PRODUCT MONOGRAPH

Pr DURELA®

Tramadol Hydrochloride

Extended-Release Capsules 100, 200, 300 mg

Opioid Analgesic

Manufacturer:
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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
oral	extended-release capsules 100, 200, 300 mg	corn starch, D & C Red #7 calcium lake (E180), D & C Yellow #10 aluminum lake, Eudragit NE 30D, FD & C Blue #2 aluminum lake (E132), gelatin, hypromellose, lactose monohydrate 200 mesh, magnesium stearate, microcrystalline cellulose, polysorbate 80, povidone K30, shellac, simethicone emulsion, sodium starch glycolate, sucrose stearate, talc and titanium dioxide

INDICATIONS AND CLINICAL USE

DURELA® (tramadol HCl extended-release capsules) is indicated for:

- the management of moderate to moderately severe pain in adults who require continuous treatment for several days or more.

Geriatrics (> 65 years of age):
In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease or other drug therapy.

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. DURELA should be administered with greater caution in patients older than 75 years, due to the greater potential for adverse events in this population (see **WARNINGS AND PRECAUTIONS, DOSAGE AND ADMINISTRATION**).

Pediatrics (< 18 years of age):
The safety and efficacy of DURELA has not been studied in the pediatric population. Therefore, use of DURELA is not recommended in patients under 18 years of age.

CONTRAINDICATIONS

- Patients who are hypersensitive to tramadol, or other opioid analgesics, or to any ingredient in the formulation. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the Product Monograph
- In patients with known or suspected mechanical gastrointestinal obstruction (e.g., bowel obstruction, strictures) or any disease/conditions that affect bowel transit (e.g., ileus of any type)
- Patients with suspected surgical abdomen (e.g., acute appendicitis or pancreatitis)
- In any situation where opioids are contraindicated, including acute intoxication with alcohol, hypnotics, centrally acting analgesics, opioids, or psychotropic drugs. Tramadol may worsen central nervous system and respiratory depression in these patients
- Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy)
- Severe renal or hepatic impairment (creatinine clearance of less than 30 mL/min and/or Child-Pugh Class C
- Patients with mild, intermittent or short-duration pain that can be managed with other pain medications
- The management of peri-operative pain
- Patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus
- 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
- Do not use DURELA while pregnant, nursing, during labour or delivery

WARNINGS AND PRECAUTIONS

SERIOUS WARNINGS AND PRECAUTIONS

Limitations of Use

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

Addiction, Abuse, and Misuse

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

DURELA must be swallowed whole; crushing, chewing, or dissolving DURELA extended release capsules can cause rapid release and absorption of a potentially fatal dose of tramadol hydrochloride (see 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 DURELA, especially by children, can result in a fatal overdose of (tramadol hydrochloride) (see DOSAGE AND ADMINISTRATION Disposal, for instructions on proper disposal).

Neonatal Opioid Withdrawal Syndrome

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

Interaction with Alcohol

The co-ingestion of alcohol with DURELA may result in increased plasma levels and a potentially fatal overdose of tramadol hydrochloride (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS).

Risks from Concomitant Use With Benzodiazepines Or Other CNS Depressants

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

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

General

DURELA must be swallowed whole and should not be broken, chewed, dissolved or crushed, since this can lead to the rapid release of tramadol and absorption of a potentially fatal dose of tramadol.

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

DURELA 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 DURELA 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.

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),
- Tricyclic antidepressants (TCAs), and other tricyclic compounds (e.g., cyclobenzaprine, promethazine, etc.),
- Opioids.

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

- MAO inhibitors (see CONTRAINDICATIONS),
- Neuroleptics, or
- 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.

Anaphylactoid Reactions

Serious and rarely fatal anaphylactoid reactions have been reported in patients receiving therapy with tramadol. When these rare reactions do occur it is often following the first dose. Other reported reactions include pruritus, hives, bronchospasm and 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 tramadol (see **CONTRAINDICATIONS**).

- Patients with acute respiratory depression, elevated carbon dioxide levels in the blood, and cor pulmonale
- Patients with acute alcoholism, delirium tremens, and convulsive disorders
- Patients with severe CNS depression, increased cerebrospinal or intracranial pressure, and head injury
- Women who are breastfeeding, pregnant, or during labour and delivery.

Drug Abuse, Addiction, Dependence and Misuse

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

DURELA is intended for oral use only. The tablets should be swallowed whole, and not chewed or crushed. Abuse of oral dosage forms can be expected to result in serious adverse events, including death.

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

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

A Risk Management program to support the safe and effective use of DURELA 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 DURELA (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 DURELA advertising and promotional materials;
c) Assurance that health-care education activities on pain management with DURELA 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.

Dependence/Tolerance
As with other opioids, tolerance and physical dependence may develop upon repeated administration of DURELA and there is a potential for development of psychological dependence.

Physical dependence and tolerance reflect the neuroadapatation 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.

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. DURELA 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 using opioids, treatment with DURELA is not recommended.

Withdrawal Symptoms
Patients on prolonged therapy should be tapered gradually from the drug if it is no longer required for pain control. Withdrawal symptoms may occur following abrupt discontinuation of therapy or upon administration of an opioid antagonist. Some of the symptoms that may be associated with abrupt withdrawal of an opioid analgesic include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, anxiety, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning (see ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION, <Adjustment or Reduction of Dosage>).

Use in Drug and Alcohol Addiction
DURELA 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 DURELA unless used under extreme caution and awareness.

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

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. Tolerance as well as both physical and psychological dependence may develop upon repeated administration of opioids, and are not by themselves evidence of an addictive disorder or abuse.

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.

Risk of Overdosage

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

Do not prescribe DURELA for patients who are suicidal or addiction prone.

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 DURELA treatment, monitoring for signs and symptoms of hyponatremia is recommended for patients with predisposing risk factors.

Gastrointestinal

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

Neonatal Opioid Withdrawal Syndrome (NOWS)

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

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific

opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn.

Use of DURELA is contraindicated in pregnant women (see **CONTRAINDICATIONS**).

Interactions with Central Nervous System Depressants (Including benzodiazepines and Alcohol):
DURELA should be used with caution and in a reduced dosage during concomitant administration of other opioid analgesics, general anesthetics, phenothiazines and other tranquilizers, sedative-hypnotics, tricyclic antidepressants, antipsychotics, antihistamines, benzodiazepines, centrally-active anti-emetics and other CNS depressants. Respiratory depression, hypotension and profound sedation, coma or death may result.

