

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: 2008

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

See full prescribing information for complete boxed warning.

- NUCYNTA® ER contains tapentadol, a Schedule II controlled substance. Monitor for signs of misuse, abuse, and addiction during NUCYNTA® ER therapy. (5.1)
- Fatal respiratory depression may occur, with highest risk at initiation and with dose increases. Instruct patients on proper administration of NUCYNTA® ER tablets to reduce the risk. (5.2)
- Accidental ingestion of NUCYNTA® ER can result in fatal overdose of tapentadol, especially in children. (5.3)
- Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products containing alcohol while taking NUCYNTA® ER because of the risk of increased and potentially fatal plasma tapentadol levels. (5.4)

RECENT MAJOR CHANGES

Boxed Warning	7/2012
Indications and Usage (1)	7/2012
Indications and Usage, Neuropathic pain associated with diabetic peripheral neuropathy (1)	8/2012
Dosage and Administration (2)	8/2012
Contraindications (4)	7/2012
Warnings and Precautions (5)	7/2012

INDICATIONS AND USAGE

NUCYNTA® ER is an opioid agonist indicated for the management of:

- moderate to severe chronic pain in adults (1)
- neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults (1)

when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

Limitations of Use

- NUCYNTA® ER is not for use:
 - As an as-needed (prn) analgesic (1)
 - For pain that is mild or not expected to persist for an extended period of time (1)
 - For acute pain (1)
 - For postoperative pain, unless the patient is already receiving chronic opioid therapy prior to surgery, or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. (1)

DOSAGE AND ADMINISTRATION

- Individualize dosing based on patient's prior analgesic treatment experience, and titrate as needed to provide adequate analgesia and minimize adverse reactions. (2.1, 2.2)
- The initial dose in patients not currently taking opioid analgesics is 50 mg twice a day. (2.1)
- Instruct patients to swallow NUCYNTA® ER tablets whole. (2.7)
- Use a gradual downward titration when NUCYNTA® ER is discontinued in a physically dependent patient. (2.3, 5.13)
- Reduce the dose of NUCYNTA® ER in patients with moderate hepatic impairment. (2.4)
- NUCYNTA® ER use in patients with severe renal impairment is not recommended. (2.5)

- Conservative initial dosing of NUCYNTA® ER in elderly patients is recommended due to possible decreased renal and hepatic function. (2.6)

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

- Significant respiratory depression (4)
- Acute or severe bronchial asthma (4)
- Known or suspected paralytic ileus (4)
- Hypersensitivity to tapentadol or to any other ingredients of the product (4)
- Concurrent use of monoamine oxidase inhibitors (MAOI) or use within the last 14 days. (4)

WARNINGS AND PRECAUTIONS

See Boxed WARNINGS

- Elderly, cachectic, and debilitated patients and patients with chronic pulmonary disease: Monitor closely because of increased risk of respiratory depression. (5.5, 5.6)
- Interaction with CNS depressants: Consider dose reduction of one or both drugs because of additive effects. (5.7, 7.3)
- Hypotensive effect: Monitor during dose initiation and titration. (5.8)
- Patients with head injury or increased intracranial pressure: Monitor for sedation and respiratory depression. Avoid use of NUCYNTA® ER in patients with impaired consciousness or coma susceptible to intracranial effects of CO₂ retention. (5.9)
- Seizures: Use with caution in patients with a history of seizures. (5.10)
- Serotonin Syndrome: Potentially life-threatening condition could result from concomitant administration of drugs with serotonergic activity. (5.11)

ADVERSE REACTIONS

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

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

DRUG INTERACTIONS

- CNS depressants: Increased risk of respiratory depression, hypotension, profound sedation, coma or death. When combined therapy with CNS depressant is contemplated, the dose of one or both agents should be reduced. (7.3)
- Mixed agonist/antagonist opioids (i.e., pentazocine, nalbuphine, and butorphanol): May reduce analgesic effect and/or precipitate withdrawal symptoms. (7.5)
- Monitor for signs of serotonin syndrome when NUCYNTA® ER is used concurrently with SSRIs, SNRIs, tricyclic antidepressants, or triptans. (7.4)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Nursing mothers: Closely monitor infants of nursing women receiving NUCYNTA® ER. (8.3)
- Renal or hepatic impairment: not recommended in patients with severe renal or hepatic impairment. Reduce dose in patients with moderate hepatic impairment. (8.7, 8.8)

See 17 for PATIENT COUNSELING INFORMATION AND MEDICATION GUIDE.

Revised: 8/2012

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RESPIRATORY DEPRESSION, ACCIDENTAL
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FULL PRESCRIBING INFORMATION

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

Abuse Potential

NUCYNTA[®] ER contains tapentadol, an opioid agonist and Schedule II controlled substance with an abuse liability similar to other opioid agonists, legal or illicit [*see Warnings and Precautions (5.1)*]. Assess each patient's risk for opioid abuse or addiction prior to prescribing NUCYNTA[®] ER. The risk for opioid abuse is increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depressive disorder). Routinely monitor all patients receiving NUCYNTA[®] ER for signs of misuse, abuse, and addiction during treatment [*see Drug Abuse and Dependence (9)*].

Life-threatening Respiratory Depression

Respiratory depression, including fatal cases, may occur with use of NUCYNTA[®] ER, even when the drug has been used as recommended and not misused or abused [*see Warnings and Precautions (5.2)*]. Proper dosing and titration are essential and NUCYNTA[®] ER should only be prescribed by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain. Monitor for respiratory depression, especially during initiation of NUCYNTA[®] ER or following a dose increase. Instruct patients to swallow NUCYNTA[®] ER tablets whole. Crushing, dissolving, or chewing NUCYNTA[®] ER can cause rapid release and absorption of a potentially fatal dose of tapentadol.

Accidental Exposure

Accidental ingestion of NUCYNTA[®] ER, especially in children, can result in a fatal overdose of tapentadol [*see Warnings and Precautions (5.3)*].

