

PRODUCT MONOGRAPH

^NNUCYNTA[®] IR

Tapentadol

Immediate-Release Tablets
50 mg, 75 mg, and 100 mg
Tapentadol (as tapentadol hydrochloride)

Opioid Analgesic

Endo Ventures Ltd
First Floor, Minerva, Simmonscourt Road
Ballsbridge, Dublin 4
Ireland

Date of Preparation:
January 13, 2012

Date of Revision:
May 22, 2018

Version 2.0

Importer/ Distributer
Paladin Labs Inc.
100 Alexis Nihon Blvd, Suite 600
Montreal, H4M 2P2
Quebec, Canada

Submission Control No: 213119

All trademarks used under license.

TABLE OF CONTENTS

PART 1: HEALTH PROFESSIONAL INFORMATION	3
SUMMARY PRODUCT INFORMATION	3
INDICATIONS AND CLINICAL USE	3
CONTRAINDICATIONS	4
WARNINGS AND PRECAUTIONS	4
ADVERSE REACTIONS	15
DRUG INTERACTIONS	21
DOSAGE AND ADMINISTRATION	23
OVERDOSAGE	277
ACTION AND CLINICAL PHARMACOLOGY	28
STORAGE AND STABILITY	32
DOSAGE FORMS, COMPOSITION AND PACKAGING	32
PART II: SCIENTIFIC INFORMATION	33
PHARMACEUTICAL INFORMATION	33
CLINICAL TRIALS	34
DETAILED PHARMACOLOGY	38
TOXICOLOGY	38
REFERENCES	41
PART III: CONSUMER INFORMATION	43

NUCYNTA[®] IR

Tapentadol

Immediate-Release Tablets
50 mg, 75 mg, and 100 mg
Tapentadol (as tapentadol hydrochloride)

Opioid Analgesic

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	Tablet / 50 mg, 75 mg, and 100 mg tapentadol, as tapentadol hydrochloride	microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, povidone, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, FD&C yellow #6 aluminum lake, D&C yellow #10 aluminum lake.

INDICATIONS AND CLINICAL USE

Adults

NUCYNTA[®] IR (tapentadol immediate-release) is indicated for the management of moderate to severe acute pain in adults.

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 (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics**).

Pediatrics (< 18 years of age):

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

CONTRAINDICATIONS

- 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 or 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).
- Patients with mild pain that can be managed with other pain medications.
- Severe renal or hepatic impairment (creatinine clearance of less than 30 mL/min and/or Child-Pugh Class C).
- Patients with acute or severe bronchial asthma, chronic obstructive airway disease, or 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.
- Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy).
- Women who are breastfeeding, pregnant, or during labour and delivery (see **SERIOUS WARNINGS AND PRECAUTIONS and WARNINGS AND PRECAUTIONS**).

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 risks of overdose and death with immediate release opioid formulations, NUCYNTA[®] IR (tapentadol) tablets should only be used in patients for

SERIOUS WARNINGS AND PRECAUTIONS

whom alternative treatment options (e.g., non-opioid analgesics) are ineffective, not tolerated, or would be otherwise inadequate to provide appropriate management of pain (see DOSAGE AND ADMINISTRATION).

Addiction, Abuse, and Misuse

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

Life-threatening Respiratory Depression: OVERDOSE

Serious, life-threatening, or fatal respiratory depression may occur with use of NUCYNTA[®] IR. Infants exposed in-utero or through breast milk are at risk of life-threatening respiratory depression upon delivery or when nursed. Patients should be monitored for respiratory depression, especially during initiation of NUCYNTA[®] IR or following a dose increase.

NUCYNTA[®] IR must be swallowed whole. Cutting, breaking, crushing, chewing, or dissolving NUCYNTA[®] IR can lead to dangerous adverse events including death (see WARNINGS AND PRECAUTIONS). Further, instruct patients of the hazards related to taking opioids including fatal overdose.

Accidental Exposure

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

Neonatal Opioid Withdrawal Syndrome

Prolonged maternal use of NUCYNTA[®] IR 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[®] IR should be avoided as it may result in dangerous additive effects, causing serious injury or death (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death (see WARNINGS AND PRECAUTIONS, Neurologic and DRUG INTERACTIONS).

- Reserve concomitant prescribing of NUCYNTA[®] IR and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.

SERIOUS WARNINGS AND PRECAUTIONS

- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

General

Patients should be instructed not to give NUCYNTA[®] IR (tapentadol) tablets to anyone other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death. NUCYNTA[®] IR should be stored securely to avoid theft or misuse.

NUCYNTA[®] IR should only be prescribed by persons knowledgeable in the administration of potent opioids, in the management of patients receiving potent opioids for the treatment of pain, and in the detection and management of respiratory depression, including the use of opioid antagonists.

Patients should be cautioned not to consume alcohol while taking NUCYNTA[®] IR as it may increase the chance of experiencing serious adverse events, including death.

Hyperalgesia that will not respond to a further dose increase of opioids can occur at particularly high doses. A tapentadol dose reduction or change in opioid may be required.

Abuse and Misuse

Like all opioids, NUCYNTA[®] IR is a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, NUCYNTA[®] IR should be prescribed and handled with caution.

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[®] IR, should be used with particular care in patients with a history of alcohol and illicit/prescription drug abuse. However, concerns about abuse, addiction, and diversion should not prevent the proper management of pain.

NUCYNTA[®] IR is intended for oral use only. The tablets should be swallowed whole with sufficient liquid and not chewed or crushed. Abuse of oral dosage forms can be expected to result in serious adverse events, including death.

Carcinogenesis and Mutagenesis

See **TOXICOLOGY** section.

Cardiovascular

Tapentadol administration may result in severe hypotension in patients whose ability to maintain adequate blood pressure is compromised by reduced blood volume, or concurrent administration of drugs such as phenothiazines and other tranquilizers, sedative/hypnotics, tricyclic antidepressants or general anesthetics. These patients should be monitored for signs of hypotension after initiating or titrating the dose of NUCYNTA[®] IR.

The use of NUCYNTA[®] IR in patients with circulatory shock should be avoided as it may cause vasodilation that can further reduce cardiac output and blood pressure.

Endocrine

Adrenal Insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

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 or 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).

Dependence/Tolerance

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

Physical dependence and tolerance reflect the neuroadaptation of the opioid receptors to chronic exposure to an opioid, 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. Some of the symptoms that may be associated with abrupt withdrawal of an opioid analgesic include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, anxiety, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning (see **ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment**).

Use in Drug and Alcohol Addiction

NUCYNTA[®] IR is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission is for the management of pain requiring opioid analgesia. Patients with a history of addiction to drugs or alcohol may be at higher risk of becoming addicted to NUCYNTA[®] IR; extreme caution and awareness is warranted to mitigate the risk.

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. In a safety study moderate withdrawal symptoms were seen in 0.3% of patients who stopped taking NUCYNTA[®] IR abruptly, while 17% experienced mild withdrawal symptoms. 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 reinstatement 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[®] IR 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[®] IR for patients who are suicidal or addiction prone.

Neurologic

Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol): Tapentadol 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. Respiratory depression, hypotension and profound sedation, coma or death may result.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics (see **DRUG INTERACTIONS**). If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when NUCYNTA[®] IR is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of

the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs (see **DRUG INTERACTIONS**).

NUCYNTA[®] IR should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects, including death (see **CONTRAINDICATIONS** and **ADVERSE REACTIONS, Sedation, and DRUG INTERACTIONS**).

Severe pain antagonizes the subjective and respiratory depressant actions of opioid analgesics. Should pain suddenly subside, these effects may rapidly become manifest.

Serotonin Syndrome

NUCYNTA[®] IR could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs (e.g. anti-depressants, migraine medications). Treatment with the serotonergic drug should be discontinued if such events (characterized by clusters of symptoms such as hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, mental status changes including confusion, irritability, extreme agitation progressing to delirium and coma) occur and supportive symptomatic treatment should be initiated. NUCYNTA[®] IR should not be used in combination with MAO inhibitors or serotonin-precursors (such as L-tryptophan, oxitriptan) and should be used with caution in combination with other serotonergic drugs (triptans, certain tricyclic antidepressants, lithium, tramadol, St. John's Wort) due to the risk of serotonergic syndrome (see **DRUG INTERACTIONS**).

Head Injury

The respiratory depressant effects of tapentadol, and the capacity to elevate cerebrospinal fluid pressure, may be greatly increased in the presence of an already elevated intracranial pressure produced by trauma. Also, tapentadol may produce confusion, miosis, vomiting and other side effects which obscure the clinical course of patients with head injury. In such patients, tapentadol must be used with extreme caution and only if it is judged essential (see **CONTRAINDICATIONS**).

