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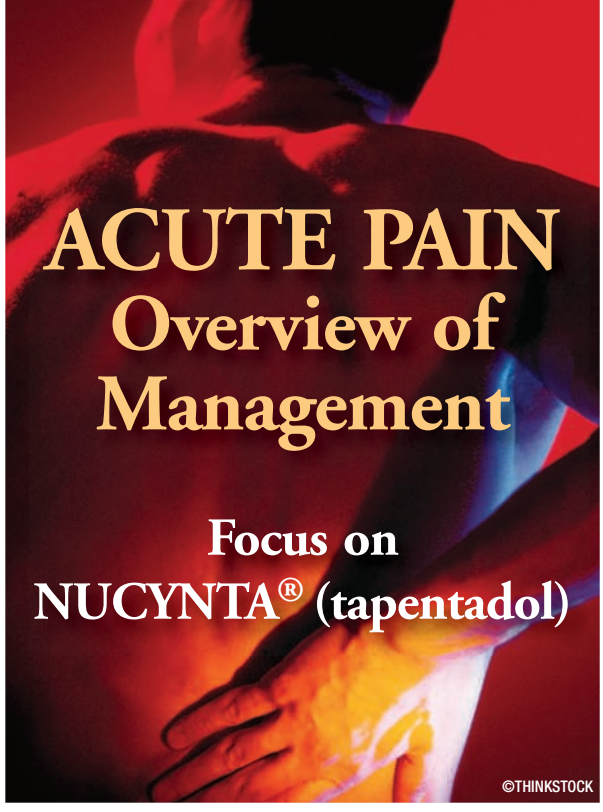
U.S. Pharmacist®
PRODUCT INFORMATION GUIDE

ACUTE PAIN
Overview of Management

Focus on NUCYNTA® (tapentadol)

SPECIAL ADVERTISING SECTION

This product information guide is sponsored by and developed in conjunction with PriCara®, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc.



Pain is defined as *an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.*[1] The experience of physical pain is familiar to everyone; however, the intensity, character, and tolerability of each person's pain is subjective. How patients perceive and react to pain is influenced by social, cultural, and psychological factors.[2] Thus, detailed examination as to the character (eg, dull, throbbing, stabbing), location, and intensity of pain, how and when it occurs, and the effects of pain is needed in order to recommend appropriate interventions.[3]

Standardized pain scales are frequently used in the clinic and in clinical trials to provide a visual clue as to the intensity of patients' pain. These scales can be used over time to assess the progression of pain and/or the effectiveness of pain therapy.[3,4]

Acute pain is defined as that associated with a sudden stimulus (eg, accident or surgery) and is generally expected to resolve as the injury heals. Acute pain lasts a relatively short time (days, weeks, or months).[3] Clinical examples of acute pain include pain following surgery and pain associated with injury.[3] In contrast, *chronic* pain may last for months to as long as years after the initial injury heals.[3]

Pain is further categorized according to the neural and biochemical mechanisms at work. *Nociceptive* pain is the normal physiological response to a noxious stimulus, such as injury or inflammation. The stimulus causes nociceptors to release the neurotransmitters glutamate, calcitonin gene-related peptide, and substance P, which transmit the signal to second-order neurons in the spinal cord. The second-order neurons form the ascending spinothalamic tract that leads to the thalamus, where they synapse with third-order neurons that project to the sensory cortex, where the pain is perceived.[5]

Pain signals are modulated by release of endorphins and enkephalins in the midbrain. These neurotransmitters interact with specific opioid receptors in descending modulatory neurons that synapse with the primary or second-order pain-transmission neurons. Descending neurons release norepinephrine and serotonin, which directly inhibit the release of pain transmitters and inhibit the activity of the second-order pain transmission neurons.[5]

Treatment Options Using Oral Medications

Pharmacological interventions for acute pain include nonopioid and opioid medications.[6] Nonopioid medications include the nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs produce pain relief by inhibition of cyclooxygenases (COX-1 and COX-2), which catalyze the production of pro-inflammatory prostaglandins from arachidonic acid. The traditional NSAIDs are nonselective inhibitors of COX-1 and COX-2. Prostaglandins are important mediators of inflammation that increase pain sensations through inflammatory mechanisms.[7] Nonopioid oral medications are recommended for mild to moderate acute pain, and most are available over the counter and by prescription. Potentially serious side effects of NSAIDs include gastrointestinal effects, such as upsets, stomach ulcers, or bleeding, as well as reduced blood clotting, decreased kidney function, and cardiovascular side effects. The risk of these events is increased by higher doses and longer-term use.[6]

Opioid medications mimic the actions of endorphins by interacting with opioid receptors in the brain and

spinal cord. Activation of mu-opioid receptors in ascending pathways may work to inhibit nociceptive signals.[5] Increase in the effect on ascending pathways activity of opioid receptors may activate the modulating descending neural pathways as detailed above and produce relief of pain.[5] Opioids are associated with the potential for abuse and addiction. Abuse refers to unacceptable behaviors with regard to the medication, such as increasing the dosage of medication without permission or obtaining prescriptions from multiple sources. Addiction is a medical diagnosis referring to a chronic neurobiological disease influenced by a patient's genetic, environmental, and psychosocial factors. It encompasses behaviors such as inability to control medication use, continued use in spite of harm, compulsive use, and cravings for the medication.[6,8] Opioids are generally indicated for moderate to severe acute pain.[6]

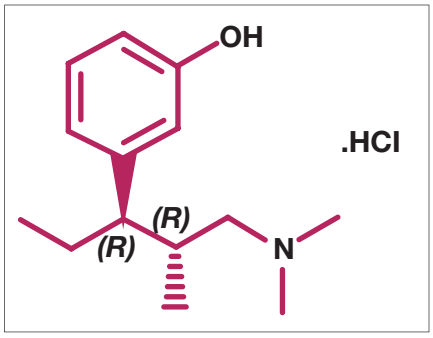


Figure 1. The molecular formula of tapentadol HCl, the active ingredient in NUCYNTA®, is $C_{14}H_{23}NO{\cdot}HCl$.

Focus on NUCYNTA® (tapentadol)

NUCYNTA® is a centrally acting synthetic oral analgesic (FIGURE 1). NUCYNTA® is indicated for relief of moderate to severe acute pain in patients 18 years of age or older.[9] Although the exact mechanism of action of NUCYNTA® is unknown, it is thought that analgesic activity is due to mu-opioid agonist activity and inhibition of norepinephrine reuptake (FIGURE 2).[9]

NUCYNTA® has been studied extensively and evaluated in three randomized, double-blind, placebo-controlled, parallel-group, multicenter, Phase 3 safety and efficacy studies and one randomized, double-blind, 90-day safety study. Of these four clinical trials, two trials in patients with acute postoperative pain following bunionectomy were conducted to evaluate the safety and efficacy of NUCYNTA®, and one study was conducted in patients with end-stage joint disease. The fourth study was a 90-day safety study in patients with osteoarthritis or low back pain (TABLE 1).

The first trial in patients post-op bunionectomy (Bunionectomy I) (n = 602 patients randomized in a 1:1:1:1:1 ratio) evaluated doses of 50-, 75-, and 100-mg tapentadol IR, oxycodone IR 15 mg, or placebo orally every 4 to 6 hours around the clock for 72 hours following surgery. The primary endpoint was the sum of pain intensity difference (SPID) over the first 48 hours ($SPID_{48}$).[10] SPID was calculated as the sum of differences in pain intensity multiplied by the number of hours since the previous observation. Higher SPID showed lower pain intensity at the specified times, compared with baseline, and greater pain relief.[10]

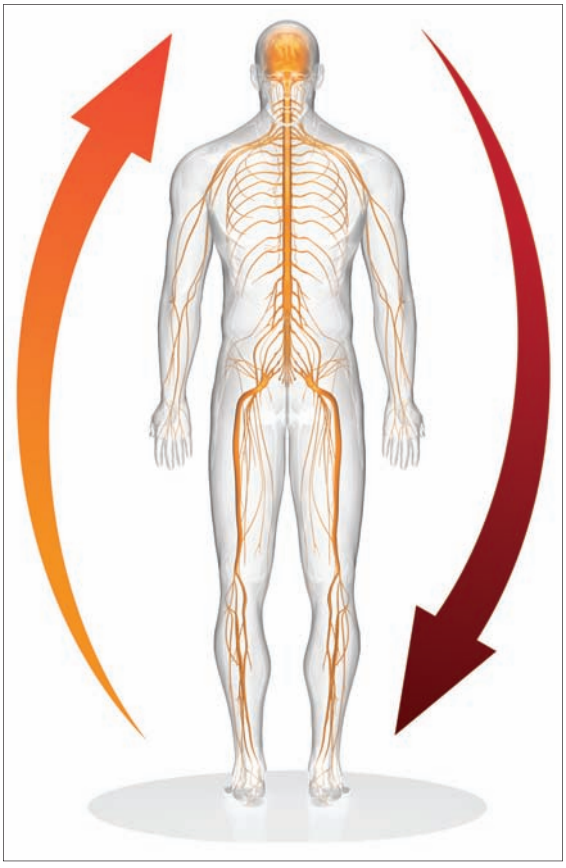


Figure 2. The mechanism of action of NUCYNTA® is thought to inhibit pain signals primarily along the ascending neural pathways through mu-opioid agonist activity, and enhance inhibition of pain signaling primarily on the descending pathways through norepinephrine reuptake inhibition.

