hydromorphone, an opioid agonist similar to morphine, and is a Schedule II controlled substance. Opioid agonists have the potential for being abused, and are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Like other opioid agonists, legal or illicit, hydromorphone can be abused. This should be considered when prescribing or dispensing EXALGO tablets in situations where the HCP is concerned about an increased risk of misuse, abuse or diversion. Prior to treatment with EXALGO, all patients should be screened for their individual risk factors for abuse and addiction. All patients treated with EXALGO require careful monitoring for signs of abuse and addiction.

6.1 Evaluation of Cases of Possible Misuse/Abuse (Including Drug Accountability)

6.1.1 Reports of Abuse, Misuse, and Diversion in Clinical Trials

Based on discussions with the FDA, Neuromed undertook a review of the Clinical Study Reports (CSRs) for previous controlled and uncontrolled studies of EXALGO in patients with chronic pain to identify cases of lost, stolen, diverted, misused/abused, or overused/overdosed study drug. For a majority of the studies, these events were evaluated by previous sponsors. Tabulations were made based upon the verbatim events reported by the investigators. Table 18 summarizes the identified cases from the individual CSRs.

Among the patients treated with EXALGO in the controlled and uncontrolled studies, there were 8 reported cases of drug loss, 9 reported cases of drug being stolen, and 10 reported cases of drug diversion. There were also 13 reported cases of misuse or abuse, and 4 reported cases of overuse or overdose. The frequency of those evaluated cases was relatively low, and provided no obvious signal for potential misuse or abuse of EXALGO within the controlled and uncontrolled studies included in the NDA.

Table 18 Summary of Evaluated Cases of Possible Misuse/Abuse Included in the Final Study Reports for the EXALGO Controlled and Uncontrolled Studies

Patients Treated with EXALGO	Patient Type	Study Duration	Potential Cases [a]				
			Drug Lost	Drug Stolen	Diversion	Misuse/ Abuse	Overuse/ Overdose
OROS-ANA-3001							
254	Chronic OA	1 y			No data		
M03-644-05							
649	Chronic OA	~17 wk	0	0	1	4	0
DO-104							
127	Cancer	20-60 d	0	0	0	0	0
DO-105							
336	Non-cancer	20-60 d	0	0	0	0	0
DO-127							
207	Chronic LBP	33-49 d	0	0	3	4	1
DO-127X							
113	Chronic LBP	6 mo	0	0	2	2	0
DO-132							
71	Chronic OA	~6 wk	0	0	2	0	0
DO-118							
77	Cancer	12-24 d	0	0	0	0	0
DO-118X							
68	Cancer	1 y	0	0	0	0	0
DO-119							
74	Chronic Pain	2-4 wk	0	0	0	1	0
DO-109							
388	Cancer and non-cancer	1-2 y	0	8	0	2	3
NMT 1077-301							
447	LBP	14-16 wk	8	1	2	0	0
Total: 2811	(N/A)	(N/A)	8	9	10	13	4

d=day(s); LBP=lower back pain; mo=month(s); N/A=not applicable; OA=Osteoarthritis; wk=week(s); y=years.
[a] Identified as reported events within CSRs

6.2 Reports of Abuse Potential or Misuse in Post-marketing Data

There were 2 cases of abuse and 9 cases of misuse that were reported during the post-marketing period of 22 December 2004 through 31 December 2008 (note that this period includes spontaneous post-marketing cases for JURNISTA, as well as some serious clinical trial reports, since although the product was first marketed only in August 2006). These cases are discussed in Section 5.3.2.2.

7 RISK EVALUATION AND MITIGATION STRATEGY (REMS): EXALGO ALLIANCE PROGRAM

Neuromed is proposing a Risk Mitigation and Evaluation Strategy (REMS) to ensure that the benefits of EXALGO outweigh the risks. The risk mitigation program is termed Exalgo Alliance (The Alliance for Responsible EXALGO Prescribing and Use). Exalgo Alliance is designed to ensure that prescribers, pharmacists, and patients understand the benefit-risk profile and responsible use and handling of EXALGO, and that only appropriate patients receive EXALGO. Exalgo Alliance is a controlled access program for dispensing EXALGO only to patients under safe use conditions and includes education and outreach to health care professionals and to patients.

Upon FDA approval of the NDA, the commercialization of EXALGO and the implementation of the REMS will be the responsibility of Covidien. Covidien will be commercially detailing only to prescribers who are experienced with prescribing multiple agents in the long acting opioid class. The Covidien REMS Oversight Committee (ROC) plans rigorous safety surveillance and monitoring, and a continuous improvement process to ensure that the REMS is effectively meeting its goals. Covidien will employ their standard operating procedures for signal identification, detection, and processing. The REMS Safety Monitoring Board (RSMB) which includes external experts in opioid safety, pharmacovigilance and risk management will provide independent assessment and recommendations regarding effective mitigation strategies.

EXALGO will only be available through the Exalgo Alliance program. Prescribers who are authorized to prescribe Schedule II drugs can only prescribe EXALGO after they have enrolled in Exalgo Alliance by acknowledging their understanding of EXALGO risks and agreeing to follow responsible EXALGO prescribing practices and other program requirements.

EXALGO can only be dispensed by enrolled pharmacies and other healthcare settings that are authorized to dispense Schedule II drugs. To become enrolled, a pharmacy representative must acknowledge understanding of EXALGO risks. They agree to responsible dispensing and use, as well as to follow the requirements of Exalgo Alliance. Wholesalers and distributors must agree to sell EXALGO only to enrolled pharmacies and healthcare settings.

EXALGO can only be used to treat patients who are enrolled in Exalgo Alliance. They must sign an agreement with their prescriber acknowledging they understand the risks and will adhere to responsible use and handling, as well as the requirements of Exalgo Alliance. Safe use conditions will be verified every time a prescription is presented. The pharmacist must verify that both the prescriber and the patient are enrolled in Exalgo Alliance, indicating they are following the program requirements. The implementation system will be monitored for program performance and stakeholder compliance. Covidien will employ comprehensive monitoring and surveillance processes to evaluate the program and take corrective actions as appropriate.

7.1 Potential Risks Associated with EXALGO

Exalgo Alliance will address the primary risks of overdose, abuse and diversion.

7.1.1 Risks of Overdose

As is the case with the use of all opioids, individuals using EXALGO who are opioid non-tolerant are at increased risk for clinically significant and life-threatening AEs such as respiratory depression. EXALGO must not be used by opioid non-tolerant individuals. Patients considered opioid tolerant are those who are taking at least 60 mg of oral morphine per day, or at least 30 mg of oral oxycodone daily, or at least 12 mg oral hydromorphone daily, or an equianalgesic dose of another opioid, for one week or longer. By restricting the use of EXALGO to those already taking opioid products for a sufficient timeframe at sufficient levels, the risk of serious outcomes such as respiratory depression may be minimized.

Patients will be instructed to take EXALGO exactly as prescribed, including taking no more than their prescribed dose of EXALGO, even if they think the drug is not working. Patients will also be instructed to avoid drinking alcohol while taking EXALGO since the combination can increase the respiratory depression effect and possibly lead to serious adverse events or death.

The risk of serious consequences due to accidental exposure to EXALGO is an important consideration for opioid-naïve patients, especially in children. The risk of serious or fatal consequences from accidental exposure to opioids like EXALGO is well-known, and epidemiologic evidence indicates that accidental ingestions occur primarily in children. Therefore, strong messages are included in all Exalgo Alliance materials describing these risks and appropriate actions to minimize risk. Therefore, strong messages are included in all Exalgo Alliance materials describing these risks and appropriate actions to minimize risk. EXALGO should not be given to anyone other than the individual for whom it is prescribed. Patients will be instructed to prevent use by others and to keep EXALGO tablets in a secure place out of the reach of children.

7.1.2 Risks of Abuse and Diversion

Hydromorphone is a potent opioid analgesic with demonstrated real-world abuse; the rate of abuse or abuse potential of hydromorphone is similar to that of other mu agonist opioids. Due to the abuse potential of hydromorphone, EXALGO will be labeled, regulated, and listed as a Schedule II opioid. Prescribers will be instructed to use caution in prescribing EXALGO to patients who may be at risk for abuse. Patients should be assessed for their clinical risks for opioid abuse or addiction before being prescribed EXALGO. As required for all patients who are prescribed Schedule II medications, patients receiving EXALGO should be routinely monitored for signs of misuse, abuse, and addiction. In addition to screening, prescribers will be instructed to employ best practices in management of pain in patients taking EXALGO. This will include universal precautions and guidelines: triaging of patients according to risk factors, stratifying patients according to risk category, initiating treatment strategies that match the risk

category, and monitoring patients and changing the treatment strategy if they move from one risk category to another. Resources will be available for prescribers regarding responsible opioid prescribing and use to identify, treat and monitor patients at risk for abuse through the ExalgoAlliance.com Resource Center.

