HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use NUCYNTA® ORAL SOLUTION safely and effectively. See full prescribing information for NUCYNTA® ORAL SOLUTION.

NUCYNTA® (tapentadol) oral solution C-II
Initial U.S. Approval: 2008

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

See full prescribing information for complete boxed warning.

- **Ensure accuracy when prescribing, dispensing, and administering NUCYNTA oral solution. Dosing errors due to confusion between mg and mL, and other tapentadol oral solution of different concentrations can result in accidental overdose and death. (2.1, 5.1)**
- **NUCYNTA oral solution exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and monitor regularly for these behaviors and conditions. (5.2)**
- **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. (5.3)**
- **Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. (5.4)**
- **Accidental ingestion of NUCYNTA oral solution, especially by children, can result in a fatal overdose of tapentadol. (5.4)**
- **Prolonged use of NUCYNTA oral solution during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.5)**
- **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 (5.6, 7).**

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

Boxed Warning	09/2018
Warnings and Precautions (5.3)	09/2018

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

NUCYNTA oral solution is an opioid analgesic indicated for the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. (1)

Limitations of Use (1)

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, reserve NUCYNTA oral solution for use in patients for whom alternative treatment options [e.g., non-opioid analgesics or opioid combination products]:

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

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

- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals. (2.1)
- Individualize dosing according to the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.1)
- Initiate treatment with NUCYNTA oral solution with or without food at a dose of 2.5 mL (50 mg), 3.75 mL (75 mg), or 5 mL (100 mg) every 4 to 6 hours depending upon pain intensity. On the first day of dosing, the second dose may be administered as soon as one hour after the first dose, if adequate pain relief is not attained with the first dose. Subsequent dosing is 2.5 mL (50 mg), 3.75 mL (75 mg), or 5 mL (100 mg) every 4 to 6 hours and should be adjusted to maintain adequate analgesia with acceptable tolerability. Daily doses greater than 700 mg on the first day of therapy and 600 mg on subsequent days have not been studied and are, therefore, not recommended. (2.2)
- Moderate Hepatic Impairment: Initiate treatment with 50 mg no more than once every 8 hours (maximum of three doses in 24 hours). Monitor closely for respiratory and central nervous system depression. (2.3)
- Do not stop NUCYNTA oral solution abruptly in a physically dependent patient. (2.5)

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

Oral Solution: 20 mg/mL (3)

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

- Significant respiratory depression (4)
- Acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitative equipment.(4)
- Known or gastrointestinal obstruction, including suspected paralytic ileus. (4)
- Hypersensitivity to tapentadol.(4)
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days. (4)

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

- Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients: Monitor closely, particularly during initiation and titration. (5.7)
- Serotonin Syndrome: Potentially life-threatening condition could result from concomitant serotonergic drug administration. Discontinue NUCYNTA oral solution if serotonin syndrome is suspected. (5.8)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.9)
- Severe Hypotension: Monitor during dosage initiation and titration. Avoid use of NUCYNTA oral solution 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 oral solution in patients with impaired consciousness or coma. (5.11)

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

The most common adverse reactions (incidence ≥10%) were nausea, dizziness, vomiting and somnolence. (6.1)

To report SUSPECTED ADVERSE REACTIONS, 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 Opioids Analgesics: Avoid use with NUCYNTA oral solution because they reduce analgesic effect of NUCYNTA oral solution or precipitate withdrawal symptoms. (7)

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

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Lactation: Closely monitor infants of nursing women receiving. NUCYNTA oral solution. (8.2)
- Severe Hepatic or Renal Impairment: Use not recommended. Reduce dose in patients with moderate hepatic impairment. (8.6, 8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 09/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

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

Risk of Medication Errors

Ensure accuracy when prescribing, dispensing, and administering NUCYNTA oral solution. Dosing errors due to confusion between mg and mL can result in accidental overdose and death *[see Dosage and Administration (2.1), Warnings and Precautions (5.1)]*.

