PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

[Pr]RALIVIA®

Tramadol Hydrochloride
Extended-Release Tablets
100 mg, 200 mg, and 300 mg

Opioid Analgesic

Bausch Health, Canada Inc.
2150 St-Elzear Blvd. West
Laval, Quebec
H7L 4A8

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RECENT MAJOR LABEL CHANGES

None

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

RALIVIA (tramadol hydrochloride) extended-release tablets are indicated for the management of moderate to moderately severe pain in adults who require continuous treatment for several days or more.

1.1 Pediatrics

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

1.2 Geriatrics

- 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.
- Healthy elderly subjects aged 65 to 75 years administered tramadol have plasma concentrations and elimination half-lives comparable to those observed in healthy subjects less than 65 years of age. RALIVIA should be administered with greater caution in patients older than 75 years, due to the greater potential for adverse events in this population (see 7 WARNINGS AND PRECAUTIONS, 4 DOSAGE AND ADMINISTRATION).

2 CONTRAINDICATIONS

- Patients who are hypersensitive to the active substance tramadol hydrochloride or other opioid analgesics or to any ingredient in the formulation. For a complete listing, 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).
- In severe renal or hepatic impairment (creatinine clearance of less than 30 mL/min and/or Child-Pugh Class C).
- Patients with mild pain that can be managed with other pain medications.
- Patients with acute or severe bronchial asthma, chronic obstructive airway, 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.
- In any situation where opioids are contraindicated, including acute intoxication with any of the following: alcohol, hypnotics, centrally acting analgesics, opioids or psychotropic drugs. RALIVIA may worsen central nervous system and respiratory depression in

these patients.

- 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).
- Pediatric patients less than 18 years of age who have undergone tonsillectomy and/or adenoidectomy for obstructive sleep apnea syndrome.
- Pediatric patients less than 12 years of age.

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 greater risks of overdose and death with extended-release opioid formulations, RALIVIA should only be used in patients for whom alternative treatment options are ineffective or not tolerated (e.g., non-opioid analgesics), or would be otherwise inadequate to provide sufficient management of pain (e.g., immediate-release opioids) (see 4 DOSAGE AND ADMINISTRATION).

Addiction, Abuse, and Misuse

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

RALIVIA must be swallowed whole; crushing, chewing, or dissolving RALIVIA extended-release tablets can cause rapid release and absorption of a potentially fatal dose of tramadol hydrochloride (see 7 WARNINGS AND PRECAUTIONS).

Further, instruct patients of the hazards related to taking opioids including fatal overdose.

Accidental Exposure
Accidental consumption of even one dose of RALIVIA, especially by children, can result in a fatal overdose of tramadol hydrochloride (active opioid) (see 4 DOSAGE AND ADMINISTRATION, 4.5 Disposal).

Neonatal Opioid Withdrawal Syndrome
Prolonged maternal use of RALIVIA 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 RALIVIA may result in increased plasma levels and a potentially fatal overdose of tramadol hydrochloride (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, 7.11 Neurologic and 9 DRUG INTERACTIONS).

- **Reserve concomitant prescribing of RALIVIA 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

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

All doses of opioids carry an inherent risk of fatal or non-fatal adverse events. This risk is increased with higher doses. For the management of pain, it is recommended that a maximum daily dosage of 300 mg (50 morphine milligram equivalent) of RALIVIA not be exceeded. Each patient should be assessed for their risk prior to prescribing RALIVIA, 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 RALIVIA (see 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment).

RALIVIA is not recommended for minor pain, or acute short-term pain that may be treated adequately through lesser means where benefit does not outweigh the possible opioid-related

side effects.

Due to possible differences in pharmacokinetic properties, RALIVIA tablets are not interchangeable with other tramadol extended-release formulations.

The maximum recommended daily dose of RALIVIA should not be exceeded

4.2 Recommended Dose and Dosage Adjustment

General

RALIVIA is designed for once-daily dosing, i.e., dosing at 24-hourly intervals. Treatment with RALIVIA should be initiated at the lowest available dose (100 mg). Clinical studies of RALIVIA have not demonstrated a clinical benefit at a total daily dose exceeding 300 mg. The maximum dose is 300 mg daily.

The correct dosage for any individual patient is that which controls the pain for a full 24 hours, with no or tolerable side effects.

As with all analgesic drugs, the dose of tramadol should be adjusted according to the severity of the pain and the clinical response of the individual patient. It is recommended that doses be slowly titrated (dosage adjustments generally separated by five days), to higher doses to minimize side effects.

Adults

RALIVIA should be initiated at a dose of 100 mg once daily and may be titrated up by 100 mg increments every five days, as necessary and depending on tolerability, to relief of pain. RALIVIA should not be administered at doses exceeding 300 mg per day.

Patients Not Receiving Opioids at the Time of Initiation of Tramadol Treatment.

The usual initial dose of RALIVIA for patients who have not previously received opioid analgesics is 100 mg q24h.

Patients Currently Receiving Opioids

RALIVIA should be used with caution and in a reduced dosage during concomitant administration of other opioid analgesics. When such combination therapy is contemplated, a substantial reduction in the dose of one or both agents should be considered, and patients should be carefully monitored.

Patients Currently Receiving Other Tramadol Formulations

Patients currently receiving oral immediate-release tramadol preparations may be transferred to RALIVIA tablets at the same or lowest nearest total daily tramadol dosage.

Patients with Renal or Hepatic Insufficiency

The elimination half-life of tramadol and its active metabolite may be prolonged in these patient populations. A starting dose of 100 mg daily is recommended. Upward dosage titration should be done with careful monitoring. Tramadol is contraindicated in patients with severe renal

impairment and/or severe hepatic impairment (creatinine clearance less than 30 mL/min and/or Child-Pugh Class C, see 2 CONTRAINDICATIONS).

Geriatrics

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.

In general, dose selection for patients over 65 years of age, who may have decreased hepatic or renal function, or other concomitant diseases, should be initiated at a low dose and slowly titrated to effect. RALIVIA should be administered with greater caution at the lowest effective dose in patients over 75 years, due to the potential for greater frequency of adverse events in this population (see 7 WARNINGS AND PRECAUTIONS and 10 CLINICAL PHARMACOLOGY).

Pediatrics (< 18 years old)

The safety and efficacy of RALIVIA has not been studied in the pediatric population. Therefore, RALIVIA is not indicated for use in children under 18 years of age.

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. RALIVIA can be safely used concomitantly with usual doses of other non-opioid analgesics.

Management of Patients Requiring Rescue Medication

If rescue medications are warranted for episodes of pain in the course of appropriate adjustments of RALIVIA dose, acetaminophen or ibuprofen may be given. If immediate release tramadol is used as rescue medication, the total daily dose of tramadol should not exceed 300 mg. Selection of rescue medication should be based on individual patient conditions. Fentanyl products should not be used as rescue medication in patients taking RALIVIA.

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 RALIVIA. 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.

Following successful relief of moderate to severe pain, periodic attempts to reduce the opioid dose should be made. Smaller doses or complete discontinuation may become feasible due to a change in the patient's condition or mental state. 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 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.

Opioid analgesics may only be partially effective in relieving dysesthetic pain, postherpetic neuralgia, stabbing pains, activity-related pain and some forms of headache. That is not to say that patients with advanced cancer suffering from some of these forms of pain should not be given an adequate trial of opioid analgesics, but it may be necessary to refer such patients at an early time to other forms of pain therapy.

4.3 Administration

RALIVIA tablets are a once-daily extended-release formulation that must be swallowed whole and should not be broken, chewed or crushed, since this can lead to the rapid release of tramadol and absorption of a potentially fatal dose of tramadol (see 7 WARNINGS AND PRECAUTIONS).

RALIVIA may be taken with or without food, with a glass of water.

RALIVIA is not indicated for rectal administration.

4.4 Missed Dose

If the patient forgets to take one or more doses, they should take their next dose at the next scheduled time and in the normal amount.

4.5 Disposal

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

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

5 OVERDOSAGE

Deaths due to overdose have been reported with abuse and misuse of tramadol, by ingesting, inhaling, or injecting the crushed tablets. Review of case reports has indicated that the risk of fatal overdose is further increased when tramadol is abused concurrently with alcohol or other CNS depressants, including other opioids.

5.1 Symptoms of Overdose

Acute overdosage with tramadol can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, bradycardia, toxic leukoencephalopathy, delayed post-hypoxic leukoencephalopathy, hypotension, and death. In addition, cases of QT prolongation have been reported during overdose.

Deaths due to overdose have been reported with abuse and misuse of tramadol, by ingesting, inhaling, or injecting the crushed tablets. Review of case reports has indicated that the risk of fatal overdose is further increased when tramadol is abused concurrently with alcohol or other CNS depressants, including other opioids.

5.2 Treatment of Overdose

In the treatment of tramadol overdosage, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

While naloxone will reverse some, but not all, symptoms caused by overdosage with tramadol, the risk of seizures is also increased with naloxone administration. Seizures may be controlled with diazepam.

In animals, convulsions following the administration of toxic doses of RALIVIA could be suppressed with barbiturates or benzodiazepines but were increased with naloxone. Naloxone administration did not change the lethality of an overdose in mice.

Hemodialysis is not expected to be helpful in an overdose because it removes less than 7% of the administered dose in a 4-hour dialysis period.

Emptying of the gastric contents is useful to remove any unabsorbed drug.

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

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablets / 100 mg, 200 mg, and 300 mg	Colloidal Silicon Dioxide, Ethylcellulose, Dibutyl Sebacate, Polyvinyl Alcohol, Polyvinyl Pyrrolidone, and Sodium Stearyl Fumarate, Black Ink (Shellac Glaze, Isopropyl Alcohol, Iron Oxide Black, n-Butyl Alcohol, Propylene Glycol and Ammonium Hydroxide.)

Physical Characteristics

RALIVIA extended-release tablets are supplied as:
100-mg, round, white tablets, imprinted with “100” over “ER” in black ink
200-mg, round, white tablets, imprinted with “200” over “ER” in black ink
300-mg, round, white tablets, imprinted with “300” over “ER” in black ink

RALIVIA 100 mg, 200 mg and 300 mg tablets are available in bottles of 90 tablets.

