

Initial Date of Approval: August 25, 2011

NDA 200533
NUCYNTA[®] ER (tapentadol) tablets
Opioid analgesic
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560
1-800-526-7736

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOALS

The goals of the NUCYNTA[®] ER REMS are:

- To inform patients and healthcare professionals about the potential for abuse, misuse, overdose, and addiction to NUCYNTA[®] ER.
- To inform patients and healthcare professionals about the safe use of NUCYNTA[®] ER.

II. REMS ELEMENTS

A. Medication Guide

In accordance with 21CFR208.24 a Medication Guide will be dispensed with each NUCYNTA[®] ER prescription.

This Medication Guide is part of the REMS and is appended.

B. Elements to Assure Safe Use

1. Healthcare professionals who prescribe NUCYNTA[®] ER will receive training.
 - a. Janssen Pharmaceuticals, Inc. will ensure that training will be provided to healthcare professionals who prescribe NUCYNTA[®] ER. To become trained, each prescriber will be provided with the NUCYNTA[®] ER educational materials. Training will address the following:
 - i. Proper patient selection;
 - ii. Appropriate NUCYNTA[®] ER dosing and administration;
 - iii. General principles of safe opioid use including information about opioid abuse and how to identify patients who are at risk for addiction;

- iv. Potential abuse, misuse, overdose, and addiction from exposure to opioids, including NUCYNTA[®] ER;
 - v. Risks of NUCYNTA[®] ER including:
 - 1. The risk of overdose caused by exposure to an essentially immediate-release form of tapentadol by consuming split, broken, chewed, crushed, or dissolved NUCYNTA[®] ER tablets;
 - 2. The risk of overdose in patients who have not developed tolerance to the sedating or respiratory-depressant effects of opioids when using an initial dose of NUCYNTA[®] ER greater than 50 mg twice daily (total daily dose of 100 mg);
 - 3. The risk of addiction from exposure to NUCYNTA[®] ER
 - vi. Information to counsel patients on the need to store opioid analgesics safely out of the reach of children and household acquaintances, and the need to properly dispose of unused drugs when no longer needed by the patient and not to share drugs with anyone for any reason; and
 - vii. The importance of dispensers providing each patient a Medication Guide with each prescription and instructing the patient to read it.
- b. Janssen Pharmaceuticals, Inc. will ensure that within 3 weeks after approval of the NUCYNTA[®] ER REMS, a Dear Healthcare Professional letter will be mailed to prescribers most experienced in treating chronic pain with opioid agonists, including pain specialists, physiatrists, and primary care physicians. This letter is designed to convey and reinforce the risks of abuse, misuse, overdose, and addiction of NUCYNTA[®] ER as well as the need to complete the NUCYNTA[®] ER REMS Education Program. This letter will be available on the Janssen Pharmaceuticals, Inc. website (www.NUCYNTAERREMS.com) for a time period of 1 year from the date of the mailing.
- c. The mailings will also include the following NUCYNTA[®] ER REMS training materials:
- i. A copy of the full Prescribing Information (PI)
 - ii. NUCYNTA[®] ER Medication Guide

iii. Prescribing NUCYNTA[®] ER Healthcare Professional Education Program: A Guide for Healthcare Professionals Who Intend to Prescribe NUCYNTA[®] ER

iv. NUCYNTA[®] ER Education Confirmation Form

- d. Additional printed training material will be available through field-force distribution and by calling the toll-free number at Janssen Pharmaceuticals, Inc. (1-800-526-7736).
- e. The training material will also be available for download at www.NUCYNTAERREMS.com.
- f. Janssen Pharmaceuticals, Inc. will maintain a list of all prescribers who have completed the NUCYNTA[®] ER REMS Education Program.

Prescribers will be re-trained every two years or following substantial changes to the NUCYNTA[®] ER REMS. Substantial changes may include changes to the NUCYNTA[®] ER Full Prescribing Information, NUCYNTA[®] ER Medication Guide, or NUCYNTA[®] ER REMS that require substantial modification of the educational materials.

The following materials are part of the REMS and are appended:

- Dear Healthcare Professional Letter,
- Prescribing NUCYNTA[®] ER Healthcare Professional Education Program: A Guide for Healthcare Professionals Who Intend to Prescribe NUCYNTA[®] ER, NUCYNTA[®] ER Education Confirmation Form, and
- NUCYNTA[®] ER REMS website screenshots.

C. Implementation System

Because NUCYNTA[®] ER can be approved without the Elements to Assure Safe Use described under FDCA 505-1(f)(3)(B), (C), and (D) of the Act, an implementation system is not required.

D. Timetable for Submission of Assessments

Janssen Pharmaceuticals, Inc. will submit REMS Assessments to the FDA every 6 months for the first year from the date of approval of the REMS, and annually thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment will

conclude no earlier than 60 days before the submission date for that assessment. Janssen Pharmaceuticals, Inc. will submit each assessment so that it will be received by the FDA on or before the due date.

APPENDIX 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.
 - 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 split, break, 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:

- 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.

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?"

