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PREVIEW EDITION!

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GET LEARNED.

RELISTOR helps provide chronic non-cancer pain patients with reliable and rapid relief from opioid-induced constipation–without compromising analgesia.[1,2]

- 6 out of 10 RELISTOR® (methylnaltrexone bromide) patients had at least 3 Spontaneous Bowel Movements (SBMs) per week[1]
- One-third of patients taking RELISTOR experienced an SBM within 4 hours of their first dose[1]

INDICATIONS

RELISTOR is indicated for the treatment of opioid-induced constipation in adult patients with chronic non-cancer pain.

RELISTOR is indicated for the treatment of opioid-induced constipation in adult patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient. Use of RELISTOR beyond four months has not been studied.

IMPORTANT SAFETY INFORMATION

RELISTOR® (methylnaltrexone bromide) Subcutaneous Injection is contraindicated in patients with known or suspected gastrointestinal obstruction and patients at increased risk of recurrent obstruction, due to the potential for gastrointestinal perforation.

Cases of gastrointestinal perforation have been reported in adult patients with opioid-induced constipation and advanced illness with conditions that may be associated with localized or diffuse reduction of structural integrity in the wall of the gastrointestinal tract (e.g., peptic ulcer disease, Ogilvie's syndrome, diverticular disease, infiltrative gastrointestinal tract malignancies or peritoneal metastases). Take into account the overall risk-benefit profile when using RELISTOR in patients with these conditions or other conditions which might result in impaired integrity of the gastrointestinal tract wall (e.g., Crohn's disease). Monitor for the development of severe, persistent, or worsening abdominal pain; discontinue RELISTOR in patients who develop this symptom.

If severe or persistent diarrhea occurs during treatment, advise patients to discontinue therapy with RELISTOR and consult their physician.

Symptoms consistent with opioid withdrawal, including hyperhidrosis, chills, diarrhea, abdominal pain, anxiety, and yawning have occurred in patients treated with RELISTOR. Patients having disruptions to the blood-brain barrier may be at increased risk for opioid withdrawal and/or reduced analgesia and should be monitored for adequacy of analgesia and symptoms of opioid withdrawal.

Avoid concomitant use of RELISTOR with other opioid antagonists because of the potential for additive effects of opioid receptor antagonism and increased risk of opioid withdrawal.

RELISTOR may precipitate opioid withdrawal in a fetus and should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In nursing mothers, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

In the clinical study in adult patients with opioid-induced constipation and chronic non-cancer pain, the most common adverse reactions (≥ 1%) were abdominal pain, nausea, diarrhea, hyperhidrosis, hot flush, tremor, and chills.

In clinical studies in adult patients with opioid-induced constipation and advanced illness, the most common adverse reactions (≥ 5%) were abdominal pain, flatulence, nausea, dizziness, and diarrhea.

Please see Brief Summary of complete Prescribing Information for RELISTOR on the adjacent page.

References

1. Michna E, Blonsky ER, Schulman S, et al. Subcutaneous methylnaltrexone for the treatment of opioid-induced constipation in patients with chronic nonmalignant pain: a randomized controlled study. *J Pain*. 2011;12(5):554-562.
2. RELISTOR® (methylnaltrexone bromide) Prescribing Information, Salix Pharmaceuticals, Inc.

www.salix.com
8510 Colonnade Center Drive, Raleigh, NC 27615
For additional information, call: 1-866-669-SLXP (7597)
To report adverse events, call: 1-800-508-0024

Salix Pharmaceuticals

RELISTOR®
methylnaltrexone bromide
subcutaneous injection

The following is a brief summary only; see full Prescribing Information for complete product information.

INDICATIONS AND USAGE

Opioid-Induced Constipation in Adult Patients with Chronic Non-Cancer Pain

RELISTOR is indicated for the treatment of opioid-induced constipation in adult patients with chronic non-cancer pain.

Opioid-Induced Constipation in Adult Patients with Advanced Illness

RELISTOR is indicated for the treatment of opioid-induced constipation in adult patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient.

Limitation of use: Use of RELISTOR beyond four months has not been studied in the advanced illness population.

CONTRAINDICATIONS

RELISTOR is contraindicated in patients with known or suspected gastrointestinal obstruction and patients at risk of recurrent obstruction, due to the potential for gastrointestinal perforation.

WARNINGS AND PRECAUTIONS

Gastrointestinal Perforation

Cases of gastrointestinal perforation have been reported in adult patients with opioid-induced constipation and advanced illness with conditions that may be associated with localized or diffuse reduction of structural integrity in the wall of the gastrointestinal tract (e.g., peptic ulcer disease, Ogilvie's syndrome, diverticular disease, infiltrative gastrointestinal tract malignancies or peritoneal metastases). Take into account the overall risk-benefit profile when using RELISTOR in patients with these conditions or other conditions which might result in impaired integrity of the gastrointestinal tract wall (e.g., Crohn's disease). Monitor for the development of severe, persistent, or worsening abdominal pain; discontinue RELISTOR in patients who develop this symptom.

Severe or Persistent Diarrhea

If severe or persistent diarrhea occurs during treatment, advise patients to discontinue therapy with RELISTOR and consult their healthcare provider.

Opioid Withdrawal

Symptoms consistent with opioid withdrawal, including hyperhidrosis, chills, diarrhea, abdominal pain, anxiety, and yawning have occurred in patients treated with RELISTOR. Patients having disruptions to the blood-brain barrier may be at increased risk for opioid withdrawal and/or reduced analgesia. Take into account the overall risk-benefit profile when using RELISTOR in such patients. Monitor for adequacy of analgesia and symptoms of opioid withdrawal in such patients.

ADVERSE REACTIONS

Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Opioid-Induced Constipation in Adult Patients with Chronic Non-Cancer Pain

The safety of RELISTOR was evaluated in a double-blind, placebo-controlled trial in adult patients with opioid-induced constipation and chronic non-cancer pain receiving opioid analgesia. This study (Study 1) included a 4-week, double-blind, placebo controlled period in which adult patients were randomized to receive RELISTOR 12 mg once daily (150 patients) or placebo (162 patients). After 4 weeks of double-blind treatment, patients began an 8-week open-label treatment period during which RELISTOR 12 mg was administered less frequently than the recommended dosage regimen of 12 mg once daily.

Adverse reactions in adult patients with opioid-induced constipation and chronic non-cancer pain receiving RELISTOR are shown in the following table. The adverse reactions in the table below may reflect symptoms of opioid withdrawal.

Adverse Reactions* in 4-Week Double-Blind, Placebo-Controlled Period of Clinical Study of RELISTOR in Adult Patients with Opioid-Induced Constipation and Chronic Non-Cancer Pain

Adverse Reaction	RELISTOR 12 mg once daily n = 150	Placebo n = 162
Abdominal Pain	21%	6%
Nausea	9%	6%
Diarrhea	6%	4%
Hyperhidrosis	6%	1%
Hot Flush	3%	2%
Tremor	1%	< 1%
Chills	1%	0%

*Adverse reactions occurring in ≥ 1 % of patients receiving RELISTOR 12 mg once daily and at an incidence greater than placebo.

During the 4-week double-blind period, in patients with opioid-induced constipation and chronic non-cancer pain that received RELISTOR 12 mg every other day, there was a higher incidence of adverse reactions, including nausea (12%), diarrhea (12%), vomiting (7%), tremor (3%), feeling of body temperature change (3%), piloerection (3%), and chills (2%) as compared to daily RELISTOR dosing. Use of RELISTOR 12 mg every other day is not recommended in patients with OIC and chronic non-cancer pain. The rates of discontinuation due to adverse reactions during the double-blind period (Study 1) were higher in the RELISTOR once daily (7%) than the placebo group (3%). Abdominal pain was the most common adverse reaction resulting in discontinuation from the double-blind period in the RELISTOR once daily group (2%).

The safety of RELISTOR was also evaluated in a 48-week, open-label, uncontrolled trial in 1034 adult patients with opioid-induced constipation and chronic non-cancer pain (Study 2). Patients were allowed to administer RELISTOR 12 mg less frequently than the recommended dosage regimen of 12 mg once daily, and took a median of 6 doses per week. A total of 624 patients (60%) completed at least 24 weeks of treatment and 477 (46%) completed the 48-week study. The adverse reactions seen in this study were similar to those observed during the 4-week double-blind period of Study 1. Additionally, in Study 2, investigators reported 4 myocardial infarctions (1 fatal), 1 stroke (fatal), 1 fatal cardiac arrest and 1 sudden death. It is not possible to establish a relationship between these events and RELISTOR.

Opioid-Induced Constipation in Adult Patients with Advanced Illness

The safety of RELISTOR was evaluated in two, double-blind, placebo-controlled trials in adult patients with opioid-induced constipation and advanced illness receiving palliative care: Study 3 included a single dose, double blind, placebo-controlled period, whereas Study 4 included a 14-day multiple dose, double-blind, placebo-controlled period.

The most common (≥5%) adverse reactions in adult patients with opioid-induced constipation and advanced illness receiving RELISTOR are shown in the following table.

Adverse Reactions from all Doses in Double-Blind, Placebo-Controlled Clinical Studies of RELISTOR in Adult Patients with Opioid-Induced Constipation and Advanced Illness*

Adverse Reaction	RELISTOR n = 165	Placebo n = 123
Abdominal Pain	29%	10%
Flatulence	13%	6%
Nausea	12%	5%
Dizziness	7%	2%
Diarrhea	6%	2%

*Adverse reactions occurring in ≥ 5 % of patients receiving all doses of RELISTOR (0.075, 0.15, and 0.30 mg/kg/dose) and at an incidence greater than placebo.

The rates of discontinuation due to adverse events during the double-blind placebo controlled clinical trials (Study 3 and Study 4) were comparable between RELISTOR (1%) and placebo (2%).

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of RELISTOR. Because they are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal

Perforation, cramping, vomiting

General Disorders and Administrative Site Disorders

Diaphoresis, flushing, malaise, pain. Cases of opioid withdrawal have been reported.

DRUG INTERACTIONS

Other Opioid Antagonists

Avoid concomitant use of RELISTOR with other opioid antagonists because of the potential for additive effects of opioid receptor antagonism and increased risk of opioid withdrawal.

Drugs Metabolized by Cytochrome P450 Isozymes

In healthy subjects, a subcutaneous dose of 0.30 mg/kg of methylnaltrexone did not significantly affect the metabolism of dextromethorphan, a CYP2D6 substrate.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies with RELISTOR in pregnant women. The use of RELISTOR during pregnancy may precipitate opioid withdrawal in a fetus due to the immature fetal blood brain barrier. In animal reproduction studies, no effects on embryo-fetal development were observed with the administration of intravenous methylnaltrexone during organogenesis in rats and rabbits at doses up to 20 times and 26 times, respectively, the maximum recommended human dose (MRHD) of 0.2 mg/kg/day. RELISTOR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether RELISTOR is present in human milk. However, methylnaltrexone bromide is present in rat milk. Because of the potential for serious adverse reactions, including opioid withdrawal, in nursing infants, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness of RELISTOR have not been established in pediatric patients.

