



## Collegium Announces 11 Poster Presentations at PAINWeek 2022 National Conference

August 30, 2022

STOUGHTON, Mass., Aug. 30, 2022 (GLOBE NEWSWIRE) -- [Collegium Pharmaceutical, Inc.](https://www.collegiumpharm.com/) (Nasdaq: COLL), a leading, diversified specialty pharmaceutical company, today announced that 11 poster presentations highlighting data regarding its product portfolio will be presented at the Annual PAINWeek National Conference, taking place September 6-9, 2022 in Las Vegas, NV.

"Collegium is excited to support 11 posters regarding our meaningfully differentiated product portfolio that will be presented at PAINWeek 2022 National Conference," said Thomas Smith, MD, EVP and Chief Medical Officer of Collegium. "We welcome opportunities to share clinical and real-world data with the medical community as part of our commitment to make a positive difference in the lives of people living with serious medical conditions."

### Poster Presentations:

Poster Title:	Budget Impact Analysis of Xtampza® ER (oxycodone extended-release) for the Treatment of Chronic Pain from a Managed Care Perspective
Authors:	Alan G. White, Todd Kunkel, Mancia Ko, Hongjue Wang
Poster Title:	Treatment Effects of Celecoxib Oral Solution in Migraine with Aura and Without Aura: Post-HOC Analysis of Results from Two Randomized, Double-Blind Placebo-Controlled Trials
Authors:	Stewart Tepper, Daniel Serrano, Mancia Ko, Todd Kunkel, Richard B. Lipton
Poster Title:	Consistency of Response to Liquid Celecoxib in Adults with Migraine: Post HOC Analysis of Results from Two Randomized, Placebo-Controlled Studies
Authors:	Daniel Serrano, Stewart Pepper, Mancia Ko, Todd Kunkel, Richard B. Lipton
Poster Title:	Efficacy of Celecoxib Oral Solution in Adults with and Without Baseline Nausea: Post-HOC Analysis of Results from Two Randomized, Double-Blind Placebo-Controlled Trials in the Acute Treatment of Migraine
Authors:	Richard B. Lipton, Daniel Serrano, Mancia Ko, Todd Kunkel, Stewart Pepper
Poster Title:	Celecoxib Oral Solution in the Acute Treatment of Migraine: Pooled Efficacy and Safety Results From 2 Randomized Placebo-controlled Trials
Authors:	Stewart Pepper, Harvey Kushner, Mancia Ko, Todd Kunkel, Richard B. Lipton
Poster Title:	Impact of Celecoxib Oral Solution on Symptomatic Improvements in the Acute Treatment of Migraine
Authors:	Stewart Pepper, Harvey Kushner, Mancia Ko, Todd Kunkel
Poster Title:	Prescription Opioid Nonmedical Use via Oral Manipulation: An Under-Recognized Risk
Authors:	Jody L. Green, Taryn Dailey-Govoni, Suzanna K. Vosburg
Poster Title:	Association between per capita prescribing and abuse of tapentadol and other opioids among individuals entering treatment for opioid use disorders
Authors:	Stevan Geoffrey Severtson, Annika M. Czizik, Matthew Ellis, Joshua C. Black, Janetta Iwanicki, Richard C. Dart
Poster Title:	Non-Medical Use of XTAMPZA ER: Motivation, Methods, and Perceptions of Tampering
Authors:	Joshua C. Black, Karilynn M. Rockhill, S. Geoff Severtson, Richard C. Dart
Poster Title:	Cross-sectional Study of Tampering in an Abuse-Deterrent Formulation of an Extended-Release Opioid in a Treatment Center Population
Authors:	Jennifer Jewell, Joshua Black, Matthew Ellis, Heather Olsen, Janetta Iwanicki, Richard Dart
Poster Title:	Differences in the severity of medical outcomes of exposures reported to poison centers involving XTAMPZA® ER and other opioid analgesics
Authors:	Stevan Geoffrey Severtson, Joshua C. Black, Janetta Iwanicki, Richard C. Dart

For more information on PAINWeek 2022, visit: <https://www.painweek.org/>

Xtampza ER (oxycodone) extended-release capsules, CII, Nucynta® ER (tapentadol) extended-release tablets, CII, and Nucynta® (tapentadol) tablets, CII, can be abused or misused, and carry a risk of addiction. These products are intended for use only in appropriate pain patients and only when other treatment alternatives are inadequate. Use of Xtampza® ER, Nucynta® ER and Nucynta® can result in serious, life-threatening or fatal respiratory depression, even when used exactly as prescribed. **See Important Safety Information including Boxed Warning on addiction, abuse, and misuse and other serious risks regarding each of these three products at the end of this press release.**

Nonsteroidal anti-inflammatory drugs (NSAIDs), including ELYXYB (celocoxib) oral solution, cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. **See Important Safety Information including Boxed Warning at the end of this press release.**

#### About Collegium Pharmaceutical, Inc.

Collegium is a diversified, specialty pharmaceutical company committed to improving the lives of people living with serious medical conditions. Collegium's headquarters are located in Stoughton, Massachusetts. For more information, please visit the Company's website at [www.collegiumpharma.com](http://www.collegiumpharma.com).