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

Advise both patients and caregivers about the risks of respiratory depression and sedation when DURELA is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs (see **DRUG INTERACTIONS**).

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

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

Increased Intracranial Pressure or Head Trauma
DURELA 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), confusion, miosis, vomiting and other side effects 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 **WARNINGS AND PRECAUTIONS, Respiratory Depression**).

Psychomotor Impairment
DURELA may impair the mental and or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using this drug should be cautioned accordingly. Patients should also be cautioned about the combined effects of tramadol hydrochloride with other CNS depressants, including other opioids, phenothiazine, sedative/hypnotics and alcohol.

Peri-operative Considerations
DURELA is contraindicated for peri-operative pain relief. DURELA is not indicated for pre-emptive analgesia (administration pre-operatively for the management of post-operative pain).

In the case of planned chordotomy or other pain-relieving operations, patients should not be treated with DURELA for at least 24 hours before the operation and DURELA should not be used in the immediate post-operative period. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. If DURELA is to be continued after the patient recovers from the post-operative period, a new dosage should be administered in accordance with the changed need for pain relief. The risk of withdrawal in opioid-tolerant patients should be addressed as clinically indicated (see **Withdrawal Symptoms**).

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

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

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

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

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of DURELA, 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 DURELA 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 DURELA are essential. Overestimating the DURELA dose when converting patients from another opioid product can result in fatal overdose with the first dose. In these patients, the use of non-opioid analgesics should be considered, if feasible (see **WARNINGS AND PRECAUTIONS**, Special Populations, Special Risk Groups, and **DOSAGE AND ADMINISTRATION**).

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 Special Populations, Nursing Women; DRUG INTERACTIONS, Overview). The prevalence of this CYP2D6 phenotype varies widely in the population (see ACTION AND CLINICAL PHARMACOLOGY, 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 preexisting respiratory depression for respiratory depression, particularly when initiating therapy and titrating with DURELA, as in these patients, even usual therapeutic doses of DURELA 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 DURELA is contraindicated in patients with acute or severe bronchial asthma, chronic obstructive airway, or status asthmaticus (see CONTRAINDICATIONS).

Serotonin Syndrome

The development of a potentially life-threatening serotonin syndrome may occur with the use of tramadol products, including DURELA, particularly with concomitant with serotonergic drugs such as SSRIs, SNRIs, TCAs, MAOIs (including linezolid and methylene blue) and triptans, with drugs which impair metabolism of serotonin (including MAOIs) and with drugs which impair metabolism of tramadol (CYP2D6 and CYP3A4 inhibitors). This may occur with recommended dose.

Acute Abdominal Conditions

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

Carcinogenesis and Mutagenesis
See animal data in **TOXICOLOGY** section.

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 DURELA.

The use of DURELA 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 **ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology**). Post-marketing experience with the use of tramadol containing products included rare reports of QT prolongation reported with an overdose (see **ADVERSE REACTIONS, Post-Marketing Reports with Tramadol; DRUG INTERACTIONS, QTc Interval-Prolonging Drugs; 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 DURELA 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, hypocalcemia);
- 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.

Patient Counselling Information

A patient information sheet should be provided when DURELA capsules are dispensed to the patient.

Patients receiving DURELA should be given the following instructions by the physician:

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

2. Patients should be advised that DURELA contains tramadol, an opioid pain medicine.

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

4. DURELA should be swallowed whole (not broken, chewed, dissolved or crushed), due to the risk of fatal tramadol overdose.

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

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

7. Patients should be advised that serious anaphylactoid reactions have rarely been reported, however patients with a history of anaphylactoid reactions to codeine and other opioids may be at increased risk and therefore should not receive tramadol.

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

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

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

11. Patients should be advised of the most common adverse reactions that may occur while taking DURELA: constipation, dizziness, nausea, somnolence and vomiting.

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

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

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

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

Special Populations

Special Risk Groups: tramadol hydrochloride 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.

Renal Impairment: DURELA is contraindicated in patients with severe renal impairment. The elimination half-life of tramadol and its active metabolite may be prolonged in patients with renal impairment.

Hepatic/Biliary/Pancreatic Impairment: DURELA is contraindicated in patients with severe hepatic impairment. The elimination half-life of tramadol and its active metabolite may be prolonged in patients with hepatic impairment. The use of DURELA in patients with liver disease is not recommended.

Pregnant Women: Animal reproduction studies have revealed no evidence of harm to the fetus due to tramadol hydrochloride. However, as studies in humans have not been conducted, the safety of tramadol in pregnancy has not been established. Since tramadol hydrochloride crosses the placental barrier, DURELA is contraindicated in pregnant patients (see **CONTRAINDICATIONS**).

The mean ratio of serum tramadol in the umbilical veins compared to maternal veins was 0.83 for 40 women given tramadol during labour. Chronic use during pregnancy may lead to physical dependence and post-partum withdrawal symptoms in the neonate. Neonatal seizures, neonatal withdrawal syndrome, fetal death and stillbirth have been reported with tramadol hydrochloride during postmarketing reports with tramadol hydrochloride immediate-release products. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening (see **WARNINGS AND PRECAUTIONS – NEONATAL OPIOID WITHDRAWAL SYNDROME**).

The effect of tramadol, if any, on the later growth, development and functional maturation of the child is unknown. Use of DURELA is contraindicated in pregnant women (see **CONTRAINDICATIONS**).

Studies in humans have not been conducted. DURELA crosses the placental barrier and is contraindicated in pregnant women.

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.

Nursing Women: DURELA is contraindicated in nursing mothers (see **CONTRAINDICATIONS**). Following a single 100 mg i.v. dose of tramadol, the cumulative excretion in breast milk within 16 hours post-dose was 100 μg of tramadol (0.1% of the maternal dose) and 27 μg of M1.

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 **WARNINGS AND PRECAUTIONS, Respiratory**).

Labour and Delivery: In view of the potential for opioids to cross the placental barrier, DURELA is contraindicated during labour. Respiratory depression may occur in the infant if opioids are administered during labour. Since its safety in infants and newborns has not been studied, tramadol should not be administered for obstetrical preoperative medication, post-

delivery analgesia or at any time during breast feeding.

