Tramadol Hydrochloride and Acetaminophen Tablets 37.5 mg/325 mg C IV
Rx only

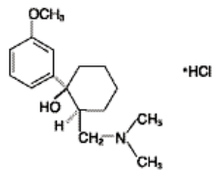
HEPATOTOXICITY

Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4,000 milligrams per day, and often involve more than one acetaminophen-containing product (see WARNINGS).

DESCRIPTION

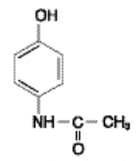
Tramadol Hydrochloride and Acetaminophen Tablets combines two analgesics, tramadol 37.5 mg and acetaminophen 325 mg.

The chemical name for tramadol hydrochloride is (±)*cis*-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride. Its structural formula is:



The molecular weight of tramadol hydrochloride is 299.84. Tramadol hydrochloride is a white, bitter, crystalline and odorless powder.

The chemical name for acetaminophen is *N*-acetyl-*p*-aminophenol. Its structural formula is:



The molecular weight of acetaminophen is 151.17. Acetaminophen is an analgesic and antipyretic agent which occurs as a white, odorless, crystalline powder, possessing a slightly bitter taste.

Tramadol Hydrochloride and Acetaminophen Tablets contain 37.5 mg tramadol hydrochloride and 325 mg of acetaminophen and are orange in color. Inactive ingredients in the tablet are crospovidone, magnesium stearate, microcrystalline cellulose, OPADRY® II Orange, povidone, pregelatinized starch, purified water, and stearic acid. OPADRY® II Orange contains: FD&C red #40; FD&C yellow #6; hypromellose 2910 3cP, 6cP, and 50cP; polydextrose; polyethylene glycol; titanium dioxide; triacetate; and triacetin.

CLINICAL PHARMACOLOGY

The following information is based on studies of tramadol alone or acetaminophen alone, except where otherwise noted:

Pharmacodynamics

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 (see **CLINICAL PHARMACOLOGY, Pharmacokinetics**).

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.

Apart from analgesia, tramadol administration may produce a constellation of symptoms (including dizziness, somnolence, nausea, constipation, sweating and puritis) similar to that of other opioids.

Acetaminophen is a non-opiate, non-salicylate analgesic.

Pharmacokinetics

Tramadol is administered as a racemate and both the [-] and [+] forms of both tramadol and M1 are detected in the circulation. The pharmacokinetics of plasma tramadol and acetaminophen following oral administration of one tramadol hydrochloride and acetaminophen tablet are shown in **Table 1**. Tramadol has a slower absorption and longer half-life when compared to acetaminophen.

Table 1: Summary of Mean (±SD) Pharmacokinetic Parameters of the (+) – and (-) Enantiomers of Tramadol and M1 and Acetaminophen Following A Single Oral Dose of One Tramadol Hydrochloride and Acetaminophen Combination Tablet (37.5 mg/325 mg) in Volunteers

Parameter[a]	(+)-Tramadol	(-)-Tramadol	(+)-M1	(-)-M1	Acetaminophen
C_{max} (ng/mL)	64.3 (9.3)	55.5 (8.1)	10.9 (5.7)	12.8 (4.2)	4.2 (0.8)
t_{max}(h)	1.8 (0.6)	1.8 (0.7)	2.1 (0.7)	2.2 (0.7)	0.9 (0.7)
CL/F (mL/min)	588 (226)	736 (244)	- -	- -	365 (84)
$t_{1/2}$ (h)	5.1 (1.4)	4.7 (1.2)	7.8 (3.0)	6.2 (1.6)	2.5 (0.6)

[a] For acetaminophen, C_{max} was measured in mcg/mL.

A single dose pharmacokinetic study of tramadol hydrochloride and acetaminophen tablets in volunteers showed no drug interactions between tramadol and acetaminophen. Upon multiple oral dosing to steady state, however, the bioavailability of tramadol and metabolite M1 was lower for the combination tablets compared to tramadol administered alone. The decrease in AUC was 14% for (+)-tramadol, 10.4% for (-)-tramadol, 11.9% for (+)-M1 and 24.2% for (-)-M1. The cause of this reduced bioavailability is not clear. Following single or multiple dose administration of tramadol hydrochloride and acetaminophen tablets, no significant change in acetaminophen pharmacokinetics was observed when compared to acetaminophen given alone.