Interaction with Alcohol

The co-ingestion of alcohol with NUCYNTA[®] ER may result in an increase of plasma levels and potentially fatal overdose of tapentadol [*see Warnings and Precautions (5.4)*]. Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products that contain alcohol while on NUCYNTA[®] ER.

1 INDICATIONS AND USAGE

NUCYNTA[®] ER (tapentadol) is indicated for the management of:

- moderate to severe chronic pain in adults
- neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults

when a continuous, around-the-clock opioid analgesic is needed for an extended period of time [*see Clinical Studies (14.1, 14.2)*].

Limitations of Usage

NUCYNTA[®] ER is not intended for use:

- As an as-needed (prn) analgesic
- For pain that is mild or not expected to persist for an extended period of time
- For acute pain
- For postoperative pain unless the patient is already receiving chronic opioid therapy prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time.

2 DOSAGE AND ADMINISTRATION

2.1 Initial Dosing

Initiate the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience. Monitor patients closely for respiratory depression, especially within the first 72 hours of initiating therapy with NUCYNTA[®] ER [*see Warnings and Precautions (5.2)*].

Consider the following factors when selecting an initial dose of NUCYNTA[®] ER:

- Total daily dose, potency, and kind of any prior analgesic the patient has been taking previously;
- Reliability of the relative potency estimate used to calculate the equivalent dose of tapentadol needed (Note: potency estimates may vary with the route of administration);
- Patient's degree of opioid experience and opioid tolerance;
- General condition and medical status of the patient;
- Concurrent medication;
- Type and severity of the patient's pain.

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

NUCYNTA[®] ER is administered at a frequency of twice daily (every 12 hours).

Discontinue all other tapentadol and tramadol products when beginning and while taking NUCYNTA[®] ER [see *Serotonin Syndrome Risk (5.11)*]. 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.

Use of NUCYNTA[®] ER as the First Opioid Analgesic

Initiate NUCYNTA[®] ER therapy with the 50 mg tablet twice daily (at 12 hour intervals).

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.

Conversion from other Opioids to NUCYNTA[®] ER

While there are useful tables of oral and parenteral equivalents, there is substantial inter-patient variation in the relative potency of different opioid drugs and formulations. Specific recommendations are not available because of a lack of systematic evidence for these types of analgesic substitutions. As such, it is safer to underestimate a patient's 24-hour NUCYNTA[®] ER requirement and provide rescue medication (e.g., immediate-release opioid or non-opioid) than to overestimate and manage an adverse reaction. In general, begin with half of the estimated daily tapentadol requirement as the initial dose, managing inadequate analgesia by supplementation with immediate-release rescue medication.

Published relative potency/equianalgesia data are available and may be referred to in clinical practice guidelines such as those published by authorities in the field of pain medicine, but such ratios are approximations. Consider contacting your specific state medical or pharmacy professional societies for further information on how to safely convert patients from one opioid to another.

2.2 Titration and Maintenance of Therapy

Individually titrate NUCYNTA[®] ER to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving NUCYNTA[®] ER to assess the maintenance of pain control and the relative incidence of adverse reactions. During chronic therapy, especially for non-cancer-related pain (or pain associated with other terminal illnesses), periodically reassess the continued need for the use of opioid analgesics.

Titrate patients to adequate analgesia with dose increases of 50 mg no more than twice daily every three days. In clinical studies, efficacy with NUCYNTA[®] ER was demonstrated relative to placebo in the dosage range of 100 mg to 250 mg twice daily [*see Clinical Studies (14)*].

If the level of pain increases, attempt to identify the source of increased pain, while adjusting the NUCYNTA[®] ER dose to decrease the level of pain.

Patients who experience breakthrough pain may require dosage adjustment or rescue medication with an appropriate dose of an immediate-release opioid or non-opioid medication.

If signs of excessive opioid-related adverse reactions are observed, the next dose may be reduced. Adjust the dose to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

During chronic, around-the-clock opioid therapy, especially for non-cancer pain syndromes, reassess the continued need for around-the-clock opioid therapy regularly (e.g., every 6 to 12 months) as appropriate.

2.3 Discontinuation of NUCYNTA[®] ER

When the patient no longer requires therapy with NUCYNTA[®] ER tablets, use a gradual downward titration of the dose to prevent signs and symptoms of withdrawal in the physically-dependent patient.

2.4 Patients with Hepatic Impairment

The use of NUCYNTA[®] ER in patients with severe hepatic impairment (Child-Pugh Score 10-15) is not recommended.

In patients with moderate hepatic impairment (Child-Pugh Score 7 to 9), initiate treatment 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 (Child-Pugh Score 5 to 6) [*see Warnings and Precautions (5.15) and Clinical Pharmacology (12.3)*].

2.5 Patients with Renal Impairment

No dosage adjustment is recommended in patients with mild or moderate renal impairment. NUCYNTA[®] ER use in patients with severe renal impairment is not recommended [*see Warnings and Precautions (5.16) and Clinical Pharmacology (12.3)*].

2.6 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 [see *Clinical Pharmacology* (12.3)].

2.7 Administration of NUCYNTA[®] ER

Instruct patients to swallow NUCYNTA[®] ER tablets whole. The tablets are not to be cut, crushed, dissolved, or chewed due to the risk of rapid release and absorption of a potentially fatal dose of tapentadol [see *Warnings and Precautions* (5.1, 5.2)].

Instruct patients to take NUCYNTA[®] ER one tablet at a time and with enough water to ensure complete swallowing immediately after placing in the mouth [see *Warnings and Precautions* (5.2), and *Patient Counseling Information* (17)].

3 DOSAGE FORMS AND STRENGTHS

NUCYNTA[®] ER 50 mg, 100 mg, 150 mg, 200 mg and 250 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
- 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
- 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
- Patients with acute or severe bronchial asthma or hypercarbia in an unmonitored setting or in the absence of resuscitative equipment
- Patients with known or suspected paralytic ileus

- Patients with hypersensitivity (e.g. anaphylaxis, angioedema) to tapentadol or to any other ingredients of the product [see *Adverse Reactions (6.2)*].
- Patients who are receiving monoamine oxidase inhibitors (MAOI) 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(7.2)*].

