TRAMADOL HCl
PARACETAMOL

DUOCETZ

37.5 mg/325 mg Film-Coated Tablet

Analgesic

MEGA We care

℞

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DUOCETZ
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FORMULATION

Each film-coated tablet contains:

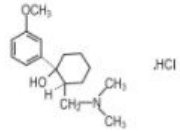
Paracetamol, EP	325 mg
Tramadol HCl, BP	37.5 mg

DESCRIPTION

TRAMADOL HCl + PARACETAMOL (DUOCETZ) combines two

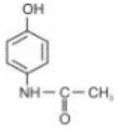
analgesics, paracetamol 325 mg and tramadol HCl 37.5 mg.

The chemical name for tramadol hydrochloride is (±)cis-2-[(dimethylamino) methyl]-1- (3-methoxy phenyl) 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 paracetamol is N-acetyl-aminophenol (4-hydroxyacetanilide). Its structural formula is:



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

Inactive ingredients in the tablet are corn starch, povidone K30, sodium starch glycolate, microcrystalline cellulose PH 101, magnesium stearate, opadry II yellow, purified water.

TRAMADOL HCl + PARACETAMOL (DUOCETZ) is available as yellow colored, oblong film-coated tablet.

CLINICAL PHARMACOLOGY

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

Pharmacodynamics

Tramadol is a centrally acting synthetic opioid analgesic. Although its mode of action is not completely understood, 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.

Paracetamol is another centrally-acting analgesic, The exact site and mechanism of its analgesic action is not clearly defined. When evaluated in standard animal model, the combination of tramadol and paracetamol exhibited a synergistic effect.

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 paracetamol following oral administration of one tablet are shown in Table 1. Tramadol has a slower absorption and longer half-life when compared to paracetamol.

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

Parameter *	(+)-Tramadol		(-)-Tramadol		(+)-M1		(-)-M1		Paracetamol	
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)
$t_{½}$ (h)	5.1	(1.4)	4.7	(1.2)	7.8	(3.0)	6.2	(1.6)	2.5	(0.6)

* For paracetamol, C_{max} was measured as μg/mL.

Absorption

Tramadol hydrochloride has a mean absolute bioavailability of approximately 75% following administration of a single 100 mg oral dose of tramadol tablets. The mean peak plasma concentration of racemic tramadol and M1 after administration of two tramadol/

paracetamol combination tablets occurs at approximately two and three hours, respectively, post-dose.

Oral absorption of paracetamol following administration of tramadol + paracetamol is rapid and almost complete and occurs primarily in the small intestine. Peak plasma concentrations of paracetamol occur within 1 hr and are not affected by co-administration with tramadol.

Food Effects: The oral administration of tramadol + paracetamol with food has no significant effect on the peak plasma concentration or extent of absorption of either tramadol or paracetamol, so that tramadol + paracetamol can be taken independently of meal times.

Distribution

The volume of distribution of tramadol was 2 and 2.5 L/kg in male and female subjects, respectively, following a 100-mg IV dose. The binding of tramadol to human plasma proteins is approximately 20%.

Paracetamol 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 paracetamol is bound to plasma protein.

Metabolism

Plasma concentration profiles for tramadol and its M1 metabolite measured following dosing of tramadol + paracetamol in volunteers

showed no significant change compared to dosing with tramadol alone.

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. Tramadol is extensively metabolized by a number of pathways, including CYP2D6.

Paracetamol is primarily metabolized in the liver by first-order kinetics and involves 3 principle separate pathways: Conjugation with glucuronide; conjugation with sulfate; and oxidation via the cytochrome P-450 enzyme pathway.

Elimination
Tramadol and its metabolites are eliminated primarily in the kidneys. The plasma elimination half-lives of racemic tramadol and M1 are approximately 6 and 7 hrs, respectively. The plasma elimination half-life of racemic tramadol increased from approximately 6-7 hrs upon multiple dosing of tramadol + paracetamol.

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

unchanged in the urine.

Toxicology: *Preclinical safety Data: Tramadol/Paracetamol Combination:* There are no animal or laboratory studies on the combination product (tramadol and paracetamol) to evaluate carcinogenesis, mutagenesis or impairment of fertility.
No drug-related teratogenic effects were observed in the progeny of rats treated orally with the combination of tramadol and paracetamol. The tramadol + paracetamol combination product was shown to be embryotoxic and fetotoxic in rats at a maternally toxic dose (50/434 mg/kg tramadol + paracetamol) 6.3 times the maximum human dose but was not teratogenic at this dose level.

Embryo and fetal toxicity consisted of decreased fetal weights and increased supernumerary ribs. Lower and less severe maternally toxic dosages (10/87 and 25/217 mg/kg tramadol + paracetamol) did not produce embryo or fetal toxicity.

