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PRODUCT MONOGRAPH

[N]NUCYNTA® CR

Tapentadol

Controlled-Release Tablets
50 mg, 100 mg, 150 mg, 200 mg, and 250 mg
Tapentadol (as tapentadol hydrochloride)

Opioid Analgesic

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Distribution Site:
Markham, Ontario
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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Controlled-release tablet 50 mg, 100 mg, 150 mg, 200 mg, and 250 mg	Silicified microcrystalline cellulose, hypromellose, magnesium stearate, polyvinyl alcohol, talc, polyethylene glycol, titanium dioxide, FD&C Blue #2 Aluminum Lake (100 mg, 150 mg, 200 mg, and 250 mg tablets), yellow iron oxide (150 mg tablets)

INDICATIONS AND CLINICAL USE

Adults

NUCYNTA® CR (tapentadol) is indicated for the management of pain severe enough to require daily, continuous, long-term opioid treatment, and:

- that is opioid-responsive; and
- for which alternative treatment options are inadequate.

NUCYNTA® CR is not indicated as an as-needed (prn) analgesic.

Geriatrics (≥ 65 years of age):

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, concomitant disease or other drug therapy.

Pediatrics (< 18 years of age):

The safety and efficacy of NUCYNTA® CR have not been studied in the pediatric population. Therefore, use of NUCYNTA® CR tablets is not recommended in patients under 18 years of age.

CONTRAINDICATIONS

NUCYNTA® CR (tapentadol) is contraindicated in:

- Patients who are hypersensitive (e.g., anaphylaxis, angioedema, anaphylactic shock) to tapentadol, to opioids, or to any ingredient in the formulation or component of the container (see **WARNINGS AND PRECAUTIONS**, **Hypersensitivity**, and **ADVERSE REACTIONS, Post-Marketing Adverse Events**). For a complete listing of ingredients, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph;
- In patients with known or suspected mechanical gastrointestinal obstruction (e.g., bowel obstruction, strictures) or any diseases/conditions that affect bowel transit (e.g., ileus of any type);
- Patients with suspected surgical abdomen (e.g., acute appendicitis or pancreatitis);
- The management of acute pain;
- Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy) (see **WARNINGS AND PRECAUTIONS**);
- Severe renal or hepatic impairment (creatinine clearance of less than 30 mL/min and/or Child-Pugh Class C);
- Patients with mild, intermittent or short-duration pain that can be managed with other pain medications;
- The management of peri-operative pain;
- Patients with acute asthma or other obstructive airway, and status asthmaticus;
- Patients with acute respiratory depression, elevated carbon dioxide levels in the blood, and cor pulmonale;
- Patients with acute alcoholism, delirium tremens, and convulsive disorders;
- Patients with severe CNS depression, increased cerebrospinal or intracranial pressure, and head injury;
- Women who are breastfeeding, pregnant, or during labour and delivery.

WARNINGS AND PRECAUTIONS

SERIOUS WARNINGS AND PRECAUTIONS

Limitations of Use

Because of the risks of addiction, abuse and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid fomulations, NUCYNTA® CR should only be used in patients for whom alternative treatment options are ineffective or not tolerated (e.g., non-opioid analgesics), or would be otherwise inadequate to provide sufficient management of pain (e.g., immediate-release opioids) (see DOSAGE AND ADMINISTRATION).

Addiction, Abuse and Misuse

NUCYNTA® CR poses risks of opioid addition, abuse, and misuse, which can lead to overdose and death. Each patient's risk should be assessed prior to prescribing NUCYNTA® CR, and all patients should be monitored regularly for the development of these behaviours or conditions (see WARNINGS AND PRECAUTIONS). NUCYNTA® CR should be stored securely to avoid theft or misuse.

Life-threatening Respiratory Depression

Serious life-threatening or fatal respiratory depression may occur with use of NUCYNTA® CR. Patients should be monitored for respiratory depression, especially during initiation of NUCYNTA® CR or following a dose increase. NUCYNTA® CR should be swallowed whole; crushing, chewing or dissolving NUCYNTA® CR can cause rapid release and absorption of a potentially fatal dose of tapentadol (see WARNINGS AND PRECAUTIONS).

Accidental Exposure

Accidental consumption of even one dose of NUCYNTA® CR, especially by children, can result in a fatal overdose of tapentadol (see DOSAGE AND ADMINISTRATION subsection Disposal, for instructions on proper disposal).

Neonatal Opioid Withdrawal Syndrome

Prolonged maternal use of NUCYNTA® CR during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening (see WARNINGS AND PRECAUTIONS).

Interaction with Alcohol

The co-ingestion of alcohol with NUCYNTA® CR may result in increased plasma levels and a potentially fatal overdose of tapentadol (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

General

NUCYNTA® CR (tapentadol) tablets must be swallowed whole with sufficient liquid. NUCYNTA® CR tablets should never be chewed, divided, dissolved or crushed. Taking broken or divided NUCYNTA® CR could lead to the uncontrolled release and rapid absorption of a potentially fatal dose of tapentadol.

Patients who have received NUCYNTA® CR should be closely monitored, especially for signs of respiratory depression, until a stable maintenance dose is reached. As with many centrally acting analgesic medications, with both central and peripheral adverse effects, the dosing regimen should be individualized according to the severity of pain being treated, the previous treatment experience, and the ability to monitor the patient. Since alcohol increases the sedative effect of opioids, the concomitant use of NUCYNTA® CR and alcohol should be avoided.

Hypersensitivity

There have been spontaneous post-marketing reports of hypersensitivity (e.g., anaphylaxis, angioedema, anaphylactic shock) in some patients during tapentadol treatment. Reported symptoms included skin redness, blisters, rash, hives, swollen face, throat tightness, dyspnea, and wheezing. Tapentadol treatment should be discontinued if such symptoms occur. Patients with hypersensitivity to tapentadol, or any other ingredient of the formulation or component of the container, should not take tapentadol (see **CONTRAINDICATIONS** and **ADVERSE REACTIONS, Post-Marketing Adverse Events**). Caution should also be exercised in patients who have had serious allergic reactions to other medications. For a complete listing of ingredients, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.

Seizure Risk

Clinical studies with tapentadol excluded patients with a history of seizure disorder or epilepsy and those with a neurological disorder that may increase the risk of seizures, such as any of the following within one year: mild/moderate traumatic brain injury, stroke, transient ischemic attack, and brain neoplasm, and severe traumatic brain injury within 15 years (consisting of at least one of the following: brain contusion, intracranial hematoma, unconsciousness of post-traumatic amnesia, lasting for more than 24 hours or residual sequelae suggesting transient change in consciousness). During the clinical trials of tapentadol one subject with a past history of seizures developed convulsion.

Spontaneous post-marketing reports of patients receiving tapentadol indicate that seizures have been reported. Although tapentadol has been given with concomitant use of selective serotonin re-uptake inhibitors (SSRIs) or serotonin norepinephrine re-uptake inhibitors (SNRIs) and other medications in clinical trials, precaution should be used when tapentadol is administered concomitantly with other medications that may cause seizures. If seizures occur, tapentadol should be discontinued.

Risk of convulsions may also increase in patients with epilepsy, those with a history of seizures, or in patients with a recognized risk for seizure (such as head trauma, metabolic disorders, alcohol and drug withdrawal, CNS infections).

Abuse, Addiction and Misuse

NUCYNTA® CR is a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, NUCYNTA® CR should be prescribed and handled with caution.

NUCYNTA® CR is intended for oral use only. NUCYNTA® CR could be abused by breaking, crushing, chewing, snorting, or injecting the dissolved product. These practices will result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death. With parenteral abuse, the tablet excipients can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury.

Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse and abuse.

Opioids, such as NUCYNTA® CR should be used with particular care in patients with a history of alcohol and illicit/prescription drug abuse. Concerns about abuse, addiction, and diversion should not prevent the proper management of pain.

Dependence/Tolerance

As with other opioids, tolerance and physical dependence may develop upon repeated administration of NUCYNTA® CR and there is a potential for development of psychological dependence.

Physical dependence and tolerance reflect the neuroadaptation of the opiate receptors to chronic exposure to an opiate, and are separate and distinct from abuse and addiction. Tolerance, as well as physical dependence, may develop upon repeated administration of opioids, and are not by themselves evidence of an addictive disorder or abuse.

Patients on prolonged therapy should be tapered gradually from the drug if it is no longer required for pain control. Withdrawal symptoms may occur following abrupt discontinuation of therapy or upon administration of an opioid antagonist.

NUCYNTA® CR should not be used in opioid-dependent patients since it cannot suppress morphine withdrawal symptoms, even though it is an opioid agonist.

Withdrawal Symptoms

The opioid withdrawal syndrome may occur following abrupt discontinuation of therapy, and 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. Patients should be cautioned about the possibility of experiencing withdrawal symptoms and counselled accordingly.

Patients on prolonged therapy may be withdrawn gradually from the drug if it is no longer required for pain control. Clinical experience suggests that withdrawal symptoms may be relieved by reinstitution of opioid therapy followed by a gradual, tapered dose reduction of the medication combined with symptomatic support.

Risk of Overdosage

Serious potential consequences of overdosage with NUCYNTA® CR are central nervous system depression, respiratory depression and death. In treating an overdose, primary attention should be given to maintaining adequate ventilation along with general supportive treatment (see **OVERDOSAGE**).

Do not prescribe NUCYNTA® CR for patients who are suicidal or addiction prone.