7 WARNINGS AND PRECAUTIONS

7.1 General

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

RALIVIA should only be prescribed by persons knowledgeable in the continuous 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 RALIVIA as it may increase the chance of experiencing serious adverse events, including death.

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

7.2 Addiction, Abuse and Misuse

Like all opioids, RALIVIA is a potential drug of abuse and misuse, which can lead to overdose and death. Therefore, RALIVIA 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 RALIVIA, should be used with particular care in patients with a history of alcohol and illicit/ prescription drug abuse.

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

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

Abuse and addiction are separate and distinct from physical dependence and tolerance. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances.

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. The development of addiction to opioid analgesics in properly managed patients with pain has been reported to be rare. However, data are not available to establish the true incidence of addiction in chronic pain patients.

Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

A Risk Management program to support the safe and effective use of RALIVIA has been established. The following are considered to be the essential components of the Risk Management program:

a. Commitment to not emphasize or highlight the scheduling status of RALIVIA (i.e., not listed under a schedule to the CDSA) in its advertising or promotional activities.
b. Inclusion of a PAAB-approved fair balance statement in all RALIVIA advertising and promotional materials.
c. Provision of progress reports to TPD, MHPD and HECSB from a drug abuse surveillance program for RALIVIA.
d. Assurance that health-care education activities on pain management with RALIVIA include balanced, evidence-based, and current information. Commitment to take reasonable actions to inform health-care professionals that there is Health Canada-approved patient information on benefits and risks, and to ensure that this information can be readily accessed through electronic and/or hard copy sources.
e. Reassessment of the risk management program 2 years post product launch.

7.3 Risk of Overdosage

Serious potential consequences of overdosage with RALIVIA are seizures, 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 RALIVIA for patients who are suicidal or addiction prone.

RALIVIA should not be taken in doses higher than those recommended by the physician. The judicious prescribing of tramadol is essential to the safe use of this drug. With patients who are depressed or suicidal, consideration should be given to the use of non-narcotic analgesics. Because of its added depressant effects, tramadol should be prescribed with caution for those

patients whose medical condition requires the concomitant administration of sedatives, tranquilizers, muscle relaxants, antidepressants, or other CNS-depressant drugs. Patients should be advised of the additive depressant effects of these combinations.

7.4 Anaphylactoid Reactions

Serious and rarely fatal anaphylactoid reactions have been reported in patients receiving therapy with tramadol. When these events do occur, it is often following the first dose. Other reported allergic reactions include pruritus, hives, bronchospasm, angioedema, toxic epidermal necrolysis and Stevens-Johnson syndrome. Patients with a history of anaphylactoid reactions to codeine and other opioids may be at increased risk and therefore should not receive RALIVIA (see 2 CONTRAINDICATIONS).

7.5 Carcinogenesis and Mutagenesis

See animal data in 16 NON-CLINICAL TOXICOLOGY section.

7.6 Cardiovascular

Tramadol hydrochloride 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 RALIVIA.

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

QTc Interval Prolongation

The effect of tramadol on the QT/QTc interval were evaluated in a dedicated randomized, double-blind, 4-way crossover, placebo- and positive-controlled, multiple dose ECG study in healthy subjects (N=62). The study involved administration of tramadol at a supra-therapeutic dose of 100 mg every 6 h on days 1-3 (400 mg/day), with a single 100 mg dose on day 4, or 150 mg every 6 h (600 mg/day) on days 1-3, with a single 150 mg dose on day 4. The maximum placebo-adjusted mean change from baseline in the QTcF interval was 5.5 ms (90% CI 3.2, 7.8) in the 400 mg/day treatment arm and 6.5 ms (90% CI 4.1, 8.8) in the 600 mg/day mg treatment arm, both occurring at the 8h time point (see 10 CLINICAL PHARMACOLOGY, 10.2 Pharmacodynamics, Cardiac Electrophysiology). Post-marketing experience with the use of tramadol containing products included rare reports of QT prolongation reported with an overdose (see 8 ADVERSE REACTIONS, 8.5 Post-Market Adverse Reactions , 9 DRUG INTERACTIONS, 9.4 Drug Interactions, QTc Interval-Prolonging Drugs and 5 OVERDOSAGE).

Many drugs that cause QTc prolongation are suspected to increase the risk of torsade de pointes. Torsade de pointes is a polymorphic ventricular tachyarrhythmia. Generally, the risk of torsade de pointes increases with the magnitude of QTc prolongation produced by the drug. Torsade de pointes may be asymptomatic or experienced by the patient as dizziness, palpitations, syncope, or seizures. If sustained, torsade de pointes can progress to ventricular fibrillation and sudden cardiac death.

Particular care should be exercised when administering RALIVIA to patients who are suspected to be at an increased risk of experiencing torsade de pointes during treatment with a QTc-prolonging drug.

Risk factors for torsade de pointes in the general population include, but are not limited to, the following:

- female gender;
- age 65 years or older;
- baseline prolongation of the QT/QTc interval;
- presence of pathological genetic variants affecting cardiac ion channels or regulatory proteins, especially congenital long QT syndromes;
- family history of sudden cardiac death at <50 years;
- cardiac disease (e.g., myocardial ischemia or infarction, congestive heart failure, left ventricular hypertrophy, cardiomyopathy, conduction system disease);
- history of arrhythmias (especially ventricular arrhythmias, atrial fibrillation, or recent conversion from atrial fibrillation);
- electrolyte disturbances (e.g., hypokalemia, hypomagnesemia, hypocalcaemia);
- bradycardia (<50 beats per minute);
- acute neurological events (e.g., intracranial or subarachnoid haemorrhage, stroke, intracranial trauma);
- nutritional deficits (e.g., eating disorders, extreme diets);
- diabetes mellitus;
- autonomic neuropathy.

When drugs that prolong the QTc interval are prescribed, healthcare professionals should counsel their patients concerning the nature and implications of the ECG changes, underlying diseases and disorders that are considered to represent risk factors, demonstrated and predicted drug-drug interactions, symptoms suggestive of arrhythmia, risk management strategies, and other information relevant to the use of the drug.

7.7 Dependence/Tolerance

Tramadol has a potential to cause psychic and physical dependence of the morphine-type (μ opioid). The drug has been associated with craving, drug-seeking behaviour and tolerance development. Cases of abuse and dependence on tramadol have been reported. RALIVIA tablets should not be used in opioid-dependent patients. Tramadol can re-initiate physical dependence in patients who have been previously dependent or chronically using other opioids. In patients with a tendency to abuse drugs or a history of drug dependence, and in patients who are chronically abusing opioids, treatment with RALIVIA is not recommended.

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

Patients on prolonged therapy should be tapered gradually from the drug if it is no longer required for pain control. Withdrawal symptoms may occur following abrupt discontinuation of therapy or upon administration of an opioid antagonist. 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, 4.2 Recommended Dose and Dose Adjustment).

Clinical experience suggests that withdrawal symptoms may be relieved by reinstitution of

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

Use in Drug and Alcohol Addiction

RALIVIA 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 RALIVIA unless used under extreme caution and awareness.

7.8 Endocrine and Metabolism

Hyponatremia

Hyponatremia has been reported very rarely with the use of tramadol, usually in patients with predisposing risk factors, such as elderly patients and/or patients using concomitant medications that may cause hyponatremia (e.g., antidepressants, benzodiazepines, diuretics). In some reports, hyponatremia appeared to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and resolved with discontinuation of tramadol and appropriate treatment (e.g., fluid restriction). During RALIVIA treatment, monitoring for signs and symptoms of hyponatremia is recommended for patients with predisposing risk factors.

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.

7.9 Gastrointestinal

Tramadol and other morphine-like opioids have been shown to decrease bowel motility. Tramadol may obscure the diagnosis or clinical course of patients with acute abdominal conditions (see 2 CONTRAINDICATIONS).

7.10 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.

7.11 Neurologic

Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol)

RALIVIA 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 RALIVIA 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).

RALIVIA 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, 8.1 Adverse Reaction Overview, 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.

"In Vitro" Dissolution Studies of Interaction with Alcohol

As drugs may be abused in conjunction with alcohol, the effect of alcohol on the rate of drug release from RALIVIA tablets was evaluated in dissolution studies using the product dissolution medium compared to 60% 0.1N HCl : 40% ethanol. Dissolution profiles for all tablet strengths in the alcohol medium were found to be within proposed dissolution specifications. The 60% 0.1N HCl : 40% ethanol medium resulted in a slight decrease in the rate of release of tramadol from RALIVIA tablets. The clinical significance of the slight decrease in dissolution rate is unknown.

Head Injury

RALIVIA should be used with caution in patients with increased intracranial pressure or head injury, since the respiratory depressant effects of opioid receptor agonism include carbon

dioxide retention and secondary elevation of cerebrospinal fluid pressure, and such effects may be markedly exaggerated in these patients. Also, pupillary changes (miosis) from tramadol may obscure the existence, extent or course of intracranial pathology. Clinicians should also maintain a high index of suspicion for adverse drug reaction when evaluating altered mental status in these patients if they are receiving tramadol (see 7 WARNINGS AND PRECAUTIONS, 7.12 Respiratory, Respiratory Depression).

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

Seizures have been reported in patients receiving tramadol within the recommended dosage range. Spontaneous post-marketing reports indicate that seizure risk is increased with doses of tramadol above the recommended range. Concomitant use of tramadol increases the seizure risk in patients taking:

- Selective serotonin re-uptake inhibitors (SSRI antidepressants or anorectics), or
- Tricyclic antidepressants (TCAs), and other tricyclic compounds (e.g., cyclobenzaprine, promethazine, etc.), or
- Opioids.

Administration of tramadol may enhance the seizure risk in patients taking:

- MAO inhibitors (see 2 CONTRAINDICATIONS),
- Neuroleptics,
- Other drugs that reduce the seizure threshold.

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). In tramadol overdose, naloxone administration may increase the risk of seizure.