Oxycodone IR was used as an active control to validate the sensitivity of the pain model. Evaluations of SPID at 12, 24, 48, and 72 hours showed that patients treated with any dose of tapentadol IR or oxycodone IR had significantly reduced pain intensity (higher SPID) compared with those treated with placebo during the treatment period ($P < .001$ for all comparisons).[10] A trend toward higher incidence of adverse events was seen with increasing dose in tapentadol IR groups (50 mg, 70%; 75 mg, 75%; 100 mg, 85%). Patients in the oxycodone IR and placebo groups reported adverse events in 87% and 41% of cases, respectively. Across all treatment groups, the most common adverse events were nausea, vomiting, constipation, dizziness, and somnolence.[10]

Table 1. Tapentadol IR Trial Data

Study	No. of Patients Randomized*	Tapentadol IR (mg)	Oxycodone IR (mg)	Duration (d)	Placebo Arm
Bunionectomy I[1]	602	50, 75, 100	15	3	✔
Bunionectomy II[2]	901	50, 75	10	3	✔
End-Stage Joint Disease (OA)[3]	666	50, 75	10	10	✔
90-day Safety[4]	849	50 or 100 PRN	10 or 15 PRN	≤90	

* And received one dose of study drugs.
OA: osteoarthritis.
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4. Hale M, Upmalis D, Okamoto A, et al. *Curr Med Res Opin*. 2009;25(5):1095-1104.

Bunionectomy II, a Phase 3b study, was conducted in 901 patients with acute postoperative pain. Patients were randomized in a 4:4:4:1 ratio to receive tapentadol IR 50 mg, tapentadol IR 75 mg, oxycodone IR 10 mg, or placebo every 4 to 6 hours for 72 hours following surgery.[11] Oxycodone IR was included in this study for assay sensitivity. The primary efficacy endpoint was $SPID_{48}$. Primary analyses were conducted to evaluate the efficacy and safety of 50- and 75-mg doses of tapentadol IR. Primary safety analyses assessed the incidence of the composite of nausea and/or vomiting for each dose.[11]

This trial showed that both doses of tapentadol IR (50 and 75 mg) were associated with significantly greater pain relief compared with placebo ($P < .001$ for both comparisons).[11] The composite incidence of nausea and/or vomiting in the 50-mg tapentadol IR group was 35%; for patients in the 75-mg tapentadol IR group, it was 51%. Patients in the oxycodone 10-mg group had a composite incidence of nausea and/or vomiting of 59%.[11]

NUCYNTA® was further evaluated for efficacy and safety in a randomized, double-blind, placebo- and active-controlled study in 666 patients with moderate to severe pain due to end-stage degenerative joint disease (osteoarthritis) that was inadequately controlled with daily doses of analgesics.[12] Oxycodone IR was included in this study for assay sensitivity. Patients were randomized in a 1:1:1:1 ratio to receive tapentadol IR 50 mg, tapentadol IR 75 mg, oxycodone IR 10 mg, or placebo every 4 to 6 hours while awake for 10 days.[12] The primary efficacy endpoint was SPID over the first 5 days of treatment. Two-day and 10-day SPID were also evaluated.[12]

Results from this trial indicated significant reductions in pain intensity (higher SPID scores) for patients in both tapentadol IR treatment groups and the oxycodone IR group compared with placebo ($P < .001$ for all comparisons).[12] Treatment-emergent adverse events (AEs) were reported in 52%, 71%, 84%, and 32% of patients who received tapentadol IR 50 mg, tapentadol IR 75 mg, oxycodone IR 10 mg, and placebo, respectively. The most frequently reported AEs in all active-treatment groups were dizziness, nausea, vomiting, somnolence, constipation, pruritus, and fatigue.[12]

Finally, a randomized, double-blind, active-control, parallel-group, multicenter clinical trial was conducted to assess longer-term tolerability of NUCYNTA® by evaluating use in patients who had a clinical diagnosis of low back pain or osteoarthritis pain of the knee or hip for at least 3 months. Patients were randomized in a 4:1 ratio to receive tapentadol IR (a flexible dose of 50 or 100 mg every 4 to 6 hours as needed to maximum 600 mg per day) or oxycodone IR (a flexible dose of 10 or 15 mg every 4 to 6 hours as needed to maximum 90 mg per day) for up to 90 days. Tolerability was assessed with AE monitoring, clinical laboratory testing, physical examinations, vital signs, and 12-lead electrocardiograms. The Clinical Opioid and Subjective Opioid Withdrawal Scales (completed 2 to 4 days after cessation of therapy) were used to assess withdrawal symptoms.[13] Patients evaluated efficacy by completing pain intensity assessments at each study visit.[13] Selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) were allowed if taken for at least 30 days prior to study screening.[13]

Over the 90-day treatment period, no relevant changes in laboratory results, urinalysis, vital signs, or ECG findings

were observed. Treatment-emergent adverse events (AEs) were reported in 76.3% of patients in the tapentadol IR group and 82.9% oxycodone IR group.[13]

Gastrointestinal AEs were reported by 44.2% of patients who received tapentadol IR and by 63.5% of those who received oxycodone IR, and included: nausea (18.4% and 29.4%, respectively,); vomiting (16.9% and 30%, respectively); constipation (12.8% and 27.1%, respectively); diarrhea (6.6% and 5.9%, respectively); and dry mouth (5.3% and 2.9%, respectively).[13]

Nervous system AEs were reported by 36.7% of patients in the tapentadol IR group and by 37.1% of those in the oxycodone IR group, and included: dizziness (18.1% and 17.1%, respectively); headache (11.5% and 10%, respectively); somnolence (10.2% and 9.4%, respectively), and fatigue (5.6% and 2.4%, respectively).[13]

Opioid-like withdrawal symptoms, recorded 2 to 4 days after cessation of treatment, were of mild to moderate intensity and were detected in 17% of patients who had taken tapentadol IR and in 29% of patients who had taken oxycodone IR.[13]

IMPORTANT SAFETY INFORMATION FOR NUCYNTA® (tapentadol)

Contraindications

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

Warnings and Precautions

- Respiratory depression is the primary risk of mu-opioid agonists. Respiratory depression occurs more frequently in elderly or debilitated patients and in those suffering from conditions accompanied by hypoxia, hypercapnia, or upper airway obstruction, in whom even moderate therapeutic doses may significantly decrease pulmonary ventilation. NUCYNTA® should be administered with caution to the elderly, debilitated patients, and patients with conditions accompanied by hypoxia, hypercapnia or decreased respiratory reserve, such as asthma, chronic obstructive pulmonary disease or cor pulmonale, severe obesity, sleep apnea syndrome, myxedema, kyphoscoliosis, CNS depression, or coma. In such patients, even usual therapeutic doses of NUCYNTA® may increase airway resistance and decrease respiratory drive to the point of apnea. Alternative non-mu-opioid agonist analgesics should be considered and NUCYNTA® should be employed only under careful medical supervision at the lowest effective dose in such patients. If respiratory depression occurs, it should be treated as any mu-opioid agonist-induced respiratory depression.
- Patients receiving other mu-opioid agonist analgesics, general anesthetics, phenothiazines, other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol) concomitantly with NUCYNTA® may exhibit additive CNS depression. Interactive effects resulting in respiratory depression, hypotension, profound sedation, coma or death may result if these drugs are taken in combination with NUCYNTA®. When such combined therapy is contemplated a dose reduction of one or both agents should be considered.
- Opioid analgesics can raise cerebrospinal fluid pressure as a result of respiratory depression with carbon dioxide retention. Therefore, NUCYNTA® should not be used in patients susceptible to the effects of raised cerebrospinal fluid pressure, such as those with head injury and increased intracranial pressure. Opioid analgesics may obscure the clinical course of patients with head injury, due to effects on pupillary response and consciousness. NUCYNTA® should be used with caution in patients with head injury, intracranial lesions, or other sources of preexisting increased intracranial pressure.
- NUCYNTA® is a mu-opioid agonist and is a Schedule II controlled substance. Such drugs are sought by drug abusers and people with addiction disorders. Diversion of Schedule II products is an act subject to criminal penalty. NUCYNTA® can be abused in a manner similar to other mu-opioid agonists, legal or illicit. This should be considered when prescribing or dispensing NUCYNTA® in situations where the physician or pharmacist is concerned about an increased risk of misuse and abuse. All patients with mu-opioid agonists require careful monitoring for signs of abuse and addiction. NUCYNTA® may be abused by crushing, chewing, snorting or injecting the product. These practices pose a significant risk to the abuser and could result in overdose and death.
- Experience with NUCYNTA® overdose is very limited. Management of overdose should be focused on treating symptoms of mu-opioid agonism. Primary atten-

(Important Safety Information continued)

tion should be given to reestablishment of a patent airway and institution of assisted or controlled ventilation when overdose of NUCYNTA® is suspected. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest and arrhythmias may require cardiac massage or defibrillation.

