PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

[N]APO-TAPENTADOL

Tapentadol Tablets

Tablets, 50 mg, 75 mg, and 100 mg Tapentadol (as tapentadol hydrochloride), oral

Opioid Analgesic

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RECENT MAJOR LABEL CHANGES

7 Warnings and Precautions, Opioid induced hyperalgesia	02/2022
7 Warnings and Precautions, Serotonin toxicity / Serotonin syndrome	02/2022
7 Warnings and Precautions, Reproductive Health: Female and Male Potential, Fertility	02/2022
7 Warnings and Precautions, Sleep apnea	02/2022

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PART I: HEALTH PROFESSIONAL INFORMATION

1. INDICATIONS

APO-TAPENTADOL (tapentadol tablets) is indicated for the management of moderate to severe acute pain in adults.

1.1 Pediatrics (<18 years)

The safety and efficacy of tapentadol have not been studied in the pediatric population. Therefore, use of APO-TAPENTADOL is not recommended in patients under 18 years of age.

1.2 Geriatrics (≥ 65 years of age)

Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness. 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 10. CLINICAL PHARMACOLOGY, Special Populations and Conditions, Geriatrics).

2. CONTRAINDICATIONS

APO-TAPENTADOL is contraindicated in:

- Patients who are hypersensitive (e.g. anaphylaxis, angioedema, anaphylactic shock) to tapentadol, to opioids, or to any ingredient in the formulation or component of the container (see 7. WARNINGS AND PRECAUTIONS, Hypersensitivity, and 8. ADVERSE REACTIONS, Post-Marketing Adverse Events). For a complete listing of ingredients, see the 6. 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 3. SERIOUS WARNINGS AND PRECAUTIONS BOX and 7. WARNINGS AND PRECAUTIONS).

3. SERIOUS WARNINGS AND PRECAUTIONS BOX

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, APO-TAPENTADOL (tapentadol) tablets should only be used in patients for 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 4. DOSAGE AND ADMINISTRATION).

Addiction, Abuse, and Misuse
APO-TAPENTADOL 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 APO-TAPENTADOL, and all patients should be monitored regularly for the development of these behaviours or conditions (see 7. WARNINGS AND PRECAUTIONS). APO-TAPENTADOL 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 APO-TAPENTADOL. 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 APO-TAPENTADOL or following a dose increase.

APO-TAPENTADOL must be swallowed whole. Cutting, breaking, crushing, chewing, or dissolving APO-TAPENTADOL can lead to dangerous adverse events including death (see 7. 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 APO-TAPENTADOL, especially by children, can result in a fatal overdose of tapentadol (see 11. STORAGE, STABILITY AND DISPOSAL for instructions on proper disposal).

Neonatal Opioid Withdrawal Syndrome

Prolonged maternal use of APO-TAPENTADOL during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening (see 7. WARNINGS AND PRECAUTIONS).

Interaction with Alcohol
The co-ingestion of alcohol with APO-TAPENTADOL should be avoided as it may result in dangerous additive effects, causing serious injury or death (see 7. WARNINGS AND PRECAUTIONS and 9. 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 7. WARNINGS AND PRECAUTIONS, Neurologic and 9. DRUG INTERACTIONS).

- Reserve concomitant prescribing of APO-TAPENTADOL and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

4. DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- **For acute pain, it is recommended that APO-TAPENTADOL 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 APO-TAPENTADOL 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) daily of APO-TAPENTADOL not be exceeded. Each patient should be assessed for their risk prior to prescribing APO-TAPENTADOL, 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 APO-TAPENTADOL** (see 4. DOSAGE AND ADMINISTRATION - Adjustment or Reduction of Dosage).
- **APO-TAPENTADOL 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 3. SERIOUS WARNINGS AND PRECAUTIONS BOX).
- APO-TAPENTADOL (tapentadol tablets) should be used with caution within 12 hours pre-operatively and within the first 12 to 24 hours post-operatively (see 7. WARNINGS AND

PRECAUTIONS, Peri-operative Considerations). Tapentadol 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.

- APO-TAPENTADOL 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.
- APO-TAPENTADOL tablets should be swallowed whole with sufficient liquid.

4.2 Recommended Dose and Dosage Adjustment

Adults: APO-TAPENTADOL tablets can be taken with or without food (see 10. CLINICAL PHARMACOLOGY, Pharmacokinetics, Food Effect).

Pediatrics (<18 years old): Health Canada has not authorized an indication for pediatric use.

Geriatrics (≥65 years of age): 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. APO-TAPENTADOL should be initiated at a low dose and slowly titrated to effect (see 7. WARNINGS AND PRECAUTIONS and 10. CLINICAL PHARMACOLOGY).

Patients Not Receiving Opioid Analgesics at the Time of Treatment: The recommended initial oral dosage of APO-TAPENTADOL 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 APO-TAPENTADOL 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 1: 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 Tapentadol Tablets and Tapentadol Extended-Release Tablets:
Clinical data indicate that tapentadol tablets may be titrated to achieve optimal analgesia with acceptable tolerability. Once on stable daily dosing, patients on tapentadol tablets can be directly converted into an approximately equivalent total daily dose of tapentadol extended-release tablets, 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 reinstitution of opioid therapy followed by a gradual, tapered dose reduction of the medication combined with symptomatic support (see 7. WARNINGS AND PRECAUTIONS, Withdrawal Symptoms and 8. ADVERSE REACTIONS).