7.2 Goals of Exalgo Alliance

The primary goals of the Exalgo Alliance program are:

- Prescribers, pharmacies and patients should understand EXALGO risks as well as responsible prescribing and use;
- EXALGO should only be used in opioid-tolerant patients;
- Overdose of EXALGO should not occur;
- Abuse and diversion of EXALGO should not occur;
- Unintended or accidental exposure to EXALGO should not occur.

7.3 Program Objectives to Meet the Exalgo Alliance Goals

In order for prescribers, pharmacists, and patients to understand EXALGO risks and prescribe, dispense, and use EXALGO appropriately, the objectives of Exalgo Alliance are to:

- Educate prescribers and pharmacists on responsible EXALGO prescribing, dispensing and use including
  - the risk-benefit of EXALGO
  - appropriate patient selection
  - proper dosing and administration
  - safe use, handling and disposal
  - patient counseling
- Educate patients on responsible EXALGO use including
  - the risk-benefit of EXALGO
  - proper dosing and administration
  - safe use, handling and disposal
- Enroll all stakeholders in the Exalgo Alliance program to ensure stakeholder
  - has received education
  - understands the risks of EXALGO and responsible prescribing , dispensing, and use
  - agrees to follow safe use procedures and other program requirements

- Ensure that wholesalers and distributors only sell EXALGO to enrolled pharmacies and healthcare settings
- Ensure EXALGO is dispensed only by enrolled pharmacies only to enrolled patients who have a prescription from an enrolled prescriber.
- Ensure appropriate supply chain controls are in place and maintained to prevent the diversion of EXALGO;
- Ensure that adequate education, surveillance, and interventions are instituted and maintained to minimize EXALGO risk;

7.4 The Exalgo Alliance Program

Exalgo Alliance is a controlled access system to ensure proper distribution, prescribing, dispensing and use. This program focuses on four critical aspects:

- education and counseling through labeling and communication materials;
- elements to assure safe use;
- an implementation system;
- comprehensive program assessment with continuous process improvement.

7.4.1 Labeling

7.4.1.1 Prescribing Information

The EXALGO PI communicates information about mitigating the risks of overdose, abuse and diversion. The EXALGO PI also provides information about the Exalgo Alliance program and instructions for prescribers, pharmacies/healthcare settings, and patients about how to enroll. The EXALGO PI is attached to each bottle. The PI is also provided with all educational material for healthcare professionals. Healthcare professionals may access the EXALGO PI through the ExalgoAlliance.com website.

There is specific language within the PI that refers to the Exalgo Alliance program, indicating that EXALGO is available only through the Exalgo Alliance™ program. Additional Exalgo Alliance program details are provided in the Warnings and Precautions Section 5.13 of the Full Prescribing Information. This section of the PI is provided below.

Warnings and Precautions [Excerpt from PI]

5.13 Exalgo Alliance Program

EXALGO is available only through the Exalgo Alliance program. The purpose of this program is to evaluate and mitigate the risks of overdose, abuse and diversion. The program is designed to ensure that only appropriate patients receive EXALGO. The program is designed to ensure that prescribers, pharmacists, and patients understand the risk-benefit profile and appropriate use and handling of EXALGO.

Under the Exalgo Alliance Program, only wholesalers, prescribers, pharmacies, and patients enrolled in the program are able to distribute, prescribe, dispense, or receive EXALGO. Please contact the Exalgo Alliance Program Contact Center at 1-XXX-XXX-XXXX or via the website at ExalgoAlliance.com for detailed information.

Prescriber Information

To enroll in the Exalgo Alliance program, prescribers must be educated to understand (1) the risks of opioids and responsible opioid prescribing and use; (2) EXALGO risks; (3) responsible EXALGO prescribing and dispensing; (4) safe EXALGO use and handling.

Prescribers are required to:

- Ensure each patient is opioid-tolerant and understands EXALGO risks and safe use and handling
- Ensure the patient has reviewed the Medication Guide
- Enroll the patient into the Exalgo Alliance Program

Patient Information

Patients should be fully counseled by their physician and pharmacist on and understand the risk-benefit profile and EXALGO safe use and handling before an initial prescription is written.

Patients who are prescribed EXALGO must be instructed to:

- Read the Medication Guide
- Not use EXALGO for short-term pain relief from injuries or surgery
- Keep EXALGO in a safe place away from children and from anyone whom has not been prescribed EXALGO
- Always protect EXALGO from theft or misuse at home or at work

Pharmacy Information

To enroll in the Exalgo Alliance program, pharmacists must be educated to understand (1) the risks of opioids and responsible opioid prescribing and use; (2) EXALGO risks; (3) responsible EXALGO prescribing and dispensing; (4) safe EXALGO use and handling.

Pharmacists are required to:

- Verify that each patient presenting a prescription is eligible to receive EXALGO
- Provide counseling to patients on EXALGO safe use and handling prior to dispensing any EXALGO prescription
- Provide the Medication Guide and instruct the patient to read it.

7.4.1.2 Bottle Labeling

The program information is reinforced to the pharmacist on the package labeling. The bottle label contains important reminders that the pharmacist must

- Verify prescription eligibility
- Dispense only to opioid-tolerant patient
- Provide a Medication Guide, and
- Counsel the patient

These messages are shown together with instructions for patients on appropriate use and handling. Counseling messages include

- EXALGO is for once daily use
- Tablets should be swallowed whole and not broken, crushed, chewed, dissolved or injected
- EXALGO should be dispensed in a childproof container with directions to keep out of reach of children

7.4.2 Medication Guide

A Medication Guide is labeling directed to patients, and should be used by prescribers and pharmacists as a tool to support patient counseling. The EXALGO Medication Guide will educate patients on the risks of EXALGO as well as EXALGO responsible use and handling procedures. The information is provided in language written at a level intended to enhance patient comprehension. The prescriber should review the EXALGO Medication Guide with the patient before they both sign the Exalgo Alliance Patient Enrollment Form, which includes a prescriber-patient medication agreement.

The EXALGO Medication Guide must be provided by the pharmacy with each EXALGO dispensed prescription in compliance with 21 Code of Federal Regulations §208.24. Covidien will provide Medication Guides to pharmacies enrolled in the Exalgo Alliance program so that the pharmacies can provide a Medication Guide with each dispensed EXALGO prescription. Medication Guides are provided in sufficient quantities shipped to each pharmacy with each order from the wholesaler or distributor. All pharmacies enrolled in the Exalgo Alliance program must agree to provide a Medication Guide each time EXALGO is dispensed and to counsel the patient to read it because information may have changed.

In addition, the EXALGO Medication Guide is provided as an attachment to the Exalgo Alliance program introductory letters sent to each stakeholder group. The Medication Guide can also be accessed through the program website, ExalgoAlliance.com.

7.4.3 Educational Communication to Healthcare Professionals

Education and outreach materials inform key stakeholders of the EXALGO risk-benefit profile and responsible use and handling of EXALGO. These materials also provide information about the Exalgo Alliance program, including direction on healthcare professional (HCP) enrollment, patient enrollment, and verification of prescription eligibility. Educational communications are directed to prescribers, and pharmacies/healthcare settings as well as to other stakeholders such as wholesalers and distributors, leadership of professional societies and patient advocacy groups, pharmaceutical compendia, and the Drug Enforcement Administration (DEA).

Education and outreach will occur via multiple media including print materials (letters, program brochures, and other program and enrollment material), web-based information (ExalgoAlliance.com), and personal communications (live meetings, webinars, and live or telephone interactions with Covidien or Exalgo Alliance Contact Center personnel).

Table 19 below provides an overview of the education and communication tools that will be utilized for each audience.

Table 19 Educational Components

Educational Components	Prescribers	Pharmacists	Patients	Other
Prescribing Information	X	X		
Bottle Label		X		
Medication Guide			X	
Prescriber Program Brochure	X			
Prescriber Introductory Letter	X			
Pharmacy Introductory Letter		X		
Wholesaler Introductory Letter				X
Pain Care Center of Excellence Introductory Letter	X			X
Association Introductory Letter	X	X	X	X
Pharmaceutical Compendia Introductory Letter		X		X
DEA Introductory Letter				X
Prescriber Education Slide Deck	X			
Pharmacy/Healthcare Setting Education Slide Deck		X		
Patient Program Brochure			X	
Resource Center (websites)	X	X	X	X
Pharmacy Guide		X		
Toll-free number	X	X	X	X

The educational elements of the Exalgo Alliance program are discussed in the sections below.

