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: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; INTERACTION WITH ALCOHOL and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

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 monitor regularly for development of these behaviors or conditions. (5.1)**
- **Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients to swallow NUCYNTA ER tablets whole to avoid exposure to a potentially fatal dose of tapentadol. (5.2)**
- **Accidental ingestion of NUCYNTA ER, especially in children, can result in fatal overdose of tapentadol. (5.2)**
- **Prolonged use of NUCYNTA ER during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available (5.3).**
- **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. (5.4)**
- **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; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation. *(5.4), (7)*.**

RECENT MAJOR CHANGES

Boxed Warning	12/2016
Warnings and Precautions (5)	12/2016

INDICATIONS AND USAGE

NUCYNTA ER is an opioid agonist indicated for the management of:

- pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate (1)
- neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. (1)

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve NUCYNTA ER for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.
- NUCYNTA ER is not indicated as an as-needed (prn) analgesic. (1)

DOSAGE AND ADMINISTRATION

- To be prescribed only by healthcare providers knowledgeable in use of
- Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (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)
- For opioid-naïve and opioid non-tolerant patients, 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. (2.2, 2.3)
- Titrate patients with dose increases of 50 mg no more than twice daily every three days. (2.3)
- Maximum daily dose is 500 mg per day. (2.1)
- Moderate Hepatic Impairment: Initiate treatment with 50 mg NUCYNTA ER no more than every 24 hours. Do not exceed 100 mg per day. Monitor closely for respiratory and central nervous system depression (2.4)
- Do not abruptly discontinue NUCYNTA® ER in a physically-dependent patient. (2.5)

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

- Risk of Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Monitor closely, particularly during initiation and titration. (5.1)
- Serotonin Syndrome: Potentially life-threatening condition could result from concomitant serotonergic drug administration. Discontinue NUCYNTA® ER if serotonin syndrome is suspected. (5.6)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.7)
- Severe Hypotension: Monitor during dosage initiation and titration. Avoid use of NUCYNTA® ER in patients with circulatory shock. (5.8)
- 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. (5.9)

ADVERSE REACTIONS

The most common (≥10%) adverse reactions were nausea, constipation, dizziness, headache, and somnolence. (6)
To report SUSPECTED ADVERSE REACTIONS, contact Depomed, Inc. at 1-866-458-6389 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. (5.12, 7)

USE IN SPECIFIC POPULATIONS

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

See 17 for PATIENT COUNSELING INFORMATION and

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; INTERACTION WITH ALCOHOL and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse, and Misuse

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

Life-threatening Respiratory Depression

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

Neonatal Opioid Withdrawal Syndrome

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

Interaction with Alcohol

Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products that contain alcohol while taking NUCYNTA ER. The co-ingestion of alcohol with NUCYNTA ER may result in increased plasma tapentadol levels and a potentially fatal overdose of tapentadol *[see Warnings and Precautions (5.4)]*.

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 [*see Warnings and Precautions (5.4), Drug Interactions (7)*].

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

1 INDICATIONS AND USAGE

NUCYNTA ER (tapentadol) is indicated for the management of:

- pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate
- neuropathic pain associated with diabetic peripheral neuropathy (DPN) severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations *[see Warnings and Precautions (5.1)]*, reserve NUCYNTA ER for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.
  - 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 in the use of potent opioids for the management of chronic pain.

- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals *[see Warnings and Precautions (5)]*.
- Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse *[see Warnings and Precautions (5.1)]*
- Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases with NUCYNTA ER and adjust the dosage accordingly *[see Warnings and Precautions (5.2)]*.

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 *[see Patient Counseling Information (17)]*. 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 (5.6)]*. 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 Initial Dosage

Use of NUCYNTA ER as the First Opioid Analgesic (opioid-naïve patients)

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 NUCYNTA to NUCYNTA ER

Patients can be converted from NUCYNTA to NUCYNTA ER using the equivalent total daily dose of NUCYNTA 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 NUCYNTA four times per day (200 mg/day) may be converted to 100 mg NUCYNTA ER twice a day.

Conversion from Other Opioids to NUCYNTA ER

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.

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.

Close observation and frequent titration are warranted until pain management is stable on the new opioid. Monitor patients for signs and symptoms of opioid withdrawal and for signs of oversedation/toxicity after converting patients to NUCYNTA ER.

Conversion from Methadone to NUCYNTA ER

Close monitoring 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.

2.3 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 and the relative incidence of adverse reactions, as well as monitoring for the development of addiction, abuse, or misuse *[see Warnings and Precautions (5.1)]*. 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 chronic therapy, 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. 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

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