Patients with Hepatic Impairment: No dosage adjustment is recommended in patients with mild hepatic impairment (see 10. CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Insufficiency).

APO-TAPENTADOL should be used with caution in patients with moderate hepatic impairment. Treatment in these patients should be initiated at 50 mg of APO-TAPENTADOL 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 10. CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Insufficiency).

Tapentadol 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 10. CLINICAL PHARMACOLOGY, Special Populations and Conditions, Renal Insufficiency).

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

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. APO-TAPENTADOL 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 APO-TAPENTADOL. 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 7. 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.

4.4 Administration

APO-TAPENTADOL tablets should be swallowed 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 (see 7. WARNINGS AND PRECAUTIONS).

4.5 Missed Dose

Patients should be advised not to take extra tablets or a double dose to make up for a missed dose. APO-TAPENTADOL should be taken approximately every 4 to 6 hours.

5. OVERDOSAGE

Human Experience

Experience with tapentadol 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, skeletal muscle flaccidity, cold and clammy skin, bradycardia, toxic leukoencephalopathy, delayed post-hypoxic leukoencephalopathy, hypotension, pneumonia aspiration, respiratory depression up to respiratory arrest, and death.

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 APO-TAPENTADOL 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.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablet / 50 mg, 75 mg, and 100 mg tapentadol, as tapentadol hydrochloride	colloidal silicon dioxide, croscarmellose sodium, D&C Yellow #10 Aluminum Lake (50 mg and 75 mg only), magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, Sunset Yellow Aluminum Lake, talc, titanium dioxide.

APO-TAPENTADOL 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 coated tablets. Engraved "APO" on one side, "T50" on the other side.

75 mg tablet: Yellow-orange, round, biconvex coated tablets. Engraved "APO" on one side, "T75" on the other side.

100 mg tablet: Orange, round, biconvex coated tablets. Engraved "APO" on one side, "T100" on the other side.

Packaging:
Bottles of 100 tablets

7 WARNINGS AND PRECAUTIONS

Please see 3. SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

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

APO-TAPENTADOL 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 APO-TAPENTADOL 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, tapentadol is a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, APO-TAPENTADOL 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 tapentadol, 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.

APO-TAPENTADOL 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 16. NON-CLINICAL TOXICOLOGY section.

Cardiovascular

Hypotension

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 tapentadol tablets.

The use of APO-TAPENTADOL in patients with circulatory shock should be avoided as it may cause vasodilation that can further reduce cardiac output and blood pressure.

Dependence/Tolerance

As with other opioids, tolerance and physical dependence may develop upon repeated administration of APO-TAPENTADOL 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 8. ADVERSE REACTIONS and 4. DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment).

Interactions with Alcohol and Drugs of Abuse
Due to its mu-opioid agonist activity, tapentadol 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 APO-TAPENTADOL with alcoholic beverages or prescription or non-prescription products containing alcohol should be avoided (see 9. DRUG INTERACTIONS).

Use in Drug and Alcohol Addiction
Tapentadol 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 APO-TAPENTADOL; extreme caution and awareness is warranted to mitigate the risk.

Driving and Operating Machinery

Patients should be cautioned that APO-TAPENTADOL 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 9. DRUG INTERACTIONS).

Endocrine and Metabolism

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.

Gastrointestinal

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 2. CONTRAINDICATIONS).

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 2. CONTRAINDICATIONS and 8. ADVERSE REACTIONS, Post-Marketing Adverse Reactions). Caution should also be exercised in patients who have had serious allergic reactions to other medications. For a complete listing of ingredients, see the 6. DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING section of the Product Monograph.

Hepatic/Biliary/Pancreatic

A study of tapentadol in subjects with hepatic impairment showed higher serum concentrations than in those with normal hepatic function. APO-TAPENTADOL should be used with caution in patients with moderate hepatic impairment (see 4. DOSAGE AND ADMINISTRATION, Patients with Hepatic Impairment and 10. CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Insufficiency).

Tapentadol has not been studied in patients with severe hepatic impairment and, therefore, use in this population is contraindicated (see 2. CONTRAINDICATIONS, 4. DOSAGE AND ADMINISTRATION, Patients with Hepatic Impairment, and 10. CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Insufficiency).

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

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 APO-TAPENTADOL is contraindicated in pregnant women (see 2. CONTRAINDICATIONS).

Neurologic

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 2. CONTRAINDICATIONS).

Opioid induced hyperalgesia

Opioid induced hyperalgesia (OIH) is a paradoxical response to an opioid in which there is an

increase in pain perception despite stable or increased opioid exposure. It differs from tolerance, in which higher opioid doses are required to achieve the same analgesic effect or treat recurring pain. Clinically, OIH may be associated with high opioid doses, long term opioid treatment, and intra-operative opioid use. OIH may manifest as an unexplained increase in pain, more diffuse pain than pre-existing, or as pain from ordinary (i.e. non-painful) stimuli (allodynia) in the absence of disease progression. When OIH is suspected, the dose of opioid should be reduced or tapered off, if possible. It is reasonable to consider opioid rotation, or the use of a non-opioid strategy for pain control. There is currently no well-established treatment for OIH.

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).