#### Xtampza ER (oxycodone)

#### INDICATIONS AND USAGE

Xtampza® ER (oxycodone) 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 Xtampza ER for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain
- Xtampza ER is not indicated as an as-needed (prn) analgesic

#### IMPORTANT SAFETY INFORMATION

**WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS**

##### Addiction, Abuse, and Misuse

Xtampza 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 Xtampza ER and monitor all patients regularly for the development of these behaviors or conditions.

##### Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- complete a REMS-compliant education program,
- counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,
- emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and
- consider other tools to improve patient, household, and community safety.

##### Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of Xtampza ER. Monitor for respiratory depression, especially during initiation of Xtampza ER or following a dose increase.

##### Accidental Ingestion

Accidental ingestion of even one dose of Xtampza ER, especially by children, can result in a fatal overdose of oxycodone.

##### Neonatal Opioid Withdrawal Syndrome

Prolonged use of Xtampza 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.

##### Cytochrome P450 3A4 Interaction

The concomitant use of Xtampza ER with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone 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 oxycodone plasma concentration. Monitor patients receiving Xtampza ER and any CYP3A4 inhibitor or inducer.

##### Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

- Reserve concomitant prescribing of Xtampza ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

#### CONTRAINDICATIONS:

- Xtampza 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 gastrointestinal obstruction, including paralytic ileus, and hypersensitivity (eg,

anaphylaxis) to oxycodone

## **WARNINGS AND PRECAUTIONS:**

### **Addiction, Abuse, and Misuse**

Xtampza ER contains oxycodone, a Schedule II controlled substance. As an opioid, Xtampza ER exposes users to the risks of addiction, abuse, and misuse. As extended-release products such as Xtampza 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 oxycodone present.

### **Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)**

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain
- Discuss with patients and/or their caregivers, with every prescription, the safe use, serious risks, and proper storage and disposal of these products. The Patient Counseling Guide (PCG) can be obtained at this link: [www.fda.gov/OpioidAnalgesicREMSPCG](http://www.fda.gov/OpioidAnalgesicREMSPCG)
- Emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist
- Consider other tools to improve patient, household, and community safety such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

For further information on the REMS and a list of accredited REMS CME/CE, call 1-800-503-0784, or visit [www.opioidanalgesicrems.com](http://www.opioidanalgesicrems.com). The FDA Blueprint can be found at [www.fda.gov/OpioidAnalgesicREMSBlueprint](http://www.fda.gov/OpioidAnalgesicREMSBlueprint).

### **Life-Threatening Respiratory Depression**

- Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, 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. Carbon dioxide (CO<sub>2</sub>) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids
- Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose
- Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper

### **Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:**

- Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with Xtampza ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered
- Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone

### **Neonatal Opioid Withdrawal Syndrome**

- Prolonged use of Xtampza ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome, and ensure that appropriate treatment will be available

### **Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers**

- Concomitant use of Xtampza ER with a CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), may increase plasma concentrations of oxycodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of Xtampza ER is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in Xtampza ER-treated patients may increase oxycodone plasma concentrations and prolong opioid adverse reactions. When using Xtampza ER with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in Xtampza ER-treated patients, monitor patients closely at frequent intervals and consider dosage reduction of Xtampza ER until stable drug effects are achieved
- Concomitant use of Xtampza ER with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease oxycodone plasma concentrations, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to oxycodone. When using Xtampza ER with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosage if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur

### **Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants**

- Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Xtampza ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate
- Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics.
- If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose

## **Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients**

- The use of Xtampza ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated

**Patients with Chronic Pulmonary Disease:** Xtampza ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive, including apnea, even at recommended dosages of Xtampza ER

**Elderly, Cachectic, or 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 Xtampza ER and when Xtampza ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients. Use an alternative analgesic for patients who require a dose of Xtampza ER less than 9 mg

### **Adrenal Insufficiency**

- Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs, including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover, and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency

### **Severe Hypotension**

- Xtampza ER may cause severe hypotension, including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of Xtampza ER. In patients with circulatory shock, Xtampza ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of Xtampza ER in patients with circulatory shock

### **Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness**

- In patients who may be susceptible to the intracranial effects of CO<sub>2</sub> retention (eg, those with evidence of increased intracranial pressure or brain tumors), Xtampza ER may reduce respiratory drive, and the resultant CO<sub>2</sub> retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with Xtampza ER
- Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of Xtampza ER in patients with impaired consciousness or coma

### **Risks of Use in Patients with Gastrointestinal Conditions**

- Xtampza ER is contraindicated in patients with gastrointestinal obstruction, including paralytic ileus
- The oxycodone in Xtampza ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in the serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms

### **Risk of Use in Patients with Seizure Disorders**

- The oxycodone in Xtampza ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during Xtampza ER therapy

### **Withdrawal**

- Do not abruptly discontinue Xtampza ER in a patient physically dependent on opioids. When discontinuing Xtampza ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of oxycodone in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain
- Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including Xtampza ER. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms

### **Risks of Driving and Operating Machinery**

- Xtampza ER may impair the mental or physical abilities needed to perform potentially hazardous activities, such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of Xtampza ER and know how they will react to the medication

### **Laboratory Monitoring**

- Not every urine drug test for "opioids" or "opiates" detects oxycodone reliably, especially those designed for in-office use. Further, many laboratories will report urine drug concentrations below a specified "cut-off" value as "negative." Therefore, if urine testing for oxycodone is considered in the clinical management of an individual patient, ensure that the sensitivity and specificity of the assay is appropriate, and consider the limitations of the testing used when interpreting results

### **ADMINISTRATION WITH FOOD:**

- Instruct patients to always take Xtampza ER capsules with food and with approximately the same amount of food in order to ensure consistent plasma levels are achieved. For patients who have difficulty swallowing, Xtampza ER can also be taken as a sprinkle on soft foods or sprinkled into a cup and administered directly into the mouth, or through a nasogastric or gastric feeding tube

### **ADVERSE REACTIONS:**

- The most common adverse reactions (>5%) reported by patients in the Phase 3 clinical trial comparing Xtampza ER with placebo were nausea, headache, constipation, somnolence, pruritus, vomiting, and dizziness

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at [XtampzaER.com/PI](http://XtampzaER.com/PI).

#### **NUCYNTA® ER (tapentadol) INDICATIONS AND USAGE**

NUCYNTA ER (tapentadol) 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
- Neuropathic pain associated with diabetic peripheral neuropathy (DPN) 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 NUCYNTA ER for use in patients for whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain
- NUCYNTA ER is not indicated as an as-needed (prn) analgesic

#### **WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; INTERACTION WITH ALCOHOL and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS**

##### **Addiction, Abuse, and Misuse**

NUCYNTA 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 NUCYNTA ER, and monitor all patients regularly for the development of these behaviors and conditions.

##### **Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)**

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- complete a REMS-compliant education program,
- counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,
- emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and
- consider other tools to improve patient, household, and community safety.

##### **Life-Threatening Respiratory Depression**

Serious, life-threatening, or fatal respiratory depression may occur with use of NUCYNTA ER. Monitor for respiratory depression, especially during initiation of NUCYNTA ER or following a dose increase. Instruct patients to swallow NUCYNTA ER tablets whole; crushing, chewing, or dissolving NUCYNTA ER tablets can cause rapid release and absorption of a potentially fatal dose of tapentadol.

##### **Accidental Ingestion**

Accidental ingestion of even one dose of NUCYNTA ER, especially by children, can result in a fatal overdose of tapentadol.

##### **Neonatal Opioid Withdrawal Syndrome**

Prolonged use of NUCYNTA 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.

##### **Interaction With Alcohol**

Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products that contain alcohol while taking NUCYNTA ER. The co-ingestion of alcohol with NUCYNTA ER may result in increased plasma tapentadol levels and a potentially fatal overdose of tapentadol.

##### **Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants**

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

- Reserve concomitant prescribing of NUCYNTA ER and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

#### **CONTRAINDICATIONS:**

NUCYNTA ER is contraindicated in patients with:

- Significant respiratory depression
- Acute or severe bronchial asthma or hypercarbia in an unmonitored setting or in the absence of resuscitative equipment
- Known or suspected gastrointestinal obstruction, including paralytic ileus
- Hypersensitivity (eg, anaphylaxis, angioedema) to tapentadol or to any other ingredients of the product
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days



## **WARNINGS AND PRECAUTIONS:**

### **Addiction, Abuse, and Misuse**

NUCYNTA ER contains tapentadol, a Schedule II controlled substance. As an opioid, NUCYNTA ER exposes users to the risks of addiction, abuse, and misuse. Because extended-release products such as NUCYNTA 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 tapentadol present.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed NUCYNTA ER. 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 NUCYNTA ER, and monitor all patients receiving NUCYNTA ER for the development of these behaviors and conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (eg, major depression). The potential for these risks should not, however, prevent the prescribing of NUCYNTA ER for the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as NUCYNTA ER, but use in such patients necessitates intensive counseling about the risks and proper use of NUCYNTA ER along with intensive monitoring for signs of addiction, abuse, and misuse.

Abuse or misuse of NUCYNTA ER by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of tapentadol and can result in overdose and death.

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing NUCYNTA 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. Contact the local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

### **Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)**

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain
- Discuss the safe use, serious risks, and proper storage and disposal of opioid analgesics with patients and/or their caregivers every time these medicines are prescribed. The Patient Counseling Guide (PCG) can be obtained at this link: [www.fda.gov/OpioidAnalgesicREMSPCG](http://www.fda.gov/OpioidAnalgesicREMSPCG)
- Emphasize to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an opioid analgesic is dispensed to them
- Consider using other tools to improve patient, household, and community safety, such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

To obtain further information on the opioid analgesic REMS and for a list of accredited REMS CME/CE, call 1-800-503-0784, or log on to [www.opioidanalgesicrems.com](http://www.opioidanalgesicrems.com). The FDA Blueprint can be found at [www.fda.gov/OpioidAnalgesicREMSBlueprint](http://www.fda.gov/OpioidAnalgesicREMSBlueprint).