NUCYNTA® CR should not be taken in doses higher than those recommended by the physician. The judicious prescribing of tapentadol is essential to the safe use of this drug.

Neurologic

Interactions with Central Nervous System Depressants (Including Alcohol)
NUCYNTA® CR should be used with caution and in a reduced dosage during concomitant administration of other opioid analgesics, general anesthetics, phenothiazines and other tranquilizers, sedative-hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, benzodiazepines, centrally-active anti-emetics and other CNS depressants including alcohol. Respiratory depression, hypotension and profound sedation, coma or death may result. When such combination therapy is contemplated, a substantial reduction in the dose of one or both agents should be considered and patients should be carefully monitored (see **DRUG INTERACTIONS**). With patients who are depressed or suicidal, consideration should be given to the use of non-narcotic analgesics.

Head Injury and Increased Intracranial Pressure

NUCYNTA® CR should be used with caution in patients with increased intracranial pressure or head injury, since the respiratory depressant effects of opioid receptor agonism include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, and such effects may be markedly exaggerated in these patients. Also, pupillary changes (miosis) from tapentadol may obscure the existence, extent or course of intracranial pathology. Clinicians should also

maintain a high index of suspicion for adverse drug reactions when evaluating altered mental status in these patients if they are receiving tapentadol (see **WARNINGS AND PRECAUTIONS, Respiratory Depression**).

Neonatal Opioid Withdrawal Syndrome (NOWS)

Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn.

Use of NUCYNTA® CR is contraindicated in pregnant women (see **CONTRAINDICATIONS**).

Respiratory Depression

Serious, life threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression from opioid use, if not immediately recognized and treated, may lead to respiratory arrest and death. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

Respiratory depression is a potential problem in elderly or debilitated patients as well as in those suffering from conditions accompanied by hypoxia or hypercapnia when even moderate therapeutic doses may dangerously decrease pulmonary ventilation.

NUCYNTA® CR should be administered with extreme caution to patients with conditions accompanied by hypoxia, hypercapnia, or decreased respiratory reserve such as: asthma, chronic obstructive pulmonary disease (COPD), cor pulmonale, severe obesity, sleep apnea syndrome, myxedema, kyphoscoliosis, CNS depression or coma. In these patients, even usual therapeutic doses of opioids may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea. Alternative non-opioid analgesics should be considered, and NUCYNTA® CR should be employed only under careful medical supervision at the lowest effective dose in such patients.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of NUCYNTA® CR, the risk is greatest during the initiation of therapy or following a dose increase. Patients should be closely monitored for respiratory depression when initiating therapy with NUCYNTA® CR and following dose increases.

Severe pain antagonizes the respiratory-depressant effects of opioids. However, should pain suddenly subside, these effects may rapidly become manifest. Patients who are scheduled for regional anesthetic procedures or other interruptions of pain transmission pathways should not receive NUCYNTA® CR within 24 hours of the procedure. Concomitant administration of

tapentadol with other opioid analgesics is associated with an increased risk of respiratory failure. Therefore, it is important to reduce the dose of tapentadol when other opioid analgesics are given concomitantly.

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

If respiratory depression does occur, it should be treated as an overdose. If naloxone is to be administered, use cautiously because it may precipitate seizures (see **WARNINGS AND PRECAUTIONS, Seizure Risk** and **OVERDOSAGE**).

Hypotensive Effect

NUCYNTA® CR may cause severe hypotension. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines, tranquilizers, sedatives, hypnotics, or general anesthetics; see **DRUG INTERACTIONS**). Monitor these patients for signs of hypotension after initiating or titrating the dose of NUCYNTA® CR. In patients with circulatory shock, NUCYNTA® CR may cause vasodilation that can further reduce cardiac output and blood pressure. Use of NUCYNTA® CR in patients with circulatory shock should be avoided.

Psychomotor Impairment

Patients should be cautioned that NUCYNTA® CR 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**).

Peri-operative Considerations

NUCYNTA® CR is contraindicated for peri-operative pain relief. In the case of planned chordotomy or other pain-relieving operations, patients should not be treated with NUCYNTA® CR for at least 48 hours before the operation and NUCYNTA® CR should not be used in the immediate post-operative period. If NUCYNTA® CR is to be continued after the patient recovers from the post-operative period, a new dosage should be administered in accordance with the changed need for pain relief. The risk of withdrawal in opioid-tolerant patients should be addressed as clinically indicated (see **Withdrawal Symptoms**).

The administration of analgesics in the peri-operative period should be managed by healthcare providers with adequate training and experience (e.g., by an anesthesiologist).

Use With Serotonin Re-uptake Inhibitors

There have been spontaneous reports of life-threatening serotonin syndrome with concomitant use of tapentadol and serotonergic drugs. The development of a potentially life-threatening serotonin syndrome can occur with use of selective serotonin re-uptake inhibitor (SSRI) or serotonin norepinephrine re-uptake inhibitor (SNRI) products, as well as NUCYNTA® CR, particularly with concomitant use of serotonergic drugs such as SSRIs, SNRIs, tricyclic antidepressants (TCAs), MAOIs (including linezolide, methylene blue and triptans) and with drugs that impair metabolism of serotonin. 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) (see **DRUG INTERACTIONS, Drugs Associated with a Risk of Serotonin Syndrome**).

Acute Abdominal Conditions

As may occur with other analgesics, the administration of NUCYNTA® CR may complicate the clinical assessment of patients with acute abdominal conditions.

Use In Drug And Alcohol Addiction

NUCYNTA® CR is an opioid with no approved use in the management of addictive disorders. Its approved usage in individuals with drug or alcohol dependence, either active or in remission is for the management of chronic pain requiring continuous treatment with an opioid analgesic.

Patient Counselling Information

A patient information sheet is included in the package of NUCYNTA® CR tablets dispensed to the patient.

Patients receiving NUCYNTA® CR should be given the following instructions by the physician:

1. Patients should be informed that accidental ingestion or use by individuals (including children) other than the patient for whom it was originally prescribed may lead to severe, even fatal, consequences.

2. Patients should be advised that NUCYNTA® CR contains tapentadol, an opioid pain medicine.

3. Patients should be advised that NUCYNTA® CR should only be taken as directed. The dose of NUCYNTA® CR should not be adjusted without consulting with a physician.

4. NUCYNTA® CR should be swallowed whole (not crushed, dissolved, divided, or chewed) due to the risk of fatal tapentadol overdose.

5. Patients should be advised to report episodes of breakthrough pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.

6. Patients should be advised not to combine NUCYNTA® CR with alcohol or other central nervous system depressants (sleep aids, tranquilizers) because dangerous additive effects may occur, resulting in serious injury or death.

7. Patients should be advised that serious anaphylactic/anaphylactoid reactions during tapentadol treatment have rarely been reported with symptoms such as skin redness, blisters, rash, hives, swollen face, throat tightness, dyspnea, and wheezing. Tapentadol treatment should be discontinued if such symptoms occur. Patients with a history of anaphylactic/anaphylactoid reactions to any other medications may be at increased risk and should be closely monitored.

8. Patients should be advised that NUCYNTA® CR may increase the risk of seizures, particularly when taken above the recommended dose range or in combination with SSRIs, tricyclic antidepressants or other tricyclic compounds or with other opioids.

9. Patients should be advised to consult their physician or pharmacist if other medications are being used or will be used with NUCYNTA® CR.

10. Patients should be advised that if they have been receiving treatment with NUCYNTA® CR and cessation of therapy is indicated, it may be appropriate to taper the NUCYNTA® CR dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms.

11. Patients should be advised of the most common adverse events that may occur while taking NUCYNTA® CR: nausea, dizziness, constipation, headache and somnolence.

12. Patients should be advised that NUCYNTA® CR may cause drowsiness, dizziness, or lightheadedness and may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating machinery). Patients started on NUCYNTA® CR or patients whose dose has been adjusted should be advised not to drive a car or operate machinery unless they are tolerant to the effects of NUCYNTA® CR.

13. Patients should be advised that NUCYNTA® CR is a potential drug of abuse. They should protect it from theft or misuse.

14. Patients should be advised that NUCYNTA® CR should never be given to anyone other than the individual for whom it was prescribed.

15. Women of childbearing potential who become or are planning to become pregnant should be advised to consult a physician prior to initiating or continuing therapy with NUCYNTA® CR. Women who are breastfeeding or pregnant should not use NUCYNTA® CR.

16. Patients should be informed that NUCYNTA® CR could cause seizures if they are at risk for seizure or have epilepsy. Such patients should be advised to use NUCYNTA® CR with care. Patients should be advised to stop taking NUCYNTA® CR if they have a seizure while taking NUCYNTA® CR and seek medical help immediately.

Special Populations

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

Hepatic Impairment
A study of tapentadol in subjects with hepatic impairment showed higher serum concentrations than in those with normal hepatic function. NUCYNTA® CR should be used with caution in patients with moderate hepatic impairment (see **DOSAGE AND ADMINISTRATION, Hepatic Impairment** and **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Insufficiency)**.

NUCYNTA® CR has not been studied in patients with severe hepatic impairment and, therefore, use in this population is contraindicated (see **CONTRAINDICATIONS, DOSAGE AND ADMINISTRATION, Hepatic Impairment**, and **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Insufficiency**).