In juvenile rats administered intravenous methylnaltrexone bromide for 13 weeks, adverse clinical signs such as convulsions, tremors and labored breathing were observed, and the juvenile rats were found to be more sensitive to the adverse effects of methylnaltrexone bromide when compared to adult animals. Juvenile dogs administered intravenous methylnaltrexone bromide for 13 weeks had a toxicity profile similar to adult dogs.

Geriatric Use

In the double-blind studies, a total of 118 (14%) patients aged 65-74 years (79 methylnaltrexone bromide, 39 placebo) and a total of 108 (13%) patients aged 75 years or older (64 methylnaltrexone bromide, 44 placebo) were enrolled. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Based on pharmacokinetic data, and safety and efficacy data from controlled clinical trials, no dose adjustment based on age is recommended.

Renal Impairment

No dose adjustment is required in patients with mild or moderate renal impairment. Dose reduction by one-half is recommended in patients with severe renal impairment (creatinine clearance less than 30 mL/min as estimated by Cockcroft-Gault).

Hepatic Impairment

No dose adjustment is required for patients with mild or moderate hepatic impairment.

OVERDOSAGE

A study of healthy volunteers noted orthostatic hypotension associated with a dose of 0.64 mg/kg administered as an intravenous bolus. Monitor for signs or symptoms of orthostatic hypotension and initiate treatment as appropriate.

If a patient on opioid therapy receives an overdose of RELISTOR, the patient should be monitored closely for potential evidence of opioid withdrawal symptoms such as chills, rhinorrhea, diaphoresis or reversal of central analgesic effect. Base treatment on the degree of opioid withdrawal symptoms, including changes in blood pressure and heart rate, and on the need for analgesia.

PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Administration

Advise all patients to:

- Inject RELISTOR subcutaneously in the upper arm, abdomen or thigh. Do not inject at the same spot each time (rotate injection sites).
- Safely dispose of needles by following the sharps disposal recommendations described in the RELISTOR Instructions for Use.
- Be within close proximity to toilet facilities once RELISTOR is administered.
- Discontinue RELISTOR if treatment with the opioid pain medication is also discontinued.

Advise chronic non-cancer pain patients receiving RELISTOR for opioid-induced constipation to:

- Discontinue all maintenance laxative therapy prior to initiation of RELISTOR. Laxative(s) can be used as needed if there is a suboptimal response to RELISTOR after three days.
- Inject one dose every day.
- Inform their healthcare provider if their opioid regimen is changed, to avoid adverse reactions, such as diarrhea.

Advise patients with advanced illness receiving RELISTOR for opioid-induced constipation to:

- Inject one dose every other day, as needed, but no more frequently than one dose in a 24-hour period.

Gastrointestinal Perforation

Advise patients to discontinue RELISTOR and to promptly seek medical attention if they develop unusually severe, persistent, or worsening abdominal pain.

Severe or Persistent Diarrhea

Advise patients to discontinue RELISTOR if they experience severe or persistent diarrhea.

Opioid Withdrawal

Advise patients that symptoms consistent with opioid withdrawal may occur while taking RELISTOR, including sweating, chills, diarrhea, abdominal pain, anxiety, and yawning.

Pregnancy

Advise females of reproductive potential, who become pregnant or are planning to become pregnant that the use of RELISTOR during pregnancy may precipitate opioid withdrawal in a fetus due to the undeveloped blood brain barrier.

Nursing

Advise females who are nursing against breastfeeding during treatment with RELISTOR due to the potential for opioid withdrawal in nursing infants.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

To report adverse events, a product complaint, or for additional information, call: 1-800-508-0024.

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Salix Pharmaceuticals, Inc.
Raleigh, NC 27615

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REL-RALAB56-102014

OVERVIEW

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NATIONAL CONFERENCE

PAINWeek is the largest U.S. pain conference for front-line clinicians with an interest in pain management. Demographically, our HCPs are 60% prescribers, 72% are PCPs, and 30% are specialists.

PAINWeek 2015 will present more than 16 course concentrations (tracks). Among them are: behavioral pain management, complementary/alternative pain management, health coaching, interventional pain management, medical and legal issues, neuropathic and musculoskeletal pain conditions, pain and chemical dependency, pharmacotherapy, and regional pain syndromes.

New this year are tracks on podiatric pain syndromes and palliative care. There is also a full-day curriculum designed especially for nurse practitioners. There are Master Classes and 30+ Special Interest Sessions including:

- The Groundhog Day Phenomenon
- The Bulletproof Prescriber
- A Tyranny of "Shoulds"
- Stem Cell Therapy: The Way to Manage the Future of Pain Management
- Suspicion: What Should I Do If I Suspect My Patient is Diverting, Abusing, or Both?
- Medical Cannabinoids: An Update on What You Need to Know for Your Practice
- Rhapsody on a Windy Night: When Pain and Sleep Share the Same Bed
- Virtual Reality: Does it Have a Role in Pain Management?

The American Society of Pain Educators (ASPE) will present the annual Pain Educators Forum (PEF) which consists of 3 days and 16 hours of clinical and educational courses! Additionally, the ASPE will again present a pre-PEF activity, "Neuropathica Galactica: A Highly Interactive Journey in Pain Management and Education." This course is limited to only 60 participants and is a hands-on, boot-camp-type workshop that will allow participants to hone their abilities on developing treatment plans for three unique case scenarios, along with presenting a diverse representation of pain syndromes (persistent post-surgical pain, rheumatoid arthritis, post-herpetic neuralgia, osteoarthritis, fibromyalgia, and others).

PAINWeek 101 – **Making the Most of Your PAINWeek Experience!**
Monday, September 7; 6:00 pm – 7:00 pm
PAINWeek 101 is a noncertified primer for first time attendees – or anyone seeking a refresher on the conference agenda, faculty, onsite technology, and venue logistics. Moderated by PAINWeek staff and faculty with Global Education Group, all questions as they pertain to course selection and CME protocol will be answered. With so much packed into the 5-day conference, PAINWeek 101 will make sure that you're fully briefed and oriented to navigate, plan, select, and make the most of your PAINWeek experience!

Faculty and schedule of sessions subject to change

ABOUT PAINWEEK

PAINWeek is an innovative single point of access designed specifically for frontline practitioners, recognized as an established leader in pain education. Active in live, print, and digital realms from its annual national conference – the largest one of its kind in the US – to its expansive web presence, *PWJ – PAINWeek Journal*, regional PAINWeekEnd conference series, learn-and-cruise PAINWeek at Sea, and ongoing coverage of pain management issues, PAINWeek is available 24/7/365 to meet the diverse clinical and practice management needs of practitioners every day of the year.

PAINWeek National Conference

Currently in its 9th year, the flagship annual conference PAINWeek will convene September 8-12 at The Cosmopolitan of Las Vegas. Featuring a multidisciplinary faculty and a range of comprehensive course offerings, satellite events, and exhibits, over 120 hours of continuing medical education activities will be presented, teaching clinicians how to maximize the quality and efficacy of their patient care.

PWE Regional Conferences and PW at Sea

More than an annual conference, PAINWeek extends its energy and expertise throughout the year via the ongoing PAINWeekEnd series, available in 15+ regional and metro areas nationwide, as well as the new PAINWeek at Sea. Adapted from the core curriculum, these events provide practitioners with 7.0-14.0 *AMA PRA Category 1 Credits*™, thereby enabling them to continually enhance their assessment, diagnostic, and treatment skills. Visit www.painweekend.org for dates and locations of the regional conference series, and www.painweek/sea for information on PAINWeek at Sea.

Location & Venue

PAINWeek is convened annually the Tuesday to Saturday following Labor Day Weekend at The Cosmopolitan of Las Vegas.

The Cosmopolitan is a 2,995-room luxury resort located on the Las Vegas Strip next to Bellagio and City Center. With 150,000 square feet of state-of-the art convention and meeting space, it offers a multitude of benefits and features to PAINWeek attendees.

PLEASE NOTE: It is IMPORTANT that you book your accommodations during your registration process at www.painweek.org, not directly with the hotel or via a third party.

> **"PAINWEEK IS THE PLACE TO COME FOR UNDERSTANDING ABOUT CHRONIC PAIN... THIS IS CLEARLY THE BIGGEST CONFERENCE, THE BEST CONFERENCE."** — TED W. JONES, PHD, CPE, CLINICAL PSYCHOLOGIST, BEHAVIORAL MEDICINE INSTITUTE

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OVERVIEW

SESSIONS AT A GLANCE

FRONTLINE PRACTITIONER FOCUS

SPECIAL PROGRAMS

MASTER CLASSES

PHARMACOTHERAPY AND MEDICAL-LEGAL

COURSE TRACK HIGHLIGHTS

SPECIAL INTEREST SESSIONS

"I TELL PEOPLE, IF YOU WANT TO GO TO THE MEETING WHERE THERE'S THE MOST CONTENT AND YOU CAN GET THE BROADEST SNAPSHOT OF WHAT'S GOING ON BOTH CLINICALLY AND IN RESEARCH RELATED TO PAIN, PAINWEEK IS YOUR MEETING." — ROGER B. FILLINGIM, PHD, PROFESSOR AND DIRECTOR, UNIVERSITY OF FLORIDA PAIN RESEARCH AND INTERVENTION CENTER

Opioid Monitoring at a Nurse Practitioner-Managed Clinic

Richard Talusan, DNP, FNP-BC, NEA-BC

A nurse practitioner-managed Opioid Monitoring Clinic (OMC) was developed in the Southern Nevada Healthcare System in Las Vegas as a quality improvement initiative to help identify patients at high risk for opioid abuse and misuse, and to provide timely treatment recommendations.

All patients admitted in the OMC are monitored for abuse and misuse of prescription pain medications through urine drug screening and use of a state prescription drug monitoring program database.

WHO should attend? This educational talk is targeted to physicians, nurse practitioners, and physician assistants who routinely prescribe opioids.

WHY should they attend? The OMC provides a thorough evaluation of patient risk factors for abuse and misuse of prescription medication through assessment of evidence-based risk factors.

WHAT will they learn? Participants will learn how to identify risk factors for opioid abuse and misuse, learn how to order and interpret urine drug testing, and learn how to minimize risks by following opioid dosing strategies including rotation and tapering.

Demystifying Pain Management: One Case at a Time

Theresa Mallick-Searle, MS, APRN-BC

The most effective way to manage pain is to use a patient-centered, multidisciplinary approach. There are several different types of therapies that are currently used in pain management.

In addition to current therapies, new methods of managing pain are on the horizon that may help personalize pain management. Opioids are being reformulated to have less potential for addiction. Additionally, scientists are using the human genome to determine how individual patients will react to specific medications, which has positive implications for patient-centered treatment.

WHO should attend? Healthcare providers who are interested in learning what is on the horizon in pain management and exploring the pathophysiology and definition of pain.

WHY should they attend? New research continues to inform both the treatment and understanding of pain. But even with these strides, involving patients in care is the key to determining the best course of treatment.

