EXALGO™ (hydromorphone HCl) Extended-Release Tablets (CII)

NDA 21-217

United States Food and Drug Administration
Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee with the Drug Safety and Risk Management Advisory Committee

September 23, 2009

Introduction and Background of EXALGO

C. Eugene Wright, PharmD, PhD

Vice President, Project Leadership

Neuromed Pharmaceuticals

Neuromed Pharmaceuticals

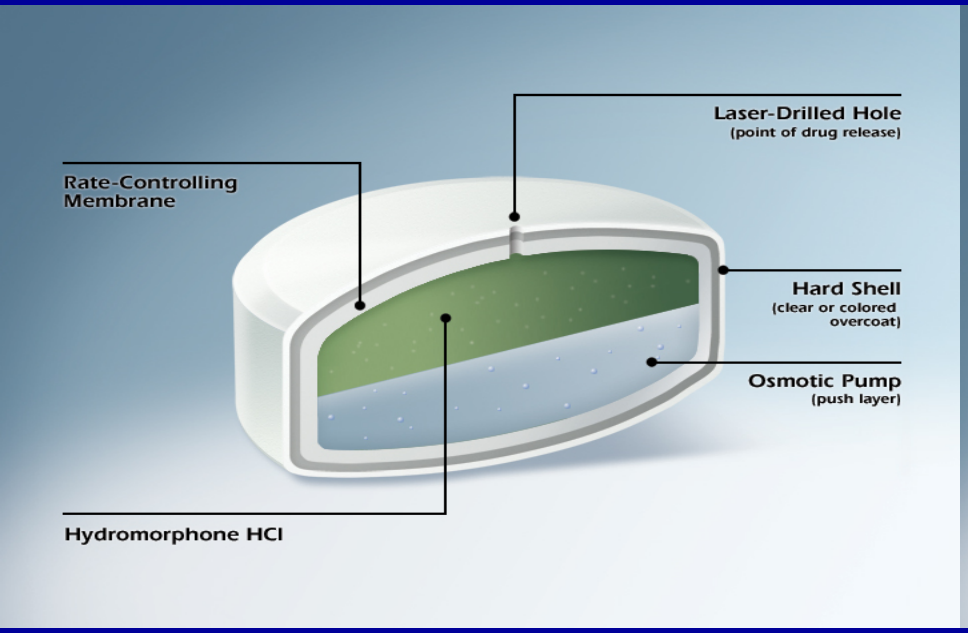
- Focus on development of pain medications
  - Developed EXALGO (acquired April 2007)
  - Designed the Exalgo Alliance™ program
- Partnered with:
  - Johnson & Johnson
    - Global manufacturer
    - Commercialization ex-US (JURNISTA™)
  - Covidien's subsidiary, Mallinckrodt
    - Implementation of Exalgo Alliance™
    - Commercialization in United States

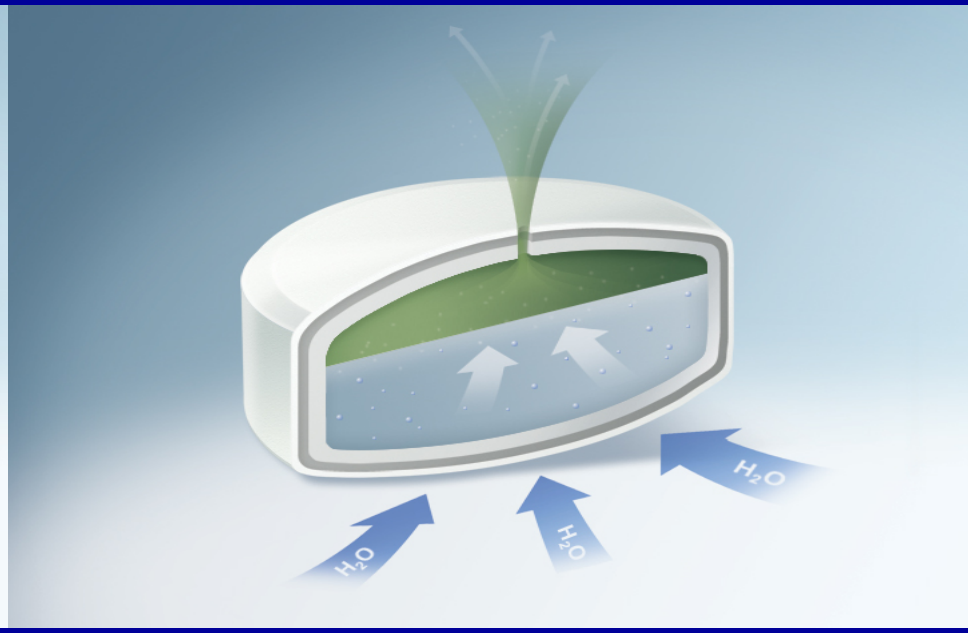
Why Are We Here?

- Hydromorphone is a well-established treatment for pain
- EXALGO is effective and well tolerated
- Once-daily hydromorphone in a proven delivery system
- Risk Evaluation and Mitigation Strategy (REMS): Exalgo Alliance™
  - Must balance patient access against the risks of overdose, abuse, and diversion

Well-Established Delivery System

- The OROS® technology
- In 13 marketed products, including a Schedule II product
  - For example: Concerta, Procardia XL, and Ditropan XL
- Marketed for 20 years





Today's Agenda

Regulatory Overview	James Ottinger, RPh
Clinical Pharmacology	C. Eugene Wright, PharmD, PhD
Clinical Overview	Christopher Gallen, MD, PhD
Extended-Release Hydromorphone for Patients With Chronic Pain	Lynn Webster, MD
Risk Evaluation and Mitigation Strategy (REMS): Exalgo Alliance	Annette Stemhagen, DrPH, FISPE
REMS Implementation, Assessment, and Commitment	Herbert Neuman, MD
Concluding Remarks	C. Eugene Wright, PharmD, PhD

External Advisors

- **Sandra D. Comer, PhD**
  Columbia University
- **James Moe, DVM, PhD, Dipl ACVP**
  JBM Consulting
- **Alan Smith, MS**
  Applied Clinical Intelligence
- **Simon Budman, PhD**
  Inflexxion

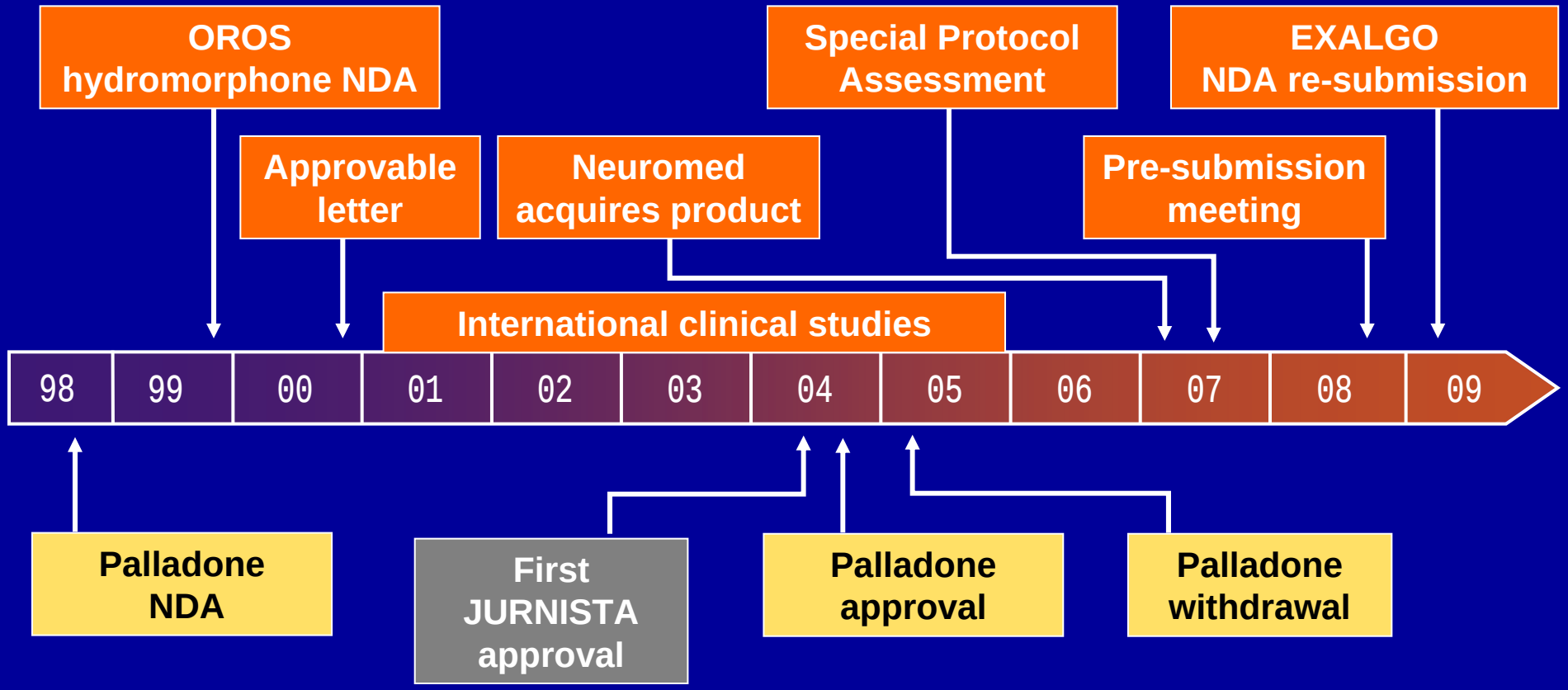
Regulatory Overview

James G. Ottinger, RPh

Vice President, Regulatory Affairs

Premier Research Group

Regulatory History of EXALGO NDA 21-217



EXALGO NDA Meets Requirements (1)

- Clinical efficacy
  - Placebo-controlled trial (Study 301)
  - Met primary endpoint
- Clinical safety
  - 2,335 patients exposed; 141 for over 1 year
  - 17 million patient-days post marketing
- Clinical pharmacokinetics
  - Well characterized
  - Alcohol interaction study
    - Not subjected to dose dumping

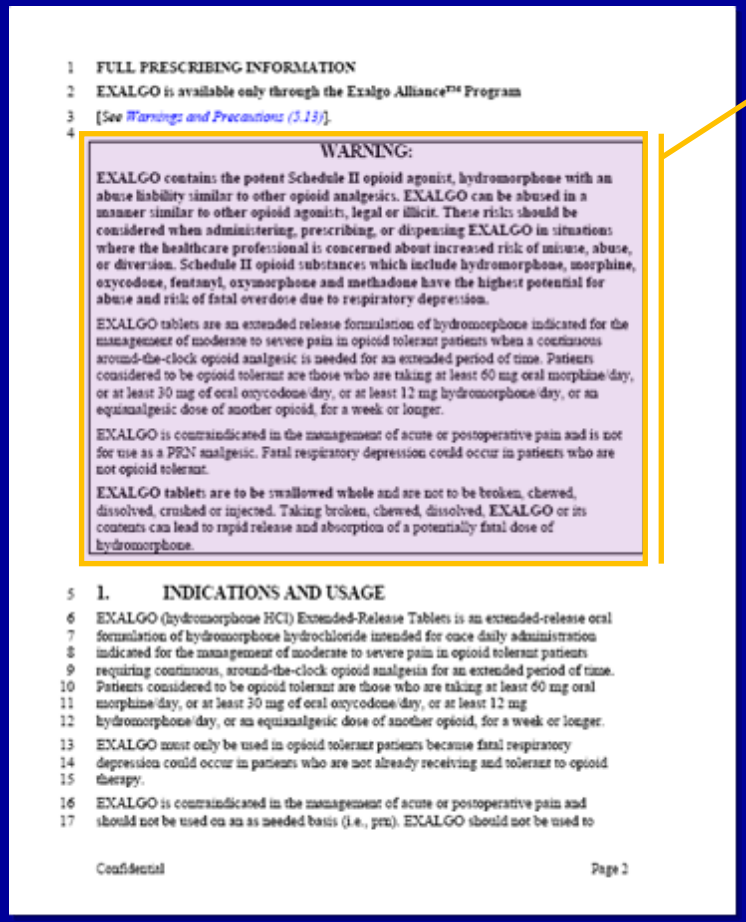
EXALGO NDA Meets Requirements (2)

- Nonclinical
  - Complete data
  - Two carcinogenicity studies initiated
- Chemistry, Manufacturing, and Controls
  - Complete data including in vitro abuse liability studies
- Proposed Risk Evaluation and Mitigation Strategy
  - Will be required for all extended release opioids
  - April Federal Register Notice
  - Onsolis REMS approved
  - Exalgo Alliance

Prescribing Information Highlights

- Indication
  - Moderate to severe pain in opioid-tolerant patients requiring continuous around-the-clock opioid therapy
- Dosage and administration
  - 12 to 64 mg once daily
- Dosage strengths
  - 8, 12, 16, and 32 mg
  - 64 mg will not be marketed
- Contraindications
  - Opioid non-tolerant patients
  - Acute pain
  - Post-operative pain
  - PRN pain

Prescribing Information Boxed Warning



FULL PRESCRIBING INFORMATION

EXALGO is available only through the Exalgo Alliance™ Program

[See *Warnings and Precautions (5.13)*].

WARNING:

EXALGO contains the potent Schedule II opioid agonist, hydromorphone with an abuse liability similar to other opioid analgesics. EXALGO can be abused in a manner similar to other opioid agonists, legal or illicit. These risks should be considered when administering, prescribing, or dispensing EXALGO in situations where the healthcare professional is concerned about increased risk of misuse, abuse, or diversion. Schedule II opioid substances which include hydromorphone, morphine, oxycodone, fentanyl, oxymorphone and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

EXALGO tablets are an extended release formulation of hydromorphone indicated for the management of moderate to severe pain in opioid tolerant patients when a continuous around-the-clock opioid analgesic is needed 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 is contraindicated in the management of acute or postoperative pain and is not for use as a PRN analgesic. Fatal respiratory depression could occur in patients who are not opioid tolerant.

EXALGO tablets are to be swallowed whole and are not to be broken, chewed, dissolved, crushed or injected. Taking broken, chewed, dissolved, EXALGO or its contents can lead to rapid release and absorption of a potentially fatal dose of hydromorphone.

1. INDICATIONS AND USAGE

EXALGO (hydromorphone HCl) Extended-Release Tablets is an extended-release oral formulation of hydromorphone hydrochloride intended for once daily administration 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.

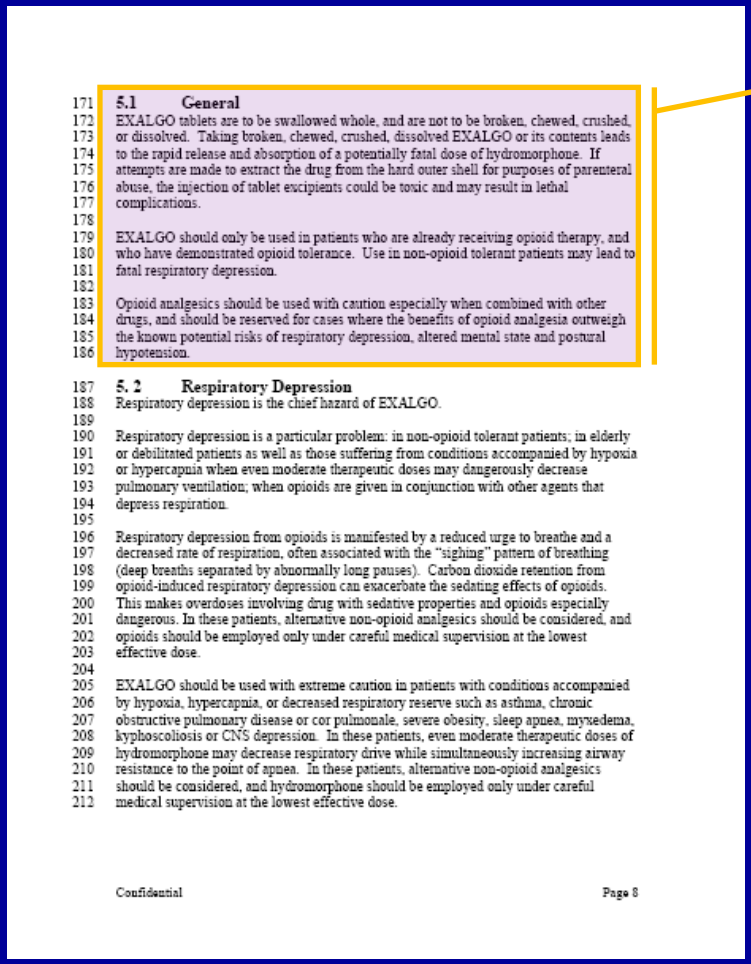
EXALGO must only be used in opioid tolerant patients because fatal respiratory depression could occur in patients who are not already receiving and tolerant to opioid therapy.

EXALGO is contraindicated in the management of acute or postoperative pain and should not be used on an as needed basis (i.e., prn). EXALGO should not be used to

Confidential Page 2

- **Boxed Warnings**
  - Opioid-tolerant patients only
  - Class Labeling
    - Risk of misuse, abuse, addiction, and diversion
    - Use in acute pain
    - Respiratory depression
    - Administration of intact tablets

Prescribing Information Warnings and Precautions



5.1 General

EXALGO tablets are to be swallowed whole, and are not to be broken, chewed, crushed, or dissolved. Taking broken, chewed, crushed, dissolved EXALGO or its contents leads to the rapid release and absorption of a potentially fatal dose of hydromorphone. If attempts are made to extract the drug from the hard outer shell for purposes of parenteral abuse, the injection of tablet excipients could be toxic and may result in lethal complications.

EXALGO should only be used in patients who are already receiving opioid therapy, and who have demonstrated opioid tolerance. Use in non-opioid tolerant patients may lead to fatal respiratory depression.

Opioid analgesics should be used with caution especially when combined with other drugs, and should be reserved for cases where the benefits of opioid analgesia outweigh the known potential risks of respiratory depression, altered mental state and postural hypotension.

5. 2 Respiratory Depression

Respiratory depression is the chief hazard of EXALGO.

Respiratory depression is a particular problem: in non-opioid tolerant patients; in elderly or debilitated patients as well as those suffering from conditions accompanied by hypoxia or hypercapnia when even moderate therapeutic doses may dangerously decrease pulmonary ventilation; when opioids are given in conjunction with other agents that depress respiration.

Respiratory depression from opioids is manifested by a reduced urge to breathe and a decreased rate of respiration, often associated with the "sighing" pattern of breathing (deep breaths separated by abnormally long pauses). Carbon dioxide retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. This makes overdoses involving drug with sedative properties and opioids especially dangerous. In these patients, alternative non-opioid analgesics should be considered, and opioids should be employed only under careful medical supervision at the lowest effective dose.

EXALGO should be used with extreme caution in patients with conditions accompanied by hypoxia, hypercapnia, or decreased respiratory reserve such as asthma, chronic obstructive pulmonary disease or cor pulmonale, severe obesity, sleep apnea, myxedema, kyphoscoliosis or CNS depression. In these patients, even moderate therapeutic doses of hydromorphone may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea. In these patients, alternative non-opioid analgesics should be considered, and hydromorphone should be employed only under careful medical supervision at the lowest effective dose.

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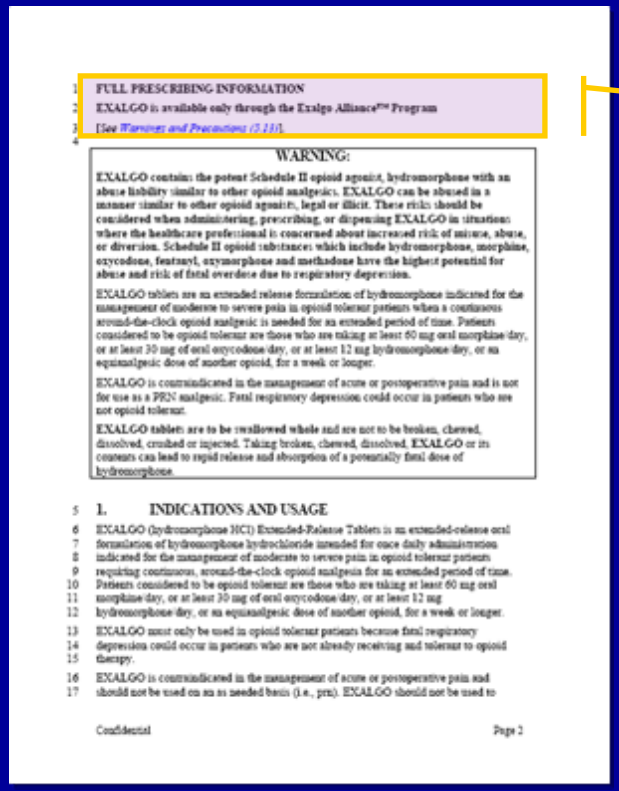
- **Warnings and Precautions Section**
  - **Risk of injection … may result in lethal complications**
  - **Class Warnings**
  - **Concomitant use with alcohol should be avoided**

Prescribing Information
Exalgo Alliance

- Provides information about the Exalgo Alliance Program



FULL PRESCRIBING INFORMATION

EXALGO is available only through the Exalgo Alliance™ Program

[*See Warnings and Precautions (5.13)*].