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:

- **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
- 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

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

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APPENDIX 2

DEAR HEALTHCARE PROFESSIONAL LETTER

Important Drug Warning

Risk of potential abuse, misuse, overdose, and addiction for NUCYNTA[®] ER (tapentadol) extended-release oral tablets C-II

[Date]

Dear Healthcare Professional:

Janssen Pharmaceuticals, Inc. is introducing NUCYNTA[®] ER, 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.

NUCYNTA[®] ER has a Risk Evaluation and Mitigation Strategy (REMS) to educate prescribers about the potential abuse, misuse, overdose and addiction from exposure to NUCYNTA[®] ER. The Food and Drug Administration (FDA) determined that a REMS was necessary for NUCYNTA[®] ER to ensure that the benefits of the drug outweigh the risks.

Prior to prescribing NUCYNTA[®] ER, prescribers are encouraged to review the NUCYNTA[®] ER Healthcare Professional Educational Program and complete the NUCYNTA[®] ER Education Confirmation Form.

You may complete and submit the NUCYNTA[®] ER Education Confirmation Form electronically at www.NUCYNTAERREMS.com or fax the completed form to Janssen Pharmaceuticals, Inc. at 1-800-282-7832. A confirmation of receipt will be emailed or faxed to you.

The goals of the REMS for NUCYNTA[®] ER are:

- Goal 1: To inform patients and healthcare professionals about the potential for abuse, misuse, overdose, and addiction to NUCYNTA[®] ER
- Goal 2: To inform patients and healthcare professionals about the safe use of NUCYNTA[®] ER

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 prescribing healthcare professional or dispensing pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

NUCYNTA[®] ER is contraindicated in:

- Patients who have impaired pulmonary function such as significant respiratory depression, acute or severe bronchial asthma or hypercapnia in unmonitored settings or the absence of resuscitative equipment.
- Patients who have or are suspected of having paralytic ileus
- Patients who are receiving monoamine oxidase (MAO) inhibitors or the use of MAO inhibitors within the last 14 days
- Patients with a known hypersensitivity to the active substance, tapentadol, or any component of the product.

NUCYNTA[®] ER is **NOT** intended for use as an as needed analgesic.

NUCYNTA[®] ER is **NOT** indicated for the management of acute or post operative pain.

Serious adverse reactions which may be associated with NUCYNTA[®] ER therapy in clinical use are those observed with opioid analgesics, including respiratory depression, impaired mental and physical abilities, seizures and additive CNS depressive effects when used in conjunction with alcohol, other opioids, or illicit drugs. The most common adverse events ($\geq 10\%$) were nausea, dizziness, constipation, headache and somnolence.

The co-administration of alcohol with NUCYNTA ER may result in increased serum levels and a potentially fatal overdose of tapentadol. Patients must not consume alcoholic beverages while using NUCYNTA[®] ER.

Refer to the full prescribing information, with boxed warning for detailed safety information

Prescribing and Dispensing

Refer to the full prescribing information for detailed prescribing and dispensing information.

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.

When prescribing and dispensing opioid products, such as NUCYNTA[®] ER, healthcare professionals should adopt behaviors that decrease the likelihood of abuse and misuse of the opioid product. Examples of these behaviors include proper assessment of the patient, periodic re-evaluation of therapy, proper dispensing, and correct storage, handling and disposal of the opioid drug. Also, healthcare professionals are advised to keep careful record-keeping of prescribing information, including quantity, frequency, and renewal requests.

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. Titrate patients to adequate analgesia with dose increases of 50 mg no more than twice daily every 3 days. The maximum allowed daily dose of NUCYNTA[®] ER is 250 mg twice daily (500 mg as a total daily dose).

There are no adequate data on the direct conversions from other opioids to NUCYNTA[®] ER. The initial dose of NUCYNTA[®] ER in patients previously taking other opioids is 50 mg twice daily, titrated to an effective and tolerable dose within the therapeutic range of 100 mg to 250 mg twice daily. Do not exceed a total daily dose of NUCYNTA[®] ER of 500 mg.

Patients receiving NUCYNTA[®] (immediate release formulation) may be converted to NUCYNTA[®] ER by using the equivalent total daily dose of NUCYNTA[®] and dividing it into two equal doses separated by approximately 12 hour intervals.

Pain relief and adverse reactions should be frequently assessed. In clinical practice, titration of the total daily dose of NUCYNTA[®] ER should be based upon the amount of supplemental opioid utilization, severity of the patient's pain, and patient's ability to tolerate NUCYNTA[®] ER. Patients should be titrated to a dose proving a meaningful improvement of pain with acceptable tolerability.

When discontinuing NUCYNTA[®] ER, potential withdrawal symptoms may be reduced by tapering the dose of NUCYNTA[®] ER.

Safe Administration

Refer to the full prescribing information for detailed safety information

NUCYNTA[®] ER tablets are to be swallowed whole, one at a time, and are not to be split, broken, chewed, dissolved, or crushed. Taking split, broken, chewed, dissolved, or crushed NUCYNTA[®] ER tablets could lead to rapid release and absorption of a potentially fatal dose of tapentadol. Patients should not pre-soak, lick or otherwise wet the tablet prior to placing into their mouth. Tablets must be taken one at a time with enough water to ensure complete swallowing immediately after placing in their mouth.