WHAT will they learn? Attendees will first hear about pain in a general sense before breaking down specific types of treatments. The discussion will then delve into case studies, noting what kind of therapies providers can combine to help patients manage their pain in the way that suits them best.

Complex Pain Patients in Chronic Pain: Addiction, Obesity, and the Elderly

Brett Badgley Snodgrass, MSN, APRN, FNP-C

Caring for patients with chronic pain can be difficult, and certain populations are more complex than others.

WHO should attend? Any healthcare professional interested in learning more about the addicted patient, the obese patient, and the elderly patient to identify special needs in this population.

WHY should they attend? Attendees will learn about the idea of addiction, as well as how to identify other terms that can be confused such as tolerance and dependence.

WHAT will they learn? Strategies for caring for the chronic pain patient with addiction will be addressed. Both obese and elderly patients can metabolize medications differently, so it is important to understand this idea to ensure safe and effective pain treatment.

AMERICAN HEADACHE SOCIETY

Comprehensive Migraine Education Program

Richard B. Lipton, MD

The last decade has yielded exciting developments in treating headaches and migraines, and new treatment options are constantly becoming available.

One of the major developments in headache treatment is new ways of delivering old therapies, including patches, inhalers, nasal sprays, and a variety of devices that are allowing for faster delivery of medication. These delivery methods offer some advantages over older treatments, in that they offer a way to bypass the gastrointestinal system, which is often a problem for patients with chronic headaches who also have stomach issues.

There are also newer molecular entities in development that offer various advantages to existing treatments.

On the topic of headache prevention, the biggest development is the current research into monoclonal antibodies. It is hoped that these monoclonal antibodies will target the calcitonin gene-related peptide (CGRP) pathway to actually prevent migraines by blocking CGRP activity.

WHO should attend? Clinicians who treat patients with migraine.

WHY should they attend? The explosion in new treatment options, different modalities for delivering headache medication, and possible ways to prevent the onset of headache represent unique opportunities for clinicians to treat patients with headache. Discussing these options with patients also opens the door for communicating about how their current treatments are working, and what may be on the horizon for them in the future.

WHAT will they learn? Attendees will hear a broad overview of the exciting progress that has taken place in the headache field during the past 10 years, with extensive discussions focusing on new ways to deliver older medications, and research into monoclonal antibodies as a way to prevent headache onset.

The session will include both lectures and cases, with ample time for questions and audience participation.

AMERICAN PAIN SOCIETY

Management of Pain and Maintaining Function in Older Adults

Roger Fillingim, PhD

The prevalence of many pain types increases with age, and pain is often more widespread and disabling among older adults.

WHO should attend? Healthcare practitioners interested in learning more about the prevalence of pain in older patients and how pain responses may change as patients age.

WHY should they attend? Data suggest that chronic pain may be associated with accelerated aging, including potential effects on biological and psychosocial processes. Pain processing seems to change with age, in that older adults shift toward a more pain-promoting rather than a pain-reducing balance in their pain modulation systems. This may help explain the increased prevalence of pain as we age.

WHAT will they learn? Attendees will hear about the multiple biological and psychosocial processes that contribute to age-related changes in the experience of pain. They will hear discussions on the importance of careful pain assessment, which can provide information related to the mechanisms driving their pain, helping to guide more effective pain treatment.

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AMERICAN SOCIETY OF PAIN EDUCATORS

SESSION HIGHLIGHT

Risk Assessment: What Is It and How To Use It

Ted Jones, PhD

Screening for patients with chronic pain who may be at risk for medication-aberrant behavior has been a hot topic as new technologies emerge to help identify these patients.

WHO should attend? Health providers involved in prescribing medications for patients with pain issues.

WHY should they attend? This session will break down the nine current screening methods validated to predict medication-aberrant behavior in patients being prescribed opioids for chronic pain.

These include the Screener and Opioid Assessment for Patients with Pain (SOAPP), the Pain Medication Questionnaire (PMQ), the Opioid Risk Tool (ORT), the Brief Risk Questionnaire (BRQ), the Narcotic Risk Manager (NRM), the Prescription Drug Use Questionnaire Self-Report (PRUQp), and others.

WHAT will they learn? In this talk, attendees will hear a detailed overview of the strengths and weaknesses of each test to help practitioners decide which one is best for their needs.

The Drug Enforcement Association (DEA) and most state licensing boards expect practitioners to screen patients for opioid abuse. Some practitioners believe it is adequate to assess their patients using just their "gut feeling." However, as this session will discuss, studies show that practitioners do not accurately predict medication-aberrant behavior in their patients when they rely only on instinct alone.

After a patient is assessed for medication abuse risk, the treatment plan should be adjusted based on risk level. Attendees will hear protocols for how to treat and monitor patients at different risk levels.

NATIONAL ASSOCIATION OF DRUG DIVERSION INVESTIGATORS

SESSION HIGHLIGHT

Addiction and Drug Histories: A Cop's Eye View from the Street to the Clinician's Office

Marc S. Gonzalez, PharmD

This course will review the aspects and mechanisms of addiction as it relates to the background and experiences of a law enforcement officer who is also a healthcare professional. Clinicians will get a better idea of the drugs people are abusing and how to better tailor treatment plans.

WHO should attend? Any physician who is interested in knowing what patients are doing with the medications they are prescribed and how drugs can be manipulated by people who are not legitimately prescribed that drug.

WHY should they attend? From this presentation, healthcare practitioners will be better able to determine whether a patient may have more serious physical and psychological issues beyond the practitioner's scope of practice, necessitating referral to another practitioner to protect the practice.

WHAT will they learn? Current methods of manipulating illicit prescription medication and an introduction to the various classes of illicit drugs will be covered. Information on various cocktails and combinations will be elucidated in an effort to assist medical practitioners in better understanding the long-term effects of all drugs when taking drug histories on new and current patients.

Actual case studies will further reinforce the information presented for a better understanding of the effect on the healthcare practitioner's treatment plan.

AMERICAN SOCIETY OF ADDICTION MEDICINE

Addiction medicine is taught in a sporadic fashion throughout U.S. medical training programs, and caring for patients with chronic pain and addiction remains a significant concern.

This track, presented by the American Society of Addiction Medicine (ASAM) is designed to enable clinicians to understand their role in treating patients with chronic pain and the use of medications with the potential for addiction or dependence.

Many healthcare providers need a greater understanding of treatment options for patients with pain and addiction, including motivational interviewing and other strategies to engage patients in safer options for pain care and to enable them to make the most out of the treatment options available.

It is a common belief that patients with addiction need to come in requesting treatment to be successful, but healthcare providers can be a key influencer in motivating patients to begin the process.

SESSION HIGHLIGHT

Nonpharmacological Management of Pain

Mel Pohl, MD

Nonpharmacological options for chronic non-cancer pain include stress-reduction techniques, addressing the cognitive aspects of pain, and physical interventions.

Emotions play a key role in chronic pain, and studies indicate that positive emotions decrease physical pain, whereas negative emotions can actually increase it.

WHO should attend? Any healthcare provider interested in learning more about treatments beyond medication.

WHY should they attend? There are risks associated with managing patients with chronic non-cancer pain using opioids alone, and emerging data show that there is more to treating chronic pain than giving medication.

WHAT will they learn? Attendees of this session will hear an in-depth discussion on cognitive behavioral therapy. Physical interventions will also be discussed including chiropractic intervention and other modalities including yoga, Tai chi, and acupuncture.

SESSION HIGHLIGHT

Medical Aspects of Marijuana

Ilena R. Robeck, MD

There are many opinions about the safety and efficacy of marijuana as a treatment option for patients with chronic pain; however, many patients are already using it to treat their pain.

Because marijuana does not come with a package insert or warning labels, it is important for healthcare providers to be able to educate patients who use marijuana – to treat pain, other medical problems, or recreationally – about its risks and benefits.

WHO should attend? Any healthcare provider with a patient who uses marijuana.

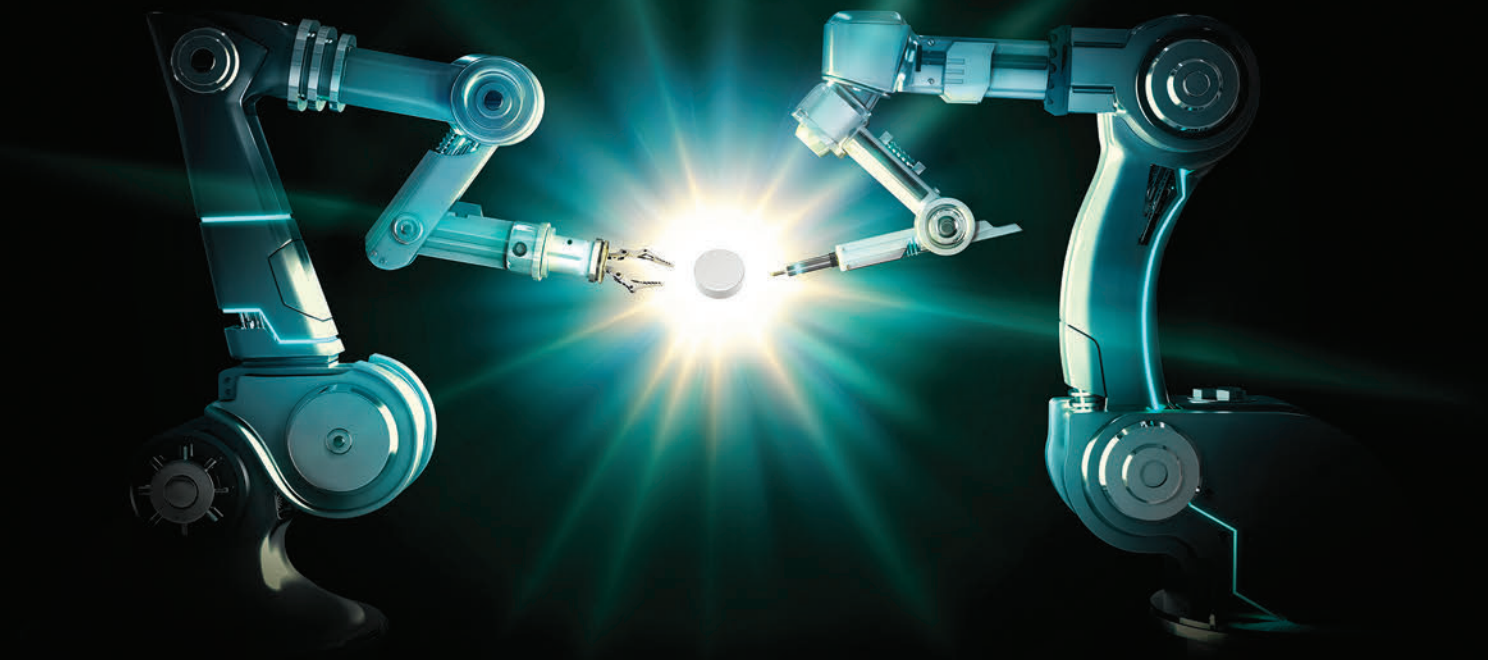
WHY should they attend? To help patients make educated decisions about marijuana use for chronic pain and whether to continue using marijuana if side effects develop.

