

# DUOCETZ

**Paracetamol 325 mg + Tramadol HCl 37.5 mg**  
**Film Coated Tablet**

**1. NAME OF THE MEDICINAL PRODUCT**

DUOCETZ  
 Paracetamol 325 mg + Tramadol HCl 37.5 mg Film Coated Tablet

**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each film-coated tablet contains:  
 Paracetamol 325 mg  
 Tramadol HCl 37.5 mg  
 For the full list of excipients, see section 6.1

**3. PHARMACEUTICAL FORM**

Film coated tablets  
 DUOCETZ is available as Odorless, yellow colored, oblong film coated tablets

**4. CLINICAL PARTICULARS**

**4.1 Therapeutic indications**

DUOCETZ is indicated for the management of moderate to severe pain.

**4.2 Posology and method of administration**

**Posology**

**Adults and children 16 years of age and over**

The maximum single dose of DUOCETZ is 1 to 2 tablets every 4 to 6 hours as needed for pain relief up to a maximum of 8 tablets per day. The lowest effective dose should be used for the shortest period of time.

**Adults and adolescents (12 years and older)**

DUOCETZ is not approved for use in patients below 12 years old.

**Paediatric population**

The safety and efficacy of DUOCETZ has not been studied in the paediatrics population. Therefore, use of DUOCETZ is not recommended in patients under 12 years of age.

**Treatment withdrawal**

Do not stop use of DUOCETZ abruptly. Withdrawal symptoms may be relieved by tapering the medication (see 4.4 Special warnings and precautions for use – Treatment withdrawal).

**Special populations**

**Children below 16 years of age**

The use of DUOCETZ is contraindicated in children below 12 years of age (see 4.3 Contraindications).

The safety and effectiveness of DUOCETZ in children aged 12 to below 16 years of age has not been established (see 4.3 Contraindications and 4.4 Special warnings and precautions for use - Other risk factors for life threatening respiratory depression in children).

**Elderly (65 years of age and older)**

No overall differences with regard to safety or pharmacokinetics were noted between subjects ≥65 years of age and younger subjects. However, 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.

**Renal impairment**

In patients with creatinine clearances of less than 30 mL/min, it is recommended that the dosing interval of DUOCETZ be increased not to exceed 2 tablets every 12 hours.

**Hepatic impairment**

The use of DUOCETZ in patients with severe hepatic impairment is not recommended.

**Method of administration**

DUOCETZ tablets are for oral administration.  
 DUOCETZ can be administered without regard to food.

**4.3 Contraindications**

DUOCETZ is contraindicated:

- in all children younger than 12 years of age.
- children younger than 18 years to treat pain after surgery to remove the tonsils and/or adenoids
- in patients who have previously demonstrated hypersensitivity to tramadol, paracetamol, any other component of this product or opioids.
- in cases of acute intoxication with alcohol, hypnotics, narcotics, centrally acting analgesics, opioids or psychotropic drugs.
- in patients using monoamine oxidase inhibitors (MAOIs) concurrently or within the last 14 days.
- adolescents between 12 and 18 years who are obese or have conditions such as obstructive sleep apnea or severe lung disease, which may increase the risk of serious breathing problems.
- in patients with significant respiratory depression (see 4.4 Special warnings and precautions for use).

**4.4 Special warning and precautions for use**

**WARNING**

This preparation contains PARACETAMOL.  
 Do not take any other paracetamol containing medicines at the same time.

**Allergy alert:** Paracetamol may cause severe skin reactions. Symptoms may include skin reddening, blisters or rash. These could be signs of a serious condition. If these reactions occur, stop use and seek medical assistance right away

**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 serotonergic drugs including: selective serotonin reuptake inhibitors (SSRI antidepressants or anorectics), tricyclic antidepressants (TCAs), and other tricyclic compounds (e.g., cyclobenzaprine, promethazine, etc.), or opioids.

Administration of tramadol may enhance the seizure risk in patients taking: monoamine oxidase inhibitors (MAOIs), 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, central nervous system [CNS] infections). In tramadol overdose, naloxone administration may increase the risk of seizure.

**Anaphylactic reactions**

Patients with a history of anaphylactic reactions to codeine and other opioids may be at increased risk and therefore should not receive DUOCETZ. Serious and rarely fatal anaphylactic reactions have been reported in patients receiving therapy with tramadol. Advise patients to seek immediate medical attention if they experience any symptoms of a hypersensitivity reaction.

