



Supplemental New Drug Application Submitted to FDA for NUCYNTA® ER (Tapentadol) Extended-Release Tablets for Diabetic Peripheral Neuropathic Pain

TITUSVILLE, N.J., Oct. 31, 2011 /PRNewswire/ -- Johnson & Johnson Pharmaceutical Research & Development, L.L.C. (J&JPRD) announced today that it has submitted a supplemental New Drug Application (sNDA) to the U.S. Food and Drug Administration (FDA) for NUCYNTA® ER (tapentadol) extended-release tablets, an oral analgesic, for the management of neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults. The FDA approved NUCYNTA® ER on August 25, 2011, for the management of moderate to severe chronic pain in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

In the United States, there are nearly 26 million people living with diabetes and, over time, they can develop a type of nerve damage called neuropathy. Approximately 60 to 70 percent of people with diabetes have some form of neuropathy. The most common type is DPN, which causes pain or loss of feeling in the toes, feet, legs, hands, and arms. It is estimated that painful DPN affects 10 to 20 percent of all patients with diabetes, and many patients on current treatments still experience considerable pain.

The submission is based on a full clinical development program, including Phase 3 double-blind, randomized, active-and placebo-controlled studies. These clinical trials explored the efficacy and safety of NUCYNTA® ER for the management of neuropathic pain associated with [DPN](#) in adults.

Data from these studies provide evidence that NUCYNTA® ER has efficacy to reduce diabetic peripheral neuropathic pain compared to placebo. The data also provide evidence of long-term safety and tolerability of NUCYNTA® ER.

J&JPRD is conducting the clinical program for NUCYNTA® ER in the United States. J&JPRD submitted the sNDA on behalf of Janssen Pharmaceuticals, Inc., an affiliated company that holds the NDA for NUCYNTA® ER. Janssen Pharmaceuticals, Inc., markets NUCYNTA® ER in the United States.

This filing represents the ongoing commitment of J&JPRD and Janssen to bring new and innovative products to patients and physicians for the treatment and management of pain.

About Tapentadol, NUCYNTA® ER and NUCYNTA®

Tapentadol is a centrally acting synthetic analgesic. The tapentadol molecule is classified as Schedule II of the Controlled Substances Act.

NUCYNTA® ER (tapentadol) extended-release tablets represents the ongoing commitment of Janssen Pharmaceuticals, Inc. and J&JPRD to bring new and innovative products to patients and physicians for the treatment and management of pain.

NUCYNTA® ER is an oral analgesic indicated for the management of moderate to severe chronic pain in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. It is taken twice daily and is available in 50 mg, 100 mg, 150 mg, 200 mg and 250 mg strengths.

NUCYNTA® (tapentadol) immediate-release tablets was approved by the FDA on November 20, 2008, for the relief of moderate to severe acute pain in patients 18 years of age or older. It is available in 50 mg, 75 mg, and 100 mg strengths.

Both NUCYNTA® and NUCYNTA® ER are available by prescription only.

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

Johnson & Johnson Pharmaceutical Research & Development, L.L.C. 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.

Please see full Product Information for NUCYNTA® ER at <http://www.nucynta.com/>

IMPORTANT SAFETY INFORMATION for NUCYNTA® ER (tapentadol) extended release

WARNING: POTENTIAL FOR ABUSE, PROPER PATIENT SELECTION, AND LIMITATIONS OF USE

Potential for Abuse

NUCYNTA® ER contains tapentadol, a mu-opioid agonist and a Schedule II controlled substance with an abuse liability similar to other opioid analgesics.

NUCYNTA® ER can be abused in a manner similar to other opioid agonists, legal or illicit. These risks should be considered when prescribing or dispensing NUCYNTA® ER in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. Schedule II opioid substances, which include hydromorphone, morphine, oxycodone, fentanyl, oxymorphone, and methadone, have the highest potential for abuse and risk of fatal overdose due to respiratory depression.

Proper Patient Selection

NUCYNTA® ER is an extended-release formulation of tapentadol indicated for the management of moderate to severe chronic pain in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

Limitations of Use

NUCYNTA® ER is not intended for use as an as-needed analgesic.

NUCYNTA® ER is not intended for the management of acute or postoperative pain.