Respiratory

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. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Tapentadol should be used with extreme caution in patients with substantially decreased respiratory reserve, pre-existing respiratory depression, hypoxia or 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[®] IR should be employed only under careful medical supervision at the lowest effective dose in such patients. (see **CONTRAINDICATIONS**).

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of NUCYNTA[®] IR 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[®] IR and following dose increases.

Life-threatening respiratory depression is more likely to occur in the elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients.

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[®] IR 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[®] IR are essential (see **DOSAGE AND ADMINISTRATION**). Overestimating the NUCYNTA[®] IR dose when converting patients from another opioid product can result in fatal overdose with the first dose. In these patients, the use of non-opioid analgesics should be considered, if feasible (see **WARNINGS AND PRECAUTIONS, Special Populations, Special Risk Groups**, and **DOSAGE AND ADMINISTRATION**). Respiratory depression has also been reported with the use of 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**).

Use in Patients with Chronic Pulmonary Disease: Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercarbia, or pre-existing respiratory depression, particularly when initiating therapy and titrating with NUCYNTA[®] IR, as in these patients, even usual therapeutic doses of NUCYNTA[®] IR may decrease respiratory drive to the point of apnea. In these patients, use of alternative non-opioid analgesics should be considered, if possible. The use of NUCYNTA[®] IR is contraindicated in patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus (see **CONTRAINDICATIONS**).

Interactions with Alcohol and Drugs of Abuse

Due to its mu-opioid agonist activity, NUCYNTA[®] IR may be expected to have additive effects when used in conjunction with alcohol, opioids, or illicit drugs that cause central nervous system depression, respiratory depression, hypotension, and profound sedation, coma, or death. If such combined therapy is necessary, a dose reduction of one or both agents should be considered. Use of NUCYNTA[®] IR with alcoholic beverages or prescription or non-prescription products containing alcohol should be avoided (see **DRUG INTERACTIONS**).

Psychomotor Impairment

Patients should be cautioned that NUCYNTA[®] IR 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 other CNS depressants, including other opioids, phenothiazine, sedative/hypnotics and alcohol (see **DRUG INTERACTIONS**).

Peri-operative Considerations

NUCYNTA[®] IR is not indicated for pre-emptive analgesia (administration pre-operatively for the management of post-operative pain).

In the case of planned chordotomy or other pain-relieving operations, patients should not be treated with NUCYNTA[®] IR for at least 24 hours before the operation and NUCYNTA[®] IR should not be used in the immediate post-operative period.

Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. Thereafter, if NUCYNTA[®] IR 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.

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).

Tapentadol and other morphine-like opioids have been shown to decrease bowel motility. Ileus is a common post-operative complication, especially after intra-abdominal surgery with opioid analgesia. Caution should be taken to monitor for decreased bowel motility in post-operative patients receiving opioids. Standard supportive therapy should be implemented.

NUCYNTA[®] IR should not be used in the early post-operative period (12 to 24 hours post-surgery) unless the patient is ambulatory and gastrointestinal function is normal.

Gastrointestinal Effects

Tapentadol and other morphine-like opioids have been shown to decrease bowel motility. Tapentadol may obscure the diagnosis or clinical course of patients with acute abdominal conditions (see **CONTRAINDICATIONS**).

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[®] IR is contraindicated in pregnant women (see **CONTRAINDICATIONS**).

Sexual Function/Reproduction

Long-term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility (see **ADVERSE REACTIONS, Post-Marketing Experience**)

Patient Counselling Information

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

Patients receiving NUCYNTA[®] IR 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[®] IR contains tapentadol, an opioid pain medicine.
3. Patients should be advised that NUCYNTA[®] IR should only be taken as directed. The dose of NUCYNTA[®] IR should not be adjusted without consulting with a physician.
4. Patients should be advised that NUCYNTA[®] IR (tapentadol) tablets are to be swallowed whole with sufficient liquid.
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[®] IR 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[®] IR 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[®] IR.
10. Patients should be advised of the most common adverse events that may occur while taking NUCYNTA[®] IR: nausea, dizziness, vomiting, somnolence and headache.
11. Patients should be advised that NUCYNTA[®] IR 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[®] IR 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[®] IR.
12. Patients should be advised that NUCYNTA[®] IR is a potential drug of abuse. They should protect it from theft or misuse.
13. Patients should be advised that NUCYNTA[®] IR should never be given to anyone other than the individual for whom it was prescribed.
14. 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[®] IR. Women who are breastfeeding or pregnant should not use NUCYNTA[®] IR.
15. Patients should be informed that NUCYNTA[®] IR could cause seizures if they are at risk for seizure or have epilepsy. Such patients should be advised to use NUCYNTA[®] IR with care. Patients should be advised to stop taking NUCYNTA[®] IR if they have a seizure while taking NUCYNTA[®] IR and seek medical help immediately.

Special Populations

Special Risk Groups: Tapentadol should be administered with caution to patients with a history of alcohol and drug abuse and in a reduced dosage to debilitated patients, and in patients with severely impaired pulmonary function, Addison's disease, hypothyroidism, myxedema, toxic psychosis, prostatic hypertrophy or urethral stricture.

Pregnant Women:

Studies in pregnant women have not been conducted. While animal reproduction studies have revealed no evidence of harm to the fetus due to tapentadol (see **TOXICOLOGY, Development Studies**) NUCYNTA[®] IR crosses the placental barrier and is contraindicated in pregnant women (see **CONTRAINDICATIONS**).

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, ADVERSE REACTIONS, Post-marketing Experience**).

Pregnant women using opioids should not discontinue their medication abruptly as this can cause pregnancy complication such as miscarriage or still-birth. Tapering should be slow and under medical supervision to avoid serious adverse events to the fetus.

Labour, Delivery and Nursing Women:

Since opioids can cross the placental barrier and are excreted in breast milk, NUCYNTA[®] IR is contraindicated in nursing women and during labour and delivery. Life-threatening respiratory depression can occur in the infant if opioids are administered to the mother. Naloxone, a drug that counters the effects of opioids, should be readily available if NUCYNTA[®] IR is used in this population.

Use in Pancreatic/Biliary Tract Disease

Drugs with mu-opioid receptor agonist activity may cause spasm of the sphincter of Oddi. NUCYNTA[®] IR should be used with caution in patients with biliary tract disease, including acute pancreatitis.

Pediatrics (< 18 years of age)

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

Geriatrics (≥ 65 years of age)

Because elderly patients are more sensitive to opioid effects and more likely to have decreased renal and hepatic function, consideration should be given to starting elderly patients within the lower range of recommended doses. Such patients should be monitored closely, particularly when initiating and titrating NUCYNTA[®] IR 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[®] IR, 16% were 65 and over, while 4% were 75 and over. No overall differences in effectiveness were observed between these patients and younger patients (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**).

Patients with Hepatic Impairment

A study of tapentadol in subjects with hepatic impairment showed higher serum concentrations than in those with normal hepatic function. NUCYNTA[®] IR 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[®] IR 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).

Patients with Renal Impairment

NUCYNTA[®] IR 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**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse effects of NUCYNTA[®] IR (tapentadol) tablets are similar to those of other opioid analgesics, and represent an extension of pharmacological effects of the drug class. The major hazards of opioids include respiratory and central nervous system depression and to a lesser degree, circulatory depression, respiratory arrest, shock and cardiac arrest.

NUCYNTA[®] IR was studied in 10 multiple-dose, active- or placebo-controlled Phase 2/3 studies. A total of 2694 subjects with moderate to severe pain were treated with NUCYNTA[®] IR every four to six hours. The population was 18 to 78 years old (median age 50 years). Of the 2694 subjects, 2212 subjects (82.1%) had no prior opioid use. 778 subjects (28.9%) had a mean total daily dose up to 200 mg, 1443 subjects (53.6%) >200 mg to 400 mg, 456 subjects (17.3%) >400 mg to 600 mg, and 6 subjects (0.6%) >600 mg to 700 mg.

Based on data from the placebo- and/or active-controlled studies that administered multiple doses of NUCYNTA[®] IR, approximately 70 % of NUCYNTA[®] IR-treated patients experienced adverse events. These were predominantly of mild and moderate severity. The most common adverse events (reported by $\geq 10\%$ in any NUCYNTA[®] IR dose group) were: nausea, dizziness, vomiting, somnolence and headache.

