Pr DURELA®

Tramadol Hydrochloride

Extended-Release Capsules 100, 200, 300 mg

Opioid Analgesic

Manufacturer:
Cipher Pharmaceuticals Inc.
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Canada, L4W 4P1

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DURELA®
Tramadol Hydrochloride Extended-Release Capsules, 100, 200, 300 mg

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Dosage Form / Strength</th>
<th>Nonmedicinal Ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>oral</td>
<td>extended-release capsules 100, 200, 300 mg</td>
<td>corn starch, D &amp; C Red #7 calcium lake (E180), D &amp; C Yellow #10 aluminum lake, Eudragit NE 30D, FD &amp; 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</td>
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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):
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. DURELA® should be administered with greater caution in patients over 75 years, due to the greater potential for adverse events in this population (see WARNINGS AND PRECAUTIONS, DOSAGE AND ADMINISTRATION) sections.

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, opioids, or to any ingredient in the formulation;
- 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);
- 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 asthma or other obstructive airway, and status asthmaticus;
- Patients with acute respiratory depression, elevated carbon dioxide levels in the blood, and cor pulmonale;
- Patients with acute alcoholism, delirium tremens, and convulsive disorders;
- Patients with severe CNS depression, increased cerebrospinal or intracranial pressure, and head injury;
- Women who are breastfeeding, pregnant, or during labour and delivery.

WARNINGS AND PRECAUTIONS

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.

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**).

**Drug Abuse, Addiction and Dependence**

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.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

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.

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.

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

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

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

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

**Withdrawal Symptoms**
Withdrawal symptoms may occur following abrupt discontinuation of therapy. 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.

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

**Risk of Overdosage**
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.

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.
Patients should be cautioned about the concomitant use of tramadol products and alcohol because of potentially serious CNS-additive effects of these agents. Because of its added depressant effects, tramadol should be prescribed with caution for those patients whose medical condition requires the concomitant administration of sedatives, tranquilizers, muscle relaxants, antidepressants, or other CNS-depressant drugs. Patients should be advised of the additive depressant effects of these combinations.

**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) 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).

**Respiratory Depression**
Administer DURELA® cautiously in patients at risk for respiratory depression. In these patients alternative non-opioid analgesics should be considered. When large doses of tramadol are administered with anesthetic medications or alcohol, respiratory depression may result. Respiratory depression should be treated as an overdose. If naloxone is to be administered, use cautiously because it may precipitate seizures (see WARNINGS AND PRECAUTIONS, Seizure Risk and OVERDOSAGE).

**Interaction With Central Nervous System (CNS) Depressants**
DURELA® should be used with caution and in reduced dosages when administered to patients receiving CNS depressants such as opioids, anesthetic agents, phenothiazines, tranquilizers or sedative hypnotics. Tramadol increases the risk of CNS and respiratory depression in these patients.

DURELA® may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

**Use in Ambulatory Patients**
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.

**Peri-operative Considerations**
DURELA® is contraindicated for peri-operative pain relief. In the case of planned chordotomy or other pain-relieving operations, patients should not be treated with DURELA® for at least 48 hours before the operation and DURELA® should not be used in the immediate post-operative period. 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).

**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.

**Use in Drug and Alcohol Addiction**
DURELA® is an opioid with no approved use in the management of addictive disorders. Its approved usage in individuals with drug or alcohol dependence, either active or in remission, is for the management of moderate to moderately severe chronic pain requiring continuous treatment with an opioid analgesic.

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

**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
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:** The safety of tramadol in pregnancy has not been established. Therefore, DURELA® is contraindicated in pregnant women and prior to or during labour.

Tramadol has been shown to cross the placenta. 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 newborn. Neonatal seizures, neonatal withdrawal syndrome, fetal death and stillbirth have been reported with tramadol hydrochloride during postmarketing reports with tramadol hydrochloride immediate-release products.

The effect of tramadol, if any, on the later growth, development and functional maturation of the child is unknown.

**Nursing Women:** DURELA® is contraindicated in nursing mothers. Tramadol and its metabolites are found in small amounts in human breast milk. 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.