NUCYNTA® ER tablets are to be swallowed whole and are not to be split, broken, chewed, dissolved, or crushed. Taking split, broken, chewed, dissolved, or crushed NUCYNTA® ER tablets could lead to rapid release and absorption of a potentially fatal dose of tapentadol.

Patients must not consume alcoholic beverages, or prescription or nonprescription medications containing alcohol. Co-ingestion of alcohol with NUCYNTA® ER may result in a potentially fatal overdose of tapentadol.

CONTRAINDICATIONS

- NUCYNTA® ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma or hypercapnia in unmonitored settings or in the absence of resuscitative equipment.
- NUCYNTA® ER is contraindicated in any patient who has or is suspected of having a paralytic ileus.
- 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.
- NUCYNTA® ER is contraindicated in patients with a known hypersensitivity to the active substance, tapentadol, or any component of the product. Angioedema has been reported in association with use of tapentadol.

WARNINGS and PRECAUTIONS

- **NUCYNTA® ER tablets are to be swallowed whole and are not to be split, broken, chewed, dissolved, or crushed.** Taking split, broken, chewed, crushed, or dissolved NUCYNTA® ER tablets leads to the rapid release and absorption of a potentially fatal dose of tapentadol.
- NUCYNTA® ER tablets must be kept in a secure place out of the reach of children. Accidental consumption of NUCYNTA® ER, especially in children, can result in a fatal overdose of tapentadol.
- Respiratory depression is the primary risk of mu-opioid agonists. Respiratory depression occurs more frequently in elderly or debilitated patients and in those suffering from conditions accompanied by hypoxia, hypercapnia, or upper airway obstruction, in whom even moderate therapeutic doses may significantly decrease pulmonary ventilation.
- Use NUCYNTA® ER with caution in patients with conditions accompanied by hypoxia, hypercapnia, or decreased respiratory reserve, such as: asthma, chronic obstructive pulmonary disease or cor pulmonale, severe obesity, sleep apnea syndrome, myxedema, kyphoscoliosis, central nervous system (CNS) depression, or coma. In such patients, even usual therapeutic doses of NUCYNTA® ER may increase airway resistance and decrease respiratory drive to the point of apnea. Alternative non-mu-opioid agonist analgesics should be considered, and NUCYNTA® ER should be employed only under careful medical supervision at the lowest effective dose in such patients. If respiratory depression occurs, it should be treated as any mu-opioid agonist-induced respiratory depression.
- Patients receiving other opioid agonist analgesics, general anesthetics, phenothiazines, other tranquilizers, sedatives,

hypnotics, centrally acting muscle relaxants, or other CNS depressants (including alcohol) concomitantly with NUCYNTA® ER may exhibit additive CNS depression. Interactive effects resulting in respiratory depression, hypotension, profound sedation, coma, or death may result if these drugs are taken in combination with NUCYNTA® ER. When such combined therapy is contemplated, a dose reduction of one or both agents should be considered.