Serotonin Toxicity/ Serotonin Syndrome

Serotonin toxicity also known as serotonin syndrome is a potentially life-threatening condition and has been reported with Tramadol Hydrochloride, including RALIVIA, 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 RALIVIA 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.

Psychomotor Impairment

RALIVIA may impair the mental and/or physical abilities needed for certain potentially hazardous activities such as driving a car or operating machinery. Patients should be cautioned accordingly. Patients should also be cautioned about the combined effects of tramadol with other CNS depressants, including other opioids, phenothiazine, sedative/hypnotics and alcohol.

7.12 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. Tramadol should be used with extreme caution in patients with substantially decreased respiratory reserve, pre-existing respiratory depression, hypoxia or hypercapnia (see 2 CONTRAINDICATIONS).

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of RALIVIA, 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 RALIVIA 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.

To reduce the risk of respiratory depression, proper dosing and titration of RALIVIA are essential. Overestimating the RALIVIA 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 7.14 Populations, 7.14.1 Special Risk Groups, and 4 DOSAGE AND ADMINISTRATION).

Cytochromes P450 (CYP) 2D6 Ultra-Rapid Metabolism

Some individuals may be CYP2D6 ultra-rapid metabolizers. These individuals convert tramadol more rapidly than other people into its more potent opioid metabolite O-desmethyltramadol (M1). This rapid conversion could result in higher than expected opioid-like side effects including life-threatening respiratory depression (see 7 WARNINGS AND PRECAUTIONS,

Special 7.14 Populations, 7.14.2 Breast-feeding and 9 DRUG INTERACTIONS, 9.2 Drug Interactions Overview). The prevalence of this CYP2D6 phenotype varies widely in the population (see 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Special Populations and Conditions, Race).

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, hypercapnia, or pre-existing respiratory depression for respiratory depression, particularly when initiating therapy and titrating with RALIVIA, as in these patients, even usual therapeutic doses of RALIVIA 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 RALIVIA 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 7 WARNINGS AND PRECAUTIONS, 7.7 Dependence/Tolerance; 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment).

7.13 Sexual Function/Reproduction

Long-term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility (see 8 ADVERSE REACTIONS, 8.5 Post-Market Adverse Reactions)

7.14 Special Populations

7.14.1 Special Risk Groups

Tramadol 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.

7.14.2 Pregnant Women

Studies in humans have not been conducted. RALIVIA crosses the placenta barrier and should not be administered to pregnant women unless in the judgment of the physician, potential benefits outweigh the risks.

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.

The mean ratio of serum tramadol in the umbilical veins compared to maternal veins was 0.83 for 40 women given tramadol during labour. Neonatal seizures, neonatal withdrawal syndrome, fetal death and stillbirth have been reported during post-marketing reports with tramadol HCl immediate-release products. The effect of RALIVIA, if any, on the later growth, development, and functional maturation of the child is unknown.

Prolonged maternal use of opioids during pregnancy can result in withdrawal signs in the neonate. Neonatal Opioid Withdrawal Syndrome (NOWS), unlike opioid withdrawal syndrome in adults, may be life-threatening (see 7 WARNINGS AND PRECAUTIONS, 7.10 Neonatal Opioid Withdrawal Syndrome).

7.14.3 Breast-feeding

Since opioids can cross the placental barrier and are excreted in breast milk, RALIVIA is not recommended to be used in nursing women and during labour and delivery unless, in the judgment of the physician, the potential benefits outweigh the risks. 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 RALIVIA is used in this population.

Some women are CYP2D6 ultra-rapid metabolizers of tramadol, which may lead to dangerously higher-than-expected serum levels of M1 that could pass to their breast-fed infants. Therefore, maternal use of tramadol can lead to serious adverse reactions, including death in nursing infants (see 7 WARNINGS AND PRECAUTIONS, 7.12 Respiratory).

7.14.4 Pediatrics

The safety and efficacy of RALIVIA has not been studied in the pediatric population. Therefore, use of RALIVIA is not recommended in patients under 18 years of age. Further, adolescent patients (12 to 18 years old) who are obese or have conditions such as obstructive sleep apnea or severe lung disease may be at increased risk of serious breathing problems; the use of RALIVIA is not recommended in these pediatrics patients.

7.14.5 Geriatrics

In general, caution should be used when selecting the dose for an elderly patient. The elimination half-life of tramadol may be prolonged in patients over 75 years, thereby increasing the potential for adverse events. Usually, dose administration should start at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy (see 4 DOSAGE AND ADMINISTRATION and 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics Special Populations and Conditions, Geriatrics).

Nine-hundred-one elderly (> 65 years of age) subjects were exposed to RALIVIA in clinical trials. Of those subjects, 156 were > 75 years of age. Based on all dosage groups combined, the incidence of adverse events was similar for patients ≥ 65 years, compared with patients < 65 years, except for constipation which was higher, and headache which was lower, in patients > 65 years of age.

7.14.6 Impaired Hepatic or Renal Function

Patients with Hepatic Impairment

Use in Hepatic Disease: Metabolism of tramadol and it's M1 metabolite is reduced in patients with advanced cirrhosis of the liver. The pharmacokinetics of RALIVIA has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). RALIVIA is contraindicated in patients with severe hepatic impairment (see 2 CONTRAINDICATIONS, 10 CLINICAL PHARMACOLOGY, and 4 DOSAGE AND ADMINISTRATION).

Patients with Renal Impairment

Impaired renal function results in a decreased rate and extent of excretion of tramadol and its active metabolite, M1. RALIVIA has not been studied in patients with severe renal impairment (CLCr < 30 mL/min). RALIVIA is contraindicated in patients with severe renal impairment (see 2 CONTRAINDICATIONS, 10 CLINICAL PHARMACOLOGY, and 4 DOSAGE AND ADMINISTRATION).

8 ADVERSE REACTIONS

8.1 Adverse Reactions Overview

Adverse effects of RALIVIA (tramadol hydrochloride) extended-release 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.

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.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, 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.

RALIVIA was administered to a total of 3108 patients in four double-blind studies in patients with chronic pain of osteoarthritis or low back pain, and one 1-year open-label study in patients with chronic non-malignant pain. A total of 901 patients were ≥ 65 years.

Incidence of Commonly Observed Adverse Events in Controlled Clinical Trials

The most common adverse events with RALIVIA were dizziness, nausea, constipation, headache.

Table 1 shows incidence of all adverse events ≥ 1% in the four randomized, placebo-controlled studies, whether considered by the clinical investigator to be related to the study drug or not. The adverse events observed in the open label study were similar to those seen in the 4 randomized, placebo-controlled, clinical trials.

Table 1: Adverse Events: Placebo-Controlled Studies Treatment – Emergent Adverse Experiences Occurring in ≥ 1% of Patients taking RALIVIA (with an incidence greater than placebo)

	Flexible* (N=133) n (%)	RALIVIA 100 mg QD (N=403) n (%)	RALIVIA 200 mg QD (N=529) n (%)	RALIVIA 300 mg QD (N=528) n (%)	Total (N=1795) n (%)	Placebo (N=664) n (%)
Eye disorders						
Vision blurred	0 (0.0)	4 (1.0)	2 (0.4)	5 (0.9)	14 (0.8)	3 (0.5)
Gastrointestinal disorders						
Nausea	33 (24.8)	61 (15.1)	102 (19.3)	128 (24.2)	377 (21.0)	51 (7.7)
Constipation	32 (24.1)	49 (12.2)	76 (14.4)	104 (19.7)	321 (17.9)	25 (3.8)
Diarrhea NOS	12 (9.0)	15 (3.7)	38 (7.2)	43 (8.1)	118 (6.6)	29 (4.4)
Vomiting NOS	10 (7.5)	20 (5.0)	36 (6.8)	44 (8.3)	129 (7.2)	13 (2.0)
Dry mouth	4 (3.0)	20 (5.0)	29 (5.5)	39 (7.4)	110 (6.1)	8 (1.2)
Abdominal pain upper	3 (2.3)	5 (1.2)	12 (2.3)	16 (3.0)	41 (2.3)	5 (0.8)
Abdominal pain NOS	3 (2.3)	5 (1.2)	6 (1.1)	6 (1.1)	24 (1.3)	3 (0.5)
Dyspepsia	2 (1.5)	7 (1.7)	10 (1.9)	14 (2.7)	38 (2.1)	8 (1.2)
Sore throat NOS	3 (2.3)	6 (1.5)	5 (0.9)	5 (0.9)	22 (1.2)	9 (1.4)
General Disorders and Administration Site Conditions						
Asthenia	10 (7.5)	14 (3.5)	29 (5.5)	32 (6.1)	98 (5.5)	10 (1.5)
Feeling hot	4 (3.0)	7 (1.7)	7 (1.3)	7 (1.3)	28 (1.6)	3(0.5)
Rigors	3 (2.3)	3 (0.7)	3 (0.6)	11 (2.1)	27 (1.5)	2 (0.3)
Influenza like illness	3 (2.3)	1 (0.2)	7 (1.3)	8 (1.5)	23 (1.3)	4 (0.6)
Chest pain NEC	3 (2.3)	3 (0.7)	4 (0.8)	4 (0.8)	17 (0.9)	4 (0.6)
Lethargy	3 (2.3)	4 (1.0)	4 (0.8)	1 (0.2)	14 (0.8)	3 (0.5)
Pain NOS	2 (1.5)	10 (2.5)	16 (3.0)	16 (3.0)	49 (2.7)	14 (2.1)
Fall	2 (1.5)	5 (1.2)	5 (0.9)	5 (0.9)	19 (1.1)	3 (0.5)
Malaise	2 (1.5)	0 (0.0)	1 (0.2)	5 (0.9)	10 (0.6)	0 (0.0)
Drug withdrawal syndrome	2 (1.5)	1 (0.2)	2 (0.4)	0 (0.0)	7 (0.4)	0 (0.0)
Weakness	1 (0.8)	3 (0.7)	11 (2.1)	15 (2.8)	39 (2.2)	5 (0.8)