No deaths were reported during the treatment period or within 30 days after treatment discontinuation in NUCYNTA[®] IR-treated groups. Approximately 0.7 % of NUCYNTA[®] IR-treated patients experienced a serious adverse event during the Phase 2/3 multi-dose studies vs. 0.4 % on placebo. The reported serious adverse events were consistent with the safety profiles of NUCYNTA[®] IR and the studied patient populations.

Approximately 10% of NUCYNTA[®] IR-treated patients with adverse events discontinued from the Phase 2/3 multi-dose studies and 0.4% (2/483) discontinued during open-label treatment. The most common reasons for discontinuation due to adverse events in these studies for NUCYNTA[®] IR and placebo-treated patients were nausea (2.0% vs. 0.5%), dizziness (2.3% vs. 0.6%), vomiting (1.3% vs. 0.1%), somnolence (1.2% vs. 0.3%), headache (0.9% vs. 0.4%), constipation (0.5% vs. 0%), and fatigue (0.5% vs. 0.1%), respectively.

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 $\geq 1\%$ of NUCYNTA[®] IR-treated patients with moderate to severe pain from ten double-blind, active and/or placebo-controlled studies are summarized in **Table 1**, if they occurred at an equivalent or higher rate with NUCYNTA[®] IR than with placebo. These adverse events were included regardless of any causal relationship to NUCYNTA[®] IR.

Table 1: Treatment Emergent Adverse Events reported by $\geq 1\%$ of NUCYNTA[®] IR-treated Patients in Phase 2/3 Double-blind, Active and/or Placebo-controlled Multi-dose Clinical Studies		
System/Organ Class MedDRA preferred Term	NUCYNTA[®] IR (n=2694) %	Placebo (n=788) %
Gastrointestinal disorders		
Nausea	27.8	12.8
Vomiting	16.4	3.8
Constipation	7.8	3.2
Dry mouth	3.5	0.3
Diarrhea	2.5	2.2
Dyspepsia	1.6	0.6
Nervous system disorders		
Dizziness	20.5	7.1
Somnolence	12.9	2.8
Headache	9.8	9.8
Tremor	1.1	0.3
Skin and subcutaneous tissue disorders		
Pruritus	4.4	0.9
Hyperhidrosis	2.3	0.9
Pruritus generalized	2.0	0.6
Psychiatric disorders		
Insomnia	1.4	1.0
Anxiety	1.3	0.9
Confusional state	1.2	0
General disorders and administration site conditions		
Pyrexia	3.4	3.4

Table 1: Treatment Emergent Adverse Events reported by $\geq 1\%$ of NUCYNTA[®] IR-treated Patients in Phase 2/3 Double-blind, Active and/or Placebo-controlled Multi-dose Clinical Studies		
System/Organ Class MedDRA preferred Term	NUCYNTA[®] IR (n=2694) %	Placebo (n=788) %
Fatigue	2.7	0.5
Feeling hot	1.0	0.5
Infections and infestations		
Nasopharyngitis	1.1	0.1
Upper respiratory tract infection	1.0	0.1
Metabolism and nutrition disorders		
Decreased appetite	1.3	0
Musculoskeletal and connective tissue disorders		
Muscle spasms	1.0	0.9

Sedation: Sedation is a common side effect of opioid analgesics, especially in opioid naïve individuals. Sedation may also occur partly because patients often recuperate from prolonged fatigue after the relief of persistent pain. Most patients develop tolerance to the sedative effects of opioids within three to five days and, if the sedation is not severe, will not require any treatment except reassurance. If excessive sedation persists beyond a few days, the dose of the opioid should be reduced and alternate causes investigated. Some of these are: concurrent CNS depressant medication, hepatic or renal dysfunction, brain metastases, hypercalcemia and respiratory failure. If it is necessary to reduce the dose, it can be carefully increased again after three or four days if it is obvious that the pain is not being well controlled. Dizziness and unsteadiness may be caused by postural hypotension, particularly in elderly or debilitated patients, and may be alleviated if the patient lies down.

Nausea and Vomiting: Nausea is a common side effect on initiation of therapy with opioid analgesics and is thought to occur by activation of the chemoreceptor trigger zone, stimulation of the vestibular apparatus and through delayed gastric emptying. The prevalence of nausea declines following continued treatment with opioid analgesics. When instituting therapy with an opioid for chronic pain, the routine prescription of an antiemetic should be considered. In the cancer patient, investigation of nausea should include such causes as constipation, bowel obstruction, uremia, hypercalcemia, hepatomegaly, tumor invasion of celiac plexus and concurrent use of drugs with emetogenic properties. Persistent nausea which does not respond to dosage reduction may be caused by opioid-induced gastric stasis and may be accompanied by other symptoms including anorexia, early satiety, vomiting and abdominal fullness. These symptoms respond to chronic treatment with gastrointestinal prokinetic agents.

Constipation: Practically all patients become constipated while taking opioids on a persistent basis. In some patients, particularly the elderly or bedridden, fecal impaction may result. It is essential to caution the patients in this regard and to institute an appropriate regimen of bowel management at the start of prolonged opioid therapy. Stimulant laxatives, stool softeners, and other appropriate measures should be used as required. As fecal impaction may present as

overflow diarrhea, the presence of constipation should be excluded in patients on opioid therapy prior to initiating treatment for diarrhea.

The following adverse effects occur less frequently with opioid analgesics and include those reported in NUCYNTA[®] IR clinical trials, whether related or not to tapentadol.

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% of NUCYNTA[®] IR-treated patients in the double-blind, placebo- or active-controlled clinical studies and were observed at a higher incidence with NUCYNTA[®] IR than with placebo:

- **Blood and lymphatic system disorders:** leukocytosis
- **Cardiac disorders:** palpitations, angina pectoris
- **Ear and labyrinth disorders:** vertigo
- **Eye disorders:** vision blurred, visual disturbance, diplopia
- **Gastrointestinal disorders:** abdominal pain, stomach discomfort, abdominal distension, gastroesophageal reflux disease, rectal hemorrhage, toothache
- **General disorders and administration site conditions:** asthenia, irritability, edema peripheral, chest pain, infusion site pain, feeling of relaxation, pain, chills, drug withdrawal syndrome, feeling abnormal, feeling drunk, feeling jittery, local reaction, gait disturbance, influenza-like illness, thirst
- **Infections and infestations:** urinary tract infection, influenza, sinusitis, bronchitis, gastroenteritis, gastroenteritis viral, acute sinusitis, cystitis, rhinitis, laryngitis, lower respiratory tract infection, viral infection
- **Injury, poisoning and procedural complications:** contusion, fall, wound secretion, muscle strain, joint injury, skin laceration
- **Investigations:** oxygen saturation decreased, blood pressure increased, blood alkaline phosphatase increased, lipase increased, blood creatinine increased, blood triglycerides increased, electrocardiogram QT prolonged, electrocardiogram T-wave abnormal, liver function test abnormal
- **Metabolism and nutrition disorders:** anorexia, gout, dehydration, hyperglycemia, hypercholesterolemia
- **Musculoskeletal and connective tissue disorders:** arthralgia, muscle twitching, back pain, myalgia, joint swelling, muscle tightness, muscular weakness, musculoskeletal stiffness, bone pain, sensation of heaviness
- **Nervous system disorders:** lethargy, disturbance in attention, hypoesthesia, paraesthesia, sedation, dysarthria, migraine, burning sensation, dyskinesia, sinus headache, amnesia, dysgeusia, presyncope, memory impairment
- **Psychiatric disorders:** abnormal dreams, euphoric mood, visual hallucination, disorientation, restlessness, agitation, nightmare, hallucination, depressed mood, depressive symptom, sleep disorder, depression, illusion, libido decreased, nervousness, affect lability, dysphoria, auditory hallucination, panic attack
- **Renal and urinary disorders:** dysuria, urinary retention, hematuria, pollakiuria, nocturia
- **Reproductive system and breast disorders:** erectile dysfunction

- **Respiratory, thoracic and mediastinal disorders:** cough, dyspnea, nasal congestion, hypoxia, nasal discomfort, sinus congestion, hiccups, dry throat
- **Skin and subcutaneous tissue disorders:** urticaria, blister, cold sweat, acne, rash pruritic
- **Vascular disorders:** hot flush, hypertension, flushing, phlebitis

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, based on patient treatment years, the frequencies 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	
<i>Rare</i>	Diarrhea
Immune system disorders	
<i>Uncommon</i>	Hypersensitivity (including rare events of angioedema, anaphylaxis and anaphylactic shock)
Psychiatric disorders	
<i>Rare</i>	Hallucination
<i>Very rare</i>	Panic attack
Nervous system disorders	
<i>Uncommon</i>	Headache
Cardiac disorders	
<i>Rare</i>	Palpitations

Androgen deficiency

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

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[®] IR (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[®] IR with caution in patients currently using specified centrally-acting drugs or alcohol.
- Do not use NUCYNTA[®] IR 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.

