NUCYNTA® (tapentadol) Tablets are immediate-release film-coated tablets for oral administration. The chemical name is 3-[(1R,2R)-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\text{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\text{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\text{max}; and 1.2 and 1.4, respectively, for t\text{1/2}. The rate of formation of tapentadol-O-glucuronide was lower in subjects with increased liver impairment.

Pharmacokinetic Drug Interactions

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

In vitro studies did not reveal any potential of tapentadol to either inhibit or induce cytochrome P450 enzymes. Thus, clinically relevant interactions mediated by the cytochrome P450 system are unlikely to occur. The pharmacokinetics of tapentadol were not affected when gastric pH or gastrointestinal motility were increased by omeprazole and metoclopramide, respectively.

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

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.

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)].

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)].

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.

6.1 Commonly-Observed Treatment-Emergent Adverse Events in Double-Blind Controlled Clinical Trials

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.

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.

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.

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Manufactured by:
Janssen Ortho, LLC
Gurabo, PR 00778

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

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NUCYNTA - tapentadol hydrochloride tablet, film coated
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
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.

**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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