WHAT will they learn? This session is about the reasons people use marijuana medically, as well as side effects and potential risks that clinicians should be able to review with patients.

It will not address whether marijuana should be legal, illegal, or whether it should be considered a medication.

HYSINGLA™ ER:

The *first and only* once-daily hydrocodone with abuse-deterrent properties and no acetaminophen



WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; AND CYTOCHROME P450 3A4 INTERACTION

Addiction, Abuse, and Misuse

HYSINGLA ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing HYSINGLA ER, and monitor all patients regularly for the development of these behaviors or conditions *[see Warnings and Precautions (5.1)]*.

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of HYSINGLA ER. Monitor for respiratory depression, especially during initiation of HYSINGLA ER or following a dose increase. Instruct patients to swallow HYSINGLA ER tablets whole; crushing, chewing, or dissolving HYSINGLA ER tablets can cause rapid release and absorption of a potentially fatal dose of hydrocodone *[see Warnings and Precautions (5.2)]*.

Accidental Ingestion

Accidental ingestion of even one dose of HYSINGLA ER, especially by children, can result in a fatal overdose of hydrocodone *[see Warnings and Precautions (5.2)]*.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of HYSINGLA ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Warnings and Precautions (5.3)]*.

Cytochrome P450 3A4 Interaction

The concomitant use of HYSINGLA ER with all cytochrome P450 3A4 inhibitors may result in an increase in hydrocodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in hydrocodone plasma concentration. Monitor patients receiving HYSINGLA ER and any CYP3A4 inhibitor or inducer *[see Warnings and Precautions (5.11), Drug Interactions (7.1), and Clinical Pharmacology (12.3)]*.

Please see Additional Warnings and Precautions on the following pages.

Please read Brief Summary of Full Prescribing Information on the following pages, including Boxed Warning.

Hysingla ER: *The same opioid molecule your hydrocodone patients are familiar with*

- **One tablet daily provides 24 hours of hydrocodone delivery**
- **Formulated with properties intended to make the tablet more difficult to misuse and abuse**
  - The *in vitro* data demonstrate that Hysingla ER has physical and chemical properties that are expected to deter intranasal and intravenous abuse. The data from the clinical abuse potential studies, along with support from the *in vitro* data, also indicate that Hysingla ER has physicochemical properties that are expected to reduce intranasal abuse and oral abuse when chewed
  - **However, abuse of Hysingla ER by the intravenous, intranasal, and oral routes is still possible**
  - With parenteral abuse, the inactive ingredients in Hysingla ER can result in death, local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury
- **Proven effective in a clinical trial**
- **Contains no acetaminophen**
- **Flexibility of 7 dosage strengths: 20, 30, 40, 60, 80, 100, and 120 mg tablets**
  - The starting dose for patients who are not opioid tolerant is Hysingla ER 20 mg orally every 24 hours. Opioid-tolerant patients are those receiving, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, or an equianalgesic dose of another opioid. Use of higher starting doses in patients who are not opioid tolerant may cause fatal respiratory depression

INDICATIONS AND USAGE

Hysingla ER (hydrocodone bitartrate) is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve Hysingla ER for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.
- Hysingla ER is not indicated as an as-needed analgesic.

CONTRAINDICATIONS

- Hysingla ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment, known or suspected paralytic ileus and gastrointestinal obstruction, hypersensitivity to any component of Hysingla ER or the active ingredient, hydrocodone bitartrate.

WARNINGS AND PRECAUTIONS

Addiction, Abuse, and Misuse

- Hysingla ER contains hydrocodone, a Schedule II controlled substance. Hysingla ER exposes users to the risks of opioid addiction, abuse, and misuse. As extended-release products such as Hysingla ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of hydrocodone present. Addiction can occur at recommended doses and if the drug is misused or abused. Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing Hysingla ER, and monitor all patients during therapy for the development of these behaviors or conditions. Abuse or misuse of Hysingla ER by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of the hydrocodone and can result in overdose and death.

Dosage and Administration

- Hysingla ER tablets must be taken whole, one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth. Crushing, chewing, or dissolving Hysingla ER tablets will result in uncontrolled delivery of hydrocodone and can lead to overdose or death.

Titration and Maintenance of Therapy

- Continually re-evaluate patients receiving Hysingla ER to assess the maintenance of pain control and the relative incidence of adverse reactions as well as monitoring for the development of addiction, abuse, or misuse.

For more information, visit HysinglaER.com

HYDROCODONE REENGINEERED

Hysingla™ ER
(Hydrocodone Bitartrate) II
EXTENDED-RELEASE TABLETS

Life-Threatening Respiratory Depression

- Serious, life-threatening, or fatal respiratory depression has been reported with modified-release opioids, even when used as recommended, and if not immediately recognized and treated, may lead to respiratory arrest and death. The risk of respiratory depression is greatest during the initiation of therapy or following a dose increase; therefore, closely monitor patients for respiratory depression. Proper dosing and titration of Hysingla ER are essential. Overestimating the Hysingla ER dose when converting patients from another opioid product can result in fatal overdose with the first dose. Accidental ingestion of even one dose of Hysingla ER, especially by children, can result in respiratory depression and death due to an overdose of hydrocodone.

Neonatal Opioid Withdrawal Syndrome

- Prolonged use of Hysingla ER during pregnancy can result in neonatal opioid withdrawal syndrome which may be life-threatening to the neonate if not recognized and treated, and requires management according to protocols developed by neonatology experts.

Interactions with Central Nervous System Depressants

- Hypotension, profound sedation, coma, respiratory depression, or death may result if Hysingla ER is used concomitantly with other CNS depressants, including alcohol or illicit drugs that can cause CNS depression. Start with a lower Hysingla ER dose than usual (i.e., 20-30% less), monitor patients for signs of sedation and respiratory depression, and consider using a lower dose of the concomitant CNS depressant.

Use in Elderly, Cachectic, and Debilitated Patients and Patients with Chronic Pulmonary Disease

- Closely monitor elderly, cachectic, and debilitated patients, and patients with chronic obstructive pulmonary disease because of the increased risk of life-threatening respiratory depression. Consider the use of alternative non-opioid analgesics in patients with chronic obstructive pulmonary disease if possible.

Use in Patients with Head Injury and Increased Intracranial Pressure

- Monitor patients closely who may be susceptible to the intracranial effects of CO_2 retention (e.g., those with evidence of increased intracranial pressure or impaired consciousness). Opioids may obscure the clinical course in a patient with a head injury. Avoid the use of Hysingla ER in patients with impaired consciousness or coma.

Hypotensive Effect

- Hysingla ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. Monitor patients during dose initiation or titration. In patients with circulatory shock, Hysingla ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Hysingla ER in patients with circulatory shock.

Gastrointestinal Obstruction, Dysphagia, and Choking

- Use caution when prescribing Hysingla ER for patients who have difficulty swallowing, or have underlying gastrointestinal disorders that may predispose them to obstruction, dysphagia, or choking. Consider use of an alternative analgesic in these patients.

Decreased Bowel Motility

- Hysingla ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus. Monitor for decreased bowel motility in post-operative patients receiving opioids. The administration of Hysingla ER may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Hydrocodone may cause spasm of the sphincter of Oddi. Monitor patients with biliary tract disease, including acute pancreatitis.

Cytochrome P450 3A4 Inhibitors and Inducers

- Concomitant use of CYP3A4 inhibitors may prolong opioid effects. Use with CYP3A4 inducers may cause lack of efficacy or development of withdrawal symptoms. If co-administration is necessary, evaluate patients frequently and consider dose adjustments until stable drug effects are achieved.

Driving and Operating Machinery

- Hysingla ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery.

Interaction with Mixed Agonist/Antagonist Opioid Analgesics

- Avoid the use of mixed agonist/antagonist analgesics in patients who have received or are receiving Hysingla ER, as they may reduce the analgesic effect and/or precipitate withdrawal.

QTc Interval Prolongation

- QTc prolongation has been observed following daily doses of 160 mg of Hysingla ER. Avoid use in patients with congenital QTc syndrome. This observation should be considered in making clinical decisions regarding patient monitoring when prescribing Hysingla ER in patients with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, or who are taking medications that are known to prolong QTc interval. In patients who develop QTc prolongation, consider reducing the dose.

ADVERSE REACTIONS

- Most common treatment-emergent adverse reactions (≥5%) reported by patients treated with Hysingla ER in the clinical trials were constipation, nausea, vomiting, fatigue, upper respiratory tract infection, dizziness, headache, and somnolence.

Please see Additional Warnings and Precautions on the preceding pages.

Please read Brief Summary of Full Prescribing Information on the following pages, including Boxed Warning.

Hysingla™ ER

(Hydrocodone Bitartrate) II

EXTENDED-RELEASE TABLETS

BRIEF SUMMARY OF PRESCRIBING INFORMATION (For complete details please see the Full Prescribing Information and Medication Guide.)

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; AND CYTOCHROME P450 3A4 INTERACTION

Addiction, Abuse, and Misuse

HYSINGLA™ ER exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing HYSINGLA ER, and monitor all patients regularly for the development of these behaviors or conditions *[see Warnings and Precautions (5.1)]*.

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of HYSINGLA ER. Monitor for respiratory depression, especially during initiation of HYSINGLA ER or following a dose increase. Instruct patients to swallow HYSINGLA ER tablets whole; crushing, chewing, or dissolving HYSINGLA ER tablets can cause rapid release and absorption of a potentially fatal dose of hydrocodone *[see Warnings and Precautions (5.2)]*.

Accidental Ingestion

Accidental ingestion of even one dose of HYSINGLA ER, especially by children, can result in a fatal overdose of hydrocodone *[see Warnings and Precautions (5.2)]*.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of HYSINGLA ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Warnings and Precautions (5.3)]*.

Cytochrome P450 3A4 Interaction

The concomitant use of HYSINGLA ER with all cytochrome P450 3A4 inhibitors may result in an increase in hydrocodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in hydrocodone plasma concentration. Monitor patients receiving HYSINGLA ER and any CYP3A4 inhibitor or inducer *[see Warnings and Precautions (5.11), Drug Interactions (7.1), and Clinical Pharmacology (12.3)]*.