Renal Impairment
NUCYNTA® CR has not been studied in controlled efficacy studies in patients with severe renal impairment; therefore, its use in this population is contraindicated (see **CONTRAINDICATIONS, DOSAGE AND ADMINISTRATION**, **Renal Impairment**, and **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Renal Insufficiency**).

Pregnant Women
Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening (see **WARNINGS AND PRECAUTIONS, Neonatal Opioid Withdrawal Syndrome**). The safety of tapentadol in pregnancy has not been studied. Therefore, NUCYNTA® CR is contraindicated in pregnant women and prior to or during labour.

Nursing Women
There is no information on the excretion of tapentadol in human milk. Therefore, NUCYNTA® CR is contraindicated during breast-feeding.

Pediatrics (< 18 years of age)
The safety and efficacy of NUCYNTA® CR have not been studied in the pediatric population. Therefore, use of NUCYNTA® CR tablets is not recommended in patients under 18 years of age.

Geriatrics (≥ 65 years of age)
In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, concomitant disease or other drug therapy. NUCYNTA® CR dosing for elderly patients with normal renal and hepatic function is the same as for younger adult patients with normal renal and hepatic function. Such patients should be monitored closely, particularly when initiating and titrating NUCYNTA® CR and when this drug is given concomitantly with other opioids or drugs that depress respiration. Of the total number of patients in Phase 2/3 double-blind, multiple-dose clinical studies of NUCYNTA® CR, 28% (1023/3613) were 65 years and over, while 7% (245/3613) were 75 years and over. No overall differences in effectiveness or tolerability were observed between these patients and younger patients (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

NUCYNTA® CR was studied in nine multiple-dose, active- or placebo-controlled Phase 2/3 studies. Patients were treated with doses ranging from 21.5 mg to 250 mg of NUCYNTA® CR dosed twice a day. A total of 3613 patients with moderate to severe pain were treated with NUCYNTA® CR, including 227 with exposure for more than 1 year. More than 60% of NUCYNTA® CR-treated subjects were opioid naïve (see **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment, Initiation of Therapy,** Patients Currently Not Taking Opioid Analgesics **(Opioid Naïve)**). The population was 18 to 91 years old (mean age 57.4 years).

Based on data from the double-blind, placebo- and/or active-controlled studies that administered multiple doses of NUCYNTA® CR, 64.4% of NUCYNTA® CR-treated patients experienced adverse events. These were predominantly of mild and moderate severity. The most common adverse events (reported by ≥10% in any NUCYNTA® CR dose group) were: nausea, dizziness, constipation and headache.

No deaths were reported during the treatment period or within 30 days after treatment discontinuation in NUCYNTA® CR-treated groups. Approximately 2.5% of NUCYNTA® CR-treated patients experienced a serious adverse event during the Phase 2/3 multi-dose studies vs. 1.0% on placebo.

Approximately 18% of NUCYNTA® CR-treated patients and 6% of patients on placebo with adverse events discontinued from the Phase 2/3 multi-dose studies. The most common reasons for discontinuation due to adverse events in the studies described above (reported by ≥1% in any NUCYNTA® CR dose group) for NUCYNTA® CR and placebo-treated patients were nausea (4.3% vs. 1.3%), dizziness (3.1% vs. 0.7%), vomiting (2.8% vs. 0.5%), somnolence (2.0% vs. 0.2%), constipation (1.4% vs. 0.2%), headache (1.2% vs. 0.3%) and fatigue (1.2% vs. 0.3%), respectively.

Withdrawal symptoms may occur if an opioid analgesic is discontinued abruptly. In all NUCYNTA® CR clinical studies, all treatment was discontinued following patient exposure up to 1 year, without a requirement for a tapering regimen. In all Phase 2/3 NUCYNTA® CR studies, patients taking NUCYNTA® CR who stopped abruptly without initiating alternative opioid therapy were assessed for withdrawal symptoms between 2 to 4 days after discontinuation, and then between 5 to 14 days after discontinuation, using the Clinical Opioid Withdrawal Scale. There were 635 patients in the NUCYNTA® CR group assessed between Day 2 and Day 4 after abrupt cessation of treatment with 11.8% and 2.0% of patients having mild or moderate withdrawal, respectively. Assessments on Day 5 or later were available for 1145 patients treated with NUCYNTA® CR (mild, 5.1%; moderate 0.3%). Withdrawal symptoms may be reduced by further tapering NUCYNTA® CR.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Double-Blind Studies

Treatment-emergent adverse events (TEAEs) reported in ≥1% of NUCYNTA® CR-treated patients with moderate to severe pain from eight double-blind, active and/or placebo-controlled studies are summarized in Table 1, if they occurred at an equivalent or higher rate with NUCYNTA® CR than with placebo. These adverse events were included regardless of any causal relationship to NUCYNTA® CR.

Table 1: Treatment-Emergent Adverse Events Reported by ≥1% of NUCYNTA® CR-Treated Patients in Phase 2/3 Double-Blind (Placebo- and/or Active-Controlled) Multiple-Dose Clinical Studies

System/Organ Class MedDRA Preferred Term	NUCYNTA® CR (n=2328) %	Placebo (n=1498) %
Any ADR		
Ear and labyrinth disorders		
Vertigo	2.2	0.8
Gastrointestinal disorders		
Nausea	18.0	8.5
Constipation	9.9	5.7
Vomiting	6.9	2.9
Dry mouth	4.6	1.7
General disorders and administration site conditions		
Fatigue	5.4	3.2

Table 1: Treatment-Emergent Adverse Events Reported by ≥1% of NUCYNTA® CR-Treated Patients in Phase 2/3 Double-Blind (Placebo- and/or Active-Controlled) Multiple-Dose Clinical Studies		
System/Organ Class MedDRA Preferred Term	**NUCYNTA® CR (n=2328) %**	**Placebo (n=1498) %**
Asthenia	1.8	0.7
Chills	1.1	0.2
Infections and infestations		
Bronchitis	1.1	0.9
Influenza	1.0	0.7
Investigations		
Electrocardiogram QT prolonged	1.0	0.3
Metabolism and nutrition disorders		
Decreased appetite	1.5	0.5
Musculoskeletal and connective tissue disorders		
Pain in extremity	1.5	1.3
Myalgia	1.0	0.6
Nervous system disorders		
Dizziness	11.8	5.1
Headache	11.4	11.3
Somnolence	8.2	2.9
Tremor	1.4	0.2
Lethargy	1.2	0.2
Psychiatric disorders		
Insomnia	3.5	1.9
Anxiety	2.7	0.9
Restlessness	1.0	0.2
Respiratory, thoracic and mediastinal disorders		
Pharyngolaryngeal pain	1.1	1.0
Skin and subcutaneous tissue disorders		
Hyperhidrosis	4.8	1.1
Pruritus	3.9	1.3
Rash	1.0	0.8
Vascular disorders		
Hot flush	1.3	0.3

Less Common Clinical Trial Adverse Events (<1%)

The following treatment-emergent adverse events (TEAEs), which have been included regardless of any causal relationship to tapentadol, occurred in less than 1% in NUCYNTA® CR-treated patients in the double-blind, placebo- or active-controlled clinical studies and were observed at a higher incidence with NUCYNTA® CR than with placebo:

- **Cardiac disorders:** tachycardia, bradycardia, extrasystoles
- **Ear and labyrinth disorders:** tinnitus
- **Endocrine disorders:** hypothyroidism
- **Eye disorders:** vision blurred, lacrimation increased, dry eye
- **Gastrointestinal disorders:** food poisoning, hematochezia, gastric disorder, rectal hemorrhage
- **General disorders and administration site conditions:** malaise, feeling jittery, drug withdrawal syndrome, feeling cold, chest pain, feeling hot, feeling abnormal, feeling of body temperature change, thirst, sluggishness
- **Infections and infestations:** gastroenteritis, cystitis, rhinitis, viral infection, localized infection, pneumonia, tooth infection, pharyngitis streptococcal, tooth abscess, infection
- **Injury, poisoning and procedural complications:** contusion, muscle strain, excoriation
- **Investigations:** blood pressure increased, gamma glutamyltransferase increased, weight decreased, electrocardiogram abnormal, electrocardiogram T-wave abnormal, blood calcium increased
- **Metabolism and nutrition disorders:** anorexia, dehydration, hypoglycemia, hypokalemia
- **Musculoskeletal and connective tissue disorders:** neck pain, bone pain, muscle twitching, osteoarthritis, muscular weakness, musculoskeletal chest pain
- **Nervous system disorders:** disturbance in attention, migraine, dysgeusia, paraesthesia, hypoesthesia, restless legs syndrome, syncope, balance disorder, sedation, depressed level of consciousness, hypersomnia, memory impairment, mental impairment, tension headache
- **Psychiatric disorders:** depression, sleep disorder, depressed mood, nervousness, abnormal dreams, nightmare, agitation, disorientation, hallucination, stress, euphoric mood, libido decreased
- **Renal and urinary disorders:** dysuria, hematuria
- **Reproductive system and breast disorders:** erectile dysfunction
- **Respiratory, thoracic and mediastinal disorders:** dyspnea, rhinorrhea, yawning, wheezing, hiccups
- **Skin and subcutaneous tissue disorders:** pruritus generalized, erythema, night sweats, piloerection, eczema, urticaria, rash macular
- **Vascular disorders:** pallor

QTc Interval in Healthy Volunteers: In a thorough QT study in healthy volunteers under stringent study conditions, tapentadol showed no clinically relevant effect on the QTc interval (see **ACTION AND CLINICAL PHARMACOLOGY**, Cardiac Safety).