**Paediatrics population**

The safety and efficacy of DUOCETZ has not been studied in the paediatrics population. Therefore, use of DUOCETZ is not recommended in patients under 12 years of age.

**Respiratory depression**

Patients with significant respiratory depression (see 4.3 Contraindications) or acute, severe bronchial asthma are at increased risk of life-threatening respiratory depression when treated with opioids. Administer DUOCETZ cautiously in patients at risk for respiratory depression, including patients with substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression, as in these patients, even therapeutic doses of DUOCETZ may decrease respiratory drive to the point of apnea. 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.

Opioids can cause sleep-related breathing disorders such as sleep apnea syndromes (including central sleep apnea [CSA]) and hypoxia (including sleep-related hypoxia) (see 4.8 Undesirable effects).

Opioid use increases the risk of CSA in a dose-dependent fashion. Evaluate patients on an ongoing basis for the onset of a new sleep apnea, or a worsening of an existing sleep apnea. In these patients, consider reducing or stopping the opioid treatment if appropriate, using best practices for tapering of opioids. (see 4.2 Posology and method of administration, Treatment withdrawal; 4.4 Special warnings and precautions for use, Treatment withdrawal).

**Cytochromes P450 (CYP) 2D6 ultra-rapid metabolism**

Some individuals may be CYP2D6 ultra-rapid metabolizers. These individuals convert tramadol more rapidly than other people into its more potent opioid metabolites O-desmethyltramadol (M1). This rapid conversion could result in higher than expected opioid-like side effects including life-threatening respiratory depression. (see section 4.9 Overdose - Symptoms and signs, Tramadol) The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 0.5 to 1% in Chinese, Japanese and Hispanics, 1 to 10% in Caucasians, 3% in African Americans, and 16-28% in North Africans, Ethiopians, and Arabs. Data are not available for other ethnic groups.

Alternative medication, dose reduction and/or increased monitoring for signs of tramadol overdose, such as respiratory depression is recommended in patients known to be CYP2D6 ultra-rapid metabolizers. (see 5.2 Pharmacokinetic Properties). Even at labeled dosage regimens, individuals who are ultra-rapid metabolizers may have life-threatening or fatal respiratory depression or experience signs of overdose (such as extreme sleepiness, confusion, or shallow breathing) (see 4.9 Overdose-Symptoms and signs, Tramadol).

**Other risk factors for life-threatening respiratory depression in children**

Life-threatening respiratory depression and death have occurred in children who received tramadol. Tramadol is subject to variability in metabolism based upon CYP2D6 genotype, which can lead to increased exposure to an active metabolite. Based upon post-marketing reports with tramadol, children younger than 12 years of age may be more susceptible to the respiratory depressant effects of tramadol (see 4.3 Contraindications). Furthermore, children with obstructive sleep apnea who are treated with opioids for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to their respiratory depressant effect (see 4.3 Contraindications). Because of the risk of life-threatening respiratory depression and death, avoid the use of DUOCETZ in adolescents younger than 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of tramadol. Risk factors include conditions associated with hypoventilation such as postoperative status, obstructive sleep apnea and concomitant use of other medications that cause respiratory depression.

As with adults, when prescribing opioids for adolescents, healthcare providers should choose the lowest effective dose for the shortest period of time and inform patients and caregivers about these risks and the signs of opioid overdose (see 4.2 Posology and method of administration and 4.9 Overdose - Symptoms and signs, Tramadol).

**Use with central nervous system (CNS) depressants, including alcohol**

The concomitant use of tramadol with CNS depressants, including alcohol, may cause additive CNS depressant effects, including profound sedation and respiratory depression. DUOCETZ should be used with caution and in reduced dosages when administered to patients receiving CNS depressants. (see 4.5 Interaction with other medicinal products and other forms of interaction)

**Increased intracranial pressure or head trauma**

DUOCETZ should be used with caution in patients with increased intracranial pressure or head injury.

**Drug dependence and potential for abuse**

A portion of the analgesic effect is attributable to the binding of the active ingredient, tramadol, to the mu-opioid receptor. Upon repeated administration of opioids, tolerance, physical dependence, and psychological dependence may develop, even at recommended dosages. Assess each patient's risk for opioid dependence and abuse prior to prescribing DUOCETZ and monitor all patients receiving DUOCETZ for development of these behaviors. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). DUOCETZ should not be used in opioid-dependent patients. Tramadol has been shown to re-initiate physical dependence in some patients that have been previously dependent on other opioids.