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

Pediatrics (<18 years of age): The safety and efficacy of DURELA has not been studied in the pediatric population. Therefore, use of DURELA capsules 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 DURELA is not recommended in these pediatrics patients.

Geriatrics (>65 years of age): In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range and titrate slowly, reflecting the greater frequency of decreased hepatic, renal or cardiac function; of concomitant disease and multiple drug therapy. The elimination half-life of tramadol may be prolonged in patients over 75 years, thereby increasing the potential for adverse events (see **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY**, **Special Populations and Conditions**, **Geriatrics**).

Monitoring and Laboratory Tests
Not Applicable.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse effects of DURELA (tramadol hydrochloride extended release capsules) 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.

The most common adverse effects with DURELA are constipation, dizziness, headache, nausea, somnolence and vomiting. These are common effects associated with other drugs with opioid-agonist activity.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug

reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

DURELA was administered to a total of 1987 patients in clinical trials. These included four double-blind and one long-term, open-label study in patients with osteoarthritis of the hip and knee. A total of 812 patients were 65 years or older.

Treatment-Emergent Adverse Events reported by patients treated with doses from 100 mg to 300 mg in the four pooled, randomized, double-blind, placebo-controlled studies in patients with chronic non-malignant pain are presented in the following table (see Table 1).

Table 1: Summary of Treatment-Emergent Adverse Events Reported by At Least 1% of Patients Receiving DURELA 100 mg - 300 mg or Placebo in Double-Blind Studies

Preferred Term	DB 100 mg (N=429) %	DB 200 mg (N=434) %	DB 300 mg (N=1054) %	DB Placebo (N=646) %
Headache	23	22	19	20
Infection	7	5	5	9
Asthenia	4	6	9	3
Pain	4	5	4	5
Back pain	5	3	4	6
Accidental injury	3	1	3	3
Abdominal pain	4	3	4	3
Flu syndrome	2	2	2	1
Chills	0.2	1	3	1
Chest pain	1	1	1	1
Neck pain	2	1	0.4	1
Fever	1	0.2	2	1
Pelvic pain	0.2		1	1
Hypertension	1	3	3	1
Vasodilatation	1	1	3	1
Nausea	16	21	25	6
Constipation	9	14	21	4
Dry mouth	5	8	13	3
Vomiting	7	10	9	2
Diarrhea	2	2	4	4
Dyspepsia	3	4	5	4
Anorexia	2	5	6	0.2
Tooth disorder	2	2	1	1
Flatulence	3	0.2	1	1
Gastrointestinal disorder	1	1	1	1
Edema	1	1	1	2

Preferred Term	DB 100 mg (N=429) %	DB 200 mg (N=434) %	DB 300 mg (N=1054) %	DB Placebo (N=646) %
Weight loss		1	2	0.2
Hyperglycemia	0.2	1	1	1
Peripheral edema	1	1	1	1
Arthralgia	5	5	5	5
Myalgia	3	1	2	2
Somnolence	12	14	16	4
Dizziness	10	12	14	5
Insomnia	2	2	5	2
Nervousness	1	2	4	1
Anxiety	1	2	3	1
Depression	1	1	2	0.3
Paresthesia	2	1	1	1
Withdrawal syndrome			2	1
Apathy			2	0.2
Tremor		1	1	1
Agitation		0.2	1	
Depersonalization	0.2	0.2	1	0.2
Confusion		1	1	1
Rhinitis	1	1	3	2
Sinusitis	1	1	4	3
Pharyngitis	2	1	2	1
Bronchitis	1	1	3	2
Cough increased	1	1	1	2
Sweating	4	5	7	1
Pruritus	3	6	7	2
Rash	2	1	3	1
Urinary tract infection	1	1	3	1
Urine abnormality	1	1	1	1

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

Nausea and Vomiting: Nausea is a common side effect on initiation of therapy with opioid

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

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

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

Less Common Clinical Trial Adverse Reactions (< 1%)

Body as a Whole: neck rigidity, viral infection, allergic reaction.

Cardiovascular: EKG abnormal, hypotension, tachycardia.

Digestive: gastroenteritis, nausea and vomiting.

Hemolytic & Lymphatic: anemia, ecchymoses, blood dyscrasia.

Metabolic & Nutritional: gout.
Musculoskeletal: arthritis, arthrosis, joint disorder, leg cramps.

Nervous: emotional lability, hyperkinesia, hypertonia, thinking abnormal, twitching, vertigo, euphoria.

Respiratory: pneumonia.

Skin: hair disorder, skin disorder, urticaria.

Special Senses: eye disorder, lacrimation disorder.

Urogenital: cystitis, dysuria, sexual function abnormality, urinary retention, prostate disorder, kidney calculus.

Abnormal Hematologic and Clinical Chemistry Findings

In clinical trials where laboratory abnormalities were recorded, the following laboratory abnormalities were reported with incidence rates > 1.0%: hyperglycemia, urine abnormality.

The following laboratory abnormalities were reported with incidence rates < 1%: GGT, SGPT/SGOT.

Other Adverse Experiences Previously Reported in Clinical Trials or Post-Marketing Reports with Tramadol hydrochloride extended release capsules

Adverse events which have been reported with the use of tramadol products include: allergic reactions (including anaphylaxis, angioneurotic edema and urticaria), bradycardia, convulsions, drug dependence, drug withdrawal (including agitation, anxiety, gastrointestinal symptoms, hyperkinesia, insomnia, nervousness, tremors), hyperactivity, hypoactivity, hypoglycemia, hypotension 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, Stevens-Johnson syndrome and suicidal tendency.

Cases of hypoglycemia 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.

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 MAO inhibitors.

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

Withdrawal Symptoms

Withdrawal symptoms may occur if tramadol is discontinued abruptly. These symptoms may include: anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhea, upper respiratory symptoms, piloerection, and rarely, hallucinations. Other symptoms that have been seen less frequently with tramadol discontinuation include: panic attacks, severe anxiety, and paresthesias. Clinical experience suggests that withdrawal symptoms may be relieved by reinstitution of opioid therapy followed by a gradual, tapered dose reduction of the medication combined with symptomatic support.

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.

Drug-Drug Interactions

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

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

Carbamazepine
Patients taking carbamazepine may have a significantly reduced analgesic effect of tramadol. Since carbamazepine increases tramadol metabolism and because of the seizure risk associated with tramadol, concomitant administration of DURELA and carbamazepine is not recommended.