**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.

**Geriatrics (>65 years of age):** In general, dose selection for an elderly patient should be cautious, 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.

**Monitoring and Laboratory Tests**

Not Applicable.

**ADVERSE REACTIONS**

**Adverse Drug Reaction Overview**

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.

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.*

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

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>DB 100 mg (N=429)</th>
<th>DB 200 mg (N=434)</th>
<th>DB 300 mg (N=1054)</th>
<th>DB Placebo (N=646)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Headache</td>
<td>23</td>
<td>22</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>Infection</td>
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<td>Back pain</td>
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<td>Accidental injury</td>
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<td>Abdominal pain</td>
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<td>Flu syndrome</td>
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<tr>
<td>Chills</td>
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<td>Nausea</td>
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<tr>
<td>Constipation</td>
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<td>Dry mouth</td>
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<td>DB 200 mg (N=434) %</td>
<td>DB 300 mg (N=1054) %</td>
<td>DB Placebo (N=646) %</td>
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<tr>
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<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Cough increased</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Sweating</td>
<td>4</td>
<td>5</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Pruritus</td>
<td>3</td>
<td>6</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Rash</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Urine abnormality</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

**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
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.

DRUG ABUSE, ADDICTION AND DEPENDENCE
Tramadol may induce psychic and physical dependence of the morphine-type (µ-opioid) (see WARNINGS AND PRECAUTIONS, Drug Abuse, Addiction and Dependence). Dependence and abuse, including drug-seeking behaviour and taking illicit actions to obtain the drug are not limited to those patients with a prior history of opioid dependence. The risk in patients with substance abuse has been observed to be higher. Tramadol is associated with craving and tolerance development.

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.

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

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).

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

**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.
**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.

**DOSAGE AND ADMINISTRATION**

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

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® can be administered without regard to food.

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

**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.

**Elderly Patients (≥ 65 years old):** Since the elimination half-life of tramadol may be prolonged in elderly patients, a starting dose of 100 mg daily is recommended. Upward dosage titration should be done with careful monitoring. DURELA® should be administered with even greater caution in patients over 75 years, due to the greater frequency of adverse events seen in this population.

**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)

**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.

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

Discontinuation
Withdrawal symptoms may occur following abrupt discontinuation of therapy. 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 DURELA® discontinuation include: panic attacks, severe anxiety, and paresthesias. Patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required for pain control.

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

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.

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.

**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 α2 adrenoceptor antagonist, yohimbine, and in animals, the serotonin antagonist rianserin reduces the antinociceptive effect of tramadol. This indicates the potential for a contribution to the analgesic effect of tramadol through modulation of monaminergic inhibitory pain pathways in the dorsal horn of the spinal cord, in addition to an opioidergic effect.
**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)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Tramadol</th>
<th>O-Desmethyl-Tramadol (M1 Metabolite)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (%CV)</td>
<td></td>
</tr>
<tr>
<td>AUC0-24 (ng\cdot h/mL)</td>
<td>6600 (25%)</td>
<td>1683 (31%)</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>364 (21%)</td>
<td>87 (32%)</td>
</tr>
<tr>
<td>Cmin (ng/mL)</td>
<td>165 (35%)</td>
<td>52 (32%)</td>
</tr>
<tr>
<td>Tmax</td>
<td>9.7 (18%)</td>
<td>10.8 (22%)</td>
</tr>
<tr>
<td>% Fluctuation</td>
<td>75 (29%)</td>
<td>51 (33%)</td>
</tr>
</tbody>
</table>

AUC0-24: 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. Therefore, use of DURELA® is not recommended in patients under 18 years of age.