Absorption:
The absolute bioavailability of tramadol from tramadol hydrochloride and acetaminophen tablets has not been determined. Tramadol hydrochloride has a mean absolute bioavailability of approximately 75% following administration of a single 100 mg oral dose of tramadol hydrochloride and acetaminophen tablets. The mean peak plasma concentration of racemic tramadol and M1 after administration of two tramadol hydrochloride and acetaminophen tablets occurs at approximately two and three hours, respectively, post-dose.

Peak plasma concentrations of acetaminophen occur within one hour and are not affected by coadministration with tramadol. Oral absorption of acetaminophen following administration of tramadol hydrochloride and acetaminophen tablets occurs primarily in the small intestine.

Food Effects:
When tramadol hydrochloride and acetaminophen tablets were administered with food, the time to peak plasma concentration was delayed for approximately 35 minutes for tramadol and almost one hour for acetaminophen. However, peak plasma concentrations, and the extents of absorption of tramadol or acetaminophen were not affected. The clinical significance of this difference is unknown.

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

Acetaminophen appears to be widely distributed throughout most body tissues except fat. Its apparent volume of distribution is about 0.9 L/kg. A relative small portion (~20%) of acetaminophen is bound to plasma protein.

Metabolism:
Following oral administration, tramadol is extensively metabolized by a number of pathways, including CYP2D6 and CYP3A4, as well as by conjugation of parent and metabolites. Approximately 30% of the dose is excreted in the urine as unchanged drug, whereas 60% of the dose is excreted as metabolites. The major metabolic pathways appear to be *N*- and *O*- demethylation and glucuronidation or sulfation in the liver. Metabolite M1 (*O*-desmethyltramadol) is pharmacologically active in animal models. Formation of M1 is dependent on CYP2D6 and as such is subject to inhibition, which may affect the therapeutic response (see **PRECAUTIONS, Drug Interactions**).

Approximately 7% of the population has reduced activity of the CYP2D6 isoenzyme of cytochrome P450. These individuals are “poor metabolizers" of debrisoquine, dextromethorphan and tricyclic antidepressants, among other drugs. Based on a population PK analysis of Phase 1 studies in healthy subjects, concentrations of tramadol were approximately 20% higher in "poor metabolizers" versus "extensive metabolizers," while M1 concentrations were 40% lower. *In vitro* drug interaction studies in human liver microsomes indicate that inhibitors of CYP2D6 such as fluoxetine and its metabolite norfluoxetine, amitriptyline and quinidine inhibit the metabolism of tramadol to various degrees. The full pharmacological impact of these alterations in terms of either efficacy or safety is unknown. Concomitant use of SEROTONIN re-uptake INHIBITORS and MAO INHIBITORS may enhance the risk of adverse events, including seizure (see **WARNINGS**) and serotonin syndrome.

Acetaminophen is primarily metabolized in the liver by first-order kinetics and involves three principal separate pathways:

a) conjugation with glucuronide;

b) conjugation with sulfate; and

c) oxidation via the cytochrome; P450-dependent, mixed-function oxidase enzyme pathway to form a reactive intermediate metabolite, which conjugates with glutathione and is then further metabolized to form cysteine and mercapturic acid conjugates. The principal cytochrome P450 isoenzyme involved appears to be CYP2E1, with CYP1A2 and CYP3A4 as additional pathways.

In adults, the majority of acetaminophen is conjugated with glucuronic acid and, to a lesser extent, with sulfate. These glucuronide-, sulfate-, and glutathione-derived metabolites lack biologic activity. In premature infants, newborns, and young infants, the sulfate conjugate predominates.

Elimination:
Tramadol is eliminated primarily through metabolism by the liver and the metabolites are eliminated primarily by the kidneys. The plasma elimination half-lives of racemic tramadol and M1 are approximately 5 to 6 and 7 hours, respectively, after administration of tramadol hydrochloride and acetaminophen tablets. The apparent plasma elimination half-life of racemic tramadol increased to 7 to 9 hours upon multiple dosing of tramadol hydrochloride and acetaminophen tablets.

The half-life of acetaminophen is about 2 to 3 hours in adults. It is somewhat shorter in children and somewhat longer in neonates and in cirrhotic patients. Acetaminophen is eliminated from the body primarily by formation of glucuronide and sulfate conjugates in a dose-dependent manner. Less than 9% of acetaminophen is excreted unchanged in the urine.