- Opioid analgesics can raise cerebrospinal fluid pressure as a result of respiratory depression with carbon dioxide retention. Therefore, NUCYNTA® ER should not be used in patients who may be susceptible to the effects of raised cerebrospinal fluid pressure, such as those with evidence of head injury and increased intracranial pressure. Opioid analgesics may obscure the clinical course of patients with head injury due to effects on pupillary response and consciousness. NUCYNTA® ER should be used with caution in patients with head injury, intracranial lesions, or other sources of preexisting increased intracranial pressure.
- Tapentadol is a mu-opioid agonist and is a Schedule II controlled substance. Such drugs are sought by drug abusers and people with addiction disorders. Diversion of Schedule II products is an act subject to criminal penalty.
- Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids.
- NUCYNTA® ER can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing NUCYNTA® ER in situations where the physician or pharmacist is concerned about an increased risk of misuse and abuse. Concerns about abuse and addiction should not prevent the proper management of pain. However, all patients treated with mu-opioid agonists require careful monitoring for signs of abuse and addiction, since use of mu-opioid agonist analgesic products carries the risk of addiction even under appropriate medical use.
- Drug abusers may attempt to abuse NUCYNTA® ER by crushing, chewing, snorting, or injecting the product. These practices may result in the uncontrolled delivery of NUCYNTA® ER and pose a significant risk to the abuser that could result in overdose and death.
- NUCYNTA® ER may cause severe hypotension. Patients at higher risk of hypotension include those with hypovolemia or those taking concurrent products that compromise vasomotor tone (eg, phenothiazines, general anesthetics).
- Patients should be cautioned that NUCYNTA® ER may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. This is to be expected, especially at the beginning of treatment, at any change of dosage, as well as in combination with alcohol or tranquilizers.
- NUCYNTA® ER may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause CNS depression, because respiratory depression, hypotension, hypertension, and profound sedation, coma, or death may result.
- NUCYNTA® ER has not been evaluated in patients with a predisposition to a seizure disorder, and such patients were excluded from clinical studies. As with other opioids, NUCYNTA® ER should be prescribed with care in patients with a history of a seizure disorder or any condition that would put the patient at risk of seizures.
- 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 symptoms (eg, nausea, vomiting, diarrhea), and can be fatal.
- Withdrawal symptoms may occur if NUCYNTA® ER is discontinued abruptly. These symptoms may include: anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhea, upper respiratory symptoms, piloerection, and rarely, hallucinations. Withdrawal symptoms may be reduced by tapering NUCYNTA® ER.
- A study with the immediate-release formulation of tapentadol in subjects with hepatic impairment showed higher serum concentrations of tapentadol than in those with normal hepatic function. Tapentadol should be used with caution in patients with moderate hepatic impairment. NUCYNTA® ER has not been studied in patients with severe hepatic impairment, and use in this population is not recommended.
- Like other drugs with mu-opioid agonist activity, NUCYNTA® ER may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis.
- NUCYNTA® ER should be used with caution in the following conditions: adrenocortical insufficiency (eg, Addison's disease); delirium tremens; myxedema or hypothyroidism; prostatic hypertrophy or urethral stricture; and toxic psychosis.
- Pregnancy Category C. There are no adequate and well-controlled studies of NUCYNTA® ER in pregnant women. NUCYNTA® ER should be used during pregnancy ONLY if the potential benefit justifies the potential risk to the fetus.

ADVERSE REACTIONS

- The most common ($\geq 10\%$) adverse reactions were nausea, constipation, headache, dizziness, and somnolence.

Please see full Product Information for NUCYNTA® at <http://www.nucynta.com/>

IMPORTANT SAFETY INFORMATION for NUCYNTA® (tapentadol) immediate release

CONTRAINDICATIONS

- Like other drugs with mu-opioid agonist activity, NUCYNTA® is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma or hypercapnia in unmonitored settings or in the absence of resuscitative equipment. NUCYNTA® is contraindicated in patients who have or are suspected to have paralytic ileus. NUCYNTA® is also contraindicated in patients currently using or within 14 days of using monoamine oxidase inhibitors (MAOIs) due to potential additive effects on norepinephrine levels, which may result in adverse cardiovascular events.

