CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200533Orig1s000

<u>LABELING</u>

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 oral tablets C-II

Initial U.S. Approval: 2011

WARNING: Potential for Abuse, proper patient selection and limitations of use

See full prescribing information for complete boxed warning.

NUCYNTA® ER contains tapentadol, a mu-opioid agonist and Schedule II controlled substance, with risk of misuse, abuse, and diversion similar to other opioid analgesics. (5.5)

NUCYNTA® ER is not intended for use as an as-needed analgesic (1).

NUCYNTA® ER is not intended for the management of acute or postoperative pain (1)

Swallow NUCYNTA® ER tablets whole. Taking split, broken, chewed, dissolved, or crushed NUCYNTA® ER tablets could lead to rapid release and absorption of a potentially fatal dose of tapentadol. (5.1)

Patients must not consume alcoholic beverages, prescription or non-prescription medications containing alcohol. Co-ingestion of alcohol with NUCYNTA® ER may result in a potentially fatal overdose of tapentadol.(12.3)

INDICATIONS AND USAGE

NUCYNTA® ER is an opioid 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. (1)

DOSAGE AND ADMINISTRATION

- As with many centrally acting analgesic medications, the dosing regimen of NUCYNTA® ER should be individualized according to the severity of pain being treated, the previous experience with similar drugs and the ability to follow-up and provide oversight of treatment. (2)
- The recommended NUCYNTA® ER total daily dose is 100 mg to 250 mg twice daily approximately every 12 hours. Patients not currently taking opioid analgesics should begin NUCYNTA® ER therapy with 50 mg twice a day.(2)
- Patients receiving NUCYNTA® (immediate-release formulation) may be converted to NUCYNTA® ER by administering the same total daily dose. Administer half the total daily dose of NUCYNTA® ER approximately every 12 hours. Do not exceed the maximum daily dose of NUCYNTA® ER of 500 mg. (2)

DOSAGE FORMS AND STRENGTHS

- Tablets: 50 mg, 100 mg, 150 mg, 200 mg, 250 mg (3)

CONTRAINDICATIONS

- Impaired pulmonary function (significant respiratory depression, acute or severe bronchial asthma or hypercapnia in unmonitored settings or the absence of resuscitative equipment) (4)
- Paralytic ileus (4)
- Concurrent use of monoamine oxidase (MAO) inhibitors or use within the last 14 day (4)
- Hypersensitivity (4)

WARNINGS AND PRECAUTIONS

- Respiratory depression: Increased risk in elderly, debilitated patients, those suffering from conditions accompanied by hypoxia, hypercapnia, or upper airway obstruction. (5.2)
- CNS effects: Additive CNS depressive effects when used in conjunction with alcohol, other opioids, or illicit drugs. (5.3)
- Elevation of intracranial pressure: Use with caution in patients with head injury, intracranial lesions, or other sources of preexisting increased intracranial pressure. (5.4)
- Abuse potential may occur. Monitor patients closely for signs of abuse and addiction. (5.5)
- Hypotension may occur, particularly in patients at high risk (5.6)
- Impaired mental/physical abilities: Caution must be used with potentially hazardous activities. (5.7)
- Interaction with alcohol and drugs of abuse: CNS, respiratory depression, hypotension and sedation effects may be additive (5.8)
- Seizures: Use with caution in patients with a history of seizures. (5 9)
- Serotonin Syndrome: Potentially life-threatening condition could result from concomitant administration of drugs with serotonergic activity. (5.10)
- Withdrawal symptoms may occur if NUCYNTA® ER is discontinued abruptly. Tapering may reduce withdrawal symptoms. (5.11)

ADVERSE REACTIONS

The most common (≥10%) adverse reactions were nausea, constipation, headache, dizziness, and somnolence. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Pharmaceuticals, Inc. at 1–800–526–7736 or FDA at 1–800–FDA–1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Use NUCYNTA® ER with caution in patients currently using specified centrally acting drugs or alcohol. (7.3)
- Do not use NUCYNTA® ER in patients currently using or within 14 days of using a monoamine oxidase inhibitor (MAOI). (7.4)
- Use NUCYNTA® ER with caution in patients currently using SSRIs, SNRIs, tricyclic antidepressants, or triptans (7.5)
- Use of NUCYNTA® ER in patients currently using mixed agonist/antagonist opioid analgesics or anticholinergic medications is not recommended (7.6, 7.7)

USE IN SPECIFIC POPULATIONS

- Labor and delivery: should not use during and immediately prior to labor and delivery. Monitor neonates, whose mothers have been taking NUCYNTA® ER, for respiratory depression. (8.2)
- Nursing mothers: should not breast-feed. (8.3)
- Pediatric use: safety and effectiveness not established in patients less than 18 years of age. (8.4)
- Renal or hepatic impairment: not recommended in patients with severe renal or hepatic impairment. Use with caution in patients with moderate hepatic impairment. (8.7, 8.8)
- Elderly: care should be taken when selecting an initial dose. (2.5)

See 17 for PATIENT COUNSELING INFORMATION AND MEDICATION GUIDE.

Revised: 08/2011

Reference ID: 3006589

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Initiating Therapy with NUCYNTA® ER
2.2 Cessation of Therapy
2.3 Renal Impairment
2.4 Hepatic Impairment
2.5 Elderly Patients
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Information Essential for Safe Administration
5.2 Respiratory Depression
5.3 CNS Depression
5.4 Head Injury and Increased Intracranial Pressure
5.5 Misuse and Abuse
5.6 Hypotension
5.7 Driving and Operating Machinery
5.8 Interactions with Alcohol and Drugs of Abuse
5.9 Seizures
5.10 Serotonin Syndrome Risk
5.11 Withdrawal
5.12 Hepatic Impairment
5.13 Use in Pancreatic/Biliary Tract Disease
5.14 Other Special Risk Groups
6 ADVERSE REACTIONS
6.1 Clinical Studies Experience
6.2 Commonly-Observed Adverse Reactions in Double-Blind Controlled Clinical Studies with NUCYNTA® ER
6.3 Other Adverse Reactions Observed During the Premarketing Evaluation of NUCYNTA® ER
6.4 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 Drugs Metabolized by Cytochrome P450 Enzymes
7.2 Drugs That Inhibit or Induce Cytochrome P450 Enzymes
7.3 Centrally Acting Drugs and Alcohol
7.4 Monoamine Oxidase Inhibitors
7.5 Serotonergic Drugs
7.6 Mixed Agonist/Antagonist Opioid Analgesics
7.7 Anticholinergics
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Neonatal Withdrawal Syndrome
8.7 Renal Impairment
8.8 Hepatic Impairment
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
10.1 Human Experience
10.2 Management of Overdose
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION
17.1 Medication Guide

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

Reference ID: 3006589

FULL PRESCRIBING INFORMATION

WARNING: POTENTIAL FOR ABUSE, PROPER PATIENT SELECTON, 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. *(9)*

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. *(1)*

NUCYNTA® ER is not intended for the management of acute or postoperative pain. *(1)*

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. *(5)*

Patients must not consume alcoholic beverages, prescription or non-prescription medications containing alcohol. Co-ingestion of alcohol with NUCYNTA® ER may result in a potentially fatal overdose of tapentadol. *(12.3)*

1 INDICATIONS AND USAGE

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.

Reference ID: 3006589

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

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

2 DOSAGE AND ADMINISTRATION

Selection of patients for treatment with NUCYNTA® ER is governed by the same principles that apply to the use of similar opioid analgesics. Physicians should individualize treatment in every case, using non-opioid analgesics, opioids on an as needed basis and/or combination products, and chronic opioid therapy in a progressive plan of pain management such as outlined by the World Health Organization and Federation of State Medical Boards Model Guidelines.

NUCYNTA® ER tablets must be swallowed whole and must not 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.

NUCYNTA® ER tablets must be taken one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth *[see Patient Counseling Information (17)]*.

2.1 Initiating Therapy with NUCYNTA® ER

It is critical to initiate the dosing regimen for each patient individually giving attention to:

- risk factors for abuse or addiction; including whether the patient has a previous or current substance abuse problem, a family history of substance abuse, or a history of mental illness or depression;
- the age, general condition and medical status of the patient;
- the patient's opioid exposure and opioid tolerance (if any);
- the daily dose, potency, and kind of the analgesic(s) the patient has been taking;
- the balance between pain management and adverse reactions.

Discontinue all other tapentadol and tramadol products when beginning and while taking NUCYNTA® ER *[see Serotonin Syndrome Risk (5.10)]*. 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.

Once therapy with NUCYNTA® ER is initiated, assess pain intensity and adverse reactions frequently.

Reference ID: 3006589

Titrate patients to adequate analgesia with dose increases of 50 mg no more than twice daily every three days.

During periods of changing analgesic requirements, including initial titration, maintain frequent contact between the healthcare provider and the patient.

Patients Currently Not Taking Opioid Analgesics

The starting dose of NUCYNTA® ER in patients currently not taking opioid analgesics is 50 mg twice a day (approximately every 12 hours). Individually titrate the dose within the therapeutic range of 100 mg to 250 mg twice daily.

Patients Currently Taking Opioid Analgesics

There are no adequate data on the direct conversion from other opioids to NUCYNTA® ER.

The initial dose of NUCYNTA® ER in patients previously taking other opioids is 50 mg titrated to an effective and tolerable dose within the therapeutic range of 100 mg to 250 mg twice daily.

In the dose selection of NUCYNTA® ER in patients currently taking opioids, give attention to the following:

- There is a substantial patient variation in the relative potency of different opioid drugs and formulations;
- It is extremely important to monitor all patients closely 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 tends to accumulate in the plasma.
- The recommended doses are only a starting point, and close observation and titration are indicated until a satisfactory dose is obtained on the new therapy.

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.

2.2 Cessation of Therapy

Periodically reassess the continued need for NUCYNTA® ER during chronic therapy. When discontinuing NUCYNTA® ER, potential withdrawal symptoms may be reduced by tapering the dose of NUCYNTA® ER *[see Withdrawal (5.11, 9.3)]*.

Reference ID: 3006589

2.3 Renal Impairment

NUCYNTA® ER has not been studied in patients with severe renal impairment; therefore, the use of NUCYNTA® ER in this population is not recommended. No dosage adjustment is recommended in patients with mild or moderate renal impairment *[see Clinical Pharmacology (12.3)]*.

2.4 Hepatic Impairment

NUCYNTA® ER has not been studied in patients with severe hepatic impairment. The use of NUCYNTA® ER in this population is not recommended.

Use NUCYNTA® ER with caution in patients with moderate hepatic impairment. Initiate treatment in these patients using 50 mg NUCYNTA® ER and administer no more frequently than once every 24 hours. The maximum recommended dose for patients with moderate hepatic impairment is 100 mg of NUCYNTA® ER once daily *[see Clinical Pharmacology (12.3)]*.