5 WARNINGS AND PRECAUTIONS

5.1 Abuse Potential

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

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

Misuse or abuse of NUCYNTA[®] ER by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of the opioid and pose a significant risk that could result in overdose and death [see *Overdosage (10)*].

Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

5.2 Life Threatening Respiratory Depression

Respiratory depression is the chief hazard of opioid agonists, including NUCYNTA[®] ER. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Respiratory depression from opioids is manifested by a reduced urge to breathe and a decreased rate of respiration, often associated with a "sighing" pattern of breathing (deep breaths separated by abnormally long pauses). Carbon dioxide (CO₂) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. Management of respiratory

depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status [*see Overdosage (10)*].

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of NUCYNTA[®] ER, the risk is greatest during the initiation of therapy or following a dose increase. Closely monitor patients for respiratory depression when initiating therapy with NUCYNTA[®] ER and following dose increases. Instruct patients against use by individuals other than the patient for whom NUCYNTA[®] ER was prescribed and to keep NUCYNTA[®] ER out of the reach of children, as such inappropriate use may result in fatal respiratory depression.

To reduce the risk of respiratory depression, proper dosing and titration of NUCYNTA[®] ER are essential [*see Dosage and Administration (2)*]. Overestimating the NUCYNTA[®] ER dose when converting patients from another opioid product can result in fatal overdose with the first dose. Respiratory depression has also been reported with use of modified-release opioids when used as recommended and not misused or abused.

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

- Proper dosing and titration are essential and NUCYNTA[®] ER should only be prescribed by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain.
- Instruct patients to swallow NUCYNTA[®] ER tablets whole. The tablets are not to be cut, crushed, dissolved, or chewed. The resulting tapentadol dose may be fatal, particularly in opioid-naïve individuals.
- NUCYNTA[®] ER is contraindicated in patients with respiratory depression and in patients with conditions that increase the risk of life-threatening respiratory depression [*see Contraindications (4)*].

5.3 Accidental Exposure

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

5.4 Interaction with Alcohol

The co-ingestion of alcohol with NUCYNTA[®] ER can result in an increase of tapentadol plasma levels and potentially fatal overdose of tapentadol. Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products containing alcohol while on NUCYNTA[®] ER therapy [*see Clinical Pharmacology (12.3)*].

5.5 Elderly, Cachectic, and Debilitated Patients

Respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients.

Therefore, monitor such patients closely, particularly when initiating and titrating NUCYNTA[®] ER and when NUCYNTA[®] ER is given concomitantly with other drugs that depress respiration [see *Warnings and Precautions (5.2)*].

5.6 Use in Patients with Chronic Pulmonary Disease

Monitor for respiratory depression those patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercarbia, or pre-existing respiratory depression, particularly when initiating therapy and titrating with NUCYNTA[®] ER, as in these patients, even usual therapeutic doses of NUCYNTA[®] ER may decrease respiratory drive to the point of apnea [see *Warnings and Precautions (5.2)*]. Consider the use of alternative non-opioid analgesics in these patients if possible.

5.7 Interactions with CNS Depressants and Illicit Drugs

Hypotension, and profound sedation, coma or respiratory depression may result if NUCYNTA[®] ER is used concomitantly with other CNS depressants (e.g., sedatives, anxiolytics, hypnotics, neuroleptics, muscle relaxants, other opioids and illicit drugs). When considering the use of NUCYNTA[®] ER in a patient taking a CNS depressant, assess the duration of use of the CNS depressant and the patient's response, including the degree of tolerance that has developed to CNS depression. Additionally, consider the patient's use, if any, of alcohol and/or illicit drugs that can cause CNS depression. If NUCYNTA[®] ER therapy is to be initiated in a patient taking a CNS depressant, start with a lower NUCYNTA[®] ER dose than usual and monitor patients for signs of sedation and respiratory depression and consider using a lower dose of the concomitant CNS depressant [see *Drug Interactions (7.3)*].

5.8 Hypotensive Effect

NUCYNTA[®] ER may cause severe hypotension. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics) [see *Drug Interactions (7.3)*]. Monitor these patients for signs of hypotension after initiating or titrating the dose of NUCYNTA[®] ER. In patients with circulatory shock, NUCYNTA[®] ER may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of NUCYNTA[®] ER in patients with circulatory shock.

5.9 Use in Patients with Head Injury or Increased Intracranial Pressure

Monitor patients taking NUCYNTA[®] ER who may be susceptible to the intracranial effects of CO₂ retention (e.g., those with evidence of increased intracranial pressure or brain tumors) for signs of sedation and respiratory depression, particularly when initiating therapy with

NUCYNTA[®] ER. NUCYNTA[®] ER may reduce respiratory drive, and the resultant CO₂ retention can further increase intracranial pressure. Opioids may also obscure the clinical course in a patient with a head injury.

Avoid the use of NUCYNTA[®] ER in patients with impaired consciousness or coma.

5.10 Seizures

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

5.11 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, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea) and can be fatal [*see Serotonergic Drugs (7.4)*].

5.12 Use in Patients with Gastrointestinal Conditions

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

5.13 Avoidance of Withdrawal

Avoid the use of mixed agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and butorphanol) in patients who have received or are receiving a course of therapy with a full opioid agonist analgesic, including NUCYNTA[®] ER. In these patients, mixed agonists/antagonists analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms.

When discontinuing NUCYNTA[®] ER, gradually taper the dose [*see Dosage and Administration (2.3)*].

5.14 Driving and Operating Heavy Machinery

NUCYNTA[®] ER may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of NUCYNTA[®] ER and know how they will react to the medication.