Serotonin toxicity / Serotonin syndrome

Serotonin toxicity also known as serotonin syndrome is a potentially life-threatening condition and has been reported with tapentadol hydrochloride, particularly during combined use with other serotonergic drugs (See 9. DRUG INTERACTIONS).

Serotonin toxicity is characterised by neuromuscular excitation, autonomic stimulation (e.g. tachycardia, flushing) and altered mental state (e.g. anxiety, agitation, hypomania). In accordance with the Hunter Criteria, serotonin toxicity diagnosis is likely when, in the presence of at least one serotonergic agent, one of the following is observed:

- Spontaneous clonus
- Inducible clonus or ocular clonus with agitation or diaphoresis
- Tremor and hyperreflexia

- Hypertonia and body temperature >38°C and ocular clonus or inducible clonus.

If concomitant treatment with APO-TAPENTADOL and other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see 9. DRUG INTERACTIONS). If serotonin toxicity is suspected, discontinuation of the serotonergic agents should be considered.

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 9. 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 APO-TAPENTADOL 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 9. DRUG INTERACTIONS).

APO-TAPENTADOL should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects, including death (see 2. CONTRAINDICATIONS and 8. ADVERSE REACTIONS, Sedation, and 9. DRUG INTERACTIONS).

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

Patient Counselling Information

A patient information sheet is included in the package of APO-TAPENTADOL tablets dispensed to the patient.

Patients receiving APO-TAPENTADOL 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 APO-TAPENTADOL contains tapentadol, an opioid pain medicine.
3. Patients should be advised that APO-TAPENTADOL should only be taken as directed. The dose of APO-TAPENTADOL should not be adjusted without consulting with a physician.
4. Patients should be advised that APO-TAPENTADOL (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 APO-TAPENTADOL 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 APO-TAPENTADOL 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 APO-TAPENTADOL.
10. Patients should be advised of the most common adverse events that may occur while taking APO-TAPENTADOL: nausea, dizziness, vomiting, somnolence and headache.
11. Patients should be advised that APO-TAPENTADOL 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 APO-TAPENTADOL 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 APO-TAPENTADOL.
12. Patients should be advised that APO-TAPENTADOL is a potential drug of abuse. They should protect it from theft or misuse.

13. Patients should be advised that APO-TAPENTADOL 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 APO-TAPENTADOL. Women who are breastfeeding or pregnant should not use APO-TAPENTADOL.
15. Patients should be informed that APO-TAPENTADOL could cause seizures if they are at risk for seizure or have epilepsy. Such patients should be advised to use APO-TAPENTADOL with care. Patients should be advised to stop taking APO-TAPENTADOL if they have a seizure while taking APO-TAPENTADOL and seek medical help immediately.

Peri-operative Considerations

APO-TAPENTADOL 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 APO-TAPENTADOL for at least 24 hours before the operation and APO-TAPENTADOL should not be used in the immediate post-operative period.

Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. Thereafter, if APO-TAPENTADOL 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.

APO-TAPENTADOL 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.

Renal

Tapentadol has not been studied in controlled efficacy studies in patients with severe renal impairment; therefore, its use in this population is contraindicated (see 2. CONTRAINDICATIONS, 4. DOSAGE AND ADMINISTRATION, Renal Impairment, and 10. CLINICAL PHARMACOLOGY, Special Populations and Conditions, Renal Insufficiency).

Reproductive health: Female and Male Potential

See sections 2. CONTRAINDICATIONS and 7.1.1 Pregnant Women.

Fertility
Animal data with Tapentadol did not show an alteration of fertility at any dose level (See section 16. NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology, IMPAIRMENT OF FERTILITY).

Function
Long-term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility (see 8. ADVERSE REACTIONS, Post-Marketing Adverse Reactions).

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 APO-TAPENTADOL should be employed only under careful medical supervision at the lowest effective dose in such patients. (see 2. CONTRAINDICATIONS).

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of APO-TAPENTADOL 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 APO-TAPENTADOL 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 APO-TAPENTADOL 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 tapentadol are essential (see 4. DOSAGE AND ADMINISTRATION). Overestimating the APO-TAPENTADOL 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 7. WARNINGS AND PRECAUTIONS, Special Populations, Special Risk Groups, and 4. 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 7. WARNINGS AND PRECAUTIONS, Seizure Risk and 5. 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 tapentadol, as in these patients, even usual therapeutic doses of APO-TAPENTADOL 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 APO-TAPENTADOL is contraindicated in patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus (see 2. CONTRAINDICATIONS).

Sleep Apnea
Opioids can cause sleep-related breathing disorders such as sleep apnea syndromes (including central sleep apnea [CSA]) and hypoxia (including sleep-related hypoxia). Opioid use increases the risk of CSA in a dose-dependent fashion. Evaluate patients on an ongoing basis for the onset of a new sleep apnea, or a worsening of an existing sleep apnea. In these patients, consider reducing or stopping the opioid treatment if appropriate, using best practices for tapering of opioids (see 4. DOSAGE AND ADMINISTRATION, Adjustment or Reduction of Dosage; 7. WARNINGS AND PRECAUTIONS, Dependence/Tolerance).

Risk of Overdosage

Serious potential consequences of overdosage with tapentadol 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 5. OVERDOSAGE).

Do not prescribe APO-TAPENTADOL for patients who are suicidal or addiction prone.

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 tapentadol 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 reinstitution of opioid therapy followed by a gradual, tapered dose reduction of the medication combined with symptomatic support.