Quinidine
Tramadol is metabolized to M1 by the CYP2D6 isoenzyme. Quinidine is a selective inhibitor of that isoenzyme, so that concomitant administration of quinidine and tramadol results in increased concentrations of tramadol and reduced concentrations of M1. The clinical consequences of these findings are unknown. 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 **ACTION AND CLINICAL PHARMACOLOGY, 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 DURELA 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 DURELA 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 **WARNINGS AND PRECAUTIONS, Cardiovascular**; **ADVERSE REACTIONS, Post-Marketing Reports with Tramadol**; **ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology**).

Cimetidine
Concomitant administration of tramadol and cimetidine is associated with a small prolongation of the half-life of tramadol, but no alteration of the DURELA dosage regimen 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 DURELA and warfarin-like compounds are administered concurrently.

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 **WARNINGS AND PRECAUTIONS**)

Drug-Food Interactions
The rate and extent of absorption of DURELA Capsules (300 mg) are similar following oral administration with or without food. Therefore, DURELA Capsules can be administered without regard to meals.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

The concomitant use of alcohol should be avoided (see **WARNINGS AND PRECAUTIONS, Serious Warnings and Precautions Box**).

DOSAGE AND ADMINISTRATION

DURELA 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).

DURELA should be swallowed whole; crushing, chewing, or dissolving DURELA extended release capsules can cause rapid release and absorption of a potentially fatal dose of tramadol hydrochloride (see WARNINGS AND PRECAUTIONS).

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 chronic non-cancer, non-palliative pain, it is recommended that a maximum daily dosage of 300 mg (50 morphine milligram equivalent) of DURELA not be exceeded. Each patient should be assessed for their risk prior to prescribing DURELA, 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 DURELA (see DOSAGE AND ADMINISTRATION, Adjustment or Reduction of Dosage and Discontinuation).

Dosing Considerations
A repeat dosage within 24 hours is not recommended; DURELA capsules have a continuous release of active ingredient over 24 hours.

DURELA (tramadol hydrochloride extended release capsules) should be used with caution within 12 hours pre-operatively and within the first 12-24 hours post-operatively (see **WARNINGS AND PRECAUTIONS, Peri-operative Considerations**).

DURELA 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.

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

Due to possible differences in pharmacokinetic properties, DURELA is not interchangeable with other extended-release tramadol-containing products.

The maximum recommended daily dose of DURELA should not be exceeded.

DURELA is contraindicated in patients with severe hepatic or renal impairment.

Administration

DURELA capsules must be swallowed whole and should not be broken, chewed, dissolved or crushed, since this can lead to the rapid release of tramadol and absorption of a potentially fatal dose of tramadol.

DURELA is not indicated for rectal administration.

Recommended Dose and Dosage Adjustment

Adults: The usual initial dose of DURELA is one 100 mg capsule daily. If adequate pain relief is not achieved, the dosage should be gradually titrated upwards. The maximum recommended daily dose is 300 mg.

General: DURELA is designed to allow for once daily dosing, i.e., dosing at 24-hourly intervals. Treatment with DURELA should be initiated at the lowest available dose (100 mg). The maximum dose is 300 mg daily.

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 regular administration of the lowest dose of controlled release tramadol (DURELA) 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. In patients receiving DURELA it is recommended that doses be slowly titrated, with dosage adjustments generally separated by 5 days, to dose which provides satisfactory pain relief for a full 24 hours, with acceptable side effects.

Patients Not Receiving Opioids or Tramadol Immediate-Release Products: The usual initial dose of DURELA for patients who have not previously received opioids or tramadol immediate-release (IR) products is 100 mg q24h.

Patients Currently Receiving Opioids or Tramadol Immediate-Release Products: Patients currently receiving other opioids or oral immediate-release tramadol preparations may be transferred to DURELA capsules at the same or lowest nearest total daily tramadol dosage.

Geriatrics: Since the elimination half-life of tramadol may be prolonged in elderly patients, a starting dose of 100 mg daily is recommended. 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. DURELA should be initiated at a low dose and slowly titrated to effect (see **WARNINGS AND PRECAUTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**).

Pediatrics (< 18 years old): The safety and efficacy of DURELA has not been studied in the pediatric population. Therefore, use of DURELA is not recommended in patients under 18 years of age.

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 **CONTRAINDICATIONS**).

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. DURELA 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 DURELA dose, medications such as acetaminophen, ibuprofen or immediate release tramadol may be given. Fentanyl products should not be used as rescue medication in patients taking DURELA. 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. For patients whose dose has been titrated to the recommended maintenance dose, without attainment of adequate analgesia, the total daily dose may be increased, unless precluded by side effects.

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 and Discontinuation:
Physical dependence with or without psychological dependence tends to occur with chronic administration of opioids, including DURELA. 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. Other symptoms that have been seen less frequently with DURELA discontinuation include: panic attacks, severe anxiety, and paresthesias.

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 **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.

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

DURELA should never be disposed of in household trash. Disposal via a pharmacy take back program is recommended. Unused or expired DURELA should be properly disposed of as soon as it is no longer needed to prevent accidental exposure to others, including children or pets. If temporary storage is required before disposal, a sealed child-proof container, such as a biohazard waste container or a lockable medication box could be obtained from a pharmacy.

Missed Dose

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

OVERDOSAGE

Deaths due to overdose have been reported with abuse and misuse of tramadol, by ingesting, inhaling, or injecting the crushed product. 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.

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, hypotension, and death. In addition, cases of QT prolongation have been reported during overdose.

Treatment of Overdose

In the treatment of tramadol overdose, primary attention should be given to the reestablishment 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.

Tramadol is minimally eliminated from the serum by hemodialysis or hemofiltration. Therefore treatment of acute tramadol intoxication with hemodialysis or hemofiltration alone is not appropriate.

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

For management of suspected drug overdose, contact your Regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Tramadol is a centrally acting synthetic opioid analgesic. Although its mode of action is not completely understood, from animal tests, 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 μ-opioid receptors. In animal models, M1 is up to 6 times more potent than tramadol in producing analgesia and 200 times more potent in μ-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 DURELA 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. At therapeutic doses, tramadol has no effect on heart rate, left-ventricular function or cardiac index. Orthostatic hypotension has been observed.

Pharmacodynamics

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 α_2 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.