5.15 Hepatic Impairment

A study with an immediate-release formulation of tapentadol in subjects with hepatic impairment showed higher serum concentrations of tapentadol than in those with normal hepatic function. Avoid use of NUCYNTA[®] ER in patients with severe hepatic impairment. Reduce the dose of NUCYNTA[®] ER in patients with moderate hepatic impairment [see *Dosage and Administration (2.4) and Clinical Pharmacology (12.3)*]. Closely monitor patients with moderate hepatic impairment for respiratory and central nervous system depression when initiating and titrating NUCYNTA[®] ER.

5.16 Renal Impairment

Use of NUCYNTA[®] ER in patients with severe renal impairment is not recommended due to accumulation of a metabolite formed by glucuronidation of tapentadol. The clinical relevance of the elevated metabolite is not known [see *Clinical Pharmacology (12.3)*].

6 ADVERSE REACTIONS

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

- Respiratory Depression [see *Warnings and Precautions (5.2)*]
- Interaction with Alcohol [see *Warnings and Precautions (5.4)*]
- Chronic Pulmonary Disease [see *Warnings and Precautions (5.6)*]
- Hypotensive Effects [see *Warnings and Precautions (5.8)*]
- Interactions with Other CNS Depressants [see *Warnings and Precautions (5.7)*]
- Drug abuse, addiction, and dependence [see *Drug Abuse and Dependence (9.2, 9.3)*]
- Gastrointestinal Effects [see *Warnings and Precautions (5.12)*]
- Seizures [see *Warnings and Precautions (5.10)*]
- Serotonin Syndrome [see *Warnings and Precautions (5.11)*]

6.1 Clinical Studies Experience

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.

Commonly-Observed Adverse Reactions in Clinical Studies with NUCYNTA[®] ER in Patients with Chronic Pain due to Low Back Pain or Osteoarthritis

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 $\geq 10\%$ in any NUCYNTA[®] ER dose group) were: nausea, constipation, dizziness, headache, and somnolence.

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

Table 1: Adverse Drug Reactions Reported by $\geq 1\%$ of NUCYNTA[®] ER-Treated Patients and Greater than Placebo-treated Patients in Pooled Parallel-Group Trials¹

	NUCYNTA [®] ER 50 to 250 mg BID ² (n=980)	Placebo (n=993)
Nausea	21%	7%
Constipation	17%	7%
Dizziness	17%	6%
Headache	15%	13%
Somnolence	12%	4%
Fatigue	9%	4%
Vomiting	8%	3%
Dry mouth	7%	2%
Hyperhidrosis	5%	<1%
Pruritus	5%	2%
Insomnia	4%	2%
Dyspepsia	3%	2%
Lethargy	2%	<1%
Asthenia	2%	<1%
Anxiety	2%	1%
Decreased appetite	2%	<1%
Vertigo	2%	<1%
Hot flush	2%	<1%
Disturbance in attention	1%	<1%
Tremor	1%	<1%
Chills	1%	0%
Abnormal dreams	1%	<1%
Depression	1%	<1%
Vision blurred	1%	<1%
Erectile dysfunction	1%	<1%

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

Commonly-Observed Adverse Reactions in Clinical Studies with NUCYNTA[®] ER in Patients with Neuropathic Pain Associated with Diabetic Peripheral Neuropathy

The types of adverse reactions seen in the studies of patients with painful diabetic peripheral neuropathy (DPN) were similar to what was seen in the low back pain and osteoarthritis trials. The safety data described in Table 2 below are based on two pooled, randomized withdrawal, double-blind, placebo-controlled, 12-week studies of NUCYNTA[®] ER (dosed 100 to 250 mg BID) in patients with neuropathic pain associated with diabetic peripheral neuropathy. These trials included 1040 NUCYNTA[®] ER-treated patients and 343 placebo-treated patients. The mean age was 60 years old; 40% were female and 60% were male; 76% were White, 12% were Black, and 12% were “Other”. The most commonly reported ADRs (incidence \geq 10% in NUCYNTA[®] ER-treated subjects) were: nausea, constipation, vomiting, dizziness, somnolence, and headache.

Table 2 lists the common adverse reactions reported in 1% or more of NUCYNTA[®] ER-treated patients and greater than placebo-treated patients with neuropathic pain associated with diabetic peripheral neuropathy in the two pooled studies.

Table 2: Adverse Drug Reactions Reported by $\geq 1\%$ of NUCYNTA[®] ER-Treated Patients and Greater than Placebo-Treated Patients in Pooled Trials (Studies DPN-1 and DPN-2)¹

	NUCYNTA [®] ER 50 to 250 mg BID ² (n=1040)	Placebo ³ (n=343)
Nausea	27%	8%
Dizziness	18%	2%
Somnolence	14%	<1%
Constipation	13%	<1%
Vomiting	12%	3%
Headache	10%	5%
Fatigue	9%	<1%
Pruritus	8%	0%
Dry mouth	7%	<1%
Diarrhea	7%	5%
Decreased appetite	6%	<1%
Anxiety	5%	4%
Insomnia	4%	3%
Hyperhidrosis	3%	2%
Hot flush	3%	2%
Tremor ⁴	3%	3%
Abnormal dreams	2%	0%
Lethargy	2%	0%
Asthenia	2%	<1%
Irritability	2%	1%
Dyspnea	1%	0%
Nervousness	1%	0%
Sedation	1%	0%
Vision blurred	1%	0%

Pruritus generalized	1%	0%
Vertigo	1%	<1%
Abdominal discomfort	1%	<1%
Hypotension	1%	<1%
Dyspepsia	1%	<1%
Hypoesthesia	1%	<1%
Depression	1%	<1%
Rash	1%	<1%
Chills ⁴	1%	1%
Feeling cold ⁴	1%	1%
Drug withdrawal syndrome	1%	<1%

¹ MedDRA preferred terms.

² NUCYNTA[®] ER dosed between 100 and 250 mg BID after a starting dose of 50 mg BID. It includes ADR reported in the open-label titration period for all subjects and in the double-blind maintenance period for the subjects who were randomized to NUCYNTA[®] ER.