Abuse and Dependence

Refer to the full prescribing information for detailed safety information

Abuse may occur by taking intact tablets without legitimate purpose, by crushing or snorting the crushed formulation or by injecting a solution from the crushed formulation. The risk of fatal overdose is further increased when tapentadol is abused concurrently with alcohol or other CNS depressants, including other opioids.

Patient Counseling

Patients should be counseled about the importance of storing opioid analgesics including NUCYNTA[®] ER, safely and out of the reach of children, other household members, visitors and pets.

Patients should be instructed against use by individuals other than the patient, for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death.

You are strongly advised to discuss the risk associated with NUCYNTA[®] ER with your patients and/or their caregivers and encourage them to read the Medication Guide. This Medication Guide contains important information on the safe and effective use of NUCYNTA[®] ER. The NUCYNTA[®] ER Medication Guide should be provided to patients each time NUCYNTA[®] ER is dispensed.

Medication Guide

Enclosed with this letter, you will find the NUCYNTA[®] ER Medication Guide. Pharmacists and other healthcare professionals who dispense NUCYNTA[®] ER have a responsibility to provide a Medication Guide directly to each patient or caregiver with each prescription according to Federal law 21 CFR 208.24(e). Additional copies of the NUCYNTA[®] ER Medication Guide are available by download from www.NUCYNTAERREMS.com, by contacting our Customer Communications Center at 1-800-526-7736 or by asking your NUCYNTA[®] ER representative.

Education Materials

Also enclosed, you will find a copy of the Prescribing NUCYNTA[®] ER Healthcare Professional Education Program: A Guide for Healthcare Professionals Who Intend to Prescribe NUCYNTA[®] ER, which contains information about the appropriate use of NUCYNTA[®] ER and information that can be shared when you counsel patients or their caregivers on the appropriate use, possible risks, and safe storage of NUCYNTA[®] ER. The Education Program also includes information on:

- General opioid risks
- Appropriate patient selection
- Appropriate dosing and administration

- Possible side effects and safety risks
- Risks associated with concomitant drug and alcohol use
- How to identify drug abuse and patients at risk for addiction
- Recommendations for the security and safe storage of the medication

Other Education Program materials include the Prescribing Information, Medication Guide, and Education Confirmation Form. We strongly recommend that you read the Education Program materials before prescribing NUCYNTA[®] ER.

You can find the Education Program and other helpful information on our website: www.NUCYNTAERREMS.com.

Adverse Event Reporting

Prescribers should report all adverse events associated with the use of NUCYNTA[®] ER to Janssen Pharmaceuticals, Inc. at 1-800-526-7736.

If you have any questions about NUCYNTA[®] ER including any information found in this letter, the Full Prescribing Information and Medication Guide for NUCYNTA[®] ER, and the NUCYNTA[®] ER Education Program, please call our Customer Communications Center at 1-800-526-7736.

Sincerely,

Paul Chang, MD
Vice President Medical Affairs
Internal Medicine

APPENDIX 3

PRESCRIBING NUCYNTA[®] ER HEALTHCARE PROFESSIONAL EDUCATION PROGRAM: A GUIDE FOR HEALTHCARE PROFESSIONALS WHO INTEND TO PRESCRIBE NUCYNTA[®] ER

NUCYNTA[®] ER Healthcare Professional Education Program: A Guide for Healthcare Professionals Who Intend to Prescribe NUCYNTA[®] ER

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

Potential for Abuse

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

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

Proper Patient Selection

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

Limitations of Use

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

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

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

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

To find this and other information about NUCYNTA[®] ER, please go to our website: www.NUCYNTAERREMS.com.

Janssen Pharmaceuticals, Inc. is dedicated to providing you with the most up-to-date knowledge about our products; if you have any questions about NUCYNTA[®] ER including information found in the Full Prescribing Information and Medication Guide for NUCYNTA[®] ER, and/or this Education Program, please call our Customer Communications Center at 1-800-526-7736.

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1. INTRODUCTION

NUCYNTA[®] ER (tapentadol) extended-release oral tablet 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

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

NUCYNTA[®] ER is not indicated for the management of acute or post operative pain.

To ensure that the benefits of NUCYNTA[®] ER outweigh the potential risks, a Risk Evaluation and Mitigation Strategy (REMS) has been implemented in response to a requirement of the United States Food and Drug Administration (FDA).

The goals of the REMS are to:

- To inform patients and healthcare professionals about the potential for abuse, misuse, overdose, and addiction to NUCYNTA[®] ER and
- To inform patients and healthcare professionals about the safe use of NUCYNTA[®] ER.

The NUCYNTA[®] ER Healthcare Professional Education Program: A Guide for Healthcare Professionals Who Intend to Prescribe NUCYNTA[®] ER is part of the REMS. The purpose of this education program is to provide prescribers with important safety information about NUCYNTA[®] ER so they can prescribe, dispense and counsel patients appropriately about the potential risk of NUCYNTA[®] ER misuse, abuse and addiction. The NUCYNTA[®] ER Healthcare Professional Education Program includes information on:

- General opioid use, including information about opioid abuse and how to identify those at risk for addiction
- The risk of abuse, misuse, overdose, and addiction from exposure to opioids, including NUCYNTA[®] ER
- The specific risks associated with NUCYNTA[®] ER
- The importance of providing each patient the NUCYNTA[®] ER Medication Guide with each prescription and instructing the patient to read it

Please note that there are two formulations for tapentadol, the active ingredient of NUCYNTA[®] and NUCYNTA[®] ER. NUCYNTA[®] ER is the extended release oral tablet

formulation of tapentadol. NUCYNTA[®] is the immediate release oral tablet formulation of tapentadol. The NUCYNTA[®] ER Healthcare Professional Education Program provides information to differentiate NUCYNTA[®] ER oral tablets from NUCYNTA[®] oral tablets.

