HIGHLIGHTS OF PRESCRIBING INFORMATION

THESE HIGHLIGHTS DO NOT INCLUDE ALL THE INFORMATION NEEDED TO USE NUCYNTA® ER SAFELY AND EFFECTIVELY. SEE FULL PRESCRIBING INFORMATION FOR NUCYNTA® ER

NUCYNTA® ER (tapentadol) extended-release tablets for oral use C-II

Initial U.S. Approval: 2008

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

See full prescribing information for complete boxed warning.

- **NUCYNTA ER exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk before prescribing and reassess regularly for development of these behaviors or conditions. (5.1)**
- **Serious, life-threatening, or fatal respiratory depression may occur, especially upon 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 to avoid exposure to a potentially fatal dose of tapentadol. (2.1, 5.2)**
- **Accidental ingestion of NUCYNTA ER, especially in children, can result in fatal overdose of tapentadol. (5.2)**
- **Instruct patients not to consume alcohol or any products containing alcohol while taking NUCYNTA ER because co-ingestion can result in fatal plasma tapentadol levels. (5.3)**
- **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 for use in patients for whom alternative treatment options are inadequate. (5.3, 7)**
- **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 management by neonatology experts will be available at delivery. (5.4)**
- **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. (5.5)**

---------- RECENT MAJOR CHANGES ----------

Boxed Warning	12/2025
Indications and Usage (1)	12/2025
Dosage and Administration (2.1, 2.3, 2.6)	12/2025
Warnings and Precautions (5.1, 5.2, 5.3, 5.12, 5.14)	12/2025

---------- INDICATIONS AND USAGE ----------

NUCYNTA ER is an opioid agonist 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. (1)
- 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. (1)

Limitations of Use

Because of the risks of addiction, abuse, misuse, overdose, and death, which can occur at any dosage or duration and persist over 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. (1, 5.1)

- NUCYNTA ER is not indicated as an as-needed (prn) analgesic. (1)

---------- DOSAGE AND ADMINISTRATION ----------

- NUCYNTA ER should be prescribed only by healthcare professionals who are knowledgeable about the use of extended-release/long-acting opioids and how to mitigate the associated risks. (2.1)
- Use the lowest effective dosage for the shortest duration of time consistent with individual patient treatment goals. Reserve titration to higher doses of NUCYNTA ER for patients in whom lower doses are insufficiently effective and in whom the expected benefits of using a higher dose opioid clearly outweigh the substantial risks (2.5).
- Initiate the dosing regimen for each patient individually, taking into account the patient's underlying cause and severity of pain, prior analgesic treatment, and response, and risk factors for addiction, abuse, and misuse. (5.1)
- Respiratory depression can occur at any time during opioid therapy, especially when initiating and following dosage increases with NUCYNTA ER. Consider this risk when selecting an initial dose and when making dose adjustments. (2.1, 5.2)
- Discuss opioid overdose reversal agents and options for acquiring them with the patient and/or caregiver, both when initiating and renewing treatment with NUCYNTA ER, especially if the patient has additional risk factors for overdose, or close contacts at risk for exposure and overdose.(2.2, 5.1, 5.2, 5.3)
- NUCYNTA ER is administered orally twice daily (approximately every 12 hours). (2.1)
- Instruct patients to swallow NUCYNTA ER tablets intact, and not to cut, break, chew, crush, or dissolve the tablets (risk of potentially fatal overdose). (2.1, 5.1)
- Instruct patients to take tablets one at a time, with enough water to ensure complete swallowing immediately after placing in mouth. (2.1)
- Do not exceed a total daily dose of NUCYNTA ER of 500 mg. (2.1)
- For patients who are not opioid tolerant, initiate treatment with 50 mg tablet orally twice daily (approximately every 12 hours). See full prescribing information for instructions on conversion, titration, and maintenance of therapy. (2.3, 2.4)
- Titrate patients with dose increases of 50 mg no more than twice daily every three days. (2.4)
- Periodically reassess patients receiving NUCYNTA ER to evaluate the continued need for opioid analgesics to maintain pain control, for the signs or symptoms of adverse reactions, and for the development of addiction, abuse, or misuse. (2.4)
- Moderate Hepatic Impairment: Initiate treatment with 50 mg NUCYNTA ER no more than every 24 hours. Do not exceed 100 mg per day. Regularly evaluate for respiratory and central nervous system depression (2.5)
- Do not rapidly reduce or abruptly discontinue NUCYNTA ER in a physically-dependent patient because rapid reduction or abrupt discontinuation of opioid analgesics has resulted in serious withdrawal symptoms, uncontrolled pain, and suicide. (2.6, 5.14)

---------- DOSAGE FORMS AND STRENGTHS ----------

Extended-release tablets: 50 mg, 100 mg, 150 mg, 200 mg, 250 mg (3)

---------- CONTRAINDICATIONS ----------

- Significant respiratory depression (4)
- Acute or severe bronchial asthma (4)
- Known or suspected paralytic ileus (4)
- Hypersensitivity to tapentadol or to any other ingredients of the product (4)
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- 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. If OIH is suspected, carefully consider appropriately decreasing the dose of the current opioid analgesic or opioid rotation. (5.6)
- Serotonin Syndrome with Concomitant Use of Serotonergic Drugs: Potentially life-threatening condition could result from concomitant serotonergic drug administration. Discontinue NUCYNTA ER if serotonin syndrome is suspected. (5.7)
- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Regularly evaluate, particularly during initiation and titration. (5.8)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.9)
- Severe Hypotension: Regularly evaluate during dosage initiation and titration. Avoid use of NUCYNTA ER in patients with circulatory shock. (5.10)
- Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness: Monitor for sedation and respiratory depression. Avoid use of NUCYNTA ER in patients with impaired consciousness or coma. (5.11)

---------- ADVERSE REACTIONS ----------

The most common (≥10%) adverse reactions were nausea, constipation, dizziness, headache, and somnolence. (6)

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

---------- DRUG INTERACTIONS ----------

- Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics: Avoid use with NUCYNTA ER because they may reduce analgesic effect of NUCYNTA ER or precipitate withdrawal symptoms. (5.13, 7)

---------- USE IN SPECIFIC POPULATIONS ----------

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Lactation: Not recommended. (8.2)
- Severe Hepatic or Renal Impairment: Use not recommended. (8.6, 8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

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

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

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 *[see Warnings and Precautions (5.1)]*.

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 *[see Warnings and Precautions (5.2)]*.

Accidental Ingestion

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

Interaction with Alcohol

Instruct patients not to consume alcoholic beverages or use prescription or nonprescription 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 *[see Warnings and Precautions (5.3)]*.

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 *[see Warnings and Precautions (5.3), Drug Interactions (7)]*.

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 management by neonatology experts will be available at delivery *[see Warnings and Precautions (5.4)]*.

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 *[see Warnings and Precautions (5.5)]*.

1 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 an 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 over the course of therapy *[see Warnings and Precautions (5.1)]*, 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.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

- NUCYNTA ER should be prescribed only by healthcare professionals who are knowledgeable about the use of extended-release/long-acting opioids and how to mitigate the associated risks.
- Use the lowest effective dosage for the shortest duration of time consistent with individual patient treatment goals *[see Warnings and Precautions (5)]*. Because the risk of overdose increases as opioid doses increase, reserve

titration to higher doses of NUCYNTA ER for patients in whom lower doses are insufficiently effective and in whom the expected benefits of using a higher dose opioid clearly outweigh the substantial risks.

- Initiate the dosing regimen for each patient individually, taking into account the patient's underlying cause and severity of pain, prior analgesic treatment and response, and risk factors for addiction, abuse, and misuse *[see Warnings and Precautions (5.1)]*
- Respiratory depression can occur at any time during opioid therapy, especially when initiating and following dosage increases with NUCYNTA ER. Consider this risk when selecting an initial dose and when making dose adjustments *[see Warnings and Precautions (5.2)]*.
- NUCYNTA ER is administered orally twice daily (approximately every 12 hours).
- Instruct patients to swallow NUCYNTA ER tablets whole, one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth.
- Crushing, chewing, or dissolving NUCYNTA ER tablets will result in uncontrolled delivery of tapentadol and can lead to overdose or death *[see Warnings and Precautions (5.1)]*.
- Discontinue all other tapentadol and tramadol products when beginning and while taking NUCYNTA ER *[see Warnings and Precautions (5.7)]*.
- Although the maximum approved total daily dose of NUCYNTA immediate-release formulation is 600 mg per day, the maximum total daily dose of NUCYNTA ER is 500 mg.
- Do not exceed a total daily dose of NUCYNTA ER of 500 mg.

2.2 Patient Access to an 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 (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 *[see Warnings and Precautions (5.1, 5.2, 5.3)]*.

Discuss the options for obtaining an opioid overdose reversal agent (e.g., prescription, over-the-counter, or as part of a community-based program) *[see Warnings and Precautions (5.2)]*.

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.

2.3 Initial Dosage

It is safer to underestimate a patient's 24-hour oral tapentadol dosage and provide rescue medication (e.g., immediate-release opioid) than to overestimate the 24-hour oral tapentadol requirements which could result in an adverse reaction due to an overdose. While useful tables of opioid equivalents are readily available, there is inter-patient variability in the potency of opioid drugs and opioid formulations. Frequently reevaluate patients for signs and symptoms of opioid withdrawal and for signs of oversedation/toxicity after converting patients to NUCYNTA ER.