Interaction with Benzodiazepines and Other Central Nervous System (CNS) Depressants

Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants (e.g. other opioids, sedatives/hypnotics, antidepressants, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, phenothiazines, neuroleptics, antihistamines, antiemetics, and alcohol) and beta-blockers, increases the risk of respiratory depression, profound sedation, coma, and death. Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation (see **WARNINGS AND PRECAUTIONS, Neurologic, Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol) and Psychomotor Impairment**). NUCYNTA[®] IR should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects.

Monoamine Oxidase Inhibitors

NUCYNTA[®] IR 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

Coadministration of tapentadol with a serotonergic agent, such as a Selective Serotonin Re-uptake Inhibitor or a Serotonin Norepinephrine Re-uptake Inhibitor, may increase the risk of serotonin syndrome, a potentially life-threatening condition (see **WARNINGS AND PRECAUTIONS**).

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[®] IR 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 linezolid, 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[®] IR 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[®] IR were observed with administration of a high fat meal. NUCYNTA[®] IR 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[®] IR may be expected to increase the sedative effect of alcohol.

DOSAGE AND ADMINISTRATION

For acute pain, it is recommended that NUCYNTA[®] IR be used for a maximum of 7 days at the lowest dose that provides adequate pain relief.

All doses of opioids carry an inherent risk of fatal or non-fatal adverse events. This risk is increased with higher doses. If NUCYNTA[®] IR is used for more than 7 days for the management of chronic non-cancer, non-palliative pain, it is recommended that 300 mg (90 morphine milligram equivalent) of NUCYNTA[®] IR not be exceeded. Each patient should be assessed for their risk prior to prescribing NUCYNTA[®] IR, as the likelihood of experiencing serious adverse events can depend upon the type of opioid, duration of treatment, level of pain as well as the patient's own level of tolerance. In addition, the level of pain should be assessed routinely to confirm the most appropriate dose and the need for further use of NUCYNTA[®] IR (see DOSAGE AND ADMINISTRATION - Adjustment or Reduction of Dosage).

NUCYNTA[®] IR should only be used in patients for whom alternative treatment options are ineffective or not tolerated (e.g., non-opioid analgesics).

Swallow whole. Do not cut, break, crush, chew, or dissolve the tablet. This can be dangerous and can lead to death or seriously harm you (see WARNINGS AND PRECAUTIONS).

Dosing Considerations

NUCYNTA[®] IR (tapentadol tablets) should be used with caution within 12 hours pre-operatively and within the first 12-24 hours post-operatively (see **WARNINGS AND PRECAUTIONS, Peri-operative Considerations**). NUCYNTA[®] IR was studied for its efficacy and safety using post-operative pain models under stringent controls. It should only be given to post-operative patients after vital signs and gastrointestinal function are adequately recovered post-operatively.

NUCYNTA[®] IR is not indicated for rectal administration.

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.

NUCYNTA[®] IR tablets should be swallowed whole with sufficient liquid.

Recommended Dose and Dosage Adjustment

Adults:

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

Patients Not Receiving Opioid Analgesics at the Time of Treatment: The recommended initial oral dosage of NUCYNTA[®] IR is 50 mg, 75 mg, or 100 mg every 4 to 6 hours depending upon the pain intensity. On the first day of dosing, the second dose may be administered as soon as one hour after the first dose, if adequate pain relief is not attained with the first dose. Subsequent dosing is 50 mg, 75 mg, or 100 mg every 4 to 6 hours and should be adjusted to achieve optimal analgesia with acceptable tolerability.

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

Patients Currently Receiving Opioids: When switching from opioids to NUCYNTA[®] IR and choosing the initial dose, the nature of the previous medication, administration and the mean daily dose should be taken into account.

Opioid switching / rotation:

Conversion ratios for opioids are subject to variations in kinetics governed by genetics and other factors. Therefore, when switching from one opioid to another, **reduce calculated dose by 25-50%** to minimize the risk of overdose. Subsequently, up-titrate the dose as required to reach appropriate maintenance dose.

Table 3: Opioid Conversion Table^a

Opioids	To convert to oral morphine equivalent	To convert from oral morphine multiply by	Daily 90 mg MED ^b
Morphine	1	1	90 mg/d
Codeine	0.15	6.67	600 mg/d
Hydromorphone	5	0.2	18 mg/d
Oxycodone	1.5	0.667	60 mg/d
Tapentadol	0.3-0.4	2.5-3.33	300 mg/d
Tramadol	0.1-0.2	6	***
Methadone	Morphine dose equivalence is not reliably established		

*** The maximum recommended daily dose of tramadol is 300 mg - 400 mg depending on the formulation.

- a. Adapted from the 2017 Canadian guideline for opioids for chronic non-cancer pain. McMaster University; 2017
- b. MED: Morphine Equivalent Dose

Conversion between NUCYNTA[®] IR and NUCYNTA[®] CR

Clinical data indicate that NUCYNTA[®] IR may be titrated to achieve optimal analgesia with acceptable tolerability. Once on stable daily dosing, patients on NUCYNTA[®] IR can be directly converted into an approximately equivalent total daily dose of NUCYNTA[®] CR, and vice-versa, if necessary, with equivalent efficacy.

Discontinuation of Treatment

Patients on prolonged therapy with any tapentadol formulation 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 reinstatement 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**).

Patients with 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[®] IR should be used with caution in patients with moderate hepatic impairment. Treatment in these patients should be initiated at 50 mg of NUCYNTA[®] IR and not be administered more frequently than once every 8 hours (maximum of three doses in 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[®] IR has not been studied in patients with severe hepatic impairment and use in this population is contraindicated.

Patients with 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[®] IR has not been studied in controlled efficacy studies in patients with severe renal impairment. The use in this population is contraindicated.

Geriatrics:

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 sensitive to opioid effects and more likely to have decreased renal and hepatic

function, consideration should be given to starting elderly patients within the lower range of recommended doses.

Respiratory depression has occurred in the elderly following administration of large initial doses of opioids to patients who were not opioid-tolerant or when opioids were co-administered with other agents that can depress respiration. NUCYNTA[®] IR should be initiated at a low dose and slowly titrated to effect (see **WARNINGS AND PRECAUTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**).

Use with Non-Opioid Medications:

If a non-opioid analgesic is being provided, it may be continued. If the non-opioid is discontinued, consideration should be given to increasing the opioid dose to compensate for the non-opioid analgesic. NUCYNTA[®] IR can be safely used concomitantly with usual doses of other non-opioid analgesics.

Dose Titration:

Dose titration is the key to success with opioid analgesic therapy. **Proper optimization of doses scaled to the relief of the individual's pain should aim at administration of the lowest dose which will achieve the overall treatment goal of satisfactory pain relief with acceptable side effects.**

Dosage adjustments should be based on the patient's clinical response.

Adjustment or Reduction of Dosage:

Physical dependence with or without psychological dependence tends to occur with chronic administration of opioids, including NUCYNTA[®] IR. Withdrawal (abstinence) symptoms may occur following abrupt discontinuation of therapy. These symptoms may include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning.

Patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required for pain control. In patients who are appropriately treated with opioid analgesics and who undergo gradual withdrawal for the drug, these symptoms are usually mild (see **WARNINGS AND PRECAUTIONS**). Tapering should be individualised and carried out under medical supervision.

Patient should be informed that reducing and/or discontinuing opioids decreases their tolerance to these drugs. If treatment needs to be re-initiated, the patient must start at the lowest dose and titrate up to avoid overdose.

Disposal

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

NUCYNTA[®] IR should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended. Unused or expired NUCYNTA[®] IR 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.

Missed Dose

Patients should be advised not to take extra tablets or a double dose to make up for a missed dose. NUCYNTA[®] IR should be taken approximately every 4 to 6 hours.

Administration

NUCYNTA[®] IR tablets should be swallowed whole with sufficient liquid.

OVERDOSAGE

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

Human Experience

Experience with NUCYNTA[®] IR 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[®] IR 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-[(1R,2R)-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.

Central Nervous System:

NUCYNTA[®] IR produces respiratory depression by direct action on brain stem respiratory centres. The respiratory depression involves both a reduction in the responsiveness of the brain stem centres to increases in CO₂ tension and to electrical stimulation.