7.1 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.

7.1.1 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 16. NON-CLINICAL TOXICOLOGY, Development Studies) tapentadol crosses the placental barrier and is contraindicated in pregnant women (see 2. 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 7. WARNINGS AND PRECAUTIONS, Neonatal Opioid Withdrawal Syndrome, 8. ADVERSE REACTIONS, Post-marketing Adverse Events).

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.

7.1.2 Breast-feeding

Since opioids can cross the placental barrier and are excreted in breast milk, APO-TAPENTADOL 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 APO-TAPENTADOL is used in this population.

7.1.3 Pediatrics (< 18 years)

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 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 tapentadol 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 tapentadol, 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 10. CLINICAL PHARMACOLOGY, Special Populations and Conditions).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Adverse effects of APO-TAPENTADOL (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.

Tapentadol 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 tapentadol 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 tapentadol, approximately 70 % of tapentadol-treated patients experienced adverse events. These were predominantly of mild and moderate severity. The most common adverse events (reported by ≥10% in any tapentadol 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 tapentadol-treated groups. Approximately 0.7 % of tapentadol-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 tapentadol and the studied patient populations.

Approximately 10% of tapentadol-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 tapentadol 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.

8.2 Clinical Trial Adverse 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 reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Double-Blind Studies

Treatment emergent adverse events (TEAEs) reported in ≥1% of tapentadol-treated patients with moderate to severe pain from ten double-blind, active and/or placebo-controlled studies are summarized in **Table 3**, if they occurred at an equivalent or higher rate with tapentadol than with placebo. These adverse events were included regardless of any causal relationship to tapentadol.

Table 3: Treatment Emergent Adverse Events reported by ≥1% of Tapentadol-treated Patients in Phase 2/3 Double-blind, Active and/or Placebo-controlled Multi-dose Clinical Studies

System/Organ Class MedDRA preferred Term	Tapentadol (n=2694) %	Placebo (n=788) %
Gastrointestinal		
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

Table 3: Treatment Emergent Adverse Events reported by ≥1% of Tapentadol-treated Patients in Phase 2/3 Double-blind, Active and/or Placebo-controlled Multi-dose Clinical Studies		
System/Organ Class MedDRA preferred Term	**Tapentadol (n=2694) %**	**Placebo (n=788) %**
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
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 tapentadol clinical trials, whether related or not to tapentadol.

8.3 Less Common Clinical Trial Adverse Reactions

The following treatment emergent adverse events (TEAEs), which have been included regardless of any causal relationship to tapentadol, occurred in less than 1% of tapentadol-treated patients in the double-blind, placebo- or active-controlled clinical studies and were observed at a higher incidence with tapentadol 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 10. CLINICAL PHARMACOLOGY, Cardiac Electrophysiology).

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

8.5 Post-Marketing Adverse Reactions

Adverse events identified during post-marketing experience with tapentadol are included in Table 4. 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 4, 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 4: Adverse Events Identified During Post-Marketing Experience with Tapentadol

Gastrointestinal disorders	
Rare	Diarrhea
Immune system disorders	
Uncommon	Hypersensitity (including rare events of angioedema, anaphylaxis and anaphylactic shock)
Psychiatric disorders	
Rare	Hallucination
Very rare	Panic attack
Not known	Delirium
Nervous system disorders	
Uncommon	Headache
Cardiac disorders	
Rare	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 tapentadol (see 2. CONTRAINDICATIONS and 7. WARNINGS AND PRECAUTIONS, Hypersensitivity). For a complete listing of ingredients, see the 6. DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING section of the Product Monograph.

Serotonin Toxicity (also known as Serotonin syndrome)
Cases of serotonin toxicity/serotonin syndrome, a potentially life-threatening condition, has been reported with tapentadol when used concomitantly with other serotonergic agents such as SSRI's and MAOIs.

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.

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

Serious Drug Interactions
• Use APO-TAPENTADOL with caution in patients currently using specified centrally-acting drugs or alcohol. • Do not use APO-TAPENTADOL in patients currently using or within 14 days of using a monoamine oxidase inhibitor (MAOI).

9.2 Drug Interactions 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.

9.3 Drug-Behavioural Interactions
The concomitant use of alcohol should be avoided. Due to its mu-opioid agonist activity, APO-TAPENTADOL may be expected to increase the sedative effect of alcohol.

9.4 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 7. WARNINGS AND PRECAUTIONS, Neurologic, Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol) and Driving and Operating Machinery). APO-TAPENTADOL should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects.

Monoamine Oxidase Inhibitors
APO-TAPENTADOL 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 2. CONTRAINDICATIONS).

Drugs Associated with a Risk of Serotonin Toxicity (also known as 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 7. WARNINGS AND PRECAUTIONS).

There have been post-marketing reports of serotonin toxicity/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]). Tapentadol can increase the risk of serotonin toxicity/serotonin syndrome when it is used concomitantly with serotonergic drugs such as SSRIs, SNRIs, and other serotonergic drugs such as tricyclic antidepressants (TCAs), MAOIs (including linezolide, methylene blue and triptans) and with drugs that impair metabolism of serotonin. This can occur within the recommended dose (see 7. WARNINGS AND PRECAUTIONS, Serotonin Toxicity/Serotonin Syndrome)**.**

Anticholinergic Drugs
The use of tapentadol 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.