- Patients should be cautioned that NUCYNTA® may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. This is to be expected especially at the beginning of treatment, at change of dosage, as well as in combination with alcohol or tranquilizers.
- NUCYNTA® has not been systematically evaluated in patients with a seizure disorder, and such patients were excluded from clinical studies. NUCYNTA® should be prescribed with care in patients with a history of a seizure disorder or any condition that would put the patient at risk of seizures.
- The development of a potentially life-threatening serotonin syndrome may occur with use of SNRI products, including NUCYNTA®, particularly with concomitant use of serotonergic drugs, such as SSRIs, SNRIs, TCAs, MAOIs and triptans, and with drugs that impair metabolism of serotonin (including MAOIs). Serotonin syndrome may include mental-status changes (eg, agitation, hallucinations, coma), autonomic instability (eg, tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (eg, hyperreflexia, incoordination) and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea).
- Withdrawal symptoms may occur if NUCYNTA® is discontinued abruptly. These symptoms may include: anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhea, upper respiratory symptoms, piloerection, and rarely, hallucinations. Withdrawal symptoms may be reduced by tapering NUCYNTA®.
- Pregnancy Category C. There are no adequate and well-controlled studies of NUCYNTA® in pregnant women. NUCYNTA® should be used during pregnancy ONLY if the potential benefit justifies the potential risk to the fetus. NUCYNTA® is not recommended for use in women during and immediately prior to labor and delivery. Neonates whose mothers have been taking NUCYNTA® should be monitored for respiratory depression. NUCYNTA® should not be used during breastfeeding.
- NUCYNTA® is not recommended in patients with severe renal or hepatic impairment. NUCYNTA® should be used with caution in patients with moderate hepatic impairment. Like other drugs with mu-opioid agonist activity, NUCYNTA® may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis.

Adverse Events

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

Please see full prescribing information starting on page 11.

Conclusions

NUCYNTA®, a molecule with mu-opioid agonist activity and norepinephrine reuptake inhibition, has been approved for the relief of moderate to severe acute pain in patients 18 years of age or older. NUCYNTA® has been clinically tested in multiple pain models and found to combine opioid efficacy with favorable gastrointestinal tolerability. ◆

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NUCYNTA® (tapentadol) is thought to work by combining mu-opioid agonist activity and norepinephrine reuptake inhibition in one centrally acting oral analgesic for relief of moderate to severe acute pain.

Description and Mechanism of Action: NUCYNTA® (tapentadol) CII is an immediate-release film-coated tablet for oral administration. The chemical name is 3-[(1R,2R)-3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol monohydrochloride. NUCYNTA® is a centrally acting synthetic analgesic. Although the exact mechanism of action is unknown, analgesia is thought to be due to mu-opioid agonist activity and inhibition of norepinephrine reuptake.

Indication: NUCYNTA® is indicated for relief of moderate to severe acute pain in persons 18 years of age or older.

Contraindications: NUCYNTA® is contraindicated in patients with impaired pulmonary function in unmonitored settings or in the absence of resuscitative equipment, in patients with paralytic ileus, and in patients receiving monoamine oxidase inhibitors (MAOIs) or who have taken MAOIs within the last 14 days. **PLEASE SEE IMPORTANT SAFETY INFORMATION ON PAGES 5 AND 6, AND FULL PRESCRIBING INFORMATION FOR NUCYNTA® STARTING ON PAGE 11 OF THIS SUPPLEMENT.**

Pharmacokinetics: Mean absolute bioavailability of tapentadol is approximately 32% due to extensive first-pass metabolism. Maximum serum concentrations of tapentadol are typically observed approximately 1.25 hours after dosing. Dose-proportional increases in AUC and C_{max} values for tapentadol are observed over the 50- to 150-mg dose range.

The AUC and C_{max} increased by 25% and 16%, respectively, when NUCYNTA® was administered after a high-fat, high-calorie breakfast. NUCYNTA® may be given with or without food.

NUCYNTA® has not been shown to inhibit or induce P450 enzymes; clinically relevant interactions mediated by the cytochrome P450 system are unlikely to occur. NUCYNTA® is primarily metabolized by glucuronidation (Phase II); there are no active metabolites. NUCYNTA® has low plasma protein binding (~20%). Pharmacokinetic drug-drug interactions by displacement from the protein binding site are unlikely to occur.

Pharmacodynamics: NUCYNTA® is a centrally acting analgesic. Tapentadol binding to the mu opioid receptor is 18 times lower than that of morphine and tapentadol is two to three times less potent than morphine for analgesia in animal models. Tapentadol inhibits norepinephrine uptake in the brains of rats, resulting in increased norepinephrine levels. In healthy subjects, NUCYNTA® had no effects on QT interval or on other electrocardiogram parameters.

Adverse Reactions: Respiratory depression is the primary risk of mu-opioid agonists and may occur more frequently in elderly or debilitated patients and in those with impaired pulmonary function. Additive CNS depression may occur in patients receiving NUCYNTA® concomitantly with mu-opioid analgesics, general anesthetics, phenothiazines, other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol).

The most common adverse events (experienced by ≥10% of patients who received NUCYNTA®) in nine Phase 2/3 trials were nausea, dizziness, vomiting, and somnolence. **PLEASE SEE IMPORTANT SAFETY INFORMATION ON PAGES 5 AND 6, AND FULL PRESCRIBING INFORMATION FOR NUCYNTA® STARTING ON PAGE 11 OF THIS SUPPLEMENT.**

Dosage and Administration: Dosing of NUCYNTA® should be individualized to the patient's severity of pain and experience with similar drugs, as well as to the ability to monitor the patient. The dose is 50 mg, 75 mg, or 100 mg every 4 to 6 hours depending on pain intensity. Daily doses of more than 700 mg on the first day and 600 mg on subsequent days have not been studied and are not recommended. NUCYNTA® may be given with or without food.

Use in Specific Populations:

- Renal impairment—no dosage adjustment is recommended for patients with mild or moderate renal impairment. NUCYNTA® has not been studied in patients with severe renal impairment in Phase 3 studies and its use is not recommended in this population.
- Hepatic impairment—no dosage adjustment is recommended for patients with mild hepatic impairment. In patients with moderate hepatic impairment, treatment should be initiated at 50 mg with no less than 8 hours between doses and subsequent therapy should maintain analgesia with acceptable tolerability by shortening or lengthening the dose interval. NUCYNTA® has not been studied in patients with severe hepatic impairment in Phase 3 studies and its use is not recommended in this population.

- Elderly patients—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, the lower ranges of recommended doses should be considered.
- Pregnancy and nursing—NUCYNTA® is Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. Due to potential harm to neonates, NUCYNTA® should not be used in women during labor and delivery or during breastfeeding.
- Pediatric patients—NUCYNTA® is not recommended in patients younger than 18 years of age.

Important Drug Interaction Information for NUCYNTA®

- Centrally acting drugs and alcohol—additive CNS depression, with respiratory depression, hypotension, profound sedation, or coma may result by coadministration of NUCYNTA® with other opioid agonist analgesics, general anesthetics, phenothiazines, antiemetics, other tranquilizers, sedatives, hypnotics, or other CNS depressants.
- Monoamine oxidase inhibitors—NUCYNTA® is contraindicated in patients who are receiving MAOIs or who have received MAOIs in the previous 14 days. Potential additive effects on norepinephrine levels may result in adverse cardiovascular events.
- In interaction studies, no clinically significant interactions were observed with acetaminophen, acetylsalicylic acid, naproxen, and probenecid. The pharmacokinetics of NUCYNTA® were not affected by omeprazole or metoclopramide.
- NUCYNTA® does not inhibit or induce cytochrome P450 enzymes and only a minor amount of NUCYNTA® is metabolized by P450 enzymes. Clinically relevant interactions mediated by P450 enzymes are unlikely to occur.
- Plasma protein binding of NUCYNTA® is low (approximately 20%). The likelihood of pharmacodynamic drug-drug interactions due to displacement of NUCYNTA® from the protein binding site is low. ◆

Patient Information Aid: Pain and Pain Relief

A basic understanding of pain physiology and the main pain medication categories will help a patient provide key information to their healthcare professional.

Pain is a familiar experience to every person and an important defense mechanism to warn individuals that injury or illness has occurred. Pain is individualized, and each person experiences pain differently. It is important for patients to provide accurate information about the nature of their pain. With this information, a program of pain relief that is appropriate for each individual can be designed.

Pain that is always noticeable or is intolerable should not be ignored. Even if the pain has lasted for only a short time—such as pain that occurs after surgery, for example—failing to treat it may cause other problems.

Some patients have trouble talking about pain because they feel that they complain too much or that the doctor or pharmacist is too busy with their other medical problems. You should know that physicians consider relief of pain and increased comfort to be an important goal of the overall treatment program. Also, patients may be very concerned about taking pain medications because of side effects, like nausea, vomiting, or constipation. There are many pain medications on the market, so alternatives are often available if a particular medication causes problems. Also, many side effects can often be counteracted with other medications (for example, constipation may be treated with laxatives) or reduced by altering the dosage.

Some patients are reluctant to take pain medications containing opioids because they are afraid to become addicted. You should know that while some pain medications produce physical dependence, this is not the same as addiction. Addiction means that people take and acquire a drug without any regard to the consequences and that they cannot control their behavior with regard to the drug. Addiction is a chronic neurobiological disease that is influenced by a patient's genetic, environmental, and psychosocial factors. Patients with addiction disease may have cravings for the drug, or use it compulsively. Patients may also be unable to control their drug use or continue to use it despite harmful consequences. You should be aware that addiction to a pain medication is unusual in people who have never had an addiction or substance abuse prob-

lem, as long as the medication is taken as directed.

On the other hand, physical dependence means that the patient may have predictable, specific withdrawal symptoms if he or she stops taking the drug suddenly or reduces the dosage suddenly. Withdrawal symptoms may also occur if the blood levels of the drug drop suddenly or the patient starts taking an antagonist to the drug. For this reason, gradually tapering off the dosage is recommended when it is time to stop taking the drug. In this way, withdrawal symptoms can often be reduced or avoided altogether. Physical dependence occurs with many classes of drugs, not just pain medications. Remember: Physical dependence is not the same thing as addiction.

Kinds of Oral Pain Medications

Medications for pain may include the following: Nonopioids and opioids. Nonopioids include drugs such as the nonsteroidal anti-inflammatory drugs (NSAIDs). These drugs are usually available over the counter and are recommended for mild to moderate pain.