No dosage adjustment is recommended in patients with mild hepatic impairment *[see Clinical Pharmacology (12.3)]*.

2.5 Elderly Patients

In general, recommended dosing for elderly patients with normal renal and hepatic function is the same as for younger adult patients with normal renal and hepatic function. Because elderly patients are more likely to have decreased renal and hepatic function, consideration should be given to starting elderly patients with the lower range of recommended doses.

3 DOSAGE FORMS AND STRENGTHS

NUCYNTA® ER 50 mg, 100 mg, and 150 mg extended-release tablets are available in the following colors and prints:

- 50 mg extended-release tablets are white oblong-shaped with a black print “OMJ 50” on one side
- 100 mg extended-release tablets are light-blue oblong-shaped with a black print “OMJ 100” on one side
- 150 mg extended-release tablets are blue-green oblong-shaped with a black print “OMJ 150” on one side

NUCYNTA® ER 200 mg and 250 mg extended-release tablets are available in the following colors and prints:

- 200 mg extended-release tablets are blue oblong-shaped with a depression in the middle running lengthwise on each side and a black print “OMJ 200” on one side

Reference ID: 3006589

- 250 mg extended-release tablets are dark blue oblong-shaped with a depression in the middle running lengthwise on each side and a white print "OMJ 250" on one side

4 CONTRAINDICATIONS

NUCYNTA® ER is contraindicated in patients with significant respiratory depression, or severe bronchial asthma or hypercapnia in unmonitored settings or in the absence of resuscitative equipment *[see Warnings and Precautions (5.1)]*.

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 (MAO) inhibitors 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 *[see Drug Interactions (7.4)]*.

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.

5 WARNINGS AND PRECAUTIONS

5.1 Information Essential for Safe Administration

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.

5.2 Respiratory Depression

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

Reference ID: 3006589

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 [*see Overdosage (10.2)*].

5.3 CNS 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.

5.4 Head Injury and Increased Intracranial Pressure

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.

5.5 Misuse and Abuse

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 carry the risk of addiction even under appropriate medical use *[see Drug Abuse and Dependence (9.2)]*.

Reference ID: 3006589

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 *[see Drug Abuse and Dependence (9)]*.

5.6 Hypotension

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 (e.g., phenothiazines, general anesthetics).

5.7 Driving and Operating Machinery

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 *[see Drug Interactions (7.3)]*.

5.8 Interactions with Alcohol and Drugs of Abuse

NUCYNTA® ER may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression, because respiratory depression, hypotension, hypertension, and profound sedation, coma or death may result *[see Drug Interactions (7.3)]*.

5.9 Seizures

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.

5.10 Serotonin Syndrome Risk

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 (e.g. 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 (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia,

Reference ID: 3006589

incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea) and can be fatal *[see Serotonergic Drugs (7.5)]*.

5.11 Withdrawal

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 *[see Drug Abuse and Dependence (9.3)]*.

5.12 Hepatic Impairment

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 *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*.

NUCYNTA® ER has not been studied in patients with severe hepatic impairment and use in this population is not recommended.

5.13 Use in Pancreatic/Biliary Tract Disease

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.

5.14 Other Special Risk Groups

NUCYNTA® ER should be used with caution in the following conditions: adrenocortical insufficiency (e.g., Addison's disease); delirium tremens; myxedema or hypothyroidism; prostatic hypertrophy or urethral stricture; and, toxic psychosis.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Respiratory Depression *[see Contraindications (4) and Warnings and Precautions (5.2)]*
- CNS Depression *[see Warnings and Precautions (5.3)]*
- Hypotension *[see Warnings and Precautions (5.6)]*
- Seizures *[see Warnings and Precautions (5.9)]*
- Serotonin Syndrome *[see Warnings and Precautions (5.10)]*

Reference ID: 3006589

6.1 Clinical Studies Experience

A causal relationship with NUCYNTA® ER often cannot be reliably established in individual cases. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety data described in Table 1 below are based on three pooled, randomized, double-blind, placebo-controlled, parallel group, 15-week studies of NUCYNTA® ER (dosed 100 to 250 mg BID after a 50 mg BID starting dose) in patients with chronic pain due to low back pain (LBP) and osteoarthritis (OA). These trials included 980 NUCYNTA® ER-treated patients and 993 placebo-treated patients. The mean age was 57 years old; 63% were female and 37% were male; 83% were White, 10% were Black, and 5% were Hispanic.

The most common adverse reactions (reported by ≥10% in any NUCYNTA® ER dose group) were: nausea, constipation, headache, dizziness, and somnolence.

The most common reasons for discontinuation due to adverse reactions in nine Phase 2/3 pooled studies reported by ≥1% in any NUCYNTA® ER dose group for NUCYNTA® ER- and placebo-treated patients were nausea (4% vs. <1%), dizziness (4% vs. <1%), vomiting (3% vs. <1%), somnolence (2% vs. <1%), constipation (1% vs. <1%), headache (1% vs. <1%), and fatigue (1% vs. <1%), respectively.

6.2 Commonly-Observed Adverse Reactions in Double-Blind Controlled Clinical Studies with NUCYNTA® ER

Table 1 lists the common adverse reactions reported in 1% or more of NUCYNTA® ER-treated patients and greater than placebo-treated patients with chronic moderate to severe pain in the three pooled studies. The types of adverse reactions seen in the study of patients with painful diabetic peripheral neuropathy (DPN) were similar to what was seen in the low back pain and osteoarthritis trials.

Reference ID: 3006589

Table 1: Adverse Drug Reactions Reported by ≥ 1% of NUCYNTA® ER-Treated Patients and Greater than Placebo-treated Patients in Pooled Parallel-Group Trials (i.e., Studies LBP-1, OA-1, and OA-2)[1]

	NUCYNTA® ER 50 to 250 mg BID[2] (n=980)	Placebo (n=993)
Gastrointestinal disorders		
Nausea	21%	7%
Constipation	17%	7%
Vomiting	8%	3%
Dry mouth	7%	3%
Dyspepsia	3%	2%
Nervous system disorders		
Dizziness	17%	7%
Headache	15%	13%
Somnolence	12%	4%
Lethargy	2%	0%
Disturbance in attention	1%	0%
Tremor	1%	0%
General disorders and administration site conditions		
Fatigue	9%	4%
Asthenia	2%	1%
Chills	1%	0%
Psychiatric disorders		
Insomnia	4%	2%
Anxiety	2%	1%
Depressed mood[3]	1%	1%
Abnormal dreams	1%	0%
Depression	1%	0%

Reference ID: 3006589

Skin and subcutaneous tissue disorders		
Hyperhidrosis	5%	1%
Pruritus	5%	2%
Rash[3]	1%	1%
Metabolism and nutrition disorders		
Decreased appetite	2%	1%
Ear and labyrinth disorders		
Vertigo	2%	1%
Vascular disorders		
Hot flush	2%	0%
Eye disorders		
Vision blurred	1%	0%
Respiratory, thoracic and mediastinal disorders		
Dyspnea[3]	1%	1%
Reproductive system and breast disorders		
Erectile dysfunction	1%	0%

[1] MedDRA preferred terms. The trials included forced titration during the first week of dosing.

[2] NUCYNTA® ER dosed between 100 and 250 mg BID after a starting dose of 50 mg BID

[3] Depressed mood was observed in 1.2% of NUCYNTA® ER-treated subjects vs. 0.5% in placebo group, rash- in 1.1 vs. 0.7 in placebo, and dyspnea- in 1.1 vs. 0.5 in placebo.

6.3 Other Adverse Reactions Observed During the Premarketing Evaluation of NUCYNTA® ER

The following adverse drug reactions occurred in less than 1% of NUCYNTA® ER-treated patients in nine Phase 2/3 clinical studies:

- **Nervous System Disorders:** Paresthesia, Hypoesthesia, Balance disorder, Sedation, Syncope, Memory impairment, Mental impairment, Depressed level of consciousness, Dysarthria, Coordination abnormal, Presyncope
- **Gastrointestinal disorders:** Impaired gastric emptying

Reference ID: 3006589

- **General disorders and administration site conditions:** Drug withdrawal syndrome, Irritability, Feeling abnormal, Feeling drunk, Feeling of relaxation
- **Psychiatric disorders:** Perception disturbances, Disorientation, Agitation, Confusional state, Euphoric mood, Drug dependence, Thinking abnormal
- **Skin and subcutaneous tissue disorders:** Urticaria
- **Metabolism and nutrition disorders:** Weight decreased
- **Cardiac disorders:** Heart rate increased, Heart rate decreased
- **Vascular Disorder:** Blood pressure decreased
- **Respiratory, thoracic and mediastinal disorders:** Respiratory depression
- **Renal and urinary disorders:** Pollakiuria, Urinary hesitation
- **Reproductive system and breast disorders:** Sexual dysfunction
- **Eye disorders:** Visual disturbance
- **Immune system disorders:** Drug hypersensitivity

6.4 Postmarketing Experience

The following adverse reactions have been identified during post approval use of tapentadol. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal disorders: diarrhea

Immune system disorders: angioedema

Psychiatric disorders: hallucination, suicidal ideation

Cardiac disorders: palpitations

7 DRUG INTERACTIONS

Tapentadol is mainly metabolized by glucuronidation. The following substances have been included in a set of interaction studies without any clinically significant finding: acetaminophen, acetylsalicylic acid, naproxen and probenecid *[see Clinical Pharmacology (12.3)]*.

The pharmacokinetics of tapentadol were not affected when gastric pH or gastrointestinal motility were increased by omeprazole and metoclopramide, respectively *[see Clinical Pharmacology (12.3)]*.

Reference ID: 3006589

7.1 Drugs Metabolized by Cytochrome P450 Enzymes

In vitro investigations indicate that tapentadol does not inhibit or induce P450 enzymes. Thus, clinically relevant interactions mediated by the cytochrome P450 system are unlikely to occur *[see Clinical Pharmacology (12.3)]*.

7.2 Drugs That Inhibit or Induce Cytochrome P450 Enzymes

The major pathway of tapentadol metabolism is conjugation with glucuronic acid to produce glucuronides, a high capacity metabolic pathway. To a lesser extent, tapentadol is additionally metabolized to N-desmethyl tapentadol (13%) by CYP2C9 and CYP2C19, and to hydroxy tapentadol (2%) by CYP2D6, which are further metabolized by conjugation. Since only a minor amount of tapentadol is metabolized via the oxidative pathway clinically relevant interactions mediated by the cytochrome P450 system are unlikely to occur *[see Clinical Pharmacology (12.3)]*.