4 CONTRAINDICATIONS HYSINGLA ER is contraindicated in patients with: • Significant respiratory depression • Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment • Known or suspected paralytic ileus and gastrointestinal obstruction • Hypersensitivity to any component of HYSINGLA ER or the active ingredient, hydrocodone bitartrate

5 WARNINGS AND PRECAUTIONS 5.1 Addiction, Abuse, and Misuse HYSINGLA ER contains hydrocodone, a Schedule II controlled substance. As an opioid, HYSINGLA ER exposes users to the risks of addiction, abuse, and misuse *[see Drug Abuse and Dependence (9.1)]*. As extended-release products such as HYSINGLA ER deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of hydrocodone present. Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed HYSINGLA ER and in those who obtain the drug illicitly. Addiction can occur at recommended doses and if the drug is misused or abused. Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing HYSINGLA ER, and monitor all patients receiving HYSINGLA ER for the development of these behaviors or conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol addiction or abuse) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the prescribing of HYSINGLA ER for the proper management of pain in any given patient. Abuse or misuse of HYSINGLA ER by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of the hydrocodone and can result in overdose and death *[see Drug Abuse and Dependence (9.1), and Overdosage (10)]*. Opioid agonists are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing HYSINGLA ER. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug *[see Patient Counseling Information (17)]*. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product. **5.2 Life-Threatening Respiratory Depression** Serious, life-threatening, or fatal respiratory depression has been reported with the use of modified-release opioids, even when used as recommended. Respiratory depression from opioid use, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status *[see Overdosage (10.2)]*. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of HYSINGLA ER, the risk is greatest during the initiation of therapy or following a dose increase. Closely monitor patients for respiratory depression when initiating therapy with HYSINGLA ER and following dose increases. To reduce the risk of respiratory depression, proper dosing and titration of HYSINGLA ER are essential *[see Dosage and Administration (2.1, 2.2)]*. Overestimating the HYSINGLA ER dose when converting patients from another opioid product can result in fatal overdose with the first dose. Accidental ingestion of even one dose of HYSINGLA ER, especially by children, can result in respiratory depression and death due to an overdose of hydrocodone. **5.3 Neonatal Opioid Withdrawal Syndrome** Prolonged use of HYSINGLA ER during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. **5.4 Interactions with Central Nervous System Depressants** Hypotension, profound sedation, coma, respiratory depression, and death may result if HYSINGLA ER is used concomitantly with alcohol or other central nervous system (CNS) depressants (e.g., sedatives, anxiolytics, hypnotics, neuroleptics, other opioids). When considering the use of HYSINGLA ER in a patient taking a CNS depressant, assess the duration use of the CNS depressant and the patient's response, including the degree of tolerance that has developed to CNS depression. Additionally, evaluate the patient's use of alcohol or illicit drugs that cause CNS depression. If the decision to begin HYSINGLA ER is made, start with a lower HYSINGLA ER dose than usual (i.e., 20-30% less), monitor patients for signs of sedation and respiratory depression, and consider using a lower dose of the concomitant CNS depressant *[see Drug Interactions (7.2)]*. **5.5 Use in Elderly, Cachectic, and Debilitated Patients** Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating HYSINGLA ER and when HYSINGLA ER is given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.2)]*. **5.6 Use in Patients with Chronic Pulmonary Disease** Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression for respiratory depression, particularly when initiating therapy and titrating with HYSINGLA ER, as in these patients, even usual therapeutic doses of HYSINGLA ER may decrease respiratory drive to the point of apnea *[see Warnings and Precautions (5.2)]*. Consider the use of alternative non-opioid analgesics in these patients if possible. **5.7 Use in Patients with Head Injury and Increased Intracranial Pressure** In the presence of head injury, intracranial lesions or a preexisting increase in intracranial pressure, the possible respiratory depressant effects of opioid analgesics and their potential to elevate cerebrospinal fluid pressure (resulting from vasodilation following CO_2 retention) may be markedly exaggerated. Furthermore, opioid analgesics can produce effects on pupillary response and consciousness, which may obscure neurologic signs of further increases in intracranial pressure in patients with head injuries. Monitor patients closely who may be susceptible to the intracranial effects of CO_2 retention, such as those with evidence of increased intracranial pressure or impaired consciousness. Opioids may obscure the clinical course of a patient with a head injury. Avoid the use of HYSINGLA ER in patients with impaired consciousness or coma. **5.8 Hypotensive Effect** HYSINGLA ER may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is an added risk to individuals whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents which compromise vasomotor tone. Monitor these patients for signs of hypotension after initiating or titrating the dose of HYSINGLA ER. In patients with circulatory shock, HYSINGLA ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of HYSINGLA ER in patients with circulatory shock. **5.9 Gastrointestinal Obstruction, Dysphagia, and Choking** In the clinical studies with specific instructions to take HYSINGLA ER with adequate water to swallow the tablet, 11 out of 2476 subjects reported difficulty swallowing HYSINGLA ER. These reports included esophageal obstruction, dysphagia, and choking, one of which had required medical intervention to remove the tablet *[see Adverse Reactions (6)]*. Instruct patients not to pre-soak, lick, or otherwise wet HYSINGLA ER tablets prior to placing in the mouth, and to take one tablet at a time with enough water to ensure complete swallowing immediately after placing in the mouth *[see Patient Counseling Information (17)]*. Patients with underlying gastrointestinal disorders such as esophageal cancer or colon cancer with a small gastrointestinal lumen are at greater risk of developing these complications. Consider use of an alternative analgesic in patients who have difficulty swallowing and patients at risk for underlying gastrointestinal disorders resulting in a small gastrointestinal lumen. **5.10 Decreased Bowel Motility** HYSINGLA ER is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus. Opioids diminish propulsive peristaltic waves in the gastrointestinal tract and decrease bowel motility. Monitor for decreased bowel motility in post-operative patients receiving opioids. The administration of HYSINGLA ER may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Hydrocodone may cause spasm of the sphincter of Oddi. Monitor patients with biliary tract disease, including acute pancreatitis. **5.11 Cytochrome P450 3A4 Inhibitors and Inducers** Since the CYP3A4 isoenzyme plays a major role in the metabolism of HYSINGLA ER, drugs that alter CYP3A4 activity may cause changes in clearance of hydrocodone which could lead to changes in hydrocodone plasma concentrations. The clinical results with CYP3A4 inhibitors show an increase in hydrocodone plasma concentrations and possibly increased or prolonged opioid effects, which could be more pronounced with concomitant use of CYP3A4 inhibitors. The expected clinical result with CYP3A4 inducers is a decrease in hydrocodone plasma concentrations, lack of efficacy or, possibly, development of an abstinence syndrome in a patient who had developed physical dependence to hydrocodone. If co-administration is necessary, caution is advised when initiating HYSINGLA ER treatment in patients currently taking, or discontinuing, CYP3A4 inhibitors or inducers. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved *[see Drug Interactions (7.1)]*. **5.12 Driving and Operating Machinery** HYSINGLA ER may impair the mental and physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Peak blood levels of hydrocodone may occur 14 – 16 hours (range 6 – 30 hours) after initial dosing of HYSINGLA ER tablet administration. Blood levels of hydrocodone, in some patients, may be high at the end of 24 hours after repeated-dose administration. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of HYSINGLA ER and know how they will react to the medication *[see Clinical Pharmacology (12.3)]*. **5.13 Interaction with Mixed Agonist/Antagonist Opioid Analgesics** Avoid the use of mixed agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and butorphanol) in patients who have received, or are receiving, a course of therapy with a full opioid agonist analgesic, including HYSINGLA ER. In these patients, mixed agonist/antagonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms. **5.14 QTc Interval Prolongation** QTc prolongation has been observed with HYSINGLA ER following daily doses of 160 mg *[see Clinical Pharmacology (12.2)]*. This observation should be considered in making clinical decisions regarding patient monitoring when prescribing HYSINGLA ER in patients with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, or who are taking medications that are known to prolong the QTc interval. HYSINGLA ER should be avoided in patients with congenital long QT syndrome. In patients who develop QTc prolongation, consider reducing the dose by 33 – 50%, or changing to an alternate analgesic.

6 ADVERSE REACTIONS The following serious adverse reactions are described elsewhere in the labeling: • Addiction, Abuse, and Misuse *[see Warnings and Precautions (5.1)]* • Life-Threatening Respiratory Depression *[see Warnings and Precautions (5.2)]* • Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.3)]* • Interactions with Other CNS Depressants *[see Warnings and Precautions (5.4)]* • Hypotensive Effects *[see Warnings and Precautions (5.8)]* • Gastrointestinal Effects *[see Warnings and Precautions (5.9, 5.10)]* **6.1 Clinical Trial Experience** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. A total of 1,827 patients were treated with HYSINGLA ER in controlled and open-label chronic pain clinical trials. Five hundred patients were treated for 6 months and 364 patients were treated for 12 months. The clinical trial population consisted of opioid-naïve and opioid-experienced patients with persistent moderate to severe chronic pain. The common adverse reactions (≥2%) reported by patients in clinical trials comparing HYSINGLA ER (20-120 mg/day) with placebo are shown in Table 2 below:

Table 2: Adverse Reactions Reported in ≥2% of Patients during the Open-Label Titration Period and Double-Blind Treatment Period: Opioid-Naïve and Opioid-Experienced Patients

	Open-label Titration Period	Double-blind Treatment Period	
MedDRA Preferred Term	(N=905) (%)	Placebo (N=292) (%)	HYSINGLA ER (N=296) (%)
Nausea	16	5	8
Constipation	9	2	3
Vomiting	7	3	6
Dizziness	7	2	3
Headache	7	2	2
Somnolence	5	1	1
Fatigue	4	1	1
Pruritus	3	<1	0
Tinnitus	2	1	2
Insomnia	2	2	3
Decreased appetite	1	1	2
Influenza	1	1	3

The adverse reactions seen in controlled and open-label chronic pain studies are presented below in the following manner: most common (≥5%), common (≥1% to <5%), and less common (<1%).

The most common adverse reactions (≥5%) reported by patients treated with HYSINGLA ER in the chronic pain clinical trials were constipation, nausea, vomiting, fatigue, upper respiratory tract infection, dizziness, headache, somnolence.

The common (≥1% to <5%) adverse events reported by patients treated with HYSINGLA ER in the chronic pain clinical trials organized by MedDRA (Medical Dictionary for Regulatory Activities) System Organ Class were:

Ear and labyrinth disorders	tinnitus
Gastrointestinal disorders	abdominal pain, abdominal pain upper, diarrhea, dry mouth, dyspepsia, gastroesophageal reflux disease
General disorders and administration site conditions	chest pain, chills, edema peripheral, pain, pyrexia

Infections and infestations	bronchitis, gastroenteritis, gastroenteritis viral, influenza, nasopharyngitis, sinusitis, urinary tract infection
Injury, poisoning and procedural complications	fall, muscle strain
Metabolism and nutrition disorders	decreased appetite
Musculoskeletal and connective tissue disorders	arthralgia, back pain, muscle spasms, musculoskeletal pain, myalgia, pain in extremity
Nervous system disorders	lethargy, migraine, sedation
Psychiatric disorders	anxiety, depression, insomnia
Respiratory, thoracic and mediastinal disorders	cough, nasal congestion, oropharyngeal pain
Skin and subcutaneous tissue disorders	hyperhidrosis, pruritus, rash
Vascular disorders	hot flush, hypertension

Other less common adverse reactions that were seen in <1% of the patients in the HYSINGLA ER chronic pain clinical trials include the following in alphabetical order: abdominal discomfort, abdominal distention, agitation, asthenia, choking, confusional state, depressed mood, drug hypersensitivity, drug withdrawal syndrome, dysphagia, dyspnea, esophageal obstruction, flushing, hypogonadism, hypotension, hypoxia, irritability, libido decreased, malaise, mental impairment, mood altered, muscle twitching, edema, orthostatic hypotension, palpitations, presyncope, retching, syncope, thinking abnormal, thirst, tremor, and urinary retention.