³ It includes ADR reported in the double-blind maintenance period for the subjects who were randomized to placebo after receiving NUCYNTA[®] ER during the open-label titration period.

⁴ Tremor was observed in 3.4% of NUCYNTA[®] ER-treated subjects vs. 3.2% in placebo group, chills- in 1.3% vs.1.2% in placebo, and feeling cold- in 1.3% vs.1.2% in placebo.

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

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

Nervous System Disorders: paresthesia, balance disorder, syncope, memory impairment, mental impairment, depressed level of consciousness, dysarthria, presyncope, coordination abnormal

Gastrointestinal disorders: impaired gastric emptying

General disorders and administration site conditions: feeling abnormal, feeling drunk

Psychiatric disorders: perception disturbances, disorientation, confusional state, agitation, euphoric mood, drug dependence, thinking abnormal, nightmare

Skin and subcutaneous tissue disorders: urticaria

Metabolism and nutrition disorders: weight decreased

Cardiac disorders: heart rate increased, palpitations, heart rate decreased, left bundle branch block

Vascular Disorder: blood pressure decreased

Respiratory, thoracic and mediastinal disorders: respiratory depression

Renal and urinary disorders: urinary hesitation, pollakiuria

Reproductive system and breast disorders: sexual dysfunction

Eye disorders: visual disturbance

Immune system disorders: drug hypersensitivity

6.2 Postmarketing Experience

The following adverse reactions, not noted in Section 6.1 above, 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.

Psychiatric disorders: hallucination, suicidal ideation

Anaphylaxis and angioedema have been reported with ingredients contained in NUCYNTA[®] ER. Advise patients how to recognize such reactions and when to seek medical attention.

7 DRUG INTERACTIONS

7.1 Alcohol

Concomitant use of alcohol with NUCYNTA[®] ER can result in an increase of tapentadol plasma levels and potentially fatal overdose of tapentadol. Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products containing alcohol while on NUCYNTA[®] ER therapy [*see Clinical Pharmacology (12.3)*].

7.2 Monoamine Oxidase Inhibitors

NUCYNTA[®] ER is contraindicated in patients who are receiving monoamine oxidase inhibitors (MAOI) 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)*].

7.3 CNS Depressants

Concurrent use of NUCYNTA[®] ER and other central nervous system (CNS) depressants including sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers, and alcohol can increase the risk of respiratory depression, hypotension, profound sedation or coma. Monitor patients receiving CNS depressants and NUCYNTA[®] ER for signs of respiratory depression and hypotension. When such combined therapy is contemplated, start NUCYNTA[®] ER at 1/3 to 1/2 of the usual dosage and consider using a lower dose of the concomitant CNS depressant.

7.4 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 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 (5.11)*].

7.5 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) may precipitate withdrawal symptoms. Avoid the use of agonist/antagonists and partial agonists with NUCYNTA[®] ER.

7.6 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 anophthalmia, 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.

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. At maternal tapentadol doses ≥ 150 mg/kg/day, a dose-related increase in pup mortality was observed to postnatal Day 4. Treatment-related developmental delay was observed in the dead pups, including incomplete ossification. In addition, significant reductions in pup body weights and body weight gains at doses associated with maternal toxicity (150 mg/kg/day and above) was seen throughout lactation.

8.2 Labor and Delivery

NUCYNTA[®] ER is not for use in women during and immediately prior to labor, where shorter acting analgesics or other analgesic techniques are more appropriate. Occasionally, opioid analgesics may prolong labor by temporarily reducing the strength, duration, and frequency of uterine contractions. However, these effects are not consistent and may be offset by an increased rate of cervical dilatation which tends to shorten labor.

Opioids cross the placenta and may produce respiratory depression and psychophysiologic effects in neonates. Closely observe neonates whose mothers received opioid analgesics during labor for signs of respiratory depression. An opioid antagonist, such as naloxone, should be available for reversal of opioid-induced respiratory depression in the neonate in such situations.

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 breastfeeding child cannot be excluded.

Because of the potential for adverse reactions in nursing infants from NUCYNTA[®] ER, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Withdrawal symptoms can occur in breast-feeding infants when maternal administration of NUCYNTA[®] ER is stopped.

8.4 Pediatric Use

The safety and efficacy of NUCYNTA[®] ER in pediatric patients less than 18 years of age have not been established.

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)*].

8.6 Neonatal Withdrawal Syndrome

Chronic maternal use of NUCYNTA[®] ER during pregnancy can affect the neonate with subsequent withdrawal signs. Neonatal withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration and severity of neonatal withdrawal syndrome vary based on the drug used, duration of use, the dose of last maternal use, and rate of elimination drug by the newborn. Neonatal opioid withdrawal syndrome may be life-threatening and should be treated according to protocols developed by neonatology experts.

8.7 Renal Impairment

The safety and effectiveness of NUCYNTA[®] ER has not been established in patients with severe renal impairment ($CL_{CR} < 30$ mL/min). Use of NUCYNTA[®] ER in patients with severe renal impairment is not recommended due to accumulation of a metabolite formed by glucuronidation of tapentadol. The clinical relevance of the elevated metabolite is not known [*see Clinical Pharmacology (12.3)*].

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)*]. The dose of NUCYNTA[®] ER should be reduced in patients with moderate hepatic impairment (Child-Pugh Score 7 to 9) [see *Dosage and Administration (2.4)*].

Use of NUCYNTA[®] ER is not recommended in severe hepatic impairment (Child-Pugh Score 10 to 15) [see *Warnings and Precautions (5.15)*].

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

NUCYNTA[®] ER contains tapentadol, a Schedule II controlled substance with a high potential for abuse similar to fentanyl, methadone, morphine, oxycodone, and oxymorphone. NUCYNTA[®] ER is subject to misuse, abuse, addiction, and criminal diversion [see *Warnings and Precautions (5.1)*]. The high drug content in the extended release formulation adds to the risk of adverse outcomes from abuse and misuse.

