Manufacturer Product Update

Janssen Pharmaceuticals, Inc. announces the availability of NUCYNTA® ER (tapentadol extended-release tablets) 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.

Please see <link> for clinical data and Prescribing Information for NUCYNTA® ER.

Link

Adobe Acrobat Document

New Product - NUCYNTA® ER (tapentadol extended-release tablets)

IMPORTANT SAFETY INFORMATION

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.

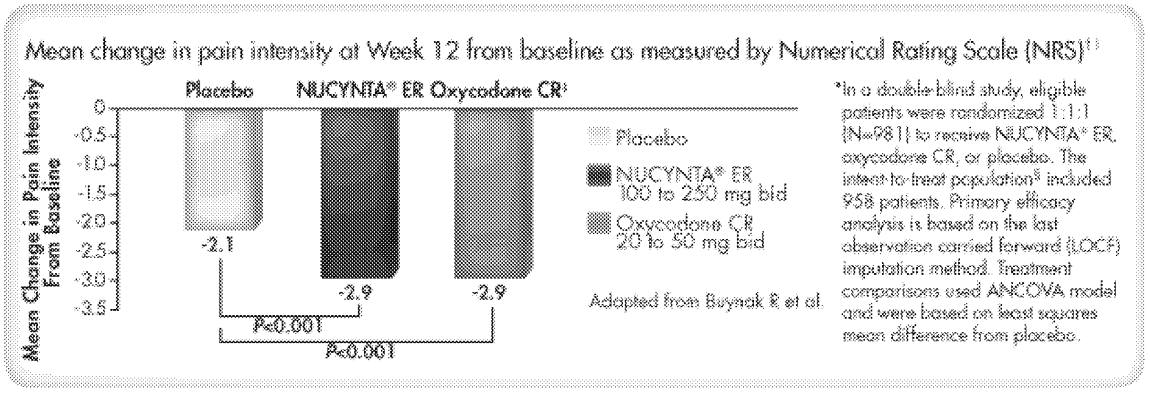
NUCYNTA® ER tablets are to be swallowed whole and are not to be split, broken, chewed, dissolved, or crushed. Taking split, broken, chewed, dissolved, or crushed NUCYNTA® ER tablets could lead to rapid release and absorption of a potentially fatal dose of tapentadol.

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.

Please see full Prescribing Information at www.NUCYNTA.com

POWERFUL PAIN MANAGEMENT

In a clinical study of chronic low back pain*
NUCYNTA® ER demonstrated powerful efficacy in chronic low back pain



- Primary efficacy endpoint was change from baseline of the mean pain intensity scores at Week 12 based on NRS[1]
- Patients had an overall mean pain intensity score of 7.5 at baseline[1]
- Oxycodone CR was included in the study for assay sensitivity[2]

TOLERABILITY PROFILE

Incidence of treatment-emergent adverse events (TEAEs) reported in at least 5% of patients in any treatment group[‖1]

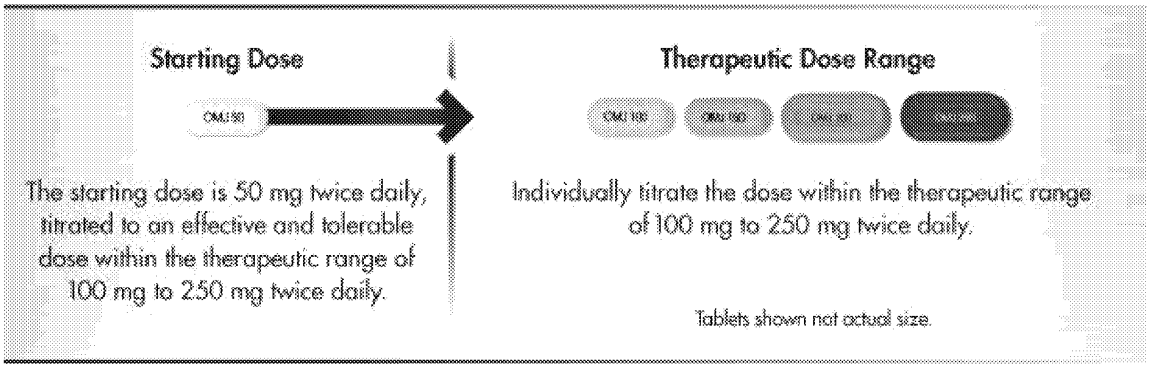
System/Organ Class Dictionary-Derived Term	% of Patients (N=965) Placebo (n=319)	NUCYNTA® ER (n=318)	Oxycodone CR‡ (n=328)
Gastrointestinal Disorders	**26**	**44**	**62**
Nausea	9	20	35
Vomiting	2	9	19
Constipation	5	14	27
Diarrhea	7	6	2
Dry Mouth	2	8	4
Dyspepsia	3	5	2
Nervous System Disorders	**23**	**40**	**45**
Dizziness	6	12	17
Somnolence	3	13	16
Headache	14	20	17
Psychiatric Disorders	**9**	**15**	**18**
Insomnia	3	4	8
General Disorders	**10**	**16**	**19**
Fatigue	4	7	7
Skin and Subcutaneous Tissue Disorders	**5**	**14**	**28**
Hyperhidrosis	0	4	5
Skin Pruritus	2	7	17