9.5 Drug-Food Interactions

No effects on the pharmacokinetics of tapentadol were observed with administration of a high fat meal. APO-TAPENTADOL can be taken with or without food (see 10. CLINICAL PHARMACOLOGY, Pharmacokinetics, Food Effect).

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

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

Tapentadol hydrochloride, the centrally-active analgesic (antinociceptive) agent has an apparent dual-mode of action. Tapentadol is a mu-opioid receptor agonist with a Ki (mean ± SD) of 0.16 ± 0.04 mcM, compared to morphine with a mean Ki of 0.009 ± 0.0035 mcM, for the human mu-opioid receptor. In the GTPγS assay using membranes from cells expressing recombinant human mu-opioid receptors, the potency (mean EC50 ± SD) of tapentadol is 0.67 ± 0.15 mcM, compared to 0.022 ± 0.003 mcM 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.

10.2 Pharmacodynamics

Tapentadol is a novel 3-[(1*R*,2*R*)-3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol with a dual mechanism of action, mu-opioid agonist and norepinephrine reuptake inhibitor. It is 18 times less potent than morphine in binding to the human mu-opioid receptor and is 2 to 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.

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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 mcM. Furthermore, there are no other metabolites which contribute to the analgesic activity of tapentadol. Tapentadol exerts its analgesic effects without a pharmacologically active metabolite.

Central Nervous System:

Tapentadol 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 CO_2 tension and to electrical stimulation.

Tapentadol 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:

Tapentadol 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:

Tapentadol may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilatation 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.

Clinical Safety Pharmacology:

Cardiac Electrophysiology

Thorough QT Study
In a randomized, double-blind, placebo- and positive-controlled crossover study, healthy subjects (N=61 to 63) were administered five consecutive doses of tapentadol 100 mg every 6 hours, tapentadol 150 mg every 6 hours, placebo and a single dose of moxifloxacin. At the doses studied, which produced mean ± SD steady-state C_{max} values of 129 ± 42.0 ng/mL for the 100 mg q6h dose and 197 ± 89.1 ng/mL for the 150 mg q6h dose, tapentadol 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, tapentadol extended-release tablets 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 tapentadol extended-release tablets (100 to 250 mg) fixed for 12 weeks in the maintenance period. Stable analgesia was maintained; there was no evidence for tolerance to tapentadol extended-release tablets, either over 15 weeks in fixed dosing, or over one year with flexible dosing.

In a randomized active-controlled safety study, tapentadol 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 tapentadol 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 tapentadol, 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. tapentadol had better gastrointestinal tolerability (e.g., with respect to nausea, vomiting and constipation) than the strong opioid comparator. tapentadol 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 tapentadol abruptly, while 17% experienced mild withdrawal symptoms.

10.3 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 tapentadol tablets. Dose-proportional increases in the C_{max} and AUC values of tapentadol have been observed after administration of tapentadol tablets over the oral therapeutic dose range.

A multiple (every 6 hours) dose study with doses ranging from 75 to 175 mg of tapentadol 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 tapentadol tablets were administered after a high-fat, high-calorie breakfast**.** Phase 3 clinical studies were conducted without restrictions to food intake. APO-TAPENTADOL may be given with or without food.

Distribution:

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

Metabolism:

In humans, 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.

Elimination:

Tapentadol and its metabolites are excreted almost exclusively (99%) via the kidneys. The terminal half-life after oral administration is on average (± standard deviation) 4.3 (±0.8) hours and the apparent clearance (CL/F) is on average 4470 (±1519) mL/min across all doses of tapentadol . The total serum clearance of tapentadol after intravenous administration is 1530 ± 177 mL/min.

Special Populations and Conditions:

- **Pediatrics (< 18 years of age):** The pharmacokinetic profile of tapentadol in children has not been studied. No clinical studies with tapentadol have been conducted in children. Individuals under 18 years of age should not take APO-TAPENTADOL.

- **Geriatrics (≥ 65 years of age):** The mean exposure (AUC) to tapentadol was similar in elderly subjects (≥ 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.

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

- **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.

- **Ethnic Origin:** No statistically significant effect of ethnic origin 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 2. 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 2. CONTRAINDICATIONS).

11 STORAGE, STABILITY AND DISPOSAL

Storage and Stability
APO-TAPENTADOL tablets should be stored at room temperature 15°C to 30°C. Protect from moisture.

Keep APO-TAPENTADOL out of the reach and sight of children.

Disposal
APO-TAPENTADOL should be kept in a safe place, out of the sight and reach of children before, during and after use. APO-TAPENTADOL should not be used in front of children, since they may copy these actions.

APO-TAPENTADOL should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended. Unused or expired APO-TAPENTADOL 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.

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

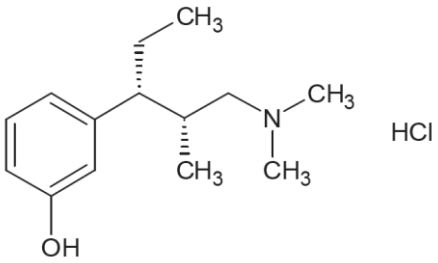
Drug Substance

Common name: Tapentadol Hydrochloride

Chemical name: 3-[(1R,2R)-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 g/mol; the molecular weight of tapentadol base is 221.34 g/mol.