**Increased risk of hepatotoxicity with alcohol use**

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

**Treatment withdrawal**

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

**Serotonin syndrome with concomitant use of serotonergic drugs**

Use DUOCETZ with great caution in patients taking serotonergic drugs including SSRIs. Concomitant use of tramadol with serotonergic drugs including SSRIs increases the risk of adverse events, including seizure and serotonin syndrome (see 4.5 Interaction with other medicinal products and other forms of interaction).

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concurrent use of DUOCETZ with serotonergic drugs (see 4.5 Interaction with other medicinal products and other forms of interaction). This may occur within the recommended dosage range.

Serotonin syndrome symptoms may include mental-status changes (e.g. agitation, hallucinations, coma), autonomic instability (e.g. tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g. hyper-reflexia, incoordination) and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea) and can be fatal (see 4.5 Interaction with other medicinal products and other forms of interaction). The onset of symptoms generally occurs within several hours to a few days of concomitant use, but may occur later than that. Discontinue DUOCETZ if serotonin syndrome is suspected.

**Adrenal insufficiency**

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, decreased appetite, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement dosing of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

**Sexual function/ reproduction**

Long term use of opioids may be associated with decreased sex hormone levels and symptoms such as low libido, erectile dysfunction, or infertility (see Postmarketing Experience).

**Renal impairment**

DUOCETZ has not been studied in patients with impaired renal function. In patients with creatinine clearances of less than 30 mL/min, it is recommended that the dosing interval of DUOCETZ be increased not to exceed 2 tablets every 12 hours. DUOCETZ is not recommended in patients with creatinine clearance of less than 10 mL/min.

**Hepatic impairment**

The use of DUOCETZ in patients with severe hepatic impairment is not recommended.

**Serious Skin Reactions**

Rarely, paracetamol 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.

**Hyponatremia**

Hyponatremia has been reported very rarely with the use of DUOCETZ usually in patients with predisposing risk factors, such as elderly patients and/or patients using concomitant medications that may cause hyponatremia. In some reports, this hyponatremia appeared to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and resolved with discontinuation of DUOCETZ and appropriate treatment (e.g. fluid restriction). During DUOCETZ treatment, monitoring for signs and symptoms of hyponatremia is recommended for patients with predisposing risk factors.

**Gastrointestinal disorders**

Patients with disorders of the biliary tract or a history of biliary surgery should be monitored for potential development of acute pancreatitis.

**Hyperprolactinemia**

Long term opioid use may be associated with increased prolactin levels and decreased sex hormone levels. Symptoms may include galactorrhea, gynaecomastia, impotence, decreased libido, infertility, or amenorrhea. If hyperprolactinemia is suspected, appropriate laboratory testing is recommended and discontinuation of treatment with DUOCETZ should be considered.

**Precautions general**

The recommended dose of DUOCETZ should not be exceeded.

DUOCETZ should not be co-administered with other tramadol or paracetamol-containing products.

**Risks from Concomitant Use with Benzodiazepines**

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of DUOCETZ with benzodiazepines. Observational studies have demonstrated that concomitant use of opioids and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

If the decision is made to newly prescribe a benzodiazepine and an opioid together, prescribe the lowest effective dosages and minimum durations of concomitant use.

If the decision is made to prescribe a benzodiazepine in a patient already receiving an opioid, prescribe a lower initial dose of the benzodiazepine than indicated in the absence of an opioid, and titrate based on clinical response.

If the decision is made to prescribe an opioid in a patient already taking a benzodiazepine, prescribe a lower initial dose of the opioid, and titrate based on clinical response.

Follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when DUOCETZ is used with benzodiazepines. Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine have been determined. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of benzodiazepines (see 4.5 Interaction with other medicinal products and other forms of interaction).