Special Populations

Renal:
The pharmacokinetics of tramadol hydrochloride and acetaminophen tablets in patients with renal impairment have not been studied. Based on studies using tramadol alone, excretion of tramadol and metabolite M1 is reduced in patients with creatinine clearance of less than 30 mL/min. Adjustment of dosing regimen in this patient population is recommended. (See **DOSAGE AND ADMINISTRATION.**) The total amount of tramadol and M1 removed during a 4-hour dialysis period is less than 7% of the administered dose based on studies using tramadol alone.

Hepatic:
The pharmacokinetics and tolerability of tramadol hydrochloride and acetaminophen tablets in patients with impaired hepatic function has not been studied. Since tramadol and acetaminophen are both extensively metabolized by the liver, the use of tramadol hydrochloride and acetaminophen tablets in patients with hepatic impairment is not recommended (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Geriatric:
A population pharmacokinetic analysis of data obtained from a clinical trial in patients with chronic pain treated with tramadol hydrochloride and acetaminophen tablets which included 55 patients between 65 and 75 years of age and 19 patients over 75 years of age, showed no significant changes in the pharmacokinetics of tramadol and acetaminophen in elderly patients with normal renal and hepatic function (see **PRECAUTIONS, Geriatric Use**).

Gender:
Tramadol clearance was 20% higher in female subjects compared to males on four phase I studies of tramadol hydrochloride and acetaminophen tablets in 50 male and 34 female healthy subjects. The clinical significance of this difference is unknown.

Pediatric:
Pharmacokinetics of tramadol hydrochloride and acetaminophen tablets has not been studied in pediatric patients below 16 years of age.

CLINICAL STUDIES

Single Dose Studies for Treatment of Acute Pain
In pivotal single dose studies in acute pain, two tablets of tramadol hyrdochloride and acetaminophen administered to patients with pain following oral surgical procedures provided greater relief than placebo or either of the individual components given at the same dose. The onset of pain relief after tramadol hydrochloride and acetaminophen tablets was faster than tramadol alone. Onset of analgesia occurred in less than one hour. The duration of pain relief after tramadol hydrochloride and acetaminophen tablets was longer than acetaminophen alone. Analgesia was generally comparable to that of the comparator, ibuprofen.

INDICATIONS AND USAGE

Tramadol hydrochloride and acetaminophen tablets are indicated for the short-term (five days or less) management of acute pain.

CONTRAINDICATIONS

Tramadol hydrochloride and acetaminophen tablets should not be administered to patients who have previously demonstrated hypersensitivity to tramadol, acetaminophen, any other component of this product or opioids. Tramadol hydrochloride and acetaminophen tablets is contraindicated in any situation where opiods are contraindicated, including acute intoxication with any of the following: alcohol, hypnotics, narcotics, centrally acting analgesics, opioids or psychotropic drugs. Tramadol hydrochloride and acetaminophen tablets may worsen central nervous system and respiratory depression in these patients.

WARNINGS

Hepatotoxicity
Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4,000 milligrams per day, and often involve more than one acetaminophen-containing product. The excessive intake of acetaminophen may be intentional to cause self-harm or unintentional as patients attempt to obtain more pain relief or unknowingly take other acetaminophen-containing products (See Boxed Warning).

The risk of acute liver failure is higher in individuals with underlying liver disease and in individuals who ingest alcohol while taking acetaminophen.

Instruct patients to look for acetaminophen or APAP on package labels and not to use more than one product that contains acetaminophen. Instruct patients to seek medical attention immediately upon ingestion of more than 4,000 milligrams of acetaminophen per day, even if they feel well.

Serious Skin Reactions
Rarely, acetaminophen may cause serious skin reactions such as acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. Patients should be informed about the signs of serious skin reactions, and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

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 reuptake inhibitors (SSRI antidepressants or anorectics),**
- **Tricyclic antidepressants (TCAs), and other tricyclic compounds (e.g., cyclobenzaprine, promethazine, etc.), or**
- **Other opioids.**

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

- **MAO inhibitors (see also WARNINGS - Use with MAO Inhibitors and Serotonin Re-uptake Inhibitors),**
- **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 or CNS infections). In tramadol overdose, naloxone administration may increase the risk of seizure.

Suicide Risk
- **Do not prescribe tramadol hydrochloride and acetaminophen tablets for patients who are suicidal or addiction-prone.**
- **Prescribe tramadol hydrochloride and acetaminophen tablets with caution for patients taking tranquilizers or antidepressant drugs and patients who use alcohol in excess and who suffer from emotional disturbance or depression.**

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.