Prior to prescribing NUCYNTA[®] ER, prescribers are encouraged to read the educational materials included in the accompanying NUCYNTA[®] ER Healthcare Professional Education Program and complete the NUCYNTA[®] ER Education Confirmation Form.

The educational materials include:

- Prescribing information
- Medication Guide
- Prescribing NUCYNTA[®] ER Healthcare Professional Education Program: A Guide for Healthcare Professionals Who Intend to Prescribe NUCYNTA[®] ER
- NUCYNTA[®] ER Education Confirmation Form

After completing the NUCYNTA[®] ER Education Confirmation Form, submit the form to Janssen Pharmaceuticals, Inc. electronically at www.NUCYNTAERREMS.com or via fax at 1-800-282-7832. A confirmation of receipt will be emailed or faxed to you.

2. GENERAL OPIOID USE: RISKS AND RISK FACTORS

Misuse, Abuse and Addiction of Prescription Opioids

All patients who are prescribed long-acting opioid analgesics, including NUCYNTA[®] ER, should be carefully monitored for signs and symptoms of abuse and addiction. Use of long-acting opioid analgesic products carries the risk of addiction even under appropriate medical use.²

Addiction is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive drug use, continued drug use despite harm, and drug craving.³ Proper assessment of the patient, proper prescribing practices, periodic re-evaluation and proper use and handling are appropriate measures that help to minimize abuse and addiction of opioid drugs. In addition, several drug abuse screening tests are available. Careful recordkeeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Overdose of Prescription Opioids

Respiratory depression is the most significant serious adverse event risk associated with opioid analgesics and it can result in death. Respiratory depression can occur with usual therapeutic doses of long-acting opioid analgesics. The risk of respiratory depression is increased in elderly or debilitated patients or following large initial opioid doses in any patient who has not been taking opioids and is not tolerant to the effects of long-acting opioids. The risk of overdose and death is greater if the opioid is taken together with alcohol, other opioids, illicit drugs, or drugs that can also depress respiratory drive or consciousness.

The co-administration of alcohol with NUCYNTA ER may result in increased serum levels and a potentially fatal overdose of tapentadol. Patients must not consume alcoholic beverages while using NUCYNTA[®] ER.

Risk Factors for Abuse²

- Personal or family history of substance abuse, including drug or alcohol abuse or addiction
- History of treatment for opioid abuse or addiction
- Presence of mental illness (e.g., major depression or general anxiety)
- Psychological stress

Risk Factors and Signs and Symptoms for Addiction^{2,4}

- Physical signs of opioid abuse (e.g., unkempt appearance, weight loss, sniffles, watery eyes, cough, nausea; lethargy, and drowsiness)
- Active substance abuse disorder
- Major, untreated psychopathology
- Skin damage caused by repeated injections
- Positive urine drug screen for illicit drugs
- Aberrant drug related behaviors
 - obtaining opioid prescriptions from more than one physician (“doctor shopping”)
 - concurrent abuse of related illicit drugs
 - altering or forging prescriptions
 - frequent reports of lost or stolen prescriptions
 - repeated unauthorized opioid dose escalations despite warnings
 - emergency calls or visits near the end of office hours
 - refusal to undergo appropriate examination, testing or referral

- reluctance to provide prior medical records or contact information for other treating healthcare professionals

Risk Factors for Overdose

- Elderly or debilitated patients
- Children
- Opioid-non tolerant patients
- Concomitant sedating agents that suppress respiration
- Impaired pulmonary function
- Abuse, especially
 - If tablets are split, broken, chewed, dissolved, crushed, or injected
 - With concurrent abuse of alcohol or other sedating substances

3. NUCYNTA[®] ER RISKS

Misuse, Abuse, and Addiction

NUCYNTA[®] ER contains tapentadol, which is a morphine-like opioid agonist and a Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing NUCYNTA[®] ER in situations where the prescribing healthcare professional or dispensing pharmacist is concerned about an increased risk of misuse, abuse, addiction, and diversion. Abuse may occur by taking intact tablets without legitimate purpose, by crushing or snorting the crushed formulation or by injecting a solution from the crushed formulation. If abused by parenteral routes, the tablet excipients may cause serious or even fatal complications. The risk of fatal overdose is increased when NUCYNTA[®] ER is abused concurrently with alcohol or other CNS depressants, including other opioids.