Seizure occurred in one volunteer with a history of seizure in a Phase 1 study.

Post-Marketing Adverse Events

Adverse events identified during post-marketing experience with tapentadol are included in Table 2. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

In Table 2, the frequencies, based on patient treatment years, are provided according to the following convention:

Very common ≥1/10
Common ≥1/100 and <1/10
Uncommon ≥1/1000 and <1/100
Rare ≥1/10,000, <1/1000
Very Rare <1/10,000
Not known (cannot be estimated from the available data)

Table 2: Adverse Events Identified During Post-Marketing Experience with Tapentadol

Gastrointestinal disorders	
Rare	Diarrhea
Immune system disorders	
Uncommon	Hypersensitity (including rare events of angioedema, anaphylaxis and anaphylactic shock)
Psychiatric disorders	
Rare	Hallucination
Very rare	Panic attack
Nervous system disorders	
Uncommon	Headache
Cardiac disorders	
Rare	Palpitations

Hypersensitivity

There have been reports of hypersensitivity (e.g., anaphylaxis, angioedema, anaphylactic shock), including fatalities, in some patients during tapentadol treatment. Reported symptoms included skin redness, blisters, rash, hives, swollen face, throat tightness, dyspnea, and wheezing. Tapentadol treatment should be discontinued if such symptoms occur. Patients with hypersensitivity to tapentadol, or any other ingredient of the formulation or component of the container, should not take NUCYNTA® CR (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS, Hypersensitivity**). For a complete listing of ingredients, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.

Suicidality

Suicidal ideation has been reported during post-market use of tapentadol. A causal relationship between suicidal ideation and tapentadol drug exposure has not been established based on data from clinical trials and post-marketing reports.

DRUG INTERACTIONS

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

Overview

Tapentadol is mainly metabolized by glucuronidation, a system with a very high capacity which is not easily saturated even in disease. As therapeutic concentrations of drugs that are subject to glucuronidation are generally well below the concentrations needed for potential inhibition of glucuronidation, the risk of clinically relevant interaction between these drugs is generally low. The following substances have been included in a set of interaction studies without any clinically significant finding: acetaminophen, acetylsalicylic acid, naproxen and probenecid. The pharmacokinetics of tapentadol were not affected when gastric pH or gastrointestinal motility were increased by omeprazole and metoclopramide, respectively.

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

Drug-Drug Interactions

Drugs Metabolized by Cytochrome P450 Enzymes
In vitro investigations indicate that tapentadol does not inhibit or induce P450 enzymes. Thus, clinically relevant interactions mediated by the cytochrome P450 system are unlikely to occur.

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

Centrally Acting Drugs and Alcohol
Concomitant use of NUCYNTA® CR with other pure mu-opioid agonists, mixed opioid agonists/antagonists (such as pentazocine, nalbuphine), or partial mu-opioid agonists has not been studied.

In vitro dissolution studies have demonstrated that NUCYNTA® CR does not release tapentadol more rapidly in 0.1 N HCl containing up to 40% ethanol than in 0.1 N HCl. In vitro studies may not predict in vivo effects.

Patients receiving other opioid agonist analgesics, general anesthetics, phenothiazines, antiemetics, other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol) concomitantly with NUCYNTA® CR may experience additive CNS depression. Interactive effects resulting in respiratory depression, hypotension, profound sedation, or coma may result if these drugs are taken in combination with NUCYNTA® CR. If such combined therapy is contemplated, a dose reduction of one or both agents should be considered. The use of NUCYNTA® CR with alcoholic beverages or prescription or non-prescription products containing alcohol should be avoided (see **WARNINGS AND PRECAUTIONS**).

Monoamine Oxidase Inhibitors
NUCYNTA® CR 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**).

Drugs Associated with a Risk of Serotonin Syndrome
There have been post-marketing reports of serotonin syndrome with the concomitant use of tapentadol and serotonergic drugs (e.g., selective serotonin re-uptake inhibitors [SSRIs] and serotonin norepinephrine re-uptake inhibitors [SNRIs]). NUCYNTA® CR can increase the risk of serotonin syndrome when it is used concomitantly with serotonergic drugs such as SSRIs, SNRIs, and other serotonergic drugs such as tricyclic antidepressants (TCAs), MAOIs (including linezolide, methylene blue and triptans) and with drugs that impair metabolism of serotonin. This can occur within the recommended dose (see **WARNINGS AND PRECAUTIONS, Use With Serotonin Re-uptake Inhibitors**).

Anticholinergic Drugs
The use of NUCYNTA® CR with anticholinergic products (e.g., oxybutynin, ipratropium bromide, tiotropium, carbamazepine, etc.) may increase the risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.

Drug-Food Interactions

No effects on the pharmacokinetics of NUCYNTA® CR were observed with administration of a high fat meal. NUCYNTA® CR can be taken with or without food (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Food Effect**).

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

The concomitant use of alcohol should be avoided. Due to its mu-opioid agonist activity, NUCYNTA® CR may be expected to increase the sedative effect of alcohol (see **WARNINGS and PRECAUTIONS, Serious Warnings and Precautions Box**).

DOSAGE AND ADMINISTRATION

NUCYNTA® CR should only be used in patients for whom alternative treatment options are ineffective or not tolerated (e.g., non-opioid analgesics), or would be otherwise inadequate to provide sufficient management of pain (e.g., immediate-release opioids).

NUCYNTA® CR should be swallowed whole; crushing, chewing or dissolving NUCYNTA® CR tablets can cause rapid release and absorption of a potentially fatal dose of tapentadol (see WARNINGS AND PRECAUTIONS, Serious Warnings and Precautions Box).

Dosing Considerations

As with many centrally acting analgesic medications, the dosing regimen should be individualized according to the severity of pain being treated, the patient's medical and analgesic history and the ability to follow-up and provide oversight of treatment. Owing to the varied response to opioids observed between individuals, it is recommended that all patients be started at the lowest possible dose of opioid therapy and titrated to an adequate level of analgesia, balanced against acceptable adverse events.

Recommended Dose and Dosage Adjustment

NUCYNTA® CR tablets can be taken with or without food (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Food Effect**).

Initiation of Therapy

Patients Currently Not Taking Opioid Analgesics **(Opioid Naïve)**

Patients currently not taking opioid analgesics should begin NUCYNTA® CR therapy with 50 mg twice a day (approximately every 12 hours) and then be individually titrated to an optimal dose within the therapeutic range of 100 mg to 250 mg twice daily.

Patients Currently Taking Opioid Analgesics **(Opioid Experienced)**
Due to the dual mechanism of action of tapentadol (see **ACTION AND CLINICAL PHARMACOLOGY**), caution should be exercised when switching from pure mu-opioids to tapentadol.

Generally, the nature of the previous analgesic, its administration and the mean total daily dose should be taken into account in choosing the initial dose. NUCYNTA® CR clinical studies demonstrated comparable pain relief between tapentadol CR and oxycodone CR at a dose ratio of 5:1. Published relative potency information may be used to calculate the relative equianalgesic dose of other opioids to oxycodone. Clinical guidelines suggest that a switch to a new drug should be accompanied by a 50% reduction in the calculated dose. Further adjustment to reach the optimal dose is recommended (see **Individualization of Dose and Maintenance of Therapy**). Patients should receive appropriate follow-up and oversight to ensure adequate analgesia and to minimize side effects.

The recommended NUCYNTA® CR dose is 100 mg to 250 mg twice daily, taken approximately every 12 hours.

Individualization of Dose and Maintenance of Therapy
Pain relief and other opioid effects should be frequently assessed. In clinical practice, titration of the total daily dose of NUCYNTA® CR should be based upon the amount of supplemental opioid utilization, severity of the patient's pain, and the patient's ability to tolerate NUCYNTA® CR. Patients should be titrated to a dose providing a meaningful improvement of pain with acceptable tolerability.

Experience from clinical studies has shown that a titration regimen in increments of 50 mg NUCYNTA® CR twice daily every 3 days was appropriate to achieve adequate pain control in most patients. Total daily doses greater than 500 mg of NUCYNTA® CR have not been studied and, therefore, are not recommended (see **CLINICAL TRIALS**).

If signs of excessive opioid-related adverse experiences are observed, the dose can be reduced depending on patient status and medical judgment. Adverse events can be treated symptomatically as well. Once adverse events are under control, upward titration can continue to an acceptable level of pain control.
During periods of changing analgesic requirement, including initial titration, frequent contact is recommended between physician and/or health care provider and the patient.

Management of Patients Requiring Rescue Medication
If rescue medications are warranted for episodes of pain in the course of appropriate adjustments of NUCYNTA® CR dose, medications such as acetaminophen, ibuprofen or tramadol may be given. Fentanyl products should not be used as rescue medication in patients taking NUCYNTA® CR. If immediate release tramadol is used as rescue medication, the total daily dose of tramadol should not exceed 400 mg. Selection of rescue medication should be based on individual patient conditions. For patients whose dose has been titrated to the recommended maintenance dose, without attainment of adequate analgesia, the total daily dose may be increased, unless precluded by side effects.

Conversion between NUCYNTA® IR and NUCYNTA® CR
Clinical data indicate that patients who have been titrated to a stable daily dose with NUCYNTA® IR and have achieved optimal analgesia with acceptable tolerability, can be directly converted to an approximately equivalent total daily dose of NUCYNTA® CR, and vice-versa, if necessary, with equivalent efficacy.