### **Life-Threatening Respiratory Depression**

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, 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. Carbon dioxide (CO<sub>2</sub>) 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 NUCYNTA ER, the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression especially within the first 24-72 hours of initiating therapy with and following dosage increases of NUCYNTA ER.

To reduce the risk of respiratory depression, proper dosing and titration of NUCYNTA ER are essential. Overestimating the NUCYNTA ER dosage when converting patients from another opioid product can result in fatal overdose with the first dose.

Accidental ingestion of even one dose of NUCYNTA ER, especially by children, can result in respiratory depression and death due to an overdose of tapentadol.

Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose.

Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper.

### **Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:**

Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with NUCYNTA ER. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered.

Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone.

### **Neonatal Opioid Withdrawal Syndrome**

Prolonged use of NUCYNTA ER during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

### **Risk From Concomitant Use With Benzodiazepines or Other CNS Depressants**

Patients must not consume alcoholic beverages or prescription or non-prescription products containing alcohol while on NUCYNTA ER therapy. The co-ingestion of alcohol with NUCYNTA ER may result in increased plasma tapentadol levels and a potentially fatal overdose of tapentadol.

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of NUCYNTA ER with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics.

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation. If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose.

Advise both patients and caregivers about the risks of respiratory depression and sedation when NUCYNTA ER is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressants have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs.

### **Risk of Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients**

The use of NUCYNTA ER in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

**Patients with Chronic Pulmonary Disease:** NUCYNTA ER-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of NUCYNTA ER.

**Elderly, Cachectic, or Debilitated Patients:** Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Alternatively, consider the use of non-opioid analgesics in these patients.

Monitor such patients closely, particularly when initiating and titrating NUCYNTA ER and when NUCYNTA ER is given concomitantly with other drugs that depress respiration.

### **Serotonin Syndrome With Concomitant Use of Serotonergic Drugs**

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of tapentadol with serotonergic drugs. Serotonergic drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT<sub>3</sub> receptor antagonists, drugs that affect the serotonergic neurotransmitter system (eg, mirtazapine, trazodone, tramadol), certain muscle relaxants (ie, cyclobenzaprine, metaxalone), and drugs that impair metabolism of serotonin (including MAO inhibitors, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue). This may occur within the recommended dosage range.

Serotonin syndrome symptoms may include mental status changes (eg, agitation, hallucinations, coma), autonomic instability (eg, tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (eg, hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). The onset of symptoms generally occurs within several hours to a few days of concomitant use, but may occur later than that. Discontinue NUCYNTA ER if serotonin syndrome is suspected.

### **Adrenal Insufficiency**

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

### **Severe Hypotension**

NUCYNTA ER may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of NUCYNTA ER. In patients with circulatory shock, NUCYNTA ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of NUCYNTA ER in patients with circulatory shock.

### **Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness**

In patients who may be susceptible to the intracranial effects of CO<sub>2</sub> retention (eg, those with evidence of increased intracranial pressure or brain tumors), NUCYNTA ER may reduce respiratory drive, and the resultant CO<sub>2</sub> retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with NUCYNTA ER.

Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of NUCYNTA ER in patients with impaired consciousness or coma.

### **Risks of Use in Patients With Gastrointestinal Conditions**

NUCYNTA ER is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

The tapentadol in NUCYNTA ER may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

### **Increased Risk of Seizures in Patients With Seizure Disorders**

The tapentadol in NUCYNTA ER may increase the frequency of seizures in patients with seizure disorders and may increase the risk of seizures in other

clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during NUCYNTA ER therapy.

#### **Withdrawal**

Do not abruptly discontinue NUCYNTA ER in a patient physically dependent on opioids. When discontinuing NUCYNTA ER in a physically dependent patient, gradually taper the dosage. Rapid tapering of tapentadol in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain.

Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including NUCYNTA ER. In these patients, mixed agonists/antagonists and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms.

#### **Risks of Driving and Operating Machinery**

NUCYNTA ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of NUCYNTA ER and know how they will react to the medication.

#### **Risk of Toxicity in Patients With Hepatic Impairment**

A study with an immediate-release formulation of tapentadol in subjects with hepatic impairment showed higher serum concentrations of tapentadol than in those with normal hepatic function. Avoid use of NUCYNTA ER in patients with severe hepatic impairment. Reduce the dose of NUCYNTA ER in patients with moderate hepatic impairment. Closely monitor patients with moderate hepatic impairment for respiratory and central nervous system depression when initiating and titrating NUCYNTA ER.

#### **Risk of Toxicity in Patients With Renal Impairment**

Use of NUCYNTA ER in patients with severe renal impairment is not recommended due to accumulation of a metabolite formed by glucuronidation of tapentadol. The clinical relevance of the elevated metabolite is not known.