Opioids are medications that interact with the natural neurological pathways of pain relief. They are generally indicated for moderate to severe pain and are available by prescription only. Opioids are controlled substances because they can be abused—so you should use them only as directed and keep them in a safe place to avoid theft. You should never sell or give them to anyone else (it is against the law), and you should tell your doctor if you or anyone in your household has had a problem with drug or substance abuse.

Information for Patients Taking NUCYNTA® (tapentadol)

There is a Medication Guide for NUCYNTA® with important information about NUCYNTA®. Your pharmacist will give you a copy of the Medication Guide with your prescription. Make sure you receive a copy of this Guide so you can read it while taking NUCYNTA®. The following is a summary of some information in the Medication Guide. Please read the Medication Guide in its entirety.

NUCYNTA® (tapentadol), a medication for moderate to severe pain relief, is an opioid. Because NUCYNTA® is a controlled substance, it is very important to handle it safely and never to sell or give it to anyone else.

Your physician should know if you have severe lung problems, have a gastrointestinal problem called paralytic ileus, or if you have taken a monoamine oxidase inhibitor (MAOI) medication (a kind of antidepressant) in the previous 14 days. You should not take NUCYNTA® if any of these apply to you. Also, if you have had a head injury, liver or kidney problems, convulsions or seizures, or pancreas or gall bladder problems, NUCYNTA® may not be right for you. NUCYNTA® is not recommended if you are pregnant or breastfeeding. If you have had addiction or substance abuse problems in the past, tell your doctor before receiving NUCYNTA®.

It is important that you know that NUCYNTA® can make you sleepy, so do not drive or operate machinery, or take part in other activities that could be dangerous, until you know how NUCYNTA® affects you. You should not drink alcohol while you are taking NUCYNTA®.

NUCYNTA® can produce serious adverse events in some patients. Patients should read the Medication Guide carefully in order to be able to take appropriate action should adverse events occur. Also, your doctor and pharmacist can answer many of the questions about side effects and what to do about them. Doctors and pharmacists may report adverse events to the manufacturer and government agencies in order to help gather important information about the safety of NUCYNTA®.◆

What Does My Doctor Need to Know About My Pain?

You, the patient, are the best source of information about your pain. Every person feels pain differently and has different ways of tolerating pain, even if the original problem that caused the pain (eg, surgery, arthritis) is similar to that of other patients.

- Intensity and tolerability—your physician may ask you to rate the intensity of pain on a scale of 0 to 10
- The location of the pain
- When it occurs—for example, only when sitting or standing, or the pain may disappear when you lie down
- A description of how it feels (eg, tingling, burning, dull, sharp)
- What makes it better or worse
- How long the pain has been going on, and whether it has changed over time
- How the pain affects your daily activities
- What medications you currently take for the pain and for other conditions
- Whether you have had any problems taking pain medications that would keep you from taking them

Frequently Asked Questions

You may find these questions and answers helpful when discussing NUCYNTA® (tapentadol) with patients. For additional information, please see the Medication Guide.

Q. What is NUCYNTA®?

A. NUCYNTA® is a strong medicine for pain that is used only for a short time for moderate to severe acute pain (eg, pain that occurs after surgery or an injury). You should not take NUCYNTA® if your pain can be controlled by other types of pain medications, such as aspirin or acetaminophen. NUCYNTA® is recommended only for adults 18 years of age and older.

Q. What are the possible side effects of NUCYNTA®?

A. NUCYNTA® 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 or have slow or shallow breathing
  - Have a slow heartbeat
  - Have severe sleepiness
  - Have cold, clammy skin
  - Feel faint, dizzy, confused or unable to talk, think, or walk normally
  - Have a seizure
  - Have hallucinations
- Physical dependence may occur, so stopping NUCYNTA® suddenly may cause withdrawal symptoms. You should discuss with your doctor how best to stop taking NUCYNTA®. Withdrawal symptoms may include feeling anxious, sweating, sleep problems, shivering, pain, nausea, tremors, diarrhea, upper respiratory symptoms, hallucinations, or hair "standing on end."
- Serotonin syndrome is a rare but life-threatening adverse event that may occur if you take NUCYNTA® in conjunction with some medications such as serotonin and norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), and triptans. Get medical help right away if you have any of these symptoms: agitation, hallucinations, coma, rapid heartbeat, overheating, loss of coordination, overactive reflexes, nausea, vomiting, or diarrhea.
- Seizures may occur in people who are at risk for seizures or have epilepsy. In this case, stop taking NUCYNTA® and contact your doctor right away.
- NUCYNTA® may cause low blood pressure in some people.

Q. What are the most common side effects reported when taking NUCYNTA®?

A. The most common side effects of NUCYNTA® are headache, nausea, dizziness, vomiting, sleepiness, and itching. Constipation may also occur, as with all opioid medicines. Tell your doctor about any side effect that is bothersome or does not go away.

Q. How should I take NUCYNTA®?

A. NUCYNTA® tablets are taken every 4 or 6 hours or as your physician has prescribed. NUCYNTA® can be taken with or without food.

Q. What will happen if I stop taking NUCYNTA®?

A. You should ask your physician before stopping NUCYNTA®. Sudden stopping may cause withdrawal symptoms, like sweating, anxiety, insomnia, or tremors. Your physician should know that you want to stop and may recommend tapering off NUCYNTA®. Withdrawal symptoms do not mean that you are addicted to NUCYNTA®.

Q. How can I avoid addiction?

A. Addiction is uncommon in people who have never had a substance abuse or addiction problem if the medication is taken as directed. Tell your physician if you have had this type of problem before taking NUCYNTA®. Take NUCYNTA® for pain exactly as prescribed by your physician. NUCYNTA® is prescribed for only a short time for moderate to severe acute pain.

Q. What about other medications?

A. Some medications may cause dangerous side effects when taken with NUCYNTA®. Tell your physician especially if you take other medicines that make you sleepy and if you use alcohol. Tell your physician if you take an MAOI; you should not take NUCYNTA® while taking an MAOI, or if you have taken an MAOI within the last 14 days. Tell your physician about other medicines as well, including prescription and over-the-counter medicines (eg, decongestants), vitamins, and herbal supplements. ◆

RESOURCES

The following organizations provide additional information about pain treatment options and resources for patients and healthcare professionals.

American Academy of Pain Management www.aapainmanage.org
American Academy of Pain Medicine www.painmed.org
American Pain Society http://ampainsoc.org
American Pain Foundation www.painfoundation.org
Pain Treatment Topics http://pain-topics.org

Please see Important Safety Information and full Prescribing Information for NUCYNTA® in this supplement.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NUCYNTA® safely and effectively. See full prescribing information for NUCYNTA®.

NUCYNTA® (tapentadol) immediate-release oral tablets C-II

Initial U.S. Approval: 2008

----------INDICATIONS AND USAGE----------

NUCYNTA® is an opioid analgesic indicated for the relief of moderate to severe acute pain in patients 18 years of age or older. (1)

----------DOSAGE AND ADMINISTRATION----------

- As with many centrally-acting analgesic medications, the dosing regimen of NUCYNTA® should be individualized according to the severity of pain being treated, the previous experience with similar drugs and the ability to monitor the patient. (2)
- Initiate NUCYNTA® with or without food at a dose of 50 mg, 75 mg, or 100 mg every 4 to 6 hours depending upon pain intensity. On the first day of dosing, the second dose may be administered as soon as one hour after the first dose, if adequate pain relief is not attained with the first dose. Subsequent dosing is 50 mg, 75 mg, or 100 mg every 4 to 6 hours and should be adjusted to maintain adequate analgesia with acceptable tolerability. Daily doses greater than 700 mg on the first day of therapy and 600 mg on subsequent days have not been studied and are, therefore, not recommended. (2)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 50 mg, 75 mg, 100 mg (3)

----------CONTRAINDICATIONS----------

- Impaired pulmonary function (significant respiratory depression, acute or severe bronchial asthma or hypercapnia in unmonitored settings or the absence of resuscitative equipment) (4.1)
- Paralytic ileus (4.2)
- Concomitant use with monoamine oxidase inhibitors (MAOI) or use within 14 days (4.3)

----------WARNINGS AND PRECAUTIONS----------

- Respiratory depression: Increased risk in elderly, debilitated patients, those suffering from conditions accompanied by hypoxia, hypercapnia, or upper airway obstruction. (5.1)
- CNS effects: Additive CNS depressive effects when used in conjunction with alcohol, other opioids, or illicit drugs. (5.2)
- Elevation of intracranial pressure: May be markedly exaggerated in the presence of head injury, other intracranial lesions. (5.3)
- Abuse potential may occur. Monitor patients closely for signs of abuse and addiction. (5.4)
- Impaired mental/physical abilities: Caution must be used with potentially hazardous activities. (5.5)
- Seizures: Use with caution in patients with a history of seizures. (5.7)
- Serotonin Syndrome: Potentially life-threatening condition could result from concomitant serotonergic administration. (5.8)

----------ADVERSE REACTIONS----------

The most common adverse events were nausea, dizziness, vomiting and somnolence. (6)

To report SUSPECTED ADVERSE REACTIONS, contact PriCara, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc. at 1-800-526-7736 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

- Use NUCYNTA® with caution in patients currently using specified centrally-acting drugs or alcohol. (7.3)
- Do not use NUCYNTA® in patients currently using or within 14 days of using a monoamine oxidase inhibitor (MAOI). (7.4)

----------USE IN SPECIFIC POPULATIONS----------

- Labor and delivery: should not use during and immediately prior to labor and delivery. Monitor neonates, whose mothers have been taking NUCYNTA®, for respiratory depression. (8.2)
- Nursing mothers: should not breast-feed. (8.3)
- Pediatric use: safety and effectiveness not established in patients less than 18 years of age. (8.4)
- Renal or hepatic impairment: not recommended in patients with severe renal or hepatic impairment. Use with caution in patients with moderate hepatic impairment. (8.6, 8.7)
- Elderly: care should be taken when selecting an initial dose. (2.3)

See 17 for PATIENT COUNSELING INFORMATION AND MEDICATION GUIDE.