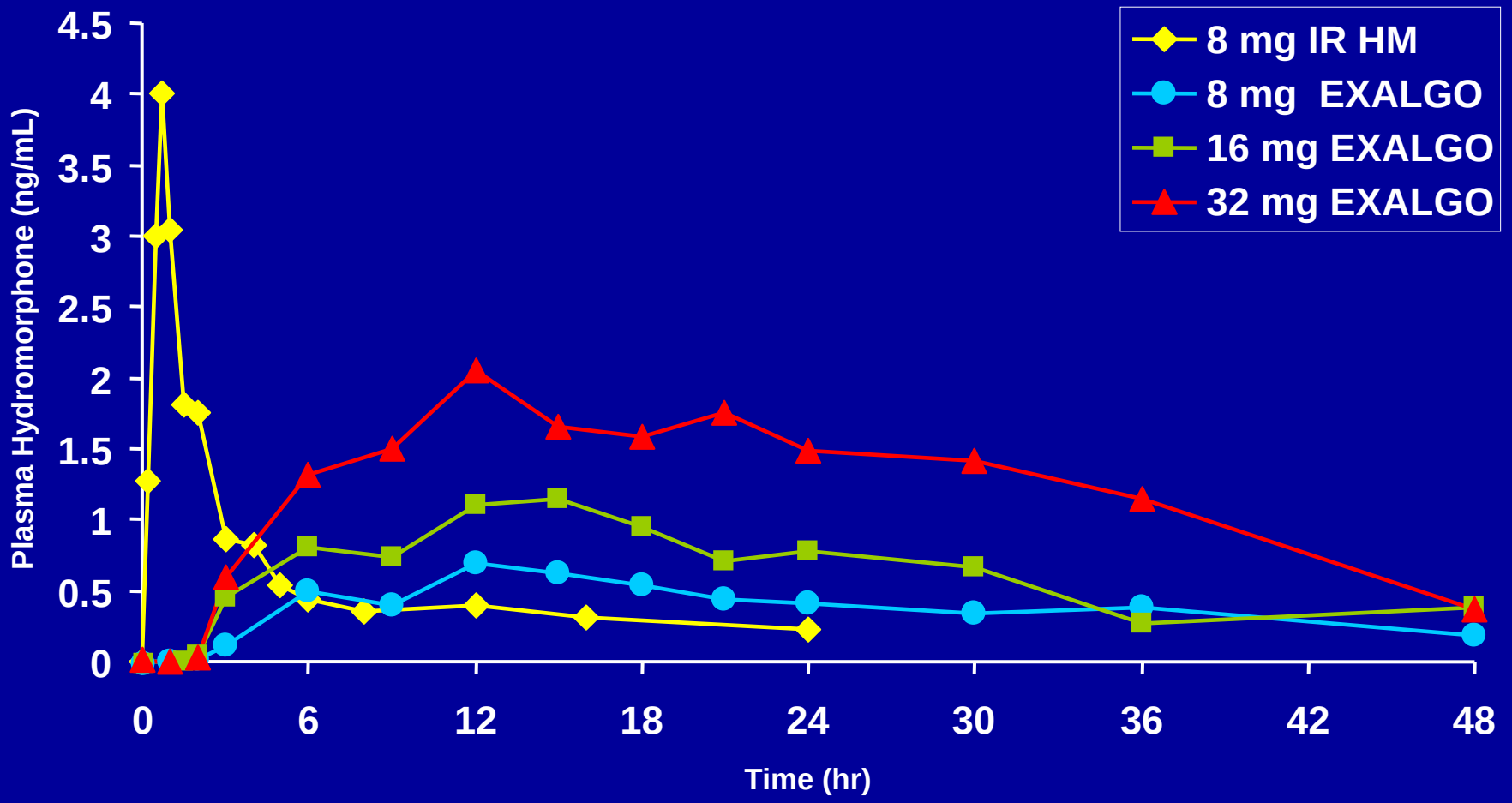
Clinical Pharmacology

C. Eugene Wright, PharmD, PhD

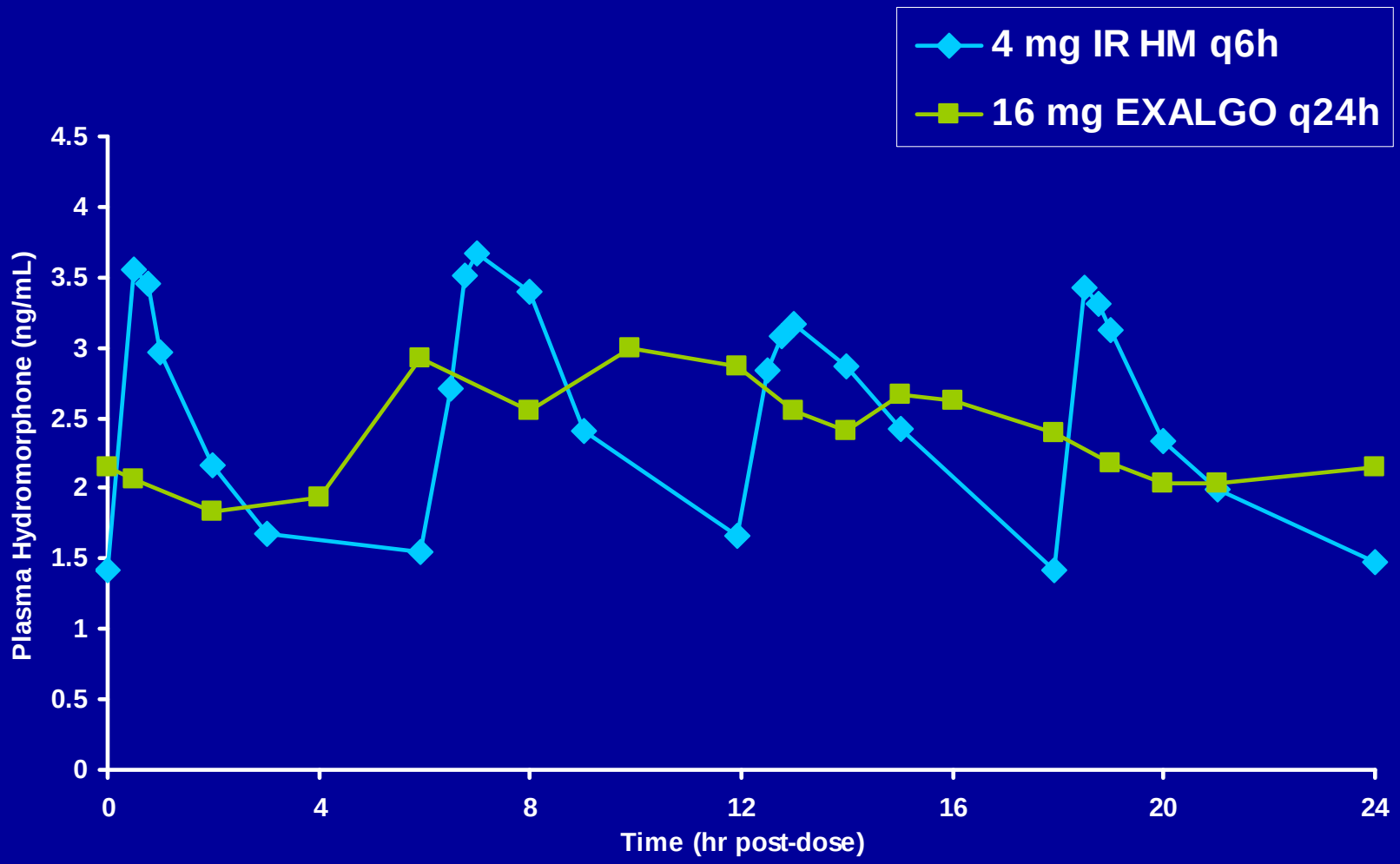
Vice President, Project Leadership

Neuromed Pharmaceuticals

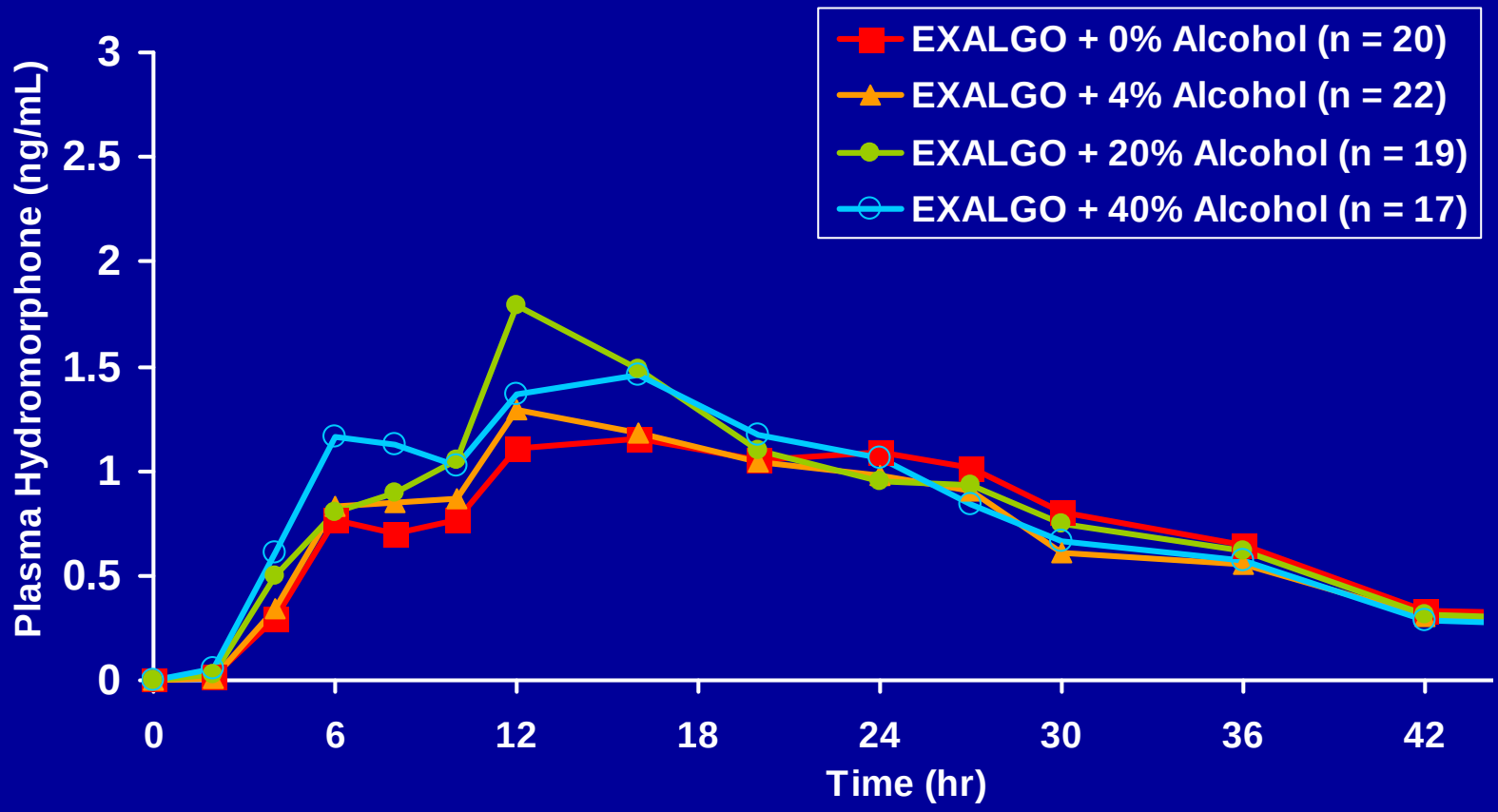
EXALGO Mean Single Dose Pharmacokinetics vs IR Hydromorphone



EXALGO Mean Steady-State Pharmacokinetics vs IR Hydromorphone



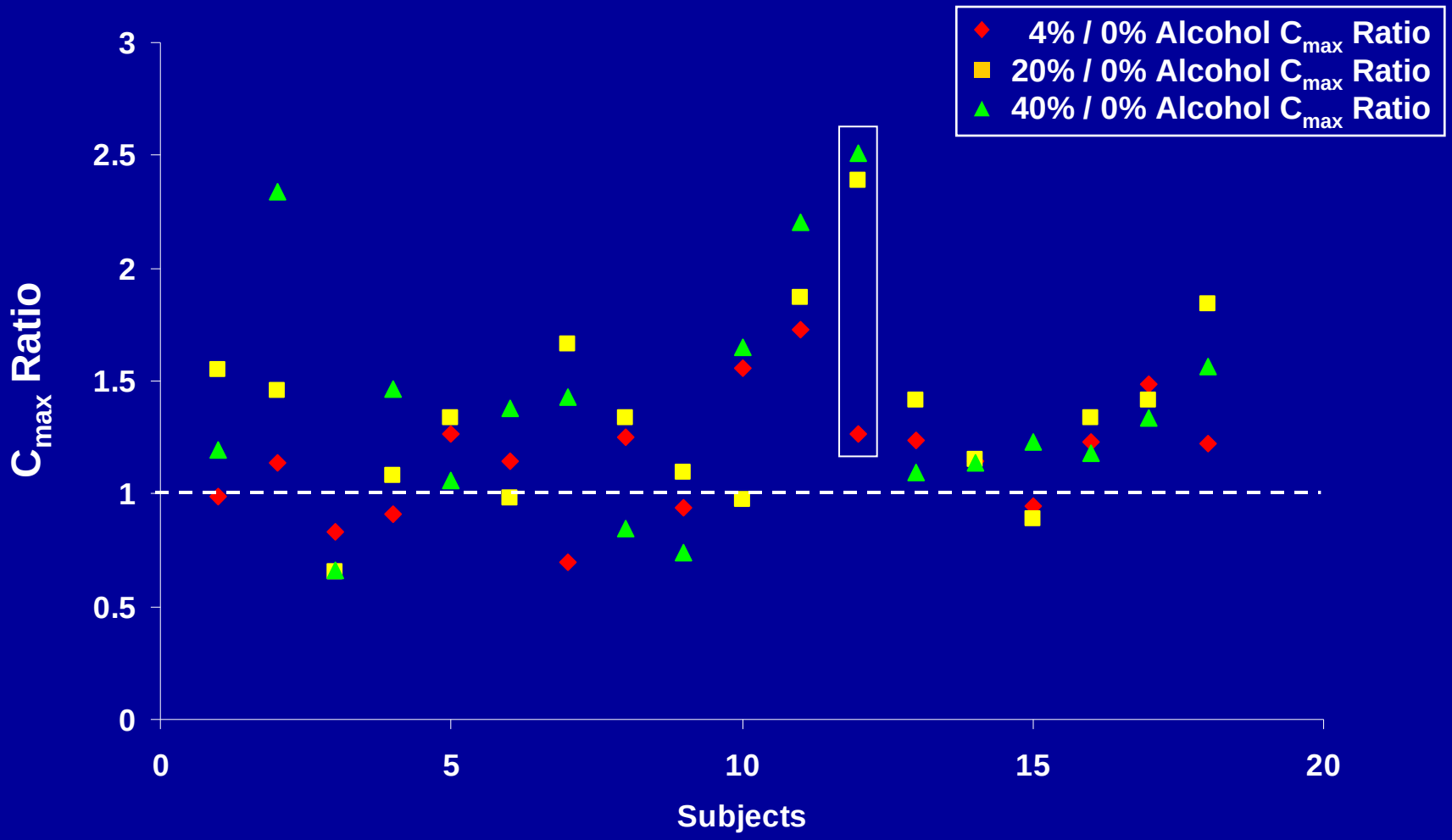
Alcohol Effect Study in Fasting Subjects



Alcohol Effect Study

C_{max} Ratio Fasted

- C_{max} ratio of EXALGO + alcohol vs EXALGO + 0% alcohol for each subject

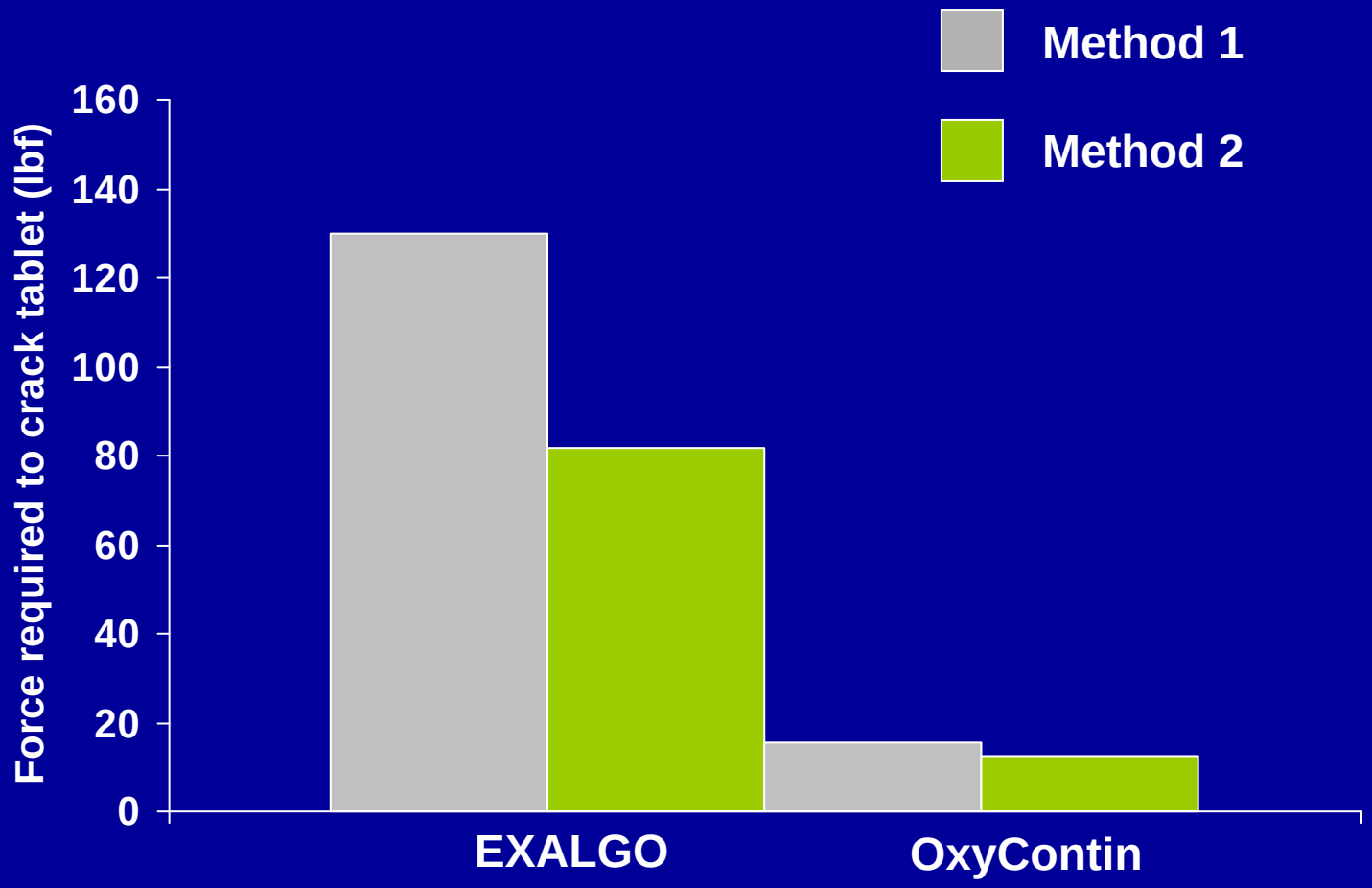


Alcohol Effect Studies

	Increase in mean C_{max} ratio relative to drug co-ingested with 0% alcohol			Maximum individual C_{max} ratio with 40% alcohol
	4% Alcohol	20% Alcohol	40% Alcohol	
EXALGO™ Hydromorphone HCl	1.2	1.4	1.4	2.5
Palladone™ Hydromorphone HCl	1	2	6	16
OPANA ER® Oxymorphone HCl	1.07	1.31	1.7	2.7
Kadian® Morphine sulfate	—	—	1.0[a]	4.54
Embeda™ Morphine sulfate/ naltrexone HCl	—	—	2	5