Tramadol-related deaths have occurred in patients with previous histories of emotional disturbances or suicidal ideation or attempts as well as histories of misuse of tranquilizers, alcohol, and other CNS-active drugs (see **WARNINGS, Risk of Overdosage**).

Serotonin Syndrome Risk
The development of a potentially life-threatening serotonin syndrome may occur with the use of tramadol products, including tramadol hydrochloride and acetaminophen tablets, particularly with concomitant use of serotonergic drugs such as SSRIs, SNRIs, TCAs, MAOIs, 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 within the recommended dose (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

Serotonin syndrome may include mental-status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea).

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

There have been post-marketing reports of hypersensitivity and anaphylaxis associated with the use of acetaminophen. Clinical signs included swelling of the face, mouth, and throat, respiratory distress, urticaria, rash, pruritus, and vomiting. There were infrequent reports of life-threatening anaphylaxis requiring emergency medical attention. Instruct patients to discontinue tramadol hydrochloride and acetaminophen tablets immediately and seek medical care if they experience these symptoms. Do not prescribe tramadol hydrochloride and acetaminophen tablets for patients with acetaminophen allergy.

Respiratory Depression
Administer tramadol hydrochloride and acetaminophen tablets 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, Seizure Risk** and **OVERDOSAGE**).

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

Interactions with Alcohol and Drugs of Abuse
Tramadol may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

Increased Intracranial Pressure or Head Trauma
Tramadol hydrochloride and acetaminophen tablets should be used with caution in patients with increased intracranial pressure or head injury. The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure and may be markedly exaggerated in these patients. Additionally, 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 reactions when evaluating altered mental status in these patients if they are receiving tramadol hydrochloride and acetaminophen tablets (see **WARNINGS**, **Respiratory Depression**).

Use In Ambulatory Patients
Tramadol 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.

Use With MAO Inhibitors and Serotonin Re-uptake Inhibitors
Use tramadol hydrochloride and acetaminophen tablets with great caution in patients taking monoamine oxidase inhibitors. Animal studies have shown increased deaths with combined administration of MAO inhibitors and tramadol. Concomitant use of tramadol with MAO inhibitors or SSRI's increases the risk of adverse events, including seizure and serotonin syndrome.

Use With Alcohol
Tramadol hydrochloride and acetaminophen tablets should not be used concomitantly with alcohol consumption. The use of tramadol hydrochloride and acetaminophen tablets in patients with liver disease is not recommended.

Use With Other Acetaminophen-containing Products
Due to the potential for acetaminophen hepatotoxicity at doses higher than the recommended dose, tramadol hydrochloride and acetaminophen tablets should not be used concomitantly with other acetaminophen-containing products.

Misuse, Abuse and Diversion
Tramadol has mu-opioid agonist activity. Tramadol hydrochloride and acetaminophen tablets, a tramadol-containing product, can be sought by drug abusers and people with addiction disorders and may be subject to criminal diversion. The possibility of illegal or illicit use should be considered when prescribing or dispensing tramadol hydrochloride and acetaminophen tablets in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. Misuse or abuse poses a significant risk to the abuser that could result in overdose and death (see **DRUG ABUSE AND DEPENDENCE** and **OVERDOSAGE**).

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.

Risk of Overdosage
Patients taking tramadol should be warned not to exceed the dose recommended by their physician. Tramadol products in excessive doses, either alone or in combination with other CNS depressants, including alcohol, are a cause of drug-related deaths. 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, tricyclic antidepressants, or other CNS depressant drugs. Patients should be advised of the additive depressant effects of these combinations.

Serious potential consequences of overdosage with tramadol are central nervous system depression, respiratory depression and death. Some deaths have occurred as a consequence of the accidental ingestion of excessive quantities of tramadol alone or in combination with other drugs. In treating an overdose, primary attention should be given to maintaining adequate ventilation along with general supportive treatment. (See **OVERDOSAGE**.)

A serious potential consequence of overdosage with acetaminophen is hepatic (centrilobular) necrosis, leading to hepatic failure and death. Emergency help should be sought immediately and treatment initiated

immediately if overdose is suspected, even if symptoms are not apparent.

Withdrawal

Withdrawal symptoms may occur if tramadol hydrochloride and acetaminophen tablets are discontinued abruptly. (See **DRUG ABUSE AND DEPENDENCE.)** Reported symptoms have included anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhea, upper respiratory symptoms, piloerection, and rarely hallucinations. Other symptoms that have been reported less frequently with tramadol hydrochloride and acetaminophen tablets discontinuation include: panic attacks, severe anxiety, and paresthesias. Clinical experience suggests that withdrawal symptoms may be avoided by tapering tramadol hydrochloride and acetaminophen tablets at the time of discontinuation.