Discontinuation of Treatment
Patients on prolonged therapy may be withdrawn gradually from the drug if it is no longer required for pain control. Mild to moderate withdrawal symptoms could occur after abrupt discontinuation of treatment with tapentadol. Clinical experience suggests that withdrawal symptoms may be relieved by reinstitution of opioid therapy followed by a gradual, tapered dose reduction of the medication combined with symptomatic support (see **WARNINGS AND PRECAUTIONS, Withdrawal Symptoms** and **ADVERSE REACTIONS**).

Renal Impairment
No dosage adjustment is recommended in patients with mild or moderate renal impairment (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Renal Insufficiency**).

NUCYNTA® CR has not been studied in controlled efficacy studies in patients with severe renal impairment. The use in this population is contraindicated.

Hepatic Impairment
No dosage adjustment is recommended in patients with mild hepatic impairment (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Insufficiency)**.

NUCYNTA® CR should be used with caution in patients with moderate hepatic impairment. Treatment in these patients should be initiated at 50 mg NUCYNTA® CR and not be administered more frequently than once every 24 hours. Further treatment, which may include dose titration, should reflect maintenance of analgesia with acceptable tolerability (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Insufficiency**).

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

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 within the lower range of recommended doses.

Missed Dose

Patients should be advised not to take extra tablets or a double dose to make up for a missed dose. NUCYNTA® CR should be taken once approximately every 12 hours.

Disposal

NUCYNTA® CR should be kept in a safe place, out of the site and reach of children before, during and after use. NUCYNTA® CR should not be used in front of children, since they may copy these actions.

Unused or expired NUCYNTA® CR should be properly disposed of as soon as it is no longer needed to prevent accidental exposure to others, including children or pets. If temporary storage is required before disposal, a sealed child-proof container, such as a biohazard waste container or a lockable medication box could be obtained from a pharmacy.

NUCYNTA® CR should never be disposed of in household trash. Disposal via a pharmacy take-back program is recommended.

OVERDOSAGE

For management of a suspected drug overdose contact your regional Poison Control Centre.

Human Experience

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

Management of Overdosage

Management of overdosage should be focused on treating symptoms of mu-opioid receptor agonism. Primary attention should be given to re-establishment of a patent airway and institution of assisted or controlled ventilation when overdosage of NUCYNTA® CR is suspected.

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 antagonist product. Overdosage with naloxone has been associated with seizure.

Gastrointestinal decontamination may be considered in order to eliminate unabsorbed drug. Gastrointestinal decontamination with activated charcoal or by gastric lavage may be considered within 2 hours after intake. Before attempting gastrointestinal decontamination, care should be taken to secure the airway.

ACTION AND CLINICAL PHARMACOLOGY

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.

Pharmacodynamics

Tapentadol is a novel 3-[(1*R*,2*R*)-3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol with a dual mechanism of action, mu-opioid agonist and norepinephrine reuptake inhibitor. 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.

Clinical Safety Pharmacology

Cardiac Safety

Thorough QT Study:

In a randomized, double-blind, placebo- and positive-controlled crossover study, healthy subjects (N=61-63) were administered five consecutive doses of immediate-release tapentadol, NUCYNTA® IR, 100 mg every 6 hours, NUCYNTA® IR 150 mg every 6 hours, placebo and a single dose of moxifloxacin. At the doses studied, which produced mean ± SD steady-state C_{max} values of 129 ± 42.0 ng/mL for the 100 mg q6h dose and 197 ± 89.1 ng/mL for the 150 mg q6h dose, immediate release tapentadol (NUCYNTA® IR) had no relevant effect on the QTc interval, the PR interval, or QRS duration.

Evaluation in Phase 2/3 Clinical Trials:

In Phase 2/3 multiple-dose clinical studies, mean blood pressure values were similar between tapentadol and placebo for up to 3 months, but the frequencies of cases with clinically significant changes in blood pressure (blood pressure increased or decreased, hypertension or hypotension),

were higher in those on tapentadol. In an objective central electrocardiogram (ECG) evaluation of Phase 2/3 clinical studies, tapentadol showed no clinically relevant effect on the QTc interval.

Dependence

Tolerance and/or a withdrawal syndrome are more likely to occur the longer a patient is on continuous opioid therapy. Withdrawal symptoms included: nausea, diarrhea, insomnia, sweating, anxiety, arthralgia, and chills. Withdrawal symptoms may be reduced by tapering.

In a randomized, open-label, parallel group safety study, NUCYNTA® CR maintained stable analgesic scores throughout the 12-month duration of the study with stable average total daily dose, indicating no development of tolerance to the tested dose ranges of 50 to 250 mg twice daily. In another clinical study in patients with neuropathic pain (safety data only), patients were allowed to titrate within 3 weeks to optimal treatment dose followed by randomization to placebo or the same dose of NUCYNTA® CR (100 to 250 mg) fixed for 12 weeks in the maintenance period. Stable analgesia was maintained; there was no evidence for tolerance to NUCYNTA® CR, either over 15 weeks in fixed dosing, or over one year with flexible dosing.

Pharmacokinetics

Absorption:

Mean absolute bioavailability after single-dose administration (fasting) of tapentadol is approximately 32% due to extensive first-pass metabolism. Maximum serum concentrations of tapentadol are observed between 3 and 6 hours after administration of NUCYNTA® CR. Dose proportional increases in serum AUC were observed following administration of NUCYNTA® CR as single doses over a range of 50-250 mg. The increase in serum C_{max} values was greater than proportional to the increase in dose over this range. The deviation from dose-proportionality for mean C_{max} values ranged from 14% to 26% with each increase in dose from 50 to 250 mg.

Steady-state exposure of tapentadol is attained following the third dose (i.e., within 36 hours after first twice-daily multiple dose administration). Mean serum tapentadol C_{max} values accumulated approximately 1.6 times following dosing with 250 mg every 12 hours, relative to single-dose administration. The serum accumulation ratio is primarily determined by the dosing interval and apparent half-life of tapentadol.

Food Effect:

The AUC and C_{max} increased by 8% and 18%, respectively, when NUCYNTA® CR tablets were administered after a high-fat, high-calorie breakfast. Phase 3 clinical studies were conducted without restrictions to food intake. NUCYNTA® CR may be given with or without food.

Distribution:

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

Metabolism 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 the 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 after oral administration is on average (± standard deviation) 5.9 (±2.0) hours and the apparent clearance (CL/F) is on average 4449 (±1199) mL/min across all doses of tapentadol CR. The total serum clearance of tapentadol after intravenous administration is 1530 ± 177 mL/min.

Special Populations and Conditions

Pediatrics (< 18 years of age): The pharmacokinetic profile of tapentadol in children has not been evaluated. No clinical studies with NUCYNTA® CR have been conducted in children. Therefore, use of NUCYNTA® CR is not recommended in patients under 18 years of age.

Geriatrics (≥ 65 years of age): The mean exposure (AUC) to tapentadol was similar in elderly subjects and young adults, with a 16% lower mean C_{max} observed in the elderly subject group compared to young adult subjects. Because elderly patients are more sensitive to opioid effects and more likely to have decreased renal and hepatic function, care should be taken in dose selection as recommended.

Gender: Gender was not identified as a statistically significant covariate in the Population Pharmacokinetic Analysis of tapentadol.

Race: No statistically significant effect of race on any of the pharmacokinetic parameters was identified.

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

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

Genetic Polymorphism: Tapentadol is primarily eliminated through glucuronidation by several uridine diphosphate glucuronyl transferase isozymes. Although there are no direct data on the impact of genetic variation of single isozymes on the pharmacokinetics of tapentadol or its glucuronide metabolite, such effect is not expected. Due to the small contribution of CYP2C9, CYP 2C19, and CYP2D6 to the metabolism of tapentadol, a contribution of genetic polymorphism of these enzymes to variability in the pharmacokinetics of tapentadol is not expected.

STORAGE AND STABILITY

NUCYNTA® CR tablets should be stored at 15-30°C.

Keep NUCYNTA® CR out of the sight and reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

NUCYNTA® CR tablets contain tapentadol hydrochloride as the medicinal ingredient and are available in dosage strengths of 50 mg, 100 mg, 150 mg, 200 mg, and 250 mg tapentadol base in bottles of 60 tablets as follows:

50 mg tablet: A white capsule-shaped tablet debossed with “O-M” on 1 side and “50” on the other side

100 mg tablet: A light blue capsule-shaped tablet debossed with “O-M” on 1 side and “100” on the other side

150 mg tablet: A blue-green capsule-shaped tablet debossed with “O-M” on 1 side and “150” on the other side

200 mg tablet: A blue capsule-shaped tablet debossed with “O-M” on 1 side and “200” on the other side

250 mg tablet: A dark blue capsule-shaped tablet debossed with “O-M” on 1 side and “250” on the other side

Composition

The following inactive ingredients are common to all tablet strengths: Silicified microcrystalline cellulose, hypromellose, magnesium stearate, polyvinyl alcohol, talc, polyethylene glycol, titanium dioxide.