Structural formula:



Physicochemical properties: Tapentadol hydrochloride is a white to off-white powder. Tapentadol hydrochloride is freely soluble in water, soluble in acetone, acetonitrile, isopropanol and methanol, and insoluble in *n*-Heptane. The melting point ranges from 193°C to 213°C. The octanol:water partition coefficient log P value is 2.87. The pKa values are 9.34 and 10.45.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Moderate to Severe Acute Pain

Table 5: Summary of patient demographics for clinical trials in moderate to severe acute pain

Study#	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Tapentadol tablets					
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: tapentadol tablets: 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: tapentadol tablets: 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: tapentadol: 50 mg, or 75 mg; Oxycodone IR: 10 mg; placebo	N=666	61.2 years (20- 79 years)	M: 338 F: 328

Table 6: Summary of patient demographics for clinical trials in tapentadol and tapentadol extended-release Dose Conversion Study

Study#	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
PAI-3019/KF39 Chronic low back pain	Randomized, double-blind, 2-period crossover	Titration phase (3-week titration to optimal effect and tolerability): tapentadol tablets 50 mg, 75 mg, or 100 mg q4-6h. Double-blind phase (two 14-day cross-over periods): Tapentadol tablets 50 mg, 75 mg, or 100 mg q4-6h at dose reached during titration; Tapentadol extended-release tablets 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

The efficacy and safety of tapentadol tablets 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 tapentadol tablets (50 mg, 75 mg, or 100 mg every 4 to 6 hours) and tapentadol extended-release tablets (100 mg, 150 mg, 200 mg, or 250 mg twice daily) while maintaining comparable efficacy.

PAI-3003/ KF 32 (Bunionectomy Pain Model)

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 tapentadol tablets 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 tapentadol tablets 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 tapentadol tablets 100 mg groups to 7.2 in the tapentadol tablets 50 mg group.

The primary efficacy endpoint was the sum of pain intensity difference over the first 48 hours ($SPID_{48}$) versus placebo. Tapentadol tablets at each dose provided a greater reduction in pain compared to placebo based on $SPID_{48}$ 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 tapentadol tablets 50 mg, 68.3% on tapentadol tablets 75 mg, and 78.8% on tapentadol tablets 100 mg.

PAI-3016/ KF35 (Hysterectomy Pain Model)

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 tapentadol tablets for the relief of moderate to severe post-operative pain following an abdominal hysterectomy. Subjects took tapentadol tablets 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 $SPID_{24}$ 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 $SPID_{24}$ calculated relative to the date and time of first dose.

Tapantadol tablets 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 tapentadol tablets 50 mg, 72.5% on tapentadol tablets 75 mg, and 73.3% on tapentadol tablets 100 mg.

PAI-3002/KF33 (Pain from End-Stage Degenerative Joint Disease Prior to Joint Replacement Surgery)

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 tapentadol 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 tapentadol treatment groups and the placebo group took such analgesia during the study. The 75 mg treatment group was dosed at 50 mg for the first day of the study, followed by 75 mg for the remaining nine days. Patients requiring rescue analgesics other than study medication were discontinued for lack of efficacy.

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

PAI-3019/KF39 (Tapentadol Tablets and Tapentadol Extended-Release Tablets Dose Conversion Study in Low Back Pain Model)

Study PAI-3019/KF39 was a randomized, double-blind, multi-center, 2-period, crossover study to establish the dose equivalence and direct conversion between tapentadol tablets and tapentadol extended-release tablets in subjects with moderate to severe Low Back Pain (LBP). Subjects were titrated open label to an optimal dose of tapentadol tablets (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 tapentadol tablets or tapentadol extended-release tablets 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 tapentadol extended-release tablets and 3.9 for the period on tapentadol tablets. The estimated difference in mean primary endpoint values (mean average pain intensity score over the last 3 days of treatment: tapentadol extended-release to tapentadol tablets) 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 tapentadol tablets 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 tapentadol extended-release tablets, or vice-versa, if necessary, with equivalent efficacy.

14.2 Comparative Bioavailability Studies

APO-TAPENTADOL 50 mg, 75 mg and 100 mg tablets have satisfied the criteria for Biopharmaceutics Classification System (BCS) – based biowaiver in comparison to the respective strengths of Nucynta IR® (tapentadol) tablets (Janssen Inc., Canada)

15. MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

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.

Carcinogenicity:

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 tapentadol 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 tapentadol 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.

Genotoxicity:

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.

Reproductive and Developmental Toxicology:

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 embryofoetal 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 tapentadol based on an area under the time-curve (AUC) comparison], no teratogenic effects were observed. Evidence of embryofoetal 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 embryofoetal 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. Embryofoetal 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.

Special Toxicology:

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.

17 SUPPORTING PRODUCT MONOGRAPHS

1. [N]NUCYNTA® IR (Tapentadol Immediate-Release Tablets 50 mg, 75 mg and 100 mg), submission control 247865, Product Monograph, Endo Ventures Ltd. Oct 15, 2021.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[N] APO-TAPENTADOL
Tapentadol Tablets

Read this carefully before you start taking **APO-TAPENTADOL** 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 **APO-TAPENTADOL**.

Serious Warnings and Precautions

- Even if you take APO-TAPENTADOL as prescribed, you are at a risk for opioid addiction, abuse and misuse. This can lead to overdose and death. Your doctor will only prescribe APO-TAPENTADOL. if other non-opioid treatment options are not effective to manage your pain. To understand your risk of opioid addiction, abuse, and misuse, you should speak to your doctor.