	Flexible* (N=133) n (%)	RALIVIA 100 mg QD (N=403) n (%)	RALIVIA 200 mg QD (N=529) n (%)	RALIVIA 300 mg QD (N=528) n (%)	Total (N=1795) n (%)	Placebo (N=664) n (%)
Infections and infestations						
Influenza	9 (6.8)	4 (1.0)	4 (0.8)	3 (0.6)	23 (1.3)	3 (0.5)
Upper respiratory tract infection NOS	5 (3.8)	15 (3.7)	12 (2.3)	13 (2.5)	49 (2.7)	20 (3.0)
Sinusitis NOS	3 (2.3)	7 (1.7)	13 (2.5)	12 (2.3)	40 (2.2)	12 (1.8)
Metabolism and nutrition disorders						
Anorexia	3 (2.3)	3 (0.7)	7 (1.3)	23 (4.4)	48 (2.7)	1 (0.2)
Appetite decreased NOS	2 (1.5)	5 (1.2)	9 (1.7)	8 (1.5)	31 (1.7)	3 (0.5)
Gout	2 (1.5)	1 (0.2)	0 (0.0)	1 (0.2)	5 (0.3)	2 (0.3)
Musculosketal, connective tissue and bone disorders						
Back pain	3 (2.3)	11 (2.7)	9 (1.7)	8 (1.5)	36 (2.0)	10 (1.5)
Muscle spasms	3 (2.3)	4 (1.0)	2 (0.4)	3 (0.6)	12 (0.7)	4 (0.6)
Nervous system disorders						
Dizziness (exc vertigo)	46 (34.6)	64 (15.9)	95 (18.0)	108 (20.5)	370 (22.6)	54 (8.1)
Headache NOS	18 (13.5)	49 (12.2)	78 (14.7)	65 (12.3)	242 (13.5)	77 (11.6)
Somnolence	10 (7.5)	33 (8.2)	46 (8.7)	32 (6.1)	162 (9.0)	11 (1.7)
Insomnia NEC	8 (6.0)	26 (6.5)	42 (7.9)	54 (10.2)	152 (8.5)	22 (3.3)
Paresthesia NEC	3 (2.3)	1 (0.2)	3 (0.6)	3 (0.6)	15 (0.8)	7 (1.1)
Irritability	3 (2.3)	2 (0.5)	3 (0.6)	3 (0.6)	12 (0.7)	3 (0.5)
Tremor NEC	1 (0.8)	3 (0.7)	4 (0.8)	14 (2.7)	24 (1.3)	1 (0.2)
Dizziness aggravated	0 (0.0)	2 (0.5)	7 (1.3)	3 (0.6)	16 (0.9)	2 (0.3)

	Flexible* (N=133) n (%)	RALIVIA 100 mg QD (N=403) n (%)	RALIVIA 200 mg QD (N=529) n (%)	RALIVIA 300 mg QD (N=528) n (%)	Total (N=1795) n (%)	Placebo (N=664) n (%)
Psychiatric disorders						
Restlessness	2 (1.5)	3 (0.7)	2 (0.4)	10 (1.9)	18 (1.0)	2 (0.3)
Nervousness	0 (0.0)	7 (1.7)	13 (2.5)	20 (3.8)	48 (2.7)	5 (0.8)
Anxiety NEC	0 (0.0)	2 (0.5)	9 (1.7)	15 (2.8)	28 (1.6)	4 (0.6)
Depression NEC	0 (0.0)	2 (0.5)	4 (0.8)	8 (1.5)	17 (0.9)	2 (0.3)
Renal and urinary disorders						
Hematuria	3 (2.3)	1 (0.2)	2 (0.4)	6 (1.1)	13 (0.7)	1 (0.2)
Difficulty in micturition	2 (1.5)	2 (0.5)	0 (0.0)	5 (0.9)	11 (0.6)	2 (0.3)
Respiratory, thoracic and mediastinal disorders						
Sneezing	0 (0.0)	10 (2.5)	10 (1.9)	12 (2.3)	36 (2.0)	2 (0.3)
Rhinorrhea	1 (0.8)	8 (2.0)	11 (2.1)	7 (1.3)	28 (1.6)	5 (0.8)
Skin and subcutaneous tissue disorders						
Pruritus NOS	9 (6.8)	25 (6.2)	36 (6.8)	31 (5.9)	125 (7.0)	6 (0.9)
Sweating increased	5 (3.8)	6 (1.5)	9 (1.7)	18 (3.4)	51 (2.8)	1 (0.2)
Dermatitis NOS	5 (3.8)	5 (1.2)	9 (1.7)	13 (2.5)	35 (1.9)	10 (1.5)
Urticaria NOS	2 (1.5)	1 (0.2)	2 (0.4)	1 (0.2)	8 (0.4)	3 (0.5)
Contusion	1 (0.8)	5 (1.2)	6 (1.1.)	4 (0.8)	17 (0.9)	1 (0.2)
Vascular disorders						
Flushing	13 (9.8)	31 (7.7)	47 (8.9)	42 (8.0)	165 (9.2)	26 (3.9)
Postural hypotension	3 (2.3)	7 (1.7)	21 (4.0)	18 (3.4)	60 (3.3)	15 (2.3)
Vasodilatation	2 (1.5)	1 (0.2)	4 (0.8)	2 (0.4)	14 (0.8)	3 (0.5)
Hot flushes NOS	0 (0.0)	4 (1.0)	11 (2.1)	13 (2.5)	32 (1.8)	5 (0.8)

*Patients in the flexible dose study received RALIVIA 200 to 400mg per day

The following listings include adverse events for the four placebo-controlled studies and the open-label study (N = 3108)

Adverse events with incidence rates ≥ 1.0% and not noted in the placebo-controlled studies.

- ***General disorders:*** pyrexia
- ***Infections and infestations:*** bronchitis, viral gastroenteritis, nasopharyngitis
- ***Musculoskeletal, connective tissue and bone disorders***: neck pain, arthralgia
- ***Nervous system disorders:*** hypoaesthesia
- ***Respiratory, thoracic, and mediastinal disorders:*** dyspnoea, nasal congestion, sinus congestion

The following adverse effects occur less frequently with opioid analgesics and include those reported in RALIVIA clinical trials, whether related or not to tramadol hydrochloride.

8.3 Less Common Clinical Trial Adverse Reactions

Cardiovascular

- ***Cardiac disorders:*** palpitations, myocardial infarction.
- ***Vascular disorders:*** hypertension aggravated, hypertension, peripheral ischemia.

Dermatologic

- ***Skin and subcutaneous tissue disorders:*** contusion, clamminess, night sweats, urticaria, piloerection.
- ***Musculoskeletal, connective tissue and bone disorders:*** joint stiffness, myalgia, muscle cramps, muscle spasms, muscle twitching, osteoarthritis aggravated.

Gastrointestinal

- ***Gastrointestinal disorders:*** flatulence, constipation aggravated, toothache, pancreatitis.

General and CNS

- ***General disorders:*** feeling jittery, edema lower limb, shivering, joint swelling, malaise, drug withdrawal syndrome, peripheral swelling.
- ***Ear and labyrinth disorders:*** tinnitus.
- ***Nervous system disorders:*** migraine, syncope, disturbance in attention, dizziness aggravated, vertigo, sedation.
- ***Psychiatric disorders:*** irritability, libido decreased, euphoric mood, sleep disorder, agitation, disorientation, abnormal dreams.

Genitourinary

- ***Renal and urinary disorders:*** difficulty in micturition, urinary frequency, urinary retention, dysuria, haematuria.

Respiratory

- ***Respiratory, thoracic and mediastinal disorders:*** yawning.

Other

- ***Hepato-biliary disorders:*** cholelithiasis, cholecystitis.
- ***Infections and infestations:*** appendicitis, cellulitis, ear infection, gastroenteritis, pneumonia, urinary tract infection, viral infection.

- ***Injury and poisoning:*** joint sprain, muscle injury.
- ***Investigations:*** heart rate increased, liver function tests abnormal, blood pressure increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood glucose increased.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

In clinical trials where clinical abnormalities were recorded (n = 230), the following clinical laboratory abnormalities were reported: alanine aminotransferase increased (0.8%), aspartate aminotransferase increased (0.7%), liver function tests NOS abnormal (0.4%), blood lactate dehydrogenase increased (0.3%), white blood cell count increased (0.3%), blood alkaline phosphatase NOS increased (0.3%), hematocrit decreased (0.3%), rectal hemorrhage (0.3%), and hypokalemia (0.3%).

The following abnormalities occurred in 0.2% of patients: red blood cell count decreased, hemoglobin decreased, blood calcium increased, blood creatinine increased, anemia NOS, blood potassium decreased, and neutrophil count increased.

The following abnormalities occurred in 0.1% of patients: thrombocythemia, blood potassium increased, blood bilirubin increased, blood in stool, hemoglobin increased, hypercalcemia, hematocrit increased, eosinophil count increased, blood sodium increased, and hyponatremia.

The following abnormalities were single occurrences in patients: blood sodium decreased, hyperkalemia, blood calcium decreased, hypophosphatemia, hemoptysis, hematemesis, red blood cell count increased, band neutrophil count increased, monocyte count increased, and lymphocyte count increased.

8.5 Post-Market Adverse Reactions

Other Adverse Experiences Previously Reported in Clinical Trials or Post-Marketing Reports with Tramadol Hydrochloride

Adverse events which have been reported with the use of tramadol products include allergic reactions (including anaphylaxis, angioneurotic edema and urticaria, Stevens-Johnson syndrome), bradycardia, convulsions, drug dependence, hyperactivity, hypoactivity, and respiratory depression. Other adverse events which have been reported with the use of tramadol products and for which a causal association has not been determined include difficulty concentrating, hepatitis liver failure, pulmonary edema, and suicidal tendency.

Serotonin syndrome (whose symptoms may include mental status change, hyperreflexia, fever, shivering, tremor, agitation, diaphoresis, seizures and coma) has been reported with tramadol when used concomitantly with other serotonergic agents such as SSRI's and MAOIs.