**High anion gap metabolic acidosis**

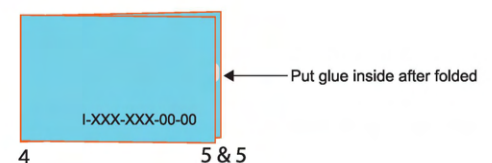
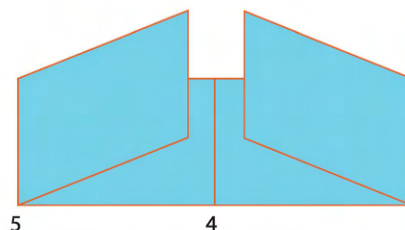
Cases of high anion gap metabolic acidosis (HAGMA) due to pyroglutamic acidosis have been reported in patients with severe illness such as severe renal impairment and sepsis, or in patients with malnutrition or other sources of glutathione deficiency (e.g. chronic alcoholism) who were treated with paracetamol at therapeutic dose for a prolonged period or a combination of paracetamol and flucoxacillin. If HAGMA due to pyroglutamic acidosis is suspected, prompt discontinuation of paracetamol and close monitoring is recommended. The measurement of urinary 5-oxoproline may be useful to identify pyroglutamic acidosis as underlying cause of HAGMA in patients with multiple risk factors.

**4.5 Interactions with other medicinal products and other forms of Interactions**

Based on its pharmacodynamic and pharmacokinetic properties, DUOCETZ exhibits a potential for pharmacodynamic and pharmacokinetic interactions. The various types of interaction, associated general recommendations and lists of examples are described below. These lists of examples are not comprehensive and therefore it is recommended that the label of each drug that is co-administered with DUOCETZ be consulted for information related to interaction pathways, potential risks, and specific actions to be taken with regards to co-administration.

**Table 1. Drug Interactions with DUOCETZ**

Inhibitors of CYP2D6	
<b>Mechanism:</b>	Enzyme inhibition resulting in decreased rate of metabolism of tramadol
<b>Clinical Impact:</b>	The concomitant use of DUOCETZ and CYP2D6 inhibitors may result in an increase in the plasma concentration of tramadol and a decrease in the plasma concentration of M1, particularly when an inhibitor is added after a stable dose of DUOCETZ is achieved. Since M1 is a more potent μ-opioid agonist, decreased M1 exposure could result in decreased therapeutic effects, and may result in signs and symptoms of opioid withdrawal in patients who had developed physical dependence to tramadol. Increased tramadol exposure can result in increased or prolonged therapeutic effects and increased risk for serious adverse events including seizures and serotonin syndrome.  After stopping an inhibitor of CYP2D6, as the effects of the inhibitor decline, the tramadol plasma concentration will decrease and the M1 plasma concentration will increase which could increase or prolong therapeutic effects but also increase adverse reactions related to opioid toxicity, and may cause potentially fatal respiratory depression (see 5. Pharmacological Properties – 5.2 Pharmacokinetic properties).
<b>Intervention:</b>	If concomitant use of an inhibitor of CYP2D6 is necessary, follow patients closely for adverse reactions including opioid withdrawal, seizures and serotonin syndrome (see 4.4 Special warnings and precautions for use – CYP2D6 ultra rapid metabolism of tramadol).  If an inhibitor of CYP2D6 is discontinued, consider lowering DUOCETZ dosage until stable drug effects are achieved. Follow patients closely for adverse events including respiratory depression and sedation.
<b>Examples</b>	Quinidine, fluoxetine, paroxetine, amitriptyline and bupropion
Inhibitors of CYP3A4	
<b>Mechanism:</b>	Enzyme inhibition resulting in decreased rate of metabolism of tramadol
<b>Clinical Impact:</b>	The concomitant use of DUOCETZ and an inhibitor of CYP3A4 can increase the plasma concentration of tramadol and may result in a greater amount of metabolism via CYP2D6 and greater levels of M1.  After stopping an inhibitor of CYP3A4, as the effects of the inhibitor decline, the tramadol plasma concentration will decrease, resulting in decreased opioid efficacy and possibly signs and symptoms of opioid withdrawal in patients who had developed physical dependence to tramadol.
<b>Intervention:</b>	If concomitant use is necessary, consider dosage reduction of DUOCETZ until stable drug effects are achieved. Follow patients closely for increased risk of serious adverse events including seizures and serotonin syndrome, and adverse reactions related to opioid toxicity including potentially fatal respiratory depression, particularly when an inhibitor is added after a stable dose of DUOCETZ is achieved.  If an inhibitor of CYP3A4 is discontinued, consider increasing the DUOCETZ dosage until stable drug effects are achieved and follow patients for signs and symptoms of opioid withdrawal.
<b>Examples</b>	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), protease inhibitors (e.g., ritonavir)
CYP3A4 Inducers	
<b>Mechanism:</b>	Enzyme induction resulting in increased rate of metabolism of tramadol.
<b>Clinical Impact:</b>	The concomitant use of DUOCETZ and an inducer of CYP3A4 can decrease the plasma concentration of tramadol, resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to tramadol.