Use of NUCYNTA ER in Patients who are not Opioid Tolerant

The starting dose for patients who are not opioid tolerant is NUCYNTA ER 50 mg orally twice daily (approximately every 12 hours). Use of higher starting doses in patients who are not opioid tolerant may cause fatal respiratory depression.

Conversion from Tapentadol Immediate-Release (IR) products to NUCYNTA ER

Patients can be converted from tapentadol IR to NUCYNTA ER using the equivalent total daily dose of tapentadol IR and dividing it into two equal doses of NUCYNTA ER separated by approximately 12-hour intervals. As an example, a patient receiving 50 mg of tapentadol IR four times per day (200 mg/day) may be converted to 100 mg NUCYNTA ER twice a day.

Conversion from Methadone to NUCYNTA ER

Frequent evaluation is of particular importance when converting from methadone to other opioid agonists. The ratio between methadone and other opioid agonists may vary widely as a function of previous dose exposure. Methadone has a long half-life and can accumulate in the plasma.

Conversion from Other Opioid Analgesics to NUCYNTA ER

When NUCYNTA ER therapy is initiated, discontinue all other opioid analgesics other than those used on an as needed basis for breakthrough pain when appropriate. There are no established conversion ratios for conversion from other opioids to NUCYNTA ER defined by clinical trials. Initiate dosing using NUCYNTA ER 50 mg orally every 12 hours.

2.4 Titration and Maintenance of Therapy

Individually titrate NUCYNTA ER to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving NUCYNTA ER to assess the maintenance of pain control, signs and symptoms of opioid withdrawal, and other adverse reactions, as well as to reassess for the development of addiction, abuse, or misuse *[see Warnings and Precautions (5.1, 5.14)]*. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration. During use of opioid therapy for an extended period of time, periodically reassess the continued need for opioid analgesics.

Patients who experience breakthrough pain may require a dosage adjustment of NUCYNTA ER or may need rescue medication with an appropriate dose of an immediate-release analgesic.

If the level of pain increases after dose stabilization, attempt to identify the source of increased pain before increasing the NUCYNTA ER dosage. If after increasing the dosage, unacceptable opioid-related adverse reactions are observed (including an increase in pain after a dosage increase), consider reducing the dosage *[see Warnings and Precautions (5)]*. Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

Titrate patients to adequate analgesia with dose increases of 50 mg no more than twice daily every three days. In clinical studies, efficacy with NUCYNTA ER was demonstrated relative to placebo in the dosage range of 100 mg to 250 mg twice daily *[see Clinical Studies (14)]*.

2.5 Dosage Modification in Patients with Hepatic Impairment

The use of NUCYNTA ER in patients with severe hepatic impairment (Child-Pugh Score 10-15) is not recommended *[see Warnings and Precautions (5.16)]*.

In patients with moderate hepatic impairment (Child-Pugh Score 7 to 9), initiate treatment using 50 mg NUCYNTA ER, administer no more frequently than once every 24 hours, and regularly evaluate for respiratory and central nervous system depression, particularly during initiation and titration of NUCYNTA ER. The maximum recommended dose for patients with moderate hepatic impairment is 100 mg of NUCYNTA ER per day. Regularly evaluate patients for respiratory and central nervous system depression *[see Clinical Pharmacology (12.2)]*.

No dosage adjustment is recommended in patients with mild hepatic impairment (Child-Pugh Score 5 to 6) *[see Warnings and Precautions (5.16), Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*.

2.6 Safe Reduction or Discontinuation of NUCYNTA ER

Do not rapidly reduce or abruptly discontinue NUCYNTA ER in patients who may be physically dependent on opioids. Rapid reduction or abrupt discontinuation of opioid analgesics in patients who are physically dependent on opioids has resulted in serious withdrawal symptoms, uncontrolled pain, and suicide. Rapid reduction or abrupt discontinuation has also been associated with attempts to find other sources of opioid analgesics, which may be confused with drug-seeking for abuse.

Patients may also attempt to treat their pain or withdrawal symptoms with illicit opioids, such as heroin, and other substances.

When a decision has been made to decrease the dose or discontinue therapy in an opioid-dependent patient taking NUCYNTA ER, there are a variety of factors that should be considered, including the total daily dose of opioid (including NUCYNTA ER) the patient has been taking, the duration of treatment, the type of pain being treated, and the physical and psychological attributes of the patient. It is important to ensure ongoing care of the patient and to agree on an appropriate tapering schedule and follow-up plan so that patient and provider goals and expectations are clear and realistic. When opioid analgesics are being discontinued due to a suspected substance use disorder, evaluate and treat the patient, or refer for evaluation and treatment of the substance use disorder. Treatment should include evidence-based approaches, such as medication assisted treatment of opioid use disorder. Complex patients with co-morbid pain and substance use disorders may benefit from referral to a specialist.

There are no standard opioid tapering schedules that are suitable for all patients. Good clinical practice dictates a patient-specific plan to taper the dose of the opioid gradually. For patients on NUCYNTA ER who are physically opioid-dependent, initiate the taper by a small enough increment (e.g., no greater than 10% to 25% of the total daily dose) to avoid withdrawal symptoms, and proceed with dose-lowering at an interval of every 2 to 4 weeks. Patients who have been taking opioids for briefer periods of time may tolerate a more rapid taper.

It may be necessary to provide the patient with lower dosage strengths to accomplish a successful taper. Reassess the patient frequently to manage pain and withdrawal symptoms, should they emerge. Common withdrawal symptoms include restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate. If withdrawal symptoms arise, it may be necessary to pause the taper for a period of time or raise the dose of the opioid analgesic to the previous dose, and then proceed with a slower taper. In addition,

evaluate patients for any changes in mood, emergence of suicidal thoughts, or use of other substances.

When managing patients taking opioid analgesics, particularly those who have been treated for an extended period of time and/or with high doses for chronic pain, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic taper. A multimodal approach to pain management may optimize the treatment of chronic pain, as well as assist with the successful tapering of the opioid analgesic *[see Warnings and Precautions (5.14), Drug Abuse and Dependence (9.3)]*.

3 DOSAGE FORMS AND STRENGTHS

NUCYNTA ER 50 mg, 100 mg, 150 mg, 200 mg and 250 mg extended-release tablets are available in the following colors and prints:

- 50 mg extended-release tablets are white oblong-shaped with a black print "OMJ 50" on one side
- 100 mg extended-release tablets are light-blue oblong-shaped with a black print "OMJ 100" on one side
- 150 mg extended-release tablets are blue-green oblong-shaped with a black print "OMJ 150" on one side
- 200 mg extended-release tablets are blue oblong-shaped with a depression in the middle running lengthwise on each side and a black print "OMJ 200" on one side
- 250 mg extended-release tablets are dark blue oblong-shaped with a depression in the middle running lengthwise on each side and a white print "OMJ 250" on one side.

4 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 (e.g., anaphylaxis, angioedema) to tapentadol or to any other ingredients of the product *[see Adverse Reactions (6.2)]*.
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days *[see Drug Interactions (7)]*.

5 WARNINGS AND PRECAUTIONS

5.1 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. In postmarketing studies, addiction, abuse, misuse, and fatal and non-fatal opioid overdose were observed in patients with long-term opioid use *[see Adverse Reactions (6.2)]*.

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 *[see Dosage and Administration (2.2), Warnings and Precautions (5.2)]*.

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 *[see Overdosage (10)]*.

Opioids are sought for nonmedical 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.

5.2 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 *[see Overdosage (10)]*.

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 *[see Dosage and Administration (2)]*. 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 *[see Dosage and Administration (2.6)]*.

Patient Access an 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 (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 *[see Warnings and Precautions (5.1, 5.3)]*.

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 *[see Dosage and Administration (2.2), Warnings and Precautions (5.1, 5.3), Overdosage (10)]*.

5.3 Risks 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 *[see Clinical Pharmacology (12.3)]*.

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 (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, gabapentinoids [gabapentin or pregabalin], and 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 *[see Drug Interactions (7)]*.

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 recommending or prescribing an opioid overdose reversal agent *[see Dosage and Administration (2.2), Warnings and Precautions (5.2), Overdosage (10)]*.

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 *[see Drug Interactions (7)]*.

5.4 Neonatal Opioid Withdrawal Syndrome

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 neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for an extended period of time of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Use in Specific Populations (8.1)]*.

5.5 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.

5.6 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 *[see Dependence (9.3)]*. 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) *[see Dosage and Administration (2.6), Warnings and Precautions (5.14)]*.

5.7 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 (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e., 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) *[see Drug Interactions (7)]*. This may occur within the recommended dosage range.

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g., 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.

5.8 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 *[see Warnings and Precautions (5.2)]*.

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 *[see Warnings and Precautions (5.2)]*.

Regularly evaluate patients, particularly when initiating and titrating NUCYNTA ER and when NUCYNTA ER is given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.2), Drug Interactions (7)]*. Alternatively, consider the use of non-opioid analgesics in these patients.

5.9 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.

5.10 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 (e.g., phenothiazines or general anesthetics) *[see Drug Interactions (7)]*. 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.

5.11 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 (e.g., 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.