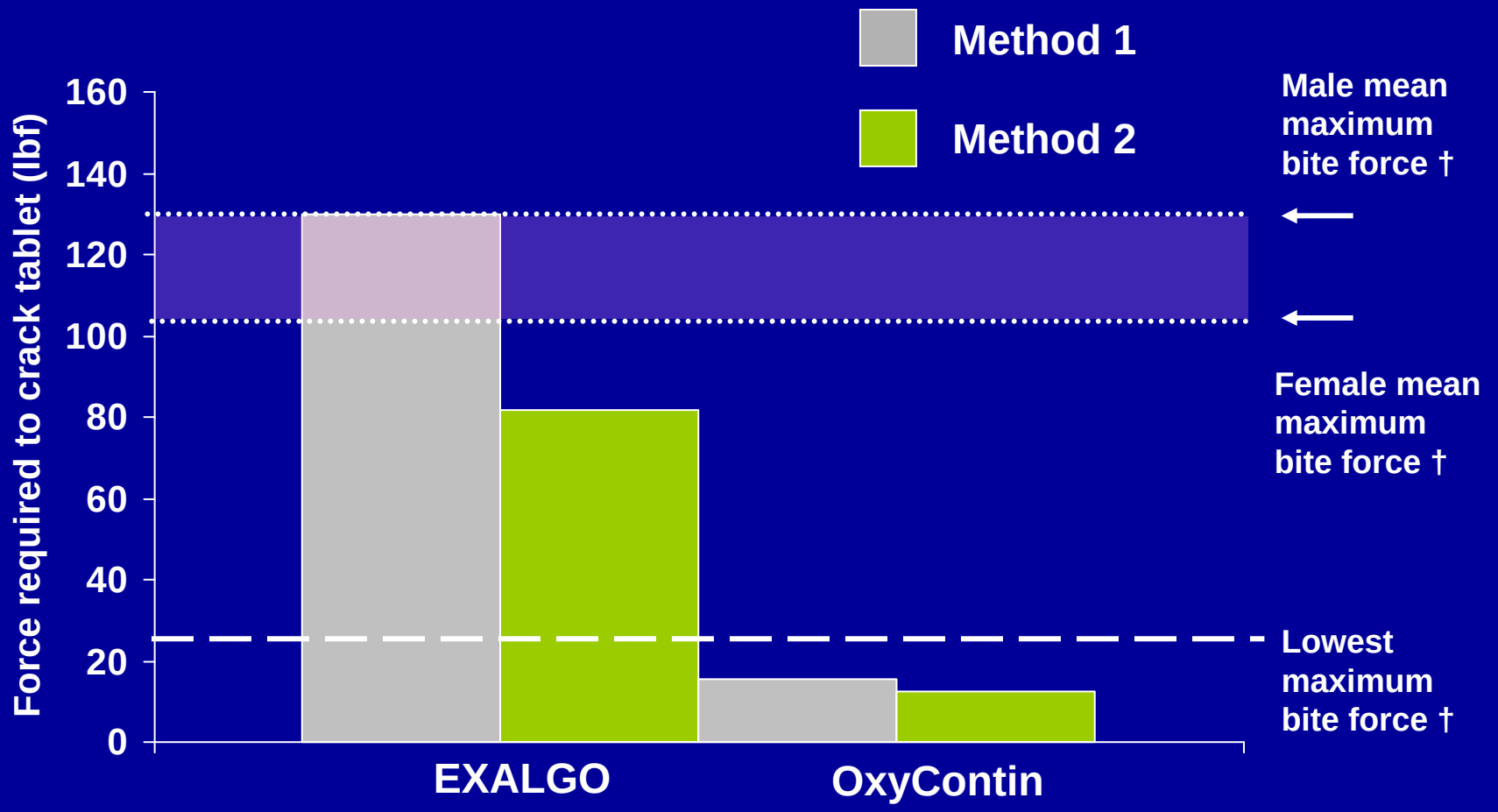
[a] Median

In Vitro Crushing Force
EXALGO and OxyContin®



In Vitro Crushing Force Related to Human Bite Force

EXALGO and OxyContin®



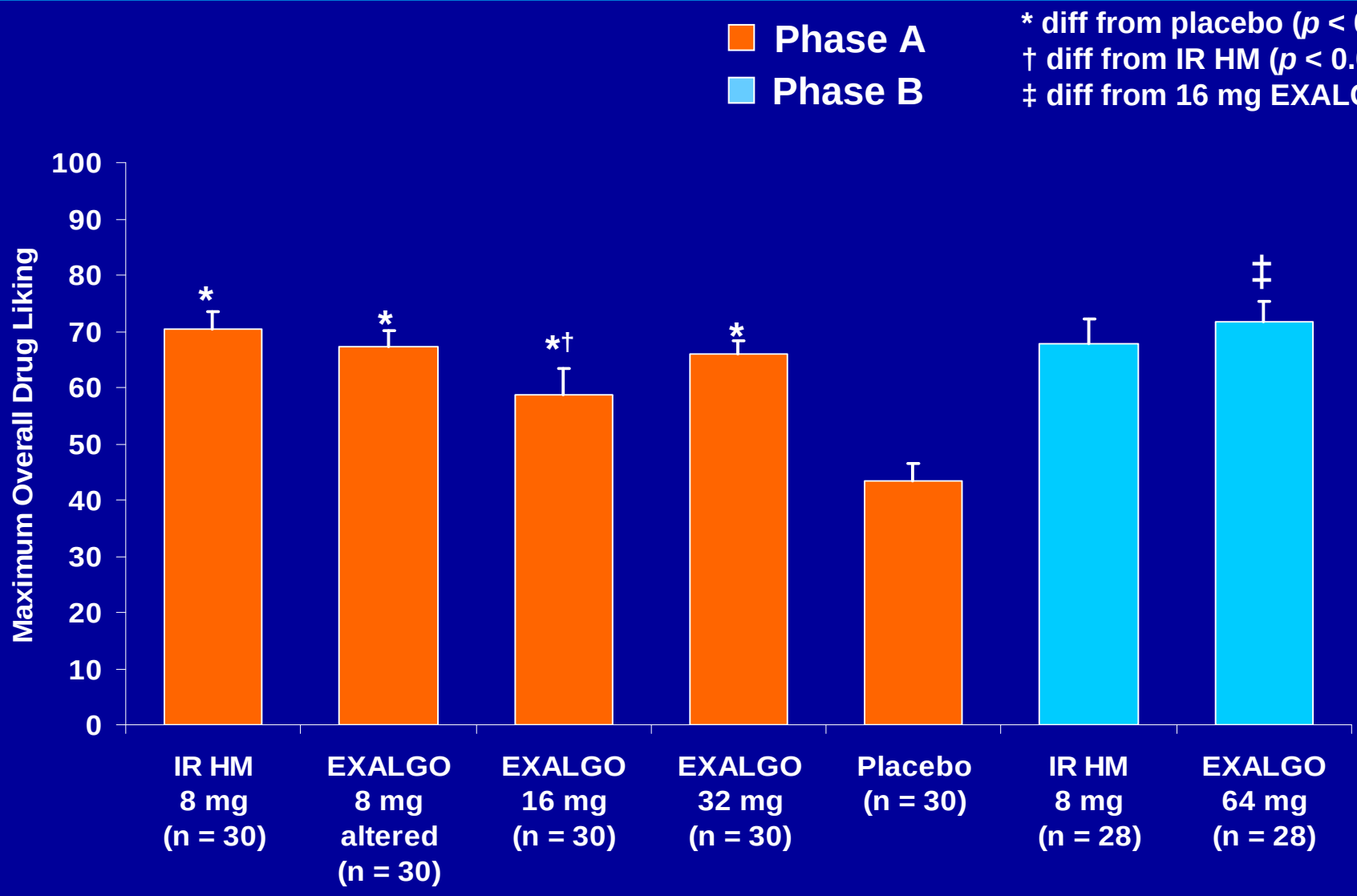
†Paulo César Rodrigues Conti, et.al. The Influence of Gender and Bruxism on the Human Maximum Bite Force, *J Appl Oral Sci.* 2006;14(6):448-53.

Abuse Liability Study Design
Study C-2005-022

Design	Single-center, single-dose, double-blind, double-dummy, placebo-controlled, randomized, crossover	
Population	Healthy subjects with history of polydrug use and moderate opiate use, but not dependent on opioids	
Comparators	**Phase A**	**Phase B**
	IR HM 8 mg	IR HM 8 mg
	EXALGO 8 mg, altered	EXALGO 64 mg, intact
	EXALGO 16 mg, intact	
	EXALGO 32 mg, intact	
	Placebo	
Primary Endpoint	Overall Drug Liking measured on Visual Analog Scale at 10 and 48 hours after dosing, maximum scores were highest of the 10 and 48 hour assessments	
Secondary Endpoints	Subjective Drug Value, Subjective Effects, Observer-rated Single-Dose Questionnaire, Subject-rated Opiate Agonist Scale, Cole/ARCI	

Abuse Liability Study Primary Endpoint—Maximum Overall Drug Liking

Mean SE



Significant Risk Factors for Abuse and Overdose

- Potency
- T_{max}
- C_{max}
- Availability
- Patient risk factors
- Prescriber inexperience

Summary of EXALGO Clinical Pharmacology

- Pharmacokinetic profile consistent with once- daily dosing
- Dose proportional
- Less fluctuation between peak and trough
- No dose dumping with alcohol
- Maximum Overall Drug Liking
  - 8 mg altered EXALGO comparable to 8 mg IR HM
  - 16 mg intact EXALGO significantly lower than 8 mg IR HM
  - 32 and 64 mg intact EXALGO not significantly different from 8 mg IR HM

EXALGO Clinical Overview

Christopher Gallen, MD, PhD

Chief Executive Officer and
Acting Chief Medical Officer

Neuromed Pharmaceuticals

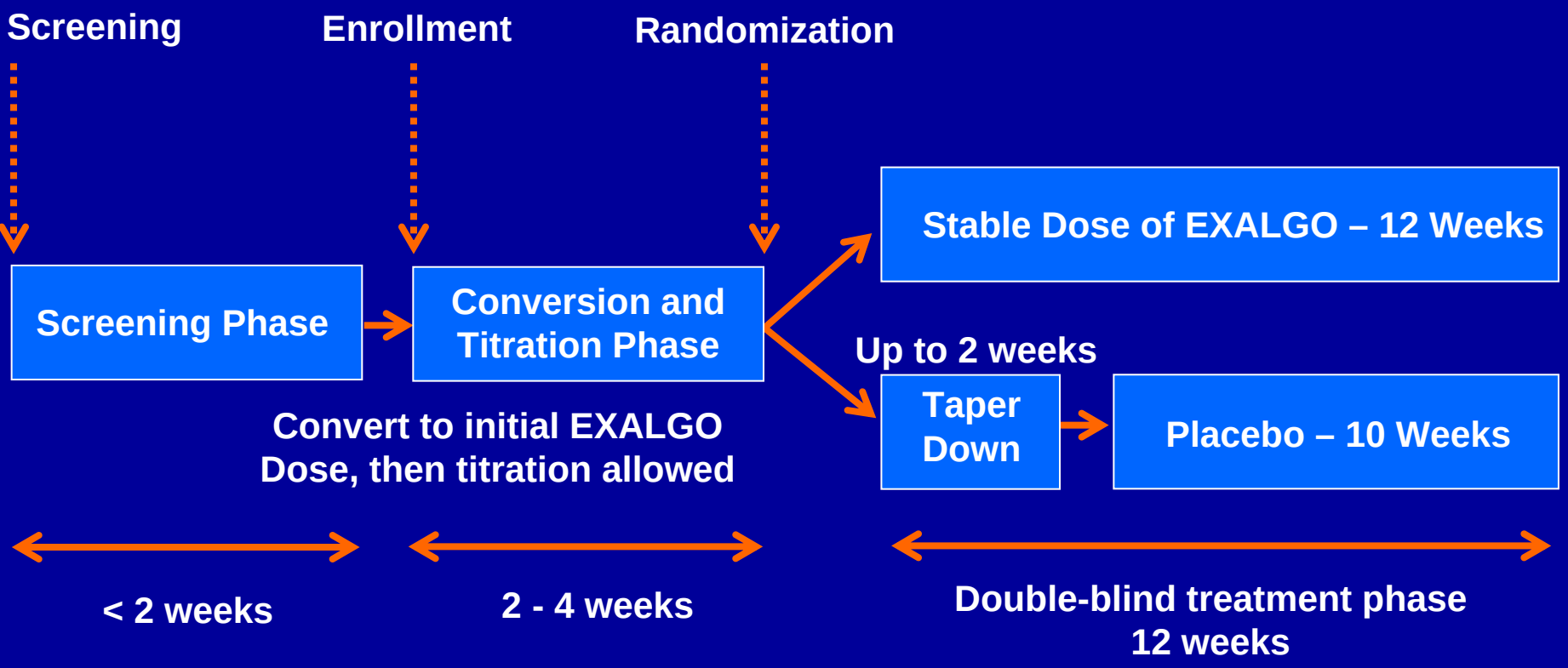
EXALGO Clinical Development Program

- Clinical pharmacology program
  - 15 studies
- Clinical program in patients with chronic pain
  - Positive pivotal Study 301
  - 12 supportive chronic pain trials
  - 2,335 EXALGO-treated patients

Study 301 in Opioid-tolerant Patients With Chronic Moderate to Severe Low-Back Pain

Trial Design

- Double-blind, placebo-controlled, randomized withdrawal design



Study 301 Discontinuation

Reason for Withdrawal[a]	Conversion and Titration Phase	Double-blind Phase	
	EXALGO, n (%) N = 459	EXALGO, n (%)[b] n = 134	Placebo, n (%)[b] n = 134
Lack of Analgesic Efficacy	56 (12.2)	16 (11.9)	40 (29.9)
Unacceptable Rescue Med Use	2 (0.4)	8 (6.0)	12 (9.0)
Opioid Withdrawal Symptoms	3 (0.7)	3 (2.2)	7 (5.2)
Adverse Event	60 (13.1)	9 (6.7)	4 (3.0)
Death	0	0	0
Protocol Violation	23 (5.0)	7 (5.2)	9 (6.7)
Withdrew Consent	21 (4.6)	7 (5.2)	4 (3.0)
Non-Compliance	16 (3.5)	11 (8.2)	11 (8.2)
Lost to Follow-up	8 (1.7)	3 (2.2)	1 (0.7)
Other	2 (0.4)	4 (3.0)	1 (0.7)
Total Withdrawn	191 (41.6)	68 (50.7)	90 (67.2)

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

Study 301 Summary of Efficacy Results

Primary efficacy endpoint	
Change from baseline to week 12 or final visit on pain intensity weekly mean diary NRS scores	$p < 0.0001$
Secondary efficacy endpoints	
Area under the curve for change in pain intensity (diary)	$p < 0.0001$
Change from baseline each office visit on pain intensity	$p < 0.0001$
Patient Global Assessment	$p < 0.0001$
Treatment failure (drop-out analysis)	$p < 0.0001$
Total patients dropped out for any reasons	$p = 0.009$
Roland-Morris Disability Questionnaire (RDQ)	$p = 0.002$
Rescue pain medication use	NS

Adverse Event (> 5%) Profile by Phase
Study 301—Safety Population

	Patients, n (%)		
		Double-blind phase (randomized population)	
MedDRA Preferred Term	Titration phase (safety population) N = 447	Placebo n = 134	EXALGO n = 134
Constipation	69 (15.4)	5 (3.7)	10 (7.5)
Nausea	53 (11.9)	10 (7.5)	12 (9.0)
Vomiting	29 (6.5)	6 (4.5)	8 (6.0)
Diarrhea	13 (2.9)	9 (6.7)	5 (3.7)
Somnolence	39 (8.7)	0	1 (0.7)
Headache	35 (7.8)	10 (7.5)	7 (5.2)
Insomnia	13 (2.9)	5 (3.7)	7 (5.2)
Withdrawal syndrome	22 (4.9)	16 (11.9)	13 (9.7)
Arthralgia	9 (2.0)	3 (2.2)	8 (6.0)
Back pain	13 (2.9)	8 (6.0)	6 (4.5)

Study 301 Drug Accountability

- Overall compliance typical of clinical trials
- Discrepancy rates between placebo and EXALGO are similar
- Study 301 not designed prospectively to assess diversion
- Low discrepancy rates in completers and in patients with medical reasons for discontinuation
- Outlier analysis indicates discrepancies in:
  - UDS positive
  - Medication lost
  - Lost to follow up
  - Withdrew consent without returning medication
  - Medication stolen

Pooled Chronic Pain Safety Analysis

	Patients, n (%) (N = 2,335)
Disease state	
Non-cancer	2,097 (89.8)
Cancer	238 (10.2)
Treatment duration (up to 20 mo)	
> 6 mo	420 (18.0)
> 12 mo	141 (6.0)
Prior opioid history	
Opioid non-tolerant	1,084 (46.4)
Opioid tolerant	1,251 (53.6)

Adverse Event Profile of EXALGO Controlled and Uncontrolled Studies

Adverse Events ≥ 5%	Patients, n (%) (N = 2,335)
Constipation	702 (30.1)
Nausea	642 (27.5)
Vomiting	322 (13.8)
Diarrhea	194 (8.3)
Insomnia	158 (6.8)
Somnolence	322 (13.8)
Headache	300 (12.8)
Anorexia	131 (5.6)
Fatigue	263 (11.3)
Dizziness	247(10.6)
Pruritis	183 (7.8)
Hyperhidrosis	136 (5.8)
Edema	132 (5.7)

Fatalities Not Related to Cancer Progression

Reason	n	Study
Sepsis	1	DO-105
Respiratory failure/dehydration	1	DO-109
Myocardial infarction	1	DO-109
Cardiac arrest	2	DO-109
Congestive heart failure	1	DO-109
Suicide[a]	1	NM-302
Total	7	

[a] Includes 1 suicide reported post-submission from study 302

Postmarketing Experience of OROS Hydromorphone

- Marketed as JURNISTA since 2006 in Germany
- Data from marketing in 9 countries

	JURNISTA	EXALGO
Indication, patients	Opioid-naive and opioid-tolerant	Opioid-tolerant
Tablet Strengths, mg	4, 8, 16, 32, 64	8, 12, 16, 32

Postmarketing Experience of OROS Hydromorphone

- 17,000,000 patient days (08/06 - 12/08)
- 170 SAEs (121 listed/49 unlisted)
- Fatal SAEs
  - Respiratory failure (3)
  - Intentional overdose (1)
  - Confusion with malignant neoplasm progression (1)
  - 1 post-submission cardiac failure / overdose (7/09)
- 11 cases of misuse by tablet manipulation
  - 9 cases—split, crushed, pulverized
  - 2 case—chewed
- No reports of accidental exposure of children

EXALGO Clinical Overview Summary

- Met the regulatory requirement for a positive, adequate, well-controlled study
  - Opioid-tolerant patients
  - Moderate to severe chronic pain
  - Significant improvements across a variety of clinical measures
- Safety and efficacy profile consistent with other strong opioid analgesics
- Extensive postmarketing experience
- Safe and well-tolerated when used as directed in this patient population

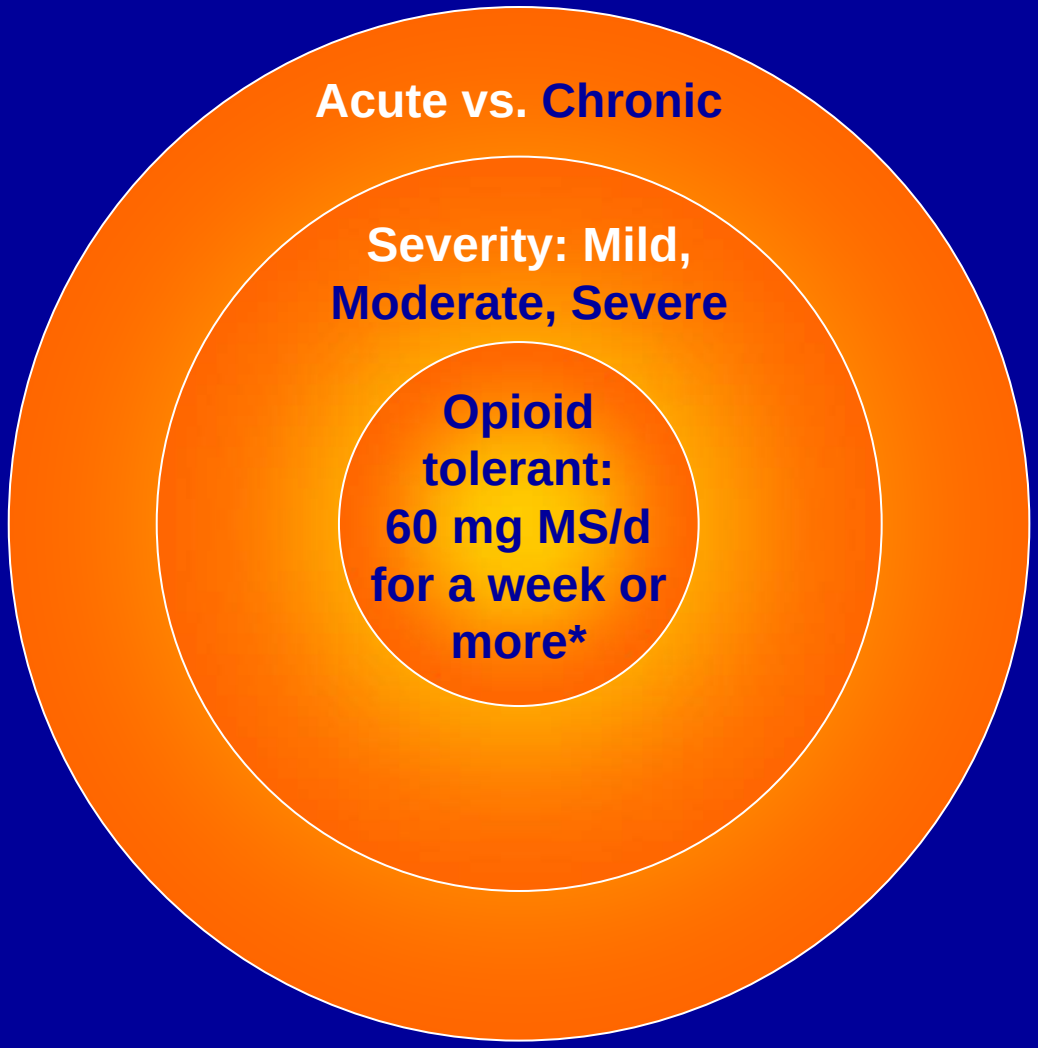
Extended-Release Hydromorphone for Patients With Chronic Pain

Lynn Webster, MD

Lifetree Clinical Research and Pain Clinic

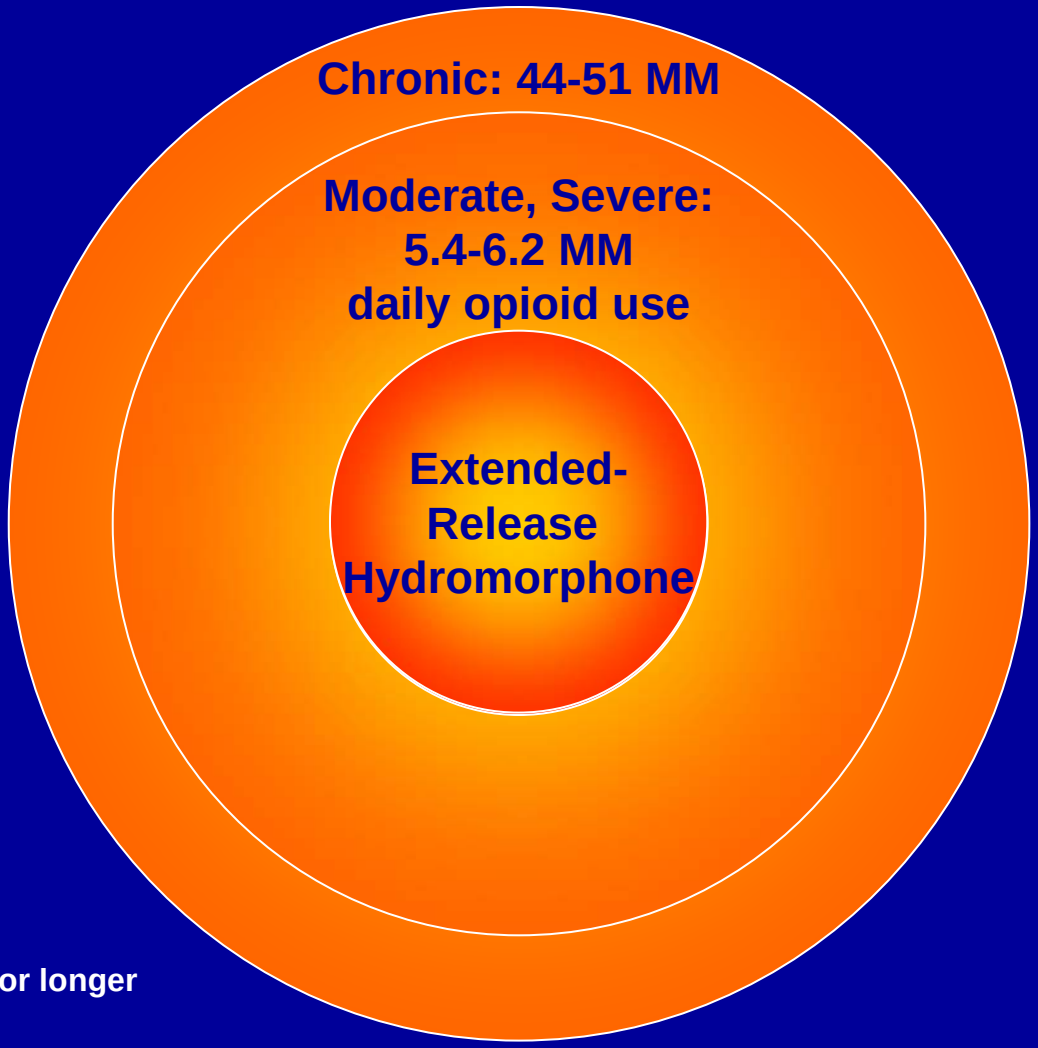
Salt Lake City, Utah

Pain Population Distribution



*Morphine sulfate equivalents/day.