- When you take APO-TAPENTADOL 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 APO-TAPENTADOL, especially If not taken as directed. 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 APO-TAPENTADOL. They could die from taking it. If a person has not been prescribed APO-TAPENTADOL, taking even one dose can cause a fatal overdose. This is especially true for children.

- If you took APO-TAPENTADOL 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 alcohol with APO-TAPENTADOL can lead to dangerous unwanted effects, serious injury, or even death. You should avoid taking alcoholic beverages or medications containing alcohol while on APO-TAPENTADOL therapy.
- Taking APO-TAPENTADOL with other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death. You should avoid taking APO-TAPENTADOL if you are taking other opioid medicines, benzodiazepines, alcohol, or other central nervous system depressants.

What is APO-TAPENTADOL used for?
APO-TAPENTADOL is used in adults to manage moderate to severe acute pain.

How does APO-TAPENTADOL work?
APO-TAPENTADOL 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 APO-TAPENTADOL?
Medicinal ingredients: tapentadol hydrochloride

Non-medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, D&C Yellow #10 Aluminum Lake (50 mg and 75 mg only), magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, Sunset Yellow Aluminum Lake (all tablet strengths), talc, titanium dioxide.

APO-TAPENTADOL comes in the following dosage forms:
APO-TAPENTADOL tablets are available in 50 mg, 75 mg, and 100 mg tapentadol (as tapentadol hydrochloride) dose strengths.

Do not use APO-TAPENTADOL if:
- your doctor did not prescribe it for you
- you are allergic to tapentadol, to opioids, to any of the other ingredients in APO-TAPENTADOL, or to any component of the container
- 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 bowel blockage, problems that affect bowel movement (e.g., ileus of any type or narrowing of the stomach or intestines
- you have severe pain in your abdomen (e.g., acute appendicitis or pancreatitis)
- you have a head injury or problem (e.g. increased pressure in the brain or disturbed consciousness)
- you are at risk for seizures or have convulsive disorders

- you have severe central nervous system (CNS) depression
- you suffer from alcoholism or have delirium tremens
- you are taking or have taken within the past 14 days a Monoamine Oxidase inhibitor (MAOi; such as phenelzine sulphate, tranylcypromine sulphate, moclobemide or selegiline)
- you have severe kidney disease or liver problems
- you are pregnant or are in labour
- you are breastfeeding

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

- have a history of using illicit or prescription drug or alcohol abuse
- are drinking or planning to drink alcoholic beverages or take medications that contain alcohol
- have low blood volume or low blood pressure
- have heart problems
- have past or current depression
- suffer from chronic or severe constipation
- have or had breathing problems (e.g., slow, fast, or shallow breathing)
- have or had brain problems (e.g., tumour, stroke, transient ischemic attack, brain neoplasm, or severe traumatic brain injury)
- have had an epileptic fit or seizures, or at a higher risk of developing these
- suffer from migraines
- have or had lung problems
- have or had pancreas problems (e.g., pancreatitis)
- have or had liver problems
- have urinary problems or problems with your adrenal or prostate gland
- have had serious allergic reactions to other medications (e.g., anaphylaxis)
- have, or had in the past, hallucinations or other severe mental problems
- have had an operation within the last 24 hours, are planning to undergo an operation within the next 24 hours or are planning to undergo an anesthetic procedure
- have sleep-related breathing disorders (e.g. central sleep apnea)
- have an underactive thyroid (hypothyroidism) or severe hypothyroidism (myxedema)
- are planning to become pregnant or to breastfeed

Other warnings you should know about:

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.

Driving and using machines: Before you do tasks which may require special attention, you should wait until you know how you react to APO-TAPENTADOL. APO-TAPENTADOL 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 APO-TAPENTADOL.

Serotonin toxicity (also known as Serotonin Syndrome): APO-TAPENTADOL 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 APO-TAPENTADOL with certain anti-depressants or migraine medications.

Serotonin toxicity 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.

Opioid withdrawal symptoms: If you are converting from a previous opioid analgesic to APO-TAPENTADOL, or converting from APO-TAPENTADOL to another opioid, you may experience opioid withdrawal symptoms. The symptoms may include: nausea, vomiting, diarrhea, anxiety and shivering. Contact your healthcare professional if you experience these symptoms when switching to or from APO-TAPENTADOL.

Seizures: APO-TAPENTADOL can cause seizures, especially if you are at a higher risk for seizures or have epilepsy. Tell your healthcare professional if you have a seizure. They will stop your treatment accordingly.

Sexual function and 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.

Sleep Apnea: Opioids can cause sleep-related breathing disorders such as sleep apnea syndromes (including central sleep apnea [CSA]) and hypoxia (including sleep-related hypoxia).

Worsened Pain: Taking opioids for pain can sometimes have the unintended effect of making your pain feel worse (opioid-induced hyperalgesia) even though your opioid dose has been unchanged or increased. This can also include feeling pain in new places in your body, or feeling pain from something that would not normally hurt, for example, feeling pain from clothing touching your skin. Tell your doctor if you notice a change like this in your pain while you are taking APO-TAPENTADOL.