7.4.3.1 Education and Awareness for Healthcare Professionals

7.4.3.1.1 Introductory Letters

The Prescriber Introductory Letter will be available to healthcare professionals at the ExalgoAlliance.com website at product launch along with other Exalgo Alliance program educational materials. The Introductory Letter will also be mailed to selected prescribers upon EXALGO launch. The mailing list includes prescribers who are in the highest deciles of prescribing long-acting opioids or hydromorphone IR and are, therefore, likely to consider prescribing EXALGO.

A similar introductory letter will be directed to pharmacies and other healthcare settings and institutions where EXALGO may be dispensed. The Pharmacy Introductory Letter will be available to pharmacists via the Exalgo Alliance Program website at product launch along with other Exalgo Alliance program educational materials. The Introductory Letter for pharmacies and healthcare settings will be mailed to selected pharmacies and healthcare settings upon EXALGO launch. The selected pharmacies include pharmacies that dispense long-acting opioids and hydromorphone IR.

Introductory letters will also be sent to other stakeholder groups such as wholesalers and distributors, leadership of associations (i.e., professional societies and patient advocacy groups), pharmaceutical compendia, and the DEA. These letters contain information about EXALGO risks and the Exalgo Alliance program.

7.4.3.1.2 Exalgo Alliance Program Website

The Exalgo Alliance program website (ExalgoAlliance.com) contains information about the Exalgo Alliance program and serves as one method by which prescribers can enroll themselves and their patients in the Exalgo Alliance program. Pharmacies can also use the site for education and enrollment. The site includes the enrollment forms and educational tools that must be reviewed before enrolling. The website is referenced in all Exalgo Alliance-related materials. It also serves as a resource for:

- Ordering all Exalgo Alliance educational materials (e.g., slides, CD-ROM, DVD);
- Obtaining a schedule of Exalgo Alliance educational activities;
- Locating pharmacies that are enrolled in the Exalgo Alliance program, including a map and search functions;
- Information on responsible opioid prescribing.

7.4.3.1.3 Prescriber and Pharmacy/Health Care Setting Educational Modules

The Exalgo Alliance Prescriber Education Slide Deck and Exalgo Alliance Pharmacy / Healthcare Setting Education Slide Deck are the primary tools for educating prescribers

and pharmacies/health care settings about EXALGO and the Exalgo Alliance program. These modules are slide presentations that contain information on (1) risks of opioids and responsible opioid prescribing and use, including universal precautions; (2) EXALGO risks; (3) responsible EXALGO prescribing and dispensing; as well as (4) responsible EXALGO use and handling. The education modules also include information for prescribers on how to enroll patients and information for pharmacies and healthcare settings on how to verify prescription eligibility. These educational modules will be available online (ExalgoAlliance.com) at the time of enrollment and for in-person training.

7.4.4 Education and Awareness for Patients

Patient education is first presented during the doctor's visit by the physician, nurse, or physician assistant. Prescribers will be provided with the Medication Guide and materials to use in counseling patients. The prescriber will review the product risks outlined in the Medication Guide along with the Exalgo Alliance Patient Program Brochure, and will discuss enrollment in the Exalgo Alliance program. Together, the prescriber and the patient will review and sign the Prescriber-Patient Medication Agreement included on the enrollment form. This Agreement ensures interactions between prescribers and their patients concerning this important risk minimization program. Once enrolled, the patient will be assigned a Patient Identification Number (PIN) that will be provided on the Exalgo Alliance Patient ID Card.

The patient will also be counseled on responsible use and handling by the pharmacist at each EXALGO dispensing when they receive the Medication Guide. The Patient Program Brochure will be available for distribution by the prescriber or through the program website. The brochure provides additional information to patients and caregivers about EXALGO risks and shows the steps that a patient must follow in Exalgo Alliance. It also reinforces the Medication Guide information by repeating the box warning, the most important information that a patient must know, and counseling messages on responsible handling and disposal of EXALGO.

The specific messages included in the communication materials are shown in Table 20 for the key risks of overdose, accidental exposure, abuse and diversion.

Table 20 Communication Messages for Key Risks

Messages	Overdose	Accidental exposure	Abuse and diversion
Risk of overdose	√	√	√
Opioid-tolerant patients only	√		
Not for short-term or acute pain	√		
Not for PRN treatment of pain	√		
Do not break, crush, chew, etc	√	√	√
Does not work immediately	√		
Take exactly as prescribed	√		√
Keep tablets in secure place	√	√	√
Keep away from children		√	
Store in childproof container		√	
Use by child is emergency		√	
Seek help immediately		√	
Immediate and proper disposal	√		√
Protect from theft			√
Screen for risk of abuse			√
Monitor for abuse			√

7.4.5 Program Material Assessment

Program materials are a critical component of the Exalgo Alliance. To assess the effectiveness of the REMS post approval, it is essential to evaluate that the materials adequately communicate the core REMS messages to each individual stakeholder prior to approval. Neuromed Pharmaceuticals, Ltd, contracted a third-party research group to conduct an independent assessment of the REMS program materials. A qualitative research study was fielded in July and August, 2009 in 3 cities (Washington, DC, New York, NY and Chicago, IL). The overall goal of the research was to determine if the product core safety messages and the REMS program requirement messages are clear, concise and easy to understand for prescribers, pharmacists and patients. The research involved a series of qualitative evaluations with these key stakeholders of the following REMS program materials* (i.e., Medication Guide, Prescriber-Patient Medication Agreement, Education Modules, Enrollment Forms and Program Brochures) to:

- Assess understanding of the risk/benefits, safe use and handling of Exalgo and the program requirements of Exalgo Alliance
- Identify confusing and/or missing information

* It should be noted that all of the materials were modified to maintain the anonymity of EXALGO (referred as Product X) and the Exalgo Alliance Program (referred as REMS Program).

- Elicit comments for how the material could be improved to enhance retention and communication of necessary information

The design of the study was to conduct Individual Depth Interviews (IDIs) with stakeholders lasting approximately 45-60 minutes. The breakdowns of the IDIs are as follows:

- 20 Prescribers (Anesthesiologists, Pain Management Doctors, Physiatrists, Oncologists and Primary Care Physicians focused in pain management)
- 12 Pharmacists (both independent and chain)
- 15 Patients (cancer, low-back and osteoarthritis patients)

The results of the research showed that all of the stakeholders understood the core safety messages for EXALGO and the program requirements associated with Exalgo Alliance. The research provided insight regarding the roles and responsibilities associated with prescribing, dispensing and use of EXALGO by each stakeholder. In addition, the research suggested enhancements to be included in the following Program Materials, "What is the most important information I should know about Exalgo?" in the EXALGO Medication Guide; additional messages to be added to the acknowledgement statements in the Prescriber-Patient Medication Agreement, Prescriber Enrollment Form and the Pharmacy Enrollment Form, as well as enhancements to the Educational Modules for Healthcare Professionals (Please see proposed enhancements indicated on the enrollment forms). Finally, a quantitative assessment is ongoing to provide a more formal evaluation regarding the effectiveness of the REMS program materials.