For submit in Malaysia  
 Artwork of insert "DUOCETZ" (PCL) code *RI-U501-H14-00-02*

Size : 250 x 320 mm

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<p>After stopping an inducer of CYP3A4, as the effects of the inducer decline, the tramadol plasma concentration will increase, which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression, seizures and serotonin syndrome.</p> <p><b>Intervention:</b> If concomitant use is necessary, consider increasing the DUOCETZ dosage until stable drug effects are achieved. Follow patients for signs of opioid withdrawal.</p> <p>If an inducer of CYP3A4 is discontinued, consider DUOCETZ dosage reduction and monitor for seizures and serotonin syndrome, and signs of sedation and respiratory depression.</p> <p>Patients taking carbamazepine, an inducer of CYP3A4, 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 DUOCETZ and carbamazepine is not recommended.</p> <p><b>Examples:</b> Rifampin, carbamazepine, phenytoin</p> <p><b>Benzodiazepines and Other Central Nervous System (CNS) Depressants including alcohol</b></p> <p><b>Mechanism:</b> Additive or synergistic pharmacodynamic effect</p> <p><b>Clinical Impact:</b> The concomitant use of tramadol with central nervous system depressants, such as benzodiazepines and other sedatives/hypnotics, anesthetic agents, phenothiazines, tranquilizers, opioids or alcohol, may produce additive CNS depressant effects, such as profound sedation and respiratory depression. If concomitant use of DUOCETZ with a CNS depressant is clinically necessary, prescribe the lowest effective dosages and minimum duration for both drugs, and follow patients closely for signs of respiratory depression. Due to additive pharmacodynamic effect, the concomitant use of opioids with benzodiazepines increase the risk of respiratory depression, profound sedation, coma, and death.</p> <p>The concomitant use of opioids and benzodiazepines increases the risk of respiratory depression because of actions at different receptor sites in the central nervous system that control respiration. Opioids interact primarily at <math>\mu</math>-receptors, and benzodiazepines interact at GABA<sub>A</sub> sites. When opioids and benzodiazepines are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists.</p> <p><b>Intervention:</b> Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate (see 4.4 Special warnings and precautions for use).</p> <p>Limit dosages and durations of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation.</p> <p><b>Examples:</b> Benzodiazepines and other sedatives/hypnotics, tranquilizers, muscle relaxants, general anesthetics, other opioids, alcohol.</p> <p><b>Serotonergic Drugs</b></p> <p><b>Mechanism:</b> Additive or synergistic pharmacodynamic effect</p> <p><b>Clinical Impact:</b> The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.</p> <p><b>Intervention:</b> If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue DUOCETZ if serotonin syndrome is suspected.</p> <p><b>Examples:</b> Examples of serotonergic drugs are selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT<sub>3</sub> receptor anti-gonists, drugs that affect the serotonin neurotransmitter system (e.g. mifepristone, trazodone, tramadol) monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue) (see 4.4 Special warnings and precautions for use).</p> <p><b>Monoamine Oxidase Inhibitors (MAOIs)</b></p> <p><b>Mechanism:</b> Additive or synergistic pharmacodynamic effect</p> <p><b>Clinical Impact:</b> The concomitant use of DUOCETZ with MAOIs, or use within 14 days of their discontinuation, is contraindicated due to the increased risk of seizures and serotonin syndrome (see 4.3 Contraindications).</p> <p>MAOI interactions with opioids may manifest as serotonin syndrome (see Warnings and Precautions – Serotonin syndrome with concomitant use of serotonergic drugs) or opioid toxicity (e.g., respiratory depression, coma) (see 4.4 Special warnings and precautions for use – Respiratory Depression).</p> <p><b>Intervention:</b> Do not use DUOCETZ in patients taking MAOIs or within 14 days of stopping such treatment.</p> <p><b>Warfarin</b></p> <p><b>Clinical Impact:</b> As medically appropriate, periodic evaluation of prothrombin time should be performed when DUOCETZ and these agents are administered concurrently due to reports of increased International Normalized Ratio (INR) in some patients. Post-marketing surveillance of tramadol has revealed rare reports of alteration of warfarin effect, including elevation of prothrombin times.</p> <p>There have been several reports that suggest that paracetamol may produce hypoprothrombemia when administered with warfarin-like compounds.