5.12 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 *[see Clinical Pharmacology (12.2)]*.

5.13 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 occurring in other clinical settings associated with seizures. Regularly evaluate patients with a history of seizure disorders for worsened seizure control during NUCYNTA ER therapy.

5.14 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 *[see Dosage and Administration (2.6), Drug Abuse and Dependence (9.3)]*.

Additionally, avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., 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 *[see Drug Interactions (7)]*.

5.15 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.

5.16 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 *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)]*.

Frequently evaluate patients with moderate hepatic impairment for respiratory and central nervous system depression when initiating and titrating NUCYNTA ER.

5.17 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 *[see Clinical Pharmacology (12.3)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are described, or described in greater detail, in other sections:

- Addiction, Abuse, and Misuse *[see Warnings and Precautions (5.1)]*
- Life-Threatening Respiratory Depression *[see Warnings and Precautions (5.2)]*
- Interaction with Benzodiazepine or Other CNS Depressants *[see Warnings and Precautions (5.3)]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.4)]*
- Opioid-Induced Hyperalgesia and Allodynia *[see Warnings and Precautions (5.6)]*
- Serotonin Syndrome *[see Warnings and Precautions (5.7)]*
- Adrenal Insufficiency *[see Warnings and Precautions (5.9)]*
- Severe Hypotension *[see Warnings and Precautions (5.10)]*
- Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.12)]*
- Seizures *[see Warnings and Precautions (5.13)]*
- Withdrawal *[see Warnings and Precautions (5.14)]*

6.1 Clinical Trial Experience

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

Commonly-Observed Adverse Reactions in Clinical Studies with NUCYNTA ER in Patients with Chronic Pain due to Low Back Pain or Osteoarthritis

The safety data described in Table 1 below are based on three pooled, randomized, double-blind, placebo-controlled, parallel group, 15-week studies of NUCYNTA ER (dosed 100 to 250 mg BID after a 50 mg BID starting dose) in patients with chronic pain due to low back pain (LBP) and osteoarthritis (OA). These trials included 980 NUCYNTA ER-treated patients and 993 placebo-treated patients. The mean age was 57 years old; 63% were female and 37% were male; 83% were White, 10% were Black, and 5% were Hispanic. The most common adverse reactions (reported by ≥10% in any NUCYNTA ER dose group) were: nausea, constipation, dizziness, headache, and somnolence.

The most common reasons for discontinuation due to adverse reactions in eight Phase 2/3 pooled studies reported by ≥1% in any NUCYNTA ER dose group for NUCYNTA ER- and placebo-treated patients were nausea (4% vs. 1%), dizziness (3% vs. <1%), vomiting (3% vs. <1%), somnolence (2% vs. <1%), constipation (1% vs. <1%), headache (1% vs. <1%), and fatigue (1% vs. <1%), respectively.

Table 1. Adverse Drug Reactions Reported by ≥1% of NUCYNTA ER-Treated Patients and Greater than Placebo-Treated Patients in Pooled Parallel-Group Trials[1]

	NUCYNTA ER 50 to 250 mg BID[2] (n=980)	Placebo (n=993)
Nausea	21%	7%
Constipation	17%	7%
Dizziness	17%	6%
Headache	15%	13%
Somnolence	12%	4%
Fatigue	9%	4%
Vomiting	8%	3%
Dry mouth	7%	2%
Hyperhidrosis	5%	<1%
Pruritus	5%	2%
Insomnia	4%	2%
Dyspepsia	3%	2%
Lethargy	2%	<1%
Asthenia	2%	<1%
Anxiety	2%	1%
Decreased appetite	2%	<1%
Vertigo	2%	<1%
Hot flush	2%	<1%
Disturbance in attention	1%	<1%
Tremor	1%	<1%
Chills	1%	0%
Abnormal dreams	1%	<1%
Depression	1%	<1%
Vision blurred	1%	<1%
Erectile dysfunction	1%	<1%

[1] MedDRA preferred terms. The trials included forced titration during the first week of dosing.

[2] NUCYNTA ER dosed between 100 and 250 mg BID after a starting dose of 50 mg BID

Commonly-Observed Adverse Reactions in Clinical Studies with NUCYNTA ER in Patients with Neuropathic Pain Associated with Diabetic Peripheral Neuropathy

The types of adverse reactions seen in the studies of patients with painful diabetic peripheral neuropathy (DPN) were similar to what was seen in the low back pain and osteoarthritis trials. The safety data described in Table 2 below are based on two pooled, randomized withdrawal, double-blind, placebo-controlled, 12-week studies of NUCYNTA ER (dosed 100 to 250 mg BID) in patients with neuropathic pain associated with diabetic peripheral neuropathy. These trials included 1040 NUCYNTA ER-treated patients and 343 placebo-treated patients. The mean age was 60 years old; 40% were female and 60% were male; 76% were White, 12% were Black, and 12% were "Other". The most commonly reported ADRs (incidence ≥10% in NUCYNTA ER-treated subjects) were: nausea, constipation, vomiting, dizziness, somnolence, and headache.

Table 2 lists the common adverse reactions reported in 1% or more of NUCYNTA ER-treated patients and greater than placebo-treated patients with neuropathic pain associated with diabetic peripheral neuropathy in the two pooled studies.

Table 2. Adverse Drug Reactions Reported by ≥ 1% of NUCYNTA ER-Treated Patients and Greater than Placebo-Treated Patients in Pooled Trials (Studies DPN-1 and DPN-2)[1]

	NUCYNTA ER 50 to 250 mg BID[2] (n=1040)	Placebo[3] (n=343)
Nausea	27%	8%
Dizziness	18%	2%
Somnolence	14%	<1%
Constipation	13%	<1%
Vomiting	12%	3%
Headache	10%	5%
Fatigue	9%	<1%
Pruritus	8%	0%
Dry mouth	7%	<1%
Diarrhea	7%	5%
Decreased appetite	6%	<1%
Anxiety	5%	4%
Insomnia	4%	3%

Hyperhidrosis	3%	2%
Hot flush	3%	2%
Tremor[4]	3%	3%
Abnormal dreams	2%	0%
Lethargy	2%	0%
Asthenia	2%	<1%
Irritability	2%	1%
Dyspnea	1%	0%
Nervousness	1%	0%
Sedation	1%	0%
Vision blurred	1%	0%
Pruritus generalized	1%	0%
Vertigo	1%	<1%
Abdominal discomfort	1%	<1%
Hypotension	1%	<1%
Dyspepsia	1%	<1%
Hypoesthesia	1%	<1%
Depression	1%	<1%
Rash	1%	<1%
Chills[4]	1%	1%
Feeling cold[4]	1%	1%
Drug withdrawal syndrome	1%	<1%

[1] MedDRA preferred terms.

[2] NUCYNTA ER dosed between 100 and 250 mg BID after a starting dose of 50 mg BID. It includes ADR reported in the open-label titration period for all subjects and in the double-blind maintenance period for the subjects who were randomized to NUCYNTA ER.

[3] It includes ADR reported in the double-blind maintenance period for the subjects who were randomized to placebo after receiving NUCYNTA ER during the open-label titration period.

[4] Tremor was observed in 3.4% of NUCYNTA ER-treated subjects vs. 3.2% in placebo group, chills- in 1.3% vs.1.2% in placebo, and feeling cold- in 1.3% vs.1.2% in placebo.

Other Adverse Reactions Observed During the Premarketing Evaluation of NUCYNTA ER

The following additional adverse drug reactions occurred in less than 1% of NUCYNTA ER-treated patients in ten Phase 2/3 clinical studies:

Nervous system disorders: paresthesia, balance disorder, syncope, memory impairment, mental impairment, depressed level of consciousness, dysarthria, presyncope, coordination abnormal

Gastrointestinal disorders: impaired gastric emptying

General disorders and administration site conditions: feeling abnormal, feeling drunk

Psychiatric disorders: perception disturbances, disorientation, confusional state, agitation, euphoric mood, drug dependence, thinking abnormal, nightmare

Skin and subcutaneous tissue disorders: urticaria

Metabolism and nutrition disorders: weight decreased

Cardiac disorders: heart rate increased, palpitations, heart rate decreased, left bundle branch block

Vascular disorder: blood pressure decreased

Respiratory, thoracic and mediastinal disorders: respiratory depression

Renal and urinary disorders: urinary hesitation, pollakiuria

Reproductive system and breast disorders: sexual dysfunction

Eye disorders: visual disturbance

Immune system disorders: drug hypersensitivity

6.2 Postmarketing Experience

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

Psychiatric disorders: hallucination, suicidal ideation, panic attack

Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.

Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.

Anaphylaxis: Anaphylaxis has been reported with ingredients contained in NUCYNTA ER.

Androgen deficiency: Cases of androgen deficiency have occurred with use of opioids for an extended period of time *[see Clinical Pharmacology (12.2)]*.

Hyperalgesia and Allodynia: Cases of hyperalgesia and allodynia have been reported with opioid therapy of any duration *[see Warnings and Precautions (5.6)]*

Hypoglycemia: Cases of hypoglycemia have been reported in patients taking opioids. Most reports were in patients with at least one predisposing risk factor (e.g., diabetes).

Opioid-induced esophageal dysfunction (OIED): Cases of OIED have been reported in patients taking opioids, and may occur more frequently in patients taking higher doses of opioid, and/or in patients taking opioids longer term *[see Warnings and Precautions (5.12)]*.