#### **ADVERSE REACTIONS:**

In clinical studies, the most common ( $\geq 10\%$ ) adverse reactions were nausea, constipation, dizziness, headache, and somnolence.

**See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at [Nucynta.com/ERpi](http://Nucynta.com/ERpi).**

#### **NUCYNTA® (tapentadol) INDICATIONS AND USAGE**

NUCYNTA (tapentadol) tablets are indicated for the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate in adults.

#### **Limitations of Use**

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, reserve NUCYNTA tablets for use in patients for whom alternative treatment options (eg, non-opioid analgesics or opioid combination products):

- Have not been tolerated, or are not expected to be tolerated
- Have not provided adequate analgesia, or are not expected to provide adequate analgesia

#### **IMPORTANT SAFETY INFORMATION**

##### **WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS**

##### **Addiction, Abuse, and Misuse**

NUCYNTA tablets expose 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 NUCYNTA tablets, and monitor all patients regularly for the development of these behaviors and conditions.

##### **Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)**

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

- complete a REMS-compliant education program,
- counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,
- emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and
- consider other tools to improve patient, household, and community safety.

##### **Life-Threatening Respiratory Depression**

Serious, life-threatening, or fatal respiratory depression may occur with use of NUCYNTA tablets. Monitor for respiratory depression, especially during initiation of NUCYNTA tablets or following a dose increase.

##### **Accidental Ingestion**

Accidental ingestion of even one dose of NUCYNTA tablets, especially by children, can result in a fatal overdose of tapentadol.

##### **Neonatal Opioid Withdrawal Syndrome**

Prolonged use of NUCYNTA tablets 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.

##### **Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants**

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.



- Reserve concomitant prescribing of NUCYNTA tablets and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

**CONTRAINDICATIONS:**

NUCYNTA tablets are 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 gastrointestinal obstruction, including suspected paralytic ileus
- Hypersensitivity to tapentadol (eg, anaphylaxis, angioedema) or to any other ingredients of the product
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days

**WARNINGS AND PRECAUTIONS:****Addiction, Abuse, and Misuse**

NUCYNTA tablets contain tapentadol, a Schedule II controlled substance. As an opioid, NUCYNTA tablets expose users to the risks of addiction, abuse, and misuse.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed NUCYNTA tablets. Addiction can occur at recommended dosages and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing NUCYNTA tablets and monitor all patients receiving NUCYNTA tablets for the development of these behaviors and conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (eg, major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as NUCYNTA tablets, but use in such patients necessitates intensive counseling about the risks and proper use of NUCYNTA tablets along with intensive monitoring for signs of addiction, abuse, and misuse.

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing NUCYNTA tablets. 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. 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.

**Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)**

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain
- Discuss the safe use, serious risks, and proper storage and disposal of opioid analgesics with patients and/or their caregivers every time these medicines are prescribed. The Patient Counseling Guide (PCG) can be obtained at this link: [www.fda.gov/OpioidAnalgesicREMSPCG](http://www.fda.gov/OpioidAnalgesicREMSPCG)
- Emphasize to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an opioid analgesic is dispensed to them
- Consider using other tools to improve patient, household, and community safety, such as patient-prescriber agreements that reinforce patient-prescriber responsibilities

To obtain further information on the opioid analgesic REMS and for a list of accredited REMS CME/CE, call 1-800-503-0784, or log on to [www.opioidanalgesicrems.com](http://www.opioidanalgesicrems.com). The FDA Blueprint can be found at [www.fda.gov/OpioidAnalgesicREMSBlueprint](http://www.fda.gov/OpioidAnalgesicREMSBlueprint).

**Life-Threatening Respiratory Depression**

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, 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. Carbon dioxide (CO<sub>2</sub>) 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 NUCYNTA tablets, the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with and following dosage increases of NUCYNTA tablets.

To reduce the risk of respiratory depression, proper dosing and titration of NUCYNTA tablets are essential. Overestimating the NUCYNTA tablets dosage when converting patients from another opioid product can result in a fatal overdose with the first dose.

Accidental ingestion of even one dose of NUCYNTA tablets, especially by children, can result in respiratory depression and death due to an overdose of tapentadol.

Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help right away in the event of a known or suspected overdose.

Opioids can cause sleep-related breathing disorders, including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the opioid dosage using best practices for opioid taper.

**Patient Access to Naloxone for the Emergency Treatment of Opioid Overdose:**

Discuss the availability of naloxone for the emergency treatment of opioid overdose with the patient and caregiver and assess the potential need for access to naloxone, both when initiating and renewing treatment with NUCYNTA tablets. Inform patients and caregivers about the various ways to obtain naloxone as permitted by individual state naloxone dispensing and prescribing requirements or guidelines (eg, by prescription, directly from a pharmacist, or as part of a community-based program). Educate patients and caregivers on how to recognize respiratory depression and emphasize the importance of calling 911 or getting emergency medical help, even if naloxone is administered.