7.3 Centrally Acting Drugs and Alcohol

Patients receiving other opioid agonist analgesics, general anesthetics, phenothiazines, antiemetics, other tranquilizers, sedatives, hypnotics, centrally acting muscle relaxants, or other CNS depressants (including alcohol) concomitantly with NUCYNTA® ER may experience additive CNS depression. Interactive effects resulting in respiratory depression, hypotension, profound sedation, or coma may result if these drugs are taken in combination with NUCYNTA® ER. If such combined therapy is contemplated, a dose reduction of one or both agents should be considered *[see Warnings and Precautions (5.3) and (5.8)]*.

The co-administration of alcohol with NUCYNTA® ER may result in increased serum levels and a potentially fatal overdose of tapentadol. Do not use NUCYNTA® ER with alcohol *[see Clinical Pharmacology (12.3)]*.

7.4 Monoamine Oxidase Inhibitors

NUCYNTA® ER is contraindicated in patients who are receiving monoamine oxidase (MAO) inhibitors 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 [*see Contraindications (4)]*.

7.5 Serotonergic Drugs

There have been post-marketing reports of serotonin syndrome with the concomitant use of tapentadol and serotonergic drugs (e.g., SSRIs and SNRIs). Caution is advised when NUCYNTA® ER is co-administered with other drugs that may affect serotonergic neurotransmitter systems such as SSRIs, SNRIs, MAOIs, and triptans. If concomitant treatment

Reference ID: 3006589

of NUCYNTA® ER with a drug affecting the serotonergic neurotransmitter system is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases *[see Warning and Precautions (5.10)]*.

7.6 Mixed Agonist/Antagonist Opioid Analgesics

The concomitant use of NUCYNTA® ER with mixed agonist/antagonists (e.g., butorphanol, nalbuphine, and pentazocine) and partial agonists (e.g., buprenorphine) could lead to a reduction of the analgesic effect by competitive blocking of opioid receptors, and/or withdrawal. Therefore, this combination is not recommended.

7.7 Anticholinergics

The use of NUCYNTA® ER with anticholinergic products may increase the risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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.

Tapentadol HCl was evaluated for teratogenic effects in pregnant rats and rabbits following intravenous and subcutaneous exposure during the period of embryofetal organogenesis. When tapentadol was administered twice daily by the subcutaneous route in rats at dose levels of 10, 20, or 40 mg/kg/day [producing up to 1.36 times the plasma exposure at the maximum recommended human dose (MRHD) of 500 mg/day for NUCYNTA® ER based on an area under the time-curve (AUC) comparison], no teratogenic effects were observed. Evidence of embryofetal toxicity included transient delays in skeletal maturation (i.e., reduced ossification) at the 40 mg/kg/day dose which was associated with significant maternal toxicity. Administration of tapentadol HCl in rabbits at doses of 4, 10, or 24 mg/kg/day by subcutaneous injection [producing 0.3, 0.8, and 2.5 times the plasma exposure at the MRHD based on an AUC comparison, respectively] revealed embryofetal toxicity at doses ≥10 mg/kg/day. Findings included reduced fetal viability, skeletal delays and other variations. In addition, there were multiple malformations including gastroschisis/thoracogastroschisis, amelia/phocomelia, and cleft palate at doses ≥10 mg/kg/day and above, and ablepharia, encephalopathy, and spina bifida at the high dose of 24 mg/kg/day. Embryofetal toxicity, including malformations, may be secondary to the significant maternal toxicity observed in the study.

Reference ID: 3006589

In a study of pre- and postnatal development in rats, oral administration of tapentadol at doses of 20, 50, 150, or 300 mg/kg/day to pregnant and lactating rats during the late gestation and early postnatal period [resulting in up to 2.28 times the plasma exposure at the MRHD on an AUC basis] did not influence physical or reflex development, the outcome of neurobehavioral tests or reproductive parameters. Treatment-related developmental delay was observed, including incomplete ossification, and significant reductions in pup body weights and body weight gains at doses associated with maternal toxicity (150 mg/kg/day and above). At maternal tapentadol doses ≥150 mg/kg/day, a dose-related increase in pup mortality was observed to postnatal Day 4.

8.2 Labor and Delivery

The effect of tapentadol on labor and delivery in humans is unknown. NUCYNTA® ER is not recommended for use in women during and immediately prior to labor and delivery. Due to the mu-opioid receptor agonist activity of NUCYNTA® ER, neonates whose mothers have been taking NUCYNTA® ER should be monitored for respiratory depression. A specific opioid antagonist, such as naloxone, should be available for reversal of opioid induced respiratory depression in the neonate.

8.3 Nursing Mothers

There is insufficient/limited information on the excretion of tapentadol in human or animal breast milk. Physicochemical and available pharmacodynamic/toxicological data on tapentadol point to excretion in breast milk and risk to the suckling child cannot be excluded. NUCYNTA® ER should not be used during breast-feeding.

8.4 Pediatric Use

The safety and effectiveness of NUCYNTA® ER in pediatric patients less than 18 years of age have not been established. NUCYNTA® ER is not recommended in this population.

8.5 Geriatric Use

Of the total number of patients in Phase 2/3 double-blind, multiple-dose clinical studies of NUCYNTA® ER, 28% (1023/3613) were 65 years and over, while 7% (245/3613) were 75 years and over. No overall differences in effectiveness or tolerability were observed between these patients and younger patients.

In general, recommended dosing for elderly patients with normal renal and hepatic function is the same as for younger adult patients with normal renal and hepatic function. Because elderly patients are more likely to have decreased renal and hepatic function, consideration should be given to starting elderly patients with the lower range of recommended doses *[see Clinical Pharmacology (12.3)]*.

Reference ID: 3006589

8.6 Neonatal Withdrawal Syndrome

Chronic maternal use of opiates or opioids during pregnancy coexposes the fetus. The newborn may experience subsequent neonatal withdrawal syndrome (NWS). Manifestations of NWS include irritability, hyperactivity, abnormal sleep pattern, high-pitched cry, tremor, vomiting, diarrhea, weight loss, and failure to gain weight. The onset, duration, and severity of the disorder differ based on such factors as the addictive drug used, time and amount of mother's last dose, and rate of elimination of the drug from the newborn.

8.7 Renal Impairment

The safety and effectiveness of NUCYNTA® ER has not been established in patients with severe renal impairment. NUCYNTA® ER is not recommended in this population *[see Dosage and Administration (2.3)]*.

8.8 Hepatic Impairment

Administration of tapentadol resulted in higher exposures and serum levels of tapentadol in subjects with impaired hepatic function compared to subjects with normal hepatic function *[see Clinical Pharmacology (12.3)]*. NUCYNTA® ER should be used with caution in patients with moderate hepatic impairment *[see Dosage and Administration (2.4)]*.

NUCYNTA® ER has not been studied in patients with severe hepatic impairment, therefore, use of NUCYNTA® ER is not recommended in this population *[see Warnings and Precautions (5.12)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

NUCYNTA® ER contains tapentadol, a mu-opioid agonist and is a Schedule II controlled substance. NUCYNTA® ER has an abuse potential similar to hydromorphone, can be abused and is subject to criminal diversion.

9.2 Abuse

Drug addiction is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Drug addiction is a treatable disease, utilizing a multidisciplinary approach, but relapse is common.

The risks of misuse and abuse should be considered when prescribing or dispensing NUCYNTA® ER. Concerns about abuse and addiction should not prevent the proper management of pain. However, all patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Reference ID: 3006589

"Drug seeking" behavior is very common in addicts, and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated claims of loss of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" (visiting multiple prescribers) to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of mu-opioid agonists can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. Careful recordkeeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Abuse of NUCYNTA® ER poses a risk of overdose and death. This risk is increased with concurrent abuse of NUCYNTA® ER with alcohol and other substances. NUCYNTA® ER tablets are intended for oral use only and must not be administered by any other route. If abused by parenteral routes, the tablet excipients may cause serious or even fatal complications. In addition, parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of drugs with mu-opioid agonist properties.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms *[see Use in Special Populations (8.6)]*. Use of NUCYNTA® ER in this population has not been characterized. As NUCYNTA® ER has mu-opioid agonist activity, infants whose mothers have taken NUCYNTA® ER should be carefully monitored.

9.3 Dependence

Tolerance to opioids is the need for increasing doses of opioids to maintain a constant effect such as analgesia (in the absence of disease progression or other external factors). The first sign of tolerance is usually a reduced duration of effect. Tolerance to different effects of opioids may develop to varying degrees and at varying rates in a given individual. There is also inter-patient variability in the rate and extent of tolerance that develops to various opioid effects, whether the

Reference ID: 3006589

effect is desirable (e.g., analgesia) or undesirable (e.g., nausea). Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist. Physical dependence and tolerance occur frequently during chronic opioid therapy.

The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, increased blood pressure, respiratory rate, or heart rate.

Tolerance and/or a withdrawal syndrome are more likely to occur the longer a patient is on continuous opioid therapy. In clinical trials, patients who stopped taking NUCYNTA® ER abruptly experienced mild (12%) or moderate (2%) withdrawal. Withdrawal symptoms included: nausea, diarrhea, insomnia, sweating, anxiety, arthralgia, and chills. Withdrawal symptoms may be reduced by tapering NUCYNTA® ER.

10 OVERDOSAGE

10.1 Human Experience

Experience with NUCYNTA® ER overdose is very limited. Preclinical data suggest that symptoms similar to those of other centrally acting analgesics with mu-opioid agonist activity are to be expected upon intoxication with tapentadol. In principle, the clinical manifestations of opioid overdose include miosis, vomiting, cardiovascular collapse, consciousness disorders up to coma, convulsions and respiratory depression up to respiratory arrest, and death.

10.2 Management of Overdose

Management of overdose should be focused on treating symptoms of mu-opioid agonism. Primary attention should be given to re-establishment of a patent airway and institution of assisted or controlled ventilation when overdose of NUCYNTA® ER is suspected. Supportive measures (including oxygen and vasopressors) should be employed in the management of cardiac and/or pulmonary failure as needed. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

Take the extended-release characteristics of NUCYNTA® ER into account when treating the overdose. Even in the face of improvement, continued medical monitoring is required because of the possibility of extended effects

Pure opioid antagonists, such as naloxone, are specific antidotes to respiratory depression resulting from opioid overdose. Respiratory depression following an overdose may outlast the

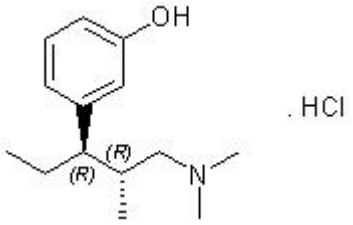
Reference ID: 3006589

duration of action of the opioid antagonist. Administration of an opioid antagonist is not a substitute for continuous monitoring of airway, breathing, and circulation following an opioid overdose. If the response to the initial administration of opioid antagonists is suboptimal or only brief in nature, repeated doses or an alternative antagonist should be administered as directed by the label of the antagonist.

Only administer opioid antagonists in the presence of clinically significant respiratory or circulatory depression secondary to tapentadol overdose. In patients who are physically dependent on any opioid agonist including NUCYNTA® ER, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered.