Electrocardiogram QT prolonged, ventricular fibrillation, and ventricular tachycardia have been reported during post-market use.

Cases of hypoglycaemia have been reported in patients taking tramadol, mostly in patients with pre-disposing risk factors, including diabetes, elderly and renal insufficiency. Caution should be exercised when prescribing tramadol to diabetic patients. More frequent monitoring of blood glucose levels may be appropriate, including at initiation or dose increase.

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.

Hallucinations

Visual and auditory hallucinations have been reported at therapeutic doses of tramadol, during post-marketing experience, in a higher rate in elderly patients compared to younger patients. Hallucinations are 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.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

In vitro studies indicated that tramadol is unlikely to inhibit the CYP3A4-mediated metabolism of other drugs when tramadol is administered concomitantly at therapeutic doses.

Tramadol does not appear to induce its own metabolism in humans, since observed maximal plasma concentrations after multiple oral doses are higher than expected based on single dose data.

Tramadol is a mild inducer of selected drug metabolism pathways measured in animals.

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

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, 7.11 Neurologic, Interactions with Central Nervous System Depressants (including benzodiazepines and alcohol) and Psychomotor Impairment). RALIVIA should not be consumed with alcohol as it may increase the chance of experiencing dangerous side effects.

Serotonergic Agents

Coadministration of tramadol 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).

9.4 Drug-Drug Interactions

MAO Inhibitors

Tramadol is contraindicated in patients receiving MAO inhibitors or who have used them within the previous 14 days (see 2 CONTRAINDICATIONS, 7 WARNINGS AND PRECAUTIONS).

Drugs that Lower Seizure Threshold

Tramadol can increase the potential for selective serotonin re-uptake inhibitors (SSRIs), tricyclic anti-depressants (TCAs), anti-psychotics and other seizure threshold lowering drugs to cause convulsions (see 7 WARNINGS AND PRECAUTIONS).

CNS Depressants

Concurrent administration of tramadol with other centrally acting drugs, including alcohol, centrally acting analgesics, opioids and psychotropic drugs may potentiate CNS depressant effects.

Carbamazepine

Carbamazepine, a CYP3A4 inducer, increases tramadol metabolism. Patients taking carbamazepine may have a significantly reduced analgesic effect of tramadol. Because of the seizure risk associated with tramadol, concomitant administration of RALIVIA and carbamazepine is not recommended (see 7 WARNINGS AND PRECAUTIONS).

Quinidine

Tramadol is metabolized to M1 by CYP2D6. A study was conducted to examine the effect of quinidine, a selective inhibitor of CYP2D6, on the pharmacokinetics of tramadol by administering 200 mg of quinidine two hours before the administration of RALIVIA 100 mg. The results demonstrated that the exposure of tramadol increased 50-60% and the exposure of M1 decreased 60-65%. In vitro drug interaction studies in human liver microsomes indicate that tramadol has no effect on quinidine metabolism.

Inhibitors of CYP2D6

Inhibitors of CYP2D6 (e.g., quinidine, fluoxetine, paroxetine, amitriptyline) may inhibit the metabolism of tramadol, resulting in increased serum concentrations of tramadol and decreased concentrations of its O-demethylated metabolite (M1). Co-administration of quinidine did not diminish the analgesic effect of tramadol in human experimental pain models.

Inhibitors or Inducers of CYP3A4

Administration of CYP3A4 inhibitors, such as ketoconazole and erythromycin, or inducers, such as rifampin and St. John's Wort may affect the metabolism of tramadol, leading to altered tramadol exposure.

Concomitant administration of CYP2D6 and/or CYP3A4 inhibitors (see 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics), such as quinidine, fluoxetine, paroxetine,

amitriptyline (CYP2D6 inhibitors), ketoconazole and erythromycin (CYP3A4 inhibitors), may reduce metabolic clearance of tramadol, increasing the risk for serious adverse events including seizures, serotonin syndrome, and QTc interval prolongation, potentially resulting in cardiac arrhythmias.

QTc Interval-Prolonging Drugs

The concomitant use of RALIVIA with QTc interval-prolonging drugs should be avoided. Drugs that have been associated with QTc interval prolongation and/or torsade de pointes include, but are not limited to, the examples in the following list. Chemical/pharmacological classes are listed if some, although not necessarily all, class members have been implicated in QTc interval prolongation and/or torsade de pointes:

- Class IA antiarrhythmics (e.g., quinidine, procainamide, disopyramide)
- Class III antiarrhythmics (e.g., amiodarone, sotalol, ibutilide, dronedarone)
- Class 1C antiarrhythmics (e.g., flecainide, propafenone)
- antipsychotics (e.g., chlorpromazine, pimozide, haloperidol, droperidol, ziprasidone, risperidone)
- antidepressants (e.g., fluoxetine, citalopram, venlafaxine, tricyclic/tetracyclic antidepressants [e.g., amitriptyline, imipramine, maprotiline])
- opioids (e.g., methadone)
- macrolide antibiotics and analogues (e.g., erythromycin, clarithromycin, azithromycin, tacrolimus)
- quinolone antibiotics (e.g., moxifloxacin, levofloxacin, ciprofloxacin)
- pentamidine
- antimalarials (e.g., quinine, chloroquine)
- azole antifungals (e.g., ketoconazole, fluconazole, voriconazole)
- domperidone
- 5-hydroxytryptamine (5-HT)3 receptor antagonists (e.g., ondansetron)
- tyrosine kinase inhibitors (e.g., sunitinib, nilotinib, ceritinib, vandetanib)
- arsenic trioxide
- histone deacetylase inhibitors (e.g., vorinostat)
- beta-2 adrenoceptor agonists (e.g., salmeterol, formoterol)

Drugs that Affect Electrolytes

The use of RALIVIA with drugs that can decrease electrolyte levels should be avoided to the extent possible. Drugs that can decrease electrolyte levels include, but are not limited to, the following:

- loop, thiazide, and related diuretics
- laxatives and enemas
- amphotericin B
- high-dose corticosteroids
- proton pump inhibitors

The above list of potentially interacting drugs is not comprehensive. Current information sources should be consulted for newly approved drugs that prolong the QTc interval or decrease electrolytes, as well as for older drugs for which these effects have recently been established (see 7 WARNINGS AND PRECAUTIONS, 7.6 Cardiovascular; 8 ADVERSE

REACTIONS, 8.5 Post-Market Adverse Reactions, Post-Marketing Reports with Tramadol; 10 CLINICAL PHARMACOLOGY, 10.2 Pharmacodynamics, Cardiac Electrophysiology).

Cimetidine

Concomitant administration of tramadol immediate-release tablets with cimetidine does not result in clinically significant changes in tramadol pharmacokinetics. No alteration of the RALIVIA dosage regimen with cimetidine is recommended.

Digoxin

Digoxin toxicity has occurred rarely during co-administration of digoxin and tramadol.

Protease inhibitors, e.g., ritonavir

Co-administered ritonavir may increase the serum concentration of tramadol, resulting in tramadol toxicity.

Warfarin and other coumarin anticoagulants

Alteration of the effect of warfarin, including elevation of prothrombin times, has been reported rarely during co-administration of warfarin and tramadol. While such changes have been generally of limited clinical significance for the individual products, periodic evaluation of prothrombin time should be performed when RALIVIA tablets and warfarin-like compounds are administered concurrently.

9.5 Drug-Food Interactions

After a single dose administration of 200 mg RALIVIA tablet with a high fat meal, the C_{max} and $AUC_{0-\infty}$ of tramadol decreased 28% and 14%, respectively, compared to fasting conditions. Mean T_{max} was increased by 3 h (from 14 h under fasting conditions to 17 h under fed conditions). While RALIVIA may be taken without regard to food, it is recommended that it be taken in a consistent manner.

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.

9.8 Drug-Lifestyle Interactions

The concomitant use of alcohol should be avoided (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX).

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Tramadol is a centrally acting synthetic opioid analgesic. Although its mode of action is not completely understood, animal tests suggest that at least two complementary mechanisms appear applicable: binding of parent and M1 metabolite to μ-opioid receptors and weak inhibition of reuptake of norepinephrine and serotonin.

Opioid activity is due to both low affinity binding of the parent compound and higher affinity binding of the O-demethylated metabolite M1 to mu-opioid receptors. In animal models, M1 is up to 6-times more potent than tramadol in producing analgesia and 200-times more potent in mu-opioid binding. Tramadol-induced analgesia is only partially antagonized by the opiate antagonist naloxone in several animal tests. The relative contribution of both tramadol and M1 to human analgesia is dependent upon the plasma concentrations of each compound.

Tramadol has been shown to inhibit reuptake of norepinephrine and serotonin in vitro, as have some other opioid analgesics. These mechanisms may contribute independently to the overall analgesic profile of tramadol. The relationship between exposure of tramadol and M1 and efficacy has not been evaluated in the RALIVIA clinical studies.

Apart from analgesia, tramadol administration may produce a constellation of symptoms (including dizziness, somnolence, nausea, constipation, sweating and pruritus) similar to that of other opioids. In contrast to morphine, tramadol has not been shown to cause histamine release. Tramadol produces less respiratory depression than other opioids and has no significant cardiac effects. At therapeutic doses, tramadol has no effect on heart rate, left-ventricular function or cardiac index. Orthostatic hypotension has been observed.

10.2 Pharmacodynamics

Tramadol is a centrally acting opioid analgesic but is atypical in having at least two complementary mechanisms of action. It is an agonist at mu-, delta- and kappa-opioid receptors, with greater affinity for the mu-receptor. Other mechanisms that contribute to its analgesic effect are inhibition of neuronal re-uptake of norepinephrine and serotonin, which are thought to result in activation of inhibitory pain pathways in the dorsal horn of the spinal cord. As a result, tramadol-induced analgesia is only partially antagonized by the opioid antagonist naloxone. It is also antagonized by α2 adrenoceptor antagonists.