Overdose

Experience with NUCYNTA[®] ER overdose is very limited. Preclinical data suggest that symptoms similar to those of other centrally acting analgesics with mu-opioid receptor agonist activity are to be expected upon taking excessive amounts of tapentadol. Any person who takes more than the recommended doses of a long-acting opioid including NUCYNTA[®] ER, especially those not tolerant to the effects of opioids, is at risk for overdose and death. The risk of a potentially fatal overdose may be increased by exposure to an essentially immediate-release form of tapentadol by consuming split, broken, chewed, dissolved, crushed, or injected NUCYNTA[®] ER tablets. The risk of overdose may be increased in patients who have not developed tolerance to the sedating

or respiratory-depressant effects of opioids when using an initial dose of NUCYNTA[®] ER greater than 50 mg twice daily (total daily dose of 100 mg).

Adverse Events

Serious adverse reactions which may be associated with opioid analgesics and NUCYNTA[®] ER therapy include respiratory depression, impaired mental and physical abilities, seizures and additive CNS depressive effects when used in combination with alcohol, other opioids or illicit drugs.

The most common adverse events ($\geq 10\%$) seen with NUCYNTA[®] ER in clinical trials were nausea, dizziness, constipation, headache and somnolence.

Please see the full Prescribing Information and Medication Guide for a complete review of the risks associated with the use of NUCYNTA[®] ER

Information Essential for Safe Administration, Storage, and Disposal

This education program is specific to NUCYNTA[®] ER, however, some information on NUCYNTA[®] (tapentadol) immediate-release oral tablets is provided.

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.

Keep NUCYNTA[®] ER in the childproof container and store it in a safe or locked away location from children and household acquaintances to protect it from being used inappropriately or stolen. Accidental exposure in children is an emergency and can result in death. Properly dispose of unused drug by flushing down the toilet. Unused drug should never be given to anyone for any reason.

Both NUCYNTA[®] (tapentadol) immediate-release oral tablets and NUCYNTA[®] ER (tapentadol) extended-release oral tablets are available in 50 mg and 100 mg tablet strengths. However, the two formulations and their package labels are designed to look very different and the tablet shape, color, and markings can be used to visually differentiate the immediate-release and extended-release formulations as described.

NUCYNTA[®] ER is available in five tablet dose strengths: 50 mg, 100 mg, 150 mg, 200 mg, and 250 mg.



- 50 mg: white, oblong-shaped tablets with a black print “OMJ 50” on one side
- 100 mg: light-blue, oblong-shaped tablets with a black print “OMJ 100” on one side
- 150 mg: blue-green, oblong-shaped tablets with a black print “OMJ 150” on one side
- 200 mg: blue, oblong-shaped tablets with a depression in the middle running lengthwise on each side and a black print “OMJ 200” on one side
- 250 mg: dark blue, oblong-shaped tablets with a depression in the middle running lengthwise on each side and a white print “OMJ 250” on one side

Tablet Appearance of NUCYNTA[®] ER (tapentadol) extended-release oral tablets



NUCYNTA[®] (tapentadol) immediate-release oral tablets are available in three dose strengths: 50 mg, 75 mg, and 100 mg.

- 50 mg: yellow, round and biconvex-shaped tablets debossed with “O-M” on one side and “50” on the other side
- 75 mg: yellow-orange, round and biconvex-shaped tablets debossed with “O-M” on one side and “75” on the other side
- 100 mg: orange, round and biconvex-shaped tablets debossed with “O-M” on one side and “100” on the other side

Tablet Appearance of NUCYNTA[®] (tapentadol) immediate-release oral tablets



4. PROPER PATIENT SELECTION

Selection of patients for treatment with NUCYNTA[®] ER should be determined by the same principles that apply to the prescribing of any opioid analgesic for continuous, around-the-clock treatment over an extended period of time. Treatment should be individualized in every case using a progressive plan of pain management as outlined by the World Health Organization⁵, the Federation of State Medical Boards Model Policy^{6,7}, and the American Pain Society².

Before prescribing an around the clock opioid analgesic, like NUCYNTA[®] ER, the following clinical guidelines have been recommended.²

- Perform a comprehensive physical examination that includes
 - patient and family history,
 - physical examination,
 - appropriate diagnostic testing before and on an ongoing basis during chronic opioid treatment.
- Obtain a comprehensive pain history including:
 - nature and intensity of the pain
 - the effect of pain on physical, mental, and social function
 - current and past medications
 - other treatments for chronic pain (e.g., surgery, anesthetic interventions, etc)

- Assess the risk of substance abuse, misuse, or addiction using patient history, examination, and/or a validated risk assessment tool
- Consider a trial period of chronic opioid treatment if:
 - chronic non-cancer pain is moderate or severe,
 - potential therapeutic benefits outweigh or are likely to outweigh potential harms
- Discuss treatment goals, expectations, potential risks, and possible treatment alternatives before starting and on an ongoing basis during chronic opioid treatment
- Ascertain patient understanding of the treatment guidelines and responsibilities that will determine continuation or discontinuation of chronic opioid treatment before treatment is started (e.g., Opioid Treatment Agreement)

All patients receiving opioids like NUCYNTA[®] ER should be routinely monitored for signs of misuse, abuse and addiction.