Adverse Reactions from Observational Studies

A prospective, observational cohort study estimated the risks of addiction, abuse, and misuse in patients initiating long-term use of Schedule II opioid analgesics between 2017 and 2021. Study participants included in one or more analyses had been enrolled in selected insurance plans or health systems for at least one year, were free of at least one outcome at baseline, completed a minimum number of follow-up assessments, and either: 1) filled multiple extended-release/long-acting opioid analgesic prescriptions during a 90-day period (n=978); or 2) filled any Schedule II opioid analgesic prescriptions covering at least 70 of 90 days (n=1,244). Those included also had no dispensing of the qualifying opioids in the previous 6 months.

Over 12 months:

- approximately 1% to 6% of participants across the two cohorts newly met criteria for addiction, as assessed with two validated interview-based measures of moderate-to-severe opioid use disorder based on Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria, and
- approximately 9% and 22% of participants across the two cohorts newly met criteria for prescription opioid abuse and misuse *[defined in Drug Abuse and Dependence (9.2)]*, respectively, as measured with a validated self-reported instrument.

A retrospective, observational cohort study estimated the risk of opioid involved overdose or opioid overdose-related death in patients with new long-term use of Schedule II opioid analgesics from 2006 through 2016 (n=220,249). Included patients had been enrolled in either one of two commercial insurance programs, one managed care program, or one Medicaid program for at least 9 months. *New long-term use* was defined as having Schedule II opioid analgesic prescriptions covering at least 70 days' supply over the 3 months prior to study entry and none during the preceding 6 months. Patients were excluded if they had an opioid-involved overdose in the 9 months prior to study entry. Overdose was measured using a validated medical code-based algorithm with linkage to the National Death Index database. The 5-year cumulative incidence estimates for opioid-involved overdose or opioid overdose-related death ranged from approximately 1.5% to 4% across study sites, counting only the first event during follow-up. Approximately 17% of first opioid overdoses observed over the entire study period (5-11 years, depending on the study site) were fatal. Higher baseline opioid dose was the strongest and most consistent predictor of opioid-involved overdose or opioid overdose-related death. Study exclusion criteria may have selected patients at lower risk of overdose, and substantial loss to follow-up (approximately 80%) also may have biased estimates.

The risk estimates from the studies described above may not be generalizable to all patients receiving opioid analgesics, such as those with exposures shorter or longer than the duration evaluated in the studies.

7 DRUG INTERACTIONS

Table 3 includes clinically significant drug interactions with NUCYNTA ER.

Table 3. Clinically Significant Drug Interactions with NUCYNTA ER Alcohol

Alcohol	
Clinical Impact:	Concomitant use of alcohol with NUCYNTA ER can result in an increase of tapentadol plasma levels and potentially fatal overdose of tapentadol.
Intervention:	Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products containing alcohol while on NUCYNTA ER therapy *[see Warnings and Precautions (5.3)]*.
Benzodiazepines and Other Central Nervous System (CNS) Depressants	
Clinical Impact:	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death *[see Warnings and Precautions (5.3)]*.

Intervention:	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. 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 recommending or prescribing an opioid overdose reversal agent *[see Dosage and Administration (2.2), Warnings and Precautions (5.1, 5.2, 5.3)]*.
Examples:	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, gabapentinoids (gabapentin or pregabalin), other opioids, alcohol
Serotonergic Drugs	
Clinical Impact:	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome *[see Warnings and Precautions (5.7)]*.
Intervention:	If concomitant use is warranted, frequently evaluate the patient, particularly during treatment initiation and dose adjustment. Discontinue NUCYNTA ER if serotonin syndrome is suspected.
Examples:	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue)
Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact:	MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma) *[see Warnings and Precautions (5.2)]*.
Intervention:	Do not use NUCYNTA ER in patients taking MAOIs or within 14 days of stopping such treatment.
Examples:	phenelzine, tranylcypromine, linezolid
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
Clinical Impact:	May reduce the analgesic effect of NUCYNTA ER and/or precipitate withdrawal symptoms.
Intervention:	Avoid concomitant use.
Examples:	butorphanol, nalbuphine, pentazocine, buprenorphine
Muscle Relaxants	
Clinical Impact:	Tapentadol may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Intervention:	Because respiratory depression may be greater than otherwise expected, decrease the dosage of NUCYNTA ER and/or the muscle relaxant as necessary. Due to the risk of respiratory depression with concomitant use of skeletal muscle relaxants and opioids, consider recommending or prescribing an opioid overdose reversal agent *[see Dosage and Administration (2.2), Warnings and Precautions (5.2, 5.3)]*
Examples:	cyclobenzaprine, metaxalone
Diuretics	
Clinical Impact:	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention:	Evaluate patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
Clinical Impact:	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention:	Evaluate patients for signs of urinary retention or reduced gastric motility when NUCYNTA ER is used concomitantly with anticholinergic drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Use of opioid analgesics for an extended period of time during pregnancy may cause neonatal opioid withdrawal syndrome *[see Warnings and Precautions (5.4)]*. Available data with NUCYNTA ER are insufficient to inform a drug-associated risk for major birth defects and miscarriage or adverse maternal outcomes. In animal reproduction studies, embryofetal mortality and structural malformations were observed with subcutaneous administration of tapentadol during organogenesis to rabbits and delays in skeletal maturation were observed in rats at exposures equivalent to and less than the maximum recommended human dose (MRHD), respectively. When administered to pregnant rats during organogenesis and through lactation, increased pup mortality was noted following oral tapentadol exposures to doses equivalent to the MRHD *[see Data]*. Based on animal data, advise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse reaction. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Fetal/neonatal adverse reactions

Use of opioid analgesics for an extended period of time during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth. Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea, and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly *[see Warnings and Precautions (5.4)]*.

Labor or Delivery

Opioids cross the placenta and may produce respiratory depression and psychophysiological effects in neonates. An opioid overdose reversal agent, such as naloxone or nalmefene must be available for reversal of opioid-induced respiratory depression in the neonate. NUCYNTA ER is not recommended for use in pregnant women during and immediately prior to labor, when use of shorter-acting analgesics or other analgesic techniques are more appropriate. Opioid analgesics, including NUCYNTA ER, can prolong labor through actions that temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Data

Animal Data

Tapentadol HCl was evaluated for teratogenic effects in pregnant rats and rabbits following intravenous and subcutaneous exposure during the period of embryofetal organogenesis. When tapentadol was administered twice daily by the subcutaneous route in rats at dose levels of 10, 20, or 40 mg/kg/day [producing up to 1.36 times the plasma exposure at the maximum recommended human dose (MRHD) of 500 mg/day for NUCYNTA ER based on an area under the time-curve (AUC) comparison], no teratogenic effects were observed. Evidence of embryofetal toxicity included transient delays in skeletal maturation (i.e., reduced ossification) at the 40 mg/kg/day dose which was associated with significant maternal toxicity. Administration of tapentadol HCl in rabbits at doses of 4, 10, or 24 mg/kg/day by subcutaneous injection [producing 0.3, 0.8, and 2.5 times the plasma exposure at the MRHD based on an AUC comparison, respectively] revealed embryofetal toxicity at doses ≥10 mg/kg/day. Findings included reduced fetal viability, skeletal delays and other variations. In addition, there were multiple malformations including gastroschisis/thoracogastroschisis, amelia/phocomelia, and cleft palate at doses ≥10 mg/kg/day and above, and ablepharia, encephalopathy, and spina bifida at the high dose of 24 mg/kg/day. Embryofetal toxicity, including malformations, may be secondary to the significant maternal toxicity observed in the study.

In a study of pre- and postnatal development in rats, oral administration of tapentadol at doses of 20, 50, 150, or 300 mg/kg/day to pregnant and lactating rats during the late gestation and early postnatal period [resulting in up to 2.28 times the plasma exposure at the MRHD on an AUC basis] did not influence physical or reflex development, the outcome of neurobehavioral tests or reproductive parameters. At maternal tapentadol doses ≥150 mg/kg/day, a dose-related increase in pup mortality was observed to

postnatal Day 4. Treatment-related developmental delay was observed in the dead pups, including incomplete ossification. In addition, significant reductions in pup body weights and body weight gains at doses associated with maternal toxicity (150 mg/kg/day and above) were seen throughout lactation.

8.2 Lactation

Risk Summary

There is insufficient/limited information on the excretion of tapentadol in human or animal breast milk. Physicochemical and available pharmacodynamic/toxicological data on tapentadol point to excretion in breast milk and risk to the breastfeeding child cannot be excluded.

Because of the potential for serious adverse reactions including excess sedation and respiratory depression in a breastfed infant, advise patients that breast feeding is not recommended during treatment with NUCYNTA ER.

Clinical Considerations

Monitor infants exposed to NUCYNTA ER through breast milk for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

8.3 Females and Males of Reproductive Potential

Infertility

Use of opioids for an extended period of time may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible *[see Adverse Reactions (6.2), Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and efficacy of NUCYNTA ER in pediatric patients less than 18 years of age have not been established.