Addiction, Abuse, and Misuse

NUCYNTA oral solution 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 oral solution, and monitor all patients regularly for the development of these behaviors and conditions *[see Warnings and Precautions (5.2)]*.

Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products *[see Warnings and Precautions (5.3)]*. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to

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

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of NUCYNTA oral solution. Monitor for respiratory depression, especially during initiation of NUCYNTA oral solution or following a dose increase *[see Warnings and Precautions (5.4)]*.

Accidental Ingestion

Accidental ingestion of even one dose of NUCYNTA oral solution, especially by children, can result in a fatal overdose of tapentadol *[see Warnings and Precautions (5.4)]*.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of NUCYNTA oral solution 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 (5.5)]*.

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 (5.6), Drug Interactions (7)]*.
- **Reserve concomitant prescribing of NUCYNTA oral solution 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 (tapentadol) oral solution is indicated for the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate in adults.

Limitations of Use
Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses *[see Warnings and Precautions (5.2)]*, reserve NUCYNTA oral solution for use in patients for whom alternative treatment options [e.g., non-opioid analgesics or opioid combination products]:

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

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

Ensure accuracy when prescribing, dispensing, and administering NUCYNTA oral solution to avoid dosing errors due to confusion between mg and mL, which could result in accidental overdose and death. Ensure the proper dose is communicated and dispensed. The oral solution contains 20 mg tapentadol per milliliter (mL), when writing prescriptions, include both the total dose in mg and the total dose in volume.

Always use the enclosed calibrated measuring syringe when administering NUCYNTA oral solution to ensure the dose is measured and administered accurately. An oral syringe is supplied with dose marks corresponding directly to 2.5 mL (equals 50 mg) oral solution, 3.75 mL (equals 75 mg) oral solution, and 5 mL (equals 100 mg) oral solution.

Do not use household teaspoons or tablespoons to measure NUCYNTA oral solution, as using a tablespoon instead of a teaspoon could lead to overdosage.

Inform patients of the availability of FDA-approved patient labeling, Instructions for Use, for step-by-step instructions for patients on how to use the medicine bottle and the oral syringe.

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 (5.2)]*.

Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases with NUCYNTA and adjust the dosage accordingly *[see Warnings and Precautions (5.4)]*

2.2 Initial Dosage

Initiate treatment with NUCYNTA oral solution in a dosing range of 50 mg (2.5 mL) to 100 mg (5 mL) every 4 to 6 hours as needed for pain.

On the first day of dosing, the second dose may be administered as soon as one hour after the first dose, if adequate pain relief is not attained with the first dose. Subsequent dosing is 2.5 mL (equivalent to 50 mg), 3.75 mL (equivalent to 75 mg), or 5 mL (equivalent to 100 mg) every 4 to 6 hours and should be adjusted to maintain adequate analgesia with acceptable tolerability.

Daily doses greater than 700 mg on the first day of therapy and 600 mg on subsequent days have not been studied and are not recommended.

NUCYNTA oral solution may be given with or without food *[see Clinical Pharmacology (12.3)]*.

Conversion from NUCYNTA oral solution to NUCYNTA ER

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

2.3 Dosage Modifications in Patients with Hepatic Impairment

The safety and efficacy of NUCYNTA oral solution has not been studied in patients with severe hepatic impairment (Child-Pugh Score 10-15) and use in this population is not recommended *[see Warnings and Precautions (5.17)]*.

Initiate treatment of patients with moderate hepatic impairment (Child-Pugh Score 7 to 9) with 50 mg no more frequently than once every 8 hours (maximum of three doses in 24 hours). Further treatment should reflect maintenance of analgesia with acceptable tolerability, to be achieved by either shortening or lengthening the dosing interval. Monitor closely for respiratory and central nervous system depression *[see Clinical Pharmacology (12.3)]*.

No dosage adjustment is recommended in patients with mild hepatic impairment (Child-Pugh Score 5 to 6) *[see Clinical Pharmacology (12.3)]*.

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