Revised: 06/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

NUCYNTA® (tapentadol) is indicated for the relief of moderate to severe acute pain in patients 18 years of age or older.

2 DOSAGE AND ADMINISTRATION

As with many centrally-acting analgesic medications, the dosing regimen should be individualized according to the severity of pain being treated, the previous experience with similar drugs and the ability to monitor the patient.

The dose is 50 mg, 75 mg, or 100 mg every 4 to 6 hours depending upon pain intensity.

On the first day of dosing, the second dose may be administered as soon as one hour after the first dose, if adequate pain relief is not attained with the first dose. Subsequent dosing is 50 mg, 75 mg, or 100 mg every 4 to 6 hours and should be adjusted to maintain adequate analgesia with acceptable tolerability.

Daily doses greater than 700 mg on the first day of therapy and 600 mg on subsequent days have not been studied and are not recommended.

NUCYNTA® may be given with or without food *[see Clinical Pharmacology (12.3)]*.

2.1 Renal Impairment

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

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

2.2 Hepatic Impairment

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

NUCYNTA® should be used with caution in patients with moderate hepatic impairment. Treatment in these patients should be initiated at 50 mg with the interval between doses no less than every 8 hours (maximum of three doses in 24 hours). Further treatment should reflect maintenance of analgesia with acceptable tolerability, to be achieved by either shortening or lengthening the dosing interval *[see Clinical Pharmacology (12.3)]*.

NUCYNTA® has not been studied in patients with severe hepatic impairment and use in this population is not recommended *[see Warnings and Precautions (5.10)]*.

2.3 Elderly Patients

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

3 DOSAGE FORMS AND STRENGTHS

NUCYNTA® Tablets are round, biconvex and film-coated and are available in the following strengths, colors, and debossings: 50 mg of tapentadol (yellow with "O-M" on one side and "50" on the other side), 75 mg of tapentadol (yellow-orange with "O-M" on one side and "75" on the other side), and 100 mg of tapentadol (orange with "O-M" on one side and "100" on the other side).

4 CONTRAINDICATIONS

4.1 Impaired Pulmonary Function

Like other drugs with mu-opioid agonist activity, NUCYNTA® is contraindicated in patients with significant respiratory depression in unmonitored settings or the absence of resuscitative equipment. NUCYNTA® is also contraindicated in patients with acute or severe bronchial asthma or hypercapnia in unmonitored settings or the absence of resuscitative equipment *[see Warnings and Precautions (5.1)]*.

NUCYNTA® (tapentadol) Tablets

4.2 Paralytic Ileus

Like drugs with mu-opioid agonist activity, NUCYNTA® is contraindicated in any patient who has or is suspected of having paralytic ileus.

4.3 Monoamine Oxidase Inhibitors

NUCYNTA® is contraindicated in patients who are receiving monoamine oxidase (MAO) inhibitors or who have taken them within the last 14 days due to potential additive effects on norepinephrine levels which may result in adverse cardiovascular events *[see Drug Interactions (7.4)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Respiratory Depression

Respiratory depression is the primary risk of mu-opioid agonists. Respiratory depression occurs more frequently in elderly or debilitated patients and in those suffering from conditions accompanied by hypoxia, hypercapnia, or upper airway obstruction, in whom even moderate therapeutic doses may significantly decrease pulmonary ventilation.

NUCYNTA® should be administered with caution to patients with conditions accompanied by hypoxia, hypercapnia or decreased respiratory reserve such as: asthma, chronic obstructive pulmonary disease or cor pulmonale, severe obesity, sleep apnea syndrome, myxedema, kyphoscoliosis, central nervous system (CNS) depression, or coma. In such patients, even usual therapeutic doses of NUCYNTA® may increase airway resistance and decrease respiratory drive to the point of apnea. Alternative non-mu-opioid agonist analgesics should be considered and NUCYNTA® should be employed only under careful medical supervision at the lowest effective dose in such patients. If respiratory depression occurs, it should be treated as any mu-opioid agonist-induced respiratory depression *[see Overdosage (10.2)]*.

5.2 CNS Depression

Patients receiving other mu-opioid agonist analgesics, general anesthetics, phenothiazines, other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol) concomitantly with NUCYNTA® may exhibit additive CNS depression. Interactive effects resulting in respiratory depression, hypotension, profound sedation, coma or death may result if these drugs are taken in combination with NUCYNTA®. When such combined therapy is contemplated, a dose reduction of one or both agents should be considered.

5.3 Head Injury and Increased Intracranial Pressure

Opioid analgesics can raise cerebrospinal fluid pressure as a result of respiratory depression with carbon dioxide retention. Therefore, NUCYNTA® should not be used in patients who may be susceptible to the effects of raised cerebrospinal fluid pressure such as those with evidence of head injury and increased intracranial pressure. Opioid analgesics may obscure the clinical course of patients with head injury due to effects on pupillary response and consciousness. NUCYNTA® should be used with caution in patients with head injury, intracranial lesions, or other sources of preexisting increased intracranial pressure.

5.4 Misuse and Abuse

Tapentadol is a mu-opioid agonist and is a Schedule II controlled substance. Such drugs are sought by drug abusers and people with addiction disorders. Diversion of Schedule II products is an act subject to criminal penalty.

NUCYNTA® can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing NUCYNTA® in situations where the physician or pharmacist is concerned about an increased risk of misuse and abuse. Concerns about abuse and addiction should not prevent the proper management of pain. However, all patients treated with mu-opioid agonists require careful monitoring for signs of abuse and addiction, since use of mu-opioid agonist analgesic products carry the risk of addiction even under appropriate medical use *[see Drug Abuse and Dependence (9.2)]*.

NUCYNTA® may be abused by crushing, chewing, snorting or injecting the product. These practices pose a significant risk to the abuser that could result in overdose and death *[see Drug Abuse and Dependence (9)]*.

5.5 Driving and Operating Machinery

Patients should be cautioned that NUCYNTA® may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. This is to be expected especially at the beginning of treatment, at any change of dosage as well as in combination with alcohol or tranquilizers *[see Drug Interactions (7.3)]*.

5.6 Interactions with Alcohol and Drugs of Abuse

Due to its mu-opioid agonist activity, NUCYNTA® may be expected to have additive effects when used in conjunction with alcohol, opioids, or illicit drugs that cause central nervous system depression, respiratory depression, hypotension, and profound sedation, coma or death *[see Drug Interactions (7.3)]*.

5.7 Seizures
NUCYNTA® has not been systematically evaluated in patients with a seizure disorder, and such patients were excluded from clinical studies. NUCYNTA® should be prescribed with care in patients with a history of a seizure disorder or any condition that would put the patient at risk of seizures.

5.8 Serotonin Syndrome Risk
The development of a potentially life-threatening serotonin syndrome may occur with use of Serotonin and Norepinephrine Reuptake Inhibitor (SNRI) products, including NUCYNTA®, particularly with concomitant use of serotonergic drugs such as Selective Serotonin Reuptake Inhibitors (SSRIs), SNRIs, tricyclic antidepressants (TCAs), MAOIs and triptans, and with 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).

5.9 Withdrawal
Withdrawal symptoms may occur if NUCYNTA® is discontinued abruptly. These symptoms may include: anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhea, upper respiratory symptoms, piloerection, and rarely, hallucinations. Withdrawal symptoms may be reduced by tapering NUCYNTA® *[see Drug Abuse and Dependence (9.3)]*.

5.10 Hepatic Impairment
A study of NUCYNTA® in subjects with hepatic impairment showed higher serum concentrations than in those with normal hepatic function. NUCYNTA® should be used with caution in patients with moderate hepatic impairment *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

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

5.11 Use in Pancreatic/Biliary Tract Disease
Like other drugs with mu-opioid agonist activity, NUCYNTA® may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis.

6 ADVERSE REACTIONS
The following treatment-emergent adverse events are discussed in more detail in other sections of the labeling:

- Respiratory Depression *[see Contraindications (4.1) and Warnings and Precautions (5.1)]*
- CNS Depression *[see Warnings and Precautions (5.2)]*

Because clinical studies are conducted under widely varying conditions, adverse event rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice. A treatment-emergent adverse event refers to any untoward medical event associated with the use of the drug in humans, whether or not considered drug-related.

Based on data from nine Phase 2/3 studies that administered multiple doses (seven placebo- and/or active-controlled, one noncontrolled and one Phase 3 active-controlled safety study) the most common adverse events (reported by ≥ 10% in any NUCYNTA® dose group) were: nausea, dizziness, vomiting and somnolence.

The most common reasons for discontinuation due to adverse events in the studies described above (reported by ≥ 1% in any NUCYNTA® dose group) were dizziness (2.6% vs. 0.5%), nausea (2.3% vs. 0.6%), vomiting (1.4% vs. 0.2%), somnolence (1.3% vs. 0.2%) and headache (0.9% vs. 0.2%) for NUCYNTA®- and placebo-treated patients, respectively.