PRECAUTIONS

General

The recommended dose of tramadol hydrochloride and acetaminophen tablets should not be exceeded.

Do not coadminister tramadol hydrochloride and acetaminophen tablets with other tramadol or acetaminophen containing products. (See **WARNINGS, Use With Other Acetaminophen-containing Products** and **Risk of Overdosage.**)

Pediatric Use

The safety and effectiveness of tramadol hydrochloride and acetaminophen tablets has not been studied in the pediatric population.

Geriatric Use

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.

Acute Abdominal Conditions

The administration of tramadol hydrochloride and acetaminophen tablets may complicate the clinical assessment of patients with acute abdominal conditions.

Use In Renal Disease

Tramadol hydrochloride and acetaminophen tablets have not been studied in patients with impaired renal function. Experience with tramadol suggests that impaired renal function results in a decreased rate and extent of excretion of tramadol and its active metabolite, M1. In patients with creatinine clearances of less than 30 mL/min, it is recommended that the dosing interval of tramadol hydrochloride and acetaminophen tablets be increased not to exceed 2 tablets every 12 hours.

Use in Hepatic Disease

Tramadol hydrochloride and acetaminophen tablets have not been studied in patients with impaired hepatic function. The use of tramadol hydrochloride and acetaminophen tablets in patients with hepatic impairment is not recommended (see **WARNINGS, Use With Alcohol**).

Information for Patients

- Do not take tramadol hydrochloride and acetaminophen tablets if you are allergic to any of its ingredients.
- If you develop signs of allergy such as a rash or difficulty breathing, stop taking tramadol hydrochloride and acetaminophen tablets and contact your healthcare provider immediately.
- Do not take more than 4,000 milligrams of acetaminophen per day. Call your doctor if you took more than the recommended dose.
- Do not take tramadol hydrochloride and acetaminophen tablets in combination with other tramadol or acetaminophen-containing products, including over-the-counter preparations.
- Tramadol hydrochloride and acetaminophen tablets may cause seizures and/or serotonin syndrome with concomitant use of serotonergic agents (including SSRIs, SNRIs, and triptans) or drugs that significantly reduce the metabolic clearance of tramadol.
- Tramadol hydrochloride and acetaminophen tablets may impair mental or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.
- Tramadol hydrochloride and acetaminophen tablets should not be taken concomitantly with alcohol-containing beverages during the course of treatment with tramadol hydrochloride and acetaminophen tablets.
- Tramadol hydrochloride and acetaminophen tablets should be used with caution when taking medications such as tranquilizers, hypnotics, or other opiate-containing analgesics.
- Inform the physician if you are pregnant, think you might become pregnant, or are trying to become pregnant (see **PRECAUTIONS, Labor and Delivery**).
- Understand the single-dose and 24-hour dose limit and the time interval between doses, since exceeding these recommendations can result in respiratory depression, seizures, hepatic toxicity, and death.

Drug Interactions

CYP2D6 and CYP3A4 Inhibitors

Concomitant administration of CYP2D6 and/or CYP3A4 inhibitors (see **CLINICAL PHARMACOLOGY, Pharmacokinetics**), such as quinidine, fluoxetine, paroxetine and amitriptyline (CYP2D6 inhibitors), and ketoconazole and erythromycin (CYP3A4 inhibitors), may reduce metabolic clearance of tramadol increasing the risk for serious adverse events including seizures and serotonin syndrome.

Serotonergic Drugs

There have been postmarketing reports of serotonin syndrome with use of tramadol and SSRIs/SNRIs or MAOIs and α2-adrenergic blockers. Caution is advised when tramadol hydrochloride and acetaminophen is coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as SSRIs, MAOIs, triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, or St. John's Wort. If concomitant treatment of tramadol hydrochloride and acetaminophen with a drug affecting the serotonergic neurotransmitter system is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see **WARNINGS, Serotonin Syndrome**).

Triptans

Based on the mechanism of action of tramadol and the potential for serotonin syndrome, caution is advised when tramadol hydrochloride and acetaminophen is coadministered with a triptan. If concomitant treatment of tramadol hydrochloride and acetaminophen with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see **WARNINGS, Serotonin Syndrome**).