8.5 Geriatric Use

Of the total number of patients in Phase 2/3 double-blind, multiple-dose clinical studies of NUCYNTA ER, 28% (1023/3613) were 65 years and over, while 7% (245/3613) were 75 years and over. No overall differences in effectiveness or tolerability were observed between these patients and younger patients.

Elderly patients (aged 65 or older) may have increased sensitivity to tapentadol. In general, use caution when selecting a dosage for an elderly patient, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy *[see Clinical Pharmacology (12.3)]*.

Respiratory depression is the chief risk for elderly patients treated with opioids and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of NUCYNTA ER slowly in geriatric patients and frequently reevaluate the patient for signs of central nervous system and respiratory depression *[see Warnings and Precautions (5.8)]*.

Tapentadol is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to regularly evaluate renal function.

8.6 Hepatic Impairment

Use of NUCYNTA ER in patients with severe hepatic impairment (Child-Pugh Score 10-15) is not recommended. In patients with moderate hepatic impairment (Child-Pugh Score 7 to 9), dosage reduction of NUCYNTA ER is recommended *[see Dosage and Administration (2.5)]*. No dosage adjustment is recommended in patients with mild hepatic impairment (Child-Pugh Score 5 to 6) *[see Warnings and Precautions (5.16), Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

Use of NUCYNTA ER in patients with severe renal impairment (creatinine clearance less than 30 mL/minute) is not recommended. No dosage adjustment is recommended in patients with mild or moderate renal impairment (creatinine clearance 30-90 mL/minute) *[see Warnings and Precautions (5.17), Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

NUCYNTA ER contains tapentadol, a Schedule II controlled substance.

9.2 Abuse

NUCYNTA ER contains tapentadol, a substance with high potential for misuse and abuse, which can lead to the development of substance use disorder, including addiction *[see Warnings and Precautions (5.1)]*.

Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a healthcare provider or for whom it was not prescribed.

Abuse is the intentional, non-therapeutic use of a drug, even once, for its desirable psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use (e.g., continuing drug use despite harmful consequences, giving a higher priority to drug use than other activities and obligations), and possible tolerance or physical dependence.

Misuse and abuse of NUCYNTA ER increases risk of overdose, which may lead to central nervous system and respiratory depression, hypotension, seizures, and death. The risk is increased with concurrent abuse of NUCYNTA ER with alcohol and/or other CNS depressants. Abuse of and addiction to opioids in some individuals may not be accompanied by concurrent tolerance and symptoms of physical dependence. In addition, abuse of opioids can occur in the absence of addiction.

All patients treated with opioids require careful and frequent reevaluation for signs of misuse, abuse, and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use. Patients at high risk of NUCYNTA ER abuse include those with a history of prolonged use of any opioid, including products containing tapentadol, those with a history of drug or alcohol abuse, or those who use NUCYNTA ER in combination with other abused drugs.

"Drug-seeking" behavior is very common in persons with substance use disorders. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing, or referral, repeated "loss" of prescriptions, tampering with prescriptions, and reluctance to provide prior medical records or contact information for other treating healthcare provider(s). "Doctor shopping" (visiting multiple prescribers to obtain additional prescriptions) is common among people who abuse drugs and people with substance use disorder. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with inadequate pain control.

NUCYNTA ER, like other opioids, can be diverted for nonmedical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic reevaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Risks Specific to Abuse of NUCYNTA ER

Abuse of NUCYNTA ER poses a risk of overdose and death. This risk is increased with the concurrent use of NUCYNTA ER with alcohol and/or other CNS depressants *[see Warnings and Precautions (5.1, 5.3), Drug Interactions (7)]*.

NUCYNTA ER is approved for oral use only. With parenteral abuse, the inactive ingredients in NUCYNTA ER can result in local tissue necrosis, infection, pulmonary granulomas, increased risk of endocarditis and valvular heart injury, embolism and death.

Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

9.3 Dependence

Both tolerance and physical dependence can develop during use of opioid therapy.

Tolerance is a physiological state characterized by a reduced response to a drug after repeated administration (i.e., a higher dose of a drug is required to produce the same effect that was once obtained at a lower dose).

Physical dependence is a state that develops as a result of a physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug.

Withdrawal may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued use.

Do not rapidly reduce or abruptly discontinue NUCYNTA ER in a patient physically dependent on opioids. Rapid tapering of NUCYNTA ER in a patient physically dependent on opioids may lead to serious withdrawal symptoms, uncontrolled pain, and suicide. Rapid discontinuation has also been associated with attempts to find other sources of opioid analgesics, which may be confused with drug-seeking for abuse.

When discontinuing NUCYNTA ER, gradually taper the dosage using a patient-specific plan that considers the following: the dose of NUCYNTA ER the patient has been taking, the duration of treatment, and the physical and psychological attributes of the patient. To improve the likelihood of a successful taper and minimize withdrawal symptoms, it is important that the opioid tapering schedule is agreed upon by the patient. In patients taking opioids for an extended period of time at high doses, ensure that a multimodal approach to pain management, including mental health support (if needed), is in place prior to initiating an opioid analgesic taper *[see Dosage and Administration (2.6), Warnings and Precautions (5.3)]*.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs *[see Use in Specific Populations (8.1)]*.

10 OVERDOSAGE

Clinical Presentation

Acute overdosage with tapentadol can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases pulmonary edema, bradycardia, hypotension, hypoglycemia, partial or complete airway obstruction, atypical snoring and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations *[see Clinical Pharmacology (12.2)]*. Toxic leukoencephalopathy has been reported after opioid overdose and can present hours, days, or weeks after apparent recovery from the initial intoxication.

Treatment of Overdose

In case of overdose, priorities are the reestablishment of a patent and protected airway and institution of assisted or controlled ventilation, if needed. Employ other supportive measures (including oxygen, vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life support measures.

For clinically significant respiratory or circulatory depression secondary to tapentadol overdose, administer an opioid overdose reversal agent such as naloxone or nalmefene.

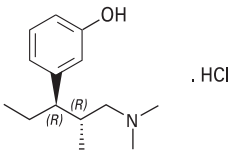
Because the duration of reversal would be expected to be less than the duration of action of tapentadol in NUCYNTA ER, carefully monitor the patient until spontaneous respiration is reliably reestablished.

NUCYNTA ER will continue to release tapentadol and add to the tapentadol load for 24 to 48 hours or longer following ingestion, necessitating prolonged monitoring. If the response to an opioid overdose reversal agent is suboptimal or only brief in nature, additional reversal agent should be given as directed in the product's prescribing information.

In an individual physically dependent on opioids, administration of the recommended usual dosage of the overdose reversal agent will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the reversal agent administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the reversal agent should be initiated with care and by titration with smaller than usual doses of the reversal agent .

11 DESCRIPTION

NUCYNTA ER (tapentadol) is an opioid agonist, supplied in extended-release film-coated tablets for oral administration, containing 58.24, 116.48, 174.72, 232.96, and 291.20 mg of tapentadol hydrochloride in each tablet strength, corresponding to 50, 100, 150, 200, and 250 mg of tapentadol free-base, respectively. The chemical name is 3-[(1*R*,2*R*)-3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol monohydrochloride. The structural formula is:



. HCl

The molecular weight of tapentadol HCl is 257.80, and the molecular formula is $C_{14}H_{23}NO \bullet HCl$. The n-octanol: water partition coefficient log P value is 2.89. The pKa values are 9.36 and 10.45. In addition to the active ingredient tapentadol HCl, tablets also contain the following inactive ingredients: alpha-tocopherol (vitamin E), hypromellose, polyethylene glycol, and polyethylene oxide. The film coating is comprised of polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, and the colorant FD&C Blue #2 aluminum lake is used for 100, 150, 200, and 250 mg strengths; and additionally, yellow iron oxide is used in 150 mg tablets.

Printing inks contain shellac glaze and propylene glycol for all strengths, and black iron oxide (50, 100, 150 and 200 mg tablets) or titanium dioxide (250 mg tablets).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tapentadol is a centrally-acting synthetic analgesic. The exact mechanism of action is unknown. Although the clinical relevance is unclear, preclinical studies have shown that tapentadol is a mu-opioid receptor (MOR) agonist and a norepinephrine reuptake inhibitor (NRI). Analgesia in animal models is derived from both of these properties.

12.2 Pharmacodynamics

Effects on the Central Nervous System (CNS)

Tapentadol produces respiratory depression, by direct action on the brainstem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to both increases in carbon dioxide tension and electrical stimulation.

Tapentadol causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings).

Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations.

Effects on the Gastrointestinal Tract and on Other Smooth Muscle

Tapentadol causes a reduction in motility and is associated with an increase in tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone is increased to the point of spasm, resulting in constipation. Other opioid induced effects may include a reduction in biliary and pancreatic secretions, spasm of the sphincter of Oddi, and transient elevations in serum amylase and opioid-induced esophageal dysfunction (OIED).

Effects on the Cardiovascular System

There was no effect of therapeutic and supratherapeutic doses of tapentadol on the QT interval. In a randomized, double-blind, placebo- and positive-controlled crossover study, healthy subjects were administered five consecutive immediate-release formulation doses of tapentadol 100 mg every 6 hours, tapentadol 150 mg every 6 hours, placebo and a single oral dose of moxifloxacin. Similarly, the immediate-release formulation tapentadol had no relevant effect on other ECG parameters (heart rate, PR interval, QRS duration, T-wave or U-wave morphology).