Seventy-six percent of NUCYNTA®-treated patients from the nine studies experienced adverse events.

NUCYNTA® was studied in multiple-dose, active- or placebo-controlled studies, or noncontrolled studies (n = 2178), in single-dose studies (n = 870), in open-label study extension (n = 483) and in Phase 1 studies (n = 597). Of these, 2034 patients were treated with doses of 50 mg to 100 mg of NUCYNTA® dosed every 4 to 6 hours.

The data described below reflect exposure to NUCYNTA® in 3161 patients, including 449 exposed for 45 days. NUCYNTA® was studied primarily in placebo- and active-controlled studies (n = 2266, and n = 2944, respectively). The population was 18 to 85 years old (mean age 46 years), 68% were female, 75% white and 67% were postoperative. Most patients received NUCYNTA® doses of 50 mg, 75 mg, or 100 mg every 4 to 6 hours.

NUCYNTA® (tapentadol) Tablets

6.1 Commonly-Observed Treatment-Emergent Adverse Events in Double-Blind Controlled Clinical Trials
Table 1 lists the adverse events reported in ≥ 1% or more of NUCYNTA®-treated patients with acute moderate to severe pain in the pooled safety data from nine Phase 2/3 studies that administered multiple doses (seven placebo- and/or active-controlled, one noncontrolled, and one Phase 3 active-controlled safety study).

Table 1 Treatment-Emergent Adverse Events* Reported by ≥ 1% of NUCYNTA®-Treated Patients In Seven Phase 2/3 Placebo- and/or Oxycodone-Controlled, One Noncontrolled, and One Phase 3 Oxycodone-Controlled Safety, Multiple-Dose Clinical Studies

System/Organ Class MedDRA Preferred Term	NUCYNTA® 21 mg – 120 mg (n=2178) %	Placebo (n=619) %
Gastrointestinal disorders		
Nausea	30	13
Vomiting	18	4
Constipation	8	3
Dry mouth	4	<1
Dyspepsia	2	<1
General disorders and administration site conditions		
Fatigue	3	<1
Feeling hot	1	<1
Infections and infestations		
Nasopharyngitis	1	<1
Upper respiratory tract infection	1	<1
Urinary tract infection	1	<1
Metabolism and nutrition disorders		
Decreased appetite	2	0
Musculoskeletal and connective tissue disorders		
Arthralgia	1	<1
Nervous system disorders		
Dizziness	24	8
Somnolence	15	3
Tremor	1	<1
Lethargy	1	<1
Psychiatric disorders		
Insomnia	2	<1
Confusional state	1	0
Abnormal dreams	1	<1
Anxiety	1	<1
Skin and subcutaneous tissue disorders		
Pruritus	5	1
Hyperhidrosis	3	<1
Pruritus generalized	3	<1
Rash	1	<1
Vascular disorders		
Hot flush	1	<1

* A treatment-emergent adverse event refers to any untoward medical event associated with the use of the drug in humans, whether or not considered drug-related.

6.2 Other Adverse Reactions Observed During the Premarketing Evaluation of NUCYNTA®

The following adverse drug reactions occurred in <1% of NUCYNTA®-treated patients in the pooled safety data from nine Phase 2/3 studies that administered multiple doses (seven were placebo- and/or active-controlled, one noncontrolled, and one Phase 3 active-controlled safety study):

Cardiac disorders: heart rate increased, heart rate decreased

Eye disorders: visual disturbance

Gastrointestinal disorders: abdominal discomfort, impaired gastric emptying

General disorders and administration site conditions: irritability, edema, drug withdrawal syndrome, feeling drunk

Immune system disorders: hypersensitivity

Investigations: gamma-glutamyltransferase increased, alanine aminotransferase increased, aspartate aminotransferase increased

Musculoskeletal and connective tissue disorders: involuntary muscle contractions, sensation of heaviness

Nervous system disorders: hypoesthesia, paresthesia, disturbance in attention, sedation, dysarthria, depressed level of consciousness, memory impairment, ataxia, presyncope, syncope, coordination abnormal, seizure

Psychiatric disorders: euphoric mood, disorientation, restlessness, agitation, nervousness, thinking abnormal

Renal and urinary disorders: urinary hesitation, pollakiuria

Respiratory, thoracic and mediastinal disorders: oxygen saturation decreased, cough, dyspnea, respiratory depression

Skin and subcutaneous tissue disorders: urticaria

Vascular disorders: blood pressure decreased

In the pooled safety data, the overall incidence of adverse reactions increased with increased dose of NUCYNTA®, as did the percentage of patients with adverse reactions of nausea, dizziness, vomiting, somnolence, and pruritus.

6.3 Post-marketing Experience

The following additional adverse reactions have been identified during post-approval use of NUCYNTA®. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency reliably.

Nervous system disorders: headache

Psychiatric disorders: hallucination

7 DRUG INTERACTIONS

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

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

7.1 Drugs Metabolized by Cytochrome P450 Enzymes

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

7.2 Drugs That Inhibit or Induce Cytochrome P450 Enzymes

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

7.3 Centrally-Acting Drugs and Alcohol

Patients receiving other opioid agonist analgesics, general anesthetics, phenothiazines, antiemetics, other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol) concomitantly with NUCYNTA® may exhibit an additive CNS depression. Interactive effects resulting in respiratory depression, hypotension, profound sedation, or coma may result if these drugs are taken in combination with NUCYNTA®. When such combined therapy is contemplated, a dose reduction of one or both agents should be considered *[see Warnings and Precautions (5.2) and (5.6)]*.

7.4 Monoamine Oxidase Inhibitors

NUCYNTA® is contraindicated in patients who are receiving monoamine oxidase (MAO) inhibitors or who have taken them within the last 14 days due to potential additive effects on norepinephrine levels which may result in adverse cardiovascular events *[see Contraindications (4.3)]*.

NUCYNTA® (tapentadol) Tablets

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

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 times the plasma exposure at the maximum recommended human dose (MRHD) of 700 mg/day 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 0.2, 0.6, and 1.85 times the plasma exposure at the MRHD based on an AUC comparison] revealed embryofetal toxicity at doses ≥10 mg/kg/day. Findings included reduced fetal viability, skeletal delays and other variations. In addition, there were multiple malformations including gastroschisis/thoracogastroschisis, amelia/phocomelia, and cleft palate at doses ≥ 10 mg/kg/day and above, and ablepharia, encephalopathy, and spina bifida at the high dose of 24 mg/kg/day. Embryofetal toxicity, including malformations, may be secondary to the significant maternal toxicity observed in the study.

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 1.7 times the plasma exposure at the MRHD on an AUC basis] did not influence physical or reflex development, the outcome of neurobehavioral tests or reproductive parameters. Treatment-related developmental delay was observed, including incomplete ossification, and significant reductions in pup body weights and body weight gains at doses associated with maternal toxicity (150 mg/kg/day and above). At maternal tapentadol doses ≥ 150 mg/kg/day, a dose-related increase in pup mortality was observed through postnatal Day 4.

There are no adequate and well controlled studies of NUCYNTA® in pregnant women. NUCYNTA® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.2 Labor and Delivery

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the total number of patients in Phase 2/3 double-blind, multiple-dose clinical studies of NUCYNTA®, 19% were 65 and over, while 5% were 75 and over. No overall differences in effectiveness were observed between these patients and younger patients. The rate of constipation was higher in subjects greater than or equal to 65 years than those less than 65 years (12% vs. 7%).

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 Renal Impairment

In patients with severe renal impairment, the safety and effectiveness of NUCYNTA® has not been established. NUCYNTA® is not recommended in this population *[see Dosage and Administration (2.1)]*.

8.7 Hepatic Impairment

Administration of NUCYNTA® resulted in higher exposures and serum levels to tapentadol in subjects with impaired hepatic function compared to

subjects with normal hepatic function *[see Clinical Pharmacology (12.3)]*. NUCYNTA® should be used with caution in patients with moderate hepatic impairment *[see Dosage and Administration (2.2)]*.

NUCYNTA® has not been studied in patients with severe hepatic impairment, therefore, use of NUCYNTA® is not recommended in this population *[see Warnings and Precautions (5.10)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

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

9.2 Abuse

Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Drug addiction is a treatable disease, utilizing a multidisciplinary approach, but relapse is common.

Concerns about abuse and addiction should not prevent the proper management of pain. However, all patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

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

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

Abuse of NUCYNTA® poses a risk of overdose and death. This risk is increased with concurrent abuse of NUCYNTA® with alcohol and other substances. In addition, parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

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

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms *[see Warnings and Precautions (5.1)]*. Use of NUCYNTA® in this population has not been characterized. As NUCYNTA® has mu-opioid agonist activity, infants whose mothers have taken NUCYNTA®, should be carefully monitored.

9.3 Dependence

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). Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist.

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

Generally, tolerance and/or withdrawal are more likely to occur the longer a patient is on continuous opioid therapy. In a safety study where drug was administered up to 90 days, 82.7% of patients taking NUCYNTA® who stopped abruptly without initiating alternative therapy and were assessed 2 to 4 days after discontinuation, did not have objective signs of opioid withdrawal using the Clinical Opiate Withdrawal Scale. Moderate withdrawal symptoms were seen in 0.3% of patients with the rest (17%) experiencing mild symptoms. Withdrawal symptoms may be reduced by tapering NUCYNTA®.