11 DESCRIPTION

NUCYNTA® ER (tapentadol) is a mu-opioid receptor agonist, supplied in extended-release film-coated tablets for oral administration, containing 58.24, 116.48, 174.72, 232.96, and 291.20 mg of tapentadol hydrochloride in each tablet strength, corresponding to 50, 100, 150, 200, and 250 mg of tapentadol free-base, respectively. The chemical name is 3-[(1*R*,2*R*)-3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol monohydrochloride. The structural formula is:



The molecular weight of tapentadol HCl is 257.80, and the molecular formula is $C_{14}H_{23}NO{\bullet}HCl$. The n-octanol: water partition coefficient log P value is 2.87. The pKa values are 9.34 and 10.45. In addition to the active ingredient tapentadol HCl, tablets also contain the following inactive ingredients: polyethylene oxide, hypromellose, polyethylene glycol and alpha-tocopherol (vitamin E). The film coating is comprised of polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and the colorant FD&C Blue #2 aluminum lake is used for 100-, 150-, 200-, and 250-mg strengths; and additionally, yellow iron oxide is used in 150-mg tablets. Printing inks contain shellac glaze and propylene glycol for all strengths, and black iron oxide (50-, 100-, 150- and 200-mg tablet) or titanium dioxide (250-mg tablet).

Reference ID: 3006589

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tapentadol is a centrally-acting synthetic analgesic. The exact mechanism of action is unknown. Although the clinical relevance is unclear, preclinical studies have shown that tapentadol is a mu-opioid receptor (MOR) agonist and a norepinephrine reuptake inhibitor (NRI), and analgesia in animal models is derived from both of these properties.

12.2 Pharmacodynamics

Tapentadol is 18 times less potent than morphine in binding to the human mu-opioid receptor and is 2-3 times less potent in producing analgesia in animal models. Tapentadol has been shown to inhibit norepinephrine reuptake in the brains of rats resulting in increased norepinephrine concentrations. In preclinical models, the analgesic activity due to the mu-opioid receptor agonist activity of tapentadol can be antagonized by selective mu-opioid antagonists (e.g., naloxone), whereas the norepinephrine reuptake inhibition is sensitive to norepinephrine modulators. Tapentadol exerts its analgesic effects without a pharmacologically active metabolite.

Effects on the cardiovascular system: There was no effect of therapeutic and supratherapeutic doses of tapentadol on the QT interval. In a randomized, double-blind, placebo- and positive-controlled crossover study, healthy subjects were administered five consecutive immediate-release formulation doses of tapentadol 100 mg every 6 hours, tapentadol 150 mg every 6 hours, placebo and a single oral dose of moxifloxacin. Similarly, the immediate-release formulation tapentadol had no relevant effect on other ECG parameters (heart rate, PR interval, QRS duration, T-wave or U-wave morphology).

12.3 Pharmacokinetics

Absorption

The mean absolute bioavailability after single-dose administration (fasting) of NUCYNTA® ER is approximately 32% due to extensive first-pass metabolism. Maximum serum concentrations of tapentadol are observed between 3 and 6 hours after administration of NUCYNTA® ER. Dose proportional increases for AUC have been observed after administration of NUCYNTA® ER over the therapeutic dose range.

Steady-state exposure of tapentadol is attained after the third dose (i.e., 24 hours after first twice daily multiple dose administration). Following dosing with 250 mg every 12 hours, minimal accumulation was observed.

Reference ID: 3006589

Food Effect

The AUC and C_{max} increased by 6% and 17%, respectively, when NUCYNTA® ER tablet was administered after a high-fat, high-calorie breakfast. NUCYNTA® ER may be given with or without food.

Distribution

Tapentadol is widely distributed throughout the body. Following intravenous administration, the volume of distribution (Vz) for tapentadol is 540 +/- 98 L. The plasma protein binding is low and amounts to approximately 20%.

Metabolism and Elimination

In humans, about 97% of the parent compound is metabolized. Tapentadol is mainly metabolized via Phase 2 pathways, and only a small amount is metabolized by Phase 1 oxidative pathways. The major pathway of tapentadol metabolism is conjugation with glucuronic acid to produce glucuronides. After oral administration approximately 70% (55% O-glucuronide and 15% sulfate of tapentadol) of the dose is excreted in urine in the conjugated form. A total of 3% of drug was excreted in urine as unchanged drug. Tapentadol is additionally metabolized to N-desmethyl tapentadol (13%) by CYP2C9 and CYP2C19 and to hydroxy tapentadol (2%) by CYP2D6, which are further metabolized by conjugation. Therefore, drug metabolism mediated by cytochrome P450 system is of less importance than phase 2 conjugation.

None of the metabolites contribute to the analgesic activity.

Tapentadol and its metabolites are excreted almost exclusively (99%) via the kidneys. The terminal half-life is on average 5 hours after oral administration. The total clearance of tapentadol is 1603 +/-227 mL/min.

Special Populations

Elderly

The mean exposure (AUC) to tapentadol was similar in elderly subjects compared to young adults, with a 16% lower mean C_{max} observed in the elderly subject group compared to young adult subjects.

Renal Impairment

AUC and C_{max} of tapentadol were comparable in subjects with varying degrees of renal function (from normal to severely impaired). In contrast, increasing exposure (AUC) to tapentadol-O-glucuronide was observed with increasing degree of renal impairment. In subjects with mild, moderate, and severe renal impairment, the AUC of tapentadol-O-glucuronide was 1.5-, 2.5-, and 5.5-fold higher compared with normal renal function, respectively.

Reference ID: 3006589

Hepatic Impairment

Administration of tapentadol resulted in higher exposures and serum levels to tapentadol in subjects with impaired hepatic function compared to subjects with normal hepatic function. The ratio of tapentadol pharmacokinetic parameters for the mild and moderate hepatic impairment groups in comparison to the normal hepatic function group were 1.7 and 4.2, respectively, for AUC; 1.4 and 2.5, respectively, for C_{max}; and 1.2 and 1.4, respectively, for $t_{1/2}$. The rate of formation of tapentadol-O-glucuronide was lower in subjects with increased liver impairment.

Pharmacokinetic Drug Interactions

Tapentadol is mainly metabolized by Phase 2 glucuronidation, a high capacity/low affinity system; therefore, clinically relevant interactions caused by Phase 2 metabolism are unlikely to occur. Naproxen and probenecid increased the AUC of tapentadol by 17% and 57%, respectively. These changes are not considered clinically relevant and no change in dose is required.

No changes in the pharmacokinetic parameters of tapentadol were observed when acetaminophen and acetylsalicylic acid were given concomitantly.

In vitro studies did not reveal any potential of tapentadol to either inhibit or induce cytochrome P450 enzymes. Thus, clinically relevant interactions mediated by the cytochrome P450 system are unlikely to occur.

The pharmacokinetics of tapentadol were not affected when gastric pH or gastrointestinal motility were increased by omeprazole and metoclopramide, respectively.

Plasma protein binding of tapentadol is low (approximately 20%). Therefore, the likelihood of pharmacokinetic drug-drug interactions by displacement from the protein binding site is low.

In Vivo NUCYNTA® ER Formulation-Alcohol Interaction

NUCYNTA® ER may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression, because respiratory depression, hypotension, hypertension, and profound sedation, coma or death may result *[see Warnings and Precautions (5.8)]*.

An *in vivo* study examined the effect of alcohol (240 mL of 40%) on the bioavailability of a single dose of 100 mg and 250 mg of NUCYNTA® ER tablet in healthy, fasted volunteers. After co-administration of a 100 mg NUCYNTA® ER tablet and alcohol, the mean C_{max} value increased by 48% compared to control with a range of 0.99-fold to 4.38-fold. The mean tapentadol AUC_{last} and AUC_{inf} were increased by 17%; the T_{max} and $t_{½}$ were unchanged. After co-administration of a 250 mg NUCYNTA® ER tablet and alcohol, the mean C_{max} value

Reference ID: 3006589

increased by 28% compared to control with a range of 0.90-fold to 2.67-fold. The mean tapentadol AUC_{last} and AUC_{inf} were increased by 16%; the T_{max} and $t_{½}$ were unchanged.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Tapentadol was administered to rats (diet) and mice (oral gavage) for two years.

In mice, tapentadol HCl was administered by oral gavage at dosages of 50, 100 and 200 mg/kg/day for 2 years (up to 0.34 times in the male mice and 0.25 times in the female mice the plasma exposure at the maximum recommended human dose [MRHD] for NUCYNTA® ER on an area under the time-curve [AUC] basis). No increase in tumor incidence was observed at any dose level.

In rats, tapentadol HCl was administered in diet at dosages of 10, 50, 125 and 250 mg/kg/day for two years (up to 0.20 times in the male rats and 0.75 times in the female rats the MRHD on an AUC basis). No increase in tumor incidence was observed at any dose level.

Mutagenesis

Tapentadol did not induce gene mutations in bacteria, but was clastogenic with metabolic activation in a chromosomal aberration test in V79 cells. The test was repeated and was negative in the presence and absence of metabolic activation. The one positive result for tapentadol was not confirmed *in vivo* in rats, using the two endpoints of chromosomal aberration and unscheduled DNA synthesis, when tested up to the maximum tolerated dose.

Impairment of Fertility

Tapentadol HCl was administered intravenously to male or female rats at dosages of 3, 6, or 12 mg/kg/day (representing exposures of up to approximately 0.56 times in the male rats and 0.50 times in the female rats the exposure at the MRHD on an AUC basis, based on extrapolation from toxicokinetic analyses in a separate 4-week intravenous study in rats). Tapentadol did not alter fertility at any dose level. Maternal toxicity and adverse effects on embryonic development, including decreased number of implantations, decreased numbers of live conceptuses, and increased pre- and post-implantation losses occurred at dosages ≥6 mg/kg/day.

13.2 Animal Toxicology and/or Pharmacology

In toxicological studies with tapentadol, the most common systemic effects of tapentadol were related to the mu-opioid receptor agonist and norepinephrine reuptake inhibition pharmacodynamic properties of the compound. Transient, dose-dependent and predominantly CNS-related findings were observed, including impaired respiratory function and convulsions,

Reference ID: 3006589

the latter occurring in the dog at plasma levels (C_{max}), which are in the range associated with the maximum recommended human dose (MRHD).

14 CLINICAL STUDIES

The efficacy of NUCYNTA® ER was studied in four studies in patients with moderate to severe chronic pain. Efficacy was demonstrated in one randomized, double-blind, placebo- and active-controlled study in patients with chronic low back pain (LBP), and one randomized, double-blind, placebo-controlled study in patients with pain related to diabetic peripheral neuropathy (DPN).