7.5 Elements to Assure Safe Use

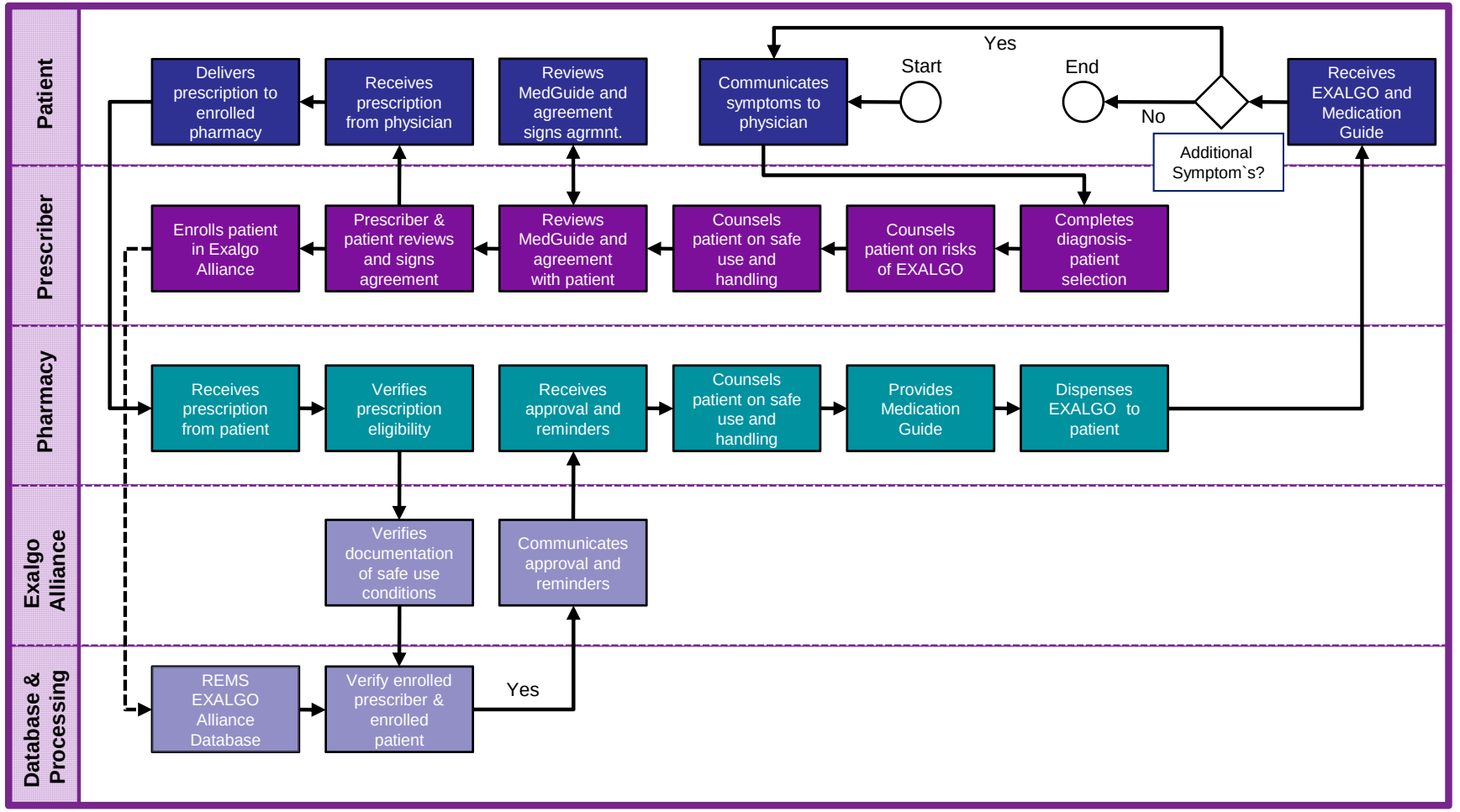
The program includes the following elements to assure the safe use of EXALGO:

- Wholesalers and distributors warehousing and distributing EXALGO will contract with Covidien to participate in the program. Wholesalers and distributors must agree to sell and distribute EXALGO only to enrolled pharmacies or healthcare settings.
- All pharmacies and healthcare settings that intend to purchase and dispense EXALGO must be enrolled in the Exalgo Alliance program after being educated on the goals and objectives of the program and acknowledging the understanding of EXALGO risks and responsible dispensing and use. Pharmacy and healthcare setting enrollment also includes acknowledgement by the pharmacist-in-charge, authorized corporate pharmacy representative or designated healthcare setting representative to educate all critical employees on the goals and objectives of the program and the risks of EXALGO and responsible dispensing and use.
- All prescribers who intend to prescribe EXALGO must enroll in the program prior to treating any patient with EXALGO. Enrollment includes prescriber education on the goals and objectives of the program and prescriber acknowledgement of the understanding of EXALGO risks and responsible prescribing and use.

- All appropriate patients who, in consultation with their prescribers, elect to be treated with EXALGO must have documentation of safe use conditions (i.e., patients must be educated on the risks and appropriate use of EXALGO in conjunction with a Prescriber-Patient Medication Agreement (PPMA) and enrolled in the Exalgo Alliance program) prior to receiving their first prescription. Enrollment involves signing a Patient Enrollment Form, which includes the PPMA. The signed enrollment form will be maintained by the prescriber in the patient chart. If a patient is unable to provide acknowledgement, the caregiver for the patient will consult with the prescriber and provide acknowledgement on the patient's behalf.
- All pharmacies and healthcare settings must obtain verification of prescription eligibility prior to each dispensing. Prescription eligibility verification is based on both the prescriber and patient being enrolled in the Exalgo Alliance Program.

The process flow for enrolling key stakeholders in the Exalgo Alliance program is shown in Figure 12.

Figure 12 Process of Elements to Assure the Safe Use of EXALGO



The overall process to ensure safe use of EXALGO includes:

- Education and enrollment of the prescriber;
- Prescriber diagnoses and educates patients, along with documentation of safe use acknowledgement and enrollment of patients into the Exalgo Alliance program;
- Presentation of prescription and patient ID number at a pharmacy enrolled in the Exalgo Alliance program;
- Pharmacist verification of prescription eligibility based on prescriber and patient enrollment;
- Pharmacist counseling of patient prior to dispensing prescription;
- Patient obtaining EXALGO prescription along with the current Medication Guide.

7.5.1 Exalgo Alliance Program for Prescribers

Healthcare professionals who have proper DEA registration and who want to prescribe EXALGO will be required to enroll into the Exalgo Alliance program and re-enroll annually. Prescribers will remain active unless a corrective action requires inactivation.

The Exalgo Alliance program will be presented on the ExalgoAlliance.com website. Prescribers who are unable or unwilling to access the website may enroll through the Exalgo Alliance Program Contact Center. Prescribers must acknowledge the statements shown in Table 21. Upon initial activation, prescribers will remain active until a corrective action of inactivation occurs or expiration of the enrollment period.

Table 21 Prescriber Enrollment into the Exalgo Alliance program

Prescribers will acknowledge the following:

- I have been educated and I understand the EXALGO risk-benefit profile as well as responsible opioid and EXALGO prescribing and use
- I have read and I understand the EXALGO full Prescribing Information and Medication Guide
- I understand that, like all strong opioids, EXALGO can be abused and this should be considered whenever prescribing or dispensing EXALGO
    - I understand that all patients should be screened according to their risk factors for abuse and diversion
    - I understand that all patients treated with EXALGO require careful monitoring for signs of abuse
- I understand that EXALGO is only approved by the FDA for the treatment of moderate to severe pain in opioid-tolerant patients requiring continuous, around-the-clock opioid analgesia for an extended period of time.
- I will prescribe EXALGO only after ensuring conditions for safe use including ensuring that each patient
    - is opioid tolerant
    - has moderate to severe pain requiring continuous, around-the-clock opioid analgesia for an extended period of time
    - has been counseled about the risks, benefits, and appropriate use of EXALGO
    - has been counseled about the risk of overdose due to giving EXALGO to someone for whom it has not been prescribed
    - has been counseled that when treatment with EXALGO is begun, it may take several hours before EXALGO begins to work. Do not take an additional dose of EXALGO. Unless prescribed by your doctor, do not take another drug if EXALGO does not start working immediately. Wait for EXALGO to work.
    - has been counseled that EXALGO must be swallowed whole; do not break, crush, or chew. Taking a broken, crushed, chewed, dissolved or injected EXALGO tablet is very dangerous as you could receive the full daily dose too quickly.
    - has reviewed the Medication Guide
    - understands EXALGO risk-benefit and agrees to follow all instructions by signing the Exalgo Alliance Patient Enrollment Form
- I will enroll patients into the Exalgo Alliance program prior to prescribing EXALGO
- I understand that Covidien will be regularly evaluating compliance with Exalgo Alliance and that Covidien reserves the right to restrict my ability to enroll future patients or take other appropriate measures at any time if I fail to comply with the program requirements.

Prescribers may enroll online by completing the Exalgo Alliance Prescriber Enrollment Form. This form is included as part of Exalgo Alliance Prescriber Enrollment Kit and can also be printed from ExalgoAlliance.com completed and faxed to the Exalgo Alliance Program Contact Center.

7.5.2 Exalgo Alliance Program for Pharmacies and Healthcare Settings

Enrollment of pharmacies and healthcare settings into the Exalgo Alliance program requires that a designated individual at the pharmacy or healthcare setting enroll in the Exalgo Alliance program. Pharmacies may enroll online by completing the Exalgo Alliance Pharmacy Enrollment Form. Healthcare settings may enroll online by completing the Exalgo Alliance Healthcare Setting Enrollment Form. These forms are included as part of Exalgo Alliance Pharmacy/Healthcare Setting Enrollment Kit and can also be printed from ExalgoAlliance.com completed and faxed to the Exalgo Alliance Program Contact Center.

Pharmacies and healthcare settings will be re-enrolled every 24 months. Pharmacies and healthcare settings will remain active unless a corrective action requires inactivation. The pharmacy or healthcare setting must acknowledge the statements described in Table 22.