NUCYNTA[®] IR depresses the cough reflex by direct effect on the cough centre in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

Tapentadol causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of tapentadol overdose.

Gastrointestinal Tract and Other Smooth Muscle:

NUCYNTA[®] IR causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary and pancreatic secretions, spasm of the sphincter of Oddi, and transient elevations in serum amylase.

Cardiovascular System:

NUCYNTA[®] IR may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, hyperhidrosis and/or orthostatic hypotension.

Endocrine System:

Opioids may influence the hypothalamic-pituitary-adrenal or -gonadal axes. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone. Clinical signs and symptoms may be manifest from these hormonal changes.

Immune System:

In vitro and animal studies indicate that opioids have a variety of effects on immune functions, depending on the context in which they are used. The clinical significance of these findings is unknown.

Clinical Safety PharmacologyCardiac 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 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 \pm SD steady-state C_{max} values of 129 \pm 42.0 ng/mL for the 100 mg q6h dose and 197 \pm 89.1 ng/mL for the 150 mg q6h dose, 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.

In a randomized active-controlled safety study, NUCYNTA[®] IR was given every 4 to 6 hours, in subjects with either low back pain, or pain from osteoarthritis of the knee or hip (present for at least 3 months). The primary objective of this study was to evaluate the safety profile of NUCYNTA[®] IR with flexible doses of either 50 mg or 100 mg taken every 4 hours to 6 hours as needed (600 mg maximum total daily dose) over 90 days in comparison with a commonly used

strong mu-opioid analgesic. For patients treated with NUCYNTA[®] IR, the incidence of adverse events leading to discontinuation was 20.2% in opioid-naïve patients and 21.3% in opioid-experienced patients (defined as using opioid analgesics at least 5 days per week in the previous 30 days). For patients treated with the strong opioid comparator, the incidence of adverse events leading to discontinuation was 36.4% in opioid-naïve patients and 24.4% in opioid-experienced patients. NUCYNTA[®] IR had better gastrointestinal tolerability (e.g., with respect to nausea, vomiting and constipation) than the strong opioid comparator. NUCYNTA[®] IR was generally well tolerated with a safety profile consistent with its molecular actions. Moderate withdrawal symptoms were seen in 0.3% of patients who stopped taking NUCYNTA[®] IR abruptly, while 17% experienced mild withdrawal symptoms.

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 typically observed at around 1.25 hours after administration of NUCYNTA[®] IR tablets. Dose-proportional increases in the C_{max} and AUC values of tapentadol have been observed after administration of NUCYNTA[®] IR tablets over the oral therapeutic dose range.

A multiple (every 6 hours) dose study with doses ranging from 75 to 175 mg of NUCYNTA[®] IR tablets showed an accumulation ratio between 1.4 and 1.7 for the parent drug and between 1.7 and 2.0 for the major metabolite tapentadol-O-glucuronide (primarily determined by the dosing interval and apparent half-life of tapentadol and its metabolite).

Food Effect:

The AUC and C_{max} increased by 25% and 16%, respectively, when NUCYNTA[®] IR tablets were administered after a high-fat, high-calorie breakfast. Phase 3 clinical studies were conducted without restrictions to food intake. NUCYNTA[®] IR 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 IR and its metabolites are excreted almost exclusively (99%) via the kidneys. The terminal half-life after oral administration is on average (\pm standard deviation) 4.3 (\pm 0.8) hours and the apparent clearance (CL/F) is on average 4470 (\pm 1519) mL/min across all doses of tapentadol IR. The total serum clearance of tapentadol after intravenous administration is 1530 \pm 177 mL/min.

Special Populations and Conditions

Pediatrics (< 18 years of age): The pharmacokinetic profile of tapentadol in children has not been studied. No clinical studies with NUCYNTA[®] IR have been conducted in children. Individuals under 18 years of age should not take NUCYNTA[®] IR.

Geriatrics (\geq 65 years of age): The mean exposure (AUC) to tapentadol was similar in elderly subjects (\geq 65 years of age) 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 of 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, CYP2C19, 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[®] IR tablets should be stored at 15-30°C.

Keep NUCYNTA[®] IR out of the sight and reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

NUCYNTA[®] IR tablets contain tapentadol (as tapentadol hydrochloride) as the medicinal ingredient and are available in 50 mg, 75 mg, and 100 mg tapentadol dose strengths in bottles of 100 tablets as follows:

50 mg tablet: Yellow round biconvex film-coated tablet debossed with 'O-M' on one side and '50' on the other side.

75 mg tablet: Yellow-orange round biconvex film-coated tablet debossed with 'O-M' on one side and '75' on the other side.

100 mg tablet: Orange round biconvex film-coated tablet debossed with 'O-M' on one side and '100' on the other side.

Composition:

Core tablet: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone (K29 to K32).

Film coat: D&C Yellow #10 aluminum lake (50 and 75 mg only), FD&C Yellow #6 aluminum lake (all tablet strengths), polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide.

Packaging:

Bottles of 100 tablets

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

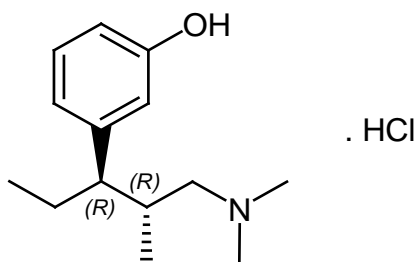
Common name: tapentadol hydrochloride

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

Molecular formula and molecular mass:

The molecular formula is $C_{14}H_{23}NO \cdot HCl$. The molecular weight of tapentadol HCl is 257.80; the 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[®] IR have been established in two studies in patients with acute moderate to severe pain. These studies were randomized, double-blind, placebo- and active-controlled studies for the relief of post-operative pain, one in patients following bunionectomy and one in patients with pain following an abdominal hysterectomy. An additional study was a randomized, double-blind, placebo-, and active-controlled study in patients with pain related to end-stage degenerative joint disease of the hip or knee within 10 days prior to a scheduled joint replacement surgery. 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
NUCYNTA[®] IR					
PAI-3003/KF32 Post-operative pain following bunionectomy	Randomized, double-blind, parallel-group; placebo- and active-controlled	Fixed oral dose q4-6h for 72 hours with an option for an early second dose on Day 1 Treatment groups: NUCYNTA [®] IR: 50 mg, 75 mg, or 100 mg; Oxycodone IR: 15 mg; placebo	n=602	46 years (18-77 years)	M: 77 F: 525
PAI-3016/KF35 Post-operative pain following abdominal hysterectomy	Randomized, double-blind, parallel-group; placebo- and active-controlled	Fixed oral dose q4-6h for 72 hours with an option for an early second dose on Day 1 Treatment groups: NUCYNTA [®] IR: 50 mg, 75 mg, or 100 mg; Morphine IR 20 mg; placebo	n=854	47.5 years (28-78 years)	M: 0 F: 854
PAI-3002/KF33 End-stage degenerative joint disease, pending surgery in 10 days	Randomized, double-blind, parallel-group; placebo- and active-controlled	Fixed oral dose q4-6h for 10 days Treatment groups: NUCYNTA [®] IR: 50 mg, or 75 mg; Oxycodone IR: 10 mg; placebo	n=666	61.2 years (20- 79 years)	M: 338 F: 328

Study	Trial design	Dosage, route of administration and duration	Study subjects treated (n = number)	Mean age (Range)	Gender
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 crossover 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

Bunionectomy Pain Model

PAI-3003/ KF 32

This study was a randomized, double-blind, parallel-group, placebo- and active-controlled, multiple-dose study evaluating the efficacy and safety of 50 mg, 75 mg, and 100 mg NUCYNTA[®] IR given every 4 h to 6 h for 72 h in patients experiencing moderate to severe acute pain following unilateral, first metatarsal bunionectomy surgery, followed by an optional 9-day open-label extension period with NUCYNTA[®] IR 50 mg or 100 mg. A total of 603 patients who qualified for the study with a baseline pain score of ≥ 4 on an 11-point numerical rating scale ranging from 0 to 10 were randomized to 1 of the 5 treatment groups in a 1:1:1:1:1 ratio and 602 subjects were treated. Patients were allowed to take a second dose of study medication as soon as 1 hour after the first dose on study Day 1, with subsequent dosing every 4 to 6 hours. If rescue analgesics were required, the patients were discontinued for lack of efficacy.