In the LBP study, patients 18 years of age or older with chronic low back pain and a baseline pain score of ≥5 on an 11-point numerical rating scale (NRS), ranging from 0 to 10 were enrolled and randomized to 1 of 3 treatments: NUCYNTA® ER, active-control (an extended-release Schedule II opioid analgesic), or placebo.

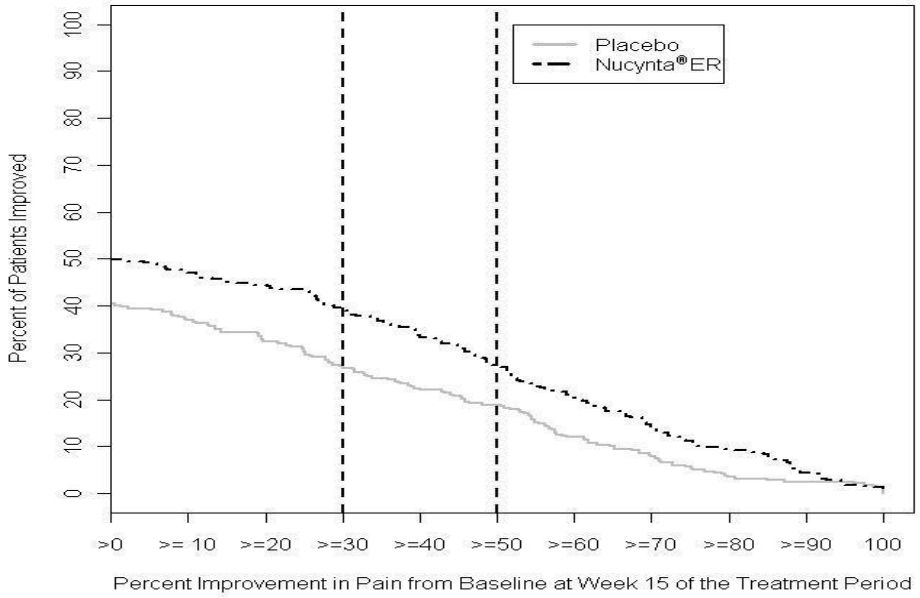
Patients randomized to NUCYNTA® ER initiated therapy with a dose of 50 mg twice daily for three days. After three days, the dose was increased to 100 mg twice daily. Subsequent titration was allowed over a 3-week titration period to a dose up to 250 mg twice daily, followed by a 12-week maintenance period. There were 981 patients randomized. The mean age of the study population was 50 (range 18 to 89) years; the mean baseline pain intensity score was 8 (SD 1). Approximately half of the patients were opioid-naïve (had not taken opioids during the three months prior to the screening visit).

The number of patients completing the study was 51% in the placebo group, 54% in the NUCYNTA® ER group and 43% in the active-control group. Lack of efficacy was the most common reason for discontinuation among placebo-treated patients (21%), whereas adverse events were the most common reason for discontinuation among the active treatment groups (17% and 32% for NUCYNTA® ER and active-control, respectively).

After 15 weeks of treatment, patients taking NUCYNTA® ER had a significantly greater pain reduction compared to placebo. The proportion of patients with various degrees of improvement is shown in Figure 1. The figure is cumulative, such that patients, whose change from baseline is, for example 50%, are also included at every level of improvement below 50%. Patients who did not complete the study were assigned 0% improvement.

Reference ID: 3006589

Figure 1: Percentage of Patients Achieving Various Levels of Improvement in Pain Intensity - Study LBP[1]



[1] The last week of Study LBP was Week 15.

In the DPN study, patients 18 years or older with pain due to diabetic peripheral neuropathy and a pain score of ≥5 on an 11-point numerical rating scale (NRS) ranging from 0 to 10 were enrolled. Following an open-label treatment period in which NUCYNTA® ER was administered to all patients for three weeks, patients who had demonstrated at least a 1-point improvement in pain intensity on the NRS at the end of the open-label titration period were randomized to either the NUCYNTA® ER dose (100 mg to 250 mg) reached during the open-label titration period, or placebo for 12 weeks of maintenance treatment.

A total of 591 patients entered open-label treatment and 389 patients met the criteria for randomization into the double-blind treatment period. The mean age of the randomized population was 60 (range 29 to 87) years; approximately two-thirds of the patients were opioid-naïve (had not taken opioids during the three months prior to the screening visit).

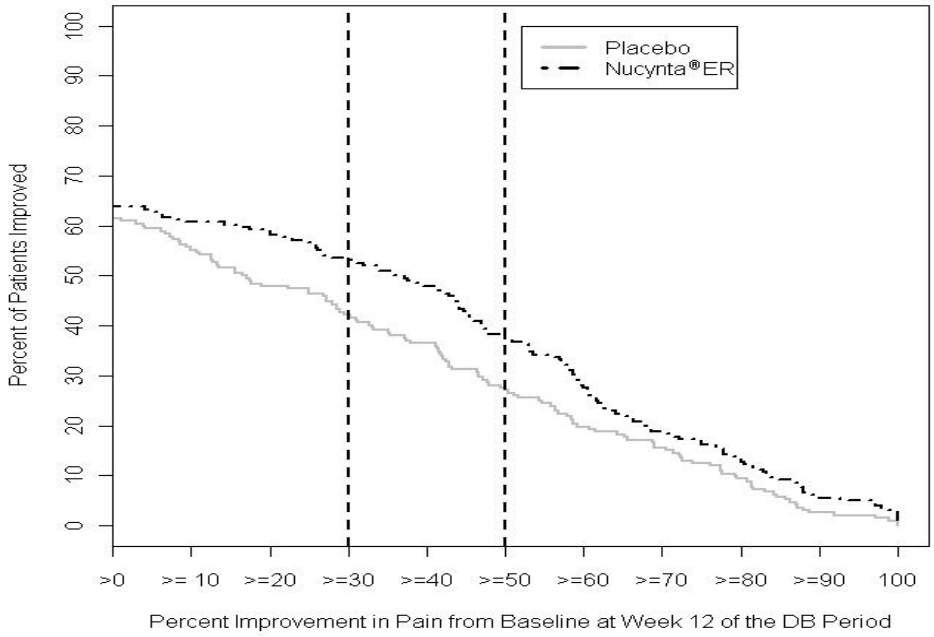
During the titration period, 34% of patients discontinued open-label NUCYNTA® ER. The most common reasons for discontinuation in the double-blind treatment period were lack of efficacy in the placebo group (14%) and adverse events in the NUCYNTA® ER group (15%).

After 12 weeks of treatment, NUCYNTA® ER provided a significantly greater reduction in pain intensity compared to placebo. Figure 2 displays the proportion of randomized patients achieving various degrees of improvement in pain intensity from the start of the open-label titration period

Reference ID: 3006589

to the last week of the randomized withdrawal period. The figure is cumulative, such that patients, whose change from baseline is, for example 50%, are also included at every level of improvement below 50%. Patients who did not complete the study were assigned 0% improvement.

Figure 2: Percentage of Patients Achieving Various Levels of Pain Relief - DPN



16 HOW SUPPLIED/STORAGE AND HANDLING

NUCYNTA® ER tablets are available in the following strengths and packages:

50 mg extended-release tablets are white oblong-shaped with a black print "OMJ 50" on one side and are available in bottles of 60 with child-resistant closure (NDC 50458-860-01) and unit dose blister packs of 10, for hospital use only (NDC 50458-860-02).

100 mg extended-release tablets are light-blue oblong-shaped with a black print "OMJ 100" on one side and are available in bottles of 60 with child-resistant closure (NDC 50458-861-01) and unit dose blister packs of 10, for hospital use only (NDC 50458-861-02).

150 mg extended-release tablets are blue-green oblong-shaped with a black print "OMJ 150" on one side and are available in bottles of 60 with child-resistant closure (NDC 50458-862-01) and unit dose blister packs of 10, for hospital use only (NDC 50458-862-02).

Reference ID: 3006589

200 mg extended-release tablets are blue oblong-shaped with a depression in the middle running lengthwise on each side and with a black print "OMJ 200" on one side, and are available in bottles of 60 with child-resistant closure (NDC 50458-863-01) and unit dose blister packs of 10, for hospital use only (NDC 50458-863-02).

250 mg extended-release tablets are dark blue oblong-shaped with a depression in the middle running lengthwise on each side and with a white print "OMJ 250" on one side, and are available in bottles of 60 with child-resistant closure (NDC 50458-864-01) and unit dose blister packs of 10, for hospital use only (NDC 50458-864-02).

Storage and Handling

Store up to 25°C (77°F); excursions permitted to 15° - 30°C (59° - 86°F) [see USP Controlled Room Temperature].

Protect from moisture.

Keep NUCYNTA® ER in a secure place out of reach of children.

NUCYNTA® ER tablets that are no longer needed should be destroyed by flushing down the toilet.

17 PATIENT COUNSELING INFORMATION

Physicians are advised to discuss the following issues with patients for whom they prescribe NUCYNTA® ER:

- Advise patients that NUCYNTA® ER should be taken only as directed and to report episodes of breakthrough pain and adverse experiences occurring during therapy to their physician.
- Advise patients not to adjust the dose of NUCYNTA® ER without consulting their physician *[see Dosage and Administration (2)]*.
- Advise patients to inform their prescriber if they are experiencing changes in their pain level or if they feel they need a change in dosage.
- Advise patients that it may be appropriate to taper dosing when discontinuing treatment with NUCYNTA® ER as withdrawal symptoms may occur *[see Drug Abuse and Dependence (9.3)]*.
- Advise patients that NUCYNTA® ER must be swallowed whole. The extended-release tablets may release all their contents at once if split, broken, chewed or crushed, or dissolved, resulting in a risk of fatal overdose of tapentadol.
- Advise patients that NUCYNTA® ER tablets should be taken one tablet at a time. Patients should not pre-soak, lick or otherwise wet the tablet prior to placing in the

Reference ID: 3006589

mouth. Advise patients to take each tablet with enough water to ensure complete swallowing immediately after placing in the mouth *[see Dosage and Administration (2)]*.

- Advise patients using NUCYNTA® ER chronically (for several weeks) to contact their healthcare providers if they notice the need to increase dosing to treat symptoms of pain or they experience symptoms of withdrawal upon abrupt cessation of dosing.

- Advise patients to flush NUCYNTA® ER tablets that are no longer needed down the toilet. Advise patients to keep NUCYNTA® ER in the childproof container and store in a safe place to protect it from being stolen.

- Advise patients that NUCYNTA® ER is a Schedule II Controlled Substance and a potential drug of abuse. Patients should protect NUCYNTA® ER from theft, and NUCYNTA® ER should never be given to anyone other than the individual for whom NUCYNTA® ER was prescribed *[see Warnings and Precautions (5.5)]*. NUCYNTA® ER tablets are intended for oral use only and must not be administered by any other route. If abused by parenteral routes, this may result in serious or even fatal complications *[see Abuse (9.2)]*.