Tapentadol produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Effects on the Endocrine System

Opioids inhibit the secretion of adrenocorticortropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans *[see Adverse Reactions (6.2)]*. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

Use of opioids for an extended period of time may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date *[see Adverse Reactions (6.2)]*.

Effects on the Immune System

Opioids have been shown to have a variety of effects on components of the immune system in *in vitro* and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

Concentration-Efficacy Relationships

The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with opioid agonists. The minimum effective analgesic concentration of tapentadol for any individual patient may increase over time due to an increase in pain, development of a new pain syndrome, and/or potential development of analgesic tolerance *[see Dosage and Administration (2.1, 2.4)]*.

Concentration-Adverse Experience Relationships

There is a relationship between increasing tapentadol plasma concentration and increasing frequency of dose-related adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions *[see Dosage and Administration (2.1, 2.3, 2.4)]*.

12.3 Pharmacokinetics

Absorption

The mean absolute bioavailability after single-dose administration (fasting) of NUCYNTA ER is approximately 32% due to extensive first-pass metabolism. Maximum serum concentrations of tapentadol are observed between 3 and 6 hours after administration of NUCYNTA ER. Dose proportional increases for AUC have been observed after administration of NUCYNTA ER over the therapeutic dose range.

Steady-state exposure of tapentadol is attained after the third dose (i.e., 24 hours after first twice daily multiple dose administration). Following dosing with 250 mg every 12 hours, minimal accumulation was observed.

Food Effect

The AUC and C_{max} increased by 6% and 17%, respectively, when NUCYNTA ER tablet was administered after a high-fat, high-calorie breakfast. NUCYNTA ER may be given with or without food.

Distribution

Tapentadol is widely distributed throughout the body. Following intravenous administration, the volume of distribution (Vz) for tapentadol is 540 +/- 98 L. The plasma protein binding is low and amounts to approximately 20%.

Elimination

Metabolism

In humans, about 97% of the parent compound is metabolized. Tapentadol is mainly

metabolized via Phase 2 pathways, and only a small amount is metabolized by Phase 1 oxidative pathways. The major pathway of tapentadol metabolism is conjugation with glucuronic acid to produce glucuronides. After oral administration approximately 70% (55% O-glucuronide and 15% sulfate of tapentadol) of the dose is excreted in urine in the conjugated form. A total of 3% of drug was excreted in urine as unchanged drug. Tapentadol is additionally metabolized to N-desmethyl tapentadol (13%) by CYP2C9 and CYP2C19 and to hydroxy tapentadol (2%) by CYP2D6, which are further metabolized by conjugation. Therefore, drug metabolism mediated by cytochrome P450 system is of less importance than phase 2 conjugation.

None of the metabolites contribute to the analgesic activity.

Excretion

Tapentadol and its metabolites are excreted almost exclusively (99%) via the kidneys. The terminal half-life is on average 5 hours after oral administration. The total clearance of tapentadol is 1603 +/-227 mL/min.

Specific Populations

Age: Geriatric Population

The mean exposure (AUC) to tapentadol was similar in elderly subjects compared to young adults, with a 16% lower mean C_{max} observed in the elderly subject group compared to young adult subjects.

Hepatic Impairment

Administration of tapentadol resulted in higher exposures and serum levels to tapentadol in subjects with impaired hepatic function compared to subjects with normal hepatic function. The ratio of tapentadol pharmacokinetic parameters for the mild hepatic impairment group (Child-Pugh Score 5 to 6) and moderate hepatic impairment group (Child-Pugh Score 7 to 9) in comparison to the normal hepatic function group were 1.7 and 4.2, respectively, for AUC; 1.4 and 2.5, respectively, for C_{max}; and 1.2 and 1.4, respectively, for $t_{1/2}$. The rate of formation of tapentadol-O-glucuronide was lower in subjects with increased liver impairment.

Renal Impairment

AUC and C_{max} of tapentadol were comparable in subjects with varying degrees of renal function (from normal to severely impaired). In contrast, increasing exposure (AUC) to tapentadol-O-glucuronide was observed with increasing degree of renal impairment. In subjects with mild (CLCR= 50 to <80 mL/min), moderate (CLCR= 30 to <50 mL/min), and severe (CLCR= <30 mL/min) renal impairment, the AUC of tapentadol-O-glucuronide was 1.5-, 2.5-, and 5.5-fold higher compared with normal renal function, respectively.

Drug Interaction Studies

Tapentadol is mainly metabolized by Phase 2 glucuronidation, a high capacity/low affinity system; therefore, clinically relevant interactions caused by Phase 2 metabolism are unlikely to occur. Naproxen and probenecid increased the AUC of tapentadol by 17% and 57%, respectively. These changes are not considered clinically relevant and no change in dose is required.

No changes in the pharmacokinetic parameters of tapentadol were observed when acetaminophen and acetylsalicylic acid were given concomitantly.

In vitro studies did not reveal any potential of tapentadol to either inhibit or induce cytochrome P450 enzymes. Only a minor amount of tapentadol is metabolized via the oxidative pathway. Thus, clinically relevant interactions mediated by the cytochrome P450 system are unlikely to occur.

The pharmacokinetics of tapentadol were not affected when gastric pH or gastrointestinal motility were increased by omeprazole and metoclopramide, respectively.

Plasma protein binding of tapentadol is low (approximately 20%). Therefore, the likelihood of pharmacokinetic drug-drug interactions by displacement from the protein binding site is low.

Alcohol

NUCYNTA ER may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression, because respiratory depression, hypotension, hypertension, and profound sedation, coma or death may result *[see Warnings and Precautions (5.5)]*.

An *in vivo* study examined the effect of alcohol (240 mL of 40%) on the bioavailability of a single dose of 100 mg and 250 mg of NUCYNTA ER tablet in healthy, fasted volunteers. After co-administration of a 100 mg NUCYNTA ER tablet and alcohol, the mean C_{max} value increased by 48% compared to control with a range of 0.99-fold to 4.38-fold. The mean tapentadol AUC_{last} and AUC_{inf} were increased by 17%; the T_{max} and $t_{½}$ were unchanged. After co-administration of a 250 mg NUCYNTA ER tablet and alcohol, the mean C_{max} value increased by 28% compared to control with a range of 0.90-fold to 2.67-fold. The mean tapentadol AUC_{last} and AUC_{inf} were increased by 16%; the T_{max} and $t_{½}$ were unchanged.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In mice, tapentadol HCl was administered by oral gavage at dosages of 50, 100 and 200 mg/kg/day for 2 years (up to 0.34 times in the male mice and 0.25 times in the female mice the plasma exposure at the maximum recommended human dose [MRHD] for NUCYNTA ER on an area under the time-curve [AUC] basis). No increase in tumor incidence was observed at any dose level.

In rats, tapentadol HCl was administered in diet at dosages of 10, 50, 125 and 250 mg/kg/day for two years (up to 0.20 times in the male rats and 0.75 times in the female rats the plasma exposure at the MRHD on an AUC basis). No increase in tumor incidence was observed at any dose level.

Mutagenesis

Tapentadol did not induce gene mutations in bacteria but was clastogenic with metabolic activation in a chromosomal aberration test in V79 cells. The test was repeated and was negative in the presence and absence of metabolic activation. The one positive result for tapentadol was not confirmed *in vivo* in rats, using the two endpoints of chromosomal aberration and unscheduled DNA synthesis, when tested up to the maximum tolerated dose.

Impairment of Fertility

Tapentadol HCl was administered intravenously to male or female rats at dosages of 3, 6, or 12 mg/kg/day (representing exposures of up to approximately 0.56 times in the male rats and 0.50 times in the female rats the exposure at the MRHD on an AUC basis, based on extrapolation from toxicokinetic analyses in a separate 4-week intravenous study in rats). Tapentadol did not alter fertility at any dose level. Maternal toxicity and adverse effects on embryonic development, including decreased number of implantations, decreased numbers of live conceptuses, and increased pre- and post-implantation losses occurred at dosages ≥6 mg/kg/day.

13.2 Animal Toxicology and/or Pharmacology

In toxicological studies with tapentadol, the most common systemic effects of tapentadol were related to the mu-opioid receptor agonist and norepinephrine reuptake inhibition pharmacodynamic properties of the compound. Transient, dose-dependent and predominantly CNS-related findings were observed, including impaired respiratory function and convulsions, the latter occurring in the dog at plasma levels (C_{max}), which are in the range associated with the maximum recommended human dose (MRHD).

14 CLINICAL STUDIES

14.1 Clinical Trials Summary

The efficacy of NUCYNTA ER was studied in five studies in patients with chronic pain and DPN. Efficacy was demonstrated in one randomized, double-blind, placebo- and active-controlled study in patients with chronic low back pain (LBP), and two randomized, double-blind, placebo-controlled studies in patients with pain related to diabetic peripheral neuropathy (DPN-1 and DPN-2).