Subjects were between 18 years and 77 years of age, inclusive. Demographics and baseline characteristics were balanced across the treatment groups. Most subjects were White (55%), Hispanic (22%), or Black (20%). Most of the subjects across the treatment groups were women (87%) and less than 65 years of age (94%). The median baseline pain intensity score was 7.0 in all groups; the mean baseline pain score ranged from 6.9 in the placebo and NUCYNTA[®] IR 100 mg groups to 7.2 in the NUCYNTA[®] IR 50 mg group.

The primary efficacy endpoint was the sum of pain intensity difference over the first 48 hours (SPID₄₈) versus placebo. NUCYNTA[®] IR at each dose provided a greater reduction in pain compared to placebo based on SPID₄₈ values adjusted for multiple comparisons. The proportions

of patients who showed reduction in pain intensity at 48 hours of 30% or greater, were 40.0% on placebo, 64.7% on NUCYNTA[®] IR 50 mg, 68.3% on NUCYNTA[®] IR 75 mg, and 78.8% on NUCYNTA[®] IR 100 mg.

Hysterectomy Pain Model

PAI-3016/ KF35

This was a multicenter, randomized, double-blind, parallel-group, placebo- and active-controlled, inpatient study that examined the efficacy, safety, and pharmacokinetics of multiple doses of 50 mg, 75 mg, and 100 mg of NUCYNTA[®] IR for the relief of moderate to severe post-operative pain following an abdominal hysterectomy. Subjects took tapentadol IR every 4 hours to 6 hours for 3 days (with the option of taking an early second dose, as early as 1 hour, but no later than 6 hours after the first study drug administration). For inclusion, a baseline pain intensity of at least 4 on the 11-point (0 to 10) pain intensity NRS and at least moderate pain on a 4-point VRS rated within 30 minutes before randomization was required. Use of any additional analgesic medication during the double-blind treatment period led to the subjects being discontinued from the study for lack of efficacy. The primary variable was SPID₂₄ based on the NRS.

The demographic data of the treatment groups were similar. The treated subjects had a mean age of 47.5 years, with 98.4% being under 65 years old, and the age ranging from 28 years to 78 years. For the Intent-to-Treat population, the mean baseline pain intensity based on the 11-point NRS was similar in all treatment groups, ranging from 5.1 to 5.2.

The primary efficacy variable for this trial was SPID₂₄ calculated relative to the date and time of first dose.

NUCYNTA[®] IR 50 mg, 75 mg, and 100 mg demonstrated statistically significant improvements in pain relief compared to placebo on the primary efficacy endpoint, adjusted for multiple comparisons. The responder rate with at least a 30% reduction at 24 hours was 53.6% on placebo, 71.2% on NUCYNTA[®] IR 50 mg, 72.5% on NUCYNTA[®] IR 75 mg, and 73.3% on NUCYNTA[®] IR 100 mg.

Pain from End-Stage Degenerative Joint Disease Prior to Joint Replacement Surgery

PAI-3002/KF 33

This was a randomized, double-blind, parallel-group, placebo- and active-controlled, multiple-dose study evaluated the efficacy and safety of 50 mg and 75 mg NUCYNTA[®] IR given every 4 to 6 hours during waking hours in patients aged 20 to 79 years, experiencing moderate to severe pain from end stage degenerative joint disease of the hip or knee, waiting for a joint replacement surgery in 10 days. The severity of the pain was defined as a 3-day mean pain score of ≥ 5 on an 11-point pain intensity scale, ranging from 0 to 10. Pain scores were assessed twice daily and assessed the pain the patient had experienced over the previous 12 hours. Patients were allowed to continue non-opioid analgesic therapy for which they had been on a stable regimen before screening throughout the study. Eighty-three percent (83%) of patients in the NUCYNTA[®] IR treatment groups and the placebo group took such analgesia during the study. The 75 mg treatment group was dosed at 50 mg for the first day of the study, followed by 75 mg for the

remaining nine days. Patients requiring rescue analgesics other than study medication were discontinued for lack of efficacy.

Efficacy was evaluated by comparing the sum of pain intensity difference (SPID) versus placebo over the first five days of treatment. NUCYNTA[®] IR 50 mg and 75 mg provided improvement in pain compared with placebo based on the 5-Day SPID ($p < 0.001$ for both NUCYNTA[®] IR treatment groups, adjusted for multiple comparisons). The responder rate of at least a 30% pain reduction was 30.2% on placebo, 43.1% on NUCYNTA[®] IR 50 mg, and 41.0% on NUCYNTA[®] IR 75 mg.

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 NUCYNTA[®] IR may be used for titration to optimal balance of efficacy and tolerability. Then the patients can be directly converted into 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 (antinociceptive) agent has an apparent dual-mode of action. Tapentadol is a mu-opioid receptor agonist with a K_i (mean \pm SD) of $0.16 \pm 0.04 \mu\text{M}$, compared to morphine with a mean K_i of $0.009 \pm 0.0035 \mu\text{M}$, for the human mu-opioid receptor. In the GTP γ S assay using membranes from cells expressing recombinant human mu-opioid receptors, the potency (mean $\text{EC}_{50} \pm \text{SD}$) of tapentadol is $0.67 \pm 0.15 \mu\text{M}$, compared to $0.022 \pm 0.003 \mu\text{M}$ 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 $10 \mu\text{M}$. 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 ~4.6x higher than the maximum recommended human daily dose. Exposure based on dose adjusted for body surface area (based on a 700 mg dose of NUCYNTA[®] IR to a 50 kg human) was ~1.2x 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 700 mg dose of NUCYNTA[®] IR to a 50 kg human) was ~2.9x 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 ~2.7x 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 0.4 times 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 times the plasma exposure at the maximum recommended human dose (MRHD)] of 700 mg/day for NUCYNTA[®] IR based on an area under the time-curve (AUC) comparison], no teratogenic effects were observed. Evidence of embryofetal toxicity included transient delays in skeletal maturation (i.e., reduced ossification) at the 40 mg/kg/day dose which was associated with significant maternal toxicity.

Administration of tapentadol HCl in rabbits at doses of 4, 10, or 24 mg/kg/day by subcutaneous injection [producing 0.2, 0.6 and 1.85 times the plasma exposure at the MRHD based on an AUC comparison] revealed embryofetal toxicity at doses ≥ 10 mg/kg/day. Findings included reduced foetal viability, skeletal delays and other variations. In addition, there were multiple malformations including gastroschisis/thoracogastroschisis, amelia/phocomelia, and cleft palate at doses ≥ 10 mg/kg/day and above, and ablepharia, encephalopathy, and spina bifida at the high dose of 24 mg/kg/day. Embryofetal toxicity, including malformations, may be secondary to the significant maternal toxicity observed in the study.

In a study of pre- and postnatal development in rats, oral administration of tapentadol at doses of 20, 50, 150, or 300 mg/kg/day to pregnant and lactating rats during the late gestation and early postnatal period [resulting in up to 1.7 times the plasma exposure at the MRHD on an AUC basis] did not influence physical or reflex development, the outcome of neurobehavioral tests or reproductive parameters. Treatment-related developmental delay was observed, including incomplete ossification, and significant reductions in pup body weights and body weight gains at doses associated with maternal toxicity (150 mg/kg/day and above). At maternal tapentadol doses ≥ 150 mg/kg/day, a dose-related increase in pup mortality was observed 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 equianalgesic 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.

