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 and pediatric patients aged 6 years and older with a body weight of at least 40 kg.

Limitations of Use

Because of the risks of addiction, abuse, misuse, overdose, and death which can occur at any dose or duration and persist over the course of therapy, reserve opioid analgesics, including NUCYNTA tablets, for use in patients for whom alternative treatment options are:

- ineffective, not been tolerated, or would be
- are otherwise inadequate to provide sufficient management of pain

IMPORTANT SAFETY INFORMATION ABOUT NUCYNTA

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

Addiction, Abuse, and Misuse

Because the use of NUCYNTA tablets 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 tablets, especially during initiation of NUCYNTA tablets or following a dosage increase. To reduce the risk of respiratory depression, proper dosing and titration of NUCYNTA tablets are essential.

Accidental Ingestion

Accidental ingestion of even one dose of NUCYNTA tablets, especially by children, can result in a 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 tablets 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 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 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 (e.g., 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. 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. In postmarketing studies, addiction, abuse, misuse, and fatal and non-fatal opioid overdose were observed in patients with long-term opioid use.
- Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing NUCYNTA tablets and reassess 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 frequent reevaluation for signs of addiction, abuse, and misuse. Consider recommending or prescribing an opioid overdose reversal agent.
- Opioids are sought for non-medical use and are subject to diversion from legitimate prescribed use. 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 careful storage of the drug during the course of treatment and 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.

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 tablets, 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 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 Opiod Overdose Reversal Agent for 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 (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.
- Discuss with the patient the options for obtaining an opioid overdose reversal agent (e.g., prescription, over-the-counter, or as part of a community-based program)
- Educate patients and caregivers on how to recognize the signs and symptoms of an overdose.
- Explain to patients and caregivers that effects of opioid overdose reversal agents like naloxone and nalmefene are temporary, and that they must call 911 or get emergency medical help right away in all cases of known or suspected opioid overdose, even if an opioid overdose reversal agent is administered

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). 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. Inform patients and caregivers of this potential interaction and educate them on the signs and symptoms of respiratory depression (including 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.

Neonatal Opioid Withdrawal Syndrome (NOWS)

- Use of NUCYNTA tablets 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 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-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 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.

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.
- Regularly evaluate 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.

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). Regularly evaluate 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_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors), NUCYNTA tablets 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 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 Complication

- 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. 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 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. Regularly evaluate 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. Regularly evaluate 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 (≥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.

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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