9.2 Abuse

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.

Drug abuse is the intentional non-therapeutic use of an over-the-counter or prescription drug, even once, for its rewarding psychological or physiological effects. Drug abuse includes, but is not limited to the following examples: the use of a prescription or over-the-counter drug to get "high", or the use of steroids for performance enhancement and muscle build up.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and include: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

"Drug-seeking" behavior is very common to 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, people suffering from untreated addiction and criminals seeking drugs to sell.

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 opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances.

NUCYNTA[®] ER can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by law, is strongly advised.

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 opioid drugs.

9.3 Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dose reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity, e.g., naloxone, nalmefene, or mixed agonist/antagonist analgesics (pentazocine, butorphanol, buprenorphine, nalbuphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

NUCYNTA[®] ER should be discontinued by a gradual downward titration [*see Dosage and Administration (2.3)*]. If NUCYNTA[®] ER is abruptly discontinued in a physically-dependent patient, an abstinence syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, piloerection, myalgia, mydriasis, irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, increased blood pressure, respiratory rate, or heart rate.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms [see *Use in Specific Populations* (8.1, 8.2,8.6)].

10 OVERDOSAGE

10.1 Clinical Presentation

Acute overdose with opioids can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and sometimes pulmonary edema, bradycardia, hypotension and death. Marked mydriasis rather than miosis may be seen due to severe hypoxia in overdose situations.

In case of overdose, priorities are the re-establishment of a patent and protected airway and institution of assisted or controlled ventilation if needed. Employ other supportive measures (including oxygen, vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life support techniques.

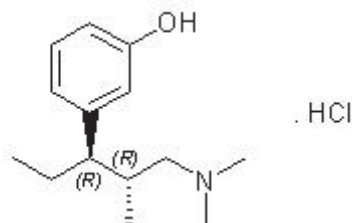
The opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to tapentadol overdose. Such agents should be administered cautiously to patients who are known, or suspected to be, physically dependent on NUCYNTA[®] ER. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute withdrawal syndrome.

Because the duration of reversal would be expected to be less than the duration of action of tapentadol in NUCYNTA[®] ER, carefully monitor the patient until spontaneous respiration is reliably re-established. NUCYNTA[®] ER will continue to release tapentadol adding to the tapentadol load for up to 24 hours after administration necessitating prolonged monitoring. If the response to opioid antagonists is suboptimal or not sustained, additional antagonist should be given as directed in the product's prescribing information.

In an individual physically dependent on opioids, administration of an opioid receptor antagonist may precipitate an acute withdrawal. The severity of the withdrawal produced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be begun with care and by titration with smaller than usual doses of the antagonist.

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 C₁₄H₂₃NO•HCl. The n-octanol: water partition coefficient log P value is 2.89. The pK_a values are 9.36 and 10.45. In addition to the active ingredient tapentadol HCl, tablets also contain the following inactive ingredients: alpha-tocopherol (vitamin E), hypromellose, polyethylene glycol, and polyethylene oxide. The film coating is comprised of polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, 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 tablets) or titanium dioxide (250 mg tablets).

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). 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).

Concentration-Efficacy Relationships

The minimum effective plasma concentration of tapentadol for analgesia varies widely among patients, especially among patients who have been previously treated with agonist opioids. As a result, individually titrate patients to achieve a balance between therapeutic and adverse effects. The minimum effective analgesic concentration of tapentadol for any individual patient may increase over time due to an increase in pain, progression of disease, development of a new pain syndrome and/or potential development of analgesic tolerance.

Concentration-Adverse Experience Relationships

There is a general relationship between increasing opioid plasma concentration and increasing frequency of adverse experiences such as nausea, vomiting, CNS effects, and respiratory depression.

Effects on the Central Nervous System (CNS)

The principal therapeutic action of tapentadol is analgesia. Tapentadol causes respiratory depression, in part by a direct effect on the brainstem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to both increases in carbon dioxide tension and electrical stimulation. Tapentadol depresses the cough reflex by direct effect on the cough center in the medulla.

Tapentadol causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations [*see Overdosage (10)*]. Other therapeutic effects of tapentadol include anxiolysis, euphoria, and feeling of relaxation, drowsiness and changes in mood.

Effects on the Gastrointestinal Tract and on Other Smooth Muscle

Gastric, biliary and pancreatic secretions are decreased by tapentadol. Tapentadol causes a reduction in motility and is associated with an increase in tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone is increased to the

point of spasm. The end result is constipation. Tapentadol can cause a marked increase in biliary tract pressure as a result of spasm of the sphincter of Oddi, and transient elevations in serum amylase. Tapentadol may also cause spasm of the sphincter of the urinary bladder.

Effects on the Cardiovascular System

Tapentadol produces peripheral vasodilation which may result in orthostatic hypotension.

Effects on the Endocrine System

Opioid agonists have been shown to have a variety of effects on the secretion of hormones. Opioids inhibit the secretion of ACTH, cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

Effects on the Immune System

Opioids have been shown to have a variety of effects on components of the immune system in *in vitro* and animal models. The clinical significance of these findings is unknown.

CNS Depressant/Alcohol Interaction

Additive pharmacodynamic effects may be expected when NUCYNTA[®] ER is used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

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.

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 (V_z) for tapentadol is 540 +/- 98 L. The plasma protein binding is low and amounts to approximately 20%.

Metabolism

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.

Excretion

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

Geriatric Patients

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 (CL_{CR} = 50 to <80 mL/min), moderate (CL_{CR} = 30 to <50 mL/min), and severe (CL_{CR} = <30mL/min) renal impairment, the AUC of tapentadol-O-glucuronide was 1.5-, 2.5-, and 5.5-fold higher compared with normal renal function, respectively.

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 hepatic impairment group (Child-Pugh Score 5 to 6) and moderate hepatic impairment group (Child-Pugh Score 7 to 9) 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.