Possible Candidates for Extended-Release Hydromorphone



*60 mg of morphine sulfate equivalents/day for 90 days or longer

Narayana A, et al. A healthcare claims database analysis to estimate the prevalence of chronic opioid use in adult patients in the United States. Presented at: American Academy of Pain Medicine 25th Annual Meeting; January 27-31, 2009; Honolulu, HI. Abstract 278.

Extended-Release Formulations

- Avoids peak and trough plasma levels
- Dosing convenience
- Reduces intra-dosing withdrawal
- Longer duration of relief
- Reduces pain induced insomnia
- Improves quality of life

Pharmacological management of persistent pain in older persons. American Geriatrics Society Panel on Pharmacological Management of Persistent Pain in Older Persons. *J Am Geriatr Soc.* 2009;57:1331-1346.

The management of chronic pain in older persons: AGS Panel on Chronic Pain in Older Persons. American Geriatrics Society. *J Am Geriatr Soc*. 1998;46:635-651.

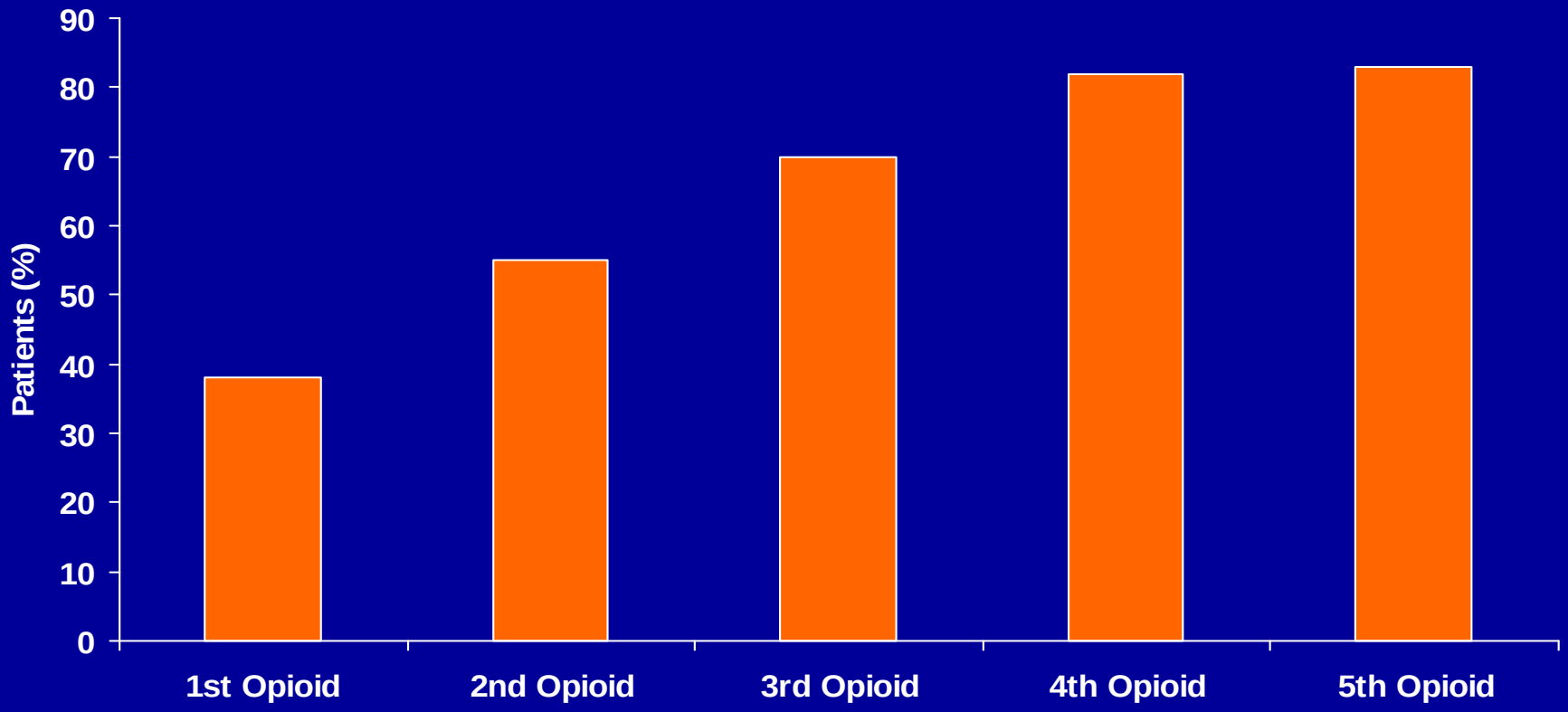
McCarberg BH, Barkin RL. Long-acting opioids for chronic pain: pharmacotherapeutic opportunities to enhance compliance, quality of life, and analgesia. *Am J Ther*. 2001;8:181-186.

Common Reasons to Rotate Opioids

- Loss of effectiveness
- Side effects
- Hyperalgesia
- Analgesic tolerance
- Interference with the P450 system
  - Induce metabolism of other drugs
  - Inhibit metabolism of other drugs
- Multiple mu-opioid receptor subtypes exist

Patients Commonly Switch Between Different Opioids

- 15% to 30% of patients switch and rotate between opioids with current treatment options[1]

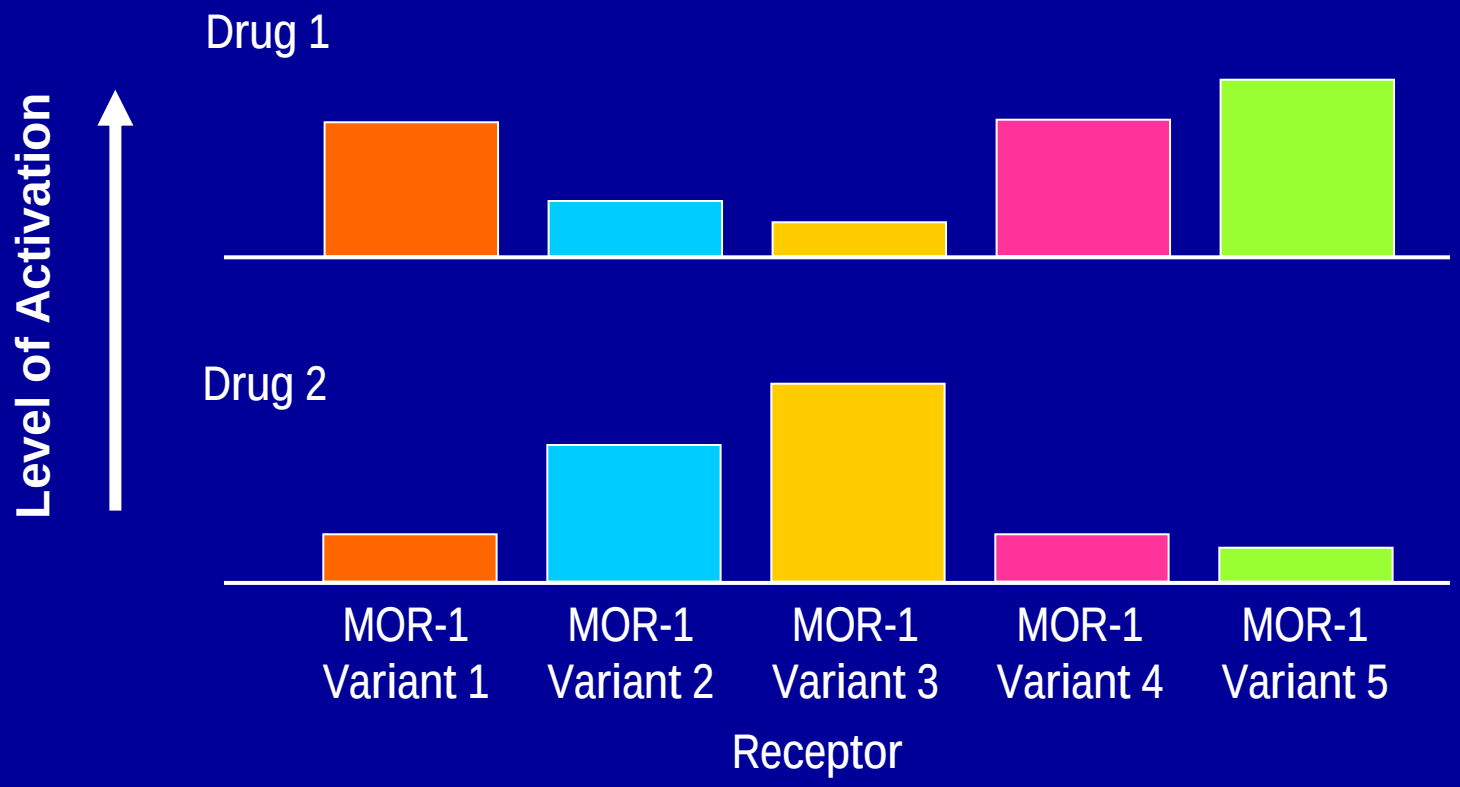


1. Slatkin, N. *Curr Med Res Opin*. 2009;25:2133-2150.

Adapted from Quang-Cantagrel ND, et al. *Anesth Analg.* 2000;90:933-937.

Variance of Mu-opioid Receptors

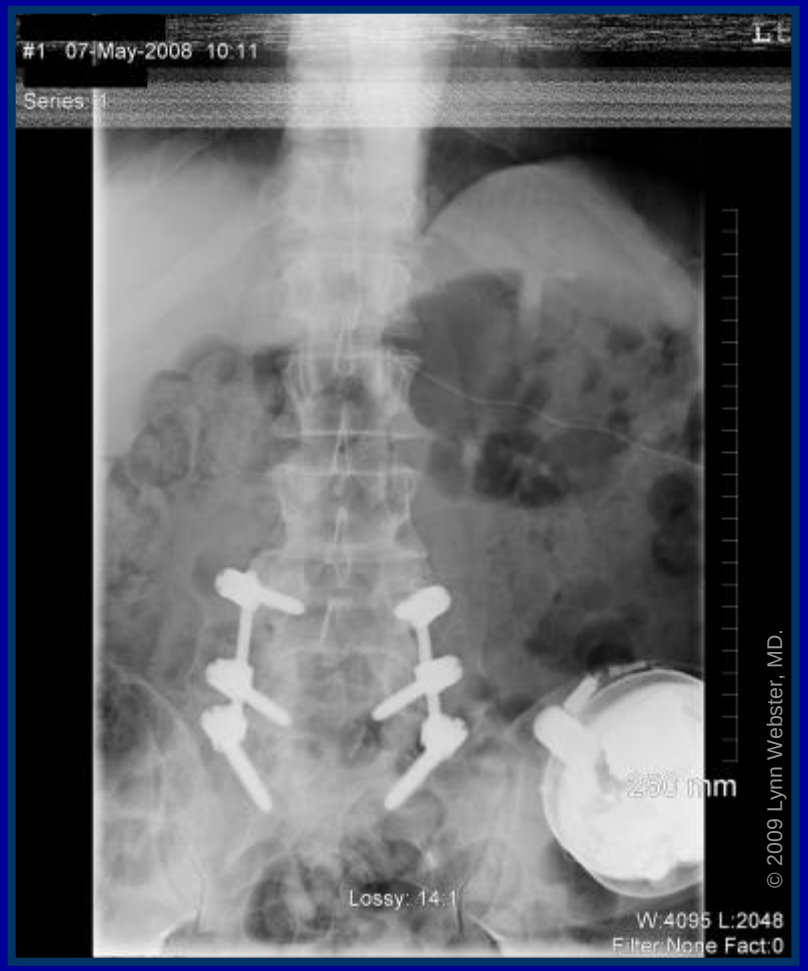
- **Receptor Variation for Same Patient With Different Drug**

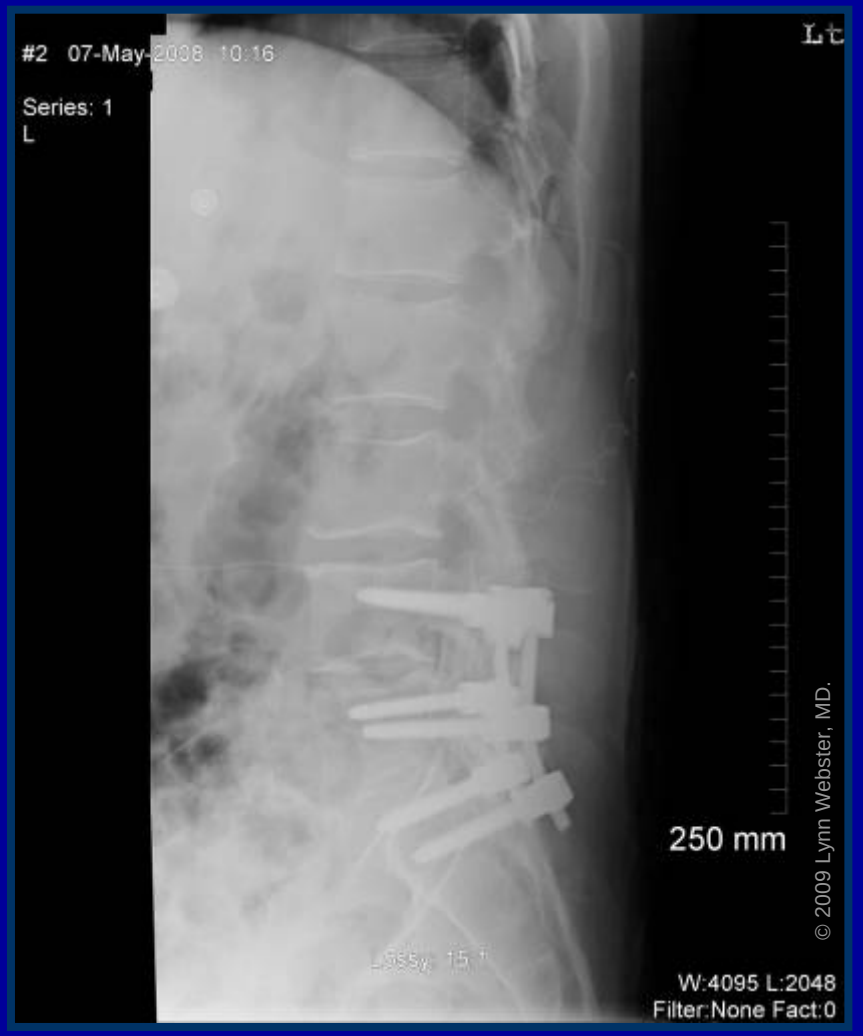


MOR, mu-opioid receptor.

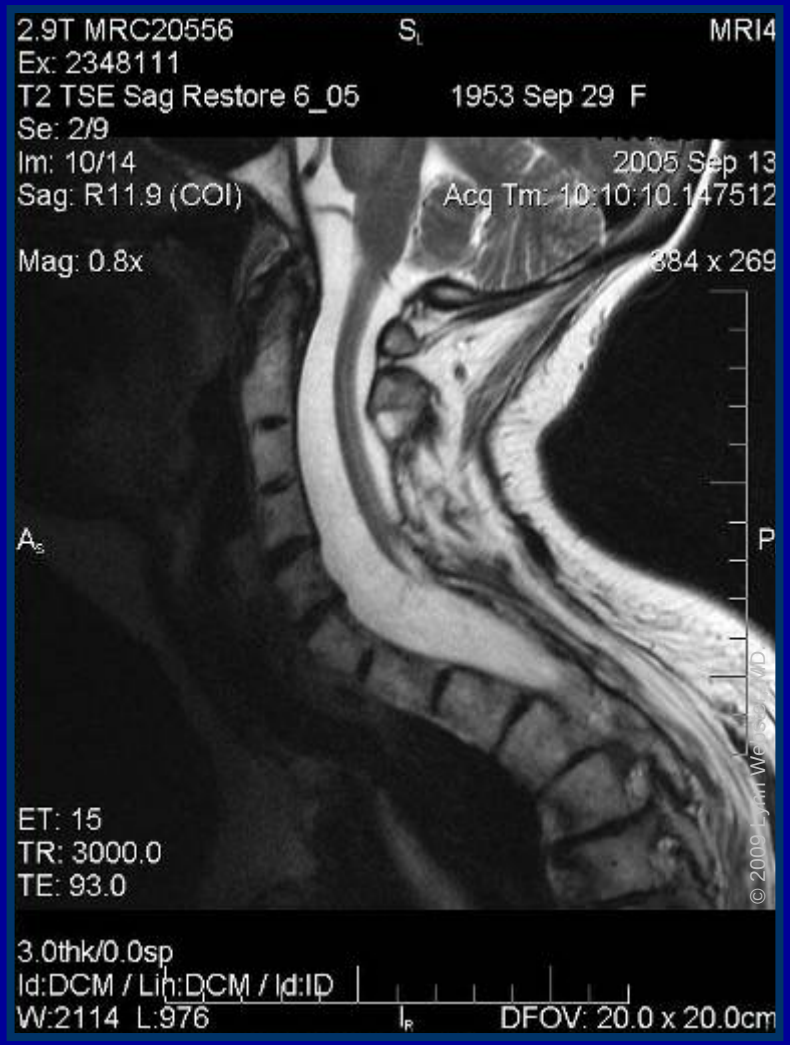
Pasternak GW. Incomplete cross tolerance and multiple mu opioid peptide receptors. *Trends Pharmacol Sci.* 2001;22:67-70.