For patients with history of psychiatric illness requiring NUCYNTA[®] ER, consider:

- Frequent and stringent monitoring
- Consulting with a mental health or addiction specialist
- Ongoing evaluations for appropriateness of opioid treatment
- Restructuring medication therapy
- Referral for assistance in chronic pain management
- Discontinuing treatment if appropriate

Who May be Appropriate for Treatment With NUCYNTA[®] ER

- Adult patients with moderate to severe chronic pain
- Patients who require a continuous, around the clock opioid analgesic for an extended period of time
 - NUCYNTA[®] ER is not intended for use as an as-needed analgesic or for patients with mild pain
 - NUCYNTA[®] ER is not indicated for acute pain expected to persist for a short period of time or for postoperative pain

Some Patients Should Never Receive NUCYNTA[®] ER

- Patients who have impaired pulmonary function (significant respiratory depression)
- Patients who have acute or severe bronchial asthma
- Patients who have hypercapnia in unmonitored settings or the absence of resuscitative equipment
- Patients who have or are suspected to have paralytic ileus

- Patients receiving concomitant treatment with a monoamine oxidase inhibitor (MAOI) or use of a MAOI within the last 14 days
- NUCYNTA[®] ER is contraindicated in patients with a known hypersensitivity to the active substance, tapentadol, or any component of the product.

5. DOSING AND ADMINISTRATION

NUCYNTA[®] ER is available in five tablet dose strengths: 50 mg, 100 mg, 150 mg, 200 mg, and 250 mg. The recommended NUCYNTA[®] ER total daily dose is 100 mg to 250 mg twice daily approximately every 12 hours with or without food. The maximum total daily dose should not exceed 500 mg.

- 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 not be split, broken, chewed, dissolved, or crushed
- NUCYNTA[®] ER tablets should be taken one tablet at a time. It is recommended to take each tablet whole with enough water to ensure complete swallowing immediately after placing in the mouth.

Individualizing the Dosage of NUCYNTA[®] ER

Individualize dosing in every case according to the patient's:

- Type, current and anticipated intensity of the patient's pain (e.g., stable, increasing, decreasing)
- Age, general condition, and medical status
- Previous experience with opioid analgesics
- Recent opioid exposure and degree of opioid tolerance (if any); consideration of incomplete cross-tolerance between opioid analgesics
- Use of concomitant medications
- The physician's ability to provide follow-up and oversight of treatment

Patients should be titrated to a dose providing a meaningful improvement of pain with acceptable tolerability.

For elderly patients with normal renal and hepatic function, in general, recommended dosing is the same as for younger adult patients with normal renal and hepatic function.

Initiating Therapy

It is critical to initiate the dosing regimen for each patient individually. Attention should be given 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.

Although the maximum approved total daily dose of immediate-release formulation NUCYNTA[®] 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.

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

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 per day 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.

Monitoring and Assessing Ongoing Treatment With NUCYNTA[®] ER

Clinical guidelines have recommended regular monitoring and reassessment of patients taking chronic opioid treatment.³

Periodic review should include the regular evaluation and documentation of:

- Pain intensity and level of physical function
- Progress toward achieving the agreed upon therapeutic goals
- Any changes in coexisting medical or psychiatric conditions
- Presence of adverse effects
- Adherence to prescribed therapies (pharmacologic and non-pharmacologic)
- Assessment of risk for aberrant drug-related behaviors, addiction, or diversion. Assessments of the patient's risk may include screening instruments (questionnaires), pill counts, urine drug screening, family member or caregiver interviews, and pharmacy-based prescription monitoring programs.

6. PATIENT COUNSELING

Healthcare professionals 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.
- 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.
- 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

mouth. Advise patients to take each tablet with enough water to ensure complete swallowing immediately after placing in the mouth.

- Advise patients using NUCYNTA[®] ER chronically (for several weeks) to contact their health care 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. 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.
- Advise patients that NUCYNTA[®] ER can cause respiratory depression and hypotension.
- 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.
- Advise patients to notify their physician if they become pregnant or intend to become pregnant during treatment with NUCYNTA[®] ER.
- Advise patients not to breast-feed an infant during treatment with NUCYNTA[®] ER.
- 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. 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).
- Advise patients not to take alcoholic beverages, or prescription or non-prescription medications containing alcohol, while on NUCYNTA[®] ER therapy. The co-administration of alcohol with NUCYNTA[®] ER may result in increased serum levels and a potentially fatal overdose of tapentadol.
- 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.

REFERENCES

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5. World Health Organization. WHO Pain Relief Ladder - <http://www.who.int/cancer/palliative/painladder/en/index.html>
6. Federation of State Medical Boards. Model Policy for the Use of Controlled Substances for the Treatment of Pain – <http://www.fsmb.org/PAIN/modelpolicy.html>
7. Federation of State Medical Boards. Resources for Pharmacovigilance and Pain Management – <http://www.fsmb.org/PAIN/resource.html>

APPENDIX 4

NUCYNTA[®] ER Education Confirmation Form

Education Confirmation Form

NUCYNTA[®] ER

The purpose of this form is to confirm you have read the REMS Educational Materials for NUCYNTA[®] ER, understand the major risks associated with NUCYNTA[®] ER, and know how to appropriately educate patients to whom NUCYNTA[®] ER is prescribed. The information you provide on this form will only be used by Janssen Scientific Affairs, LLC for this purpose and shared with affiliates and third parties involved in the fulfillment of this activity. All information you provide below will be governed by our Privacy Policy found at www.NUCYNTAERREMS.com. By submitting this form, you have read, understand, and agree to these conditions.