Only a minor amount of tapentadol is metabolized via the oxidative pathway. In addition, *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.

Drug Interaction/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* (5.4)].

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 $t_{1/2}$ were unchanged. After co-administration of a 250 mg NUCYNTA[®] ER tablet and alcohol, the mean C_{max} value

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 $t_{1/2}$ 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,

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 five studies in patients with moderate to severe chronic pain and DPN. Efficacy was demonstrated in one randomized, double-blind, placebo- and active-controlled study in patients with chronic low back pain (LBP), and two randomized, double-blind, placebo-controlled studies in patients with pain related to diabetic peripheral neuropathy (DPN-1 and DPN-2).

14.1 Moderate to Severe Chronic Low Back Pain

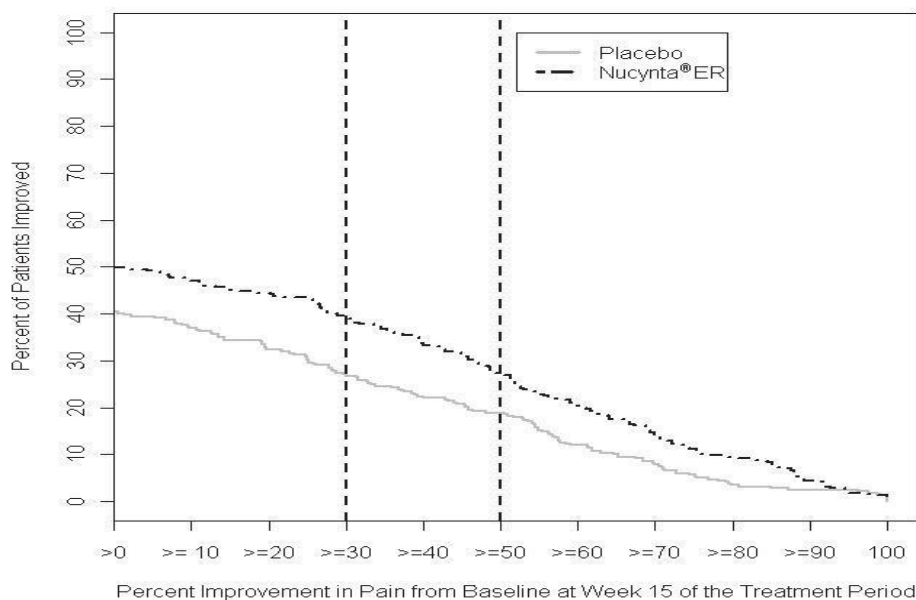
In the LBP study, patients 18 years of age or older with chronic low back pain and a baseline pain score of ≥ 5 on an 11-point numerical rating scale (NRS), ranging from 0 to 10 were enrolled and randomized to 1 of 3 treatments: NUCYNTA[®] ER, active-control (an extended-release Schedule II opioid analgesic),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

Figure 1: Percentage of Patients Achieving Various Levels of Improvement in Pain Intensity - Study LBP¹



¹ The last week of Study LBP was Week 15.

14.2 Neuropathic Pain Associated with Diabetic Peripheral Neuropathy

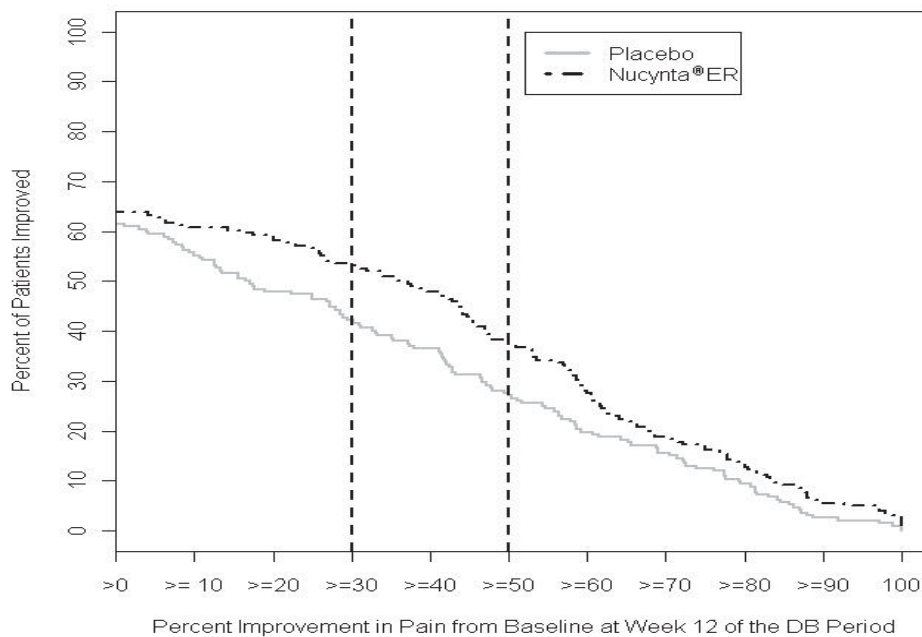
In the two DPN studies, patients 18 years of age or older with pain due to diabetic peripheral neuropathy and a pain score of ≥ 5 on an 11-point numerical rating scale (NRS) ranging from 0 (no pain) to 10 (worst possible pain) were enrolled. Following an open-label treatment period in which NUCYNTA[®] ER was administered to all patients for three weeks and titrated to an individually stable dose, patients who had tolerated the drug and 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 continue the NUCYNTA[®] ER dose (100 mg to 250 mg twice a day) reached during the open-label titration period, or receive placebo for 12 weeks of maintenance treatment. During the first 4 days of the double-blind maintenance period patients were permitted to take tapentadol ER 25 mg up to two times a day as additional medication. After the first 4 days, patients were allowed to take tapentadol ER 25 mg once daily as needed for pain, in addition to the patient's assigned study drug. Patients recorded their pain in a diary twice daily.