- Advise patients that NUCYNTA® ER can cause respiratory depression and hypotension *[see Warnings and Precautions (5.2 and 5.6)]*.

- Advise patients to exercise caution about operating hazardous machinery, including automobiles while taking NUCYNTA® ER, as NUCYNTA® ER has the potential to impair judgment, thinking, or motor skills *[see Warnings and Precautions (5.7)]*.

- Advise patients to notify their physician if they become pregnant or intend to become pregnant during treatment with NUCYNTA® ER *[see Use in Specific Populations (8.1)]*.

- Advise patients not to breast-feed an infant during treatment with NUCYNTA® ER *[see Use in Specific Populations (8.3)]*.

- Advise patients not to take NUCYNTA® ER while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking NUCYNTA® ER.

- Advise patients that NUCYNTA® ER could cause seizures if they are at risk for seizures or have epilepsy. Such patients should be advised to use NUCYNTA® ER with care *[see Warnings and Precautions (5.9)]*. Patients should be advised to stop taking NUCYNTA® ER if they have a seizure while taking NUCYNTA® ER and call their healthcare provider right away.

- Advise patients that NUCYNTA® ER could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs (including Serotonin Reuptake Inhibitors, Serotonin and Norepinephrine Reuptake Inhibitors and tricyclic antidepressants) *[see Warnings and Precautions (5.10)]*.

- Advise patients not to take alcoholic beverages, or prescription or non-prescription medications containing alcohol, while on NUCYNTA® ER therapy. The co-

Reference ID: 3006589

administration of alcohol with NUCYNTA® ER may result in increased serum levels and a potentially fatal overdose of tapentadol *[see Drug Interactions (7.3)]*.

- Advise patients to inform their physicians if they are taking, or plan to take additional medications including CNS Depressants, MAO inhibitors, mixed agonists/antagonist opioid analgesics, anticholinergics, SSRIs, SNRIs, or tricyclic antidepressants *[see Drug Interactions (7)]*.

See Medication Guide.

Issued: August 2011

Manufactured by:
Janssen Ortho, LLC
Gurabo, PR 00778

Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

© Janssen Pharmaceuticals, Inc. 2011

17.1 Medication Guide

MEDICATION GUIDE

NUCYNTA® ER (new-SINN-tah E-R) C-II

(tapentadol)

extended-release oral tablets

Important:

Keep NUCYNTA® ER in a safe place away from children. Accidental use by a child is a medical emergency and can result in death. If a child accidentally takes NUCYNTA® ER, get emergency help right away.

Read the Medication Guide that comes with NUCYNTA® ER before you start taking it and each time you get a new prescription. There may be new information. This Medication Guide does not take the place of talking to your doctor about your medical condition or your treatment. Talk to your doctor if you have any questions.

What is the most important information I should know about NUCYNTA® ER?

1. **NUCYNTA® ER overdose can cause life-threatening breathing problems that can lead to death.**
    - **Take NUCYNTA® ER exactly as prescribed by your doctor.**
    - NUCYNTA® ER is not for use for short-term pain relief from injuries or surgery.
    - NUCYNTA® ER is not for use to treat pain that you only have once in a while (“as needed”).
    - **Swallow NUCYNTA® ER tablets whole. Do not break, split, chew, dissolve, or crush NUCYNTA® ER tablets before swallowing, or inject the contents. If NUCYNTA® ER is taken in this way, the tapentadol in NUCYNTA® ER may be released too fast. This is dangerous. It may cause you to have trouble breathing and lead to death.**
    - If you cannot swallow NUCYNTA® ER tablets whole, tell your doctor. You will need a different pain medicine.

Reference ID: 3006589

- Do not drink alcohol, or use prescription or non-prescription medicines that contains alcohol while you are being treated with NUCYNTA® ER. Alcohol can cause very high levels of tapentadol in your blood and you can die due to an overdose of tapentadol.

- It is important to stay under the care of your doctor while taking NUCYNTA® ER.

2. **Prevent theft, misuse, or abuse. Keep NUCYNTA® ER in a safe place to protect it from being stolen. NUCYNTA® ER can be a target for people who misuse or abuse prescription medicines or street drugs.**

3. **Never give NUCYNTA® ER to anyone else, even if they have the same symptoms you have. It may harm them or even cause death. Selling or giving away this medicine is against the law.**

What is NUCYNTA® ER?

- NUCYNTA® ER is a prescription medicine that contains the opioid (narcotic) pain medicine tapentadol. The medicine in NUCYNTA® ER is slowly released over time. **If you break, split, chew, dissolve, or crush NUCYNTA® ER before swallowing, or inject the contents, the tapentadol may be released too fast and you may overdose.** See "What is the most important information I should know about NUCYNTA® ER?"

- NUCYNTA® ER is a strong opioid pain medicine. NUCYNTA® ER is used in adults to treat moderate to severe pain that continues around-the-clock and is expected to last for a long period of time.

- NUCYNTA® ER is not for use for short-term pain relief from injuries or surgery.

- NUCYNTA® ER is not for use to treat pain that you only have once in a while ("as needed").

- **NUCYNTA® ER is a federally controlled substance (CII)** because it contains strong opioid pain medicine that can be a target for people who abuse prescription medicines or street drugs.

- It is not known if NUCYNTA® ER is safe and works in children less than 18 years of age. NUCYNTA® ER should not be used in children.

Who should not take NUCYNTA® ER?

Do not take NUCYNTA® ER if you:

Reference ID: 3006589

- have trouble breathing or lung problems such as severe asthma, wheezing, or shortness of breath.
- have a bowel blockage called paralytic ileus.
- **take a monoamine oxidase inhibitor (MAOI) medicine or have taken an MAOI medicine within the last 14 days.** Ask your doctor or pharmacist if any of your medicines is a MAOI.
- are allergic to tapentadol or any of the ingredients in NUCYNTA® ER. See the end of this Medication Guide for a complete list of ingredients in NUCYNTA® ER.

What should I tell my doctor before taking NUCYNTA® ER?

NUCYNTA® ER may not be right for you.

Before taking NUCYNTA® ER, tell your doctor if you:

- have trouble breathing or lung problems such as asthma, wheezing, or shortness of breath
- have had a head injury or a brain problem
- have liver or kidney problems
- have adrenal gland problems, such as Addison's disease
- have thyroid problems
- have convulsions or seizures
- have pancreas or gallbladder problems
- have problems urinating or prostate problems
- have constipation
- have severe scoliosis that affects your breathing
- have low blood pressure
- have or had a drinking problem or alcoholism or a family history of this problem
- have mental problems including depression, anxiety, or hallucinations (seeing or hearing things that are not really there)
- have or had drug abuse or addiction problems or a family history of this problem
- plan to have surgery
- **are pregnant or plan to become pregnant.**

  If you take NUCYNTA® ER right before your baby is born, your baby could have breathing problems.

Reference ID: 3006589

If you take NUCYNTA® ER regularly before your baby is born, your newborn baby may have withdrawal symptoms, because his/her body has become used to the medicine.

Symptoms of withdrawal in a newborn baby may include:

- irritability
- crying more than usual
- shaking (tremors)
- jitteriness
- breathing faster than normal
- diarrhea or more stools than normal
- vomiting
- fever

- **are breastfeeding.** You should not breastfeed while taking NUCYNTA® ER. Talk to your doctor about the best way to feed your baby if you take NUCYNTA® ER.

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines may cause serious or life-threatening medical problems when taken with NUCYNTA® ER. Sometimes, the doses of certain other medicines and NUCYNTA® ER need to be changed.

Especially tell your doctor if you take:

- Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs), tricyclic antidepressants, tramadol, and triptan medicines. See “What are the possible side effects of NUCYNTA® ER?”
- Other medicines that make you sleepy such as:
  - other pain medicines
  - antidepressant medicines, including those listed above
  - sleeping pills
  - antihistamines
  - anti-anxiety medicines
  - muscle relaxants
  - anti-nausea medicines
  - tranquilizers

Do not take NUCYNTA® ER if you take a monoamine oxidase inhibitor (MAOI) medicine. See "Who should not take NUCYNTA® ER?"

Reference ID: 3006589

Do not take any new medicine while using NUCYNTA® ER until you have talked to your doctor or pharmacist. They will tell you if it is safe to take other medicines while you are taking NUCYNTA® ER. **Ask your doctor if you are not sure if your medicine is one of the listed above.**

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take NUCYNTA® ER?

- **Take NUCYNTA® ER exactly as prescribed by your doctor. Do not change the dose unless your doctor tells you to.**
- Your doctor may change your dose after seeing how NUCYNTA® ER affects you.
- You can take NUCYNTA® ER with or without food.
- **Swallow NUCYNTA® ER whole**. You must take NUCYNTA® ER one tablet at a time, with enough water to make sure that you completely swallow the tablet right away. Do not soak, lick, or wet the tablet before putting it in your mouth.
- **Do not break, split, chew, dissolve, or crush NUCYNTA® ER tablets before swallowing, or inject the contents.** If you cannot swallow tablets, tell your doctor. See "What is the most important information I should know about NUCYNTA® ER?"
- **If you miss a dose**, take it as soon as possible. If it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. **Do not take 2 doses at the same time unless your doctor tells you to.** If you are not sure about your dosing call your doctor.
- **If you take too much NUCYNTA® ER or overdose, get emergency help right away.**
- Call your doctor if your pain is not well controlled while taking NUCYNTA® ER.
- Follow your doctor's instructions about how to slowly stop taking NUCYNTA® ER to help prevent uncomfortable withdrawal symptoms.

What should I avoid while taking NUCYNTA® ER?

- **Do not drive, operate machinery, or do other dangerous activities,** until you know how NUCYNTA® ER affects how alert you are. NUCYNTA® ER can make you sleepy.

What are the possible side effects of NUCYNTA® ER?

NUCYNTA® ER can cause serious side effects including:

Reference ID: 3006589

- **Life-threatening breathing problems. Call your doctor right away or get emergency medical help if you:**
    - have trouble breathing
    - have extreme drowsiness with slowed breathing
    - have shallow breathing (little chest movement with breathing)
    - feel faint, dizzy, confused, or have other unusual symptoms
    - have a seizure
- **Decreased blood pressure.** This can make you feel dizzy and faint if you get up too fast from sitting or lying down. Low blood pressure is more likely to happen if you take other medicines that can also lower your blood pressure. Severe low blood pressure can happen if you lose blood or take certain other medicines.
- **Serotonin syndrome.** Serotonin syndrome is a rare, life-threatening condition that could happen if you take NUCYNTA® ER with SSRIs, SNRIs, MAOIs, triptans, tricyclic antidepressants, tramadol, or certain other medicines. Serotonin syndrome can cause death. See "What should I tell my doctor before taking NUCYNTA® ER?"