14.2 Moderate to Severe Chronic Low Back Pain

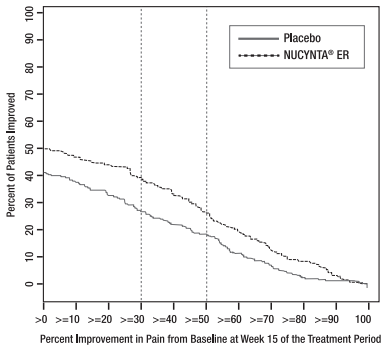
In the LBP study, patients 18 years of age or older with chronic low back pain and a baseline pain score of ≥5 on an 11-point numerical rating scale (NRS), ranging from 0 to 10 were enrolled and randomized to 1 of 3 treatments: NUCYNTA ER, active-control (an extended-release Schedule II opioid analgesic), or placebo.

Patients randomized to NUCYNTA ER initiated therapy with a dose of 50 mg twice daily for three days. After three days, the dose was increased to 100 mg twice daily. Subsequent titration was allowed over a 3-week titration period to a dose up to 250 mg twice daily, followed by a 12-week maintenance period. There were 981 patients randomized. The mean age of the study population was 50 (range 18 to 89) years; the mean baseline pain intensity score was 8 (SD 1). Approximately half of the patients had not taken opioids during the three months prior to the screening visit.

The number of patients completing the study was 51% in the placebo group, 54% in the NUCYNTA ER group and 43% in the active-control group. Lack of efficacy was the most common reason for discontinuation among placebo-treated patients (21%), whereas adverse events were the most common reason for discontinuation among the active treatment groups (17% and 32% for NUCYNTA ER and active-control, respectively).

After 15 weeks of treatment, patients taking NUCYNTA ER had a significantly greater pain reduction compared to placebo. The proportion of patients with various degrees of improvement is shown in Figure 1. The figure is cumulative, such that patients, whose change from baseline is, for example 50%, are also included at every level of improvement below 50%. Patients who did not complete the study were assigned 0% improvement.

Figure 1. Percentage of Patients Achieving Various Levels of Improvement in Pain Intensity - Study LBP[1]



[1] The last week of Study LBP was Week 15.

14.3 Neuropathic Pain Associated with Diabetic Peripheral Neuropathy

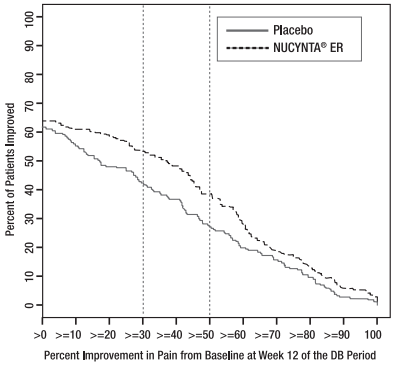
In the two DPN studies, patients 18 years of age or older with pain due to diabetic peripheral neuropathy and a pain score of ≥5 on an 11-point numerical rating scale (NRS) ranging from 0 (no pain) to 10 (worst possible pain) were enrolled. Following an open-label treatment period in which NUCYNTA ER was administered to all patients for three weeks and titrated to an individually stable dose, patients who had tolerated the drug and demonstrated at least a 1-point improvement in pain intensity on the NRS at the end of the open-label titration period were randomized to either continue the NUCYNTA ER dose (100 mg to 250 mg twice a day) reached during the open-label titration period, or receive placebo for 12 weeks of maintenance treatment. During the first 4 days of the double-blind maintenance period patients were permitted to take tapentadol ER 25 mg up to two times a day as additional medication. After the first 4 days, patients were allowed to take tapentadol ER 25 mg once daily as needed for pain, in addition to the patient's assigned study drug. Patients recorded their pain in a diary twice daily.

Study DPN-1: A total of 591 patients entered open-label treatment and 389 patients met the criteria for randomization into the double-blind treatment period. The mean age of the randomized population was 60 (range 29 to 87) years; approximately two-thirds of the patients had not taken opioids during the three months prior to the screening visit.

During the titration period, 34% of patients discontinued open-label NUCYNTA ER. The most common reasons for discontinuation in the double-blind treatment period were lack of efficacy in the placebo group (14%) and adverse events in the NUCYNTA ER group (15%).

After 12 weeks of treatment, NUCYNTA ER provided a significantly greater reduction in pain intensity from baseline to the end of the 12-week double-blind period compared to placebo. Figure 2 displays the proportion of randomized patients achieving various degrees of improvement in pain intensity from the start of the open-label titration period to the last week of the randomized withdrawal period. The figure is cumulative, such that patients, whose change from baseline is, for example 50%, are also included at every level of improvement below 50%. Patients who did not complete the study were assigned 0% improvement.

Figure 2. Percentage of Patients Achieving Various Levels of Improvement in Pain Intensity - PN-1



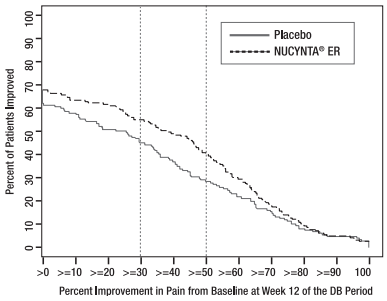
PN-1ACCE

Study DPN-2: A total of 459 patients entered open-label treatment and 320 patients met the criteria for randomization into the double-blind treatment period. The mean age of the randomized population was 59 (range 28 to 83) years; approximately two-thirds of the patients had not taken opioids during the three months prior to the screening visit.

During the titration period, 22% of patients discontinued open-label NUCYNTA ER and 6% of patients were not subsequently randomized because they failed to have at least 1-point improvement in pain intensity. The most common reason for discontinuation in the double-blind treatment period was adverse events in both the placebo group (9%) and the NUCYNTA ER group (14%).

After 12 weeks of treatment, NUCYNTA ER provided a significantly greater reduction in pain intensity from baseline to the end of the 12-week double-blind period compared to placebo. Figure 3 displays the proportion of randomized patients achieving various degrees of improvement in pain intensity from the start of the open-label titration period to the last week of the randomized withdrawal period. The figure is cumulative, such that patients, whose change from baseline is, for example 50%, are also included at every level of improvement below 50%. Patients who did not complete the study were assigned 0% improvement.

Figure 3. Percentage of Patients Achieving Various Levels of Improvement in Pain Intensity - DPN-2



16 HOW SUPPLIED/STORAGE AND HANDLING

NUCYNTA ER tablets are available in the following strengths and packages:

50 mg extended-release tablets are white oblong-shaped with a black print "OMJ 50" on one side and are available in bottles of 60 with child-resistant closure (NDC 24510-058-60) and unit dose blister packs of 100 (10 blister strips of 10 tablets each), for hospital use only (NDC 24510-058-01).

100 mg extended-release tablets are light-blue oblong-shaped with a black print "OMJ 100" on one side and are available in bottles of 60 with child-resistant closure (NDC 24510-116-60) and unit dose blister packs of 100 (10 blister strips of 10 tablets each), for hospital use only (NDC 24510-116-01).

150 mg extended-release tablets are blue-green oblong-shaped with a black print "OMJ 150" on one side and are available in bottles of 60 with child-resistant closure (NDC 24510-174-60) and unit dose blister packs of 100 (10 blister strips of 10 tablets each), for hospital use only (NDC 24510-174-01).

200 mg extended-release tablets are blue oblong-shaped with a depression in the middle running lengthwise on each side and with a black print "OMJ 200" on one side, and are available in bottles of 60 with child-resistant closure (NDC 24510-232-60) and unit dose blister packs of 100 (10 blister strips of 10 tablets each), for hospital use only (NDC 24510-232-01).

250 mg extended-release tablets are dark blue oblong-shaped with a depression in the middle running lengthwise on each side and with a white print "OMJ 250" on one side, and are available in bottles of 60 with child-resistant closure (NDC 24510-291-60) and unit dose blister packs of 100 (10 blister strips of 10 tablets each), for hospital use only (NDC 24510-291-01).

Storage and Handling

Store at 20°C – 25°C (68°F – 77°F); excursions permitted to 15° C – 30°C (59° F – 86°F) [see USP Controlled Room Temperature].

Protect from moisture.

Store NUCYNTA ER securely and dispose of properly.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Storage and Disposal

Because of the risks associated with accidental ingestion, misuse, and abuse, advise patients to store NUCYNTA ER securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home. Inform patients that leaving NUCYNTA ER unsecured can pose a deadly risk to others in the home *[see Warnings and Precautions (5.1, 5.2), Drug Abuse and Dependence (9.2)]*.

Advise patients and caregivers that when medicines are no longer needed, they should be disposed of promptly. Expired, unwanted, or unused NUCYNTA ER Tablets should be disposed of by flushing the unused medication down the toilet if a drug take-back option is not readily available. Inform patients that they can visit www.fda.gov/drugdisposal for a complete list of medicines recommended for disposal by flushing, as well as additional information on disposal of unused medicines.

Addiction, Abuse, and Misuse

Inform patients that the use of NUCYNTA ER, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose or death *[see Warnings and Precautions (5.1)]*. Instruct patients not to share NUCYNTA ER with others and to take steps to protect NUCYNTA ER from theft or misuse.

Life-threatening Respiratory Depression

Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting NUCYNTA ER or when the dosage is increased, and that it can occur even at recommended dosages.

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 *[see Warnings and Precautions (5.2)]*.

Accidental Ingestion

Inform patients that accidental ingestion, especially by children, may result in respiratory depression or death *[see Warnings and Precautions (5.2)]*.