Inadequate Pain Relief

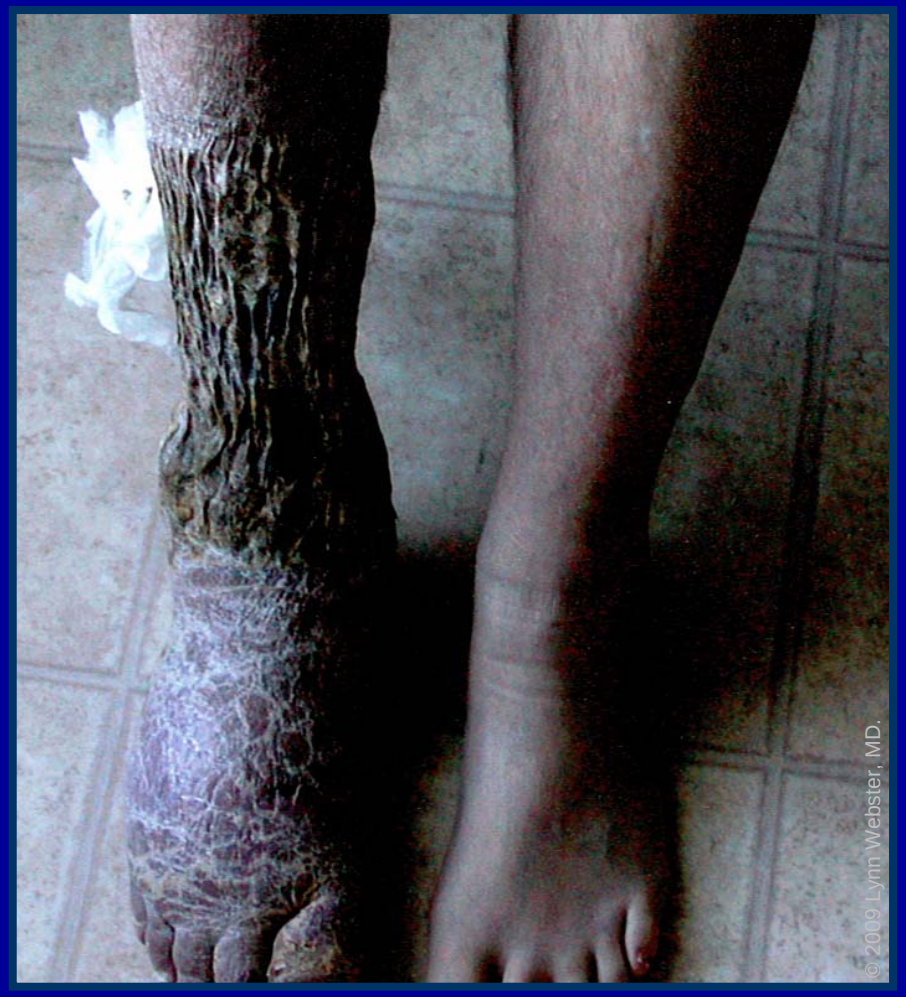




Only Transmucosal Fentanyl and Hydromorphone Provided Relief



Failed Available Sustained Release Oral and Transdermal Opioids



Extended-Release Hydromorphone Summary

- Hydromorphone is widely accepted as an effective short-acting analgesic
- Hydromorphone is not significantly metabolized by cytochrome P450
  - Reduced likelihood of drug-drug interactions affecting drug plasma concentration
- Hydromorphone has been used effectively in prolonged continuous intrathecal infusions
- Extended-release hydromorphone would provide another option to meet the need of patients not receiving adequate pain relief from current therapies

Risk Evaluation and Mitigation Strategy (REMS): Exalgo Alliance

Annette Stemhagen, DrPH, FISPE

Senior Vice President Epidemiology, Registries and Risk Management

United BioSource Corporation

Primary Risks

The primary risks of EXALGO

- Overdose
- Abuse and diversion

Risk Factors for Overdose and Respiratory Depression

- Non-opioid tolerance
- Elderly
- Debilitated health
- Co-morbid conditions
  - Impaired respiration
  - CNS depression
- Drug-drug interactions
  - Other sedating agents that depress respiration
- Abuse
  - Concurrent abuse of alcohol or other sedating substances

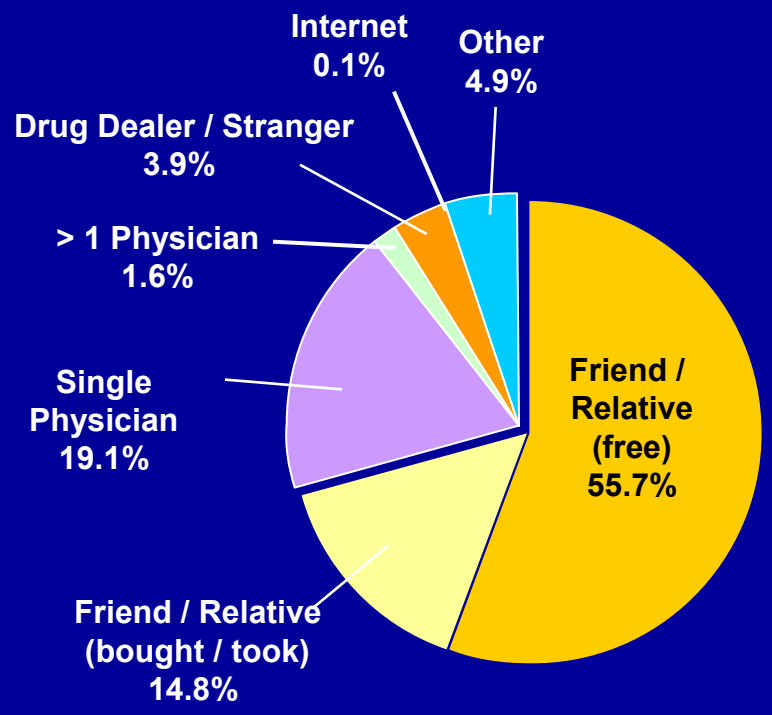
Patient Risk Factors for Abuse

- History of substance abuse[1]
  - Personal
  - Family
- Young age[1]
- History of preadolescent sexual abuse[1]
- Mental disease[1]
- Social patterns of drug use[2]
- Psychological stress[2]

1. Webster LR, Webster RM. Predicting aberrant behaviors in opioid-treated patients: preliminary validation of the Opioid Risk Tool. *Pain Med* 2005;6:432–42;
2. Savage SR. Assessment for addiction in pain-treatment settings. *Clin J Pain* 2002;18(4 Suppl.):S28–38;

Source of Non-Medical use of Prescription Opioids

In ~90% of non-medical users the source was a friend, relative, or a single physician



- **70% of respondents reported getting pain relievers from a friend or relative**
- **19% reported directly abusing the drug they had been prescribed by a single physician**

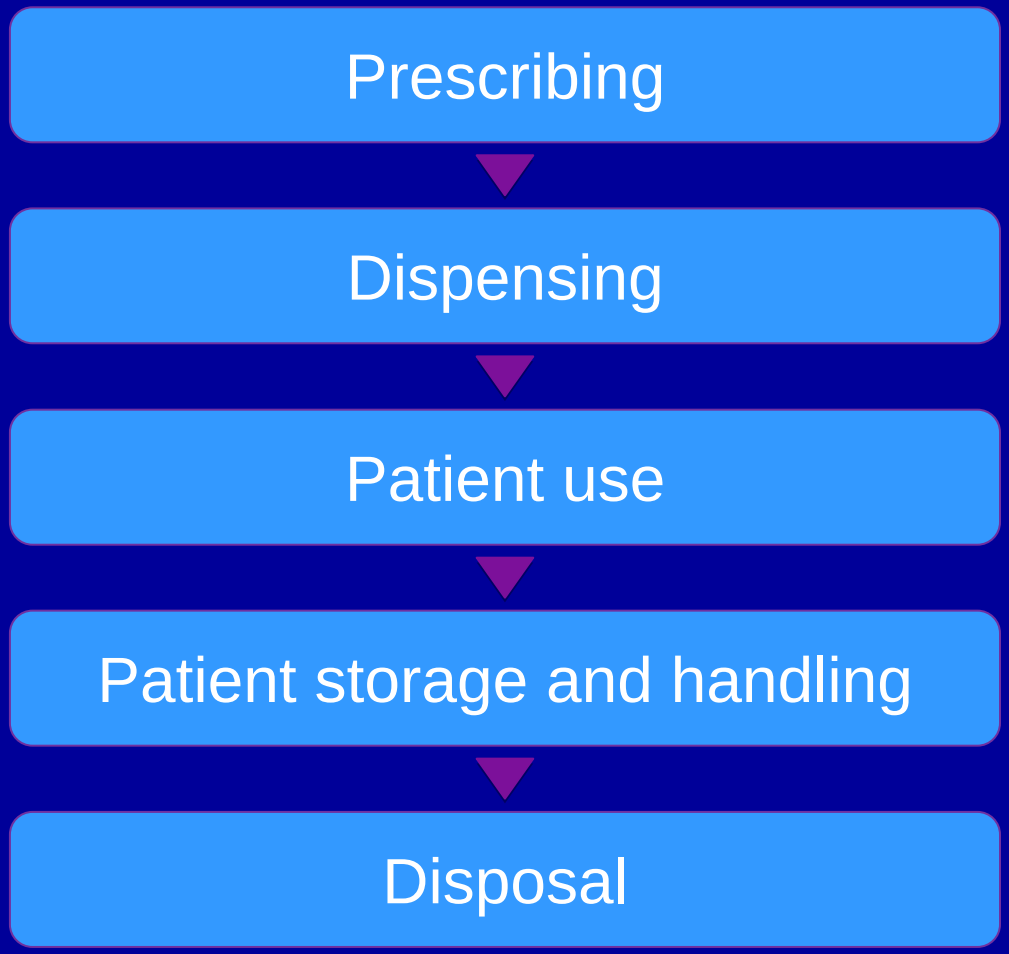
SAMHSA. Results from the 2006 National Survey on Drug Use and Health: National Findings, 2007. Available at: http://www.oas.samhsa.gov/nsduh/2k6nsduh/2k6Results.pdf. Accessed June 19, 2008.

Primary Goals of Exalgo Alliance

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

Exalgo Alliance Program Design

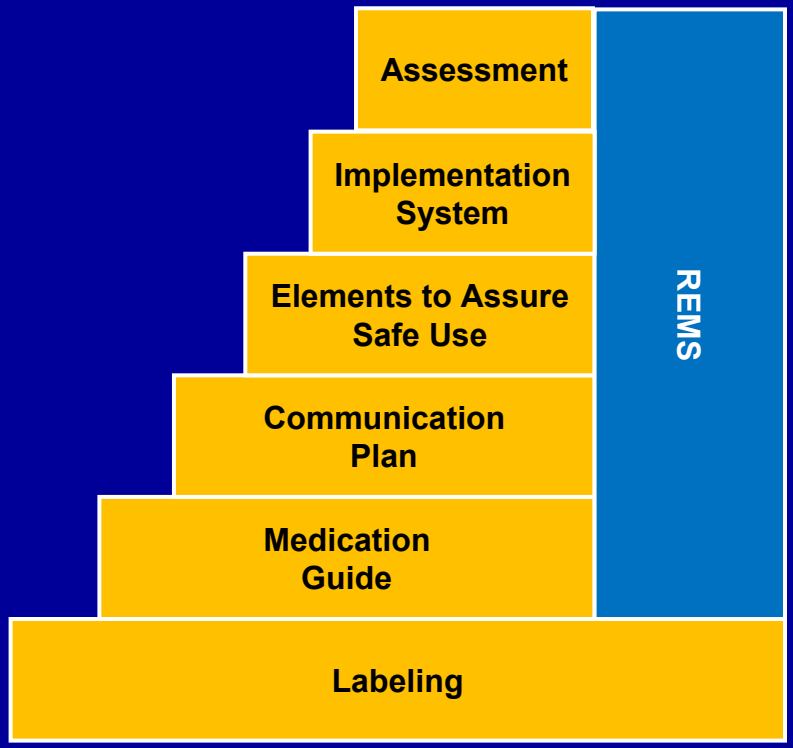
Points of Intervention



Aspects of the Exalgo Alliance Program

- Education and counseling
- Controlled access to those who:
  - Acknowledge understanding Exalgo Alliance
  - Follow safe use procedures
- Surveillance and monitoring
- Continuous program improvement

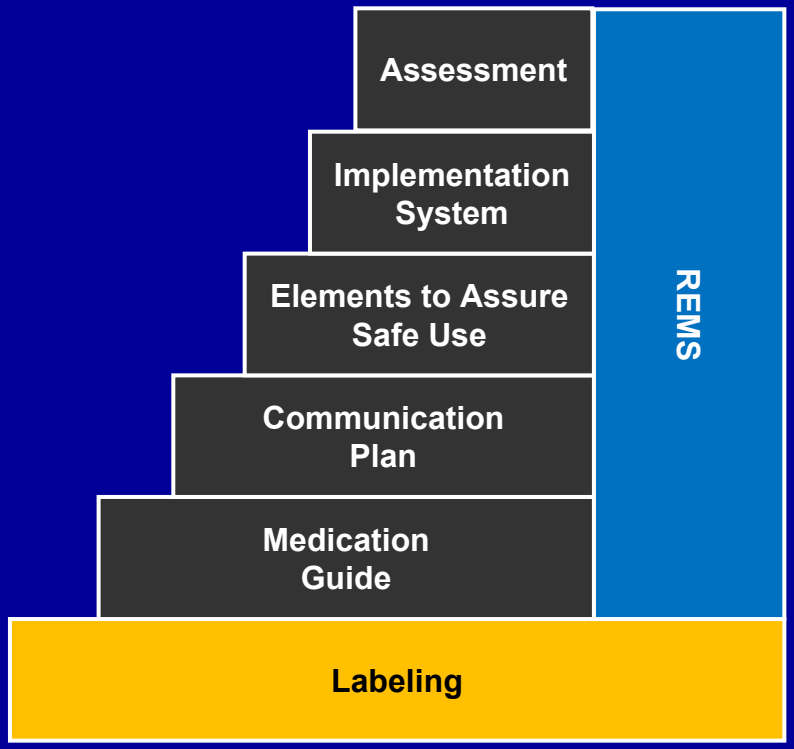
Components of the Exalgo Alliance Program



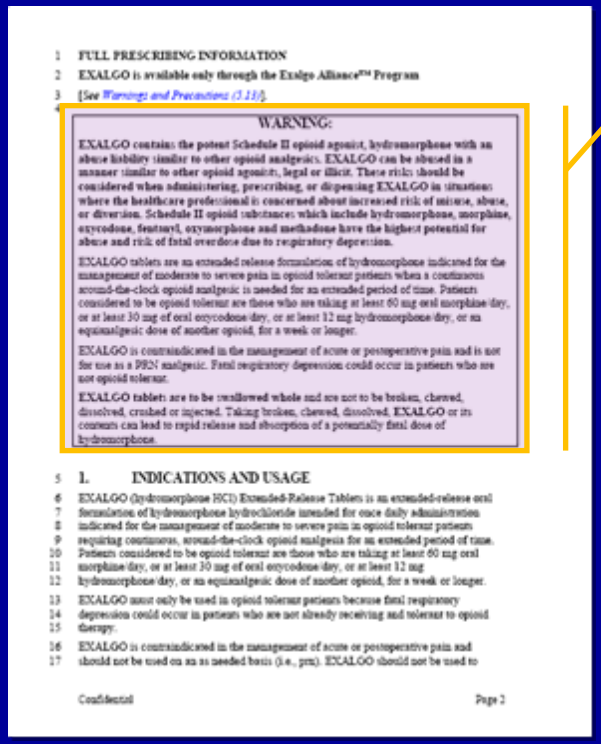
Components of the Exalgo Alliance Program

Labeling educates HCPs about:

- Risks and responsible prescribing, dispensing, and use
- Program requirements



Prescribing Information Boxed Warning



FULL PRESCRIBING INFORMATION

EXALGO is available only through the Exalgo Alliance™ Program

[See Warnings and Precautions (5.11)].

WARNING:

EXALGO contains the potent Schedule II opioid agonist, hydromorphone with an abuse liability similar to other opioid analgesics. EXALGO can be abused in a manner similar to other opioid agonists, legal or illicit. These risks should be considered when administering, prescribing, or dispensing EXALGO in situations where the healthcare professional is concerned about increased risk of misuse, abuse, or diversion. Schedule II opioid substances which include hydromorphone, morphine, oxycodone, fentanyl, oxymorphone and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

EXALGO tablets are an extended release formulation of hydromorphone indicated for the management of moderate to severe pain in opioid tolerant patients when a continuous around-the-clock opioid analgesic is needed 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 is contraindicated in the management of acute or postoperative pain and is not for use as a PRN analgesic. Fatal respiratory depression could occur in patients who are not opioid tolerant.

EXALGO tablets are to be swallowed whole and are not to be broken, chewed, dissolved, crushed or injected. Taking broken, chewed, dissolved, EXALGO or its contents can lead to rapid release and absorption of a potentially fatal dose of hydromorphone.

1. INDICATIONS AND USAGE

EXALGO (hydromorphone HCl) Extended-Release Tablets is an extended-release oral formulation of hydromorphone hydrochloride intended for once daily administration 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.

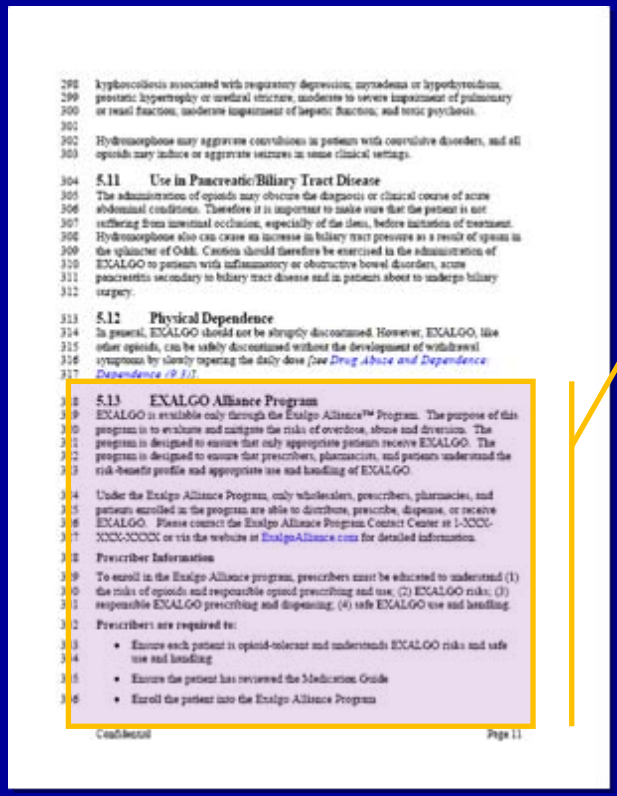
EXALGO is contraindicated in the management of acute or postoperative pain and should not be used on an as needed basis (i.e., prn). EXALGO should not be used to

Confidential Page 2

Provides information about mitigating primary risks of:

- **Overdose**
- **Abuse and diversion**

Prescribing Information Warnings Section 5.13



hypercoagulemia associated with respiratory depression, myxedema or hypothyroidism, prostatic hypertrophy or urethral stricture, moderate to severe impairment of pulmonary or renal function, moderate impairment of hepatic function, and toxic psychosis.

Hydromorphone may aggravate convulsions in patients with convulsive disorders, and all opioids may induce or aggravate seizures in some clinical settings.

5.11 Use in Pancreatic/Biliary Tract Disease

The administration of opioids may obscure the diagnosis or clinical course of acute abdominal conditions. Therefore it is important to make sure that the patient is not suffering from intestinal occlusion, especially of the ileus, before initiation of treatment. Hydromorphone also can cause an increase in biliary tract pressure as a result of spasm in the sphincter of Oddi. Caution should therefore be exercised in the administration of EXALGO to patients with inflammatory or obstructive bowel disorders, acute pancreatitis secondary to biliary tract disease and in patients about to undergo biliary surgery.

5.12 Physical Dependence

In general, EXALGO should not be abruptly discontinued. However, EXALGO, like other opioids, can be safely discontinued without the development of withdrawal symptoms by slowly tapering the daily dose *[see Drug Abuse and Dependence Dependence (9.3)]*.

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

Confidential Page 11

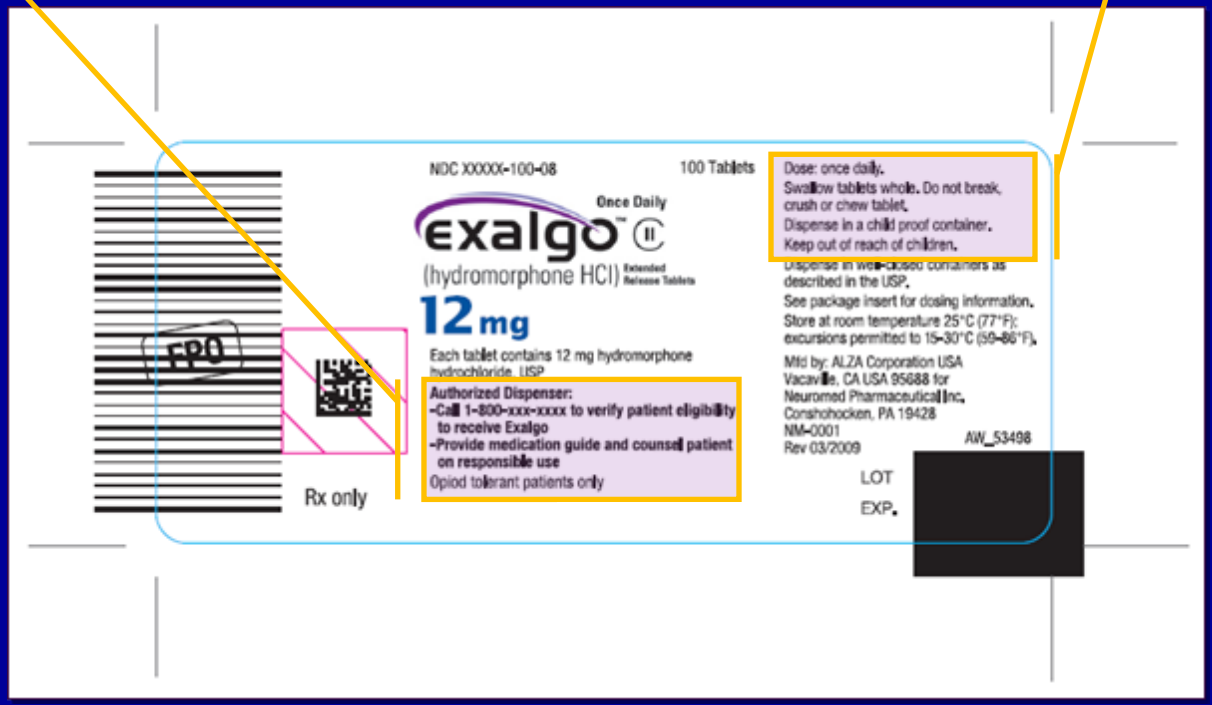
Provides information about Exalgo Alliance Program:

- **Program requirements**
- **Stakeholder enrollment**
- **Prescription verification**