Carcinogenicity, Mutagenicity & Impairment of Fertility: Tramadol HCl: A slight but statistically significant increase in 2 common murine tumors, pulmonary and hepatic, was observed in a mouse carcinogenicity study with tramadol, particularly in aged mice (dosing orally up to 30 mg/kg for approximately 2 years, although the study was not done with maximum tolerated dose). This finding is not believed to suggest risk in humans. No such finding occurred

in a rat carcinogenicity study.
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 hamster 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.

Impairment of Fertility/Effect on Reproduction: 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 was evaluated in peri- and postnatal studies in rats. Progeny of dams receiving oral (gavage) dose levels of 50 mg/kg or greater had decreased weights, and pup survival was decreased early in lactation at 80 mg/kg (6-10 times the maximum human dose). No toxicity was observed for progeny of dams receiving 8, 10, 20, 25 or 4O mg/kg.
Maternal toxicity was observed at all dose levels of tramadol in this study, but effects on progeny were evident only at higher dose levels where maternal toxicity was more severe.

Special Populations

Renal
The pharmacokinetics of Tramadol/Paracetamol Combination Tablet (37.5 mg/325 mg) in patients with renal impairment has 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. 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/Paracetamol Combination Tablet (37.5 mg/325 mg) in patients with impaired hepatic function has not been studied. Since tramadol and paracetamol are both extensively metabolized by the liver, the use of Tramadol/Paracetamol Combination Tablet (37.5 mg/325 mg) in patients with hepatic impairment is not recommended.

A population pharmacokinetic analysis of data obtained from a clinical trial in patients with chronic pain treated with Tramadol/Paracetamol Combination Tablet (37.5 mg/325 mg) which included 55 patients between 65 and 75 years of age and 19 patients over 75 years of age, showed no significant changes in

pharmacokinetics of tramadol and paracetamol in elderly patients with normal renal and hepatic function.

Gender
Tramadol clearance was 20% higher in female subjects compared to males on four phase I studies of Tramadol/Paracetamol Combination Tablet (37.5 mg/ 325 mg) in 50 male and 34 female healthy subjects. The clinical significance of this difference is unknown.

Pediatric
Pharmacokinetics of Tramadol/Paracetamol Combination Tablet (37.5 mg/ 325 mg) has not been studied in pediatric patients below

16 years of age.

THERAPEUTIC INDICATIONS
TRAMADOL HCl + PARACETAMOL (DUOCETZ) is indicated for the management of moderate to severe pain.

DOSAGE AND ADMINISTRATION
- Adults and children over 16 years
The maximum single dose is 1 to 2 tablets every 4 to 6 hours as needed for pain relief up to a maximum of 8 tablets per day.

- Pediatric (Children below 16 years)
The safety and effectiveness has not been established.

- Elderly
No overall differences with regard to safety or pharmacokinetics were noted between subjects ≥ 65 years of age and younger subjects.
TRAMADOL HCl + PARACETAMOL (DUOCETZ) can be administered without regard to food.

CONTRAINDICATIONS
TRAMADOL HCl + PARACETAMOL (DUOCETZ) should not be administered to patients who have previously demonstrated hypersensitivity to tramadol, paracetamol, any other component of this product or opioids. It is contraindicated in any situation where

opioids are contraindicated, including acute intoxication with any of the following: alcohol, hypnotics, narcotics, centrally acting analgesics, opioids or psychotropic drugs.

PRECAUTIONS
Seizures: 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 (eg, cyclobenzaprine, promethazine, etc,), or opioids.

Administration of tramadol may enhance the seizure risk in patients taking: MAO 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 (eg, head trauma, metabolic disorders, alcohol and drug withdrawal, CNS infections). In tramadol overdose, naloxone administration may increase the risk of seizure.
Anaphylactoid Reactions: Patients with a history of anaphylactoid reactions to codeine and other opioids may be at increased risk and therefore should not receive TRAMADOL HCl + PARACETAMOL (DUOCETZ).

Respiratory Depression: Administer TRAMADOL HCl + PARACETAMOL (DUOCETZ) cautiously in patients at risk for respiratory depression. When large doses of tramadol are administered with anesthetic medications or alcohol, respiratory depression may result. Treat such cases as an overdose. If naloxone is to be administered, use cautiously because it may precipitate seizures.

Use with CNS Depressants: TRAMADOL HCl + PARACETAMOL (DUOCETZ) should be used with caution and in reduced dosages when administered to patients receiving CNS depressants eg. alcohol, opioids, anesthetic agents, phenothiazines, tranquilizers or sedative hypnotics.