  You or someone else should call your doctor or get medical help right away if you have any of these symptoms:
    - you feel agitated or restless, or have hallucinations
    - you pass out (become unconscious). Serotonin syndrome can cause you to go into coma
    - you have a fast heartbeat or feel overheated
    - you have heavy sweating that is not due to activity, or loss of coordination

  You may have nausea, vomiting, or diarrhea with any of the symptoms listed above.
- **NUCYNTA® ER could cause seizures in people who are at risk for having seizures or who have epilepsy. If you have a seizure while taking NUCYNTA® ER, stop taking NUCYNTA® ER and call your doctor right away.**
- **Physical Dependence.** Do not stop taking NUCYNTA® ER or any other opioid without talking to your doctor. You could become sick with uncomfortable withdrawal symptoms because your body has become used to these medicines. Physical dependence is not the same as drug addiction.
- **There is a chance of abuse or addiction with NUCYNTA® ER.** The chance is higher if you are, or have been addicted to or abused other medicines, street drugs, or alcohol, or if you have a history of mental problems.

The most common side effects with NUCYNTA® ER are:

- nausea
- constipation
- headache
- dizziness

Reference ID: 3006589

- sleepiness

Constipation (not enough or hard bowel movements) is a common side effect of pain medicines (opioids), including NUCYNTA® ER, and is unlikely to go away without treatment. Talk to your doctor about dietary change, and the use of laxatives (medicines to treat constipation) and stool softeners to prevent or treat constipation while taking NUCYNTA® ER.

Talk to your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of NUCYNTA® ER. For a complete list, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store NUCYNTA® ER?

- **Keep NUCYNTA® ER in a safe place away from children.**
- **Keep NUCYNTA® ER in the container it comes in.**
- Store NUCYNTA® ER between 68°F to 77°F (20°C to 25°C). Keep NUCYNTA® ER tablets dry.
- **After you stop taking NUCYNTA® ER, flush the unused tablets down the toilet.**

General information about NUCYNTA® ER

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use NUCYNTA® ER for a condition for which it was not prescribed. Do not give NUCYNTA® ER to other people, even if they have the same symptoms you have. It may harm them and even cause death. **Sharing NUCYNTA® ER is against the law.**

This Medication Guide summarizes the most important information about NUCYNTA® ER. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about NUCYNTA® ER that is written for healthcare professionals. For more information about NUCYNTA® ER call 1-800-526-7736 or go to www.NUCYNTAERREMS.com.

What are the ingredients in NUCYNTA® ER?

Active Ingredient: tapentadol HCl

Reference ID: 3006589

Inactive ingredients: polyethylene oxide, hypromellose, polyethylene glycol and alpha-tocopherol (vitamin E).

The film coating contains polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and the colorant FD&C Blue #2 aluminum lake is used for 100-, 150-, 200-, and 250-mg strengths; and additionally, yellow iron oxide is used in 150-mg tablets.

Printing inks for all strengths contain shellac glaze and propylene glycol. The 50, 100, 150, and 200 mg tablet printing ink also contains black iron oxide. The 250 mg tablet printing ink also contains titanium dioxide.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

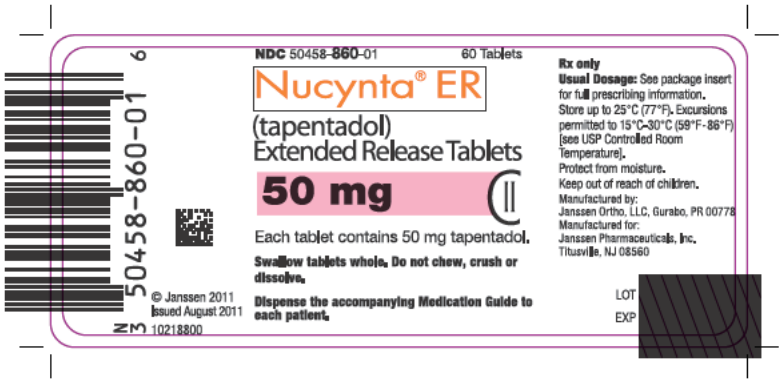
Manufactured by:
Janssen Ortho, LLC
Gurabo, PR 00778

Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

Issued: August 2011

© Janssen Pharmaceuticals, Inc. 2011

Reference ID: 3006589


NDC 50458-860-01
60 Tablets
Nucynta® ER
(tapentadol)
Extended Release Tablets
50 mg
II
Each tablet contains 50 mg tapentadol.
Swallow tablets whole. Do not chew, crush or dissolve.
Dispense the accompanying Medication Guide to each patient.
Rx only
Usual Dosage: See package insert for full prescribing information.
Store up to 25°C (77°F). Excursions permitted to 15°C-30°C (59°F-86°F) [see USP Controlled Room Temperature].
Protect from moisture.
Keep out of reach of children.
Manufactured by:
Janssen Ortho, LLC, Gurabo, PR 00778
Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
LOT
EXP
© Janssen 2011
Issued August 2011
10218800
N 50458-860-01 6

LPI-1013
or
FI-1024

(b) (4)

Nucynta® ER
(tapentadol)
Extended Release Tablets
50 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458860020
LOT:
EXP:

Nucynta® ER
(tapentadol)
Extended Release Tablets
50 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458860020
LOT:
EXP:

10230000

Nucynta® ER
(tapentadol)
Extended Release Tablets
50 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458860020
LOT:
EXP:

Nucynta® ER
(tapentadol)
Extended Release Tablets
50 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458860020
LOT:
EXP:

Nucynta® ER
(tapentadol)
Extended Release Tablets
50 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458860020
LOT:
EXP:

Nucynta® ER
(tapentadol)
Extended Release Tablets
50 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458860020
LOT:
EXP:

Nucynta® ER
(tapentadol)
Extended Release Tablets
50 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458860020
LOT:
EXP:

Nucynta® ER
(tapentadol)
Extended Release Tablets
50 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458860020
LOT:
EXP:

Nucynta® ER
(tapentadol)
Extended Release Tablets
50 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458860020
LOT:
EXP:

Nucynta® ER
(tapentadol)
Extended Release Tablets
50 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458860020
LOT:
EXP:

Nucynta® ER
(tapentadol)
Extended Release Tablets
50 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458860020
LOT:
EXP:

(b) (4)

NDC 50458-**560**-02

Nucynta® ER

(tapentadol) Extended Release Tablets

Swallow tablets whole. Do not chew, crush or dissolve.

Dispense the accompanying Medication Guide to each patient.

Rx only

100 tablets (10 x 10 count blister cards)

Ⅱ

50 mg

PACKAGING NOT CHILD RESISTANT

FOR SCAN INSPECTION OF DATA MATRIX CODE

N 50458-560-02 2

This carton made from recycled materials.

NDC 50458-**560**-02

Nucynta® ER (tapentadol) Extended Release Tablets

Rx only

100 tablets (10 x 10 count blister cards)

PACKAGING NOT CHILD RESISTANT

50 mg

Ⅱ

Usual Dosage: See package insert for full prescribing information.

Store up to 25°C (77°F). Excursions permitted to 15°C-30°C (59°F–86°F) [see USP Controlled Room Temperature].

Protect from moisture.

Keep out of reach of children.

For hospital use only.

Caution: Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed.

PACKAGING NOT CHILD RESISTANT

janssen

© Janssen 2011

Issued August 2011
10230500

Manufactured by:
Janssen Ortho, LLC
Gurabo, PR 00778

Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

LOT

EXP

NDC 50458-**560**-02

Nucynta® ER

(tapentadol) Extended Release Tablets

Rx only

100 tablets (10 x 10 count blister cards)

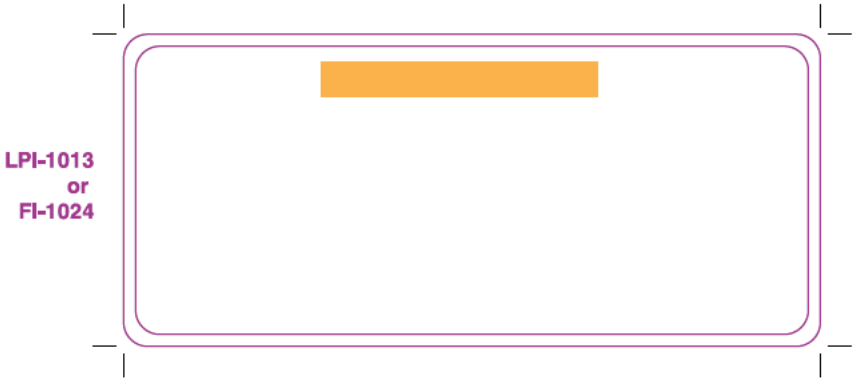
Ⅱ

50 mg

PACKAGING NOT CHILD RESISTANT

(b) (4)

N 50458-861-01 3
NDC 50458-861-01
60 Tablets
Nucynta® ER
(tapentadol)
Extended Release Tablets
100 mg
CII
Each tablet contains 100 mg tapentadol.
Swallow tablets whole. Do not chew, crush or dissolve.
Dispense the accompanying Medication Guide to each patient.
© Janssen 2011
Issued August 2011
10218900
Rx only
Usual Dosage: See package insert for full prescribing information.
Store up to 25°C (77°F). Excursions permitted to 15°C-30°C (59°F-86°F) [see USP Controlled Room Temperature].
Protect from moisture.
Keep out of reach of children.
Manufactured by:
Janssen Ortho, LLC, Gurabo, PR 00778
Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
LOT
EXP


LPI-1013
or
FI-1024

(b) (4)

Nucynta® ER
(tapentadol)
Extended Release Tablets
100 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458861027
LOT:
EXP:

Nucynta® ER
(tapentadol)
Extended Release Tablets
100 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458861027
LOT:
EXP:

10230100

Nucynta® ER
(tapentadol)
Extended Release Tablets
100 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458861027
LOT:
EXP:

Nucynta® ER
(tapentadol)
Extended Release Tablets
100 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458861027
LOT:
EXP:

Nucynta® ER
(tapentadol)
Extended Release Tablets
100 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458861027
LOT:
EXP:

Nucynta® ER
(tapentadol)
Extended Release Tablets
100 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458861027
LOT:
EXP:

Nucynta® ER
(tapentadol)
Extended Release Tablets
100 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458861027
LOT:
EXP:

Nucynta® ER
(tapentadol)
Extended Release Tablets
100 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458861027
LOT:
EXP:

Nucynta® ER
(tapentadol)
Extended Release Tablets
100 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458861027
LOT:
EXP:

Nucynta® ER
(tapentadol)
Extended Release Tablets
100 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458861027
LOT:
EXP:

Nucynta® ER
(tapentadol)
Extended Release Tablets
100 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458861027
LOT:
EXP:

(b) (4)

NDC 50458-**561**-02

Nucynta® ER

(tapentadol) Extended Release Tablets

Swallow tablets whole. Do not chew, crush or dissolve.

Dispense the accompanying Medication Guide to each patient.