7 DRUG INTERACTIONS **7.1 Drugs Affecting Cytochrome P450 Isoenzymes** *Inhibitors of CYP3A4* Co-administration of HYSINGLA ER with ketoconazole, a strong CYP3A4 inhibitor, significantly increased the plasma concentrations of hydrocodone. Inhibition of CYP3A4 activity by inhibitors, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may prolong opioid effects. Caution is advised when initiating therapy with, currently taking, or discontinuing CYP3A4 inhibitors. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved *[see Clinical Pharmacology (12.3)]*. *Inducers of CYP3A4* CYP3A4 inducers may induce the metabolism of hydrocodone and, therefore, may cause increased clearance of the drug which could lead to a decrease in hydrocodone plasma concentrations, lack of efficacy or, possibly, development of a withdrawal syndrome in a patient who had developed physical dependence to hydrocodone. If co-administration with HYSINGLA ER is necessary, monitor for signs of opioid withdrawal and consider dose adjustments until stable drug effects are achieved *[see Clinical Pharmacology (12.3)]*. **7.2 Central Nervous System Depressants** The concomitant use of HYSINGLA ER with other CNS depressants including sedatives, hypnotics, tranquilizers, general anesthetics, phenothiazines, other opioids, and alcohol can increase the risk of respiratory depression, profound sedation, coma and death. Monitor patients receiving CNS depressants and HYSINGLA ER for signs of respiratory depression, sedation and hypotension. When combined therapy with any of the above medications is considered, the dose of one or both agents should be reduced *[see Warnings and Precautions (5.4)]*. **7.3 Interactions with Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics** Mixed agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and butorphanol) and partial agonist analgesics (buprenorphine) may reduce the analgesic effect of HYSINGLA ER or precipitate withdrawal symptoms in these patients. Avoid the use of mixed agonist/antagonist and partial agonist analgesics in patients receiving HYSINGLA ER. **7.4 MAO Inhibitors** HYSINGLA ER is not recommended for use in patients who have received MAO inhibitors within 14 days, because severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics. No specific interaction between hydrocodone and MAO inhibitors has been observed, but caution in the use of any opioid in patients taking this class of drugs is appropriate. **7.5 Anticholinergics** Anticholinergics or other drugs with anticholinergic activity when used concurrently with opioid analgesics may increase the risk of urinary retention or severe constipation, which may lead to paralytic ileus. Monitor patients for signs of urinary retention and constipation in addition to respiratory and central nervous system depression when HYSINGLA ER is used concurrently with anticholinergic drugs. **7.6 Strong Laxatives** Concomitant use of HYSINGLA ER with strong laxatives (e.g., lactulose), that rapidly increase gastrointestinal motility, may decrease hydrocodone absorption and result in decreased hydrocodone plasma levels. If HYSINGLA ER is used in these patients, closely monitor for the development of adverse events as well as changing analgesic requirements.

8 USE IN SPECIFIC POPULATIONS **8.1 Pregnancy** *Pregnancy Category C Risk Summary* There are no adequate and well-controlled studies of HYSINGLA ER use during pregnancy. Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome. In animal reproduction studies with hydrocodone in rats and rabbits no embryotoxicity or teratogenicity was observed. However, reduced pup survival rates, reduced fetal/pup body weights, and delayed ossification were observed at doses causing maternal toxicity. In all of the studies conducted, the exposures in animals were less than the human exposure (see Animal Data). HYSINGLA ER should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. *Clinical Considerations* Fetal/neonatal adverse reactions Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth. Observe newborns for symptoms of neonatal opioid withdrawal syndrome, such as poor feeding, diarrhea, irritability, tremor, rigidity, and seizures, and manage accordingly *[see Warnings and Precautions (5.3)]*. *Data* Animal Data No evidence of embryotoxicity or teratogenicity was observed after oral administration of hydrocodone throughout the period of organogenesis in rats and rabbits at doses up to 30 mg/kg/day (approximately 0.1 and 0.3-fold, respectively, the human hydrocodone dose of 120 mg/day based on AUC exposure comparisons). However, in these studies, reduced fetal body weights and delayed ossification were observed in rat at 30 mg/kg/day and reduced fetal body weights were observed in in rabbit at 30 mg/kg/day (approximately 0.1 and 0.3-fold, respectively, the human hydrocodone dose of 120 mg/day based on AUC exposure comparisons). In a pre- and post-natal development study pregnant rats were administered oral hydrocodone throughout the period of gestation and lactation. At a dose of 30 mg/kg/day decreased pup viability, pup survival indices, litter size and pup body weight were observed. This dose is approximately 0.1-fold the human hydrocodone dose of 120 mg/day based on AUC exposure comparisons. **8.2 Labor and Delivery** Opioids cross the placenta and may produce respiratory depression in neonates. HYSINGLA ER is not recommended for use in women immediately prior to and during labor, when use of shorter acting analgesics or other analgesic techniques are more appropriate. HYSINGLA ER may prolong labor through actions which temporarily reduce the strength, duration and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor. **8.3 Nursing Mothers** Hydrocodone is present in human milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue HYSINGLA ER, taking into account the importance of the drug to the mother. Infants exposed to HYSINGLA ER through breast milk should be monitored for excess sedation and respiratory depression. Withdrawal symptoms can occur in breast-fed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped. **8.4 Pediatric Use** The safety and effectiveness of HYSINGLA ER in pediatric patients have not been established. Accidental ingestion of a single dose of HYSINGLA ER in children can result in a fatal overdose of hydrocodone *[see Warnings and Precautions (5.2)]*. HYSINGLA ER gradually forms a viscous hydrogel (i.e., a gelatinous mass) when exposed to water or other fluids. Pediatric patients may be at increased risk of esophageal obstruction, dysphagia, and choking because of a smaller gastrointestinal lumen if they ingest HYSINGLA ER *[see Warnings and Precautions (5.9)]*. **8.5 Geriatric Use** In a controlled pharmacokinetic study, elderly subjects (greater than 65 years) compared to young adults had similar plasma concentrations of hydrocodone *[see Clinical Pharmacology (12.3)]*. Of the 1827 subjects exposed to HYSINGLA ER in the pooled chronic pain studies, 241 (13%) were age 65 and older (including those age 75 and older), while 42 (2%) were age 75 and older. In clinical trials with appropriate initiation of therapy and dose titration, no untoward or unexpected adverse reactions were seen in the elderly patients who received HYSINGLA ER. Hydrocodone may cause confusion and oversedation in the elderly. In addition, because of the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease and concomitant use of CNS active medications, start elderly patients on low doses of HYSINGLA ER and monitor closely for adverse events such as respiratory depression, sedation, and confusion. **8.6 Hepatic Impairment** No adjustment in starting dose with HYSINGLA ER is required in patients with mild or moderate hepatic impairment. Patients with severe hepatic impairment may have higher plasma concentrations than those with normal hepatic function. Initiate therapy with 1/2 the initial dose of HYSINGLA ER in patients with severe hepatic impairment and monitor closely for adverse events such as respiratory depression *[see Clinical Pharmacology (12.3)]*. **8.7 Renal Impairment** No dose adjustment is needed in patients with mild renal impairment. Patients with moderate or severe renal impairment or end stage renal disease have higher plasma concentrations than those with normal renal function. Initiate therapy with 1/2 the initial dose of HYSINGLA ER in these patients and monitor closely for adverse events such as respiratory depression *[see Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE **9.1 Controlled Substance** HYSINGLA ER contains hydrocodone bitartrate, a Schedule II controlled substance with a high potential for abuse similar to fentanyl, methadone, morphine, oxycodone, and oxymorphone. HYSINGLA ER can be abused and is subject to misuse, abuse, addiction and criminal diversion. The high drug content in the extended-release formulation adds to the risk of adverse outcomes from abuse and misuse. **9.2 Abuse** All patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use. Drug abuse is the intentional non-therapeutic use of an over-the-counter or prescription drug, even once, for its rewarding psychological or physiological effects. Drug abuse includes, but is not limited to the following examples: the use of a prescription or over-the-counter drug to get "high," or the use of steroids for performance enhancement and muscle build up. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and include: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal. "Drug-seeking" behavior is very common to addicts and drug abusers. Drug seeking tactics include, but are not limited to, emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated claims of "loss" of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" (visiting multiple prescribers) to obtain additional prescriptions is common among drug abusers, people with untreated addiction, and criminals seeking drugs to sell. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control. Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction. HYSINGLA ER can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by law, is strongly advised. Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs. Abuse may occur by taking intact tablets in quantities greater than prescribed or without legitimate purpose, by crushing and chewing or snorting the crushed formulation, or by injecting a solution made from the crushed formulation. The risk is increased with concurrent use of HYSINGLA ER with alcohol or other central nervous system depressants. *Risks Specific to Abuse of HYSINGLA ER* HYSINGLA ER is for oral use only. Abuse of HYSINGLA ER poses a risk of overdose and death.. Taking cut, broken, chewed, crushed, or dissolved HYSINGLA ER increases the risk of overdose and death. With parenteral abuse, the inactive ingredients in HYSINGLA ER can result in death, local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases, such as hepatitis and HIV. Abuse Deterrence Studies *Summary* The *in vitro* data demonstrate that HYSINGLA ER has physical and chemical properties that are expected to deter intranasal and intravenous abuse. The data from the clinical abuse potential studies, along with support from the *in vitro* data, also indicate that HYSINGLA ER has physicochemical properties that are expected to reduce intranasal abuse and oral abuse when chewed. However, abuse of HYSINGLA ER by the intravenous, intranasal, and oral routes is still possible. Additional data, including epidemiological data, when available, may provide further information on the impact of HYSINGLA ER on the abuse liability of the drug. Accordingly, this section may be updated in the future as appropriate. HYSINGLA ER contains hydrocodone, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit, including fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone. HYSINGLA ER can be abused and is subject to misuse, addiction, and criminal diversion *[See Warnings and Precautions (5.1) and Drug Abuse and Dependence (9)]*. **9.3 Dependence** Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects. Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dose reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity, e.g., naloxone, nalmefene, or mixed agonist/antagonist analgesics (pentazocine, butorphanol, nalbuphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage. HYSINGLA ER should be discontinued by a gradual downward titration *[see Dosage and Administration (2.6)]*. If HYSINGLA ER is abruptly discontinued in a physically dependent patient, an abstinence syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, piloerection, myalgia, mydriasis, irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, increased blood pressure, respiratory rate, or heart rate. Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.3)]*.