Instructions: Please complete and submit the Education Confirmation Form either electronically by visiting www.NUCYNTAERREMS.com or by completing this printed form and faxing all 3 pages to Janssen Pharmaceuticals, Inc. at 1-800-282-7832. Tear along perforation before faxing. A confirmation of receipt will be emailed or faxed to you.

Completion, submission, and results of this confirmation form will not affect your ability to prescribe NUCYNTA[®] ER.

Prescriber Information (please fill in all fields completely)

Prescriber Name, Credentials _____

DEA Registration Number _____

Specialty _____

Affiliation _____

Address _____

City _____ State _____ Zip _____

Office Phone _____ Office Fax _____

E-mail _____

Office Manager Name _____

By signing this form, I acknowledge that I have read and understand the REMS Educational Materials for NUCYNTA[®] ER.

Prescriber's Signature _____

How do you want to be confidentially informed of the results of your NUCYNTA[®] ER Education Confirmation Form?

Via E-mail _____ Via Fax _____

Date the form was completed _____

For additional educational information, go to www.NUCYNTAERREMS.com or call 1-800-526-7736.

1. For which of the following conditions can NUCYNTA[®] ER be appropriately prescribed?

- For moderate-to-severe acute pain in patients 18 years of age or older when pain relief is needed for a short period of time
- For moderate-to-severe chronic pain in adults when a continuous, around-the-clock opioid analgesic is needed for an extended time
- For moderate-to-severe post-operative pain in patients not tolerant to opioid analgesics
- For mild pain in adults who need treatment with a long-acting opioid
- For sudden or episodic pain that requires treatment with an as-needed analgesic

2. Which of the following are risk factors for addiction? (check all that apply)

- Prior treatment for alcoholism
- History of major untreated psychopathology
- Chronic severe pain
- Positive urine drug test for illicit drugs
- Aberrant drug-related behaviors, like forging prescriptions

3. The recommended starting dose of NUCYNTA[®] ER for patients who are not tolerant to opioids is 100 mg twice daily approximately every 12 hours with or without food.

- True
- False

4. What is the only safe way to take NUCYNTA[®] ER?

- Chewing the tablet before swallowing
- Swallowing the tablet after it has been crushed
- Swallowing the tablet whole with the aid of liquids
- Dissolving the tablet in a glass of water before swallowing
- Breaking the tablet before swallowing

5. Which of the following are risks of NUCYNTA[®] ER treatment? (check all that apply)

- Respiratory depression
- Opioid Abuse

- Drug Addiction
- Overdose
- Serotonin Syndrome

6. Patients should be counseled to read the NUCYNTA[®] ER Medication Guide that they receive with each and every prescription because important information may have changed.

- True
- False

7. Which of the following statements are true about the safe storage of NUCYNTA[®] ER? (check all that apply)

- NUCYNTA[®] ER should be kept in the childproof container and out of reach of children
- NUCYNTA[®] ER should be kept in a convenient and easily accessible location such as an unlocked medicine cabinet
- NUCYNTA[®] ER should be kept hidden and inaccessible to children and household acquaintances
- NUCYNTA[®] ER should be given to a friend for safe-keeping

8. Which of the following statements regarding NUCYNTA[®] ER dosing is not correct?

- The recommended NUCYNTA[®] ER total daily dose is 100 mg to 250 mg twice daily approximately every 12 hours with or without food
- After initiating the recommended starting dose in patients who are not opioid tolerant, the dose of NUCYNTA[®] ER may be titrated up by 50 mg twice daily every 3 days. The dose should be titrated within the therapeutic range of 100 mg to 250 mg twice daily.
- Daily doses of NUCYNTA[®] ER above 500 mg are recommended in patients who have refractory chronic pain
- For appropriate patients with chronic pain, NUCYNTA[®] (tapentadol) immediate-release oral tablets can be switched to NUCYNTA[®] ER by dividing the total daily dose of NUCYNTA[®] into 2 equal doses that will be taken twice daily approximately every 12 hours with or without food

Appendix 4

NUCYNTA ER Website Screenshots

www.NUCYNTAERREMS.com

When accessing NUCYNTAERREMS.COM, the user will proceed to the page below.

This page will summarize the program, provide downloadable PDFs, and link to the Prescribing NUCYNTA® ER Healthcare Professional Education Program Brochure and Confirmation Form.

Access the Prescribing
NUCYNTA® ER Healthcare
Professional Education
Program Brochure and
Confirmation Form

Start Here >

NUCYNTA® ER Risk Evaluation and Mitigation Strategy (REMS)

A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage the known or potential serious risk(s) associated with a drug product, and is required by the Food and Drug Administration (FDA) to ensure that the benefits of the drug outweigh its risks.

In order for Janssen Pharmaceuticals, Inc. to communicate the serious risks of NUCYNTA® ER, Janssen Pharmaceuticals, Inc. has worked with the FDA to develop materials to communicate these risks.

The REMS program is designed to inform patients and healthcare professionals (HCPs) about the risks of NUCYNTA® ER. To learn more about the serious risks, including potential for abuse, misuse, overdose, and addiction, [click here](#).

