NUCYNTA® ER (tapentadol) Extended-Release Oral Tablets
Fact Sheet

What is NUCYNTA® ER (pronounced 'new-sinn-tah')?

- NUCYNTA® ER (tapentadol) extended-release tablets, a centrally-acting oral opioid analgesic taken twice daily, is available by prescription only for the following indications:[1]
    - moderate to severe chronic pain in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.[1]
    - neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.[1]
  - NUCYNTA® ER is the first and only opioid approved by the U.S. Food and Drug Administration (FDA) for neuropathic pain associated with DPN.
  - NUCYNTA® ER is taken twice daily and available in 50 mg, 100 mg, 150 mg, 200 mg and 250 mg strengths.[1]

Efficacy and Safety in DPN Pain Studies

- NUCYNTA® ER has demonstrated proven efficacy in patients with neuropathic pain associated with DPN.[2,3]
  - Phase 3 data showed, among patients who had at least a one-point reduction in pain intensity during three weeks of treatment with NUCYNTA® ER, those who continued on the same dose of NUCYNTA® ER that was titrated to balance individual tolerability and efficacy (100-250 mg twice daily) for an additional 12 weeks experienced significantly better pain control compared to those who switched to placebo.[2,3]
  - The most common (≥10% in NUCYNTA® ER-treated patients) adverse reactions were nausea, constipation, vomiting, dizziness, headache and somnolence.[1]

Safety and Tolerability Overall

- Throughout its clinical trial program NUCYNTA® ER demonstrated:
  - Proven efficacy[2,3,5]
  - Favorable tolerability profile[2,3,4,5]
  - Proven safety profile[2,3,4,5]

- In addition to the Phase 3 studies on chronic low back pain and painful DPN, safety also was evaluated in a Phase 3 study in more than 1,100 patients with moderate to severe chronic pain over a 1-year period.[4]
  - The most common (≥10% of NUCYNTA® ER-treated patients) treatment emergent adverse events in the one year safety trial were constipation, nausea, dizziness, somnolence and headache.[4]

Additional Information about NUCYNTA® ER

- The tapentadol molecule is classified as Schedule II of the Controlled Substances Act. NUCYNTA® ER was approved by the FDA in August 2011.

- Outside the United States, tapentadol is marketed by Janssen Inc. in Canada. Grünenthal GmbH discovered tapentadol and markets immediate- and extended-release formulations of tapentadol (PALEXIA®) in several countries worldwide.

- Janssen Research & Development, LLC and Janssen Pharmaceutical KK, Japan, are developing tapentadol in Japan. In addition, Janssen Pharmaceutical companies have rights to develop and market immediate- and extended-release formulations of tapentadol in select European countries and certain countries in Latin America, the Asia-Pacific region, Africa and the Middle East.

IMPORTANT SAFETY INFORMATION FOR NUCYNTA® ER (tapentadol) Extended-Release Oral Tablets

WARNING: ABUSE POTENTIAL, LIFE-THREATENING RESPIRATORY DEPRESSION, ACCIDENTAL EXPOSURE, and INTERACTION WITH ALCOHOL

Abuse Potential
NUCYNTA® ER contains tapentadol, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit. Assess each patient's risk for opioid abuse or addiction prior to prescribing NUCYNTA® ER. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (eg, major depressive disorder). Routinely monitor all patients receiving NUCYNTA® ER for signs of misuse, abuse, and addiction during treatment.

Life-threatening Respiratory Depression
Respiratory depression, including fatal cases, may occur with use of NUCYNTA® ER, even when the drug has been used as recommended and not misused or abused. Proper dosing and titration are essential, and NUCYNTA® ER should only be prescribed by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain. Monitor for respiratory depression, especially during initiation of NUCYNTA® ER or following a dose increase. Instruct patients to swallow NUCYNTA® ER tablets whole. Crushing, dissolving, or chewing NUCYNTA® ER can cause rapid release and absorption of a potentially fatal dose of tapentadol.

Accidental Exposure
Accidental ingestion of NUCYNTA® ER, especially in children, can result in a fatal overdose of tapentadol.

Interaction With Alcohol

The co-ingestion of alcohol with NUCYNTA® ER may result in an increase of plasma levels and potentially fatal overdose of tapentadol. Instruct patients not to consume alcoholic beverages or use prescription or nonprescription products that contain alcohol while on NUCYNTA® ER.

CONTRAINDICATIONS

- NUCYNTA® ER is contraindicated in patients with significant respiratory depression.