100 mg, 150 mg, 200 mg, and 250 mg tablets also contain FD&C Blue #2 Aluminum Lake. 150 mg tablets also contain yellow iron oxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

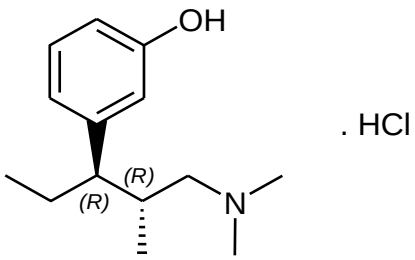
Drug Substance

Common name: tapentadol hydrochloride

Chemical name: 3-[(1*R*,2*R*)-3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol hydrochloride.

Molecular formula and molecular mass:
The molecular formula is $C_{14}H_{23}NO \bullet HCl$. The molecular weight of tapentadol HCl is 257.80, molecular weight of tapentadol base is 221.34.

Structural formula:



Physicochemical properties:
Tapentadol hydrochloride is a white to off-white powder. Tapentadol hydrochloride is freely soluble in water, 0.1 N HCl, and simulated intestinal fluid (SIF), soluble in ethanol, sparingly soluble in methanol and slightly soluble in 2-propanol. The melting point ranges from 204 to 210 °C. The n-octanol:water partition coefficient log P value is 2.89. The pKa values are 9.36 and 10.37.

CLINICAL TRIALS

The efficacy and safety of NUCYNTA® CR have been established in two studies in patients with moderate to severe chronic pain. The studies were randomized, double-blind, placebo- and active-controlled studies – one in patients with low back pain (LBP) and one in patients with pain related to osteoarthritis. An additional double-blind crossover study was also conducted to test whether subjects with moderate to severe chronic low back pain titrated to stable efficacy and tolerability could be switched between NUCYNTA® IR (50 mg, 75 mg, or 100 mg every 4

to 6 hours) and NUCYNTA® CR (100 mg, 150 mg, 200 mg, or 250 mg twice daily) while maintaining comparable efficacy.

Study Demographics and Trial Design

Table 3: Summary of Patient Demographics for Clinical Trials in Specific Indication

Study	Trial design	Dosage, route of administration and duration	Study subjects treated (n = number)	Mean age (Range)	Gender
Chronic low back pain PAI-3011	Randomized, double-blind, parallel-group; placebo and active	3-week titration to effect then 12 weeks maintenance with controlled dose adjustment NUCYNTA® CR: 100 mg to 250 mg BID Oxycodone CR: 20 mg to 50 mg BID placebo	n=965 (Randomized n=981)	49.9 (18 to 89)	M: 406 F: 559
Pain from Osteoarthritis of the knee PAI-3008	Randomized, double-blind, parallel-group; placebo and active	3-week titration to effect then 12 weeks maintenance with controlled dose adjustment NUCYNTA® CR: 100 mg to 250 mg BID Oxycodone CR: 20 mg to 50 mg BID placebo	n=1023 (Randomized n= 1030)	58.3 (40 to 91)	M: 405 F: 618
NUCYNTA® IR and NUCYNTA® CR					
PAI-3019/KF39 Chronic low back pain	Randomized, double-blind, 2-period crossover	Titration phase (3-week titration to optimal effect and tolerability): NUCYNTA® IR 50 mg, 75 mg, or 100 mg q4-6h. Double-blind phase (two 14-day cross-over periods): NUCYNTA® IR 50 mg, 75 mg, or 100 mg q4-6h at dose reached during titration; NUCYNTA® CR 100 mg, 150 mg, 200 mg, or 250 mg BID at the same total daily dose as for IR	n=116 (open-label) n=87 (for safety during double-blind treatment) n=60 (per protocol for non-inferiority)	53.6 years (21-88 years)	M: 51 F: 65

Studies in Chronic Pain

Low Back Pain (LBP)

Study PAI-3011 was a randomized, multi-centre, double-blind, parallel-group study in patients with moderate to severe chronic LBP, comparing controlled dose-adjustment regimens of NUCYNTA® CR (100 to 250 mg b.i.d.) to oxycodone controlled release (CR, 20 to 50 mg b.i.d.), and placebo b.i.d. Efficacy was evaluated in patients 18 years of age or older with chronic low back pain and a baseline pain score of ≥5 on an 11-point numerical rating scale (NRS), ranging from 0 to 10. Patients were randomized in a 1:1:1 ratio to 1 of 3 treatments: NUCYNTA® CR, oxycodone CR, or placebo.

Following a screening and a wash-out period, patients randomized to NUCYNTA® CR and oxycodone CR initiated the titration period with NUCYNTA® CR 50 mg and oxycodone CR 10 mg twice daily respectively for three days. The dose was increased to NUCYNTA® CR 100 mg b.i.d., oxycodone CR 20 b.i.d., or placebo b.i.d. for the next 4 days. Thereafter, increases in dose were allowed in increments of NUCYNTA® CR 50 mg b.i.d., oxycodone CR 10 mg b.i.d., or placebo for the remaining of the three weeks titration period to achieve a stable optimal dose. Subsequent titrations in increments of NUCYNTA® CR 50 mg b.i.d., oxycodone CR 10 mg b.i.d. were allowed over a 3-week titration period to a dose of 100 mg to 250 mg twice daily to achieve an optimal therapeutic dose. A 12-week maintenance period followed the titration period with allowed controlled dose adjustments in increments of NUCYNTA® CR 50 mg b.i.d., oxycodone CR 10 mg b.i.d. every three days.

Efficacy was evaluated by comparing the difference in pain intensity from baseline to the last week of the maintenance period between NUCYNTA® CR and placebo, and the difference in pain intensity from baseline to overall maintenance period between NUCYNTA® CR and placebo. The primary efficacy analyses were performed using the last observation carried forward (LOCF) imputation method for missing values. Sensitivity analyses were performed with various imputation methods (baseline observation carried forward [BOCF], worst observation carried forward [WOCF], placebo mean imputation [PMI], and modified BOCF to evaluate the robustness of the observed treatment effects on the primary efficacy endpoints.

There were 981 patients randomized; 965 patients received study drug. The mean age of the study population was 49.9 (range 18 to 89) years; the mean baseline pain intensity score was 7.6 (SD 1.29). Approximately half of the patients (46.6%) were opioid-naïve (had not taken opioids during the three months prior to the screening visit).

The number of patients completing the study was 50.5% in the placebo group, 54.1% in the NUCYNTA® CR group and 43.3% in the oxycodone CR group. Lack of efficacy was the most common reason for discontinuation among placebo-treated patients (20.7%), whereas adverse events were the most common reason for discontinuation among the active treatment groups (16.7% and 32.3% for NUCYNTA® CR and oxycodone CR, respectively).

Table 4: Results of Study PAI-3011 in Chronic Low Back Pain

Primary Efficacy Point	Statistics	Placebo	Tapentadol CR
Change from Baseline to Week 12 of Maintenance	Mean (SD)	-2.1 (2.33)	-2.9 (2.66)
	LS Mean Change	-2.1	-2.9
	LS Mean Difference versus placebo (SE)		-0.8 (0.19)
	95% CI (versus placebo)		[-1.22, -0.47]
	P-value (versus placebo)		<0.001

NUCYNTA® CR provided significantly greater analgesia compared to placebo throughout the entire 12-week maintenance period. Results of the primary endpoint using additional imputation methods were consistent with the primary analysis with significant improvement of pain for the NUCYNTA® CR group compared with the placebo group for all imputations methods (BOCF, WOCF, modified BOCF, and PMI).

A significantly higher proportion of NUCYNTA® CR patients had a 30% or 50% reduction in pain score from baseline to the end of Week 12 of the maintenance period compared to placebo (NUCYNTA® CR vs. placebo: 39.7% vs. 27.1% and 27.0% vs. 18.9%, respectively).

Other secondary efficacy points such as, change from baseline to 12-week overall maintenance, BPI, and SF36 are supportive.

Osteoarthritis (OA) Pain

Study PAI-3008 was a randomized, multi-centre, double-blind, parallel-group study, comparing controlled dose-adjustment regimens of NUCYNTA® CR (100 to 250 mg b.i.d.) to oxycodone controlled release (CR, 20 to 50 mg b.i.d.), and placebo in patients with moderate to severe chronic pain due to OA of the knee. Efficacy was evaluated in patients 40 years of age or older with pain due to osteoarthritis and a pain score of ≥5 on an 11-point numerical rating scale ranging from 0 to 10. Patients were randomized in a 1:1:1 ratio to 1 of 3 twice-daily treatments: NUCYNTA® CR, oxycodone CR, or placebo.

Following a screening and a wash-out period, patients randomized to NUCYNTA® CR and oxycodone CR initiated the titration period with NUCYNTA® CR 50 mg and oxycodone CR 10 mg twice daily respectively for three days. The dose was increased to NUCYNTA® CR 100 mg b.i.d., oxycodone CR 20 b.i.d., or placebo b.i.d. for the next 4 days. Thereafter, increases in dose were allowed in increments of NUCYNTA® CR 50 mg b.i.d., oxycodone CR 10 mg b.i.d., or placebo for the remaining of the three weeks titration period to achieve a stable optimal dose. Subsequent titrations in increments of NUCYNTA® CR 50 mg b.i.d., oxycodone CR 10 mg b.i.d. were allowed over a 3-week titration period to a dose of 100 mg to 250 mg twice daily to achieve an optimal therapeutic dose. A 12-week maintenance period followed the titration period with allowed controlled dose adjustments in increments of NUCYNTA® CR 50 mg b.i.d., oxycodone CR 10 mg b.i.d. every three days.