Central Nervous System

Tramadol hydrochloride extended release capsules produces respiratory depression by direct action on brain stem respiratory centres. The respiratory depression involves both a reduction in the responsiveness of the brain stem centres to increases in CO_2 tension and to electrical stimulation.

Tramadol hydrochloride extended release capsules 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 extended release capsules 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 oxycodone overdose.

Gastrointestinal Tract and Other Smooth Muscle

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

Cardiovascular System
Tramadol hydrochloride extended release capsules may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilatation may include pruritus, flushing, red eyes, hyperhidrosis and/or orthostatic hypotension.

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 DURELA 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 **WARNINGS AND PRECAUTIONS, Cardiovascular; ADVERSE REACTIONS, Post-Marketing Reports with Tramadol; DRUG INTERACTIONS, QTc Interval-Prolonging Drugs; DOSAGE AND ADMINISTRATION**, **Recommended Dose and Dosage Adjustment; OVERDOSAGE**).

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.

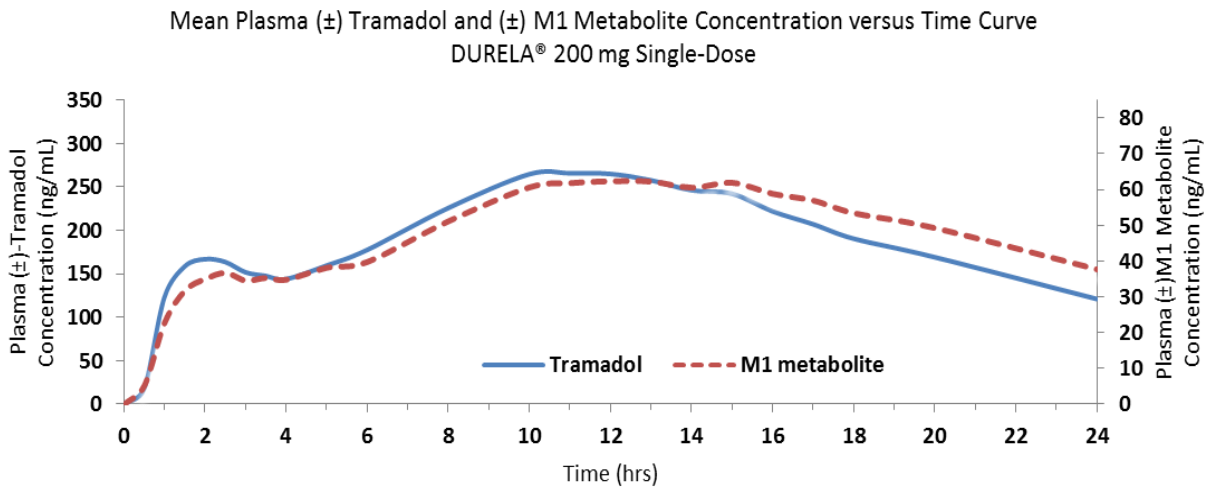
Immune System
In vitro and animal studies indicate that opioids have a variety of effects on immune functions, depending on the context in which they are used. The clinical significance of these findings is unknown.

Pharmacokinetics
The analgesic activity of tramadol is due to both parent drug and the M1 metabolite. DURELA is administered as a racemate and both tramadol and M1 are detected in the circulation. The Cmax and AUC of DURELA have been observed to be dose-proportional over an oral dose range of 100 to 300 mg in healthy subjects.

Absorption: After a single dose administration of DURELA, Tmax occurs around 12 hours.

DURELA's initial rapid release of tramadol is attributed to the immediate-release tablet in the capsule.

Figure 1: Mean Tramadol and M1 Metabolite Concentration of DURELA Capsules 200 mg, single-dose



DURELA's immediate release tablet provides rapid release of tramadol following administration of DURELA. DURELA has an initial plasma/time concentration profile similar to immediate-release tramadol formulations, followed by a sustained release over a 24-hour period.

The mean bioavailability Cmax and AUC of DURELA after a 300 mg single dose were 422 ng/mL and 9644 ng·hr/mL, respectively under fasting conditions: the half-life was approximately 9 hours.

Table 2: Pharmacokinetic parameters for DURELA

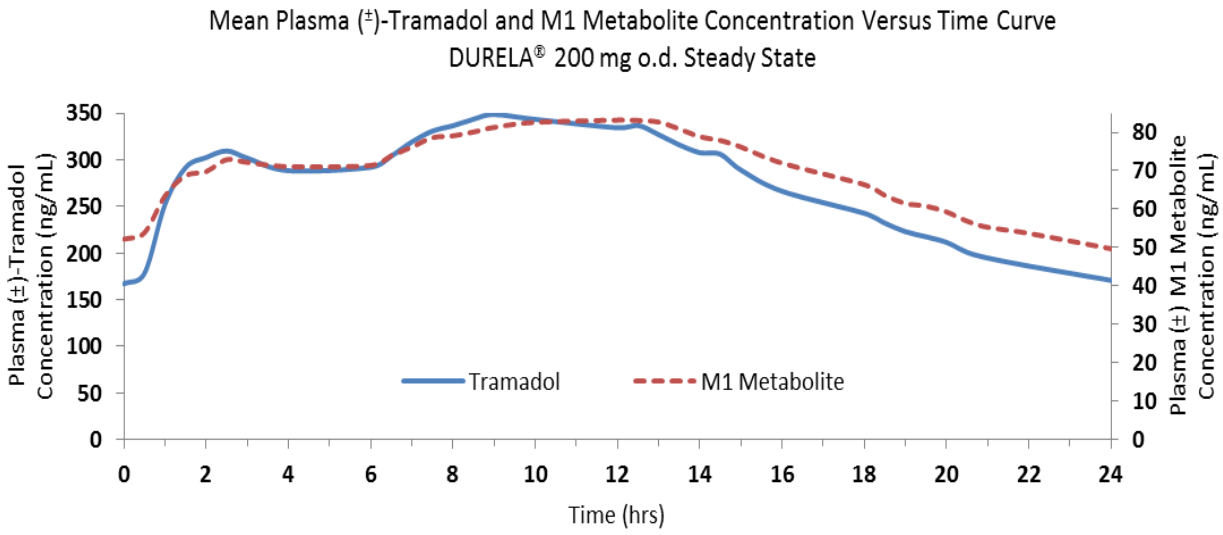
Mean (%CV) Steady-State Pharmacokinetic Parameter Values (N= 22)

Parameter	**Tramadol**	**O-Desmethyl-Tramadol (M1 Metabolite)**
AUC_{0-24} (ng·h/mL)	6600 (25%)	1683 (31%)
Cmax (ng/mL)	364 (21%)	87 (32%)
Cmin (ng/mL)	165 (35%)	52 (32%)
Tmax	9.7 (18%)	10.8 (22%)
% Fluctuation	75 (29%)	51 (33%)

AUC_{0-24}: Area Under the Curve in a 24-hour dosing interval
Cmax: Peak Concentration in a 24-hour dosing interval
Cmin: Trough Concentration in a 24-hour dosing interval
Tmax: Time to Peak Concentration

Steady-state plasma concentrations of both tramadol and M1 are achieved within five days of once-daily dosing.