- NUCYNTA® ER is contraindicated in patients with acute or severe bronchial asthma or hypercarbia in an unmonitored setting or in the absence of resuscitative equipment.

- NUCYNTA® ER is contraindicated in patients with known or suspected paralytic ileus.

- NUCYNTA® ER is contraindicated in patients with hypersensitivity (eg, anaphylaxis, angioedema) to tapentadol or to any other ingredients of the product.

- NUCYNTA® ER is contraindicated in patients who are receiving monoamine oxidase inhibitors (MAOIs) or who have taken them within the last 14 days due to potential additive effects on norepinephrine levels which may result in adverse cardiovascular events.

WARNINGS and PRECAUTIONS

- NUCYNTA® ER contains tapentadol, an opioid agonist and a Schedule II controlled substance. Tapentadol can be abused in a manner similar to other opioid agonists, legal or illicit. Opioid agonists are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing NUCYNTA® ER in situations where there is concern about increased risks of misuse, abuse, or diversion. Concerns about abuse, addiction, and diversion should not, however, prevent the proper management of pain.

- Assess each patient's risk for opioid abuse or addiction prior to prescribing NUCYNTA® ER. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (eg, major depression). Patients at increased risk may still be appropriately treated with modified-release opioid formulations; however, these patients will require intensive monitoring for signs of misuse, abuse, or addiction. Routinely monitor all patients receiving opioids for signs of misuse, abuse, and addiction because these drugs carry a risk for addiction even under appropriate medical use.

- Misuse or abuse of NUCYNTA® ER by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of the opioid and pose a significant risk that could result in overdose and death.

- Contact local state professional licensing board or state-controlled substances authority for information on how to prevent and detect abuse or diversion of this product.
- Respiratory depression is the chief hazard of opioid agonists, including NUCYNTA® ER. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Respiratory depression from opioids is manifested by a reduced urge to breathe and a decreased rate of respiration, often associated with a "sighing" pattern of breathing (deep breaths separated by abnormally long pauses). Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status.

- 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 dose increase. Closely monitor patients for respiratory depression when initiating therapy with NUCYNTA® ER and following dose increases. Instruct patients

against use by individuals other than the patient for whom NUCYNTA® ER was prescribed and to keep NUCYNTA® ER out of the reach of children, as such inappropriate use may result in fatal respiratory depression.

- To reduce the risk of respiratory depression, proper dosing and titration of NUCYNTA® ER are essential. Overestimating the NUCYNTA® ER dose when converting patients from another opioid product can result in a fatal overdose with the first dose. Respiratory depression has also been reported with use of modified-release opioids when used as recommended and not misused or abused.

- To further reduce the risk of respiratory depression, consider the following:

    - Proper dosing and titration are essential and NUCYNTA® ER should only be prescribed by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain.
    - Instruct patients to swallow NUCYNTA® ER tablets whole. The tablets are not to be cut, crushed, dissolved, or chewed. The resulting tapentadol dose may be fatal, particularly in opioid-naïve individuals.
    - NUCYNTA® ER is contraindicated in patients with respiratory depression and in patients with conditions that increase the risk of life-threatening respiratory depression.

- Accidental ingestion of NUCYNTA® ER, especially in children, can result in a fatal overdose of tapentadol.

- The co-ingestion of alcohol with NUCYNTA® ER can result in an increase of tapentadol plasma levels and potentially fatal overdose of tapentadol. Instruct patients not to consume alcoholic beverages or use prescription or nonprescription products containing alcohol while on NUCYNTA® ER therapy.

- Respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Therefore, monitor such patients closely, particularly when initiating and titrating NUCYNTA® ER and when NUCYNTA® ER is given concomitantly with other drugs that depress respiration.

- Monitor for respiratory depression those patients with significant chronic obstructive pulmonary disease or cor pulmonale and patients having a substantially decreased respiratory reserve, hypoxia, hypercarbia, or pre-existing respiratory depression, particularly when initiating therapy and titrating with NUCYNTA® ER, as in these patients even usual therapeutic doses of NUCYNTA® ER may decrease respiratory drive to the point of apnea. Consider the use of alternative nonopioid analgesics in these patients, if possible.