Discontinuation rates due to TEAEs[‖]
placebo: **4%**
NUCYNTA® ER: **17%**
oxycodone CR: **32%**

†An 11-point pain intensity scale. A score of 0 being "no pain"; a score of 10 being "pain as bad as you can imagine."
‡Clinical trials were conducted with controlled-release oxycodone, which is the opioid ingredient in OxyContin®.
§Intent-to-treat population included all randomized subjects who received at least one dose of the study drug.
‖Safety population included all subjects who received at least one dose of study drug (N=965). Patients had a mean baseline pain intensity score of 7.5. Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
OxyContin is a registered trademark of Purdue Pharma Inc.

NUCYNTA® ER DOSING & TITRATION

- **NUCYNTA® ER is available in 50 mg, 100 mg, 150 mg, 200 mg, and 250 mg tablets**



- Tapentadol has not been shown to induce or inhibit P450 enzymes
  - Clinically relevant interactions mediated by the cytochrome P450 system are unlikely to occur
- Primarily metabolized by glucuronidation (Phase II)
- No known active metabolites
- Tapentadol has low plasma protein binding (~20%)
  - The likelihood of pharmacokinetic drug-drug interactions by displacement from the protein-binding site is low
- There were no clinically significant findings in drug interaction studies of tapentadol and acetaminophen, acetylsalicylic acid, naproxen, and probenecid. The pharmacokinetics of tapentadol were not affected when gastric pH or GI motility were increased by omeprazole and metoclopramide, respectively. No drug interaction studies were conducted with the extended-release formulation

Available in 5 tablet strengths:
50 mg, 100 mg, 150 mg, 200 mg, and 250 mg

NUCYNTA® ER STRENGTH	NDC NUMBER	PACKAGE QUANTITY	CASE SIZE	MINIMUM ORDER QUANTITY	CASE DIMENSIONS
NUCYNTA® ER 50 mg	50458-860-01	60-count bottle	24 bottles	1 case	8.125"(W) x 3.5"(H) x 11.438"(D)
NUCYNTA® ER 100 mg	50458-861-01	60-count bottle	24 bottles	1 case	8.125"(W) x 3.5"(H) x 11.438"(D)
NUCYNTA® ER 150 mg	50458-862-01	60-count bottle	24 bottles	1 case	8.125"(W) x 3.5"(H) x 11.438"(D)
NUCYNTA® ER 200 mg	50458-863-01	60-count bottle	24 bottles	1 case	8.125"(W) x 3.5"(H) x 11.438"(D)
NUCYNTA® ER 250 mg	50458-864-01	60-count bottle	24 bottles	1 case	8.125"(W) x 3.5"(H) x 11.438"(D)

If you have questions about NUCYNTA® ER, please contact us at 1-800-JANSSEN (526-7736) between 9:00 AM and 5:00 ET or visit www.NUCYNTA.com for more information.

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 (=10%) adverse events were nausea, constipation, headache, dizziness, and somnolence.

References: 1. 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*. 2010;11(11):1787-1804. **2.** Data on file. Johnson & Johnson Pharmaceutical Research & Development, LLC.

Janssen Pharmaceuticals, Inc.

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