REFERENCES

1. Christoph T, De Vry J, Tzschentke TM. Tapentadol, but not morphine, selectively inhibits disease-related thermal hyperalgesia in a mouse model of diabetic neuropathic pain. *Neurosci Lett*. 2010; 470(2):91-94.
2. Daniels S, Casson E, Stegmann J-U, et al. A randomized, double-blind, placebo-controlled phase 3 study of the relative efficacy and tolerability of tapentadol IR and oxycodone IR for acute pain. *Curr Med Res Opin*. 2009; 25:1551-1561.
3. Daniels SE, Upmalis D, Okamoto A, et al. A randomized, double-blind, phase III study comparing multiple doses of tapentadol IR, oxycodone IR, and placebo for postoperative (bunionectomy) pain. *Curr Med Res Opin*. 2009; 25:765-776.
4. Etropolski M, Okamoto A, Shapiro DY, et al. Dose conversion between tapentadol immediate release and extended release for low back pain. *Pain Physician* 2010; 13: 61-70.
5. Etropolski MS, Kelly K, Okamoto A, Rauschkolb C. Comparable Efficacy and Superior Gastrointestinal Tolerability (Nausea, Vomiting, Constipation) of Tapentadol Compared with Oxycodone Hydrochloride. *Adv Ther* 2011; 28(5):401-417.
6. Hale M, Upmalis D, Okamoto A. Tolerability of tapentadol immediate release in patients with lower back pain or osteoarthritis of the hip or knee over 90 days: a randomized, double-blind study. *Curr Med Res Opin*. 2009; 25:1095-1104.
7. Hartrick C, Van Hove I, Stegmann J-U, et al. Efficacy and tolerability of tapentadol immediate release and oxycodone HCl immediate release in patients awaiting primary joint replacement surgery for end-stage joint disease: a 10-day, phase III, randomized, double-blind, active- and placebo-controlled study. *Clin Ther*. 2009; 31:260-271.
8. Hartrick C. Tapentadol immediate release for the relief of moderate-to-severe acute pain. *Expert Opin Pharmacother*. 2009; 10:2687-2696.
9. Kneip C, Terlinden R, Beier H, Chen G. Investigations into the drug-drug interaction potential of tapentadol in human liver microsomes and fresh human hepatocytes. *Drug Metab Lett*. 2008; 2(1):67-75.
10. Miaskowski C. A review of the incidence, causes, consequences, and management of gastrointestinal effects associated with postoperative opioid administration. *J Peri Anesth Nurs*. 2009; 24(4):222-228.
11. Oh C, Rengelshausen J, Mangold B, Etropolski M, Rauschkolb C, Wang SS, Upmalis D, Häufel T. A thorough QT/QT_c study of multiple doses of tapentadol immediate release in healthy subjects. *Int J Clin Pharmacol Ther*. 2010; 48:678-687.
12. Porreca F, Ossipov MH. Nausea and vomiting side effects with opioid analgesics during treatment of chronic pain: mechanisms, implications, and management options. *Pain*

Med. 2009; 10(4):654-662.

13. Schneider J, Jahnel U, Linz K. Neutral effects of the novel analgesic tapentadol on cardiac repolarization due to mixed ion channel inhibitory activities. *Drug Development Research*. 2010; 71:197-208.
14. Schröder W, Tzschentke TM, Terlinden R, et al. Synergistic Interaction between the Two Mechanisms of Action of Tapentadol in Analgesia. *J Pharmacol Exp Ther*. 2011; 337(1): 312-320.
15. Smit JW, Oh C, Rengelshausen J, et al. Effects of acetaminophen, naproxen, and acetylsalicylic acid on tapentadol pharmacokinetics: results of two randomized, open-label, crossover, drug-drug interaction studies. *Pharmacotherapy*. 2010; 30:25-34.
16. Tayal G, Grewal A, Mittal R, et al. Tapentadol - a novel analgesic. *J Anaesth Clin Pharmacol*. 2009; 25:463-466.
17. Terlinden R, Ossig J, Fliegert F, et al. Absorption, metabolism, and excretion of ¹⁴C-labeled Tapentadol HCl in healthy male subjects. *Eur J Drug Metab Pharmacokinet*. 2007; 32(3):163-169.
18. Terlinden R, Kogel BY, Englberger W, et al. In vitro and in vivo characterization of tapentadol metabolites. *Methods Find Exp Clin Pharmacol*. 2010; 32: 31-38.
19. Tzschentke TM, Christoph T, Kogel B, et al. (-) - (1R,2R) - 3 - (3-Dimethylamino-1-ethyl-2-methyl-propyl)-phenol Hydrochloride (Tapentadol HCl): a Novel μ -Opioid Receptor Agonist / Norepinephrine Reuptake Inhibitor with Broad Spectrum Analgesic Properties. *J Pharmacol Exp Ther*. 2007; 323(1):265-276.
20. Tzschentke TM, de Vry J, Terlinden R, et al. Tapentadol hydrochloride. *Drugs Future*. 2006; 31(12):1053-1061.
21. Tzschentke TM, Jahnel U, Kogel B, et al. Tapentadol hydrochloride: a next-generation, centrally-acting analgesic with two mechanisms of action in a single molecule. *Drugs Today*. 2009; 45:483-96.
22. Vorsanger G, Xiang J, Biondi DO, Upmalis D, Delfgaauw J, Allard R, Moskovitz B. Post hoc analysis of data from a 90-day clinical trial evaluating the tolerability and efficacy of tapentadol immediate release and oxycodone immediate release for the relief of moderate to severe pain in elderly and nonelderly patients. *Pain Res Manage* 2011; 16: 245-51.
23. Wade WE, Spruill WJ. Tapentadol hydrochloride: a centrally acting oral analgesic. *Clin Ther*. 2009; 31:2804-2818.
24. Xu XS, Smit JW, Lin R, et al. Population pharmacokinetics of tapentadol immediate release (IR) in healthy subjects and patients with moderate or severe pain. *Clin Pharmacokinet* 2010; 49 (10): 671-68.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

**^NNUCYNTA[®] IR
Tapentadol Immediate-Release Tablets**

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

Serious Warnings and Precautions

- **Even if you take NUCYNTA[®] IR as prescribed you are at a risk for opioid addiction, abuse and misuse. This can lead to overdose and death.**
- **When you take NUCYNTA[®] IR it must be swallowed whole. Do not cut, break, crush, chew, dissolve the tablet. This can be dangerous and can lead to death or seriously harm you.**
- **You may get life-threatening breathing problems while taking NUCYNTA[®] IR. This is less likely to happen if you take it as prescribed by your doctor. Babies are at risk of life-threatening breathing problems if their mothers take opioids while pregnant or nursing.**
- **You should never give anyone your NUCYNTA[®] IR. They could die from taking it. If a person has not been prescribed NUCYNTA[®] IR, taking even one dose can cause a fatal overdose. This is especially true for children.**
- **If you took NUCYNTA[®] IR while you were pregnant, whether for short or long periods of time or in small or large doses, your baby can suffer life-threatening withdrawal symptoms after birth. This can occur in the days after birth and for up to 4 weeks after delivery. If your baby has any of the following symptoms:**
 - **has changes in their breathing (such as weak, difficult or fast breathing)**
 - **is unusually difficult to comfort**
 - **has tremors (shakiness)**
 - **has increased stools, sneezing, yawning, vomiting, or fever****Seek immediate medical help for your baby.**
- **Taking NUCYNTA[®] IR with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including some street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.**

What is NUCYNTA® IR used for?

NUCYNTA® IR is used for the management of moderate to severe acute pain in adults.

How does NUCYNTA® IR work?

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

What are the ingredients in NUCYNTA® IR ?

Medicinal ingredients: tapentadol hydrochloride

Non-medicinal ingredients: Microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, povidone, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, FD&C yellow #6 aluminum lake, D&C yellow #10 aluminum lake.

NUCYNTA® IR comes in the following dosage forms:

NUCYNTA® IR tablets are available in 50 mg, 75 mg, and 100 mg tapentadol dose strengths.

Do not use NUCYNTA® IR if:

- your doctor did not prescribe it for you
- you are allergic to tapentadol or any of the other ingredients in NUCYNTA® IR
- you can control your pain by the occasional use of other pain medications. This includes those available without a prescription
- you have severe asthma, trouble breathing, or other breathing problems
- you have any heart problems
- you have bowel blockage or narrowing of the stomach or intestines
- you have severe pain in your abdomen
- you have a head injury
- you are at risk for seizures
- you suffer from alcoholism
- you are taking or have taken within the past 2 weeks a Monoamine Oxidase inhibitor (MAOi) (such as phenelzine sulphate, tranylcypromine sulphate, moclobemide or selegiline)
- you have severe kidney disease
- you have severe liver disease
- you are going to have, or recently had, a planned surgery
- you are pregnant or planning to become pregnant or you are in labour
- you are breastfeeding

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take NUCYNTA® IR. 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 low blood pressure
- have heart disease
- have past or current depression

- suffer from chronic or severe constipation
- have slow, fast, or shallow breathing
- suffer from increased pressure in the brain or disturbed consciousness
- have had a brain tumour
- have had an epileptic fit, or if you have an increased risk of having epileptic fits
- suffer from migraines
- have severe kidney, liver or lung disease
- suffer from a pancreatic or biliary tract disease, including pancreatitis
- have problems with your adrenal or prostate gland
- have had serious allergic reactions to other medications (anaphylaxis)
- have, or had in the past, hallucinations or other severe mental problems
- are planning to become pregnant.

Other warnings you should know about:

Swallow NUCYNTA[®] IR tablets whole with sufficient liquid.

Avoid taking alcoholic beverages, or prescription or non-prescription medications containing alcohol, while on NUCYNTA[®] IR therapy. The co-administration of alcohol with NUCYNTA[®] IR may increase the sedative effects of alcohol.

