Tracetol® 37.5/325 mg Tablets

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(Tramadol Hydrochloride/ Paracetamol Tablets)

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:
Tramadol Hydrochloride U.S.P. …….. 37.5mg.
Acetaminophen U.S.P ……325mg

DESCRIPTION

Tracetol (Tramadol hydrochloride + Acetaminophen) tablet combines two analgesics, Tramadol and Acetaminophen. The chemical name for Tramadol Hydrochloride (±)cis-2-[(dimethylamino-)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride. The molecular weight of tramadol hydrochloride is 299.84. The chemical name for acetaminophen is N-acetyl-p-aminophenol. The molecular weight of acetaminophen is 151.17.

WARNING: ADDICTION, ABUSE, AND MISUSE; RISK EVALUATION AND MITIGATION STRATEGY (REMS); LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; ULTRA-RAPID METABOLISM OF TRAMADOL AND OTHER RISK FACTORS FOR LIFE-THREATENING RESPIRATORY DEPRESSION IN CHILDREN; NEONATAL OPIOID WITHDRAWAL SYNDROME; INTERACTIONS WITH DRUGS AFFECTING CYTOCHROME P450 ISOENZYMES; HEPATOTOXICITY; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

•Tramadol + Acetaminophen exposes users to the risks of addiction, abuse and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Tramadol + Acetaminophen, and monitor regularly for these behaviors or conditions.
• To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, FDA require a Risk Evaluation and Mitigation Strategy (REMS) for these products.
• Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially during initiation or following a dose increase.
• Accidental ingestion of Tramadol + Acetaminophen, especially by children, can result in a fatal overdose of tramadol.
• Life-threatening respiratory depression and death is known to occur in children who receive tramadol. Some of the known cases followed tonsillectomy and/or adenoidectomy; in at least one case, the child is known to have evidence of being an ultra-rapid metabolizer of tramadol due to a CYP2D6 polymorphism.
Tramadol + Acetaminophen are contraindicated in children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy.
Avoid the use of Tramadol + Acetaminophen in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of tramadol.
• Prolonged use of Tramadol + Acetaminophen, during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life threatening if not recognized and treated If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.
• The effects of concomitant use or discontinuation of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with tramadol are complex. Use of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with Tramadol + Acetaminophen requires careful consideration of the effects on the parent drug, tramadol, and the active metabolite, M1.
• Tramadol+ Acetaminophen contains acetaminophen, which is known to be associated with 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.
• Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation.

CLINICAL INFORMATION

Indications

Tracetol (Tramadol hydrochloride+Acetaminophen) tablets are indicated for the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

Limitations of Use

Tracetol (Tramadol + Acetaminophen) tablets are indicated for short-term use of five days or less.
Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, reserves Tracetol for use in patients for whom alternative treatment options [e.g., non-opioid analgesics]:
• Have not been tolerated, or are not expected to be tolerated,
• Have not provided adequate analgesia, or are not expected to provide adequate analgesia.

Dosage and administration

Usual adult dose for pain

The initial dose of Tracetol is 2 tablets every 4 to 6 hours as needed for pain relief.
Maximum dose: 8 tablets per day.

Renal dose adjustment

In patients with creatinine clearances of < 30 mL/min, do not exceed 2 tablets every 12 hours.

Liver dose adjustments

The use of Tracetol (Tramadol+Acetaminophen) in patients with liver disease is not recommended.

Safe reduction or discontinuation of Tracetol

Rapid discontinuation of opioid analgesics in patients who are physically dependent on opioids has resulted in serious withdrawal symptoms, uncontrolled pain, and suicide. It is important to ensure ongoing care of the patient and to agree on an appropriate tapering schedule and follow-up plan so that patient and provider goals and expectations are clear and realistic.

Administration requirements

• Tracetol is not approved for use for more than 5 days.
• Do not exceed the recommended dose and do not co-administer Tracetol with other tramadol or acetaminophen containing products.
• Use lowest effective dosage for shortest duration consistent with individual treatment goals.
• Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases with Tracetol and adjust the dosage accordingly.