Figure 2: Mean Steady-State Tramadol and M1 Metabolite Plasma Concentration of DURELA Capsules 200 mg, o.d.



The rate and extent of absorption of DURELA (300 mg) are similar following oral administration with or without food. Therefore, DURELA can be administered without regard to meals.

Distribution: Tramadol has a great affinity for tissues (V_d = 203 + 40 L) and the plasma protein binding is approximately 20%.

Metabolism: Tramadol is extensively metabolized after oral administration. The major metabolic pathways appear to be N- and O-demethylation and glucuronidation or sulfation in the liver. Only one metabolite (mono-O-desmethyltramadol - denoted M1) is pharmacologically active. Production of M1 is dependent on the CYP2D6 isoenzyme of cytochrome P-450 and as such is subject to inhibition, which may affect the therapeutic response (see **DRUG INTERACTIONS**).

Excretion: 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.

Special Populations and Conditions

Pediatrics:

The safety and efficacy of DURELA has not been studied in the pediatric population. Individuals under 18 years of age should not take DURELA capsules.

Geriatrics (>65 years of age): The effect of age on pharmacokinetics of DURELA has not been studied. Healthy elderly subjects aged 65 to 75 years administered an immediate-release formulation of tramadol have plasma tramadol concentrations and elimination half-lives comparable to those observed in healthy subjects less than 65 years of age. In subjects over 75 years maximum serum concentrations are slightly elevated (208 vs. 162 ng/mL) and the elimination half-life is slightly prolonged (7 vs. 6 hours) compared to subjects 65 to 75 years of age. Adjustment of the daily dose is recommended for patients older than 75 years (see **DOSAGE AND ADMINISTRATION**).

Gender: The absolute bioavailability of tramadol was 73% in males and 79% in females. The plasma clearance was 6.4 mL/min/kg in males and 5.7 mL/min/kg in females following a 100 mg IV dose of tramadol. Following a single oral dose, and after adjusting for body weight, females had a 12% higher peak tramadol concentration and a 35% higher area under the concentration-time curve compared to males. This difference may not be of any clinical significance.

Race: 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 **WARNINGS AND PRECAUTIONS**, Respiratory, Special Populations, Nursing Women).

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 **DRUG INTERACTIONS**, Overview). The prevalence of this CYP2D6 phenotype is about 5-10 percent in Caucasians and 1 percent of Asians.

Hepatic Insufficiency: Metabolism of tramadol and M1 is reduced in patients with advanced cirrhosis of the liver, resulting in a larger area under the serum-concentration time curve for tramadol and longer tramadol and M1 elimination half-lives (13 hrs. for tramadol and 19 hrs. for M1). DURELA is contraindicated in patients with severe hepatic impairment (Child-Pugh Class C) (see **CONTRAINDICATIONS**).

Renal Insufficiency: Impaired renal function results in a decreased rate and extent of excretion of tramadol and its active metabolite M1. DURELA is contraindicated in patients with creatinine clearances of less than 30 mL/min (see **CONTRAINDICATIONS**). The total amount of tramadol and M1 removed during a dialysis period is less than 7% of the administered dose.

Genetic Polymorphism: Not applicable.

STORAGE AND STABILITY

Store at room temperature (15-30°C).

SPECIAL HANDLING INSTRUCTIONS

Protect from light, moisture and high humidity. Dispense in a tight container. Keep out of sight and reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

The DURELA capsule contains both a tablet which provides rapid release of tramadol, as well as microporous beads which allow for a continuous diffusion of tramadol over a 24-hour dosing cycle.

DURELA (tramadol HCl extended-release capsules) is supplied as opaque white hard gelatin capsules, imprinted as follows.

100 mg Capsules: White Capsule imprinted with blue ink "**G 252**" on cap and "**100**" between lines on the body, in bottles of 30 capsules.

200 mg Capsules: White capsule imprinted with violet ink "**G 253**" on cap and "**200**" between lines on the body, in bottles of 30 capsules.

300 mg Capsules: White capsule imprinted with red ink "**G 254**" on cap and "**300**" between lines on the body, in bottles of 30 capsules.

The capsules have both immediate-release and extended-release components, as follows:

Dosage	Immediate-release tablet	Extended-release beads
100 mg	25 mg	75 mg
200 mg	50 mg	150 mg
300 mg	50 mg	250 mg

Composition:

Active Ingredient(s): Tramadol hydrochloride extended release capsules USP

Non-medicinal Ingredients: Corn starch, D & C Red #7 calcium lake (E180), D & C Yellow #10 aluminum lake, Eudragit NE 30D, FD & C Blue #2 aluminum lake (E132), gelatin, hypromellose, lactose monohydrate 200 mesh, magnesium stearate, microcrystalline cellulose, polysorbate 80, povidone K30, propylene glycol, shellac, simethicone emulsion, sodium starch glycolate, sucrose stearate, talc and titanium dioxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

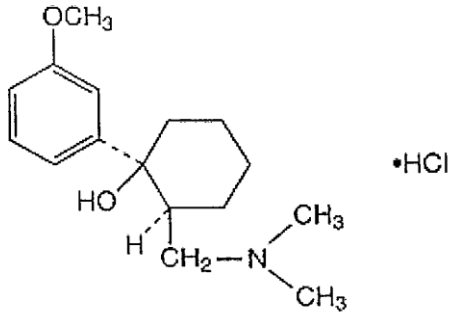
Proper name: Tramadol Hydrochloride extended release capsules USP

Chemical name: (1 RS, 2 RS)-2-(Dimethylaminomethyl)-1-(3-methoxyphenyl) cyclohexan-1-ol hydrochloride

Molecular formula: $C_{16}H_{26}ClNO_2.HCl$

Molecular mass: 299.84

Structural formula:



Physicochemical properties: Tramadol is a white to off-white crystalline powder, readily soluble in water and methanol.