Increased Intracranial Pressure or Head Trauma: TRAMADOL HCl + PARACETAMOL (DUOCETZ) should be used with caution in patients with increased intracranial pressure or head injury.

Use in Opioid-Dependent Patients: TRAMADOL HCl + PARACETAMOL (DUOCETZ) should not be used in opioid-dependent patients. Tramadol has been shown to reinitiate physical dependence in some patients that have been previously dependent on other opioids.

Use with Alcohol: Chronic heavy alcohol abusers may be at increased risk of liver toxicity from excessive paracetamol use.

Withdrawal: Withdrawal symptoms may occur if TRAMADOL HCl + PARACETAMOL (DUOCETZ) is discontinued abruptly. Panic attacks, severe anxiety, hallucinations, paresthesia, tinnitus and unusual CNS symptoms have also been rarely reported with abrupt discontinuation of tramadol HCl. Clinical experience suggests that withdrawal symptoms may be relieved by tapering the medication.

Use with MAO Inhibitors and Serotonin Reuptake Inhibitors: Use TRAMADOL HCl + PARACETAMOL (DUOCETZ) with great caution in patients taking monoamine oxidase inhibitors. Concomitant use of tramadol with MAO inhibitors or SSRIs increases the risk of adverse events, including seizure and serotonin syndrome.

Use in Renal Disease: TRAMADOL HCl + PARACETAMOL (DUOCETZ) has not been studied in patients with impaired renal function. In patients with creatinine clearances of <30 mL/min, it is recommended that the dosing interval of TRAMADOL HCl + PARACETAMOL (DUOCETZ) be increased not to exceed 2 tablets every 12 hrs.

Use in Hepatic Disease: The use of TRAMADOL HCl + PARACETAMOL (DUOCETZ) in patients with severe hepatic impairment is not recommended.

General:
The recommended dose of TRAMADOL HCl + PARACETAMOL

(DUOCETZ) should not be exceeded. TRAMADOL HCl + PARACETAMOL (DUOCETZ) should not be co-administered with other tramadol or paracetamol-containing products.
Effects on the Ability to Drive or Operate Machinery: TRAMADOL HCl + PARACETAMOL (DUOCETZ) may impair mental and physical abilities required for the performance of potentially hazardous task eg. driving car or operating machinery.

Use in pregnancy & lactation: Tramadol has been shown to cross the placenta. There are no adequate and well-controlled studies in pregnant women. Safe use in pregnancy has not been established.

TRAMADOL HCl + PARACETAMOL (DUOCETZ) is not recommended for nursing mothers because its safety in infants and newborns has not been studied.

Drug Interactions
Use with MAO inhibitors and SSRIs: Interaction with MAO inhibitors have been reported for some centrally-acting drugs (see precautions).

Use with Carbamazepine: Concomitant administration of tramadol HCl and carbamazepine causes a significant increase in tramadol metabolism. Patients taking carbamazepine may have a significantly reduced analgesic effect from the tramadol component

of TRAMADOL HCl + PARACETAMOL (DUOCETZ).

Use with Quinidine: Tramadol is metabolized to M1 by CYP2D6. Concomitant administration of quinidine and tramadol results in increased concentrations of tramadol. The clinical consequences of these findings are unknown.

Use with Warfarin-Like Compounds: As medically appropriate, periodic evaluation of prothrombin time should be performed when TRAMADOL HCl + PARACETAMOL (DUOCETZ) and these agents are administered concurrently due to reports of increased International Normalized Ratio (INR) in some patients.

Use with Inhibitors of CYP2D6: In vitro interaction studies in human liver microsomes indicate that concomitant administration with inhibitors of CYP2D6 eg. fluoxetine, paroxetine and amitriptyline could result in some inhibition of the metabolism of tramadol.

Use with Cimetidine: Concomitant administration of TRAMADOL HCl + PARACETAMOL (DUOCETZ) and cimetidine has not been studied. Concomitant administration of tramadol and cimetidine does not result in clinically significant changes in tramadol pharmacokinetics.

Incompatibilities: None known.

Use in pregnancy & lactation: Tramadol has been shown to cross the placenta. There are no adequate and well-controlled studies in pregnant women. Safe use in pregnancy not been established.
TRAMADOL HCl + PARACETAMOL (DUOCETZ) is not recommended for nursing mothers because its safety in infants and newborns has not been studied.
Preg Safety (US)

Category C: Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the

potential benefit justifies the potential risk to the fetus.

ADVERSE REACTIONS
The most frequently reported events were in the central nervous system and gastrointestinal system.
The most common reported events were nausea, dizziness and somnolence.
In addition, the following effects have been frequently observed, though the frequency is generally lower: Body as a Whole: Asthenia, fatigue, hot flushes.
Central and Peripheral Nervous System: Headache, tremor.
Gastrointestinal System: Abdominal pain, constipation, diarrhea, dyspepsia, flatulence, dry mouth, vomiting.