Efficacy was evaluated by comparing the difference in pain intensity from baseline to the last week of the maintenance period between NUCYNTA® CR and placebo, and the difference in

pain intensity from baseline to overall maintenance period between NUCYNTA® CR and placebo. The primary efficacy analyses were performed using the last observation carried forward (LOCF) imputation method for missing values.

There were 1030 patients randomized with 1023 patients received study drug. The mean age was 58.3 (range 40 to 91) years; the mean baseline pain intensity score was 7.3 (SD 1.31). Approximately two-thirds of the patients (67.6%) were opioid-naïve (had not taken opioids during the three months prior to the screening visit).

The number of patients completing the study was 61.4% in the placebo group, 57.3% in the NUCYNTA® CR group and 35.4% in the oxycodone CR group. Lack of efficacy was the most common reason for discontinuation among placebo-treated patients (16.7%), whereas adverse events were the most common reason for discontinuation among the active treatment groups (19.2% and 40.0% for NUCYNTA® CR and oxycodone CR, respectively).

Table 5: Results of Study PAI-3008 in Pain Due to Osteoarthritis

Primary Efficacy Point	Statistics	Placebo	Tapentadol CR
Change from Baseline to Week 12 of Maintenance	Mean (SD)	-2.2 (2.54)	-3.0 (2.39)
	LS Mean Change	-2.3	-2.9
	LS Mean Difference versus placebo (SE)		-0.7 (0.18)
	95% CI (versus placebo)		[-1.04, -0.33]
	P-value (versus placebo)		<0.001

NUCYNTA® CR provided significantly greater analgesia compared to placebo throughout the entire 12-week maintenance period.

A significantly higher proportion of NUCYNTA® CR patients had a 50% reduction in pain score from baseline to the end of Week 12 of the maintenance period compared to placebo (NUCYNTA® CR vs. placebo: 32.0% vs. 24.3%).

Other secondary endpoints, such as change from baseline to 12-week overall maintenance, 30% responder data, and WOMAC Health Survey were also supportive of efficacy.

NUCYNTA® IR and NUCYNTA® CR Dose Conversion Study in Low Back Pain Model

PAI-3019/KF39

Study PAI-3019/KF39 was a randomized, double-blind, multi-center, 2-period, crossover study to establish the dose equivalence and direct conversion between NUCYNTA® IR and NUCYNTA® CR in subjects with moderate to severe Low Back Pain (LBP). Subjects were titrated open label to an optimal dose of NUCYNTA® IR (50 mg, 75 mg, or 100 mg every 4 hours or 6 hours, with a maximum total daily dose of 500 mg) for 21 days. This was followed by 2 double-blind fixed dose crossover periods (using the total daily dose given either as NUCYNTA® IR or NUCYNTA® CR in the titration phase) each for a 14-day duration. The primary efficacy endpoint, assessed using a non-inferiority test, was the mean average pain intensity score during the last 3 days of each double-blind treatment period, measured twice daily with the 11-point NRS.

A total of 116 subjects were enrolled in the open-label Titration Period, 88 subjects were randomized, 87 subjects were included in the double-blind Safety Analysis Set and 60 subjects were included in the Per-Protocol Analysis Set. For the patients in the open-label Safety Analysis Set, the median age was 53.0 years (range 21 to 88) and the majority of subjects were women (56%), white (77.6%), and under 65 years of age (74.1%). The mean pre-treatment pain intensity, based on the 11-point NRS, at the start of the open-label titration was 7.3. Slightly more than half of the subjects (53.4%) were opioid naïve, they had not taken opioids during the 3 months prior to the screening visit.

The total mean pain intensity score decreased from a pre-treatment value of 7.3 to a mean score of 4.2 after 3 weeks of open-label titration (before the start of the double-blind crossover) (n=60, per protocol). The estimated mean average pain intensity score over the last 3 days of treatment from the primary analysis per protocol was 4.0 for the period on NUCYNTA® CR and 3.9 for the period on NUCYNTA® IR. The estimated difference in mean primary endpoint values (mean average pain intensity score over the last 3 days of treatment: NUCYNTA® CR to NUCYNTA® IR) was 0.1 with a 95% CI of (-0.09, 0.28) which was within the pre-specified margin of non-inferiority (-2, 2). This study demonstrated that patients who have been titrated to a stable daily dose with NUCYNTA® IR and have achieved optimal analgesia with acceptable tolerability, can be directly converted to an approximately equivalent total daily dose of NUCYNTA® CR, or vice-versa, if necessary, with equivalent efficacy.

DETAILED PHARMACOLOGY

Tapentadol hydrochloride, the centrally-active analgesic (anti-nociceptive) agent has an apparent dual-mode of action. Tapentadol is a mu-opioid receptor agonist with a K_i (mean ± SD) of 0.16 ± 0.04 μM, compared to morphine with a mean K_i of 0.009 ± 0.0035 μM, for the human mu-opioid receptor. In the GTPγS assay using membranes from cells expressing recombinant human μ-opioid receptors, the potency (mean EC_{50} ± SD) of tapentadol is 0.67 ± 0.15 μM, compared to 0.022 ± 0.003 μM for morphine.

Tapentadol also inhibits, in vitro, the reuptake of norepinephrine via the norepinephrine transporter. Both mechanisms are likely to contribute to the analgesic effects of the compound. In a microdialysis study in the rat, tapentadol elicited a dose-dependent increase of extracellular concentrations of norepinephrine whereas morphine did not increase extracellular concentrations of norepinephrine.

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-O-glucuronide, the major metabolite in man has no mu-opioid binding affinity and has no effects on norepinephrine – and 5-hydroxy tryptophan uptake mechanisms, up to a concentration of 10 μM. Furthermore, there are no other metabolites which contribute to the

analgesic activity of tapentadol. Tapentadol exerts its analgesic effects without a pharmacologically active metabolite.

TOXICOLOGY

Overview

Studies were conducted in mice, rats, guinea pigs, rabbits, dogs and monkeys to establish the toxicological profile of tapentadol hydrochloride following administration via different routes.

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).

Acute and Repeat-Dose Toxicity Studies

In acute toxicity studies in rodents with p.o. and i.v. administration, tapentadol HCl demonstrated a low acute toxicity. LD50 values were clearly above 300 (p.o.) or 40 (i.v.) mg/kg in mice and rats, respectively.

Tapentadol was evaluated in repeat-dose toxicity studies in mice, rats, dogs and monkeys up to a duration of 3, 6 or 12 months or 14 days, respectively. At high doses of tapentadol, transient, dose dependent and predominantly CNS-related findings, e.g., fearfulness, sedation or excited behaviour, recumbency and hunched posture, impaired respiratory function, rarely convulsions, were observed.

In dogs, salivation, vomiting and retching were additionally observed. The CNS- and gastrointestinal symptoms are concordant with the pharmacodynamic effects of MOR agonists. In rats, adaptive changes of the liver were seen. These changes are considered to be related to the xenobiotic overload of hepatocytes due to substantial phase II metabolism and are not regarded as a sign of overt hepatotoxicity. Additionally; there was a lack of relevant tumour formation in the liver in both rodent species (rats and mice) in the 2-year carcinogenicity studies.

In dogs, transient prolongation of the QTc-time was observed in repeat-dose studies. The effects increased with dose and were significant only at the beginning of the studies. No other electrocardiographic findings were observed. Some late toxicity, including convulsions and deaths in rats and dogs occurred in the high dose groups with a delay of several hours following intravenous or oral administration. The cause of these deaths remained unclear, but is regarded as a result of exaggerated pharmacodynamic effects of the compound.

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 (200 mg/kg/day = maximum tolerated dose in mice) for 2 years. Exposures based on mean plasma C_{max} were ~4.9x higher than the maximum recommended human daily dose. Exposure based on dose adjusted for body surface area (based on a 500 mg dose of NUCYNTA® CR to a 50 kg human) was ~1.6x higher in mice than the maximum recommended human daily dose. No increase in tumour incidence was observed at any dose level. In rats, tapentadol HCl was administered in the diet at dosages of 10, 50, 125 and 250 mg/kg/day for two years. Exposure based on dose adjusted for body surface area (based on a 500 mg dose of NUCYNTA® CR to a 50 kg human) was ~4.0x higher in rats than at the maximum recommended human daily dose. C_{max} values were not measured in this carcinogenicity study and therefore a direct C_{max} exposure multiple cannot be calculated. However, in 3- and 6-month oral gavage toxicity studies, at exposures similar to the AUC exposures in the rat carcinogenicity study, C_{max} exposures were on average ~2.5x higher than in humans at the maximum recommended daily dose. No increase in tumour incidence was observed at any dose level.

Mutagenesis

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

Impairment of Fertility

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

Developmental Studies

Tapentadol HCl was evaluated for teratogenic effects in pregnant rats and rabbits following intravenous and subcutaneous exposure during the period of embryofetal organogenesis. When tapentadol was administered twice daily by the subcutaneous route in rats at dose levels of 10, 20, or 40 mg/kg/day [producing up to 1.36 times the plasma exposure at the maximum recommended human dose (MRHD) of 500 mg/day for NUCYNTA® CR 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 up to 2.48 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 2.28 times the plasma exposure at the MRHD on an AUC basis] did not influence physical or reflex development, the outcome of neurobehavioral tests or reproductive parameters. Treatment-related developmental delay was observed, including incomplete ossification, and significant reductions in pup body weights and body weight gains at doses associated with maternal toxicity (150 mg/kg/day and above). At maternal tapentadol doses ≥150 mg/kg/day, a dose-related increase in pup mortality was observed to postnatal Day 4.