Use With Carbamazepine

Patients taking **carbamazepine** may have a significantly reduced analgesic effect of tramadol. Because carbamazepine increases tramadol metabolism and because of the seizure risk associated with tramadol, concomitant administration of tramadol hydrochloride and acetaminophen tablets and carbamazepine is not recommended.

Use With Quinidine

Tramadol is metabolized to M1 by CYP2D6. **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.

Potential for Other Drugs to Affect Tramadol

In vitro drug interaction studies in human liver microsomes indicate that concomitant administration with inhibitors of CYP2D6 such as fluoxetine, paroxetine, and amitriptyline could result in some inhibition of the metabolism of tramadol. Administration of CYP3A4 inhibitors, such as ketoconazole and erythromycin, or inducers, such as rifampin and St. John's Wort, with tramadol hydrochloride and acetaminophen tablets may affect the metabolism of tramadol leading to altered tramadol exposure.

Potential for Tramadol to Affect Other Drugs

In vitro studies indicate 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.

Use With Cimetidine

Concomitant administration of tramadol hydrochloride and acetaminophen tablets and **cimetidine** has not been studied. Concomitant administration of tramadol and cimetidine does not result in clinically significant changes in tramadol pharmacokinetics. Therefore, no alteration of the tramadol hydrochloride and acetaminophen tablets dosage regimen is recommended.

Use With Digoxin

Post-marketing surveillance of tramadol has revealed rare reports of **digoxin** toxicity.

Use With Warfarin Like Compounds

Post-marketing surveillance of both tramadol and acetaminophen individual products have revealed rare alterations of warfarin effect, including elevation of prothrombin times.

While such changes have been generally of limited clinical significance for the individual products, periodic evaluation of prothrombin time should be performed when tramadol hydrochloride and acetaminophen tablets and warfarin-like compounds are administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility

There are no animal or laboratory studies on the combination product (tramadol and acetaminophen) to evaluate carcinogenesis, mutagenesis, or impairment of fertility.

A slight but statistically significant increase in two common murine tumors, pulmonary and hepatic, was observed in a mouse carcinogenicity study, particularly in aged mice. Mice were dosed orally up to 30 mg/kg (90 mg/m^2 or 0.5 times the maximum daily human tramadol dosage of 185 mg/m^2) for approximately two years, although the study was not done with the Maximum Tolerated Dose. This finding is not believed to suggest risk in humans. No such finding occurred in a rat carcinogenicity study (dosing orally up to 30 mg/kg, 180 mg/m^2, or 1 time the maximum daily human tramadol dosage).

Tramadol was not mutagenic in the following assays: Ames *Salmonella* microsomal activation test, CHO/HPRT mammalian cell assay, mouse lymphoma assay (in the absence of metabolic activation), dominant lethal mutation tests in mice, chromosome aberration test in Chinese hamsters, and bone marrow micronucleus tests in mice and Chinese hamsters. Weakly mutagenic results occurred in the presence of metabolic activation in the mouse lymphoma assay and micronucleus test in rats. Overall, the weight of evidence from these tests indicates that tramadol does not pose a genotoxic risk to humans.

No effects on fertility were observed for tramadol at oral dose levels up to 50 mg/kg (350 mg/m^2) in male rats and 75 mg/kg (450 mg/m^2) in female rats. These dosages are 1.6 and 2.4 times the maximum daily human tramadol dosage of 185 mg/m^2.

Pregnancy

Teratogenic Effects: Pregnancy Category C

No drug-related teratogenic effects were observed in the progeny of rats treated orally with tramadol and acetaminophen. The tramadol/acetaminophen combination product was shown to be embryotoxic and fetotoxic in rats at a maternally toxic dose, 50/434 mg/kg tramadol/acetaminophen (300/2604 mg/m^2 or 1.6 times the maximum daily human tramadol/acetaminophen dosage of 185/1591 mg/m^2), but was not teratogenic at this dose level. Embryo and fetal toxicity consisted of decreased fetal weights and increased supernumerary ribs.

Non-teratogenic effects:

Tramadol alone was evaluated in peri- and post-natal studies in rats. Progeny of dams receiving oral (gavage) dose levels of 50 mg/kg (300 mg/m^2 or 1.6 times the maximum daily human tramadol dosage) or greater had decreased weights, and pup survival was decreased early in lactation at 80 mg/kg (480 mg/m^2 or 2.6 times the maximum daily human tramadol dosage).

There are no adequate and well-controlled studies in pregnant women. Tramadol hydrochloride and acetaminophen tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Neonatal seizures, neonatal withdrawal syndrome, fetal death and still birth have been reported with tramadol hydrochloride during post-marketing.