10 OVERDOSAGE **10.1 Symptoms** Acute overdosage with opioids is often characterized by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, sometimes, pulmonary edema, bradycardia, hypotension, and death. Marked mydriasis rather than miosis may be seen due to severe hypoxia in overdose situations *[see Clinical Pharmacology (12.2)]*. **10.2 Treatment** In the treatment of HYSINGLA ER overdosage, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. Employ other supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias will require advanced life support techniques. The opioid antagonist naloxone hydrochloride is a specific antidote against respiratory depression that may result from opioid overdosage. Nalmefene is an alternative opioid antagonist, which may be administered as a specific antidote to respiratory depression resulting from opioid overdose. Since the duration of action of HYSINGLA ER may exceed that of the antagonist, keep the patient under continued surveillance and administer repeated doses of the antagonist according to the antagonist labeling, as needed, to maintain adequate respiration. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression. Administer opioid antagonists cautiously to persons who are known, or suspected to be, physically dependent on HYSINGLA ER. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome. In an individual physically dependent on opioids, administration of the usual dose of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be initiated with care and by titration with smaller than usual doses of the antagonist.

CAUTION
DEA FORM REQUIRED

Healthcare professionals can telephone Purdue Pharma's Medical Services Department (1-888-726-7535) for information on this product.

Purdue Pharma L.P.
Stamford, CT 06901-3431

U.S. Patent Numbers: 6,488,963; 6,733,783; 8,309,060; 8,361,499; 8,529,948; 8,551,520; 8,647,667 and 8,808,740.

This brief summary is based on Hysingla ER Prescribing Information 303511-0C, Revised 02/2015 (A)

A Case-Based Examination of Patient-Centered Urine Drug Testing

Howard Heit, MD, and Douglas Gourlay, MD

Testing patients for aberrant drug use is one of several controversies in pain management today. This case-based session is designed to encourage interactivity and discussion among participants.

WHO should attend? Healthcare professionals wishing to discuss clinical issues relating to drug testing and prescribing that may relate to their practice.

WHY should they attend? Participating in this workshop will give attendees a more patient-centered selection of choices when dealing with aberrant behavior.

WHAT will they learn? The focus in this presentation will be to address many of the clinical challenges associated with asking and answering the sometimes difficult questions associated with treating patients with chronic pain, using a case-based learning approach. Issues such as unexpected urine drug test (UDT) results and strategies for approaching UDT in clinical practice will be examined.

Total Recovery: Solving the Mystery of Chronic Pain and Depression

Gary Kaplan, DO, DABFP, DABPM, FAAMA

Chronic pain and depression are a silent epidemic in the United States. There are more than 100 million individuals who have chronic pain and more than 38 million with a neuropsychiatric disease.

Comorbid neuropsychiatric diseases and chronic pain are common – approximately 50% to 65% of people with major depressive disorder also deal with chronic pain. The cost of this epidemic is more than $1.5 trillion annually.

Chronic pain and depression are not diseases, but symptoms of an underlying inflammation in the brain. The economic and personal costs of this epidemic are a consequence of our healthcare system's failure to treat the underlying causes of these conditions.

In the brain, microglia cells are integral for the regulation of the central nervous system. Injury to neural tissue can activate an inflammatory response in microglia. This tissue injury can be caused by a variety of factors, including physical trauma, ischemia, obesity, psychological trauma, autoimmune disease, toxins, infections, and medications.

The inflammatory response from the microglia can produce symptoms that include depression, anxiety, fatigue/malaise, sleep disturbances, endocrine dysfunction, pain, gastrointestinal dysfunction, fever, and postural orthostatic tachycardia syndrome (POTS).

When the inflammation is limited to the spinal cord the result is neuropathic pain. When the higher centers of the CNS are involved the disease is more appropriately referred to as Central Sensitization Syndrome (CSS) due to the multiplicity of symptoms that result.

WHO should attend? All healthcare providers interested in learning more about the interplay between inflammation, neuronal dysregulation, and their roles in depression and chronic pain.

WHY should they attend? An integrative approach is essential to clinical success in the treatment of CSS. Understanding the pathophysiology of CSS is key to creating a truly individualized and successful treatment approach.

This session will explain how the underlying pathophysiology of chronic pain is a neuroimmunologically mediated neuroinflammatory disease of which chronic pain is a symptom.

"The therapeutic approach to effectively treating chronic pain then requires an understanding of all of the factors (and there are typically multiple issues) that caused the inflammation in the first place, addressing those issues in a comprehensive manner, and then addressing the secondary factors that are maintaining the inflammation," said Dr. Kaplan.

WHAT will they learn? Attendees of this session will hear methods of treating CSS, which include addressing confounding issues, meditation, exercise, nutrition, sleep interventions, medications, acupuncture, psychotherapy, and physical therapy.

Could Levorphanol Levitate Above Methadone Misadventure?

Jeffrey Fudin, BS, PharmD, FCCP, FASHP,

Levorphanol has been noted to provide analgesic effects for those patients with pain who do not respond well to other medications, including methadone. The talk will focus on the applications, hazards, and pharmacokinetics of both drugs.

WHO should attend? Pharmacists and prescribers of pain medications.

WHY should they attend? To discuss the pros and cons of levorphanol over methadone as well as safety concerns and misconceptions.

WHAT will they learn? Fudin will lead a debate to educate prescribers about the particular usefulness and hazards associated with treating pain with levorphanol vs methadone. The data on levorphanol vs methadone for pain treatment are limited. Currently, the only study that directly compares their effects is an 8-year observational case study that compared the two drugs in palliative care pain patients with severe, chronic, non-cancer pain. Overall, the drugs had similar response rates (75% for methadone and 70% for levorphanol).

Fudin's debate will focus on three key points: (1) How the pharmacology of methadone and levorphanol make them uniquely suited for pain, especially neuropathic pain; (2) The danger of inexperienced patients and clinicians using these drugs; and (3) The vast differences in pharmacokinetics of the two drugs, in terms of metabolism.

On the topic of methadone, Fudin will discuss the importance of recognizing drug interactions. "Especially concerning is the potential for p-glycoprotein inhibitors to increase absorption through the gut and the blood-brain barrier, which could result in death and that these interactions more frequently than not are lacking in pharmacy drug interaction software," said Fudin. He will also discuss how polymorphisms affect the half-life of methadone as well as methadone's two enantiomers.

As for levorphanol, Fudin said it is difficult to speak to the challenges of the drug. Although it has existed since the 1950s, few prescribers are familiar or even aware of the treatment.

"The most dangerous attributes of both levorphanol and methadone for patients is that their half-lives are at least 15 hours," said Fudin. "While levorphanol is less variable, patients may not notice any lethargy with a few extra doses until saturation occurs, resulting in an overdose. These drugs are very potent and can creep up on patients without them realizing they are headed for doom."

This session will stress the importance of education to combat misconceptions and ensure safe, effective prescribing of these two drugs.

Focus on Changes in Billing/Coding Clinical Laboratory

Jennifer Bolen, JD

Coding changes for laboratories have been drastic in recent months and may present significant reimbursement challenges if coding directives, coverage determinations, and medical policies are not considered.

Essentially, physicians need to make sure their billing and coding staff know whether a commercial payor is using the AMA Current Procedural Terminology (CPT) codes for clinical laboratory or the CMS Healthcare Common Practice Coding System (HCPCS) codes.

WHO should attend? Physicians who own laboratories, practice administrators, clinical practice directors, laboratory directors, and staff who may be involved in implementing laboratory coding changes.

WHY should they attend? An understanding of the difference between presumptive and definitive testing, and how that factors into claims for reimbursement and medical necessity documentation, is necessary.

WHAT will they learn? Attendees will learn about the new CPT and HCPCS codes. They will hear a review of current payor coverage determinations and policies for clinical laboratory, and the importance of developing practice protocols for clinical drug testing. Clinical Laboratory Fee Schedule updates and changing coverage determinations and policies will also be discussed.

REGIONAL PAIN SYNDROMES

When Sex Hurts

Georgine Lamvu, MD, MPH, FACOG

Dyspareunia affects 1% to 5% of men and 3% to 16% of women. The prevalence of vulvar pain, which may occur with or without intercourse, has been estimated to be 8% among U.S. women.

WHO should attend? All healthcare providers who treat women.

WHY should they attend? Some research suggests vulvar pain is more common in Hispanic women compared with white women, but researchers are uncertain if these findings reflect a true difference in prevalence or just differences in symptom reporting.

WHAT will they learn? Attendees will learn the multitude of organic, musculoskeletal, and psychosocial etiologies of dyspareunia and vulvodynia and will also learn about various treatment options including hormonal treatments for pain associated with post-menopausal vaginal atrophy, topical steroids for pain associated with vaginal skin dermatoses, and physical therapy for pain associated with pelvic floor myalgias.

Simplifying the Gender Specific Complexities of Female Chronic Pelvic Pain (CPP)

Georgine Lamvu, MD, MPH, FACOG

In the United States there are nearly 25 million women who suffer from some form of chronic pelvic pain (CPP).

WHO should attend? Any provider who treats women and who is interested in gender differences or disparities.

WHY should they attend? CPP is reported by women more frequently than by men, and yet research shows that most women suffer for years without receiving treatment.

WHAT will they learn? This lecture will provide an overview of female pelvic neuroanatomy, hormonal variations, sexual function, and pain behavior. The talk will then integrate this information into recommendations for a more structured approach to the evaluation and treatment of CPP.

NEUROLOGY

Peripheral Neuropathies

Natalie Strand, MD

New research is helping healthcare providers better understand the brain and nervous system and is leading to improved treatments and therapies for peripheral neuropathies.

The options for treatment include medications, non-invasive devices, injections, invasive devices, therapy, and/or complementary or integrative treatments. Surgical interventions may even be considered for some types of neuropathies.

WHO should attend? Clinicians who treat patients with neuropathies.

WHY should they attend? Often if patients fail to respond to the first couple of rounds of antidepressants or anti-epileptic drugs the prognosis seems poor, but there may be other options.

WHAT will they learn? Dr. Strand will explain how advances in treatment strategies can enable clinicians to maximize the use of a multimodal approach tailored to each patient to improve quality of life.

BEHAVIORAL PAIN MANAGEMENT

'It Could Be Worse' and Other Things Not to Say to Patients With Chronic Pain

Melissa E. A. Geraghty, PsyD

One key concept that is most crucial for working with patients in pain is the ability to discuss difficult thoughts and feelings. Many people in the life of a person with chronic pain say things such as, "It'll get better" or "It could be worse." These people may genuinely say these things out of care, but they also say them due to their own discomfort. For most people, it is extremely uncomfortable to acknowledge everything with which a person with pain deals. Instead of truly listening and allowing patients to express themselves, many rush to speak words of comfort or advice. This is invalidating as it does not allow the person in pain to feel heard.

WHO should attend? Any healthcare provider interested in better communication with patients and their families.

WHY should they attend? There are two highly effective tools for communication. The first is the clinician him or herself. Clinicians should be immersed in the pain community in ways beyond the standard expectation of reading pain-specific journal articles and receiving pain-based education (although, of course, these are very important as well). Clinicians can further immerse themselves through peer supervision, looking at pain advocacy Websites, and looking at patient forum Websites to hear directly what patients have to say.

The second tool is the patient. When the patient feels truly listened to, and not like the physician is just waiting to speak, better communication will happen. Show a genuine interest in learning how conditions affect patients individually instead of placing them in a standardized box.