CLINICAL TRIALS

Study demographics and trial design

Table 3: Summary of patient demographics for clinical trials in specific indication

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
02.01	Randomized, double-blind, placebo-controlled, multi-dose, Phase III, parallel group, study	100, 200, 300 mg oral 12 weeks	430	63 (45 – 85)	162 M 268 F
02.02	Randomized, double-blind, placebo-controlled, multi-dose, Phase III, parallel group, study	100, 200, 300 mg oral 12 weeks	445	66 (42 – 89)	122 M 323 F
02.04	Randomized, double-blind, placebo-controlled, multi-dose, Phase III, parallel group, study	300 mg Placebo 52 weeks	837	62 (41 – 90)	355 M/482 F
02.05	Randomized, double-blind, placebo-controlled, multi-dose, Phase III, parallel group, study	100, 200 300 mg oral 12 weeks	851	61 (40-86)	285M 566F

Study results

The efficacy of DURELA (tramadol HCl extended-release capsules) was evaluated following 12 to 14 weeks of treatment in four, randomized, placebo-controlled, studies (TRAMCT.02.01, TRAMCT.02.02, TRAMCT.02.04 and TRAMCT.02.05) in patients with moderate to severe pain from osteoarthritis of the knee or hip. Moderate to severe pain was defined as a Pain Intensity Score in the study joint of $\geq$ 40 mm on a 100 mm visual analog scale (VAS) off analgesic or anti-arthritic medication. In TRAMCT.02.05, patients also had to meet pre-specified flare criteria. Three of the studies TRAMCT.02.01, TRAMCT.02.02 and TRAMCT.02.05 were multi-dose (100, 200 and 300 mg) studies, whereas TRAMCT.02.04 investigated only the highest dose 300 mg. A fixed-dose, forced-titration, design was employed in all of the studies. The primary efficacy parameter was the WOMAC Pain Index. Key secondary endpoints included Pain Intensity in the Study Joint, assessed using a visual analogue scale (VAS) and the WOMAC function Index.

Data from studies TRAMCT.02.01, TRAMCT.02.02 and TRAMCT.02.04 are presented below.

TRAMCT.02.01

Table 4: LS Mean Change from Baseline in the WOMAC Pain Index

Study 02-01		Tramadol ER 100 mg	Tramadol ER 200 mg	Tramadol ER 300 mg	Placebo
WOMAC Pain Index					
		N = 106	N = 103	N = 112	N = 108
Baseline	Mean ± SD	11.80 ± 3.424	11.05 ± 3.356	11.29 ± 3.558	12.13 ± 3.133
Change to Wk 12[§]	LS Mean ± SE	-5.25 ± 1.096	-4.75 ± 1.100	-4.51 ± 1.052	-4.12 ± 1.103
	p value[†]	**0.0351**	0.2448	0.4702	

TRAMCT.02.02

Table 5: LS Mean Change from Baseline in the WOMAC Pain Index

Study 02-02		Tramadol ER 100 mg	Tramadol ER 200 mg	Tramadol ER 300 mg	Placebo
WOMAC Pain Index					
		N = 110	N = 113	N = 110	N = 111
Baseline	Mean ± SD	10.77 ± 3.608	11.06 ± 3.647	11.64 ± 3.216	11.46 ± 3.207
Change to Wk 12[§]	LS Mean ± SE	-3.18 ± 1.049	-2.89 ± 1.036	-3.45 ± 1.020	-2.06 ± 1.034
	p value[†]	**0.0417**	0.1254	**0.0110**	

Bolded p-values significant based on protocol specified analysis.

TRAMCT.02.04

Table 6: LS Mean Change from Baseline in the WOMAC Pain Index

Study 02-04		Tramadol ER 300 mg	Placebo
WOMAC Pain Index			
		N = 430	N = 139
Baseline	Mean ± SD	11.66 ± 3.170	11.72 ± 3.142
Change to Wk 12[§]	LS Mean ± SE	-3.51 ± 0.186	-2.59 ± 0.324
	p value[†]	**0.0129**	

Bolded p-values significant based on protocol specified analysis.

TRAMCT.02.05

In study TRAMCT.02.05, a high placebo response and a baseline pain/treatment interaction confounded the ability to distinguish the effects of treatment from placebo.

DETAILED PHARMACOLOGY

Tramadol is a centrally acting 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 α_2 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.

TOXICOLOGY

After a single oral administration in mice, rats, guinea pigs, rabbits and dogs, the LD_{50} of tramadol was 228-850 mg/kg; after s.c. injection in mice, rats and guinea pigs the LD_{50} range was 200-286 mg/kg; after i.m. injection in rabbits and dogs, the LD_{50} was 75-225 mg/kg; and after i.v. injection in mice, rabbits and dogs, the LD_{50} was 45-68 mg/kg.

Clinical, hematological, clinical chemistry and histological investigations revealed no drug related changes following repeated oral and parenteral administration for 6 and 26 weeks to rats and dogs, as well as oral administration for 12 months to dogs. Only with doses far above those used in therapy, changes in general behaviour and CNS effects, such as weight loss (probably due to reduced food intake), decreased grooming activity, restlessness, salivation and convulsions were observed.

No effects on fertility were observed for tramadol at oral dose levels up to 50 mg/kg in male rats and 75 mg/kg in female rats. Tramadol has been shown to be embryotoxic (delayed ossification) and fetotoxic in mice, rats and rabbits at maternally toxic doses 3 to 15 times the maximum human dose or higher (120 mg/kg in mice, 25 mg/kg or higher in rats and 75 mg/kg or higher in rabbits), but was not teratogenic at those dose levels. No harm to the fetus due to tramadol was observed at doses that were not maternally toxic.

The drug had no mutagenic effect in either the micro-nucleus test, which was carried out with mice, rats and hamsters administered two single oral and parenteral doses, or in the dominant lethal test, in which mice were administered single and repeated oral and parenteral doses.