Contraindications

Tramadol + Acetaminophen are contraindicated for:
• All children < 12 years of age.
• Post-operative management in children < 18 years of age following tonsillectomy and/or adenoidectomy.
Tramadol + Acetaminophen are also contraindicated in patients with:
• Significant respiratory depression
• Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment.
• Patients with known or suspected gastrointestinal obstruction, including paralytic ileus
• Any situation in which opioids are contraindicated, including acute intoxication with any of the following: alcohol, centrally acting analgesics, hypnotics, narcotics, opioids, or psychotropic drugs; hypersensitivity to any component of the product or opioids.
• Concurrent use of monoamine oxidase inhibitors (maois) or use within the last 14 days

Warnings and Precautions

Addiction, Abuse and Misuse

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing Tramadol + Acetaminophen, and monitor all patients.

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression is known to occur with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death.

Ultra-Rapid Metabolism of Tramadol and Other Risk Factors for Life-threatening Respiratory Depression in Children

Because of the risk of life-threatening respiratory depression and death, this drug is
• Contraindicated in children < 12 years of age.
• Contraindicated for postoperative management in pediatric patients, <18 years of age
• Avoid the use in adolescents 12 to 18 years of age who have other risk factors

Nursing Mothers

Breastfeeding is not recommended during treatment with Tramadol + Acetaminophen.

Neonatal Opioid Withdrawal Syndrome

Prolonged use during pregnancy can result in withdrawal in the neonate.

Risks of Interactions with Drugs Affecting Cytochrome P450 Isoenzymes

The effects of concomitant use or discontinuation of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors on levels of tramadol and M1 from Tramadol + Acetaminophen are complex. Careful consideration is required.

Risks of Concomitant Use or Discontinuation of Cytochrome P450 2D6 Inhibitors

The concomitant use with all cytochrome P450 2D6 inhibitors (e.g., amiodarone, quinidine) may result in an increase in tramadol plasma levels and a decrease in the levels of the active metabolite, M1. The effect of increased tramadol levels may be an increased risk for serious adverse events including seizures and serotonin syndrome.

Cytochrome P450 3A4 Interaction

The concomitant use with cytochrome P450 3A4 inhibitors, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir) or discontinuation of a cytochrome P450 3A4 inducer such as rifampin, carbamazepine, and phenytoin, may result in an increase in tramadol plasma concentrations, which could increase or prolong adverse reactions, increase the risk for serious adverse events.

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

Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Profound sedation, respiratory depression, coma, and death may result from the concomitant use with benzodiazepines or other CNS depressants. Keep concomitant use reserve for patients, in whom alternative treatment options are inadequate and use lowest initial dose.

Serotonin Syndrome Risk

Serotonin syndrome, a potentially life-threatening condition, is known to occur with the use of tramadol, including Tramadol + Acetaminophen, during concomitant use with serotonergic drugs including SSRIs, SNRIs, TCAs, triptans, 5-HT3 receptor antagonists, drugs affecting serotonergic neurotransmitter system (e.g., mirtazapine, trazodone), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), and drugs that impair metabolism of serotonin (including MAO inhibitors, and linezolid). This may occur within the recommended dosage range. Discontinue Tramadol + Acetaminophen if serotonin syndrome is suspected.

Increased Risk of Seizures

Seizure risk is increased with doses of tramadol above the recommended range. And with Concomitant use with drugs like SSRIs, SNRIs, TCAs, Anorectics and other tricyclic compounds (e.g., cyclobenzaprine, promethazine, etc.), Other opioids, MAO inhibitors, Neuroleptics etc.
Risk of seizures 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.

Suicide Risk

Do not prescribe Tramadol + Acetaminophen for patients who are suicidal or addiction-prone. Consideration should be given to the use of non-narcotic analgesics in patients who are suicidal or depressed.

Adrenal Insufficiency

Adrenal insufficiency is known to occur with opioid use, more often following greater than one month of use.

Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

The use of Tramadol + Acetaminophen in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.
Monitor such patients closely, particularly when initiating and titrating Tramadol + Acetaminophen and when it is given concomitantly with other drugs that depress respiration. Alternatively, consider the use of non-opioid analgesics in these patients.

Severe Hypotension

Tramadol + Acetaminophen may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. Monitor these patients for hypotension. Avoid use in patients with circulatory shock.

Risk of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness

Tramadol + Acetaminophen may reduce respiratory drive, and the resultant CO_2 retention can further increase intracranial pressure.
Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use in patients with impaired consciousness or coma.

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.

Risk of Use in Patients with Gastrointestinal Conditions

Contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus. It may cause spasm of the sphincter of Oddi.