The opioid activity of tramadol is due to both low affinity binding of the parent compound and higher affinity binding of the O-demethylated metabolite (M1) to the mu opioid receptor. The affinity of tramadol for the mu receptor is 10 times less than codeine, 200 times less than O desmethyl tramadol, and 6,000 times less than morphine. The affinity of tramadol for delta and kappa opioid receptors is 20-25 times less than to mu receptors. The (+) enantiomer has 20 times greater affinity for the mu opioid receptor than the (-) enantiomer.

Tramadol inhibits the neuronal re-uptake of serotonin and also increases its release through a pre-synaptic mechanism. The (+) enantiomer is more potent than the (-) enantiomer in inhibiting serotonin reuptake. Conversely, the (-) enantiomer is more potent than the (+) enantiomer in inhibiting norepinephrine reuptake, and also increases norepinephrine release through stimulation of a pre-synaptic autoreceptor.

Both enantiomers have anti-nociceptive effects in animals and analgesic effects in humans, and the interaction between the two enantiomers is synergistic. However, for adverse effects, the interaction is less than additive (rotarod performance), additive (colonic motility) or antagonistic (cardiovascular and respiratory endpoints). Effects on gastrointestinal motility and

respiration are less than with morphine, consistent with clinical observations of less constipation and respiratory depression at recommended doses.

The administration of naloxone only partially antagonizes tramadol's antinociceptive and analgesic effects in animals and man, indicating a contribution from non-opioid analgesic mechanisms. In animals and man, the effect of tramadol is attenuated by the α2-adrenoceptor antagonist, yohimbine, and in animals, the serotonin antagonist rianserin reduces the antinociceptive effect of tramadol. This indicates the potential for a contribution to the analgesic effect of tramadol through modulation of monaminergic inhibitory pain pathways in the dorsal horn of the spinal cord, in addition to an opioidergic effect.

Cardiac Electrophysiology

In a randomized, double-blind, 4-way crossover, placebo- and positive-controlled, multiple dose ECG assessment study in healthy subjects (N=62), the following tramadol treatments were tested: A) 100 mg every 6 h on days 1-3 (400 mg/day), with a single 100 mg dose on day 4 and B) 150 mg every 6 h (600 mg/day) on days 1-3, with a single 150 mg dose on day 4. The maximum dose for RALIVIA is 300 mg/day. In both treatment arms, the maximum difference from placebo in the mean change from baseline QTcF interval occurred at the 8 h time point: 5.5 ms (90% CI 3.2, 7.8) in the 400 mg/day treatment arm and 6.5 ms (90% CI 4.1, 8.8) in the 600 mg/day mg treatment arm. Both treatment groups were within the 10 ms threshold for QT prolongation (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular; 8 ADVERSE REACTIONS, 8.5 Post-Market Adverse Reactions, Post-Marketing Reports with Tramadol, 9 DRUG INTERACTIONS, 9.2 Drug Interactions Overview, QTc Interval-Prolonging Drugs, 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment and 5 OVERDOSAGE).

Central Nervous System

Tramadol hydrochloride produces respiratory depression by direct action on brain stem respiratory centres. The respiratory depression involves both a reduction in the responsiveness of the brain stem centres to increases in CO2 tension and to electrical stimulation.

Tramadol hydrochloride 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.

Tramadol hydrochloride 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 tramadol overdose.

Gastrointestinal Tract and Other Smooth Muscle

Tramadol hydrochloride 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.

Endocrine System

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

Immune System

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

10.3 Pharmacokinetics

The analgesic activity of tramadol is due to both parent drug and the M1 metabolite. RALIVIA is administered as a racemate and both the [-] and [+] forms of both tramadol and M1 are detected in the circulation.

The pharmacokinetics of RALIVIA are approximately dose-proportional over a 100 400 mg dose range in healthy subjects. However, the observed tramadol AUC values for the 400-mg dose were 26% higher than predicted based on the AUC values for the 200-mg dose. The clinical significance of this finding has not been studied and is not known.

Absorption

Consistent with the extended-release nature of the formulation, there is a lag time in drug absorption following RALIVIA administration. The mean peak plasma concentrations of tramadol and M1 after administration of RALIVIA tablets to healthy volunteers are attained at about 12 h and 15 h, respectively, after dosing. Following administration of the RALIVIA, steady-state plasma concentrations of both tramadol and M1 are achieved within four days with once daily dosing.

Distribution

The volume of distribution of tramadol was 2.6 and 2.9 L/kg in male and female subjects, respectively, following a 100-mg intravenous dose. The binding of tramadol to human plasma proteins is approximately 20% and binding also appears to be independent of concentration up to 10 mcg/mL. Saturation of plasma protein binding occurs only at concentrations outside the clinically relevant range.

Metabolism

Tramadol is extensively metabolized after oral administration. The major metabolic pathways appear to be N- (mediated by CYP3A4 and CYP2B6) and O- (mediated by CYP2D6) demethylation and glucuronidation or sulfation in the liver. One metabolite (O-desmethyl tramadol, denoted M1) is pharmacologically active in animal models. Formation of M1 is dependent on CYP2D6 and as such is subject to inhibition, which may affect the therapeutic response (see 9 DRUG INTERACTIONS).

Excretion

Tramadol is eliminated primarily through metabolism by the liver and the metabolites are eliminated primarily by the kidneys. Approximately 30% of the dose is excreted in the urine as unchanged drug, whereas 60% of the dose is excreted as metabolites. The remainder is excreted either as unidentified or as unextractable metabolites. The mean terminal plasma elimination half-lives of racemic tramadol and racemic M1 after administration of RALIVIA are approximately 7.9 and 8.8 h, respectively.

Food Effects

After a single dose administration of 200 mg RALIVIA tablet with a high fat meal, the C_{max} and $AUC_{0-\infty}$ of tramadol decreased 28% and 14%, respectively, compared to fasting conditions. Mean T_{max} was increased by 3 h (from 14 h under fasting conditions to 17 h under fed conditions). While RALIVIA may be taken without regard to food, it is recommended that it be taken in a consistent manner.

Special Populations and Conditions

- **Pediatrics:** The pharmacokinetics of RALIVIA in individuals under 18 years old has not been evaluated. Individuals under 18 years of age should not take RALIVIA.
- **Geriatrics:** Healthy elderly subjects aged 65 to 75 years administered tramadol have plasma concentrations and elimination half-lives comparable to those observed in healthy subjects less than 65 years of age. RALIVIA should be administered with greater caution in patients older than 75 years due to the greater potential for adverse events in this population (see 7 WARNINGS AND PRECAUTIONS, 4 DOSAGE AND ADMINISTRATION).
- **Gender:** Based on pooled multiple-dose pharmacokinetics studies for RALIVIA in 166 healthy subjects (111 males and 55 females), the dose-normalized AUC values for tramadol were somewhat higher in females than in males. There was a considerable degree of overlap in dose normalized AUC values for males and females, thus, dosage adjustment based on gender is not recommended.
- **Race:** Due to the small sample size for Asian, Hispanic, and other populations, conclusions cannot be drawn about the pharmacokinetics of tramadol in these populations.

  Some patients are CYP2D6 ultra-rapid metabolizers of tramadol due to a specific genotype. These individuals convert tramadol into its active metabolite, M1, more rapidly and completely than other people leading to higher-than-expected serum M1 levels. The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 0.5 to 1% in Chinese, Japanese and Hispanics, 1 to 10% in Caucasians, 3% in African Americans, and 16 to 28% in North Africans, Ethiopians, and Arabs. Data are not available for other ethnic groups (see 7 WARNINGS AND PRECAUTIONS, 7.12 Respiratory, 7.14 Special Populations, 7.14.2 Breast-feeding).

  In contrast, some patients exhibit the CYP2D6 poor metabolizer phenotype and do not convert tramadol to the active M1 metabolite sufficiently to benefit from the analgesic effect of the drug (see 9 DRUG INTERACTIONS, 9.2 Drug Interactions Overview). The prevalence of this CYP2D6 phenotype is about 5-10 percent in Caucasians and 1 percent of Asians.

- **Hepatic Insufficiency:** Pharmacokinetics of tramadol was studied in patients with mild or moderate hepatic impairment after receiving multiple doses of RALIVIA 100 mg. The exposure of (+)- and (-)-tramadol was similar in mild and moderate hepatic impairment patients in comparison to patients with normal hepatic function. However, exposure of (+)- and (-)-M1 decreased ~50% with increased severity of the hepatic impairment (from normal to mild and moderate). The pharmacokinetics of tramadol after the administration of RALIVIA has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). After the administration of tramadol immediate-release tablets to patients with advanced cirrhosis of the liver, tramadol area under the plasma concentration time curve was larger and the tramadol and M1 half-lives were longer than subjects with normal hepatic function. RALIVIA is contraindicated in patients with severe hepatic impairment (see 2 CONTRAINDICATIONS, 7 WARNINGS AND PRECAUTIONS, 7.14.6 Impaired Hepatic or Renal Function and 4 DOSAGE AND ADMINISTRATION).
- **Renal Insufficiency:** Impaired renal function results in a decreased rate and extent of excretion of tramadol and its active metabolite, M1. The pharmacokinetics of tramadol were studied in patients with mild or moderate renal impairment after receiving multiple doses of RALIVIA 100 mg. There is no consistent trend observed for tramadol exposure related to renal function in patients with mild (CLCr: 50-80 mL/min) or moderate (CLCr: 30-50 mL/min) renal impairment in comparison to patients with normal renal function. However, exposure of M1 increased 20-40% with increased severity of the renal impairment (from normal to mild and moderate). RALIVIA has not been studied in patients with severe renal impairment (CLCr < 30 mL/min). RALIVIA is contraindicated in patients with severe renal impairment (see 2 CONTRAINDICATIONS, 7 WARNINGS AND PRECAUTIONS, 7.14.6 Impaired Hepatic or Renal Function, and 4 DOSAGE AND ADMINISTRATION). The total amount of tramadol and M1 removed during a 4-hour dialysis period is less than 7% of the administered dose.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15–30ºC).