Bottle Labeling

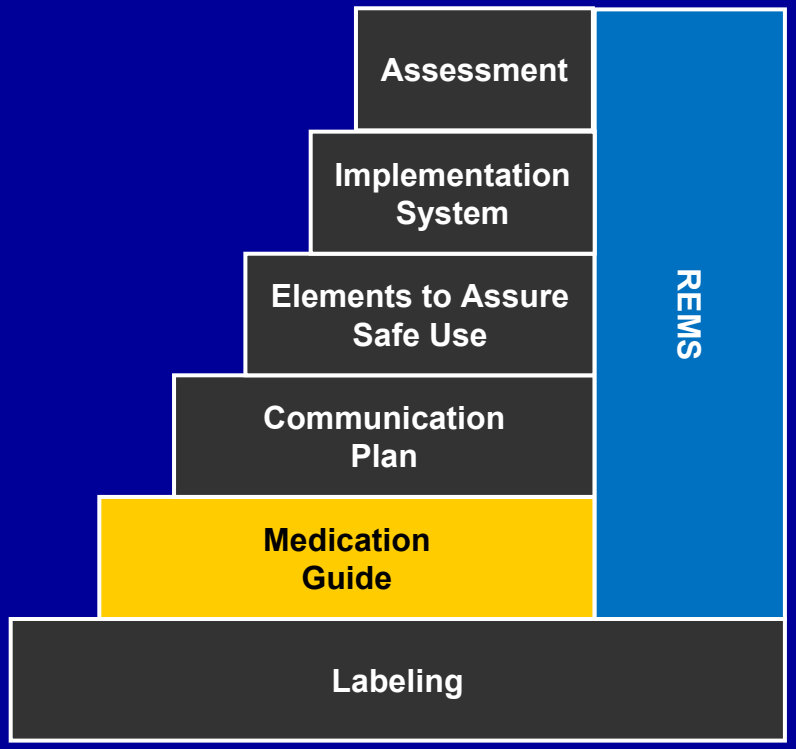
- Verify patient eligibility
- Opioid-tolerant patients only
- Provide Medication Guide
- Counsel patient

- Once daily
- Swallow tablets whole
- Do not break, crush or chew
- Dispense in child-proof container
- Keep out of reach of children

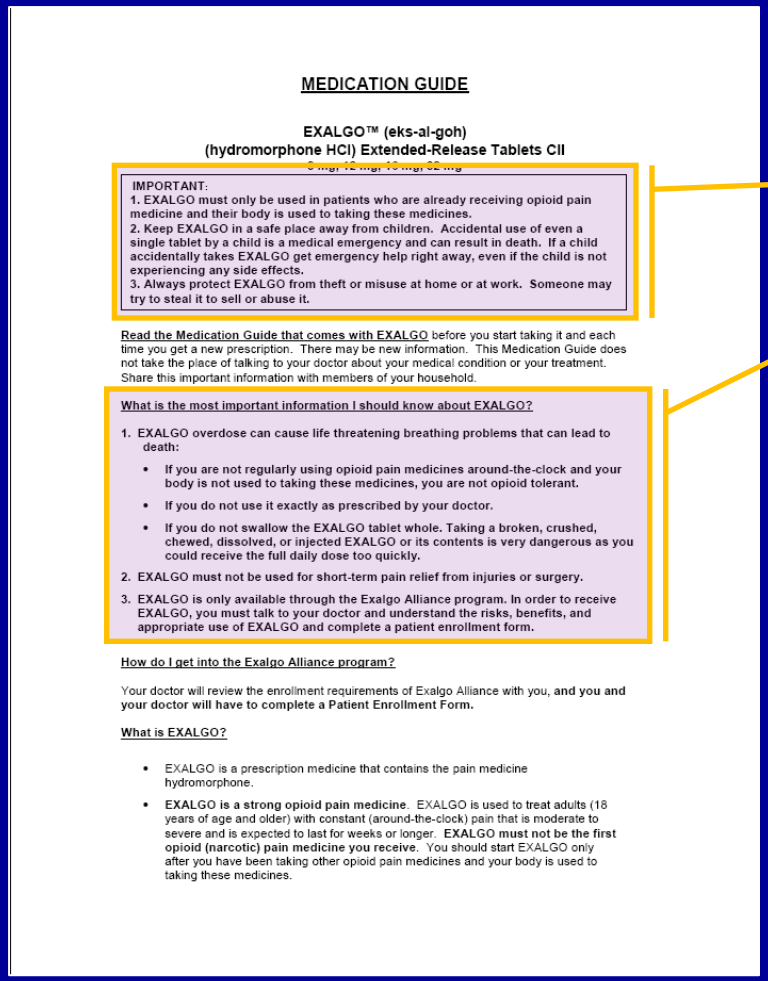


Components of the Exalgo Alliance Program

- Medication Guide educates patients about:
  - Risks and safe use and handling
  - Program requirements



Medication Guide



MEDICATION GUIDE

EXALGO™ (eks-al-goh)
(hydromorphone HCl) Extended-Release Tablets CII

IMPORTANT:
1. EXALGO must only be used in patients who are already receiving opioid pain medicine and their body is used to taking these medicines.
2. Keep EXALGO in a safe place away from children. Accidental use of even a single tablet by a child is a medical emergency and can result in death. If a child accidentally takes EXALGO get emergency help right away, even if the child is not experiencing any side effects.
3. Always protect EXALGO from theft or misuse at home or at work. Someone may try to steal it to sell or abuse it.

Read the Medication Guide that comes with EXALGO before you start taking it and each time you get a new prescription. There may be new information. This Medication Guide does not take the place of talking to your doctor about your medical condition or your treatment. Share this important information with members of your household.

What is the most important information I should know about EXALGO?

1. EXALGO overdose can cause life threatening breathing problems that can lead to death:
   - If you are not regularly using opioid pain medicines around-the-clock and your body is not used to taking these medicines, you are not opioid tolerant.
   - If you do not use it exactly as prescribed by your doctor.
   - If you do not swallow the EXALGO tablet whole. Taking a broken, crushed, chewed, dissolved, or injected EXALGO or its contents is very dangerous as you could receive the full daily dose too quickly.
2. EXALGO must not be used for short-term pain relief from injuries or surgery.
3. EXALGO is only available through the Exalgo Alliance program. In order to receive EXALGO, you must talk to your doctor and understand the risks, benefits, and appropriate use of EXALGO and complete a patient enrollment form.

How do I get into the Exalgo Alliance program?

Your doctor will review the enrollment requirements of Exalgo Alliance with you, **and you and your doctor will have to complete a Patient Enrollment Form.**

What is EXALGO?

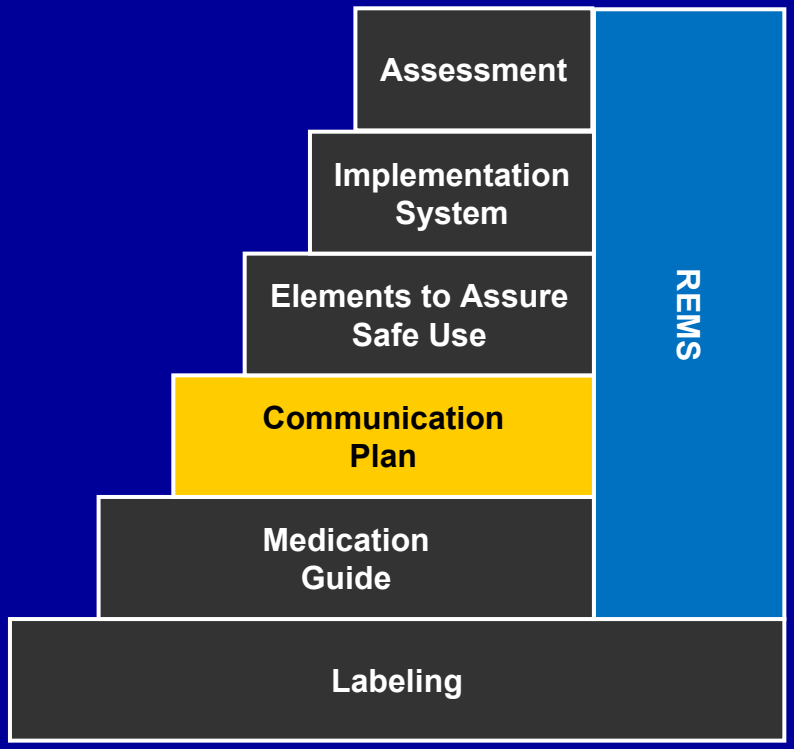
- EXALGO is a prescription medicine that contains the pain medicine hydromorphone.
- **EXALGO is a strong opioid pain medicine.** EXALGO is used to treat adults (18 years of age and older) with constant (around-the-clock) pain that is moderate to severe and is expected to last for weeks or longer. **EXALGO must not be the first opioid (narcotic) pain medicine you receive.** You should start EXALGO only after you have been taking other opioid pain medicines and your body is used to taking these medicines.

- Patients must be opioid tolerant
- Keep EXALGO in a safe, secure place from children
  - Accidental ingestion by a child is considered a medical emergency
- Protect EXALGO against theft and misuse
- Overdose can cause life-threatening breathing problems that can lead to death
- EXALGO must not be used for short-term pain
- EXALGO is only available through the Exalgo Alliance

Components of the Exalgo Alliance Program

Communication Plan educates all stakeholders about:

- Risks and responsible prescribing, dispensing, and use
- Program requirements



Exalgo Alliance Education and Communication Components

REMS components	Prescriber	Pharmacy/HCS	Patient
Labeling and scheduling			
Schedule II restrictions	☑	☑	☑
Prescribing Information (PI)	☑	☑	
Bottle label		☑	
Medication Guide			☑
Program and enrollment material			
Introductory letters	☑	☑	
Program brochures	☑	☑	☑
Enrollment kit	☑	☑	☑
Education slide module	☑	☑	
Enrollment forms	☑	☑	☑
Prescriber-Patient Medication Agreement	☑		☑
Website / Resource center			
ExalgoAlliance.com website	☑	☑	☑

Core Safety Messages

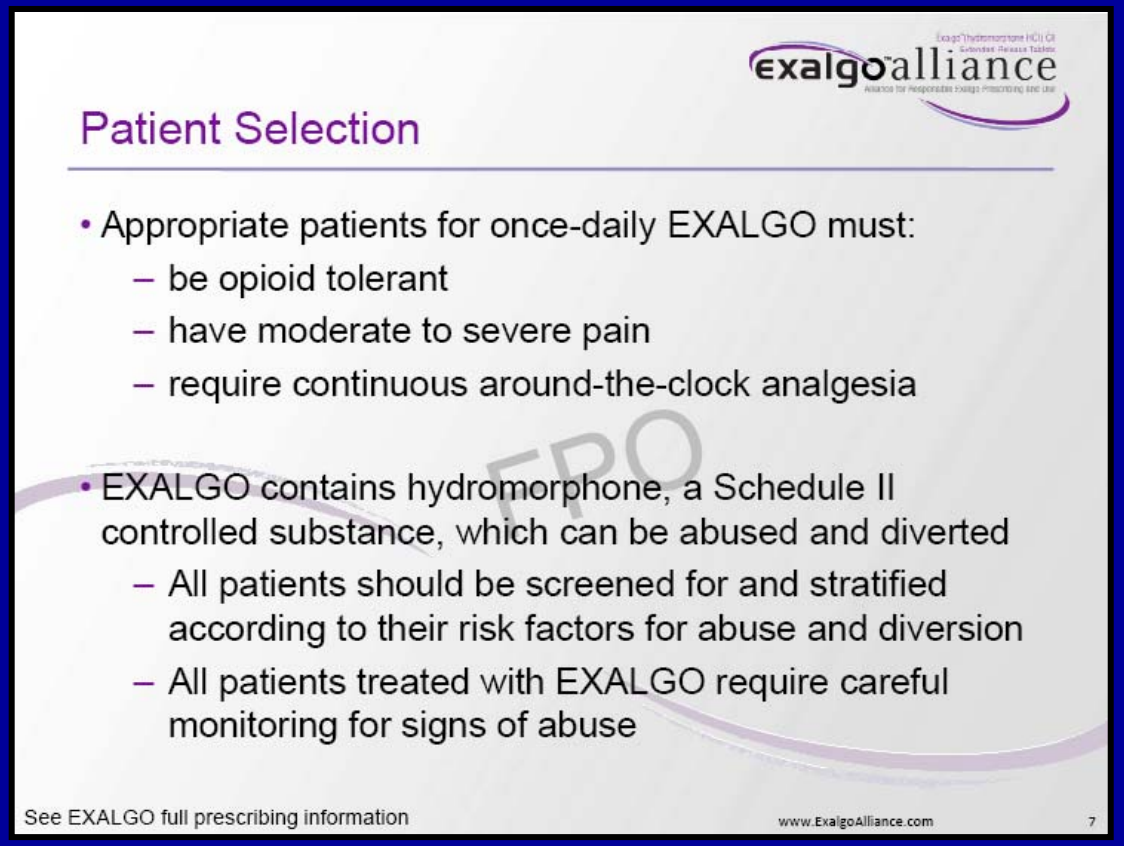
	Messages	Overdose	Abuse	Diversion
Patient selection and monitoring	Risk of overdose	✓	✓	✓
	Screen for risk of abuse		✓	✓
	Monitor for abuse		✓	✓
	Opioid-tolerant patients only	✓	✓	✓
	Not for short-term, acute, prn pain	✓		
	Proper dosing and administration	✓		
Safe use	Do not break, crush, chew, etc	✓	✓	✓
	Does not work immediately	✓	✓	✓
	Take exactly as prescribed	✓	✓	
Protect from accidental exposure and diversion	Keep tablets in secure place	✓	✓	✓
	Keep away from children	✓		
	Store in child-proof container	✓		
	Use by child is emergency	✓		
	Seek help immediately	✓		
	Immediate and proper disposal	✓	✓	✓
	Protect from theft		✓	✓

ExalgoAlliance.com

- Program information
- Education on responsible EXALGO prescribing and use
- Access to support resources
  - Printable versions of forms and tools

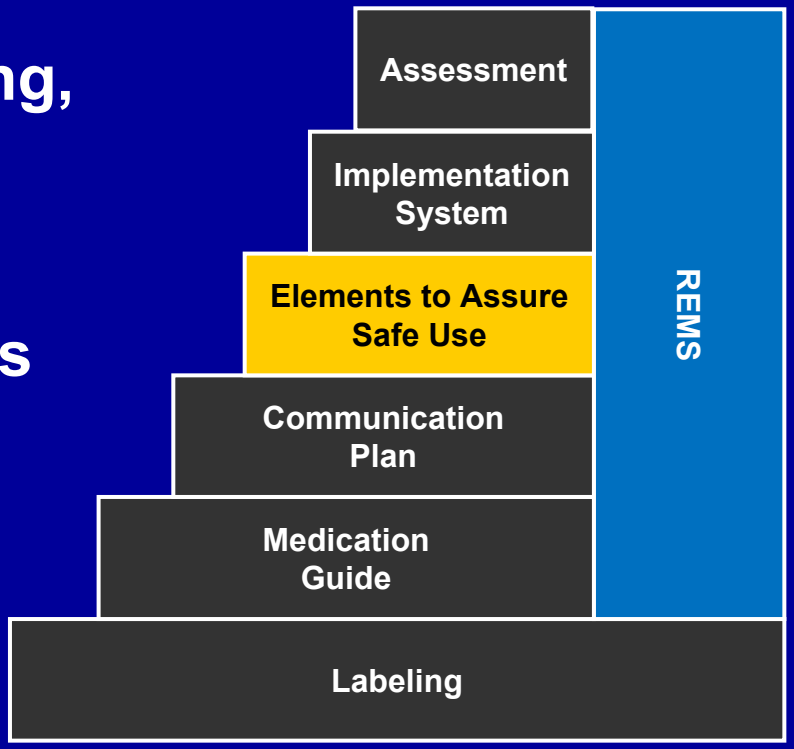
Training and Acknowledgement of Proper Patient Selection

- Indication
- Contraindications
- Patient selection
  - Risk stratification



Components of the Exalgo Alliance Program

- **Elements to Assure Safe Use:**
  - Educate stakeholders about
    - Risks
    - Responsible prescribing, dispensing, and use
  - Enroll stakeholders
  - Verify safe use procedures

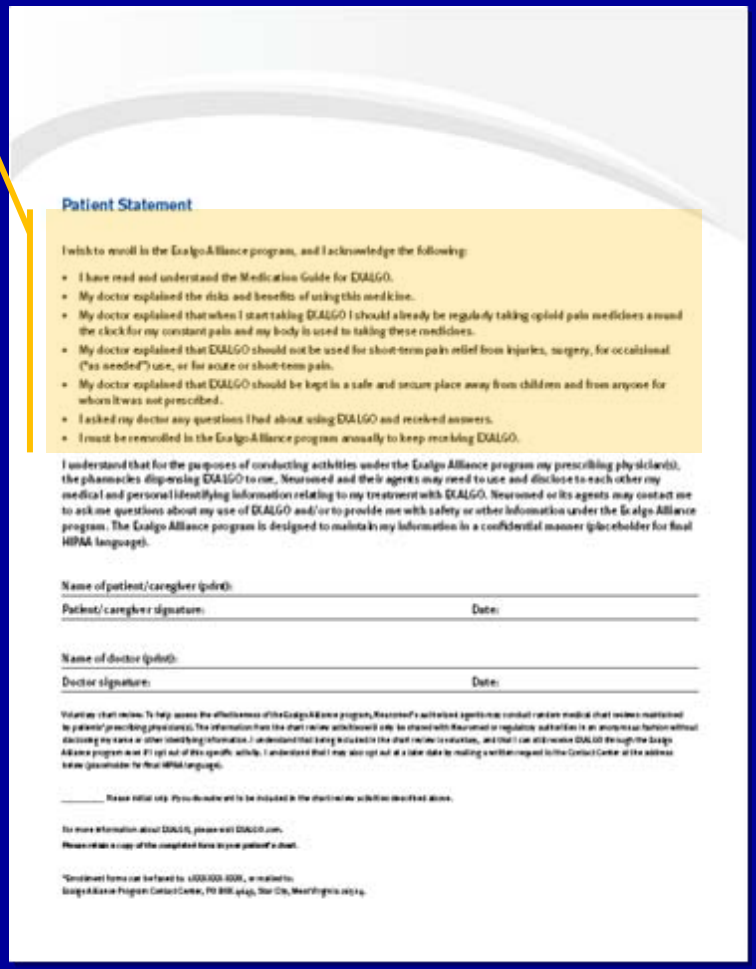


Elements to Assure Safe Use

- Prescribers must be enrolled to prescribe and re-enrolled annually
- Patients must sign a Prescriber-Patient Medication Agreement and be enrolled annually
- Pharmacies must be enrolled to purchase and dispense and re-enrolled every 2 years
- Pharmacists must obtain verification of prescription eligibility prior to each dispensing
- Wholesalers and distributors agree to sell and distribute only to enrolled pharmacies and healthcare settings

Prescriber-Patient Medication Agreement

- Patient read and understood Medication Guide
- Doctor explained the risks and benefits
- Doctor explained opioid tolerance as a necessary condition
- Doctor explained EXALGO is not for
  - Short-term pain relief from injuries or surgery
  - Occasional (“as needed”) use
  - Acute or short-term pain
- Doctor explained that EXALGO must be taken exactly as prescribed including
  - Taken once daily
  - Swallowed whole; do not break, crush or chew
  - May take several hours to begin working; do not take additional dose
- Doctor explained keeping EXALGO safe and secure
  - Away from children
  - Away from anyone for whom it was not prescribed
- Doctor answered patient’s questions



Patient Statement

I wish to enroll in the Exalgo Alliance program, and I acknowledge the following:

- 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 to 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 should be kept 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 re-enrolled in the Exalgo Alliance program annually to keep receiving EXALGO.

I understand that for the purposes of conducting activities under the Exalgo Alliance program my prescribing physician(s), the pharmacies dispensing EXALGO to me, Neurosmed and their agents may need to use and disclose to each other my medical and personal identifying information relating to my treatment with EXALGO. Neurosmed or its agents may contact me to ask me questions about my use of EXALGO and/or to provide me with safety or other information under the Exalgo Alliance program. The Exalgo Alliance program is designed to maintain my information in a confidential manner (placeholder for final HIPAA language).

Name of patient/caregiver (print):

Patient/caregiver signature: Date:

Name of doctor (print):

Doctor signature: Date:

Print Enrollment Form

Program Testing

- Objectives
  - Qualitative and quantitative assessment of core Exalgo Alliance materials and program elements
  - Conducted with prescribers, pharmacists, and patients to:
    - Assess clarity/comprehension
    - Identify how to improve retention/communication

GfK Healthcare: Exalgo Alliance Communication Study. August 2009.

Respondents Were Provided the Following REMS Materials

Physicians

- Medication Guide
- Patient Enrollment Form with PPMA
- Prescriber Enrollment Form
- Prescriber REMS Program Brochure
- Prescriber Education Module

Pharmacists

- Medication Guide
- Pharmacy Enrollment Form
- Pharmacy Education Module

Patients

- Medication Guide
- Patient Enrollment Form with PPMA
- Patient REMS Program Brochure

GfK Healthcare: Exalgo Alliance Communication Study. August 2009.

Qualitative and Quantitative Study Sample

	Physician[a]	Pharmacy[b]	Patient[c]
Qualitative	20	12	15
Quantitative	150	35	75
Total	170	47	90

[a] Physician = see ≥10 patients with CIIs/mo.

[b] Pharmacy = independent and chain

[c] Patient = chronic pain patients

GfK Healthcare: Exalgo Alliance Communication Study. August 2009.