Anaphylaxis and Other Hypersensitivity Reactions

Serious and rarely fatal anaphylactic reactions are known to occur in patients receiving therapy with tramadol. When these events do occur it is often following the first dose.

Increased Risk of Hepatotoxicity with Concomitant Use of Other Acetaminophen-containing Products

It should not be used concomitantly with other acetaminophen containing products.

Withdrawal

When discontinuing Tramadol + Acetaminophen in a physically dependent patient, gradually

taper the dosage. Rapid tapering of dose may lead to a withdrawal syndrome and return of pain.

Drug Interactions

Clinically Significant Drug Interactions with Tramadol + Acetaminophen

Inhibitors of CYP2D6	
Clinical Impact and Intervention.	If concomitant use of a CYP2D6 inhibitor is necessary, follow patients closely for adverse reactions due to increase plasma levels. e.g. Quinidine, fluoxetine, paroxetine and bupropion
Inhibitors of CYP3A4	
Clinical Impact and Intervention:	If concomitant use is necessary, consider dosage reduction of Tramadol + Acetaminophen until stable drug effects are achieved. Follow patients closely for adverse reactions. e.g. Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), protease inhibitors (e.g., ritonavir)
CYP3A4 Inducers	
Clinical Impact and Intervention:	If concomitant use is necessary, consider increasing the Tramadol + Acetaminophen dosage until stable drug effects are achieved. Follow patients for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider Tramadol + Acetaminophen dosage reduction and monitor for adverse reactions. Concomitant administration with carbamazepine is not recommended.
Examples:	Rifampin, carbamazepine, phenytoin
Benzodiazepines and Other Central Nervous System (CNS) Depressants	
Clinical Impact:	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.
Intervention:	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation.
Examples:	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.
Serotonergic Drugs	
Clinical Impact:	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
Intervention:	If concomitant use is warranted, carefully observe the patient. Discontinue treatment if serotonin syndrome is suspected.
Examples:	SSRIs, SNRIs, TCAs, triptans, 5-HT3 receptor antagonists, and drugs that affect the serotonin neurotransmitter system, certain muscle relaxants, MAO inhibitors.
Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact:	MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma)
Intervention:	Do not use in patients taking MAOIs or within 14 days of stopping such treatment.
Examples:	phenelzine, tranylcypromine, linezolid
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
Clinical Impact:	May reduce the analgesic effect of Tramadol + Acetaminophen and/or precipitate withdrawal symptoms.
Intervention:	Avoid concomitant use.
Examples:	butorphanol, nalbuphine, pentazocine, buprenorphine
Muscle Relaxants	
Clinical Impact:	Tramadol may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Intervention:	Monitor patients for signs and decrease the dosage and/or the muscle relaxant as necessary.
Diuretics	
Clinical Impact:	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention:	Monitor patients for signs
Anticholinergic Drugs	
Clinical Impact:	Concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention:	Monitor patients for signs
Digoxin	
Clinical Impact:	Rare reports of digoxin toxicity.
Intervention:	Follow patients for signs of digoxin toxicity and adjust dosage of digoxin as needed.
Warfarin	
Clinical Impact:	Rare reports of alteration of warfarin effect, including elevation of prothrombin times.
Intervention:	Monitor prothrombin time in patients on warfarin

Pregnancy and Breastfeeding

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome.

Tramadol+Acetaminophen is not recommended for obstetrical preoperative medication or for post-delivery analgesia in nursing mothers. Tramadol and its metabolite, *O*-desmethyltramadol (M1), are present in human milk.

Advise patients that breastfeeding is not recommended.

Effects on ability to drive and use machines

Inform patients that Tramadol + Acetaminophen may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication.

Adverse Reactions

Tabulated list of adverse reactions

	Very common	**Common**
Psychiatric disorders		Confessional state, mood altered, anxiety, nervousness, euphoric mood, sleep disorders
Nervous system disorders	dizziness, somnolence	headache, trembling
Gastrointestinal disorders	nausea	vomiting, constipation, dry mouth, diarrhea, abdominal pain, dyspepsia, flatulence
Skin and subcutaneous tissue disorders		hyperhidrosis, pruritus

*Reported in post marketing surveillance.