Consider prescribing naloxone, based on the patient's risk factors for overdose, such as concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose. The presence of risk factors for overdose should not prevent the proper management of pain in any given patient. Also consider prescribing naloxone if the patient has household members (including children) or other close contacts at risk for accidental ingestion or overdose. If naloxone is prescribed, educate patients and caregivers on how to treat with naloxone.

### **Neonatal Opioid Withdrawal Syndrome**

Prolonged use of NUCYNTA tablets during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

### **Risks From Concomitant Use With Benzodiazepines or Other CNS Depressants**

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of NUCYNTA tablets with benzodiazepines or other CNS depressants (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics.

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation. If concomitant use is warranted, consider prescribing naloxone for the emergency treatment of opioid overdose.

Advise both patients and caregivers about the risks of respiratory depression and sedation when NUCYNTA tablets are used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs.

### **Life-Threatening Respiratory Depression in Patients With Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients**

The use of NUCYNTA tablets in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

**Patients with Chronic Pulmonary Disease:** NUCYNTA tablets-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of NUCYNTA tablets.

**Elderly, Cachectic, or Debilitated Patients:** Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients.

Monitor such patients closely, particularly when initiating and titrating NUCYNTA tablets and when NUCYNTA tablets are given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients.

### **Serotonin Syndrome With Concomitant Use of Serotonergic Drugs**

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concurrent use of tapentadol with serotonergic drugs. Serotonergic drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT<sub>3</sub> receptor antagonists, drugs that affect the serotonergic neurotransmitter system (eg, mirtazapine, trazodone, tramadol), certain muscle relaxants (ie, cyclobenzaprine, metaxalone), and drugs that impair metabolism of serotonin (including MAO inhibitors, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue). This may occur within the recommended dosage range.

Serotonin syndrome symptoms may include mental-status changes (eg, agitation, hallucinations, coma), autonomic instability (eg, tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (eg, hyperreflexia, incoordination) and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea) and can be fatal. The onset of symptoms generally occurs within several hours to a few days of concomitant use, but may occur later than that. Discontinue NUCYNTA tablets if serotonin syndrome is suspected.

### **Adrenal Insufficiency**

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

### **Severe Hypotension**

NUCYNTA tablets may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dosage of NUCYNTA tablets. In patients with circulatory shock, NUCYNTA tablets may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of NUCYNTA tablets in patients with circulatory shock.

### **Risks of Use in Patients With Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness**

In patients who may be susceptible to the intracranial effects of CO<sub>2</sub> retention (eg, those with evidence of increased intracranial pressure or brain tumors), NUCYNTA tablets may reduce respiratory drive, and the resultant CO<sub>2</sub> retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with NUCYNTA tablets.

Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of NUCYNTA tablets in patients with impaired consciousness or coma.

### Risks of Use in Patients With Gastrointestinal Conditions

NUCYNTA tablets are contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

The tapentadol in NUCYNTA tablets may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis for worsening symptoms.

### Increased Risk of Seizures in Patients With Seizure Disorders

The tapentadol in NUCYNTA tablets may increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical settings associated with seizures. Monitor patients with a history of seizure disorders for worsened seizure control during NUCYNTA tablets therapy.

### Withdrawal

Do not abruptly discontinue NUCYNTA tablets in a patient physically dependent on opioids. When discontinuing NUCYNTA tablets in a physically dependent patient, gradually taper the dosage. Rapid tapering of tapentadol in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain.

Additionally, avoid the use of mixed agonist/antagonist (eg, pentazocine, nalbuphine, and butorphanol) or partial agonist (eg, buprenorphine) analgesics in patients who are receiving a full opioid agonist analgesic, including NUCYNTA tablets. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or precipitate withdrawal symptoms.

### Risks of Driving and Operating Machinery

NUCYNTA tablets may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of NUCYNTA tablets and know how they will react to the medication.

### Interactions With Alcohol, Other Opioids, and Drugs of Abuse

Due to its mu-opioid agonist activity, NUCYNTA tablets may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression, respiratory depression, hypotension, and profound sedation, coma or death. Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products containing alcohol, other opioids, or drugs of abuse while on NUCYNTA tablets therapy.

### Risk of Toxicity in Patients With Hepatic Impairment

A study with NUCYNTA tablets in subjects with hepatic impairment showed higher serum concentrations of tapentadol than in those with normal hepatic function. Avoid use of NUCYNTA tablets in patients with severe hepatic impairment. Reduce the dose of NUCYNTA tablets in patients with moderate hepatic impairment. Closely monitor patients with moderate hepatic impairment for respiratory and central nervous system depression when receiving NUCYNTA tablets.

### Risk of Toxicity in Patients With Renal Impairment

Use of NUCYNTA tablets in patients with severe renal impairment is not recommended due to accumulation of a metabolite formed by glucuronidation of tapentadol. The clinical relevance of the elevated metabolite is not known.

### ADVERSE REACTIONS:

In clinical studies, the most common ( $\geq 10\%$ ) adverse reactions were nausea, dizziness, vomiting, and somnolence.

See full Prescribing Information, including Boxed Warning on Addiction, Abuse and Misuse and other serious risks, accompanying this piece or at [Nucynta.com/IRpi](http://Nucynta.com/IRpi).