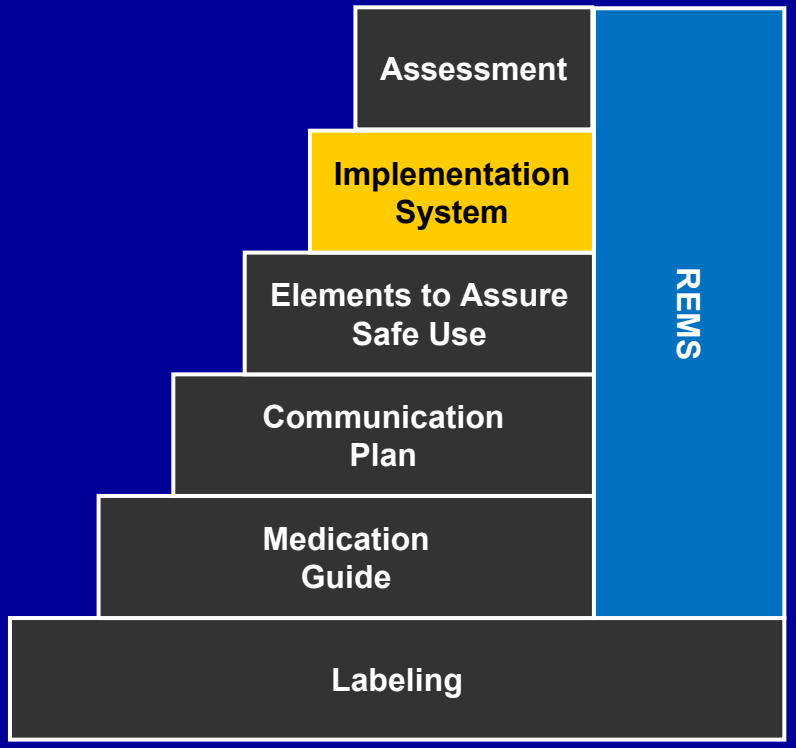
Quantitative Testing Results:
Stakeholder Response to Exalgo Alliance

- Clear and effective communication of
  - Core safety messages
  - Safe use procedures
  - Program requirements
- Identified gaps resulted in proposed modifications
  - (e.g., Medication Guide, PPMA, enrollment forms)
- Stakeholders expressed willingness to participate in the program:
  - Patients (93%)
  - Prescribers (83%)
  - Pharmacists (91%)

GfK Healthcare: Exalgo Alliance Communication Study. August 2009.

Components of the Exalgo Alliance Program

- Implementation System establishes the infrastructure of the Elements to Assure Safe Use



REMS Implementation, Assessment, and Commitment

Herbert Neuman, MD
Vice President of Medical Affairs
and Chief Medical Officer
Covidien Pharmaceuticals

Covidien Commitment

- Covidien is a global healthcare company
- Covidien's pharmaceutical subsidiary, Mallinckrodt Inc., has been an active producer of opioid analgesics since 1898
- We will be building upon an existing foundation of safety surveillance and monitoring for all our products
- Covidien will be a responsible steward of this product

Responsible Stewardship

- Responsible commercialization
- Responsible distribution
- Rational and achievable Risk Evaluation and Mitigation Strategy
- Open communication with governmental and scientific communities

Responsible Commercialization

- Drive appropriate education and enrollment of experienced pain practitioners
- No direct to consumer advertising
- Relevant Covidien personnel will be required to support REMS activities and adhere to all policies and practices
  - PhRMA Guidelines
  - Covidien SOPs
- Zero tolerance for infractions

Responsible Distribution

- Long-term relationships with select distributors
- Distributors will be contractually prohibited from delivering to non-enrolled pharmacies
- Regular distributors audits

Responsible REMS Design

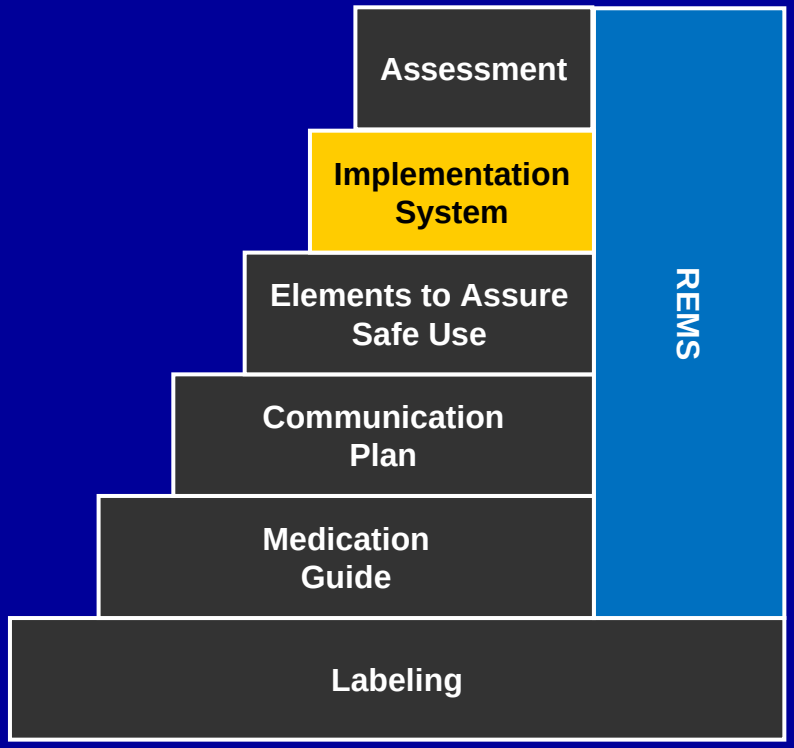
- Existing stakeholder workflow process compatibility
- Designed to minimize risks
  - Addresses known risk factors for overdose/abuse
  - Targets primary sources of diversion
    - 80% to 90% result from a patient or physician
- Adapts to evolution in risk management or a long-acting opioid-class REMS

Responsible REMS Implementation

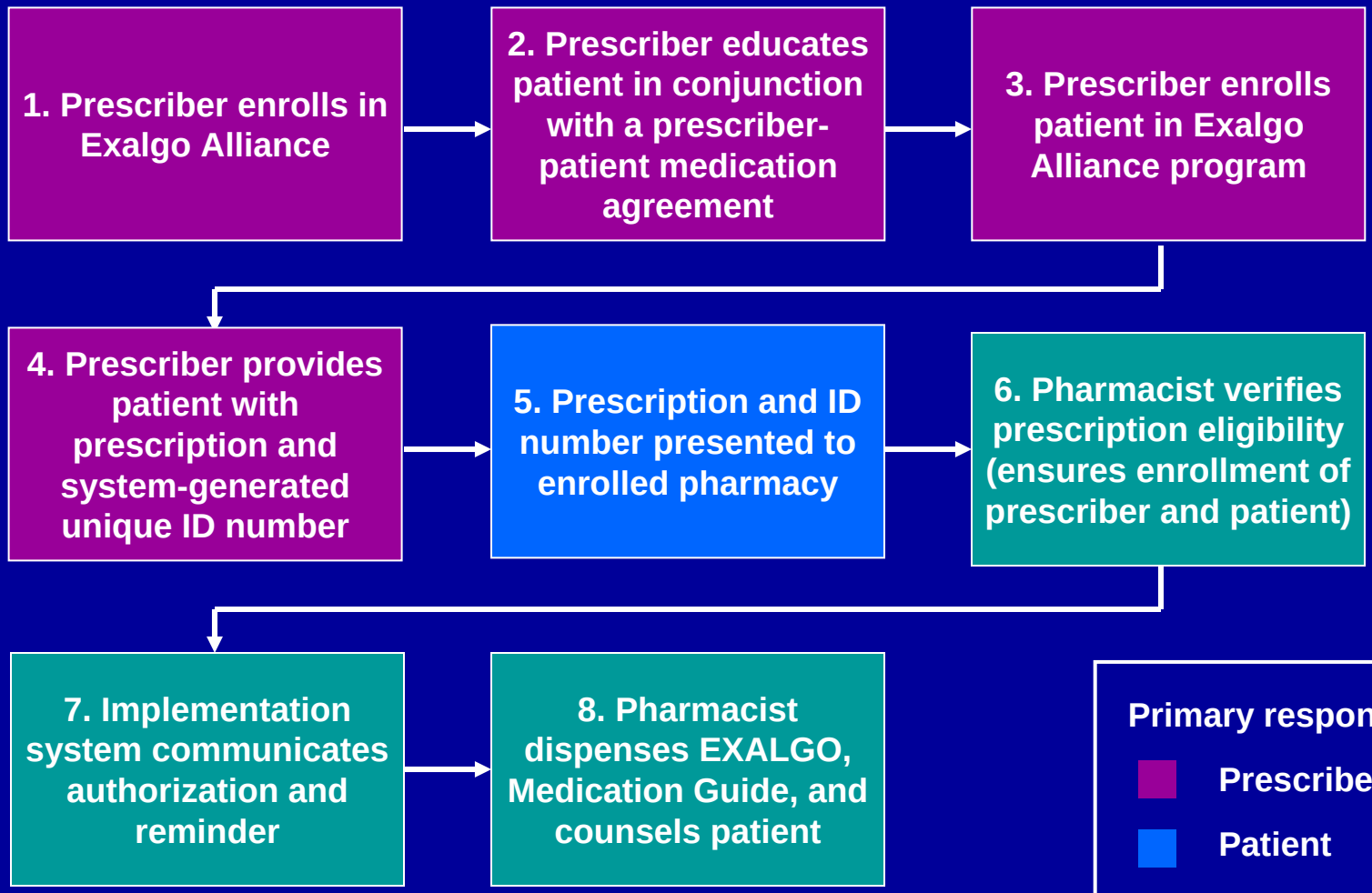
- Appropriate patient access enabled
- Deviations to guidelines aggressively addressed
- Information suggesting possible criminal conduct will be forwarded to relevant law enforcement officials
- De-identified data will be responsibly studied and results shared as appropriate

Components of the Exalgo Alliance Program

- Implementation System establishes the infrastructure of the Elements to Assure Safe Use



Exalgo Alliance Overall Process Flow

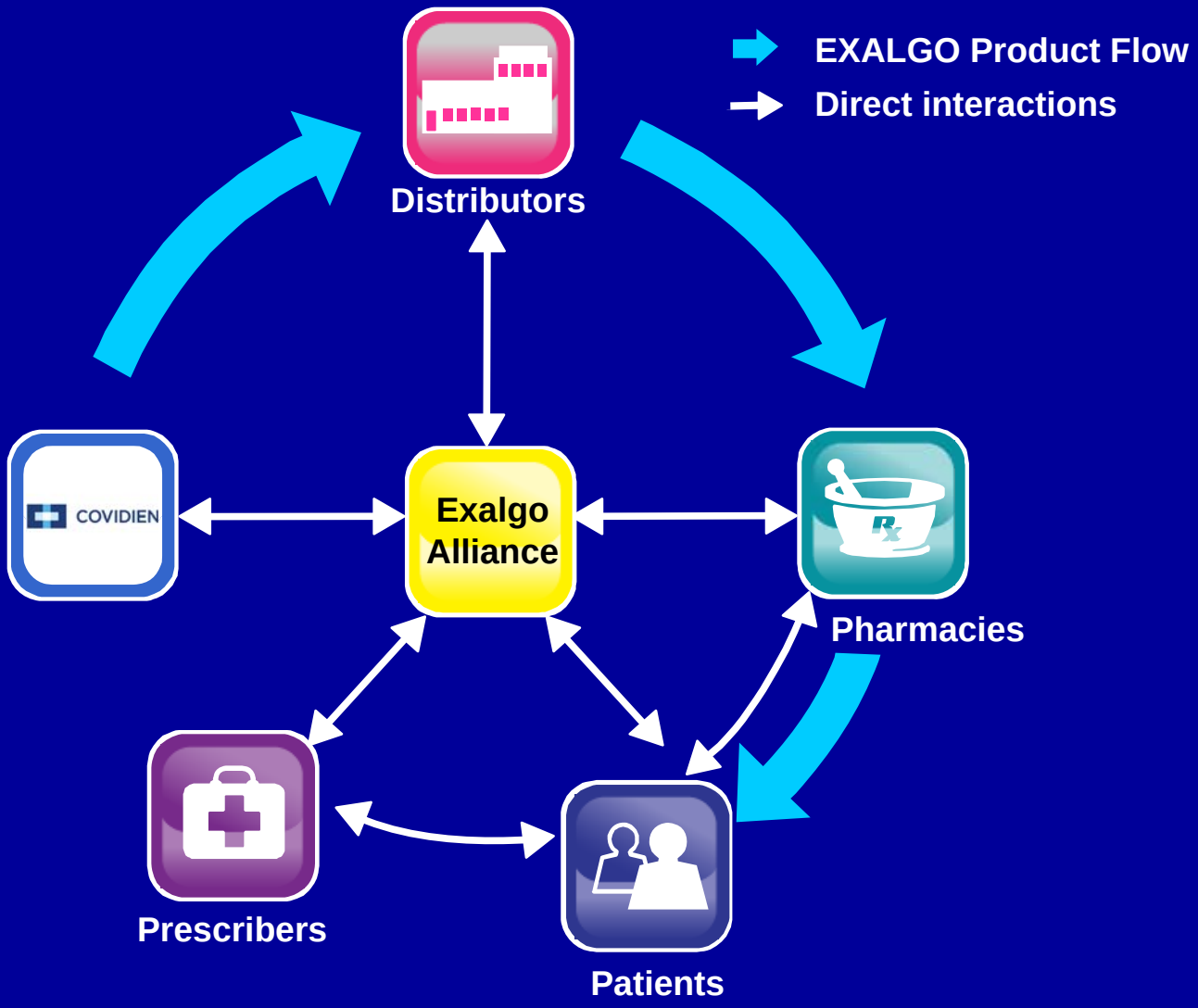


ExalgoAlliance.com Features

- Prescriber enrollment
- Patient enrollment
  - Unique PIN provided
- Pharmacy enrollment
- Prescription verification
- Access to support resources and tools
  - Electronic forms and tools

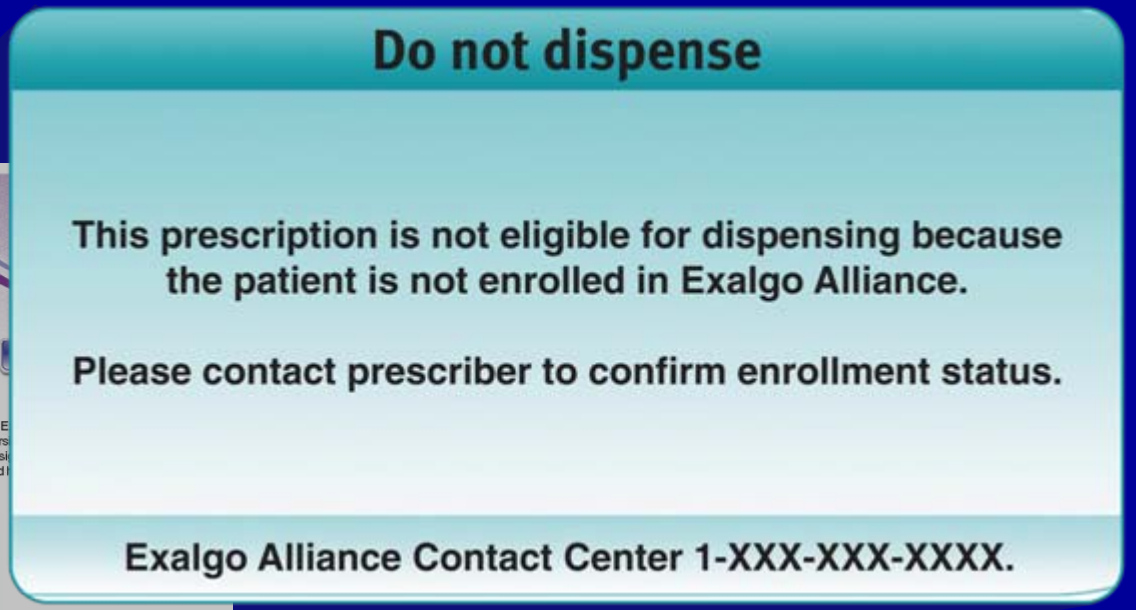
Controlled Access System

Distribution to Appropriate Patients



Verification of Safe Use Procedures

- System links the prescriber, patient, and pharmacy to ensure safe use procedures, including alerts to pharmacist as needed

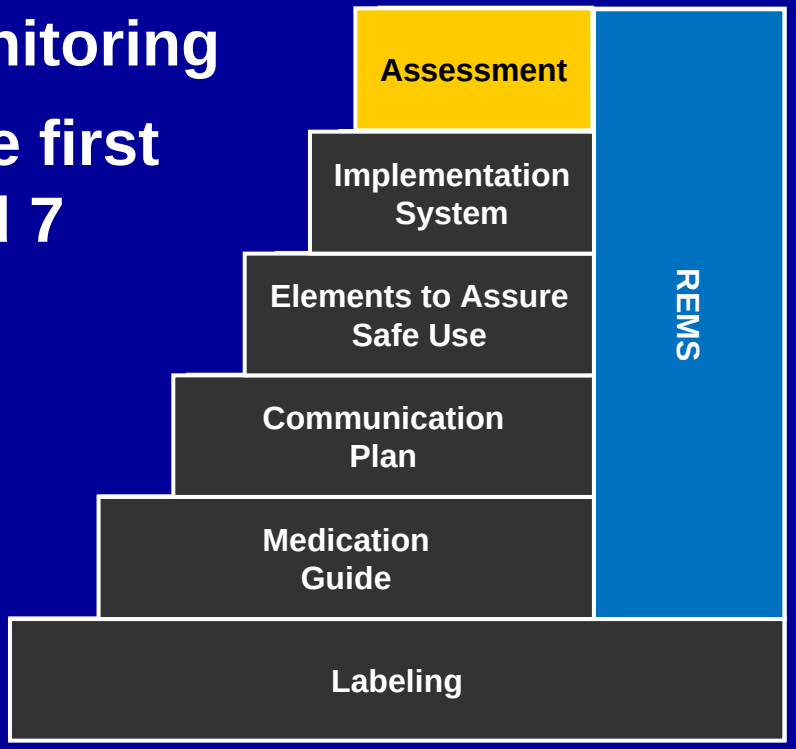


Corrective Actions

- Communication to specific stakeholders
- Escalation
  - One intervention with re-education
  - De-enrollment with potential for appeal
  - Re-education and re-enrollment opportunities

Components of the Exalgo Alliance Program

- **Assessment**
  - Program performance and effectiveness
  - Risk surveillance and monitoring
  - Submitted annually for the first 3 years and at years 5 and 7



Effectiveness Assessments

- Program performance metrics
- Prospective surveys and studies
- Retrospective claims analysis

Exalgo Alliance Safety Assessment

Exalgo Alliance Implementation Database

Stakeholder enrollment and tablet dispensing

Covidien Pharmacovigilance Database

Spontaneously reported AEs

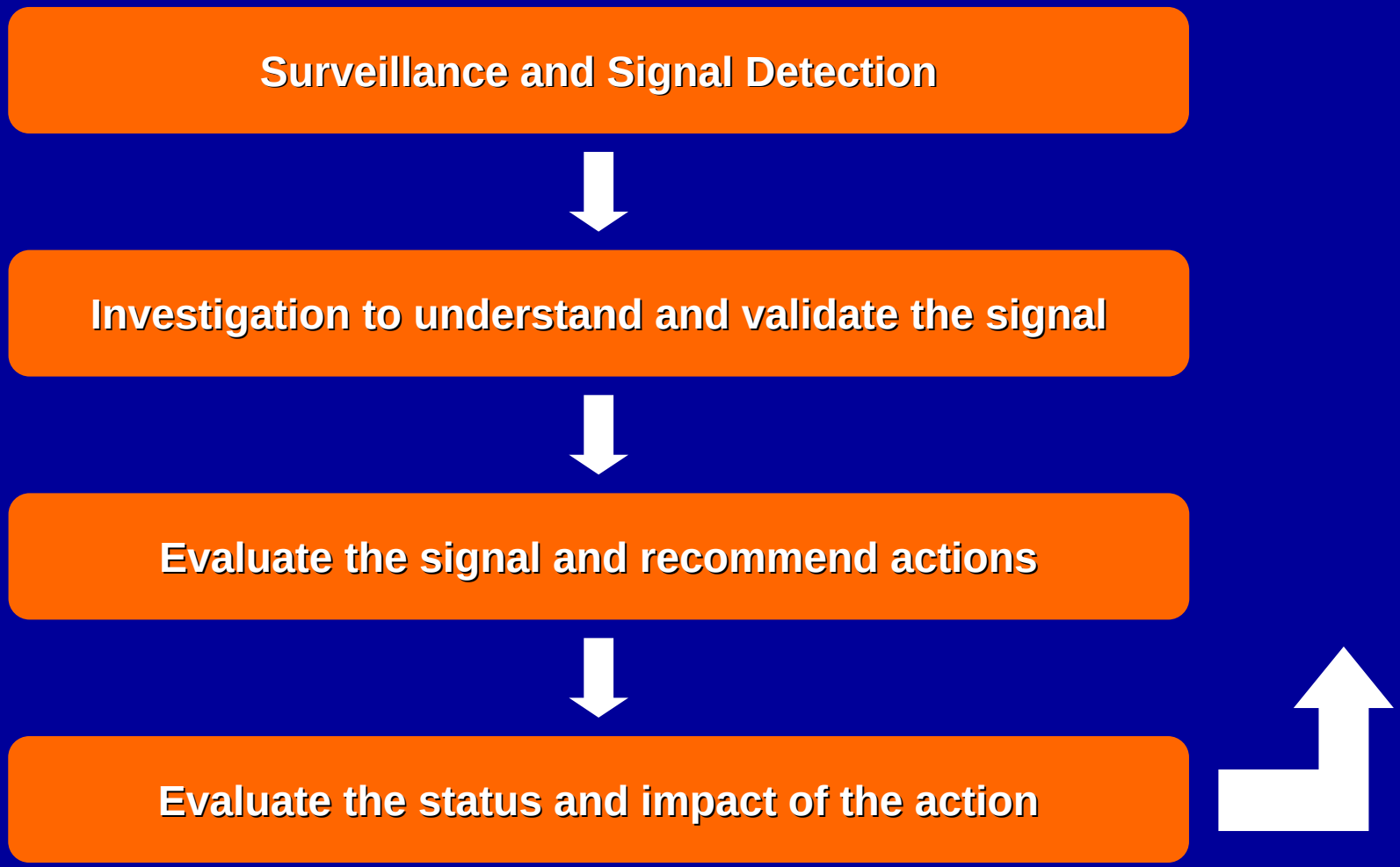
Surveillance and Monitoring

Primary risks (overdose, abuse, diversion)