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 APO-TAPENTADOL:

- alcohol. This includes prescription and non-prescription medications that contain alcohol. Do not drink alcohol while you are taking APO-TAPENTADOL. It can lead to:
    - drowsiness
    - unusually slow or weak breathing
    - serious side effects or
    - a fatal overdose
- other sedative medications which may enhance the drowsiness caused by APO-TAPENTADOL
- other opioid analgesics (used to treat pain)
- cough medicines containing opioids such as codeine
- general anesthetics (used during surgery)
- benzodiazepines (used to help you sleep or that help reduce anxiety)
- antidepressants (used for depression and mood disorders). Do not **take** APO-TAPENTADOL with MAO inhibitors (MAOi) or if you have taken MAOi's in the last 14 days (e.g., linezolid and methylene blue)
- medications used to treat serious mental or emotional disorders such as schizophrenia (e.g., tranquillizers, hypnotics, antipsychotics, beta-blockers, neuroleptics, phenothiazines, and serotonergic agents). Talk to your healthcare professional, if you are unsure.
- antihistamines (used to treat allergies)
- anti-emetics (used to prevent vomiting)
- medications used to treat muscle spasms and back pain (e.g., muscle relaxants)
- medications used to treat migraines (e.g., triptans)
- St. John's Wort

- medications used to treat high blood pressure (e.g., central-acting agents)
- medications known as anticholinergic drugs (e.g., oxybutynin, ipratropium bromide, tiotropium, and carbamazepine)

How to take APO-TAPENTADOL:
APO-TAPENTADOL is usually taken every 4 to 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.

APO-TAPENTADOL is for oral use. You may take the tablets with or without food.

Always swallow APO-TAPENTADOL 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 Dose:
Your dose is tailored/personalized just for you. Be sure to follow your doctor's dosing instructions exactly. Do not increase, decrease your dose, or stop without consulting your doctor.

Your doctor will prescribe the lowest dose that works to control your pain. It is recommended that you only take APO-TAPENTADOL for up to 7 days. If you need to take APO-TAPENTADOL 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 or death.

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

If your pain increases or you develop any side effect as a result of taking APO-TAPENTADOL, tell your doctor immediately.

Stopping your Medication:
If you have been taking APO-TAPENTADOL 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 APO-TAPENTADOL.

You should do it slowly to avoid uncomfortable symptoms such as having:
- body aches
- diarrhea

- goosebump
- a loss of appetite
- nausea
- a feeling nervousness or restlessness
- a runny nose or sneezing
- tremors or shivering
- stomach cramps
- rapid heart rate (tachycardia)
- 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 more sensitive 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 APO-TAPENTADOL.

Refilling your Prescription for APO-TAPENTADOL:
A new written prescription is required from your doctor each time you need more APO-TAPENTADOL. 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:

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
- slow, shallow, or stopped breathing

If you think you, or a person you are caring for, have taken too much APO-TAPENTADOL, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

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

What are possible side effects from using APO-TAPENTADOL?
These are not all the possible side effects you may have when taking APO-TAPENTADOL. If you experience any side effects not listed here, tell your healthcare professional.

Like all medicines, APO-TAPENTADOL 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. APO-TAPENTADOL can cause serious side effects including life-threatening breathing problems

Side effects may include:
- drowsiness
- insomnia (difficult to fall asleep and/or stay asleep)
- dizziness
- nausea, vomiting, or a poor appetite
- dry mouth
- headache
- problems with vision
- weakness
- fatigue
- uncoordinated muscle movement
- itching
- constipation
- low sex drive (libido)
- impotence (erectile dysfunction)
- infertility

Talk with your doctor or pharmacist about ways to prevent constipation when you start using APO-TAPENTADOL.

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, dizziness, floppy muscles/low muscle tone, cold and clammy skin.			√
Respiratory Depression (hypoventilation): slow, shallow or weak breathing, blue lips.			√
Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing, wheezing, drop in blood pressure, feeling sick to your stomach and throwing up			√
Bowel Blockage (impaction): abdominal pain, severe constipation, nausea, vomiting, liquid stool, urge to move bowels, poor appetite, weight loss, malaise			√
Withdrawal: nausea, vomiting, diarrhea, anxiety, shivering, cold and clammy skin, body aches, loss of appetite, sweating		√	
Cardiac arrhythmias: fast, slow or irregular heartbeat, heart palpitations, shortness of breath		√	
Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, fatigue (may occur when you go from lying or sitting to standing up)	√		
Serotonin toxicity: a reaction which may cause feeling of agitation or restlessness, flushing, muscle twitching, involuntary eye movements heavy sweating, high body temperature (>38 °C), or rigid muscles, coordination problems, uncontrolled muscle spasms,			√

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	
shaking, shivering, racing or fast heartbeat, high or low blood pressure, fever, nausea, vomiting, diarrhea, tremor, coma, loss of muscle control			

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
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store APO-TAPENTADOL at room temperature 15°C to 30°C. Protect from moisture.
- **Keep unused or expired APO-TAPENTADOL in a secure place to prevent theft, misuse or accidental exposure.**
- **Keep APO-TAPENTADOL 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 APO-TAPENTADOL, get emergency help right away.**

Do not use APO-TAPENTADOL after the expiry date.

Disposal:

APO-TAPENTADOL 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 APO-TAPENTADOL:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient 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); Find the Patient Medication Information on the manufacturer's website http://www.apotex.ca/products, or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

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