NUCYNTA® ER (tapentadol)
INDICATIONS AND USAGE
NUCYNTA ER (tapentadol) is indicated for the management of:

- severe and persistent pain in adults that requires an opioid analgesic and that cannot be adequately treated with alternative options, including immediate-release opioids
- severe and persistent neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults that requires opioid analgesic and that cannot be adequately treated with alternative options, including immediate-release opioids

Limitations of Use

- Because of the risks of addiction, abuse, misuse, overdose and death, which can occur at any dosage or duration, and persist the course of therapy, reserve opioid analgesics, including NUCYNTA ER, for use in patients for whom alternative treatment options 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.

IMPORTANT SAFETY INFORMATION ABOUT NUCYNTA ER

WARNING: SERIOUS AND LIFE-THREATENING RISKS FROM USE OF NUCYNTA ER

Addiction, Abuse, and Misuse
Because the use of 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 and reassess all patients regularly for the development of these behaviors and conditions.

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of NUCYNTA ER, especially during initiation or following a dosage increase. To reduce the risk of respiratory depression, proper dosing and titration of NUCYNTA ER are essential. 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.

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.

Neonatal Opioid Withdrawal Syndrome (NOWS)
Advise pregnant women using opioids for an extended period of time of the risk of Neonatal Opioid Withdrawal Syndrome, which may be life-threatening if not recognized and treated. Ensure that neonatology experts will be available at delivery.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)
Healthcare providers are strongly encouraged to complete a REMS-compliant education program and to counsel patients and caregivers on serious risks, safe use, and the importance of reading the Medication Guide with each prescription.

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.
- 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. The risk of opioid-related overdose or overdose-related death is increased with higher opioid doses, and this risk persists over the course of therapy
- Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing NUCYNTA ER, and reassess 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 (e.g., 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 frequent reevaluation for signs of addiction, abuse, and misuse. Consider recommending or prescribing an opioid overdose reversal agent.
- 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 for non-medical use and are subject to diversion from legitimate prescribed use. 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 careful storage of the drug during the course of treatment and 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.

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 overdose reversal agents, depending on the patient's clinical status.
- 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 NUCYNTA ER, the risk is greatest during the initiation of therapy or following a dosage increase.
- 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 Opioid Overdose Reversal Agent for the Emergency Treatment of Opioid Overdose:

- Inform patients and caregivers about opioid overdose reversal agents (e.g., naloxone, nalmefene).
- Discuss the importance of having access to an opioid overdose reversal agent, especially if the patient has risk factors for overdose, such as (e.g., concomitant use of CNS depressants, a history of opioid use disorder, or prior opioid overdose or if there are household members (including children) or other close contacts at risk for accidental ingestion or opioid overdose. The presence of risk factors for overdose should not prevent the management of pain in any patient.
- Discuss the options for obtaining an opioid overdose reversal agent (e.g., prescription, over-the-counter, or as part of a community-based program).
- There are important differences among the opioid overdose reversal agents, such as route of administration, product strength, approved patient age range, and pharmacokinetics. Be familiar with these differences, as outlined in the approved labeling for those products, prior to recommending or prescribing such an agent.
- Educate patients and caregivers on how to recognize respiratory depression, and how to use an opioid overdose reversal agent for the emergency treatment of opioid overdose. Emphasize the importance of calling 911 or getting emergency medical help, even if an opioid overdose reversal agent is administered.

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 and/or other CNS depressants, including alcohol (eg, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, gabapentinoids [gabapentin or pregabalin], and 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. 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. Inform patients and caregivers of this potential interaction and educate them on the signs and symptoms of respiratory depression (including sedation).
- 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.

Neonatal Opioid Withdrawal Syndrome (NOWS)

- Use of NUCYNTA ER for an extended period of time 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 NOWS and manage accordingly. Advise pregnant women using opioids for an extended period of time of the risk of NOWS and ensure that appropriate treatment will be available.

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
- 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. The FDA Blueprint can be found at www.fda.gov/OpioidAnalgesicREMSBlueprint.

Opioid-Induced Hyperalgesia and Allodynia

- Opioid-Induced Hyperalgesia (OIH) occurs when an opioid analgesic paradoxically causes an increase in pain, or an increase in sensitivity to pain. This condition differs from tolerance, which is the need for increasing doses of opioids to maintain a defined effect. Symptoms of OIH include (but may not be limited to) increased levels of pain upon opioid dosage increase, decreased levels of pain upon opioid dosage decrease, or pain from ordinarily non-painful stimuli (allodynia). These symptoms may suggest OIH only if there is no evidence of underlying disease progression, opioid tolerance, opioid withdrawal, or addictive behavior.
- Cases of OIH have been reported, both with short-term and longer-term use of opioid analgesics. Though the mechanism of OIH is not fully understood, multiple biochemical pathways have been implicated. Medical literature suggests a strong biologic plausibility between opioid analgesics and OIH and allodynia. If a patient is suspected to be experiencing OIH, carefully consider appropriately decreasing the dose of the current opioid analgesic or opioid rotation (safely switching the patient to a different opioid moiety).

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-HT3 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 monoamine oxidase 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.

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.
- Regularly evaluate patients, particularly when initiating and titrating NUCYNTA ER and when NUCYNTA ER is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients.

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). Regularly evaluate 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_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), NUCYNTA ER may reduce respiratory drive, and the resultant CO_2 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 Gastrointestinal Complications

- 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. Regularly evaluate patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.
- Cases of opioid-induced esophageal dysfunction (OIED) have been reported in patients taking opioids. The risk of OIED may increase as the dose and/or duration of opioids increases. Regularly evaluate patients for signs and symptoms of OIED (e.g., dysphagia, regurgitation, non-cardiac chest pain) and, if necessary, adjust opioid therapy as clinically appropriate.

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. Regularly evaluate patients with a history of seizure disorders for worsened seizure control during NUCYNTA ER therapy.

Withdrawal

- Do not rapidly reduce or 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. Frequently evaluate 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 (≥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.

To report SUSPECTED ADVERSE REACTIONS, contact Collegium Pharmaceutical, Inc. at 1-855-331-5615 or FDA at 1-800–FDA–1088 or http://www.fda.gov/medwatch.

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