**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:** No data available.

**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**

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:

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Immediate-release tablet</th>
<th>Extended-release beads</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg</td>
<td>25 mg</td>
<td>75 mg</td>
</tr>
<tr>
<td>200 mg</td>
<td>50 mg</td>
<td>150 mg</td>
</tr>
<tr>
<td>300 mg</td>
<td>50 mg</td>
<td>250 mg</td>
</tr>
</tbody>
</table>
Composition:

Active Ingredient(s): 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.
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Tramadol Hydrochloride 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:

![Structural formula of tramadol hydrochloride](image)

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

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

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 ≥ 40 mm on a 100 mm visual analog scale (VAS) off analgesic or antiarthritic 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

<table>
<thead>
<tr>
<th>Study 02-01</th>
<th>Tramadol ER 100 mg</th>
<th>Tramadol ER 200 mg</th>
<th>Tramadol ER 300 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>WOMAC Pain Index</td>
<td>N = 106</td>
<td>N = 103</td>
<td>N = 112</td>
<td>N = 108</td>
</tr>
<tr>
<td>Baseline</td>
<td>Mean ± SD</td>
<td>11.80 ± 3.424</td>
<td>11.05 ± 3.356</td>
<td>11.29 ± 3.558</td>
</tr>
<tr>
<td>Change to Wk 12†</td>
<td>LS Mean ± SE</td>
<td>-5.25 ± 1.096</td>
<td>-4.75 ± 1.100</td>
<td>-4.51 ± 1.052</td>
</tr>
<tr>
<td>p value†</td>
<td>0.0351</td>
<td>0.2448</td>
<td>0.4702</td>
<td></td>
</tr>
</tbody>
</table>

Bolded p-values significant based on protocol specified analysis.

TRAMCT.02.02

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

<table>
<thead>
<tr>
<th>Study 02-02</th>
<th>Tramadol ER 100 mg</th>
<th>Tramadol ER 200 mg</th>
<th>Tramadol ER 300 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>WOMAC Pain Index</td>
<td>N = 110</td>
<td>N = 113</td>
<td>N = 110</td>
<td>N = 111</td>
</tr>
<tr>
<td>Baseline</td>
<td>Mean ± SD</td>
<td>10.77 ± 3.608</td>
<td>11.06 ± 3.647</td>
<td>11.64 ± 3.216</td>
</tr>
<tr>
<td>Change to Wk 12†</td>
<td>LS Mean ± SE</td>
<td>-3.18 ± 1.049</td>
<td>-2.89 ± 1.036</td>
<td>-3.45 ± 1.020</td>
</tr>
<tr>
<td>p value†</td>
<td>0.0417</td>
<td>0.1254</td>
<td>0.0110</td>
<td></td>
</tr>
</tbody>
</table>

Bolded p-values significant based on protocol specified analysis.

TRAMCT.02.04

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

<table>
<thead>
<tr>
<th>Study 02-04</th>
<th>Tramadol ER 300 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>WOMAC Pain Index</td>
<td>N = 430</td>
<td>N = 139</td>
</tr>
<tr>
<td>Baseline</td>
<td>Mean ± SD</td>
<td>11.66 ± 3.170</td>
</tr>
<tr>
<td>Change to Wk 12†</td>
<td>LS Mean ± SE</td>
<td>-3.51 ± 0.186</td>
</tr>
<tr>
<td>p value†</td>
<td>0.0129</td>
<td></td>
</tr>
</tbody>
</table>

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 α2 adrenoceptor antagonists.

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

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

Both enantiomers have anti-nociceptive effects in animals and analgesic effects in humans, and the interaction between the two enantiomers is synergistic. However, for adverse effects, the interaction is less than additive (rotarod performance), additive (colonic motility) or antagonistic (cardiovascular and respiratory endpoints). Effects on gastrointestinal motility and respiration are less than with morphine, consistent with clinical observations of less constipation and respiratory depression at recommended doses.

TOXICOLOGY

After a single oral administration in mice, rats, guinea pigs, rabbits and dogs, the LD₅₀ of tramadol was 228-850 mg/kg; after s.c. injection in mice, rats and guinea pigs the LD₅₀ range was 200-286 mg/kg; after i.m. injection in rabbits and dogs, the LD₅₀ was 75-225 mg/kg; and after i.v. injection in mice, rabbits and dogs, the LD₅₀ 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.
REFERENCES


12. Parr WD, Frankus P, Dengler JH. The metabolism of tramadol by human liver