Study DPN-1: 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 from baseline to the end of the 12-week double-blind period 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 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 Improvement in Pain Intensity – DPN-1



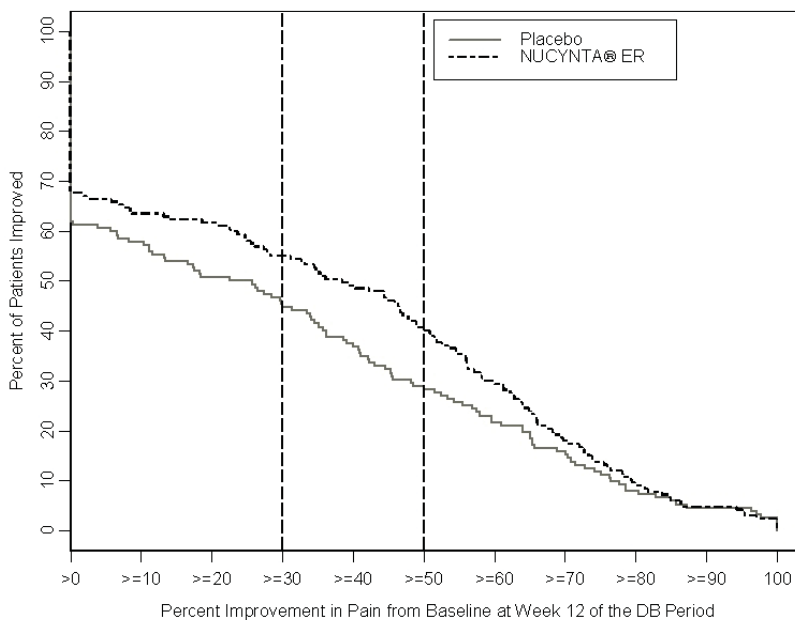
Study DPN-2: A total of 459 patients entered open-label treatment and 320 patients met the criteria for randomization into the double-blind treatment period. The mean age of the randomized population was 59 (range 28 to 83) years; approximately two-thirds of the patients were opioid-naïve (had not taken opioids during the three months prior to the screening visit).

During the titration period, 22% of patients discontinued open-label NUCYNTA[®] ER and 6% of patients were not subsequently randomized because they failed to have at least 1-point improvement in pain intensity. The most common reason for discontinuation in the double-blind

treatment period was adverse events in both the placebo group (9%) and the NUCYNTA[®] ER group (14%).

After 12 weeks of treatment, NUCYNTA[®] ER provided a significantly greater reduction in pain intensity from baseline to the end of the 12-week double-blind period compared to placebo. Figure 3 displays the proportion of randomized patients achieving various degrees of improvement in pain intensity from the start of the open-label titration period 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 3: Percentage of Patients Achieving Various Levels of Improvement in Pain Intensity-DPN-2



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 100 (10 blister strips of 10 tablets each), 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 100 (10 blister strips of 10 tablets each), 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 100 (10 blister strips of 10 tablets each), for hospital use only (NDC 50458-862-02).

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 100 (10 blister strips of 10 tablets each), 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 100 (10 blister strips of 10 tablets each), 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

See *FDA-approved patient labeling (Medication Guide)*

Abuse Potential

Inform patients that NUCYNTA[®] ER contains tapentadol, a Schedule II controlled substance that is subject to abuse. Instruct patients not to share NUCYNTA[®] ER with others and to take steps to protect NUCYNTA[®] ER from theft or misuse.

Life-threatening Respiratory Depression

Discuss the risk of respiratory depression with patients, explaining that the risk is greatest when starting NUCYNTA[®] ER or when the dose is increased. Advise patients how to recognize respiratory depression and to seek medical attention if they are experiencing breathing difficulties.

Accidental Exposure

Instruct patients to take steps to store NUCYNTA[®] ER securely. Accidental exposure, especially in children, may result in serious harm or death. Advise patients to dispose of unused NUCYNTA[®] ER by flushing the tablets down the toilet.

Risks from Concomitant Use of Alcohol and other CNS Depressants

Inform patients that the concomitant use of alcohol with NUCYNTA[®] ER can increase the risk of life-threatening respiratory depression. Instruct patients not to consume alcoholic beverages, as well as prescription and over-the-counter drug products that contain alcohol, during treatment with NUCYNTA[®] ER.

Inform patients that potentially serious additive effects may occur if NUCYNTA[®] ER is used with other CNS depressants, and not to use such drugs unless supervised by a health care provider.

Concurrent use of MAOI

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

Seizures

Inform patients that NUCYNTA[®] ER could cause seizures if they are at risk for seizures or have epilepsy. 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.

Serotonin Syndrome

Inform 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. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop.

Instruct 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.

Important Administration Instructions

Instruct patients how to properly take NUCYNTA[®] ER, including the following:

- Swallowing NUCYNTA[®] ER tablets whole
- Not cutting, crushing, chewing, or dissolving the tablets

- Using NUCYNTA[®] ER exactly as prescribed to reduce the risk of life-threatening adverse reactions (e.g., respiratory depression)
- Not discontinuing NUCYNTA[®] ER without first discussing the need for a tapering regimen with the prescriber
- To take each tablet with enough water to ensure complete swallowing immediately after placing in mouth.

Hypotension

Inform patients that NUCYNTA[®] ER may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position).

Driving or Operating Heavy Machinery

Inform patients that NUCYNTA[®] ER may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication.

Constipation

Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention.

Anaphylaxis

Inform patients that anaphylaxis has been reported with ingredients contained in NUCYNTA[®] ER. Advise patients how to recognize such a reaction and when to seek medical attention.

Pregnancy

Advise female patients that NUCYNTA[®] ER can cause fetal harm and to inform the prescriber if they are pregnant or plan to become pregnant.

Manufactured by:

Janssen Ortho, LLC

Gurabo, PR 00778

Manufactured for:

Janssen Pharmaceuticals, Inc.

Titusville, NJ 08560

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Revised: August 2012