Table 22 Pharmacy and Healthcare Settings Enrollment into the Exalgo Alliance program

Pharmacies and healthcare settings will acknowledge the following:
• I have been educated and I understand the EXALGO risk-benefit profile as well as responsible EXALGO dispensing and use • I will educate all pharmacists and other staff involved in dispensing EXALGO using the Exalgo Alliance program materials. • I understand that, like all strong opioids, EXALGO can be abused and this should be considered whenever prescribing or dispensing EXALGO. • I understand that EXALGO is only approved by the FDA for the treatment of moderate to severe pain in opioid-tolerant patients requiring continuous, around-the-clock opioid analgesia for an extended period of time. • I or my designee agree(s): – to verify eligibility prior to dispensing or administering EXALGO – to provide counseling to patients on appropriate product use prior to dispensing any EXALGO prescription. ▪ EXALGO should be kept in a childproof container in a safe and secure place away from children and from anyone for whom it was not prescribed ▪ EXALGO should not be used for short term pain relief from injuries, from surgery, from occasional use or for acute or short term pain ▪ EXALGO should only be used by patients who are already regularly taking pain medicines around the clock for chronic pain and their body is used to taking these medicines ▪ EXALGO must be taken only once per day ▪ EXALGO must always be swallowed whole. Taking a broken, crushed, chewed, dissolved, or injected EXALGO tablet is very dangerous as you could receive the full daily dose too quickly – to provide a Medication Guide with each prescription and instruct the patient to read it • I understand that Covidien will be regularly evaluating compliance with Exalgo Alliance and that Covidien reserves the right to restrict my ability to dispense EXALGO or take other appropriate measures at any time if I or my staff fails to comply with the program requirements.

EXALGO will only be distributed to enrolled pharmacies/healthcare settings through approved wholesalers. Pharmacies/healthcare settings may enroll online by completing the Exalgo Alliance Program Pharmacy/Healthcare Setting Enrollment Form. This can also be printed from ExalgoAlliance.com, completed and faxed to the Exalgo Alliance Program Contact Center or the enrolling pharmacist may call the Contact Center directly to enroll.

7.5.3 Exalgo Alliance Program for Patients

Prior to receiving their first prescription of EXALGO, patients must be educated on the risks and appropriate use of EXALGO and sign the Exalgo Alliance Patient Enrollment Form. Patients will be reminded that opioids are categorized as federally controlled substances because they can lead to dependence or be abused, and that selling or giving away opioid medicine is against the law.

The specific requirements which the patient must acknowledge are shown in Table 23. Patients will be re-enrolled (including re-counseling, review of the Medication Guide, and completion of a new Prescriber-Patient Medication Agreement) annually or following substantial changes to the Exalgo Alliance Program. Substantial changes may include:

1. Changes in operations of the program that affect the manner in which eligible patients are identified and screened for enrollment

2. Changes to the Medication Guide that require modification of educational materials

3. Changes that modify the operations of the Exalgo Alliance program in a way that changes the program procedures for the patients.

Table 23 Patient Enrollment into the Exalgo Alliance program

Patients must acknowledge:
• I have read and understand the Medication Guide for EXALGO • My doctor explained the risks and benefits of using this medicine • My doctor explained that when I start taking EXALGO I should already be regularly taking opioid pain medicines around the clock for my constant pain and my body is used taking these medicines • My doctor explained that EXALGO should not be used for short-term pain relief from injuries, surgery, for occasional ("as needed") use, or for acute or short-term pain • My doctor explained that EXALGO must be taken exactly as prescribed, including o EXALGO must be taken only once per day o EXALGO must be swallowed whole; do not break, crush, or chew. Taking a broken, crushed, chewed, dissolved or injected EXALGO tablet is very dangerous as I could receive the full daily dose too quickly o The initial dose of EXALGO may take several hours to begin working. I must not take an additional dose of EXALGO. • My doctor explained that EXALGO should be kept in a childproof container in a safe and secure place away from children and from anyone for whom it was not prescribed • I asked my doctor any questions I had about using EXALGO and received answers • I must be reenrolled in the Exalgo Alliance program annually to keep receiving EXALGO

7.5.4 Drug Dispensing and Supply Chain

EXALGO is a Schedule II prescription opioid analgesic and will be dispensed to patients only in a DEA-regulated setting. All movements of Schedule II products in the supply chain are regulated by the DEA. Movements of Schedule II drugs from a research setting to the manufacturer, then to the distributor, and finally to the retail pharmacy are accompanied by submission of a DEA Form 222, which indicates how much of the Schedule II substance is being moved, where, and when.

Covidien will establish contracts with distributors. The contract will stipulate that the distributor must restrict shipments only to pharmacies enrolled in the Exalgo Alliance program and abide by applicable laws and regulations. The contract will also stipulate that distributors will provide data to Covidien including information on shipment to enrolled pharmacies. Table 24 describes the requirements for wholesalers and distributors for Schedule II products.

Table 24 Requirements for Wholesalers and Distributors

Wholesalers and distributors
• Distribute or exporting manufacturers, distributors, importers, and exporters of List I chemicals are also required to: o Register with DEA (21 USC. § 822 (a)(1) and 21 CFR §1309.21), and o Provide controls and procedures to guard against theft and diversion. • It is the responsibility of the manufacturers to ensure that all their direct purchasing customers are properly registered with the DEA. • DEA laws and regulations also require regulated persons (manufacturers, distributors, importers, and exporters of listed chemicals) to implement measures that prevent diversion by: o Obtaining proof of identity from their customers (21 USC. § 830 (a)(3) and 21 CFR §1310.07) o Maintaining retrievable receipt and distribution records (21 USC. § 830 (a) and 21 CFR Part 1310) o Reporting to the DEA any suspicious orders (21 USC. § 830 (b)(1) and 21 CFR §1310.05 (a)(1)). The reports are required to be filed with the DEA ARCOS unit in the time and manner specified by the regulations (21 CFR 1304.33). o Exercising due diligence to avoid filling suspicious orders that might be diverted o Confirming the legitimacy of the order

Prescribers and pharmacists must follow specific processes when prescribing and dispensing a Schedule II product. Selected requirements are summarized in Table 25 below.

Table 25 Selected Code of Federal Regulation Requirements for Prescribing and Dispensing a Schedule II Product

Code of Federal Regulations for Controlled Substances
• Must be issued by written prescription only • Must be written in ink or indelible pencil or typewritten • May be faxed, but the original must be presented to the pharmacist before the drug is dispensed • Must be signed by the registrant and include his or her full name, address, and registration number • Must be dated and signed on the day issued • Must include the drug name, dose, dosage formulations, quantity prescribed, and directions for use • Emergency verbal prescriptions must be confirmed within • 72 hours and must be nonrefillable • Must not be restricted in terms of quantity or prescription expiration (state rules may apply)

7.6 Implementation System

The Exalgo Alliance program will be implemented through a controlled access program. The Implementation System includes the following:

- The Exalgo Alliance program will maintain a database of all enrolled prescribers, pharmacies and healthcare settings, and patients. The Exalgo Alliance program will also record wholesalers and distributors contracted to participate in the program;
- All pharmacies and healthcare settings must verify prescription eligibility prior to each dispensing of EXALGO. Eligibility verification is based on both the prescriber and patient being enrolled in the Exalgo Alliance program. The pharmacist will enter the prescriber DEA number and the patient ID number into the system at each dispensing. The system will provide the pharmacist with the name of the patient for verification against the prescription, with a reminder to verify patient identification. The system will confirm that both the prescriber and the patient are enrolled in Exalgo Alliance and that the prescription can be dispensed. If one or both are not enrolled, then the prescription cannot be dispensed and the pharmacist must reach out to the Contact Center for resolution. The NDC number of the EXALGO strengths dispensed is added to the system at each successful dispensing;
- Exalgo Alliance Program Contact Center will monitor distribution of EXALGO to determine whether EXALGO is being shipped only to enrolled pharmacies/healthcare settings who are approved to dispense EXALGO;

- Exalgo Alliance Program Contact Center will monitor prescriptions through secondary data sources to ensure that EXALGO is only dispensed from prescriptions written by enrolled prescribers.

7.7 Exalgo Alliance Assessment Plan

The Exalgo Alliance will undergo periodic review to evaluate the effectiveness of the strategies and tools in accomplishing the goals and objectives of the program. Covidien will propose revisions to the program based on thorough surveillance and evaluations.

7.7.1 Surveillance

Covidien is committed to monitoring the effectiveness of the Exalgo Alliance program. Covidien supports a number of passive and active surveillance systems to monitor the occurrences of fatal and nonfatal overdose, addiction, misuse, abuse, diversion of, and accidental exposure to EXALGO. Table 26 provides a list of surveillance tools and the risks that are addressed.