NUCYNTA® (tapentadol) Tablets

10 OVERDOSAGE

10.1 Human Experience

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

10.2 Management of Overdose

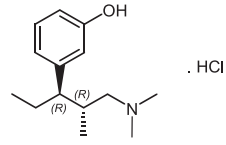
Management of overdose should be focused on treating symptoms of mu-opioid agonism. Primary attention should be given to re-establishment of a patent airway and institution of assisted or controlled ventilation when overdose of NUCYNTA® is suspected. Supportive measures (including oxygen and vasopressors)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

Pure opioid antagonists, such as naloxone, are specific antidotes to respiratory depression resulting from opioid overdose. Respiratory depression following an overdose may outlast the duration of action of the opioid antagonist. Administration of an opioid antagonist is not a substitute for continuous monitoring of airway, breathing, and circulation following an opioid overdose. If the response to opioid antagonists is suboptimal or only brief in nature, an additional antagonist should be administered as directed by the manufacturer of the product.

Gastrointestinal decontamination may be considered in order to eliminate unabsorbed drug. Gastrointestinal decontamination with activated charcoal or by gastric lavage is only recommended within 2 hours after intake. Gastrointestinal decontamination at a later time point may be useful in case of intoxication with exceptionally large quantities. Before attempting gastrointestinal decontamination, care should be taken to secure the airway.

11 DESCRIPTION

NUCYNTA® (tapentadol) Tablets are immediate-release film-coated tablets for oral administration. The chemical name is 3-[(1*R*,2*R*)-3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol monohydrochloride. The structural formula is:



The molecular weight of tapentadol HCl is 257.80, and the molecular formula is $C_{14}H_{23}NO{\cdot}HCl$. The n-octanol:water partition coefficient log P value is 2.87. The pKa values are 9.34 and 10.45. In addition to the active ingredient tapentadol HCl, tablets also contain the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, povidone, magnesium stearate, and Opadry® II, a proprietary film-coating mixture containing polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and aluminum lake coloring.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tapentadol is a centrally-acting synthetic analgesic. Although its exact mechanism is unknown, analgesic efficacy is thought to be due to mu-opioid agonist activity and the inhibition of norepinephrine reuptake.

12.2 Pharmacodynamics

Tapentadol is a centrally-acting synthetic analgesic. It 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 doses of NUCYNTA® 100 mg every 6 hours, NUCYNTA® 150 mg every 6 hours, placebo and a single oral dose of moxifloxacin. Similarly, NUCYNTA® had no relevant effect on other ECG parameters (heart rate, PR interval, QRS duration, T-wave or U-wave morphology).

12.3 Pharmacokinetics

Absorption

Mean absolute bioavailability after single-dose administration (fasting) is approximately 32% due to extensive first-pass metabolism. Maximum serum concentrations of tapentadol are typically observed at around 1.25 hours after dosing.

Dose-proportional increases in the C_{max} and AUC values of tapentadol have been observed over the 50 to 150 mg dose range.

A multiple (every 6 hour) dose study with doses ranging from 75 to 175 mg tapentadol showed a mean accumulation factor of 1.6 for the parent drug and 1.8 for the major metabolite tapentadol-O-glucuronide, which are primarily determined by the dosing interval and apparent half-life of tapentadol and its metabolite.

Food Effect

The AUC and C_{max} increased by 25% and 16%, respectively, when NUCYNTA® was administered after a high-fat, high-calorie breakfast. NUCYNTA® may be given with or without food.

Distribution

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

Metabolism and Elimination

In humans, the metabolism of tapentadol is extensive. 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 contributes to the analgesic activity.

Tapentadol and its metabolites are excreted almost exclusively (99%) via the kidneys. The terminal half-life is on average 4 hours after oral administration. The total clearance is 1530 +/- 177 ml/min.

Special Populations

Elderly

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

Renal Impairment

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

Hepatic Impairment

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

Pharmacokinetic Drug Interactions

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

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

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

NUCYNTA® (tapentadol) Tablets

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.

13 NON-CLINICAL 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 0.2 times the plasma exposure at the maximum recommended human dose [MRHD] 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 0.2 times in the male rats and 0.6 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 0.4 times 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

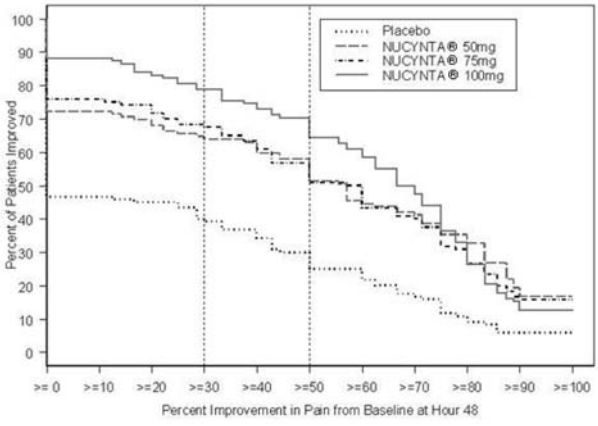
The efficacy and safety of NUCYNTA® in the treatment of moderate to severe acute pain has been established in two randomized, double-blind, placebo- and active-controlled studies of moderate to severe pain from first metatarsal bunionectomy and end-stage degenerative joint disease.

14.1 Orthopedic Surgery – Bunionectomy

A randomized, double-blind, parallel-group, active- and placebo-controlled, multiple-dose study demonstrated the efficacy of 50 mg, 75 mg, and 100 mg NUCYNTA® given every 4 to 6 hours for 72 hours in patients aged 18 to 80 years experiencing moderate to severe pain following unilateral, first metatarsal bunionectomy surgery. Patients who qualified for the study with a baseline pain score of ≥ 4 on an 11-point rating scale ranging from 0 to 10 were randomized to 1 of 5 treatments. Patients were allowed to take a second dose of study medication as soon as 1 hour after the first dose on study Day 1, with subsequent dosing every 4 to 6 hours. If rescue analgesics were required, the patients were discontinued for lack of efficacy. Efficacy was evaluated by comparing the sum of pain intensity difference over the first 48 hours (SPID48) versus placebo. NUCYNTA® at each dose provided a greater reduction in pain compared to placebo based on SPID48 values.

For various degrees of improvement from baseline to the 48-hour endpoint, Figure 1 shows the fraction of patients achieving that level of improvement. The figures are cumulative, such that every patient that achieves a 50% reduction in pain from baseline is included in every level of improvement below 50%. Patients who did not complete the 48-hour observation period in the study were assigned 0% improvement.

Figure 1: Percentage of Patients Achieving Various Levels of Pain Relief as Measured by Pain Severity at 48 Hours Compared to Baseline- Post Operative Bunionectomy



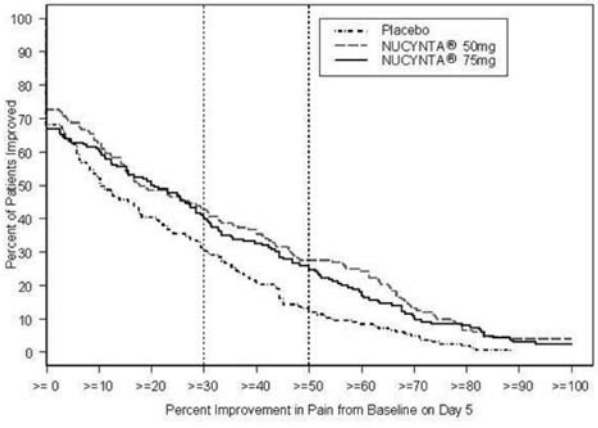
The proportions of patients who showed reduction in pain intensity at 48 hours of 30% or greater, or 50% or greater were significantly higher in patients treated with NUCYNTA® at each dose versus placebo.

14.2 End-Stage Degenerative Joint Disease

A randomized, double-blind, parallel-group, active- and placebo-controlled, multiple-dose study evaluated the efficacy and safety of 50 mg and 75 mg NUCYNTA® given every 4 to 6 hours during waking hours for 10 days in patients aged 18 to 80 years, experiencing moderate to severe pain from end stage degenerative joint disease of the hip or knee, defined as a 3-day mean pain score of ≥ 5 on an 11-point pain intensity scale, ranging from 0 to 10. Pain scores were assessed twice daily and assessed the pain the patient had experienced over the previous 12 hours. Patients were allowed to continue non-opioid analgesic therapy for which they had been on a stable regimen before screening throughout the study. Eighty-three percent (83%) of patients in the tapentadol treatment groups and the placebo group took such analgesia during the study. The 75 mg treatment group was dosed at 50 mg for the first day of the study, followed by 75 mg for the remaining nine days. Patients requiring rescue analgesics other than study medication were discontinued for lack of efficacy. Efficacy was evaluated by comparing the sum of pain intensity difference (SPID) versus placebo over the first five days of treatment. NUCYNTA® 50 mg and 75 mg provided improvement in pain compared with placebo based on the 5-Day SPID.

For various degrees of improvement from baseline to the Day 5 endpoint, Figure 2 shows the fraction of patients achieving that level of improvement. The figures are cumulative, such that every patient that achieves a 50% reduction in pain from baseline is included in every level of improvement below 50%. Patients who did not complete the 5-day observation period in the study were assigned 0% improvement.

Figure 2: Percentage of Patients Achieving Various Levels of Pain Relief as Measured by Average Pain Severity for the Previous 12 hours, Measured on Study Day 5 Compared to Baseline — End Stage Degenerative Joint Disease



NUCYNTA® (tapentadol) Tablets

The proportions of patients who showed reduction in pain intensity at 5 days of 30% or greater, or 50% or greater were significantly higher in patients treated with NUCYNTA® at each dose versus placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

NUCYNTA® Tablets are available in the following strengths and packages. All tablets are round and biconvex-shaped.