Labor and Delivery

Tramadol hydrochloride and acetaminophen tablets should not be used in pregnant women prior to or during labor unless the potential benefits outweigh the risks. Safe use in pregnancy has not been established. Chronic use during pregnancy may lead to physical dependence and post-partum withdrawal symptoms in the newborn. (See **DRUG ABUSE AND DEPENDENCE.**) 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 labor.

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

Nursing Mothers

Tramadol hydrochloride and acetaminophen tablets are not recommended for obstetrical preoperative medication or for post-delivery analgesia in nursing mothers because its safety in infants and newborns has not been studied.

Following a single IV 100 mg dose of tramadol, the cumulative excretion in breast milk within 16 hours post-dose was 100 mcg of tramadol (0.1% of the maternal dose) and 27 mcg of M1.

ADVERSE REACTIONS

Table 2 reports the incidence rate of treatment-emergent adverse events over five days of tramadol hydrochloride and acetaminophen tablets use in clinical trials (subjects took an average of at least 6 tablets per day).

Table 2: Incidence of Treatment-Emergent Adverse Events (≥2.0%)

Body System Preferred Term	Tramadol Hydrochloride and Acetaminophen Tablets (N=142) (%)
Gastrointestinal System Disorders	
Constipation	6
Diarrhea	3
Nausea	3
Dry Mouth	2
Psychiatric Disorders	
Somnolence	6
Anorexia	3
Insomnia	2
Central & Peripheral Nervous System	
Dizziness	3
Skin and Appendages	
Sweating Increased	4
Pruritus	2
Reproductive Disorders, Male*	
Prostatic Disorder	2

* Number of males = 62

Incidence at least 1%, causal relationship at least possible or greater: The following lists adverse reactions that occurred with an incidence of at least 1% in single-dose or repeated-dose clinical trials of tramadol hydrochloride and acetaminophen tablets.

Body as a Whole - Asthenia, fatigue, hot flushes.

Central and Peripheral Nervous System - Dizziness, headache, tremor.

Gastrointestinal System - Abdominal pain, constipation, diarrhea, dyspepsia, flatulence, dry mouth, nausea, vomiting.

Psychiatric Disorders - Anorexia, anxiety, confusion, euphoria, insomnia, nervousness, somnolence.

Skin and Appendages - Pruritus, rash, increased sweating.

Selected Adverse events occurring at less than 1%: The following lists clinically relevant adverse reactions that occurred with an incidence of less than 1% in tramadol hydrochloride and acetaminophen tablets clinical trials.

Body as a Whole - Chest pain, rigors, syncope, withdrawal syndrome.

Cardiovascular Disorders - Hypertension, aggravated hypertension, hypotension.

Central and Peripheral Nervous System - Ataxia, convulsions, hypertonia, migraine, aggravated migraine, involuntary muscle contractions, paraesthesia, stupor, vertigo.

Gastrointestinal System - Dysphagia, melena, tongue edema.

Hearing and Vestibular Disorders - Tinnitus.

Heart Rate and Rhythm Disorders - Arrhythmia, palpitation, tachycardia.

Liver and Biliary System - Hepatic function abnormal.

Metabolic and Nutritional Disorders - Weight decrease.

Psychiatric Disorders - Amnesia, depersonalization, depression, drug abuse, emotional lability, hallucination, impotence, paroniria, abnormal thinking.

Red Blood Cell Disorders - Anemia.

Respiratory System - Dyspnea.

Urinary System - Albuminuria, micturition disorder, oliguria, urinary retention.

Vision Disorders - Abnormal vision.

Other clinically significant adverse experiences previously reported with tramadol hydrochloride;

Other events which have been reported with the use of tramadol products and for which a causal association has not been determined include: vasodilation, orthostatic hypotension, myocardial ischemia, pulmonary edema, allergic reactions (including anaphylaxis and urticaria, Stevens-Johnson syndrome/TENS), cognitive dysfunction, difficulty concentrating, depression, suicidal tendency, hepatitis, liver failure and gastrointestinal bleeding. Reported laboratory abnormalities included elevated creatinine and liver function tests. 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 SSRIs and MAOIs.

Other clinically significant adverse experiences previously reported with acetaminophen;

Allergic reactions (primarily skin rash) or reports of hypersensitivity secondary to acetaminophen are rare and generally controlled by discontinuation of the drug and, when necessary, symptomatic treatment.