Overview of Surveillance Tools

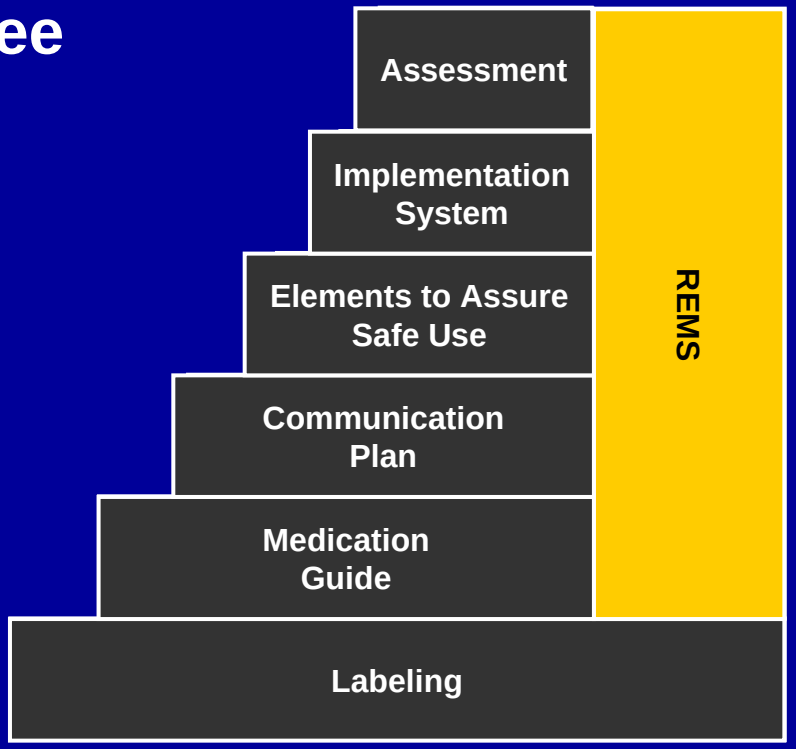
	Overdose			Abuse and Diversion			
Outcome/ behavior measured	Overdose	Accidental ingestion	Inappropriate prescribing	Misuse	Abuse	Teen abuse	Diversion
Covidien Pharmacovigilance	☑	☑	☑	☑	☑	☑	☑
Adult and Adolescent Abuse & Addiction Inventories					☑	☑	☑
Internet Monitoring				☑	☑	☑	
Media Monitoring	☑	☑	☑	☑	☑	☑	☑
DAWN, Drug Abuse Warning Network-Live	☑	☑		☑	☑		
FDA-AERS	☑	☑	☑	☑	☑	☑	
Poison Control Centers	☑	☑		☑	☑	☑	☑
Law Enforcement					☑	☑	☑
Opioid Treatment Program					☑	☑	☑
Impaired Healthcare Workers					☑	☑	☑

Intervention Process for Surveillance and Signal Detection



Exalgo Alliance Program Governance

- Established Covidien Risk Management policies and procedures
  - REMS Oversight Committee
- Well defined escalation procedures to ensure executive governance



Exalgo Alliance Summary

- Comprehensive program to ensure EXALGO's benefits outweigh the risks
- Controlled access to ensure only appropriate patients receive EXALGO
- Defined responses to potential program deviations
- Continuous monitoring with improvement as needed
- Reflects Covidien's commitment to good stewardship

Concluding Remarks

Conclusions

- EXALGO represents an important addition to the armamentarium for opioid-tolerant patients with moderate to severe chronic pain
- EXALGO administered once a day is safe and effective for this intended patient population
- Post-marketing data confirm the safety profile established in the clinical program
- The Exalgo Alliance will assure responsible distribution, prescribing, dispensing and use of EXALGO
- The EXALGO data together with the Exalgo Alliance program support the proposed indication

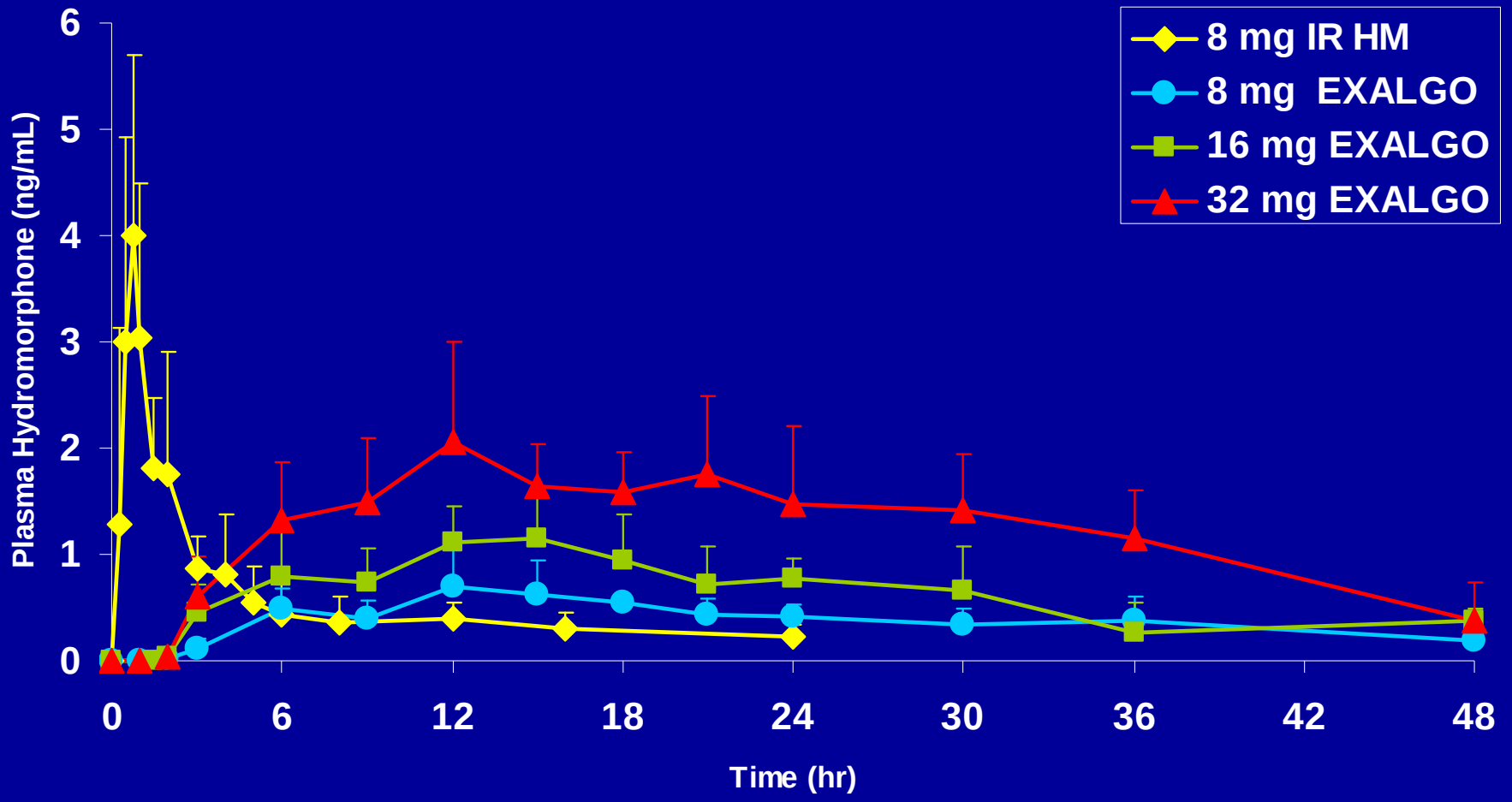
EXALGO™ (hydromorphone HCl) Extended-Release Tablets (CII)

NDA 21-217

United States Food and Drug Administration
Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee with the Drug Safety and Risk Management Advisory Committee

September 23, 2009

EXALGO Mean (SD) Single-Dose Pharmacokinetics Versus IR Hydromorphone Variability

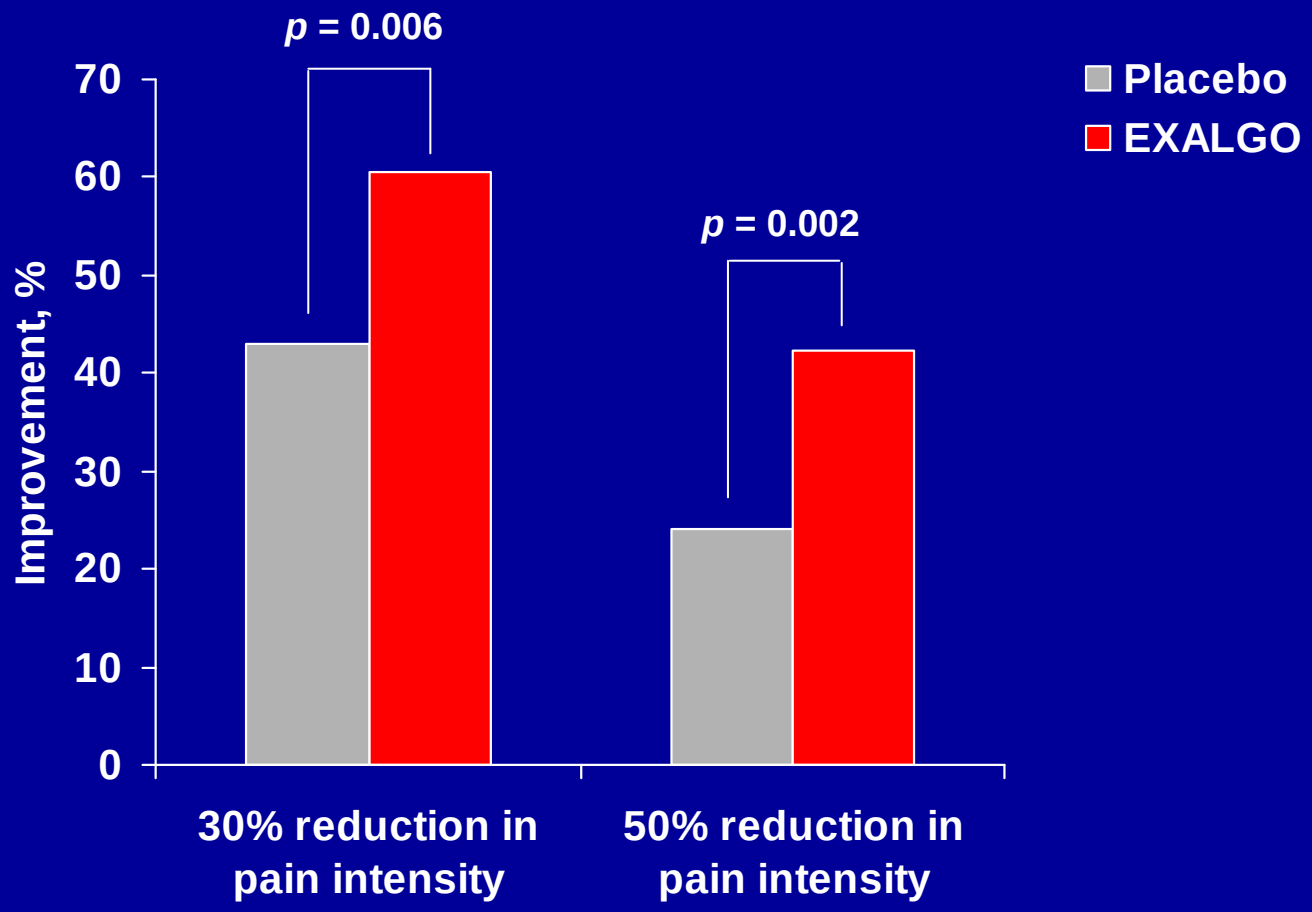


Explanation for Dropouts

- Patients inappropriately treated
  - Screen average score of 6.4
- Those inappropriately treated pts then receive 75% of prior dose
- Patients then entered a protracted titration

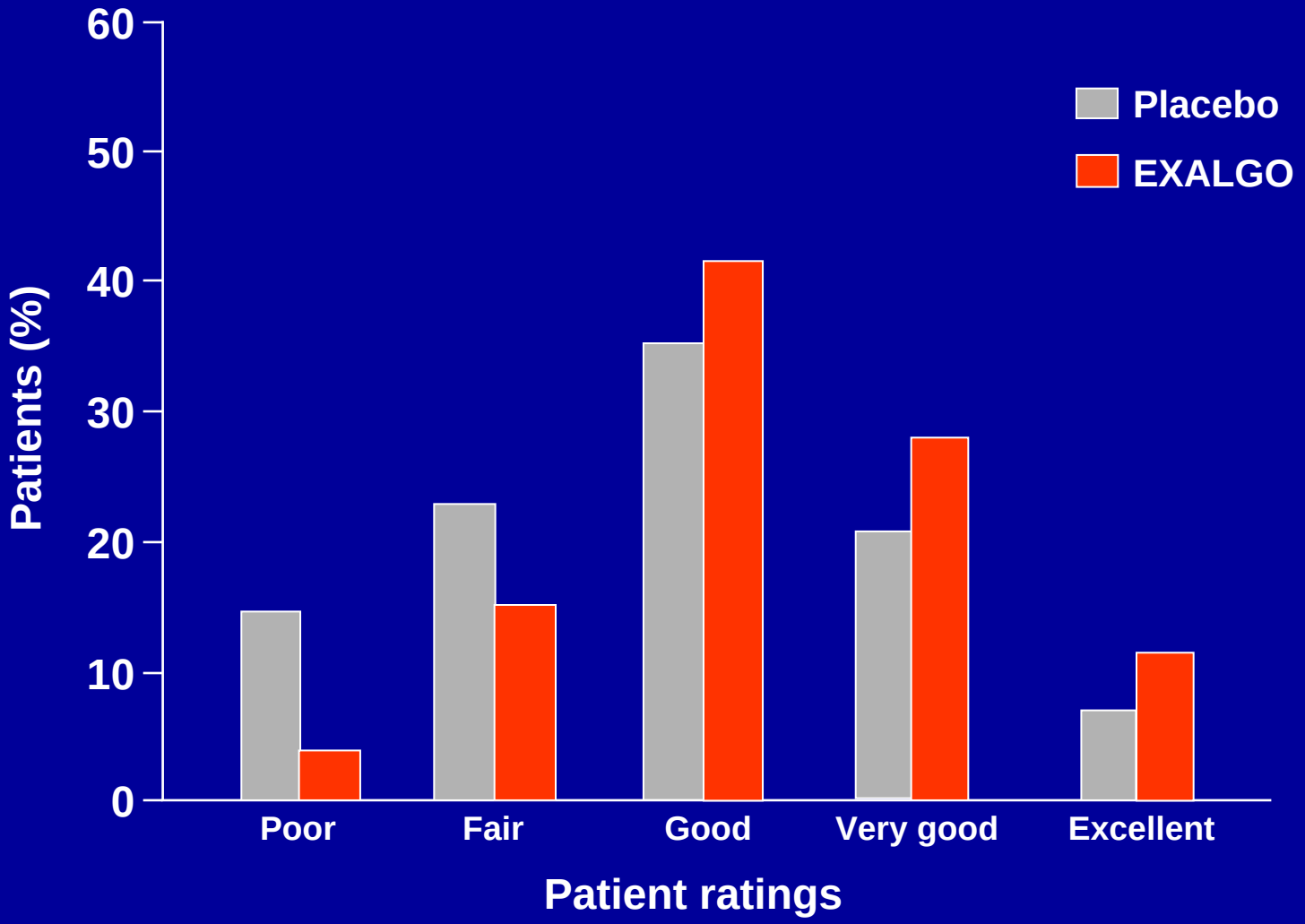
Percent Reduction in Average Pain Intensity From Screening to Final Visit

Study 301—ITT Population



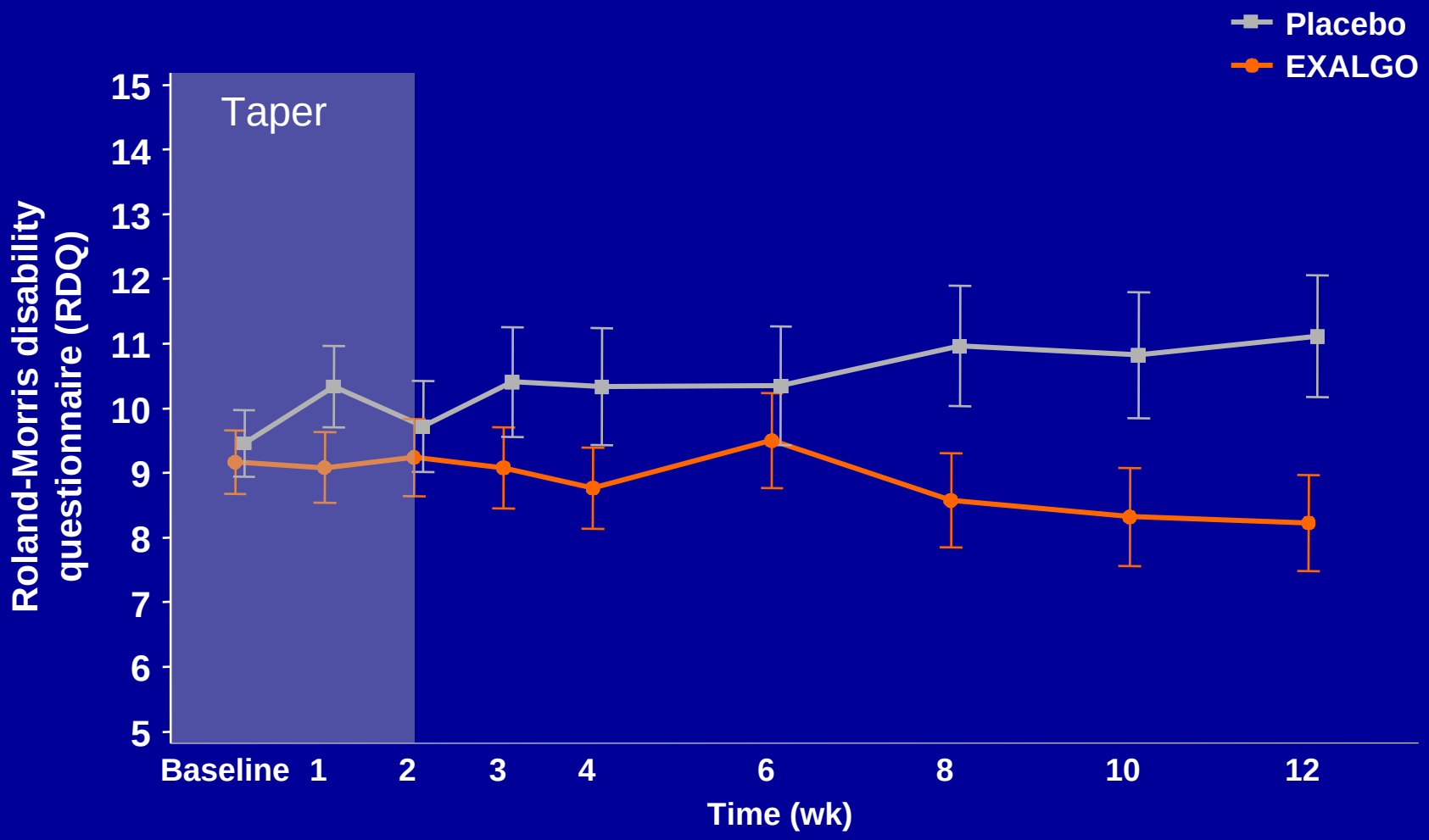
Patient Global Assessment Rating at Final Visit or 12 weeks

Study 301—ITT Population



Observed Mean Roland-Morris Disability Scores

Study 301—ITT Population



Mean ± SEM

Overview of Post-Marketing Safety Data: Abuse / Intentional Misuse

- Monitored in surveillance of spontaneous cases reported to the J&J safety database and to the WHO Vigibase
- Covered in standard section in JURNISTA® Periodic Safety Update Report (PSUR)
- Broad range of events in PSUR review of possible abuse / misuse cases, including cases of withdrawal, which are reviewed for evidence of abuse
- Trending of spontaneous reports by quarter is part of the EU-RMP PV Plan
- No cases reporting drug abuse
- 2 case reporting intentional misuse
  - Patient took JURNISTA® 16 mg instead of the prescribed 8 mg (no further details provided); experienced sleepiness, tiredness and hypertension, which subsequently resolved
  - Patient increased prescribed 16 mg/day to 48 mg/day, acting on her own authority, due to sudden increase in pain. Hospitalized for an accidental overdose, from which she recovered 2-3 days later
- 1 case describing withdrawal syndrome and drug-seeking behavior

JURNISTA® EU-RMP: Overview

- Pharmacovigilance Plan
  - Routine surveillance activities
    - Intra-product signaling of SCEPTRE* to monitor AE reporting trends and lot-trend review to detect potential manufacturing issues
    - Data mining of the WHO Vigibase
  - Product-specific Surveillance Activities
    - Monitor reporting trends and demographic profile of cases reporting an AE of interest identified in the EU-RMP in the SCEPTRE database
- Risk Minimization Action Plan (RiskMAP)
  - Supply chain integrity
  - Manufacturing quality controls
  - Launch activities
  - Educational program

*Part of the worldwide safety database of Benefit Risk Management, a division of J&J PRD.

Database Security

- Patient identifiable information saved in a separate database from clinical data
- Private patient information is de-identified and encrypted in the database preventing even Database Administrators from reading the data
- Secured database and infrastructure
- Stakeholders have access to limited information through a secured connection with individual user name and password
- System is compliant with all HIPAA and Health and Human Services standards