Rx only

100 tablets (10 x 10 count blister cards)

CII

100 mg

PACKAGING NOT CHILD RESISTANT

FOR SCAN INSPECTION OF DATA MATRIX CODE

N 50458-561-02 9

This carton made from recycled materials.

NDC 50458-**561**-02

Nucynta® ER (tapentadol) Extended Release Tablets

Rx only
100 tablets
(10 x 10 count blister cards)

PACKAGING NOT CHILD RESISTANT

100 mg

CII

Usual Dosage: See package insert for full prescribing information.

Store up to 25°C (77°F). Excursions permitted to 15°C-30°C (59°F–86°F) [see USP Controlled Room Temperature].

Protect from moisture.

Keep out of reach of children.

For hospital use only.

Caution: Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed.

PACKAGING NOT CHILD RESISTANT

janssen

© Janssen 2011

Issued August 2011
10230600

Manufactured by:
Janssen Ortho, LLC
Gurabo, PR 00778

Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

LOT

EXP

NDC 50458-**561**-02

Nucynta® ER

(tapentadol) Extended Release Tablets

Rx only

100 tablets (10 x 10 count blister cards)

CII

100 mg

PACKAGING NOT CHILD RESISTANT

(b) (4)

NDC 50458-862-01
60 Tablets
Nucynta® ER
(tapentadol)
Extended Release Tablets
150 mg
II
Each tablet contains 150 mg tapentadol.
Swallow tablets whole. Do not chew, crush or dissolve.
Dispense the accompanying Medication Guide to each patient.
Rx only
Usual Dosage: See package insert for full prescribing information.
Store up to 25°C (77°F). Excursions permitted to 15°C-30°C (59°F-86°F) [see USP Controlled Room Temperature].
Protect from moisture.
Keep out of reach of children.
Manufactured by:
Janssen Ortho, LLC, Gurabo, PR 00778
Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
LOT
EXP
© Janssen 2011
Issued August 2011
10219000
N 50458-862-01 0

LPI-1013
or
FI-1024

(b) (4)

Nucynta® ER
(tapentadol)
Extended Release Tablets
150 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458862024
LOT:
EXP:

Nucynta® ER
(tapentadol)
Extended Release Tablets
150 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458862024
LOT:
EXP:

10230200

Nucynta® ER
(tapentadol)
Extended Release Tablets
150 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458862024
LOT:
EXP:

Nucynta® ER
(tapentadol)
Extended Release Tablets
150 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458862024
LOT:
EXP:

Nucynta® ER
(tapentadol)
Extended Release Tablets
150 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458862024
LOT:
EXP:

Nucynta® ER
(tapentadol)
Extended Release Tablets
150 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458862024
LOT:
EXP:

Nucynta® ER
(tapentadol)
Extended Release Tablets
150 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458862024
LOT:
EXP:

Nucynta® ER
(tapentadol)
Extended Release Tablets
150 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458862024
LOT:
EXP:

Nucynta® ER
(tapentadol)
Extended Release Tablets
150 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458862024
LOT:
EXP:

Nucynta® ER
(tapentadol)
Extended Release Tablets
150 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458862024
LOT:
EXP:

Nucynta® ER
(tapentadol)
Extended Release Tablets
150 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458862024
LOT:
EXP:

(b) (4)

NDC 50458-**562**-02

Nucynta® ER

(tapentadol) Extended Release Tablets

Swallow tablets whole. Do not chew, crush or dissolve.

Dispense the accompanying Medication Guide to each patient.

Rx only

100 tablets (10 x 10 count blister cards)

CII

150 mg

PACKAGING NOT CHILD RESISTANT

FOR SCAN INSPECTION OF DATA MATRIX CODE

N 3 50458-562-02 6

This carton made from recycled materials.

NDC 50458-**562**-02

Nucynta® ER

(tapentadol) Extended Release Tablets

Rx only

100 tablets

(10 x 10 count blister cards)

CII

150 mg

PACKAGING NOT CHILD RESISTANT

Usual Dosage: See package insert for full prescribing information.

Store up to 25°C (77°F). Excursions permitted to 15°C-30°C (59°F-86°F) [see USP Controlled Room Temperature].

Protect from moisture.

Keep out of reach of children.

For hospital use only.

Caution: Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed.

PACKAGING NOT CHILD RESISTANT

janssen

© Janssen 2011

Issued August 2011

10230700

Manufactured by:
Janssen Ortho, LLC
Gurabo, PR 00778

Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

LOT

EXP

NDC 50458-**562**-02

Nucynta® ER

(tapentadol) Extended Release Tablets

Rx only

100 tablets (10 x 10 count blister cards)

CII

150 mg

PACKAGING NOT CHILD RESISTANT

(b) (4)

NDC 50458-863-01
60 Tablets
Nucynta® ER
(tapentadol)
Extended Release Tablets
200 mg
II
Each tablet contains 200 mg tapentadol.
Swallow tablets whole. Do not chew, crush or dissolve.
Dispense the accompanying Medication Guide to each patient.
Rx only
Usual Dosage: See package insert for full prescribing information.
Store up to 25°C (77°F). Excursions permitted to 15°C-30°C (59°F-86°F) [see USP Controlled Room Temperature].
Protect from moisture.
Keep out of reach of children.
Manufactured by:
Janssen Ortho, LLC, Gurabo, PR 00778
Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
LOT
EXP
© Janssen 2011
Issued August 2011
10219100
N 50458-863-01 7

LPI-1013
or
FI-1024

(b) (4)

Nucynta® ER
(tapentadol)
Extended Release Tablets
200 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458863021
LOT:
EXP:

Nucynta® ER
(tapentadol)
Extended Release Tablets
200 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458863021
LOT:
EXP:

10230300

Nucynta® ER
(tapentadol)
Extended Release Tablets
200 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458863021
LOT:
EXP:

Nucynta® ER
(tapentadol)
Extended Release Tablets
200 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458863021
LOT:
EXP:

Nucynta® ER
(tapentadol)
Extended Release Tablets
200 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458863021
LOT:
EXP:

Nucynta® ER
(tapentadol)
Extended Release Tablets
200 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458863021
LOT:
EXP:

Nucynta® ER
(tapentadol)
Extended Release Tablets
200 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458863021
LOT:
EXP:

Nucynta® ER
(tapentadol)
Extended Release Tablets
200 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458863021
LOT:
EXP:

Nucynta® ER
(tapentadol)
Extended Release Tablets
200 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458863021
LOT:
EXP:

Nucynta® ER
(tapentadol)
Extended Release Tablets
200 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458863021
LOT:
EXP:

Nucynta® ER
(tapentadol)
Extended Release Tablets
200 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458863021
LOT:
EXP:

(b) (4)

NDC 50458-**563**-02

Nucynta® ER

(tapentadol) Extended Release Tablets

Swallow tablets whole. Do not chew, crush or dissolve.

Dispense the accompanying Medication Guide to each patient.

Rx only

100 tablets (10 x 10 count blister cards)

CII

200 mg

PACKAGING NOT CHILD RESISTANT

FOR SCAN INSPECTION OF DATA MATRIX CODE

N 50458-563-02 3

This carton made from recycled materials.

NDC 50458-**563**-02

Nucynta® ER (tapentadol) Extended Release Tablets

Rx only
100 tablets
(10 x 10 count blister cards)

200 mg

CII

PACKAGING NOT CHILD RESISTANT

Usual Dosage: See package insert for full prescribing information.

Store up to 25°C (77°F). Excursions permitted to 15°C-30°C (59°F–86°F) [see USP Controlled Room Temperature].

Protect from moisture.

Keep out of reach of children.

For hospital use only.

Caution: Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed.

PACKAGING NOT CHILD RESISTANT

janssen

Manufactured for: Janssen Pharmaceuticals, Inc. Titusville, NJ 08560

Manufactured by: Janssen Ortho, LLC Gurabo, PR 00778

Issued August 2011 10230800

© Janssen 2011

LOT

EXP

NDC 50458-**563**-02

Nucynta® ER

(tapentadol) Extended Release Tablets

Rx only

100 tablets (10 x 10 count blister cards)

CII

200 mg

PACKAGING NOT CHILD RESISTANT

(b) (4)

LPI-1013
or
FI-1024

(b) (4)

Nucynta® ER
(tapentadol)
Extended Release Tablets
250 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458864028
LOT:
EXP:

Nucynta® ER
(tapentadol)
Extended Release Tablets
250 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458864028
LOT:
EXP:

Nucynta® ER
(tapentadol)
Extended Release Tablets
250 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458864028
LOT:
EXP:

Nucynta® ER
(tapentadol)
Extended Release Tablets
250 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458864028
LOT:
EXP:

Nucynta® ER
(tapentadol)
Extended Release Tablets
250 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458864028
LOT:
EXP:

Nucynta® ER
(tapentadol)
Extended Release Tablets
250 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458864028
LOT:
EXP:

Nucynta® ER
(tapentadol)
Extended Release Tablets
250 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458864028
LOT:
EXP:

Nucynta® ER
(tapentadol)
Extended Release Tablets
250 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458864028
LOT:
EXP:

Nucynta® ER
(tapentadol)
Extended Release Tablets
250 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458864028
LOT:
EXP:

Nucynta® ER
(tapentadol)
Extended Release Tablets
250 mg
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
(01)10350458864028
LOT:
EXP:

10230400

(b) (4)

NDC 50458-**564**-02

Nucynta® ER

(tapentadol) Extended Release Tablets

Swallow tablets whole. Do not chew, crush or dissolve.

Dispense the accompanying Medication Guide to each patient.

Rx only

100 tablets (10 x 10 count blister cards)

Ⓒ II

250 mg

PACKAGING NOT CHILD RESISTANT

FOR SCAN INSPECTION OF DATA MATRIX CODE

N 50458-564-02 0

This carton made from recycled materials.

NDC 50458-**564**-02

Nucynta® ER (tapentadol) Extended Release Tablets

250 mg

Ⓒ II

PACKAGING NOT CHILD RESISTANT

Rx only

100 tablets

(10 x 10 count blister cards)

Usual Dosage: See package insert for full prescribing information.

Store up to 25°C (77°F). Excursions permitted to 15°C-30°C (59°F–86°F) [see USP Controlled Room Temperature].

Protect from moisture.

Keep out of reach of children.

For hospital use only.

Caution: Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed.

PACKAGING NOT CHILD RESISTANT

janssen

Manufactured for: Janssen Pharmaceuticals, Inc. Titusville, NJ 08560

Manufactured by: Janssen Ortho, LLC Gurabo, PR 00778

Issued August 2011 10230900

© Janssen 2011

LOT

EXP

NDC 50458-**564**-02

Nucynta® ER (tapentadol) Extended Release Tablets

250 mg

Ⓒ II

PACKAGING NOT CHILD RESISTANT

Rx only

100 tablets

(10 x 10 count blister cards)

(b) (4)