Interactions with Benzodiazepines and other CNS Depressants

Instruct patients not to consume alcoholic beverages, as well as prescription and over-the-counter products that contain alcohol, during treatment with NUCYNTA ER. The co-ingestion of alcohol with NUCYNTA ER may result in increased plasma levels and a potentially fatal overdose of oxymorphone *[see Warnings and Precautions (5.3)]*.

Inform patients and caregivers that potentially fatal additive effects may occur if NUCYNTA ER is used with benzodiazepines or other CNS depressants, including alcohol (e.g., non-benzodiazepine sedative/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, gabapentinoids [gabapentin or pregabalin], and other opioids), and not to use these concomitantly unless supervised by a health care provider *[see Warnings and Precautions (5.3), Drug Interactions (7)]*.

Patient Access to an 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 (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) *[see Dosage and Administration (2.2), Warnings and Precautions (5.2)]*.

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 agent 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 [see Overdosage (10)].

Advise patients and caregivers:

- how to treat with the overdose reversal agent in the event of an opioid overdose.
- to tell family and friends about their opioid overdose reversal agent, and to keep it in a place where family and friends can access it in an emergency.
- to read the Patient Information (or other educational material) that will come with their opioid overdose reversal agent. Emphasize the importance of doing this before an opioid emergency happens, so the patient and caregiver will know what to do.

Hyperalgesia and Allodynia

Inform patients and caregivers not to increase opioid dosage without first consulting a clinician. Advise patients to seek medical attention if they experience symptoms of hyperalgesia, including worsening pain, increased sensitivity to pain, or new pain *[see Warnings and Precautions (5.6); Adverse Reactions (6.2)]*.

Serotonin Syndrome

Inform patients that opioids could cause a rare but potentially life-threatening condition called serotonin syndrome resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their healthcare providers if they are taking, or plan to take serotonergic medications *[see Warnings and Precautions (5.7), Drug Interactions (7)]*.

Seizures

Inform patients that NUCYNTA ER could cause seizures if they are at risk for seizures or have epilepsy. Patients should be advised to stop taking NUCYNTA ER if they have a seizure while taking NUCYNTA ER and call their healthcare provider right away *[see Warnings and Precautions (5.13)]*.

MAOI Interaction

Inform patients not to take NUCYNTA ER while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking NUCYNTA ER *[see Drug Interactions (7)]*.

Important Administration Instructions

Instruct patients how to properly take NUCYNTA ER, including the following:

- Using NUCYNTA ER exactly as prescribed to reduce the risk of life-threatening adverse reactions (e.g., respiratory depression) *[see Dosage and Administration (2)]*
- Swallowing NUCYNTA ER tablets whole *[see Dosage and Administration (2.1)]*
- To take each tablet with enough water to ensure complete swallowing immediately after placing in mouth *[see Dosage and Administration (2.1)]*
- Not cutting, crushing, chewing, or dissolving the tablets *[see Dosage and Administration (2.1)]*

Important Discontinuation Instructions

In order to avoid developing withdrawal symptoms, instruct patients not to discontinue NUCYNTA ER without first discussing a tapering plan with the prescriber *[see Dosage and Administration (2.6)]*

Driving or Operating Heavy Machinery

Inform patients that NUCYNTA ER may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication *[see Warnings and Precautions (5.15)]*.

Constipation

Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention.

Adrenal Insufficiency

Inform patients that NUCYNTA ER could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms *[see Warnings and Precautions (5.9)]*.

Hypotension

Inform patients that NUCYNTA ER may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position) *[see Warnings and Precautions (5.10)]*.

Anaphylaxis

Inform patients that anaphylaxis has been reported with ingredients contained in NUCYNTA ER. Advise patients how to recognize such a reaction and when to seek medical attention *[see Contraindications (4), Adverse Reactions (6.2)]*.

Pregnancy

Neonatal Opioid Withdrawal Syndrome

Inform female patients of reproductive potential that use of NUCYNTA ER for an extended period of time during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated *[see Warnings and Precautions (5.4), Use in Specific Populations (8.1)]*.

Embryo-Fetal Toxicity

Advise female patients that NUCYNTA ER can cause fetal harm and to inform the prescriber if they are pregnant or plan to become pregnant *[see Use in Specific Populations (8.1)]*.

Lactation

Advise patients that breastfeeding is not recommended during treatment with NUCYNTA ER *[see Use in Specific Populations (8.2)]*

Infertility

Inform patients that use of opioids for an extended period of time may cause reduced fertility. It is not known whether these effects on fertility are reversible *[see Use in Specific Populations (8.3)]*.

Distributed by: Collegium Pharmaceutical, Inc., Stoughton, MA 02072

U.S. Patent Nos. 6071970, 7994364, 8075872, 8114383, 8309060, 8420056, 8536130, and RE39593.

NUCX-011-C.11

Revised: December 2025

Medication Guide

NUCYNTA® ER (new-SINN-tah E-R) (tapentadol) extended-release oral tablets, CII

NUCYNTA ER is:

- A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage severe and persistent pain in adults that requires an extended treatment period with a daily opioid pain medicine, when other pain medicines do not treat your pain well enough or you cannot tolerate them.
- Also used in adults to manage severe and persistent pain from damaged nerves (neuropathic pain) that happens with diabetes, and that requires an extended treatment period with a daily opioid pain medicine, when other pain medicines do not treat your pain well enough or you cannot tolerate them.
- A long-acting (extended-release) opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death.
- Not to be taken on an "as needed" basis.

Important information about NUCYNTA ER:

- **Get emergency help or call 911 right away if you take too much NUCYNTA ER (overdose).** When you first start taking NUCYNTA ER, when your dose is changed, or if you take too much (overdose), serious or life-threatening breathing problems that can lead to death may occur. Ask your healthcare provider about medicines like naloxone or nalmefene that can be used in an emergency to reverse an opioid overdose.
- Taking NUCYNTA ER with other opioid medicines, benzodiazepines, gabapentinoids (gabapentin or pregabalin), alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.
- Never give anyone else your NUCYNTA ER. They could die from taking it. Selling or giving away NUCYNTA ER is against the law.
- Store NUCYNTA ER securely, out of sight and reach of children, and in a location not accessible by others, including visitors to the home.

Do not take NUCYNTA ER if you have:

- severe asthma, trouble breathing, or other lung problems.
- a bowel blockage or have narrowing of the stomach or intestines.

Before taking NUCYNTA ER, tell your healthcare provider if you have a history of:

- head injury, seizures
- liver, kidney, thyroid problems
- problems urinating
- pancreas or gallbladder problems
- abuse of street or prescription drugs, alcohol addiction, opioid overdose, or mental health problems.

Tell your healthcare provider if you are:

- noticing your pain getting worse. If your pain gets worse after you take NUCYNTA ER, do not take more of NUCYNTA ER without first talking to your healthcare provider. Talk to your healthcare provider if the pain that you have increases, if you feel more sensitive to pain, or if you have new pain after taking NUCYNTA ER.
- **pregnant or planning to become pregnant.** Use of NUCYNTA ER for an extended period of time during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **breastfeeding.** Not recommended during treatment with NUCYNTA ER. It may harm your baby.
- living in a household where there are small children or someone who has abused street or prescription drugs.
- taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking NUCYNTA ER with certain other medicines can cause serious side effects.

When taking NUCYNTA ER:

- Do not change your dose. Take NUCYNTA ER exactly as prescribed by your healthcare provider. Use the lowest effective dose for the shortest time needed.
- Take your prescribed dose every 12 hours, at the same time every day. Do not take more than your prescribed dose in 24 hours. If you miss a dose, take your next dose at your usual time.
- Swallow NUCYNTA ER whole. Do not cut, break, chew, crush, dissolve, snort, or inject NUCYNTA ER because this may cause you to overdose and die.
- **Call your healthcare provider if the dose you are taking does not control your pain.**
- **Do not stop taking NUCYNTA ER without talking to your healthcare provider.**
- Dispose of expired, unwanted, or unused NUCYNTA ER by promptly flushing down the toilet, if a drug take-back option is not readily available. Visit www.fda.gov/drugdisposal for additional information on disposal of unused medicines.

While taking NUCYNTA ER DO NOT:

- Drive or operate heavy machinery until you know how NUCYNTA ER affects you. NUCYNTA ER can make you sleepy, dizzy, or lightheaded.
- Drink alcohol or use prescription or over-the-counter medicines containing alcohol. Using products containing alcohol during treatment with NUCYNTA ER may cause you to overdose and die.

The possible side effects of NUCYNTA ER are:

- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain. Call your healthcare provider if you have any of these symptoms and they are severe.

Get emergency medical help or call 911 right away if you have:

- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue, or throat, extreme drowsiness, light-headedness when changing positions, feeling faint, agitation, high body temperature, trouble walking, stiff muscles, or mental changes such as confusion.
- agitation, hallucinations, coma, feeling overheated, or heavy sweating.

These are not all the possible side effects of NUCYNTA ER. Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. **For more information go to *dailymed.nlm.nih.gov***

Distributed by: Collegium Pharmaceutical, Inc., 100 Technology Center Drive Suite 300, Stoughton, MA, 02072, www.collegiumpharma.com or call 1-855-331-5615.

This Medication Guide has been approved by the U.S. Food and Drug Administration

NUCX-012-C.5 Revised: 12/2025

Collegium PHARMACEUTICAL