In carcinogenicity studies using tramadol, survival analysis did not show any statistically significant positive linear trend or differences in mortality among the placebo and tramadol treatment groups.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PART III: PATIENT MEDICATION INFORMATION

Pr DURELA®
Tramadol hydrochloride extended release capsules
Extended-Release Capsules

Read this carefully before you start taking DURELA 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 DURELA.

Serious Warnings and Precautions

- **Even if you take DURELA as prescribed you are at risk for opioid addiction, abuse, and misuse. This can lead to overdose and death.**
- **When you take DURELA it must be swallowed whole. Do not cut, break, crush, chew, dissolve the capsules. This can be dangerous and can lead to death or seriously harm you.**
- **You may get life-threatening breathing problems while taking DURELA. 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 DURELA. They could die from taking it. If a person has not been prescribed DURELA, taking even one dose can cause a fatal overdose. This is especially true for children.**
- **If you took DURELA 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 DURELA 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 DURELA used for?
DURELA is an oral capsule that slowly releases tramadol (an opioid analgesic) over a 24 hour period to manage moderate or moderately severe pain that is expected to persist for several days or more.

How does DURELA work?
DURELA is a painkiller belonging to the class of medicines known as opioids. It relieves pain by acting on specific nerve cells of the spinal cord and brain.

What are the ingredients in DURELA?
Medicinal ingredients: Tramadol hydrochloride USP
Non-medicinal ingredients: Corn starch, D & C Red #7 calcium lake (E180), D & C Yellow #10 aluminum lake, Eudragit NE 30D, FD & C Blue #2 aluminum lake (E132), gelatin, hypromellose, lactose monohydrate 200 mesh, magnesium stearate, microcrystalline cellulose, polysorbate 80, povidone K30, propylene glycol, shellac, simethicone emulsion, sodium starch glycolate, sucrose stearate, talc and titanium dioxide.

DURELA comes in the following dosage forms:
Extended-release capsules: 100 mg, 200 mg, and 300 mg. DURELA capsules are white, marked as follows:

100 mg: "**G 252**" on cap and "**100**" between lines on the body in blue ink
200 mg: "**G 253**" on cap and "**200**" between lines on the body in violet ink
300 mg: "**G 254**" on cap and "**300**" between lines on the body in red ink

Do not use DURELA if:

- you are allergic to tramadol or any of the other ingredients of DURELA
- 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 than 18 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
- you are pregnant or plan to become pregnant, or you are in labour
- you are breastfeeding
- 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 DURELA. Talk about any health conditions or problems you may have, including if you:

- have a history of illicit or prescription drug or alcohol abuse
- have low blood pressure
- have past or current depression
- suffer from chronic or severe constipation
- have been told that you metabolize tramadol or other pain medications rapidly
- have problems with your thyroid, adrenal or prostate gland, diabetes, epilepsy, liver or kidney disease
- have, or had in the past hallucinations or other severe mental problems

Other warnings you should know about:
DURELA 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.

Seizures have been reported at therapeutic doses of tramadol and this risk may be increased at doses exceeding the usual upper daily dose limit.

You should take the following precautions while taking DURELA capsules:
Alcohol: You must not consume alcohol while taking DURELA capsules, 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:
Do not use DURELA while pregnant, nursing, during labour or delivery. Opioids can be transferred to your baby through breast milk, or while still in the womb. DURELA can then cause life-threatening breathing problems in your unborn baby or nursing infant.

If you are pregnant and are taking DURELA, 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 DURELA. This may help avoid serious harm to your unborn baby.

Adolescents (12 to 18 years old): You should not use DURELA 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 DURELA 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 DURELA. DURELA can cause:

- drowsiness
- dizziness, or
- lightheadedness

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, and slowly take you off DURELA.

Serotonin Syndrome: DURELA 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 DURELA 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.

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.

There are other medications that may cause DURELA capsules to be less effective, or may cause you to have some side effects or drug reactions. There are also other drugs, such as tranquillizers, antidepressants, hypnotics, sleeping pills, or other pain relief medications, that can cause some serious reactions when taken at the same time as DURELA capsules.

The following may interact with DURELA:

- alcohol. This includes prescription and non-prescription medications that contain alcohol. Do not drink alcohol while taking DURELA. 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 DURELA 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
- St. John's Wort

How to take DURELA:

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.

DURELA is not recommended for rectal administration.

Usual adult starting dose:

Take the dose prescribed by your doctor as your dose is tailored/personalized just for you. Do not increase or decrease your dose without consulting your doctor. Taking higher doses can lead to more side effects and a greater chance of overdose. DURELA capsules should be taken regularly every 24 hours (with 4 to 6 oz. of water) to prevent pain all day and night. The usual starting dose of DURELA is 100 mg per day.

You should not take more than the maximum recommended dose of 300 mg of DURELA® per day. Exceeding this recommendation can result in respiratory depression (shallow, slow breathing), seizures, coma, heart stoppage and death.

DURELA capsules may be taken with or without food.

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

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

Stopping your Medication

If you have been taking DURELA 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 having:

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

Refilling your Prescription for DURELA:

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

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

Overdose:

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

Signs of overdose may include:

- unusually slow or weak breathing
- dizziness
- confusion
- extreme drowsiness
- fits (seizures)
- irritation and discomfort in the stomach and gut
- loss of appetite
- nausea
- vomiting
- feeling unwell
- unusually pale color and sweating

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

Missed Dose:

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

Should your pain increase, or any other complaint develop as a result of taking DURELA, contact your doctor immediately.

What are possible side effects from using DURELA?

These are not all the possible side effects you may feel when taking DURELA. 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

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

DURELA 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.	√		
UNCOMMON **Decreased Blood Sugar (hypo-glycemia):** dizziness, lack of energy, drowsiness, headache, trembling, sweating.			√

The most common side effects you may experience are constipation, dizziness, drowsiness, headache, nausea, and vomiting. Your doctor may order a laxative and stool softener to help relieve your constipation while you are taking DURELA. Tell your doctor about these problems if they arise.

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

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

- Online at MedEffect; https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator1908C
    Ottawa, ON
    K1A 0K9

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

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

Storage:
Store at room temperature (15-30°C). **Keep unused and expired DURELA in a secure place to prevent theft, misuse or accidental exposure. Keep DURELA out of sight and reach of children and pets.**

Disposal:
DURELA 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 DURELA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this consumer medication information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the importer/distributor's website, www.aralez.com or by calling 1-866-391-4503

This leaflet was prepared by Cipher Pharmaceuticals Inc.

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