WARNINGS & PRECAUTIONS

- Respiratory depression is the primary risk of mu-opioid agonists. Respiratory depression occurs more frequently in elderly or debilitated patients and in those suffering from conditions accompanied by hypoxia, hypercapnia, or upper airway obstruction, in whom even moderate therapeutic doses may significantly decrease pulmonary ventilation. NUCYNTA® should be administered with caution to the elderly, debilitated patients, and patients with conditions accompanied by hypoxia, hypercapnia or decreased respiratory reserve such as: asthma, chronic obstructive pulmonary disease or cor pulmonale, severe obesity, sleep apnea syndrome, myxedema, kyphoscoliosis, CNS depression, or coma. In such patients, even usual therapeutic doses of NUCYNTA® may increase airway resistance and decrease respiratory drive to the point of apnea. Alternative non-mu-opioid agonist analgesics should be considered and NUCYNTA® should be employed only under careful medical supervision at the lowest effective dose in such patients. If respiratory depression occurs, it should be treated as any mu-opioid agonist-induced respiratory depression.
- Patients receiving other mu-opioid agonist analgesics, general anesthetics, phenothiazines, other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol) concomitantly with NUCYNTA® may exhibit additive CNS depression.
- Interactive effects resulting in respiratory depression, hypotension, profound sedation, coma or death may result if these drugs are taken in combination with NUCYNTA®. When such combined therapy is contemplated, a dose reduction of one or both agents should be considered.
- Opioid analgesics can raise cerebrospinal fluid pressure as a result of respiratory depression with carbon dioxide retention. Therefore, NUCYNTA® should not be used in patients susceptible to the effects of raised cerebrospinal fluid pressure such as those with head injury and increased intracranial pressure. Opioid analgesics may obscure the clinical course of patients with head injury due to effects on pupillary response and consciousness. NUCYNTA® should be used with caution in patients with head injury, intracranial lesions, or other sources of preexisting increased intracranial pressure.
- NUCYNTA® is a mu-opioid agonist and is a Schedule II controlled substance. Such drugs are sought by drug abusers and people with addiction disorders. Diversion of Schedule II products is an act subject to criminal penalty. NUCYNTA® can be abused in a manner similar to other mu-opioid agonists, legal or illicit. This should be considered when prescribing or dispensing NUCYNTA® in situations where the physician or pharmacist is concerned about an increased risk of misuse and abuse. All patients treated with mu-opioid agonists require careful monitoring for signs of abuse and addiction. NUCYNTA® may be abused by crushing, chewing, snorting or injecting the product. These practices pose a significant risk to the abuser that could result in overdose and death.
- Experience with NUCYNTA® overdose is very limited. Management of overdose should be focused on treating symptoms of mu-opioid agonism. Primary attention should be given to reestablishment of a patent airway and institution of assisted or controlled ventilation when overdose of NUCYNTA® is suspected. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.
- Patients should be cautioned that NUCYNTA® may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. This is to be expected especially at the beginning of treatment, at any change of dosage as well as in combination with alcohol or tranquilizers.
- NUCYNTA® has not been systematically evaluated in patients with a seizure disorder, and such patients were excluded from clinical studies. NUCYNTA® should be prescribed with care in patients with a history of a seizure disorder or any condition that would put the patient at risk of seizures.
- The development of a potentially life-threatening serotonin syndrome may occur with use of SNRI products, including NUCYNTA®, particularly with concomitant use of serotonergic drugs such as SSRIs, SNRIs, TCAs, MAOIs and triptans, and with drugs which impair metabolism of serotonin (including MAOIs). 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 symptoms (eg, nausea, vomiting, diarrhea).
- Withdrawal symptoms may occur if NUCYNTA® is discontinued abruptly. These symptoms may include: anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhea, upper respiratory symptoms, piloerection, and rarely, hallucinations. Withdrawal symptoms may be reduced by tapering NUCYNTA®.
- Pregnancy Category C. There are no adequate and well-controlled studies of NUCYNTA® in pregnant women. NUCYNTA® should be used during pregnancy ONLY if the potential benefit justifies the potential risk to the fetus. NUCYNTA® is not recommended for use in women during and immediately prior to labor and delivery. Neonates whose mothers have been taking NUCYNTA® should be monitored for respiratory depression. NUCYNTA® should not be used during breastfeeding.
- NUCYNTA® is not recommended in patients with severe renal or hepatic impairment. NUCYNTA® should be used with caution in patients with moderate hepatic impairment. Like other drugs with mu-opioid agonist activity, NUCYNTA® may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including

acute pancreatitis.

Adverse Events

- The most common adverse events are nausea, dizziness, vomiting, somnolence and headache.

Please see full Product Information (<http://nucynta.com/sites/default/files/pdf/nucyntaer-pi.pdf>)

About Janssen Pharmaceuticals, Inc.

Janssen Pharmaceuticals, Inc. is dedicated to addressing and resolving the major unmet medical needs of our time. Driven by our commitment to patients, healthcare professionals, and caregivers, we strive to develop sustainable and integrated healthcare solutions by working in partnership with all stakeholders on the basis of trust and transparency. Our daily work is guided by meeting goals of excellence in quality, innovation, safety, and efficacy in order to advance patient care.

For more information on Janssen Pharmaceuticals, Inc., visit us at www.janssenpharmaceuticalsinc.com, or follow us on Twitter at www.twitter.com/JanssenUS.

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

Johnson & Johnson Pharmaceutical Research & Development, L.L.C., (J&JPRD) is a wholly owned subsidiary of Johnson & Johnson, the world's most broadly based producer of health care products. J&JPRD is headquartered in Raritan, N.J., and has facilities in Europe, the United States and Asia. J&JPRD is leveraging drug discovery and drug development in a variety of therapeutic areas, including Neuroscience, Oncology, Immunology, Infectious Diseases, and Cardiovascular and Metabolism to address unmet medical needs worldwide. More information can be found at www.jnjpharmarnd.com