DRUG ABUSE AND DEPENDENCE

Tramadol is classified as a Schedule IV controlled substance by federal regulation.

Abuse

Tramadol has mu-opioid agonist activity. Tramadol hydrochloride and acetaminophen tablets, a tramadol-containing product, can be abused and may be subject to criminal diversion.

Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. Drug addiction is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, use for nonmedical purposes, continued use despite harm or risk of harm, and craving. Drug addiction is a treatable disease, utilizing a multidisciplinary approach, but relapse is common.

"Drug-seeking" behavior is very common in addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated "loss" of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of tramadol hydrochloride and acetaminophen tablets can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances.

Concerns about abuse and addiction should not prevent the proper management of pain. However all patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Proper assessment of the patient and periodic re-evaluation of therapy are appropriate measures that help to limit the potential abuse of this product.

Tramadol hydrochloride and acetaminophen tablets are intended for oral use only.

Dependence

Tolerance is the need for increasing doses of drugs to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist (see also **WARNINGS, Withdrawal**).

The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

Generally, tolerance and/or withdrawal are more likely to occur the longer a patient is on continuous therapy with tramadol hydrochloride and acetaminophen tablets.

OVERDOSAGE

Tramadol hydrochloride and acetaminophen tablets is a combination product. The clinical presentation of overdose may include the signs and symptoms of tramadol toxicity, acetaminophen toxicity or both. The initial symptoms of tramadol overdosage may include respiratory depression and or seizures.The initial symptoms seen within the first 24 hours following an acetaminophen overdose are: anorexia, nausea, vomiting, malaise, pallor and diaphoresis. An overdosage of tramadol hydrochloride and acetaminophen tablets may be a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended.

Tramadol

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, seizures, bradycardia, hypotension, cardiac arrest, and death.

Deaths due to overdose have been reported with abuse and misuse of tramadol (see **WARNINGS, Misuse, Abuse, and Diversion**). 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.

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

While naloxone will reverse some, but not all, symptoms caused by overdosage with tramadol, the risk of seizures is also increased with naloxone administration. In animals, convulsions following the administration of toxic doses of tramadol hydrochloride and acetaminophen tablets could be suppressed with barbiturates or benzodiazepines but were increased with naloxone. Naloxone administration did not change the lethality of an overdose in mice. Hemodialysis is not expected to be helpful in an overdose because it removes less than 7% of the administered dose in a 4-hour dialysis period.

Acetaminophen

In ***acetaminophen*** overdosage, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and coagulation defects also may occur. Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis, and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

In the treatment of acetaminophen overdosage, gastric decontamination with activated charcoal should be administered just prior to N-acetylcysteine (NAC) to decrease systemic absorption if acetaminophen ingestion is known or suspected to have occurred within a few hours of presentation. Serum acetaminophen levels should be obtained immediately if the patient presents 4 or more hours after ingestion to assess potential risk of hepatotoxicity, acetaminophen levels drawn less than 4 hours post-ingestion may be misleading. To obtain the best possible outcome, NAC should be administered as soon as possible where impending or evolving liver injury is suspected. Intravenous NAC may be administered when circumstances preclude oral administration.

Vigorous supportive therapy is required in severe intoxication. Procedures to limit the continuing absorption of the drug must be readily performed since the hepatic injury is dose-dependent and occurs early in the course of intoxication.

DOSAGE AND ADMINISTRATION

For the short-term (five days or less) management of acute pain, the recommended dose of Tramadol Hydrochloride and Acetaminophen Tablets is 2 tablets every 4 to 6 hours as needed for pain relief up to a maximum of 8 tablets per day.

Individualization of Dose

In patients with creatinine clearances of less than 30 mL/min, it is recommended that the dosing interval of Tramadol Hydrochloride and Acetaminophen Tablets be increased not to exceed 2 tablets every 12 hours. Dose selection for an elderly patient should be cautious, in view of the potential for greater sensitivity to adverse events.

HOW SUPPLIED

Tramadol Hydrochloride and Acetaminophen Tablets 37.5 mg/325 mg, (orange, film-coated capsule-shaped tablets) debossed "083" on one side and "KALI" on the other are available as follows:

Bottles of 100 tablets NDC 49884-946-01
Bottles of 500 tablets NDC 49884-946-05

Dispense in a tight container. Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F).

Manufactured by:
PAR PHARMACEUTICAL COMPANIES, INC.
Spring Valley, NY 10977

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