Tramadol

- Postural hypotension, bradycardia, collapse.
- Rare alterations of warfarin effect, including elevation of prothrombin times.
- Symptoms of withdrawal reactions

Acetaminophen

- Hypersensitivity may occur rarely

Over dosage

Symptoms of overdose from tramadol

In principle, on intoxication with tramadol, symptoms similar to those of other centrally acting analgesics (opioids) are to be expected, including miosis, vomiting, cardiovascular collapse, consciousness disorders up to coma, convulsions and respiratory depression.

Symptoms of overdose from Acetaminophen

In the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. In severe poisoning (7.5-10 g), hepatic failure may progress to encephalopathy, coma and death. Acute tubular necrosis, arrhythmias and pancreatitis may develop.

Emergency treatment

• Transfer immediately to a specialised unit, maintain respiratory and circulatory functions.
• Take a blood sample to measure plasma concentration of Acetaminophen and tramadol.
• Perform hepatic tests at the start (of overdose) and repeat every 24 hours.
• Empty the stomach by causing the patient to vomit (when the patient is conscious) by irritation or gastric lavage.
• Take Supportive measures, Naloxone should be used to reverse respiratory depression; fits can be controlled with diazepam.
• Tramadol is minimally eliminated from the serum by haemodialysis or haemofiltration..

PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Analgesics, opioids in combination with non-opioid analgesics, tramadol and Acetaminophen, ATC code: N02AJ13.

Mechanism of action:

Tramadol is an opioid analgesic that acts on the central nervous system. Tramadol is pure nonselective agonists of the μ, δ, and κ opioid receptors with a higher affinity for the μ receptors. Other mechanisms which contribute to its analgesic effect are inhibition of neuronal reuptake of noradrenaline and enhancement of serotonin release. Tramadol has an antitussive effect. Unlike morphine, a broad range of analgesic doses of tramadol has no respiratory depressant effect.

The precise mechanism of the analgesic properties of Acetaminophen is unknown and may involve central and peripheral effects.

Tramadol hydrochloride + Acetaminophen is positioned as a step II analgesic in the WHO pain ladder and should be utilized accordingly by the physician.

Pharmacokinetic properties

Absorption

The absolute bioavailability of tramadol from Tramadol + Acetaminophen tablets has not been evaluated. Tramadol has a mean absolute bioavailability of approximately 75% following administration of a single 100 mg oral dose of tramadol tablets. Tramadol has a slower absorption and longer half-life when compared to acetaminophen.

Upon multiple oral dosing to steady state, however, the bioavailability of tramadol and metabolite M1 is lower for the combination tablets compared to tramadol administered alone.

Peak plasma concentrations of acetaminophen occur within one hour and are not affected by co-administration with tramadol.

Distribution

The volume of distribution of tramadol was 2.6 and 2.9 L/kg in male and female individuals, respectively, following a 100 mg intravenous dose. Plasma protein binding is ~ 20% and binding also appears to be independent of concentration up to 10 mcg/mL.

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

Tramadol is eliminated primarily through metabolism by the liver and the metabolites are eliminated primarily by the kidneys. The mean (SD) apparent total clearance of tramadol after a single 37.5 mg dose is 588 (226) mL/min for the (+) isomer and 736 (244) mL/min for the (-) isomer. The plasma elimination half-lives of racemic tramadol and M1 are approximately 5-6 and 7 hours, respectively, after administration of Tramadol + Acetaminophen. The apparent plasma elimination half-life of racemic tramadol increased to 7-9 hours upon multiple dosing of Tramadol + Acetaminophen.

The half-life of acetaminophen is about 2 to 3 hours in adults. Acetaminophen is primarily metabolized in the liver by first-order kinetics. 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.

Excretion

Approximately 30% of the tramadol dose is excreted in the urine as unchanged drug, whereas 60% of the dose is excreted as metabolites.

Less than 9% of acetaminophen is excreted unchanged in the urine.

PHARMACEUTICAL INFORMATION

Shelf life

2 years

Special Precautions for storage

To be sold on the prescription of a registered medical practitioner only.
Avoid exposure to heat and light.
Store below 30 C.
Keep out of the reach of children.

Nature and contents of container / Packaging

TRACETOL(Tramadol hydrochloride + Acetaminophen) 37.5/325 mg tablets are available in a blister pack of 10's (1 X 10's).

Manufactured By

ASPIN
An OBS Group Company
Aspin Pharma (Pvt.) Ltd.
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