Table 26 Overview of Surveillance Tools

	Overdose			Abuse and Diversion			
Outcome/ behavior measured	Overdose	Accidental ingestion	Inappropriate prescribing	Misuse	Abuse	Teen abuse	Diversion
Covidien Pharmacovigilance[a]	☑	☑	☑	☑	☑	☑	☑
NAVIPPRO®							
ASI-MV Connect[a]					☑		☑
Adolescent ASI-MV (CHAT)[a]					☑	☑	☑
Internet monitoring (WIS)[a]				☑	☑	☑	
Media monitoring (MediaGRIID)[b]	☑	☑	☑	☑	☑	☑	☑
DAWN, Drug Abuse Warning Network-Live[b]	☑	☑		☑	☑		
Adverse Event Reporting System[b]	☑	☑	☑	☑	☑	☑	
American Association of Poison Control Centers AAPCC[b]	☑	☑		☑	☑	☑	☑
RADARS[a]	☑				☑	☑	☑
Knowledge, attitude, and behavior			☑	☑	☑		
Chart review study			☑				
Claims database[b]	☑		☑	☑			

[a] product-specific
[b] limited product specificity

7.7.1.1 Passive Surveillance

Important safety information can be identified through various voluntary and observational sources as part of Covidien's post-marketing surveillance. Continued

review and assessment of all data received from these sources will provide valuable insight into the EXALGO safety profile.

Spontaneous reports of AEs remain one of the most important ways to gather safety information about EXALGO. Spontaneous AE reports meeting the criteria for expedited reporting to the agency, as defined in 21 CFR § 314.80, as well as other reports designated as events of special interest, will be submitted to the FDA within 15 calendar days. All other reportable AEs will be submitted to the agency in the Periodic Safety Update Reports (PSURs). Table 27 indicates specific AEs that will be monitored.

Table 27 Covidien Post-approval Adverse Event Monitoring

Outcomes
• Death - All spontaneous and possibly related reports of death • Overdose - All overdose • Misuse, abuse, addiction, and diversion • All serious AE associated with suspected misuse • All AEs associated with manipulation of the tablet • All AEs associated with suspected abuse, addiction, and diversion • Inappropriate prescribing/medication errors • All non-accidental pediatric exposures associated with an AE (serious and non-serious) • All actual and potential medication error reports regardless of patient outcome • All AEs associated with use in opioid non-tolerant tolerant patients • All AEs associated with use in patients with acute or post-operative pain or "as needed" (prn) use • All AEs associated with HCP-directed manipulation of the tablet • Accidental exposures - All accidental exposures including asymptomatic reports (children and adults) o Non-accidental pediatric exposures that are not associated with an AE will be included in the quarterly report under off- label use. o Off- label use that does not fall into these categories shall be reported in the quarterly report under off- label use.

7.7.1.2 Active Surveillance Using Databases

Active surveillance systems require regular periodic collection of case reports from health care providers or facilities. The focus of active surveillance is on the events, settings, or drugs of interest and allows for collection of data more complete than that obtained by passive surveillance systems. Since no one system is likely to address all safety problems, multiple surveillance systems will be employed. These systems will include systems that follow a large number of patients exposed to the drug of interest after launch (drug-based), systems implemented in hospitals to detect relevant drug-related events (setting-based), and data for selected drug-induced diseases (disease-based).

Applicable setting-based system surveillance for EXALGO events will include the Drug Abuse Warning Network (DAWN), which is funded by substance abuse and mental

health services and collects data from multiple metropolitan areas (chart review of drug-related cases for individuals aged 6 to 97 years), and the Toxic Exposure Surveillance System (TESS) a poisoning surveillance database that has been maintained by the American Association of Poison Control Centers (AAPCC) since 1993 and collects data from 64 poison control centers in the US (serving nearly the entire US population). These surveillance systems provide information regarding events.

Table 28 describes the multiple systems and outcome measures to be used for active surveillance.

Table 28 Active Surveillance and Exalgo Alliance Assessment Methods

Abbreviation of Addiction Severity Index – Multimedia Version (ASI-MV):	
Description	**Outcomes**
A self-administered computer-based assessment given to patients entering addiction treatment that assesses specific outcomes related to abuse of prescription opioids	• Abuse of EXALGO™ • Route of administration if abused • Source, severity of problems: employment, medical, legal, drug and alcohol, psychiatric, and family/social
Teenage version of ASI-MV	
Description	**Outcomes**
A self-administered computer-based assessment given to patients entering addiction treatment that assesses specific outcomes related to abuse of prescription opioids	• Abuse of EXALGO™ • Route of administration if abused • Source, severity of problems: academic, medical, legal, drug and alcohol, psychiatric, and family/social
Web Informed Services (WIS)	
Description	**Outcomes**
A qualitative monitoring proprietary data source of internet discussions that provides a temporally sensitive "snapshot" of user knowledge and attractiveness of opioid products	• Opinions and knowledge regarding prescription opioid abuse, diversion, and attempts or instructions for defeating the extended-release system • Actions and information regarding the attractiveness of a product to the opiate-abusing population
RADARS™ (Researched Abuse, Diversion and Addiction-Related Surveillance System) - Key Informants	
Description	**Outcomes**
• Drug diversion investigators from across the US • Rural, urban, suburban areas • Key informant - clinician, epidemiologist, treatment counselor, other observer knowledgeable about new and emerging drug problems	• Diversion
RADARS™ -Law Enforcement	
Description	**Outcomes**
Drug diversion investigators from across the US	• Diversion

• Rural, urban, suburban areas
• Quarterly Survey
  • In the week following the end of a quarter, each informant is sent a survey
  • Number of new cases, dosage form and street price in which each drug is mentioned is documented by the informant
  • Survey is returned to Drug Diversion staff	

RADARS – Opioid/Methadone Treatment Programs	
Description	**Outcomes**

• 75 treatment centers which are members of the American Association for the Treatment of Opioid Dependence
• All new admissions are asked to complete a one page questionnaire anonymously
  • Opioid use (past month, lifetime, age at 1st use)
  • Primary opioid of abuse
  • Source of opioid drug
	• Abuse

RADARS – Impaired Healthcare Workers	
Description	**Outcomes**
• A subset of both the Drug Diversion and Key Informant systems • Informants are regulatory agencies, criminal justice systems, professional boards • Further details on methodology can be found in the Drug Diversion and Key Informant descriptions	• Abuse • Diversion
Legislative activity and law enforcement news	
Description	**Outcomes**
NAVIPPRO system for monitoring the media for stories pertaining to legislative activity involving drug abuse, controlled substances, prescribing of opioids, and other related topics. Additionally, staff member-based searches for articles about law enforcement events involving prescription opioids.	• Legislative activity involving prescription opioids • Law enforcement events involving prescription opioids
Food and Drug Administration Adverse Event Reporting System (FDA-AERS)	
Description	**Outcomes**
A database that provides not only comprehensive data on reports of adverse events associated with physician visits as well as consumer and pharmaceutical industry reports, but also allows for comparison of proportional reporting rates and empirical Bayes geometric means of adverse events among drugs.	• Death • Overdose (fatal and non-fatal) • Misuse, abuse, addiction, and diversion • Inappropriate prescribing • Medication errors • Accidental exposures/ingestion

Drug Abuse Warning Network (DAWN) Live	
Description	**Outcomes**
A public health surveillance system that monitors and assesses drug-related visits to hospital emergency departments and drug-related deaths investigated by medical examiners and coroners.	• Overdose (fatal and non-fatal) • Addiction • Abuse • Misuse • Accidental ingestion particularly in children • Inappropriate prescribing
(AAPCC) National Poison Data System (NPDS)-	
Description	**Outcomes**
An AAPCC-maintained national database of information logged by 64 poison control centers throughout the United States, including poisoning events and information on actual or potential exposures to substances including prescription drugs	• Accidental ingestion associated with EXALGO™ • Overdose (fatal and non-fatal) associated with EXALGO™

7.7.1.3 Knowledge, Attitude and Behavior Surveys

In addition to surveillance, it will be important to actively monitor ongoing feedback from prescribers, pharmacists and patients to determine outcome measures regarding the effectiveness of the Exalgo Alliance program education and communication. A series of surveys will be used to measure knowledge, attitudes and behaviors. Separate surveys will be targeted at prescribers, pharmacists and patients.

Representative samples of prescribers and patients will be surveyed periodically on their knowledge of the Exalgo Alliance program key risk messages and program requirements. The goal of this survey initiative will be to determine whether the Exalgo Alliance program is effective in educating about the key risk messages and the procedures to be followed in the Exalgo Alliance program.

All surveys will be conducted according to industry standards and will assess prescribers that have prescribed EXALGO. Structured questionnaire will be utilized to conduct the survey with each stakeholder group at approximately 8 and 20 months after launch, thus enabling REMS Assessments to be submitted to FDA at 12 and 24 months following launch. The survey will be repeated periodically as needed, to be determined in consultation with the FDA.