### ELYXYB™ (celecoxib) oral solution

#### INDICATION

ELYXYB™ (celecoxib) oral solution is a nonsteroidal anti-inflammatory drug (NSAID) indicated for the acute treatment of migraine with or without aura in adults.

#### Limitations of Use

ELYXYB is not indicated for the preventive treatment of migraine.

#### IMPORTANT SAFETY INFORMATION about ELYXYB™

##### WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

###### Cardiovascular Thrombotic Events

- Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in the treatment and may increase with duration of use.
- ELYXYB is contraindicated in the setting of coronary artery bypass graft (CABG) surgery.

###### Gastrointestinal Bleeding, Ulceration, and Perforation

- NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious (GI) events.

#### CONTRAINDICATIONS

ELYXYB is contraindicated in the following patients:

- Known hypersensitivity to celecoxib or any components of the drug product or sulfonamides.
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs.
- In the setting of coronary artery bypass graft (CABG) surgery.

#### WARNINGS AND PRECAUTIONS

**Post-MI Patients:** Avoid the use of ELYXYB in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If ELYXYB is used in patients with a recent MI, monitor patients for signs of cardiac ischemia.

**Hepatotoxicity:** Elevations of ALT or AST have been reported in patients with NSAIDs. In addition, rare, sometimes fatal, cases of severe hepatic injury, including fulminant hepatitis, liver necrosis, and hepatic failure, have been reported. Inform patients of warning signs and symptoms of hepatotoxicity. Discontinue if abnormal liver tests persist or worsen or if clinical signs and symptoms of liver disease develop.

**Hypertension:** NSAIDs, including ELYXYB, can lead to new onset of hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events. Patients taking some antihypertension medications may have impaired response to these therapies when taking NSAIDs. Monitor blood pressure.

**Heart Failure and Edema:** Avoid the use of ELYXYB in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If ELYXYB is used in patients with severe heart failure, monitor patients for signs of worsening heart failure.

**Renal Toxicity:** Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury and may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia. Avoid use of ELYXYB in patients with severe renal impairment unless benefits are expected to outweigh the risk of worsening renal function. If ELYXYB is used in patients with advanced renal disease, monitor patients for signs of worsening renal function.

**Hyperkalemia:** Increases in serum potassium concentration, including hyperkalemia, have been reported with use of NSAIDs, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninemic-hypoaldosteronism state.

**Anaphylactic Reactions:** Celecoxib has been associated with anaphylactic reactions in patients with and without known hypersensitivity to celecoxib and in patients with aspirin-sensitive asthma. Celecoxib is a sulfonamide and both NSAIDs and sulfonamides may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people.

**Exacerbation of Asthma Related to Aspirin Sensitivity:** ELYXYB is contraindicated in patients with aspirin-sensitive asthma. Monitor patients with preexisting asthma (without known aspirin sensitivity).

**Serious Skin Reactions:** Serious skin reactions have occurred following treatment with celecoxib, including erythema multiforme, exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP). These serious events may occur without warning and can be fatal. Discontinue ELYXYB at the first appearance of skin rash or any other sign of hypersensitivity.

**Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS):** DRESS has been reported in patients taking NSAIDs. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Eosinophilia is often present. If such signs or symptoms are present, discontinue ELYXYB and evaluate the patient immediately.

**Medication Overuse Headache:** Overuse of acute migraine drugs (e.g., ergotamine, triptans, opioids, NSAIDs, or combination of these drugs for 10 or more days per month), including ELYXYB, may lead to exacerbation of headache (medication overuse headache). Detoxification of patients, including withdrawal of the overused drugs and treatment of withdrawal symptoms may be necessary.

**Premature Closure of Fetal Ductus Arteriosus:** ELYXYB may cause premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including ELYXYB, in pregnant women starting at about 30 weeks gestation and later.

**Oligohydramnios/Neonatal Renal Impairment:** Use of NSAIDs, including ELYXYB, at about 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. If NSAID treatment is necessary between about 20 weeks and 30 weeks gestation, limit ELYXYB use to the lowest effective dose and shortest duration possible. Discontinue ELYXYB if oligohydramnios occurs.

**Hematological Toxicity:** Anemia has occurred in NSAID-treated patients. Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia or blood loss. NSAIDs, including ELYXYB, may increase the risk of bleeding events. Monitor patients for signs of bleeding.

**Masking of Inflammation and Fever:** The pharmacological activity of celecoxib in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infections.

**Laboratory Monitoring:** Because serious GI bleeding, hepatotoxicity, and renal injury can occur without warning symptoms or signs, consider monitoring patients on long-term NSAID, including ELYXYB, treatment with a CBC and a chemistry profile periodically.

**Disseminated Intravascular Coagulation (DIC):** ELYXYB is not indicated in pediatric patients or for the treatment of juvenile rheumatoid arthritis (JRA). Disseminated intravascular coagulation has occurred with use of celecoxib capsules in pediatric patients with systemic-onset JRA, which required monitoring for signs and symptoms of abnormal clotting or bleeding.