50 mg tablets are yellow and debossed with "O-M" on one side and "50" on the other side, and are available in bottles of 100 (NDC 50458-820-04) and hospital unit dose blister packs of 10 (NDC 50458-820-02).

75 mg tablets are yellow-orange and debossed with "O-M" on one side and "75" on the other side, and are available in bottles of 100 (NDC 50458-830-04) and hospital unit dose blister packs of 10 (NDC 50458-830-02).

100 mg tablets are orange and debossed with "O-M" on one side and "100" on the other side, and are available in bottles of 100 (NDC 50458-840-04) and hospital unit dose blister packs of 10 (NDC 50458-840-02).

Store up to 25ºC (77ºF); excursions permitted to 15º - 30ºC (59º - 86ºF) [see USP Controlled Room Temperature]. Protect from moisture.

Keep out of reach of children.

17 PATIENT COUNSELING INFORMATION

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

17.1 Instructions for Use

Patients should be advised NUCYNTA® should be taken only as directed and to report episodes of breakthrough pain and adverse experiences occurring during therapy to their physician. Individualization of dosage is essential to make optimal use of this medication. Patients should be advised not to adjust the dose of NUCYNTA® without consulting their physician *[see Dosage and Administration (2)]*. Patients should be advised that it may be appropriate to taper dosing when discontinuing treatment with NUCYNTA® as withdrawal symptoms may occur *[see Drug Abuse and Dependence (9.3)]*. The physician can provide a dose schedule to accomplish a gradual discontinuation of the medication.

17.2 Misuse and Abuse

Patients should be advised that NUCYNTA® is a potential drug of abuse. Patients should protect NUCYNTA® from theft, and NUCYNTA® should never be given to anyone other than the individual for whom NUCYNTA® was prescribed *[see Warnings and Precautions (5.4)]*.

17.3 Interference with Cognitive and Motor Performance

As NUCYNTA® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles *[see Warnings and Precautions (5.5)]*.

17.4 Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with NUCYNTA® *[see Use in Specific Populations (8.1)]*.

17.5 Nursing

Patients should be advised not to breast-feed an infant during treatment with NUCYNTA® *[see Use in Specific Populations (8.3)]*.

17.6 Monoamine Oxidase Inhibitors

Patients should be informed not to take NUCYNTA® while using any drugs that inhibit monoamine oxidase. Patients should not start any new medications while taking NUCYNTA® until they are assured by their healthcare provider that the new medication is not a monoamine oxidase inhibitor.

17.7 Seizures

Patients should be informed that NUCYNTA® could cause seizures if they are at risk for seizures or have epilepsy. Such patients should be advised to use NUCYNTA® with care *[see Warnings and Precautions (5.7)]*. Patients should be advised to stop taking NUCYNTA® if they have a seizure while taking NUCYNTA® and call their healthcare provider right away.

17.8 Serotonin Syndrome

Patients should be informed that NUCYNTA® could cause rare but potentially life-threatening conditions resulting from concomitant administration of serotonergic drugs (including Serotonin Reuptake Inhibitors, Serotonin and Norepinephrine Reuptake Inhibitors and tricyclic antidepressants) *[see Warnings and Precautions (5.8)]*.

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs as there is a potential for interactions *[see Drug Interactions (7)]*.

17.9 Alcohol
Patients should be advised to avoid alcohol while taking NUCYNTA® *[see Drug Interactions (7.3)]*.

17.10 Medication Guide
See Medication Guide.

Revised: June 2010

Manufactured by:
Janssen Ortho, LLC
Gurabo, PR 00778

Manufactured for:
PriCara®, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc.
Raritan, NJ 08869

PriCara
Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc.

 10169802

MEDICATION GUIDE

NUCYNTA® (new-SINN-tah)
(tapentadol)
immediate-release oral tablets C-II

- **NUCYNTA® is a federally controlled substance (C-II) because it can be abused. Keep NUCYNTA® in a safe place to prevent theft. Selling or giving away NUCYNTA® may harm others, and is against the law.**
- **Tell your doctor if you (or a family member) have ever abused or been dependent on alcohol, prescription medicines, or street drugs.**

Read the Medication Guide that comes with NUCYNTA® 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®?

NUCYNTA® is a tablet that contains tapentadol, a strong medicine that is a pain medicine.

Use NUCYNTA® exactly how your doctor tells you to. Do not use NUCYNTA® if it has not been prescribed for you.

You should not take NUCYNTA® if your pain is mild and can be controlled with other pain medicines such as non-steroidal anti-inflammatory medicines (NSAIDS) or acetaminophen.

What is NUCYNTA®?

- NUCYNTA® is a prescription medicine that is used in adults 18 years of age or older to treat moderate to severe pain that is expected to last a short time.

  NUCYNTA® is for short-term use only because the risks for withdrawal symptoms, abuse and addiction are higher when NUCYNTA® is used longer.

Who should not take NUCYNTA®?

Do not take NUCYNTA® if you:

- have severe lung problems
- have a gastrointestinal problem called paralytic ileus in which the intestines are not working normally.
- take a monoamine oxidase inhibitor (MAOI) medicine or have taken an MAOI within the last 14 days. Ask your doctor or pharmacist if any of your medicines is an MAOI.

What should I tell my doctor before taking NUCYNTA®?

NUCYNTA® may not be right for you. Tell your doctor about all your medical conditions, including if you have:

- trouble breathing or lung problems
- or had a head injury
- liver or kidney problems
- convulsions or seizures
- dependency problems with alcohol
- pancreas or gall bladder problems
- past or present substance abuse or drug addiction. There is a risk of abuse or addiction with narcotic pain medicines. If you have abused drugs in the past, you may have a higher chance of developing abuse or addiction again while using NUCYNTA®.
- are pregnant or plan to become pregnant
- are breast-feeding. You should not breast-feed while taking NUCYNTA®.

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. Using NUCYNTA® with other medicines can cause serious side effects. The doses of some other medicines may need to be changed. Your doctor can tell you what medicines can be safely taken with NUCYNTA®. Especially tell your doctor if you take:

- **Monoamine Oxidase Inhibitors (MAOIs).** See "Who should not take NUCYNTA®."
- **any medicine that makes you sleepy.** NUCYNTA® can make you sleepy and affect your breathing. Taking these medicines together can be dangerous.

How should I take NUCYNTA®?

- Do not take NUCYNTA® unless it has been prescribed for you by your doctor.
- Take NUCYNTA® exactly as prescribed by your doctor.
- **Do not change the dose of NUCYNTA® unless your doctor tells you to**. Your doctor may change your dose after seeing how the medicine affects you. Do not use NUCYNTA® more often than prescribed. Call your doctor if your pain is not well controlled while taking NUCYNTA®.
- Follow your doctor's instructions about how to slowly stop taking NUCYNTA® to help lessen withdrawal symptoms.
- NUCYNTA® can be taken with or without food.

What should I avoid while taking NUCYNTA®?

- Do not drive, operate machinery, or participate in any other possibly dangerous activities until you know how you react to this medicine. NUCYNTA® can make you sleepy.
- You should not drink alcohol while using NUCYNTA®. Alcohol increases your chance of having dangerous side effects.

What are the possible side effects of NUCYNTA®?

NUCYNTA® 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, or have slow or shallow breathing
  - have a slow heartbeat
  - have severe sleepiness
  - have cold, clammy skin
  - feel faint, dizzy, confused, or can not think, walk or talk normally
  - have a seizure
  - have hallucinations
- **Physical Dependence.** NUCYNTA® can cause physical dependence. Talk to your doctor about slowly stopping NUCYNTA® to avoid getting sick with withdrawal symptoms. You could become sick with uncomfortable symptoms because your body has become used to the medicine. Tell your doctor if you have any of these symptoms of withdrawal: feeling anxious, sweating, sleep problems, shivering, pain, nausea, tremors, diarrhea, upper respiratory symptoms, hallucinations, hair "standing on end." Physical dependence is not the same as drug addiction. Your doctor can tell you more about the differences between physical dependence and drug addiction.
- **Serotonin syndrome.** Serotonin syndrome is a rare, life-threatening problem that could happen if you take NUCYNTA® with Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs), Monoamine Oxidase Inhibitors (MAOIs), triptans or certain other medicines. Call your doctor or get medical help right away if you have any one or more of the these symptoms: you feel agitated, have hallucinations, coma, rapid heart beat, feel overheated, loss of coordination, over active reflexes, nausea, vomiting, or diarrhea.
- **Seizures.** NUCYNTA® can cause seizures in people who are at risk for seizures or who have epilepsy. Tell your doctor right away if you have a seizure and stop taking NUCYNTA®.
- **Low blood pressure.** This can make you feel dizzy if you get up too fast from sitting or lying down.

The common side effects with NUCYNTA® are nausea, dizziness, vomiting, sleepiness, and itching.

Constipation is a common side effect of all opioid medicines. Talk to your doctor about the use of laxatives and stool softeners to prevent or treat constipation while taking NUCYNTA®.

Tell your doctor about any side effect that bothers you or that does not go away. These are not all the possible side effects of NUCYNTA®. 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®?

- Store NUCYNTA® at 59°F to 86°F (15°C to 30°C). Keep NUCYNTA® tablets dry.
- Dispose of NUCYNTA® tablets you no longer need.

NUCYNTA® (tapentadol) Tablets

Keep NUCYNTA® in a safe place out of the reach of children.

General information about NUCYNTA®

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

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

What are the ingredients in NUCYNTA®?

Active Ingredient: tapentadol

Inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, povidone, magnesium stearate, and Opadry® II, a proprietary film-coating mixture containing polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and aluminum lake coloring.

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

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