12 SPECIAL HANDLING INSTRUCTIONS

RALIVIA does not have special handling instructions.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Tramadol hydrochloride

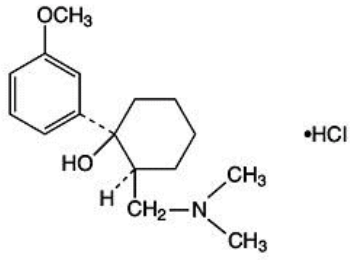
Chemical name: (±) cis-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride

(1RS,2RS)-2[(dimethylamino)methyl]-1-(3-methoxyphenl)cyclohexanol hydrochloride

Molecular formula: $C_{16}H_{25}NO_2 \cdot HCl$

Molecular mass: 299.8 g/mol

Structural formula:



Physicochemical properties

Description: Tramadol hydrochloride is a white, crystalline powder.

Solubility: Freely soluble in water and in methanol, very soluble in acetone.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Tramadol HCl ER was studied in patients with chronic, moderate-to-severe pain due to osteoarthritis of the knee and/or hip, and low back pain, in four 12-week, randomized, double-blind, parallel-group, placebo-controlled trials. To qualify for inclusion into these studies, patients were required to have moderate-to-severe pain as defined by a pain intensity score of ≥ 40 mm, off previous medications, on a 0 – 100 mm visual analog scale (VAS). The primary outcome variables were pain intensity VAS for studies 015 and 014. Studies 023 and 021 had 3 co-primary outcomes: WOMAC Osteoarthritis Index pain, WOMAC OA physical function subscales, and patient global assessment of disease activity.

14.2 Study Results

Data from the 2 pivotal studies are shown in Tables 2 and 3.

Table 2: Study Demographics, Trial Design and Results of Study (015)

Study #	**Trial design**	**Dosage, route of administration and duration**	**Study subjects (n = number)**	**Mean age (Range)**	**Gender**
Study (015)	Randomized, double-blind, parallel-group, flexible dosing – **Tramadol HCl ER** vs. Placebo	**Tramadol HCl ER:** 200 – 400 mg/day, oral vs. Placebo, oral; 12 weeks duration	n = 246	61.4 years (30 – 85)	M = 95 F = 151
Primary Endpoints		**Associated value and statistical significance for LS mean change from baseline over weeks 1 to 12 for Tramadol HCl ER**		**Associated value and statistical significance for LS mean change from baseline over weeks 1 to 12 for Placebo**	
Pain intensity (100 mm VAS)		Baseline (mean ± SD) 78.2 ± 15.2 **Tramadol HCl ER** (LS mean) 30.4 *(p<0.001)*		Baseline (mean ± SD) 75.5 ± 16.5 Placebo (LS mean) 17.7 *(p<0.001)*	
		LS mean difference in change from baseline over weeks 1 to 12 between **Tramadol HCl ER** and Placebo = 12.7 *(p<0.001)*			

Table 3: Study Demographics, Trial Design and Results of Study (023)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n = number)	Mean age (Range)	Gender
Study (023)	Randomized, double-blind, dose-ranging, fixed-dose, parallel-group – 4 doses of **Tramadol HCl ER** vs. Placebo	**Tramadol HCl ER:** 100, 200, 300, and 400 mg/day, oral vs. Placebo, oral; 12 weeks duration	n = 1011 (evaluable efficacy and safety population)	58.2 years (22 – 74)	M = 380 F = 631

Primary Endpoints	**Associated value and statistical significance for LS mean change at endpoint for Tramadol HCl ER 100, 200, 300 and 400 mg, and Placebo vs. baseline & the LS mean differences in change from baseline between Tramadol HCl ER doses and Placebo**				
	Treatments	**Baseline VAS scores (mean ± SD)**	**LS mean ± SE change at endpoint**	**LS mean ± SE difference vs. Placebo**	**p-value vs. placebo**
WOMAC OA Index pain subscale (5 X 100 mm VAS)	**Tramadol HCl ER 400 mg**	298.0 ± 93.7	107.8 ± 8.7 *(p<0.001)*	33.6 ± 11.7	0.004
	Tramadol HCl ER 300 mg	296.6 ± 96.3	103.9 ± 8.7 *(p<0.001)*	29.7 ± 11.7	0.012
	Tramadol HCl ER 200 mg	315.2 ± 92.4	111.5 ± 8.7 *(p<0.001)*	37.3 ± 11.8	0.002
	Tramadol HCl ER 100 mg	308.0 ± 99.3	107.2 ± 8.6 *(p<0.001)*	32.9 ± 11.7	0.005
	Placebo	305.9 ± 95.2	74.2 ± 8.5 *(p<0.001)*	N/A	N/A
WOMAC OA Index physical function subscale (17 X 100 mm VAS)	**Tramadol HCl ER 400 mg**	1010.9 ± 331.7	329.8 ± 28.8 *(p<0.001)*	95.5 ± 38.9	0.014
	Tramadol HCl ER 300 mg	1026.6 ± 337.6	336.1 ± 28.8 *(p<0.001)*	101.8 ± 38.9	0.009
	Tramadol HCl ER 200 mg	1096.2 ± 298.7	350.2 ± 29.0 *(p<0.001)*	115.9 ± 39.0	0.003

	Tramadol HCl ER 100 mg	1071.6 ± 331.2	331.7 ± 28.5 *(p<0.001)*	97.4 ± 38.8	0.012
	Placebo	1058.7 ± 340.3	234.3 ± 28.1 *(p<0.001)*	N/A	N/A
Patient global assessment of disease activity (100 mm VAS)	**Tramadol HCl ER 400 mg**	61.4 ± 22.6	20.8 ± 2.0 *(p<0.001)*	4.6 ± 2.7	0.084
	Tramadol HCl ER 300 mg	64.6 ± 20.7	23.5 ± 2.0 *(p<0.001)*	7.2 ± 2.7	0.006
	Tramadol HCl ER 200 mg	67.4 ± 20.1	21.8 ± 2.0 *(p<0.001)*	5.5 ± 2.7	0.037
	Tramadol HCl ER 100 mg	65.4 ± 22.3	21.3 ± 1.9 *(p<0.001)*	5.1 ± 2.6	0.055
	Placebo	66.6 ± 21.5	16.2 ± 1.9 *(p<0.001)*	N/A	N/A

Study (014)

A 12-week, randomized, double-blind, parallel-group, placebo-controlled trial was conducted in 619 patients with moderate-to-severe chronic low back pain to compare the analgesic efficacy and safety of tramadol HCl ER 200 mg and 300 mg QD with placebo, each administered orally. Only patients who achieved pain relief, tolerated and completed an initial 3-week open-label, run-in period during which tramadol HCl ER was administered to all patients and titrated up to 300 mg/day were randomized (without washout) into the 12-week double-blind period (n = 386). Tramadol HCl ER 300 mg QD statistically significantly maintained baseline improvement in pain intensity VAS score over weeks 1 to 12 compared to placebo (p=0.009). The tramadol HCl ER 200 mg QD dose did not significantly (p=0.052) maintain baseline improvement in pain intensity VAS score over weeks 1 to 12 compared to placebo.

Study (021)

This was a 12-week, randomized, double-blind, dose-ranging, fixed-dose, parallel-group, placebo-controlled trial conducted in 1020 patients with moderate-to-severe pain of osteoarthritis of the knee and/or hip to compare the analgesic efficacy and safety of tramadol HCl ER 100, 200, and 300 mg QD versus a Cox2 control, and placebo, each administered orally. With the tramadol HCl ER treatments, the magnitude of the LS mean change scores from baseline increased with dose, however, only the 300 mg dose was associated with a statistically significant reduction from baseline compared to placebo in the patient global assessment of disease activity scores (p=0.023).

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenic effect of tramadol was observed in p53(+/–)-heterozygous mice at oral doses up to 150 mg/kg/day (approximately 2-fold maximum daily human dose [MDHD] of 400 mg/day for a 60 kg adult based on body surface conversion) for 26 weeks and in rats at oral doses up to 75 mg/kg/day for males and 100 mg/kg/day for females (approximately 2 fold MDHD) for two years. However, the excessive decrease in body weight gain observed in the rat study might have reduced their sensitivity to any potential carcinogenic effect of the drug.

Tramadol was not mutagenic in the following assays: a bacterial reverse mutation assay using Salmonella and E. coli, a mouse lymphoma assay (in the absence of metabolic activation), and a bone marrow micronucleus test in mice. Mutagenic results occurred in the presence of metabolic activation in the mouse lymphoma assay. Overall, the weight of evidence from these tests indicates that tramadol does not pose a genotoxic risk to humans.

No effects on fertility were observed for tramadol at oral dose levels up to 50 mg/kg/day in male and female rats (approximately equivalent to MDHD).

Reproduction and Teratology

Tramadol was not teratogenic at oral dose levels up to 50 mg/kg/day (approximately equivalent to MDHD) in rats and 100 mg/kg (approximately 5-fold MDHD) in rabbits during organogenesis. However, embryo fetal lethality, reductions in fetal weight and skeletal ossification, and increased supernumerary ribs were observed at a maternal toxic dose of 140 mg/kg in mice (approximately 2 fold MDHD), 80 mg/kg in rats (2 fold MDHD) or 300 mg/kg in rabbits (approximately 15 fold MDHD).

Tramadol caused a reduction in neonatal body weight and survival at an oral dose of 80 mg/kg (approximately 2-fold MDHD) when rats were treated during late gestation throughout lactation period.

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

PrRALIVIA®
Tramadol Hydrochloride
Extended-Release Tablets

Read this carefully before you start taking **RALIVIA** 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 **RALIVIA**.

Serious Warnings and Precautions

- **Even if you take RALIVIA as prescribed you are at risk for opioid addiction, abuse, and misuse. This can lead to overdose and death.**
- **When you take RALIVIA 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 RALIVIA. 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 RALIVIA. They could die from taking it. If a person has not been prescribed RALIVIA, taking even one dose can cause a fatal overdose. This is especially true for children.**
- **If you took RALIVIA 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 RALIVIA 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.**

What is RALIVIA used for?

- RALIVIA (tramadol hydrochloride) is an extended-release oral tablet that slowly releases tramadol (an opioid analgesic) over a 24-hour period to manage continuous pain that is expected to persist for several days or more. Your doctor is the person who knows if RALIVIA tablets are a good choice for you.