- Hypotension and profound sedation, coma or respiratory depression may result if NUCYNTA® ER is used concomitantly with other CNS depressants (eg, sedatives, anxiolytics, hypnotics, neuroleptics, muscle relaxants, other opioids, and illicit drugs). When considering the use of NUCYNTA® ER in a patient taking a CNS depressant, assess the duration of use of the CNS depressant and the patient's response, including the degree of tolerance that has developed to CNS depression. Additionally, consider the patient's use, if any, of alcohol and/or illicit drugs that can cause CNS depression. If NUCYNTA® ER therapy is to be initiated in a patient taking a CNS depressant, start with a lower NUCYNTA® ER dose than usual and monitor patients for signs of sedation and respiratory depression and consider using a lower dose of the concomitant CNS depressant.

- NUCYNTA® ER may cause severe hypotension. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (eg, phenothiazines or general anesthetics). Monitor these patients for signs of hypotension after initiating or titrating the dose 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.

- Monitor patients taking NUCYNTA® ER who may be susceptible to the intracranial effects of CO_2 retention (eg, those with evidence of increased intracranial pressure or brain tumors) for signs of sedation and respiratory depression, particularly when initiating therapy with NUCYNTA® ER. NUCYNTA® ER may reduce respiratory drive and the resultant CO_2 retention can further increase intracranial pressure. 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.

- NUCYNTA® ER has not been evaluated in patients with a predisposition to a seizure disorder, and such patients were excluded from clinical studies. The active ingredient tapentadol in NUCYNTA® ER may aggravate convulsions in patients with convulsive disorders and may induce or aggravate seizures in some clinical settings. Monitor patients with a history of seizure disorders for worsened seizure control during NUCYNTA® ER therapy.

- Cases of life-threatening serotonin syndrome have been reported with the concurrent use of tapentadol and serotonergic drugs. Serotonergic drugs comprise selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, drugs that affect the serotonergic neurotransmitter system (eg, mirtazapine, trazodone, and tramadol), and drugs that impair metabolism of serotonin (including MAOIs). This may occur within the recommended dose. Serotonin syndrome may include mental-status changes (eg, agitation, hallucinations, coma), autonomic instability (eg, tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (eg, hyperreflexia, incoordination), and/or gastrointestinal (GI) symptoms (eg, nausea, vomiting, diarrhea), and can be fatal.

- NUCYNTA® ER is contraindicated in patients with GI obstruction, including paralytic ileus. The tapentadol in NUCYNTA® ER may cause spasm of the sphincter of Oddi. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

- Avoid the use of mixed agonist/antagonist analgesics (ie, pentazocine, nalbuphine, and butorphanol) 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 analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms.

- When discontinuing NUCYNTA® ER, gradually taper the dose.

- 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.

- 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. Closely monitor patients with moderate hepatic impairment for respiratory and CNS depression when initiating and titrating NUCYNTA® ER.

- Use of NUCYNTA® ER in patients with severe renal impairment is not recommended due to accumulation of a metabolite formed by glucuronidation of tapentadol. The clinical relevance of the elevated metabolite is not known.

ADVERSE REACTIONS IN CLINICAL STUDIES

- **Management of moderate to severe chronic pain:** The most common (≥10%) adverse reactions were nausea, constipation, dizziness, headache, and somnolence.

- **Management of neuropathic pain associated with diabetic peripheral neuropathy (DPN):** The most common (≥10%) adverse reactions were nausea, constipation, vomiting, dizziness, somnolence, and headache.

For full prescribing information for NUCYNTA® ER, including boxed warnings, please click here**.**

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References

1. NUCYNTA® ER (tapentadol) [Prescribing Information]. Raritan, NJ: Janssen Pharmaceuticals, Inc.

2. Vinik A, et al. Efficacy and tolerability of tapentadol extended release (ER) in patients with chronic, painful diabetic peripheral neuropathy (DPN): results of a phase 3, randomized-withdrawal, placebo-controlled study. Abstract. http://www.ampainsoc.org/abstract/view/5160/.

3. Schwartz S, et al. Safety and efficacy of tapentadol ER in patients with painful diabetic peripheral neuropathy: results of a randomized-withdrawal, placebo-controlled trial. *Cur Med Research and Op*. 2011;27(1):151-162.

4. Wild JE, Grond S, Kuperwasser B, et al. Long-term safety and tolerability of tapentadol extended release for the management of chronic low back pain or osteoarthritis pain. *Pain Pract*. 2010;10(5):416-427.

5. Buynak R, Shapiro DY, Okamoto A, et al. Efficacy and safety of tapentadol extended release for the management of chronic low back pain: results of a prospective, randomized, double-blind, placebo- and active-controlled phase III study. *Expert Opin Pharmacother*. August 2010;11(11):1787-1804.