Data from the prescriber and patient surveys will be reported as descriptive statistics for the survey administration, study population, and knowledge, attitude, and behavior (KAB) questions. Statistics will be reported for each stakeholder group surveyed.

7.7.1.4 Chart Review Study

A chart review study will collect data from a sample of enrolled prescribers regarding two aspects of Exalgo Alliance:

- The percent of patients who are opioid tolerant
- The percent of patients with evidence of a signed Prescriber-Patient Medication Agreement in the patient chart

The results from this study will be used to evaluate the effectiveness of the Exalgo Alliance program in minimizing the risk of EXALGO use by patients who are not opioid tolerant. This chart review will supplement the KAB surveys and provide the most complete and accurate information on the patient's opioid use status since patient charts represent direct source data. The Exalgo Alliance Patient Enrollment Form informs the patient that his/her records may be used to evaluate the program and provides an option for opting out of the study. Only charts of patients who have not opted out will be sampled.

7.7.1.5 System and Program Performance Metrics

Exalgo Alliance program assessments include the following information:

- An assessment of enrollment and utilization statistics for prescribers, pharmacy/healthcare settings, and patients;
- A narrative summary written by Covidien Product Safety with analysis and evaluation of the Exalgo Alliance program;
- The total number of written prescriptions requested, filled, and denied during the reporting period [from pharmacy interactions with the Exalgo Alliance system];
- The total number of written prescriptions requested, filled, and denied during the reporting period from health care settings [from healthcare setting interactions with the Exalgo Alliance system];
- The number of prescribers not complying with enrollment requirements as well as Covidien's corrective action;
- The number of pharmacies/healthcare settings not complying with Exalgo Alliance requirements and Covidien's corrective action;

  Pursuant to 21 CFR§ 314.80, Covidien will submit a quarterly periodic progress report for EXALGO to FDA. Narrative summary and analysis of the surveillance activities during the reporting period (and cumulative);
- A summary and analysis of unintended interruptions or delays in treatment (e.g., interruption or delay in dispensing due to logistical issues associated with the Exalgo Alliance program). This summary should describe any corrective actions taken;

- A summary and analysis of non-compliance in the supply chain and distribution process as well as any corrective actions taken;
- A summary of all changes to the Exalgo Alliance program that were implemented during the reporting period;
- A report of periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24;
- An assessment of healthcare professional and patient understanding of the safe-use of EXALGO (the results of surveys administered to prescribers and patients);
- Based on the information provided, an assessment and conclusion of whether the Exalgo Alliance program is meeting its goals, and whether modifications to the program are needed.

7.7.2 Oversight and Review Committees

7.7.2.1 REMS Oversight Committee

An EXALGO REMS Oversight Committee (ROC) will be comprised of representatives from multiple functional areas within the Covidien organization, including Risk Management, Legal, Regulatory Affairs, Drug Safety and Pharmacovigilance, Medical Affairs, and Marketing. The mission of the ROC is to coordinate and review the Exalgo Alliance program. The ROC will review all cases of special interest. The ROC will meet in person, electronically, or otherwise as often as necessary to fulfill its mission, but no less than quarterly. The ROC will identify actions to be taken if stakeholders are found to be out of compliance with the program. The possible actions will be determined based on the situations identified and may include modification to educational materials, visits by MSLs or other Covidien personnel to the noncompliant prescribers or pharmacies, or deactivation of a distributor, prescriber, pharmacy or patient.

Signals may be allocated to more than one category. The specific characteristics of the signal will determine the type of intervention, the target population, and the magnitude of the response. If the responsibility or jurisdiction for responding to a specific signal belongs to a stakeholder other than Covidien, the intervention may be limited to contacting the responsible authority.

Each intervention deployed in response to each signal, and the approach to measuring the result of that intervention, will be determined by the ROC. The ROC will carefully consider the appropriateness of each intervention in each specific case. All decisions will be documented. The documentation of signals, interventions, results of interventions, and modifications to the interventions will be summarized in the quarterly risk management reports to FDA.

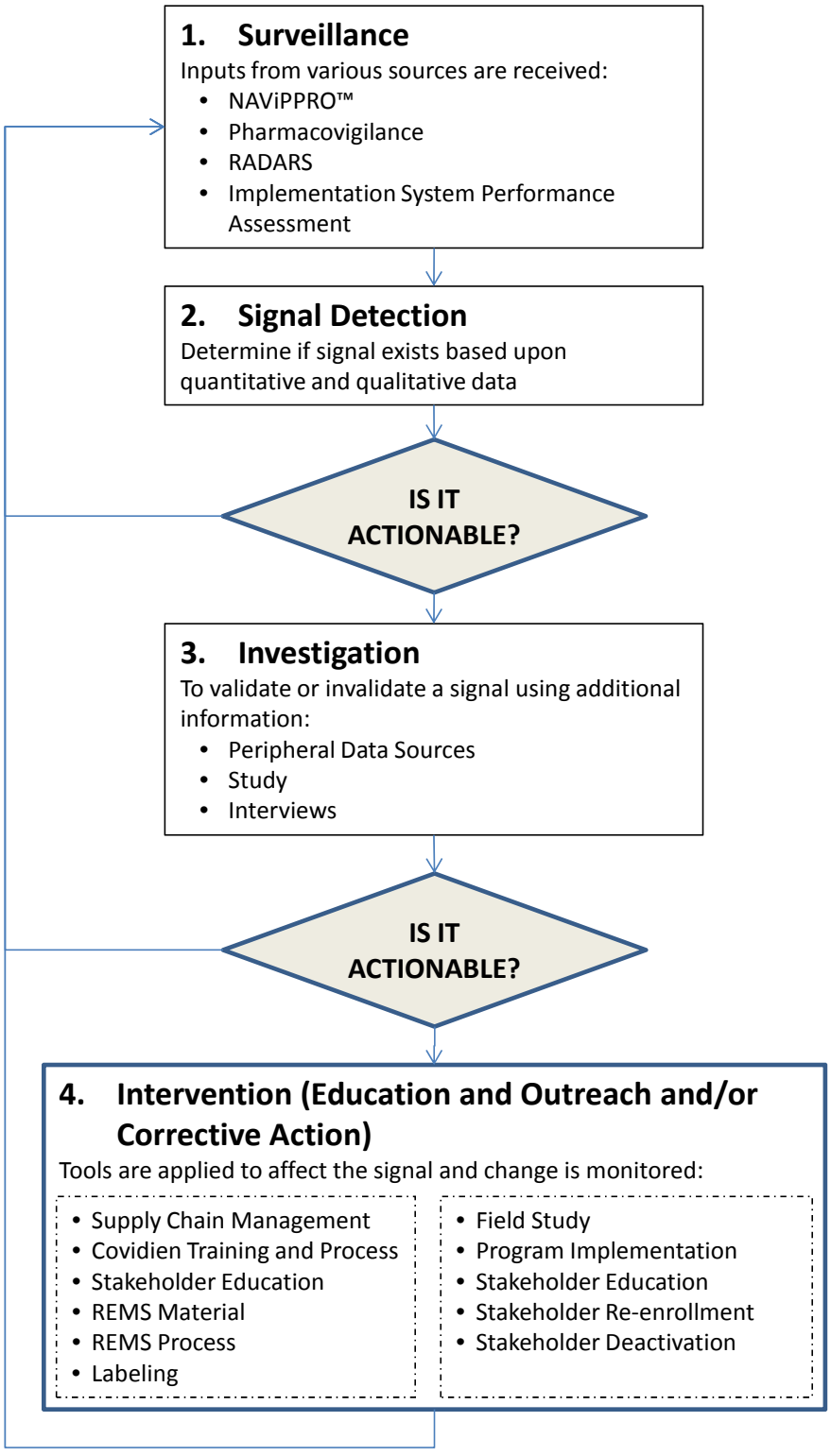
Signals that will trigger an evaluation and potential response include, but are not limited to the following:

- Fatal or nonfatal overdose of EXALGO

- Use in opioid non-tolerant patients
- Use for acute or postoperative pain
- Pediatric exposure, whether accidental or intentional
- Abuse or addiction associated with EXALGO
- AEs due to misuse by patients
- Diversion of EXALGO
- AEs associated with inappropriate prescribing, particularly:
    - Prescribing of EXALGO to an opioid non-tolerant patient
    - Prescribing of EXALGO for acute pain
    - Prescribing for prn use

The signal will be analyzed against the current strategies of the program to determine if any modifications are needed to improve the effectiveness of the Exalgo Alliance and prevent the occurrence of similar signals.

Figure 13 REMS Process Flow



Surveillance systems will generate signals indicating that either isolated events or patterns of overdose (fatal and nonfatal), addiction, misuse, abuse, diversion, or accidental ingestion may have occurred. The ROC will respond to each signal as follows.