Opioid dependence and addiction: There are important differences between physical dependence and addiction. It is important that you talk to your doctor if you have questions or concerns about abuse, addiction or physical dependence.

Pregnancy, nursing, labour and delivery: Do not use NUCYNTA[®] IR while pregnant, nursing, during labour or delivery. Opioids can be transferred to your baby through breast milk, or while still in the womb. NUCYNTA[®] IR can then cause life-threatening breathing problems in your unborn baby or nursing infant.

If you are pregnant and are taking NUCYNTA[®] IR, it is important that you don't stop taking your medication all of a sudden. If you do, it can cause a miscarriage or a still-birth. Your doctor will monitor and guide you on how to slowly stop taking NUCYNTA[®] IR. This may help avoid serious harm to your unborn baby.

Driving and using machines: Before you do tasks which may require special attention, you should wait until you know how you react to NUCYNTA[®] IR. NUCYNTA[®] IR can cause:

- drowsiness
- dizziness or
- lightheadedness

This can usually occur after you take your first dose and when your dose is increased.

Disorder of the adrenal gland: You may develop a disorder of the adrenal gland called adrenal insufficiency. This means that your adrenal gland is not making enough of certain hormones. You may experience symptoms such as:

- nausea, vomiting

- feeling tired, weak or dizzy
- decreased appetite

You may be more likely to have problems with your adrenal gland if you have been taking opioids for longer than one month. Your doctor may do tests, give you another medication, and slowly take you off NUCYNTA[®] IR.

Serotonin Syndrome: NUCYNTA[®] IR can cause Serotonin Syndrome, a rare but potentially life-threatening condition. It can cause serious changes in how your brain, muscles and digestive system work. You may develop Serotonin Syndrome if you take NUCYNTA[®] IR with certain antidepressants or migraine medications.

Serotonin Syndrome symptoms include:

- fever, sweating, shivering, diarrhea, nausea, vomiting;
- muscle shakes, jerks, twitches or stiffness, overactive reflexes, loss of coordination;
- fast heartbeat, changes in blood pressure;
- confusion, agitation, restlessness, hallucinations, mood changes, unconsciousness, and coma.

Sexual Function/Reproduction: Long term use of opioids may lead to a decrease in sex hormone levels. It may also lead to low libido (desire to have sex), erectile dysfunction or being infertile.

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

The following may interact with NUCYNTA[®] IR :

- Alcohol. This includes prescription and non-prescription medications that contain alcohol. **Do not** drink alcohol while you are taking NUCYNTA[®] IR. It can lead to:
 - drowsiness
 - unusually slow or weak breathing
 - serious side effects or
 - a fatal overdose
- other sedative drugs which may enhance the drowsiness caused by NUCYNTA[®] IR
- other opioid analgesics (drugs used to treat pain)
- general anesthetics (drugs used during surgery)
- benzodiazepines (drugs used to help you sleep or that help reduce anxiety)
- antidepressants (for depression and mood disorders). **Do not** take NUCYNTA[®] IR with MAO inhibitors (MAOi) or if you have taken MAOi's in the last 14 days.
- drugs used to treat serious mental or emotional disorders (such as schizophrenia)
- antihistamines (drugs used to treat allergies)
- anti-emetics (drugs used for the prevention of vomiting)
- drugs used to treat muscle spasms and back pain
- drugs used to treat migraines (e.g. triptans)
- St. John's Wort

How to take NUCYNTA® IR :

NUCYNTA® IR is usually taken every 4-6 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.

NUCYNTA® IR is for oral use. You may take the tablets with or without food.

Always swallow NUCYNTA® IR tablets whole with sufficient liquid.

Swallow whole. Do not cut, break, crush, chew or dissolve the tablet. This can be dangerous and can lead to death or seriously harm you.

Usual Adult Starting Dose:

Your dose is tailored/personalized just for you. Be sure to follow your doctor's dosing instructions exactly. Do not increase or decrease your dose without consulting your doctor.

Your doctor will prescribe the lowest dose that works to control your pain. It is recommended that you only take NUCYNTA® IR for up to 7 days . If you need to take NUCYNTA® IR for longer, your doctor will determine the best dose for you to lower the risk of side effects and overdose. Higher doses can lead to more side effects and a greater chance of overdose.

Review your pain regularly with your doctor to determine if you still need NUCYNTA® IR. Be sure to use NUCYNTA® IR only for the condition for which it was prescribed.

If your pain increases or you develop any side effect as a result of taking NUCYNTA® IR, tell your doctor immediately.

Stopping your Medication:

If you have been taking NUCYNTA® IR for more than a few days you should not stop taking it all of a sudden. Your doctor will monitor and guide you on how to slowly stop taking NUCYNTA® IR.

You should do it slowly to avoid uncomfortable symptoms such as having:

- body aches
- diarrhea
- goosebump
- loss of appetite
- nausea
- feeling nervous or restless
- runny nose
- sneezing
- tremors or shivering
- stomach cramps
- rapid heart rate (tachycardia)

- having trouble sleeping
- an unusual increase in sweating
- heart palpitations
- an unexplained fever
- weakness
- yawning

By reducing or stopping your opioid treatment, your body will become less used to opioids. If you start treatment again, you will need to start at the lowest dose. You may overdose if you restart at the last dose you took before you slowly stopped taking NUCYNTA[®] IR.

Refilling your Prescription for NUCYNTA[®] IR :

A new written prescription is required from your doctor each time you need more NUCYNTA[®] IR . Therefore, it is important that you contact your doctor before your current supply runs out.

Only obtain prescriptions for this medicine from the doctor in charge of your treatment. Do not seek prescriptions from other doctors unless you switch to another doctor for your pain management.

Overdose:

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

Signs of overdose may include:

- unusually slow or weak breathing
- dizziness
- confusion
- extreme drowsiness

After taking very high doses, the following may be experienced:

- pin-point pupils, vomiting, drop in blood pressure, fast heart beat, collapse, disturbed consciousness or coma (deep unconsciousness), epileptic fits, dangerously slow or shallow breathing or stopped breathing.

If this happens, seek medical help immediately.

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 a row, talk to your doctor before restarting your medication.

What are possible side effects from using NUCYNTA[®] IR?

Like all medicines, NUCYNTA[®] IR may cause unwanted effects, although not everybody gets them. Some of these effects are on the nervous system and some are outside of the nervous system. The most frequently reported unwanted effects were nausea, dizziness, vomiting,

sleepiness, headache, constipation, and fatigue. NUCYNTA[®] IR can cause serious side effects including life-threatening breathing problems (see **SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM**). Tell your doctor if you have any other medical conditions.

Opioid withdrawal symptoms such as nausea, vomiting, diarrhea, anxiety and shivering are possible after converting from your previous opioid analgesic to NUCYNTA[®] IR, or converting from NUCYNTA[®] IR to another opioid. Contact your doctor if you experience these symptoms when switching to or from NUCYNTA[®] IR.

Seizures: NUCYNTA[®] IR 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[®] IR.

These are not all the possible side effects you may feel when taking NUCYNTA[®] IR . If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- drowsiness
- insomnia
- dizziness
- fainting
- nausea, vomiting, or a poor appetite
- dry mouth
- headache
- problems with vision
- weakness, uncoordinated muscle movement
- itching
- sweating
- constipation
- low sex drive, impotence (erectile dysfunction), infertility

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

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.	√		
Serotonin Syndrome: agitation or restlessness, loss of muscle control or muscle twitching, tremor, diarrhea			√

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:

- Online at **MedEffect**: <https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
 - Fax to 1-866-678-6789 (toll-free), or
 - Mail to: Canada Vigilance Program
Health Canada, Postal Locator 1908C
Ottawa, ON
K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at **MedEffect**. (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>).

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® IR in a secure place to prevent theft, misuse, or accidental exposure.**

- Store NUCYNTA[®] IR at room temperature (15-30°C).
- **Keep NUCYNTA[®] IR under lock, out of sight and reach of children and pets**
- **Never take medicine in front of small children as they will want to copy you. Accidental ingestion by a child is dangerous and may result in death. If a child accidentally takes NUCYNTA[®] IR, get emergency help right away.**

Do not use NUCYNTA[®] IR after the expiry date.

Disposal:

NUCYNTA[®] IR 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[®] IR:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this consumer medication information by visiting the Health Canada website (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the distributor's website www.paladinlabs.com, or by calling Paladin Labs Inc. at 1-888-867-7426

This leaflet was prepared by Endo Ventures Ltd.

Dublin 4, Ireland

Last Revised: May 22, 2018