## DRUG INTERACTIONS

**Drugs that Interfere with Hemostasis (e.g., warfarin, aspirin, SSRIs/SNRIs):** Monitor patients for bleeding who are concomitantly taking ELYXYB with drugs that interfere with hemostasis. Concomitant use of ELYXYB and oral corticosteroids, antiplatelet drugs (e.g., aspirin), anticoagulants, or selective serotonin reuptake inhibitors (SSRIs), is not recommended.

**ACE Inhibitors, Angiotensin Receptor Blockers (ARB), or Beta-Blockers:** Concomitant use with ELYXYB may diminish the antihypertensive effect of these drugs. Monitor blood pressure.

**ACE Inhibitors and ARBs:** Concomitant use with ELYXYB in the elderly, volume-depleted, or those with renal impairment may result in deterioration of renal function. In such high-risk patients, monitor for signs of worsening renal function.

**Diuretics:** NSAIDs can reduce natriuretic effect of furosemide and thiazide diuretics. Monitor patients to assure diuretic efficacy including antihypertensive effects.

**Digoxin:** Concomitant use with ELYXYB can increase serum concentration and prolong half-life of digoxin. Monitor serum digoxin levels.

## USE IN SPECIFIC POPULATIONS

**Pregnancy:** Use of NSAIDs during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs in pregnant women starting at 30 weeks gestation.

**Infertility:** NSAIDs are associated with reversible infertility. Consider withdrawal of ELYXYB in women who have difficulties conceiving.

## ADVERSE REACTIONS

Most common adverse reaction (at least 3% and greater than placebo) reported by patients treated with ELYXYB in the clinical trials was dysgeusia.

Please see [full Prescribing Information](#), including [Boxed Warning](#) and [Medication Guide](#) for ELYXYB.

To report SUSPECTED ADVERSE REACTIONS, contact BioDelivery Sciences International, Inc. at 1-800-469-0261 or FDA at 1-800-FDA-1088 or [www.fda.gov/safety/medwatch](http://www.fda.gov/safety/medwatch).

Intended for healthcare professionals of the United States of America only.

## Forward-Looking Statements

This press release contains forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. We may, in some cases, use terms such as "predicts," "forecasts," "believes," "potential," "proposed," "continue," "estimates," "anticipates," "expects," "plans," "intends," "may," "could," "might," "should" or other words that convey uncertainty of future events or outcomes to identify these forward-looking statements. Examples of forward-looking statements contained in this press release include, among others, statements related to our full-year 2022 financial guidance, including total projected product revenue, adjusted operating expenses and adjusted EBITDA, current and future market opportunities for our products and our assumptions related thereto, expectations (financial or otherwise) and intentions, and other statements that are not historical facts. Such statements are subject to numerous important factors, risks and uncertainties that may cause actual events or results, performance, or achievements to differ materially from the company's current expectations. Actual results may differ materially from management's expectations and such forward-looking statements in this press release could be affected as a result of various important factors, including risks relating to, among others: risks related to the ability to realize the anticipated benefits of our acquisition of BDSI, including the possibility that the expected benefits from the BDSI acquisition will not be realized or will not be realized within the expected time period; the risk that BDSI's business will not be integrated successfully; unknown liabilities; risks related to future opportunities and plans for the products acquired with BDSI, including uncertainty of the expected financial performance of such products; the impact of the COVID-19 pandemic on our ability to conduct our business, reach our customers, and supply the market with our products; our ability to commercialize and grow sales of our products; our ability to manage our relationships with licensors; the success of competing products that are or become available; our ability to obtain and maintain regulatory approval of our products and any product candidates, and any related restrictions, limitations, and/or warnings in the label of an approved product; the size of the markets for our products and product candidates, and our ability to service those markets; our ability to obtain reimbursement and third-party payor contracts for our products; the rate and degree of market acceptance of our products and product candidates; the costs of commercialization activities, including marketing, sales and distribution; changing market conditions for our products; the outcome of any patent infringement, opioid-related or other litigation that may be brought by or against us, including litigation with Purdue Pharma, L.P.; the outcome of any governmental investigation related to our business; our ability to secure adequate supplies of active pharmaceutical ingredient for each of our products and manufacture adequate supplies of commercially saleable inventory; our ability to obtain funding for our operations and business development; regulatory developments in the U.S.; our expectations regarding our ability to obtain and maintain sufficient intellectual property protection for our products; our ability to comply with stringent U.S. and foreign government regulation in the manufacture of pharmaceutical products, including U.S. Drug Enforcement Agency, or DEA, compliance; our customer concentration; and the accuracy of our estimates regarding expenses, revenue, capital requirements and need for additional financing. These and other risks are described under the heading "Risk Factors" in our Annual Reports on Form 10-K and Quarterly Reports on Form 10-Q and other filings with the SEC. Any forward-looking statements that we make in this press release speak only as of the date of this press release. We assume no obligation to update our forward-looking statements whether as a result of new information, future events or otherwise, after the date of this press release.

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