- Individual case reports and/or full data reports will be obtained
- The signal will be carefully and thoroughly evaluated to determine:
  - Its validity
  - Its characteristic (population involved, geographical area, magnitude, etc.)
  - Whether it occurred due to the poor effectiveness of the Exalgo Alliance program.
- The event(s) will be reported immediately if appropriate
- The signal may be further investigated by telephone or in- person, or by conducting studies or surveys
- Action will be taken if appropriate.

A description of the methods utilized in processing signals will be included within the Exalgo Alliance Assessment Report.

7.7.2.2 REMS Safety Monitoring Board (RSMB)

An external clinical advisory board of practicing clinicians in the field of pain and addiction management and other relevant experts will be established as a REMS Safety Monitoring Board (RSMB). This board will interface with the ROC in reviewing safety events regarding:

- Inappropriate prescribing
- Inappropriate use and handling
- Prescribing and use as directed

The RSMB will make recommendations to the ROC regarding actions to be taken to minimize risk, and identify areas for program improvement.

7.7.2.3 Liaising with Local and Regional Authorities

In situations that involve regulatory or legal action, Covidien will alert appropriate government authorities when issues are identified that require a comprehensive approach by those with the appropriate responsibility, jurisdiction, and authority.

7.8 Summary

Exalgo Alliance is a comprehensive program to mitigate the primary risks of overdose, abuse and diversion in order to ensure that EXALGO's benefits outweigh the risks. EXALGO will only be available through a controlled access program. The program is designed to ensure that all key stakeholders understand EXALGO's risk-benefit profile

and responsible prescribing, dispensing, and use and agree to follow the Exalgo Alliance program requirements. Only appropriate patients should receive EXALGO. The implementation of the Exalgo Alliance will not impede the ability of appropriate patients to have access to EXALGO. The effectiveness of the program will be evaluated with a comprehensive surveillance and monitoring program, with continuous process improvement and corrective actions taken as appropriate.

8 BENEFIT / RISK PROFILE

Chronic pain is defined by the International Association for the Study of Pain as persistent pain lasting longer than the time required for normal tissue healing (IASP 1994). More than 50 million Americans experience chronic pain from a wide variety of sources, most commonly back pain, joint pain and headache (Ruoff 2002; Vo et al. 2008). Chronic pain, the nation's leading cause of disability, exacts a huge toll on individual patients including not just physical distress but profound psychosocial and economic distress as well as functional losses and vocational dysfunction. Chronic pain can be a devastating problem for patients that can become associated with depression, anxiety, sleep disturbances, and can impact family life as well. This problem is increasingly well recognized, such that the US government has designated the next 10 years as the "Decade of Pain Control and Research." The classical model for pain treatment captured in the WHO Analgesic Ladder includes complete and comprehensive assessment based on the needs of the patient, disease targeted remediation of causes, multi-modal therapy with an escalation of therapeutic modalities through a variety of non-opioid therapies up to weak and then strong opioid therapy when appropriate, together with continual reappraisal of the patient's adherence to treatment.

The beneficial use of opioids is well-established for the treatment of a broad range of states associated with chronic pain including cancer and non-malignant pains such as arthritis, back pain and many other inflammatory and neuropathic pain conditions. For example, more than 80% of cancer patients require opioid analgesics for pain. As the understanding of chronic pain as a medical syndrome has advanced over the last decade or more, the number of prescriptions for opioids – both short-acting agents prescribed multiple times a day and long-acting agents and patches requiring less frequent dosing – has steadily grown. Both short- and long-acting opioids can be effective in the treatment of chronic pain. Commonly long-acting opioids are used to provide a stable level of pain relief when around-the-clock relief is needed, while short-acting opioids are used for breakthrough and more transient pain. Patient treatment is individualized, but long-acting agents have become increasingly commonly used for their convenience and potential to improve sleep compared to short-acting opioids. Decades of clinical practice as well as observational studies have demonstrated that in many cases poor opioid responsiveness can be remedied by a switch to a new drug yielding better analgesia and fewer side effects. Opioid rotation is a well-accepted clinical practice used in a variety of clinical situations. Longitudinal study of patient opioid use has shown that it is common for patients to move through multiple opioids until they find the opioid that is optimal in their case (Kroenke et al. 2009; Fine 2009). The specific mechanisms underlying this phenomenon are not known, but the theoretical basis relates broadly to significant individual variations in response to different mu-opioid agonists. The implication of this

phenomenon is that availability of a range of clinical opioid choices facilitates optimal clinical management of the devastating condition of chronic pain.

Because opioids are known to have significant potential AEs and a pattern of known very common AEs, a benefit versus risk assessment and decision has to be made for each patient at the time that opioids are prescribed, and has to be kept in mind as the patient's condition progresses. Beyond the risk of AEs in an individual patient and the risk of abuse or addiction in any patient, the abuse liability of opioids, a known public health problem for decades, extends both to patients and non-patients. The significant clinical benefit of opioids for the patients must be considered in context and balanced relative to the potential risks of addiction and abuse both by patients and non-patients and in the context of programmatic controls to detect and minimize the risks to both patients and non-patients.

Hydromorphone has been in use for the treatment of pain since the first clinical report in 1926 and remains widely used today. The chief clinical limitation of available formulations of hydromorphone is that its rapid absorption and short half-life have led both to the requirement for very frequent dosing, the risk of significant pain on awakening, and to a blood level pattern of high peaks and low troughs. Hydromorphone is currently available in both IR and a long-acting formulation in 9 countries globally but is only available in an IR formulation in the US at this time. EXALGO, marketed in those 9 countries under the brand name JURNISTA, was developed as an extended release formulation of hydromorphone intended to provide clinical benefit to the subset of patients who respond well to hydromorphone and require around-the-clock therapy. The unique PK characteristics of EXALGO produce relatively stable and effective blood levels of hydromorphone for analgesic coverage throughout 24 hours. EXALGO does not have an IR component and is intended and effective for chronic pain but not acute pain. EXALGO bioavailability is not affected by food, and its extended-release properties are maintained in the presence of alcohol with no acute dose dumping of hydromorphone.

Efficacy of EXALGO used together with rescue medication was demonstrated relative to placebo supplemented with rescue medication in the pivotal study NMT 1077-301 in opioid-tolerant patients with chronic pain. Throughout the double-blind phase of the study, EXALGO treated patients showed a clinically and statistically significant reduction in pain intensity through 12 weeks of treatment, compared to placebo treated patients supplemented with rescue medication. The EXALGO treatment response was also reflected in a variety of secondary outcome measures detecting subjective, behavioral and disability-related improvements compared to placebo supplemented with rescue medication. These data were consistent with the response in a series of supportive trials showing EXALGO superiority to half dose hydromorphone and non-inferiority to full dose hydromorphone, morphine and oxycontin. Pooled safety data from over 3000 patients in 13 controlled and uncontrolled studies of EXALGO in patients with chronic pain showed a safety profile that was characteristic of that seen with other strong opioids and revealed no unexpected safety concerns. Similarly, post-marketing surveillance data from worldwide experience has to date produced only a modification of the label to note a reduced blood level and risk of opioid withdrawal in patients with

syndromes producing a markedly shortened bowel transit time (consistent with the steady release properties expected from this formulation), and addition of 2 terms to the undesirable effects section.

Like other opioids, EXALGO has the risk of overdose, misuse and abuse, which must be considered when the product is prescribed, administered and dispensed. To minimize these risks, EXALGO should be prescribed to the appropriate opioid-tolerant patient population. EXALGO is therefore contraindicated in the management of acute or postoperative pain, and should not be prescribed to treat mild pain. It is important that the initiation of dosage is individualized for each patient being prescribed EXALGO with appropriate conversion from other pain medications and subsequent dose titration in order to properly manage analgesic relief. Patients being considered for EXALGO or any other opioid should be assessed for their clinical risks for opioid addiction or abuse, and should be monitored for signs of misuse, abuse, and addiction. Patients should be counseled regarding the risks of using EXALGO and the importance of not allowing anyone access to the medication.

In conclusion, the data presented in this Briefing Document demonstrate that EXALGO is effective in controlling pain over a 12-week period in opioid-tolerant patients with moderate to severe chronic pain using a variety of predetermined measures of efficacy. The safety profile across the EXALGO clinical development program is well-understood and is similar to other strong opioids. The primary risks of overdose, misuse, and abuse will be addressed through a comprehensive REMS program. EXALGO will provide an option for clinicians who treat opioid-tolerant patients whose chronic pain is not adequately or optimally controlled by their current opioid therapy. Overall the benefits of EXALGO for patients exceed the risks associated with this new formulation. The risks of EXALGO can be reduced, detected and managed through the comprehensive EXALGO REMS.

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