How does RALIVIA work?

RALIVIA is a painkiller belonging to the class of medicines known as opioids. It relieves pain by acting on specific nerve cells of the spinal cord and brain. It contains tramadol, a medicine used to treat moderate to moderately severe pain and should relieve your pain and help the pain relief last longer.

Your pain may increase or decrease from time to time and your doctor may need to change the amount of tramadol you take daily (daily dosage).

What are the ingredients in RALIVIA?

Medicinal ingredients: Tramadol hydrochloride

Non-medicinal ingredients: Colloidal Silicon Dioxide, Ethylcellulose, Dibutyl Sebacate, Polyvinyl Alcohol, Polyvinyl Pyrrolidone, and Sodium Stearyl Fumarate, Black Ink (containing: Shellac Glaze, Isopropyl Alcohol, Iron Oxide Black, n-Butyl Alcohol, Propylene Glycol and Ammonium Hydroxide).

RALIVIA comes in the following dosage forms:

Extended-release tablets: 100 mg, 200 mg and 300 mg

Do not use RALIVIA if:

- you are allergic to tramadol hydrochloride or any of the other ingredients of RALIVIA
- your pain can be controlled by the occasional use of painkillers including those available without a prescription
- you have severe asthma, trouble breathing, or other breathing problems
- you have any heart problems
- you have bowel blockage or narrowing of the stomach or intestines
- you have severe pain in your abdomen
- you have a head injury
- you are at risks for seizures
- you have severe kidney disease
- you have severe liver disease
- you suffer from alcoholism
- you are taking or have taken within the past 2 weeks a Monoamine Oxidase inhibitor (MAOi) (such as phenelzine sulphate, tranylcypromine sulphate, moclobemide or selegiline)
- you are less than18 years old and are having (or have recently had) your tonsils or adenoids removed because of frequent interruption of breathing during sleep
- you are less than 12 years old

- your doctor did not prescribe it for you

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

- are taking any other medications
- are planning surgery, or about to undergo surgery
- have diabetes
- are over 65 years of age
- have a history of illicit or prescription drug or alcohol abuse
- have low blood pressure
- have past or current depression
- suffer from chronic or severe constipation
- have been told that you metabolize tramadol or other pain medications rapidly
- suffer from migraines
- are pregnant or planning to become pregnant
- are breast-feeding

Other warnings you should know about:

Low blood sugar levels: RALIVIA can decrease your blood sugar levels. Diabetic patients may need to monitor their blood sugar more often. If you notice changes, discuss this with your doctor.

Alcohol: You must not consume alcohol while taking RALIVIA tablets, as it may increase the chance of experiencing dangerous side effects. Also, you should tell your doctor if you drink alcohol regularly or have a history of alcoholism.

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

Pregnancy, nursing, labour and delivery: Opioids can be transferred to your baby through breast milk, or while still in the womb. RALIVIA can then cause life-threatening breathing problems in your unborn baby or nursing infant. Your doctor will determine if the benefits of using RALIVIA outweigh the risks to your unborn baby or nursing infant.

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

Adolescents (12 to 18 years old): You should not use RALIVIA if your child:

- is overweight (obese)
- has obstructive sleep apnea (a condition where your breathing starts and stops while you sleep)
- has severe lung disease

There is a higher risk of serious breathing problems if your child takes RALIVIA and has any of the above conditions.

Driving and using machines: Before you perform tasks which may require special attention, wait until you know how you respond to RALIVIA. RALIVIA can cause:

- drowsiness
- dizziness, or
- light-headedness

This can usually occur after the first dose and when the 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, or slowly take you off RALIVIA.

Serotonin Syndrome (also known as Serotonin Toxicity): RALIVIA 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 RALIVIA with certain anti-depressants or migraine medications.

Serotonin Syndrome symptoms include:

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

Sleep apnea: Opioids can cause a problem called sleep apnea (stopping breathing from time to time while sleeping). Tell your doctor if you have a history of sleep apnea or if anyone notices you stop breathing from time to time while sleeping.

Worsening 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 RALIVIA.

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

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

The following may interact with RALIVIA:

- carbamazepine (TEGRETOL®) may increase the metabolism of tramadol and reduce the analgesic effect;
- tricyclic antidepressants, selective serotonin re-uptake inhibitors (SSRIs), antipsychotics;
- protease inhibitors (e.g., ritonavir);
- digoxin (LANOXIN®), warfarin or warfarin-like;
- alcohol. This includes prescription and non-prescription medications that contain alcohol. **Do not drink** alcohol while taking RALIVIA. It can lead to:
  - drowsiness,
  - unusually slow or weak breathing
  - serious side effects or
  - a fatal overdose
- other opioid analgesics (drugs used to treat pain);
- general anesthetics (drugs used during surgery);
- benzodiazepines (drugs used to help you sleep or that help reduce anxiety);
- antidepressants (for depression and mood disorders). **Do not** take RALIVIA with MAO inhibitors (MAOi) or if you have taken MAOi's in the last 14 days;
- drugs used to treat serious mental or emotional disorders (such as schizophrenia);
- antihistamines (drugs used to treat allergies);
- anti-emetics (drugs used for the prevention of vomiting);
- drugs used to treat muscle spasms and back pain;
- warfarin (such as coumadin) and other anticoagulants (used for prevention or treatment of blood clots);
- anti-retroviral drugs (used to treat viral infections);
- anti-fungal drugs (used to treat fungal infections);
- antibiotic drugs (used to treat bacterial infections);
- some heart medication (such as beta blockers);
- grapefruit juice;
- drugs used to treat migraines (e.g. triptans);
- St. John's Wort;

How to take RALIVIA:

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

Usual Adult Starting Dose:

Your dose is tailored/personalized just for you. Be sure to follow your doctor's dosing instructions exactly. **Do not increase or decrease your dose or stop taking RALIVIA all of a sudden without talking to your doctor**. Taking higher doses can lead to more side effects and a greater chance of overdose.

You may take RALIVIA tablets with or without food, with a glass of water.

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

If your pain increases or you develop any side effect as a result of taking RALIVIA, tell your doctor **right away**.

Stopping RALIVIA or reducing your dose:

If you have been taking RALIVIA for more than a few days you should not stop taking it all of a sudden. You should check with your doctor for directions on how to slowly stop taking it. You should do it slowly to avoid uncomfortable symptoms such as:

- body aches;
- diarrhea;
- gooseflesh;
- loss of appetite;
- nausea;
- feeling nervous or restless;
- runny nose;
- sneezing;
- tremors or shivering;
- stomach cramps;
- rapid heart rate (tachycardia);
- having trouble sleeping;
- an unusual increase in sweating;
- an unexplained fever;
- weakness;
- yawning.

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

Refilling your Prescription for RALIVIA:

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

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

Overdose:

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

Accidental swallowing of RALAVIA tablets, especially by children, can result in breathing difficulties, with slow or shallow breathing, and/or fits (seizures). Deaths have been reported.

Signs of overdose may include:

- unusually slow or weak breathing;
- dizziness;
- confusion;
- extreme drowsiness;
- fits (seizures);
- irritation and discomfort in the stomach and gut;
- loss of appetite;
- nausea;
- vomiting;
- feeling unwell;
- unusually pale color and sweating;
- toxic leukoencephalopathy (a brain disorder affecting the brain's white matter).

Cases of abnormal electrical conduction in the heart (QT prolongation) have been reported.

Missed Dose:

It is very important that you do not miss taking your dose.

If you miss:

- **1 one or more doses:** take your next dose at the next scheduled time. **Do not** try to make-up for the missed dose by taking a double dose.

- **Several doses in a row:** talk to your doctor before restarting your medication.

What are possible side effects from using RALIVIA?

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

Side effects may include:

- Drowsiness
- Insomnia
- Dizziness
- Fainting
- Nausea, vomiting, poor appetite
- Dry mouth
- Headache
- Problems with vision
- Weakness, uncoordinated muscle movement
- Itching

- Sweating
- Constipation
- Low sex drive, impotence (erectile dysfunction), infertility

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

RALIVIA can cause abnormal blood test results including decreased blood sugar. Your doctor will decide when to perform blood tests and will interpret the results.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
RARE			
Overdose: hallucinations, confusion, inability to walk normally, slow or weak breathing, extreme sleepiness, sedation, or dizziness, floppy muscles/low muscle tone, cold and clammy skin.			√
Respiratory Depression: Slow, shallow or weak breathing.			√
Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			√
Bowel Blockage (impaction): abdominal pain, severe constipation, nausea			√
Withdrawal: nausea, vomiting, diarrhea, anxiety, shivering, cold and clammy skin, body aches, loss of appetite, sweating.		√	
Fast, Slow or Irregular Heartbeat: heart palpitations.		√	
Low Blood Pressure: dizziness, fainting, light-headedness.	√		

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**	
Serotonin Syndrome: agitation or restlessness, loss of muscle control or muscle twitching, tremor, diarrhea			√
VERY RARE			
Hypoglycemia (low blood sugar): thirst, frequent urination, hunger, nausea and dizziness, fast heartbeat, tingling, trembling, nervousness, sweating, low energy			√
Hallucinations: seeing or hearing things that are not there			√

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

- **Keep unused or expired RALIVIA in a secure place to prevent theft, misuse or accidental exposure.**
- **Keep RALIVIA out of sight and reach of children and pets.**
- **Accidental overdose with RALIVIA by a child is dangerous and may result in death**
- **Do not give any of it to anyone other than the person for whom it was prescribed, since it may seriously harm them. If a child accidentally takes RALIVIA, get emergency help right away.**

- Store RALIVIA at room temperature (15-30ºC)

Disposal:

RALIVIA 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 RALIVIA:

- 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; the manufacturer's website www.bauschhealth.ca, or by calling 1-800-361-4261.

This leaflet was prepared by

Bausch Health, Canada Inc.
2150 St-Elzear Blvd., West
Laval, QC, H7L 4A8
www.bauschhealth.ca

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