The goals of the REMS for NUCYNTA® ER are:

Goal 1: To inform patients and HCPs about the potential for abuse, misuse, overdose, and addiction to NUCYNTA® ER.

Goal 2: To inform patients and Healthcare Professionals about the safe use of NUCYNTA® ER.

NUCYNTA® ER should only be prescribed in accordance with the NUCYNTA® ER REMS, including HCP education on responsible prescribing and use of NUCYNTA® ER.

You can complete the NUCYNTA® ER REMS education in 3 easy steps:

Step 1: To review the Prescribing NUCYNTA® ER Healthcare Professional Education Program Brochure, [click here](#). Please review the Full US Prescribing Information and Medication Guide by clicking on the links below.

Step 2: [Click here](#) to register, complete, and submit the NUCYNTA® ER Education Confirmation Form online.

Step 3: Once you have submitted the NUCYNTA® ER Education Confirmation Form, you will receive confirmation of your registration via e-mail or fax.

To review printable versions of all NUCYNTA® ER REMS materials, please click on the links below:

- ["Dear Healthcare Professional" Letter](#)
- [Prescribing Information](#)
- [Medication Guide](#)
- [Prescribing NUCYNTA® ER Healthcare Professional Education Program Brochure](#)
- [NUCYNTA® ER Education Confirmation Form](#)

For additional information, please call our Customer Communications Center at 1-800-526-7736.

Completed NUCYNTA® ER Education Confirmation Forms may be faxed to Janssen Pharmaceuticals, Inc. at 1-800-292-7832.

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

NUCYNTA® ER IMPORTANT SAFETY INFORMATION

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

POTENTIAL FOR ABUSE

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

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

PROPER PATIENT SELECTION

FULL ISI WILL APPEAR ON EVERY PAGE OF NUCYNTA.ERREMS.COM. SEE NEXT PAGE FOR FULL ISI.

CLICK THROUGHS

Access the Prescribing NUCYNTA® ER Healthcare Professional Education Program Brochure and Confirmation Form
Start Here >

NUCYNTA® ER Risk Evaluation and Mitigation Strategy (REMS)

A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage the known or potential serious risks associated with a drug product, and is required by the Food and Drug Administration (FDA) to ensure that the benefits of the drug outweigh its risks.

In order for Janssen Pharmaceuticals, Inc. to communicate the serious risks of NUCYNTA® ER, Janssen Pharmaceuticals, Inc. has worked with the FDA to develop strategies to communicate these risks.

The REMS program is designed to inform patients and healthcare professionals (HCPs) about the risks of NUCYNTA® ER and to help them learn more about the serious risks, including potential for abuse, misuse, overdose, and addiction.

Click here

The goals of the REMS for NUCYNTA® ER are:

- Goal 1:** To inform patients and HCPs about the potential for abuse, misuse, overdose, and addiction to NUCYNTA® ER.
- Goal 2:** To inform patients and Healthcare Professionals about the safe use of NUCYNTA® ER.

NUCYNTA® ER should only be prescribed in accordance with the NUCYNTA® ER REMS, including HCP education on acceptable prescribing and use of NUCYNTA® ER.

You can complete the NUCYNTA® ER REMS education in 3 easy steps:

- Step 1:** To receive the Prescribing NUCYNTA® ER Healthcare Professional Education Program Brochure, **Click here** to view the FULL US Prescribing Information and Medication Guide by clicking on the **Prescribe** link.
- Step 2:** **Click here** to register, complete, and submit the NUCYNTA® ER Education Confirmation Form online.
- Step 3:** Once you have completed the NUCYNTA® ER Education Confirmation Form, you will receive confirmation of your registration via e-mail or fax.

To review printable versions of the NUCYNTA® ER REMS materials, please click on the links below:

- Dear Healthcare Professional Letter
- Prescribing Information
- Medication Guide
- Prescribing NUCYNTA® ER Healthcare Professional Education Program Brochure
- NUCYNTA® ER Education Confirmation Form

WHEN THE USER CLICKS ON ANY OF THE LINKS ABOVE, THE PRESCRIBING NUCYNTA® ER HEALTHCARE PROFESSIONAL EDUCATION PROGRAM BROCHURE WILL OPEN. THE USER WILL HAVE THE OPTION TO ADVANCE DIRECTLY TO THE CONFIRMATION FORM FROM EACH SPREAD, OR UPON CLICKING THROUGH THE ENTIRE BROCHURE.

REMS Home | REMS

Access the NUCYNTA® ER REMS Educational Program

NUCYNTA® ER Risk Evaluation and Mitigation Strategy

← Cover →

EDUCATION PROGRAM

NUCYNTA® ER
tapentadol extended-release tablets

HEALTHCARE PROFESSIONAL EDUCATION PROGRAM:
A GUIDE FOR HEALTHCARE PROFESSIONALS WHO INTEND TO PRESCRIBE NUCYNTA® ER

Please see boxed WARNING on page 2, and accompanying Full Prescribing Information and Medication Guide.

Complete NUCYNTA® ER Education Confirmation forms should be mailed to (180) at 1-800-444-4444.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BOB A RAPPAPORT
08/25/2011