Dependence and Tolerance

Tapentadol is a mu-opioid receptor agonist. The potential to induce drug dependence and the abuse liability of tapentadol was studied in animal models in rats and monkeys. Tapentadol produced physical dependence as shown in an acute (mouse) and a chronic (rat) model. In both cases, however, tapentadol produced fewer withdrawal symptoms than morphine at equi-analgesic doses. In rat models of reward and reinforcement, tapentadol had potency comparable to morphine at equianalgesic doses. Tapentadol produced a conditioned place preference, was intravenously self administered, and generalized to a morphine cue (but not to an amphetamine cue) in a drug discrimination procedure.

Development of tolerance to the analgesic effects of tapentadol was much slower than that of morphine (at equianalgesic doses) in an acute and a chronic pain model in rats.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

[N]NUCYNTA® CR

tapentadol controlled-release tablets

Read this carefully before you start taking NUCYNTA® CR and each time you get a refill. This leaflet is a summary and will not tell you everything about NUCYNTA® CR tablets. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about NUCYNTA® CR.

Serious Warnings and Precautions

- **Even if you take NUCYNTA® CR as prescribed you are at risk for opioid addiction, abuse and misuse that can lead to overdose and death.**
- **Life-threatening breathing problems can happen while taking NUCYNTA® CR, especially if not taken as directed.**
- **Never give anyone your NUCYNTA® CR. They could die from taking it. If a person has not been prescribed NUCYNTA® CR, taking even one dose can cause a fatal overdose. This is especially true for children.**
- **Babies born to mothers who have taken NUCYNTA® CR (for short or long periods in small or large doses) during their pregnancy can suffer life-threatening withdrawal symptoms. This can occur in the days after birth and for up to 4 weeks after delivery. If your baby has breathing changes (weak, difficult or fast), is unusually difficult to comfort, has tremors (shakiness) or has increased stools, sneezing, yawning, vomiting, or fever, seek immediate medical help for your baby.**

What is NUCYNTA® CR used for:

NUCYNTA® CR is used for the long-term management of pain, when:

- the pain is severe enough to require daily, around the clock painkillers
- the doctor determines that other treatment options are not able to effectively treat your pain

NUCYNTA® CR is NOT used ("as needed") to treat pain that you only have once in a while.

How does NUCYNTA® CR work:

NUCYNTA® CR is a painkiller belonging to the class of medicines known as opioids. It relieves pain by acting on specific nerve cells of the spinal cord and brain.

What are the ingredients in NUCYNTA® CR:

Medicinal ingredients: tapentadol hydrochloride

Non-medicinal ingredients: Hypromellose, magnesium stearate, polyethylene glycol, polyvinyl alcohol, talc, silicified microcrystalline cellulose, titanium dioxide, FD&C Blue #2 Aluminum Lake (100 mg, 150 mg, 200 mg, and 250 mg tablets), yellow iron oxide (150 mg tablets).

NUCYNTA® CR comes in the following dosage forms:
NUCYNTA® CR is available as controlled-release tablets containing 50 mg, 100 mg, 150 mg, 200 mg and 250 mg tapentadol, as tapentadol hydrochloride.

Do not use NUCYNTA® CR if:

- you are allergic (hypersensitive) to tapentadol or any of the other ingredients of NUCYNTA® CR
- you have acute pain
- your pain can be controlled by occasional use of painkillers including those available without a prescription
- you have severe asthma, trouble breathing or any heart problems
- you have bowel blockage or narrowing of the stomach or intestines
- you have a head injury or other risks for seizures
- you suffer from alcoholism
- you are pregnant or plan to be pregnant, in labour or are breast-feeding
- you have paralysis of the gut
- you are also taking MAO inhibitors (certain medicines used for treatment of depression) or have taken them in the last 14 days before treatment with NUCYNTA® CR
- you have severe kidney or liver dysfunction
- you suffer from seizures
- you are under 18 years of age

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take NUCYNTA® CR. Talk about any health conditions or problems you may have, including if you:

- have a history of illicit or prescription drug or alcohol abuse
- have severe liver, kidney or heart disease
- have low blood pressure
- have past or current depression
- suffer from chronic or severe constipation
- have problems with your pancreas
- have slow or shallow breathing
- suffer from increased pressure in the brain or disturbed consciousness
- have had a head injury or brain tumours
- have had an epileptic fit, or if you have an increased risk of having epileptic fits
- have had serious allergic reactions to other medications (anaphylaxis)
- are going to have, or recently had planned surgery

Other warnings you should know about:
Driving and using machines: Before you perform tasks which may require special attention, wait until you know how you respond to NUCYNTA® CR. Drowsiness, dizziness or lightheadedness, can especially occur after the first dose and when the dose is increased.

Tell your healthcare professional about all the medications you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with NUCYNTA® CR:

- alcohol, including prescription and non-prescription medication containing alcohol. Do not drink alcohol while taking NUCYNTA® CR. This can lead to drowsiness, depressed breathing, serious side effects or a fatal overdose
- other sedative drugs which may enhance the drowsiness caused by NUCYNTA® CR
- other opioid analgesics (for pain)
- cough medicines containing opioids such as codeine
- general anaesthetics (used during surgery)
- drugs used to help you sleep or to reduce anxiety
- antidepressants (for depression and mood disorders). Do not take NUCYNTA® CR with MAO inhibitors or if you have taken MAO inhibitors in the last 14 days before treatment with NUCYNTA® CR
- other serotonin and norepinephrine re-uptake inhibitors
- triptan medicines
- drugs used to treat serious mental or emotional disorders such as schizophrenia
- antihistamines (for allergies)
- anti-emetics (for prevention of vomiting)
- drugs used to treat muscle spasms and back pain
- warfarin and other coumarin anticoagulants (for prevention/treatment of blood clots)
- anti-retroviral, anti-fungal and antibiotic drugs

How to take NUCYNTA® CR:

Swallow whole. Do not break, chew, dissolve or crush as it would cause too much drug to be released into your blood at one time and expose yourself to a potentially toxic dose of tapentadol.

Usual Adult Starting dose:
Dosage is individualized. Be sure to follow your doctor's dosing instructions exactly.
The usual dose is 1 tablet every 12 hours.

Your doctor may prescribe a different, more appropriate dose or interval of dosing, if this is necessary for you. If you feel that the effect of these tablets is too strong or too weak, talk to your doctor or pharmacist.

Overdose:

Signs of overdose may include abnormally slow or weak breathing, dizziness, confusion, extreme drowsiness, pin-point pupils, vomiting, drop in blood pressure, fast heart beat, collapse, disturbed consciousness or coma (deep unconsciousness), epileptic fits.

If you think you have taken too much NUCYNTA® CR, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed dose:
If you miss one dose, take it as soon as possible. However, if it is almost time for your next dose, then skip the missed dose. Do not take two doses at once. If you miss several doses in succession, talk to your doctor before restarting your medication.

Refilling Prescriptions for NUCYNTA® CR:
A new written prescription is required from your doctor each time you need more NUCYNTA® CR. Therefore, it is important that you contact your doctor before your current supply runs out.

What are the possible side effects from using NUCYNTA® CR?
These are not all the possible side effects you may feel when taking NUCYNTA® CR. If you experience any side effects not listed here, contact your health care professional.

Side effects may include:
- Drowsiness, insomnia
- Dizziness, fainting
- Nausea, vomiting, poor appetite, dry mouth
- Headache
- Problems with vision
- Weakness, uncoordinated muscle movement
- Itching
- Sweating
- Constipation

Talk with your doctor or pharmacist about ways to prevent constipation when you start using NUCYNTA® CR.

Seizures NUCYNTA® CR 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® CR.

Serious side effects and what to do about them			
Symptom/effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE **Overdose:** hallucinations, confusion, inability to walk normally, slow or weak breathing, extreme sleepiness, sedation, or dizziness,			✓

floppy muscles/low muscle tone, cold and clammy skin			
Respiratory Depression: Slow, shallow or weak breathing			✓
Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			✓
Bowel Blockage (impaction): abdominal pain, severe constipation, nausea			✓
Withdrawal: nausea, vomiting, diarrhea, anxiety, shivering, cold and clammy skin, body aches, loss of appetite, sweating		✓	
Fast, Slow or Irregular Heartbeat: heart palpitations		✓	
Low Blood Pressure: dizziness, fainting, light-headedness	✓		

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

We encourage you to report serious or unexpected side effects to Health Canada. The information is used to check for new safety concerns about health products. As a consumer, your report contributes to the safe use of health products for everyone**. 3 ways to report:**

- Report online at MedEffect
- By calling 1-866-234-2345 (toll free)
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

Storage:

Keep unused or expired NUCYNTA® CR in a secure place to prevent theft, misuse or accidental exposure.

Keep NUCYNTA® CR out of the sight and reach of children and pets.

Store NUCYNTA® CR at 15-30°C.

Do not use NUCYNTA® CR after the expiry date.

Disposal:

NUCYNTA® CR should never be thrown into household trash, where children and pets may find it. It should be returned to a pharmacy for proper disposal.

If you want more information about NUCYNTA® CR:

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for health professionals and includes this patient medication information by visiting the Health Canada website, the manufacturer's website http://www.janssen.ca, or by contacting the sponsor, Janssen Inc., at: 1-800-567-3331 or at: 1-800-387-8781.

This leaflet was prepared by
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