Psychiatric Disorders: Anorexia, anxiety, confusion, euphoria, insomnia, nervousness.
Skin and Appendages: Pruritus, rash, increased sweating.
Uncommon reported clinically significant adverse experiences with at least a possible causal link to tramadol + paracetamol include:
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, paresthesia, 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: Liver test abnormalities.
Metabolic and Nutritional Disorders: Decreased weight.
Psychiatric Disorders: Amnesia, depersonalization, depression, drug abuse, emotional lability, hallucination, impotence, bad dreams, 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 in Clinical Trials or Post-Marketing Reports with Tramadol HCl: Other events which have been reported with the use of tramadol products include: Orthostatic hypotension, hypotension, allergic reactions (including anaphylaxis and urticaria, Stevens-Johnson syndrome/TENS), cognitive dysfunction, suicidal tendency and hepatitis. Reported laboratory abnormalities include elevated creatinine. Serotonin syndrome (whose symptoms may include fever, excitation, shivering and agitation) has been reported with tramadol when used concomitantly with other serotonergic agents eg, SSRIs and MAO inhibitors. Post-marketing surveillance of tramadol has revealed rare alterations of warfarin effect, including elevation of prothrombin

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times.
Other Clinically Significant Adverse Experiences Previously Reported in Clinical Trials or Post-Marketing Reports with Paracetamol Allergic reactions (primarily skin rash) or reports of hypersensitivity secondary to paracetamol are rare and generally controlled by discontinuation of the drug, and when necessary symptomatic treatment. There have been several reports that suggest that paracetamol may produce hypoprothrombinemia when administered with warfarin-like compounds. In other studies, prothrombin time did not change.

OVERDOSE
TRAMADOL HCl + PARACETAMOL (DUOCETZ) is a combination

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product. The clinical presentation of overdose may include the signs and symptoms of tramadol toxicity, paracetamol toxicity or both. The initial symptoms of tramadol overdosage may include respiratory depression and or seizures.
The initial symptoms seen within the first 24 hrs following a paracetamol overdose may include: Gastrointestinal irritability, anorexia, nausea, vomiting, malaise, pallor and diaphoresis.

Human Experience: Tramadol: Serious potential consequences of overdosage of the tramadol component are respiratory depression, lethargy, coma, seizure, cardiac arrest and death.
Paracetamol: Paracetamol in massive overdosage may cause hepatic toxicity in some patients. Early symptoms following a

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potentially hepatotoxic overdosage may include: Gastrointestinal irritability, anorexia, nausea, vomiting, malaise, pallor, and diaphoresis.
Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48-72 hrs post-ingestion.

Treatment: A single or multiple overdose of tramadol + paracetamol may be a potentially lethal polydrug overdose, and appropriate expert consultation, if available, is recommended.
While naloxone will reverse some, but not all, symptoms caused by overdosage with tramadol, the risk of seizures is also increased with naloxone administration. Based on experience with tramadol, hemodialysis is not expected to be helpful in an overdose because

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it removes <7% of the administered dose in a 4-hr dialysis period.
In treating an overdosage of tramadol + paracetamol, primary attention should be given to maintaining adequate ventilation along with general supportive treatment. Measures should be taken to reduce drug absorption. Vomiting should be induced mechanically, or with syrup of ipecac, if the patient is alert (adequate pharyngeal and laryngeal reflexes). Oral activated charcoal (1 g/kg) should follow gastric emptying. The 1st dose should be accompanied by an appropriate cathartic. If repeated doses are used, the cathartic might be included with alternate doses as required. Hypotension is usually hypovolemic in etiology and should respond to fluids. Vasopressors and other supportive measures should be employed as indicated. A cuffed endotracheal tube should be inserted before

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gastric lavage of the unconscious patient and, when necessary to provide assisted respiration.

In adult and pediatric patients, any individual presenting with an unknown amount of paracetamol ingested or with questionable or unreliable history about the time of ingestion should have a plasma paracetamol level drawn and be treated with acetylcysteine. If an assay cannot be obtained and the estimated paracetamol ingestion exceeds 7.5-10 g for adults and adolescents or 150 mg/kg for children, dosing with N-acetylcysteine should be initiated and continued for a full course of therapy.

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STORAGE:
Store at temperatures not exceeding 30°C, in a dry place.
Keep away from direct sunlight.
Keep out of reach of children.

AVAILABILITY:
Alu/Clear PVC/PVDC Blister Pack x 10's (Box of 30's)

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For suspected adverse drug reaction, report to the FDA:
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