WHAT will they learn? This session will focus on discussing what not to say to patients who have pain. Patients will sense the clinicians' investment in their well-being, which will form the basis of open communication.

Depression and Suicidal Behavior in Patients With Pain and Concomitant Substance Use Disorders: Conceptual Theory, Risk Assessment, and Mitigation

Martin Cheatle, PhD

Individuals suffering from chronic pain can present with a number of equally-debilitating comorbidities including depression, substance use disorders, and suicidal ideation and behavior.

Although there has been considerable focus on the misuse and abuse of prescription opioids and the rising rate of opioid-related overdoses, depression, and suicidal ideation in patients with pain, those with pain and substance abuse are becoming a silent epidemic.

This presentation will review the current conceptual model of depression and suicidal ideation in patients with chronic pain who have a history of substance use disorder. It will examine possible mediators, outline risk assessment strategies, and discuss interventions to mitigate the risk of suicide in this vulnerable population.

WHO should attend? Any clinician who actively cares for patients with chronic pain.

WHY should they attend? Clinicians need to be cognizant of screening for depression and suicidal ideation in these vulnerable patient populations. Clinics that manage these complex patients should have a plan of action if a patient screens positive for severe depression and/or suicide.

WHAT will they learn? A review of the literature on pain, substance use disorders and suicidal ideation, and a conceptual model of the association between pain, depression, and suicidal ideation will be discussed.

Attendees will learn to identify risk factors for suicidal ideation in this patient population, examine the strengths and weaknesses of risk assessment tools, and understand risk mitigation strategies.

Virtual Reality: Does It Have a Role in Pain Management?

Theresa Mallick-Searle, MS, APRN-BC

Social and psychological factors unique to individuals are known to influence pain. Now, new research shows that life experience affects people even more dramatically than previously thought. Thus, manipulating how a patient feels during pain treatment using virtual reality has important implications.

WHO should attend? For those unfamiliar with virtual reality, Mallick-Searle's lecture will provide an overview of the technology before discussing how it can be applied to pain management.

WHY should they attend? Research has already established virtual reality as a potential treatment for post-traumatic stress disorder, anxiety, depression, phobias, and rehabilitation. It also helps reduce the amount of medication these patients may otherwise have to take.

Attendees will learn how to use virtual reality most effectively to treat pain, including the combination of virtual reality and cognitive behavioral techniques. They will also learn about potential future applications for virtual reality in pain.

As virtual reality becomes more widely available, Mallick-Searle hopes that pain management practitioners will learn how it can benefit patients and how to integrate it into their arsenal of treatment options.

WHAT will they learn? Virtual reality is still too new and expensive to be widely used, but this session will discuss how virtual reality can benefit patients with pain if clinicians choose to embrace this new technology. Virtual reality can be used to make patients feel relaxed even during painful episodes.

Electronic Prescribing of Controlled Substances

Sean Kelly, MD

Electronic prescribing of controlled substances (EPCS) is a hot topic of late, but many questions remain about how this technology can best be incorporated into pain management practices.

WHO should attend? Pharmacists and practitioners who prescribe controlled substances to patients with pain.

WHY should they attend? To learn how EPCS can help combat the public health crisis of prescription drug abuse while still allowing patients to get the medications they need.

WHAT will they learn? For pain practitioners, one of the most prevalent issues is addressing prescription drug abuse, diversion, and fraud – all without creating barriers for patients who genuinely need these drugs.

"With EPCS, a paper prescription and a physician's DEA number are never in the hands of the patient, which minimizes the opportunity for fraud or theft," said Dr. Kelly. "Furthermore, the strong authentication and audit trail allows for greater transparency and more proactive visibility into prescriber patterns."

E-prescribing for non-controlled substances is already a widely-used technology. In its early days, providers were unfamiliar with the system, but e-prescribing was quickly adopted as they recognized its efficiency. The session will discuss the potential of EPCS to follow in the footsteps of its predecessor, as it has many of the same advantages.

EPCS is a technology still in its infancy, but it is currently being developed to fit Drug Enforcement Administration (DEA) standards. Dr. Kelly has high hopes for the technology, but he will discuss what needs to happen to ensure the success of EPCS.

Stem Cell Therapy: The Way to Manage the Future of Pain Medicine

Orlando Florete Jr., MD

For the past several years, stem cell therapy has become an ever-expanding area of clinical application and research. Cumulative data support the use of stem cells in a variety of clinical conditions including regeneration of human bones and cartilages in osteoarthritis, hematopoietic cell transplantation in hematologic malignancies and other hematologic abnormalities, and in various neurological disorders, including spinal cord injury, Parkinson's disease, and multiple sclerosis, to mention a few. Its application in plastic surgery is well known.

Recent clinical data indicate that stem cell therapy is highly effective in the management of various chronic pain syndromes, both nociceptive and neuropathic.

WHO should attend? Healthcare practitioners interested in hearing the latest clinical research on stem cell therapy.

WHY should they attend? Stem cell therapy as a way to treat pain is no longer medically controversial. The controversy lies in the source of stem cells. Although the use of embryonic/fetal stem cells has been widely blocked, with the application of autologous stem cells as the source, the objection to the use of stem cell therapy has quieted. Considered experimental in the United States, the technology has been used extensively for years in Europe and in Asia. However, there are a significant number of U.S. pain physicians who are incorporating this technology as part of the treatment modalities available for pain management.

WHAT will they learn? Attendees will hear data from clinical research and reports from the medical literature that show the efficacy and safety of stem cell therapy in pain management. From simple injection of stem cells in peripheral joints such as the ankles, knees, shoulders, and hips, as well as its intradiscal application, the preliminary findings are encouragingly positive. More extensive data are needed to affirm this treatment modality as a standard of care.

Attendees will also hear about the more recent development of biological three dimensional printers, that may pave the way for potential reproduction of cartilages, joints, bones, and other body parts. This will have a major effect not only in pain management but in almost all areas of medicine.

Pain Management and the Groundhog Day Phenomenon

Kevin Zacharoff, MD, FACPE, FACIP, FAAP

Although pain management policies, procedures, and practices are being discussed at a national and international level, there are often hurdles to implementing widespread change.

"The Groundhog Day Phenomenon" – named after the popular film in which Bill Murray's character relives the same day – will center around some of the issues surrounding pain policies, particularly the need to share information about pain treatment among different prescribers of pain medications.

WHO should attend? This talk is designed to help bring policymakers and prescribers to the same page regarding pain management policies.

WHY should they attend? "From healthcare system to healthcare system and practice to practice, it seems that everyone who thinks the time has come for a 'pain policy and procedure set' feels as if they've discovered this on their own. In actuality it has been promoted in many different ways and forms during the past 15-20 years or more," said Dr. Zacharoff. "This 'reinventing the wheel' phenomenon, despite a plethora of writings, guidelines, national meetings, and debates, certainly seems like a 'Groundhog Day' phenomenon to me and doesn't seem to be changing."

WHAT will they learn? Attendees will hear ways to help address the "Groundhog Day Phenomenon," through PAINWeek 2015 and other regional meetings.

"Reproducible and clinically relevant and implementable information that resonates with clinicians providing treatment for people with chronic pain needs to happen. People must share this information with each other and become vectors for knowledge transfer to continue using existing 'wheels,' not new ones," said Dr. Zacharoff.

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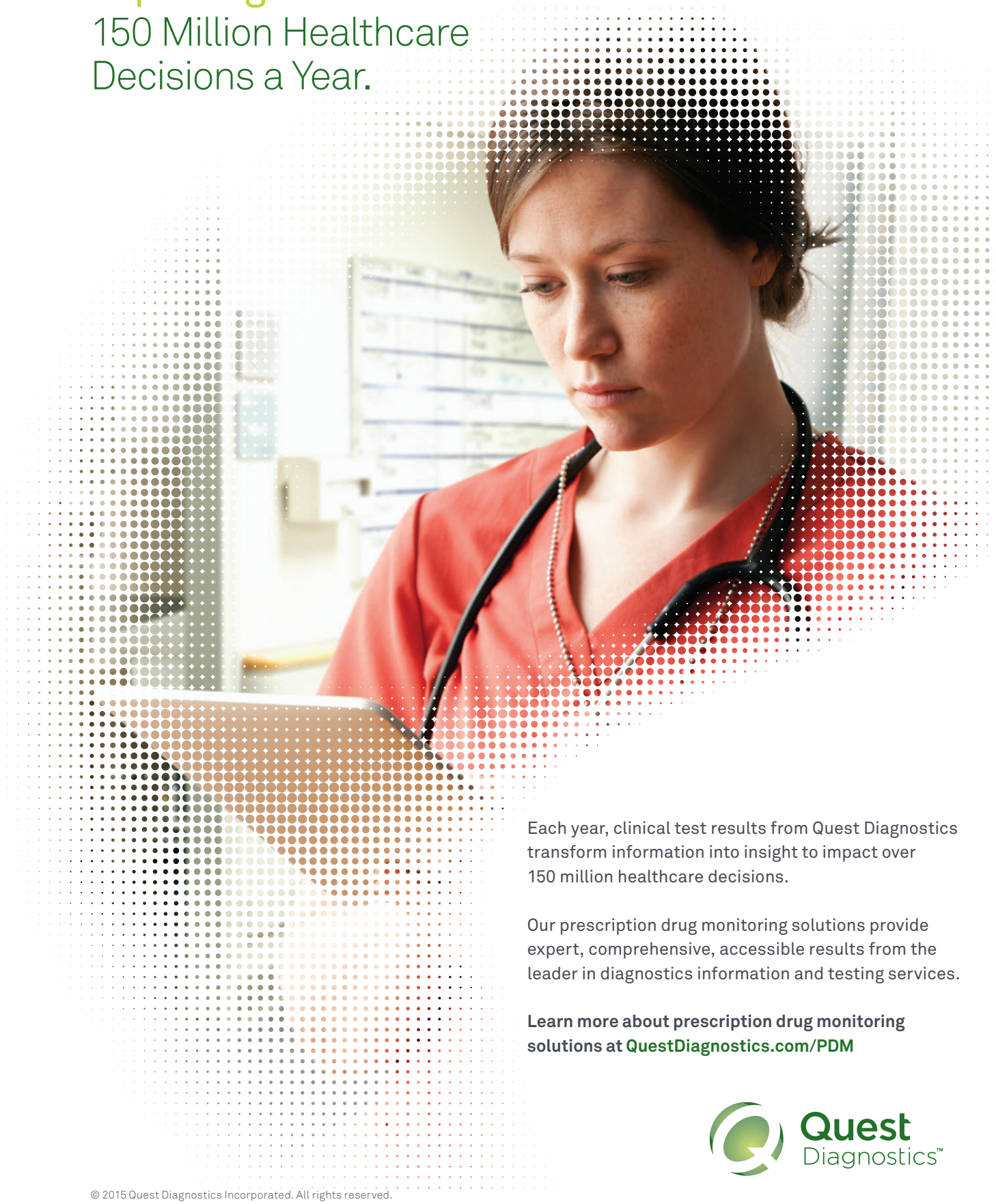

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