</p> <p><b>Intervention:</b> Monitor the prothrombin time of patients on warfarin for signs of an interaction and adjust the dosage of warfarin as needed.</p> <p><b>Fluoxacinil</b></p> <p><b>Mechanism:</b> Additive or synergistic pharmacodynamic effect</p> <p><b>Clinical Impact:</b> High anion gap metabolic acidosis (HAGMA) from pyroglutamic acid (5-oxoprolinemia) has been reported with concomitant use of therapeutic doses of acetaminophen and fluoxacinil. Patients reported to be most at risk are elderly females with underlying disease such as sepsis, renal function abnormality, and malnutrition. Most patients improve after stopping one or both of the drugs</p> <p><b>Intervention:</b> Caution should be taken when fluoxacinil is used concomitantly with acetaminophen as concurrent intake has been associated with HAGMA, especially in patients with risk factors. Discontinue DUOCETZ and/or fluoxacinil if HAGMA is suspected.</p> <p><b>Cimetidine</b></p> <p><b>Clinical Impact:</b> Concomitant administration of tramadol and cimetidine does not result in clinically significant changes in tramadol pharmacokinetics.</p> <p><b>4.6 Fertility, pregnancy and lactation</b></p> <p><b>Pregnancy</b></p> <p>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. DUOCETZ is not recommended for pregnant women.</p> <p>The use of opioids during childbirth might result in respiratory depression in the newborn infant.</p> <p>Prolonged use of DUOCETZ, or other opioids, during pregnancy may lead to neonatal opioid withdrawal syndrome. This risk is particularly increased during the last trimester of pregnancy.</p> <p><b>Breast-feeding</b></p> <p>DUOCETZ is not recommended for breast-feeding mothers because its safety in infants and newborns has not been studied.</p> <p>Tramadol is subject to the same polymorphic metabolism as codeine, with ultra-rapid metabolizers of CYP2D6 substrate being potentially exposed to life-threatening levels of O-desmethyltramadol (M1). At least one death was reported in a breast-feeding infant who was exposed to high levels of morphine in breast milk because the mother was an ultra-rapid metabolizer of codeine. A baby breast-feeding from an ultra-rapid metabolizer mother taking DUOCETZ could potentially be exposed to high levels of M1, and experience life-threatening respiratory depression. For this reason, breast-feeding is not recommended during treatment with DUOCETZ.</p> <p>Approximately 0.1% of the maternal dose of tramadol is excreted in breast milk. In the immediate post-partum period, for maternal oral daily dosage up to 400 mg, this corresponds to a mean amount of tramadol ingested by breast-fed infants of 3% of the maternal weight-adjusted dosage. For this reason tramadol should not be used during lactation or alternatively, breast-feeding should be discontinued during treatment with tramadol. Discontinuation of breast-feeding is generally not necessary following a single dose of tramadol.</p> <p><b>Fertility</b></p> <p>The effect of tramadol or tramadol/paracetamol combination on human fertility has not been evaluated.</p> <p><b>4.7 Effects on ability to drive and use machines</b></p> <p>DUOCETZ may impair mental or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.</p> <p><b>4.8 Undesirable effects</b></p> <p>Cutaneous hypersensitivity reactions including skin rashes, angioedema, Stevens Johnson Syndrome/Toxic Epidermal Necrolysis have been reported.</p> <p>Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that have been considered to be reasonably causally associated with the use of tramadol hydrochloride/paracetamol based on a comprehensive assessment of the available adverse event information. A causal relationship with tramadol hydrochloride/paracetamol cannot be reliably established in individual cases.</p> <p>The following adverse reactions have been reported during postmarketing experience. The frequencies are provided according to the following convention:</p> <ul style="list-style-type: none"> <li>Very common <math>\geq 1/10</math></li> <li>Common <math>\geq 1/100</math> and <math>&lt; 1/10</math></li> <li>Uncommon <math>\geq 1/1000</math> and <math>&lt; 1/100</math></li> <li>Rare <math>\geq 1/10000</math> and <math>&lt; 1/1000</math></li> <li>Very rare <math>&lt; 1/10000</math></li> <li>Not known (cannot be estimated from the available data)</li> </ul> <p><b>Adverse Reactions Identified During Postmarketing Experience with tramadol and paracetamol by Frequency Category Estimated from Spontaneous Reporting Rates</b></p> <table border="1"> <tr> <td><b>System Organ Class</b></td> <td><b>Frequency: Adverse Reaction</b></td> </tr> <tr> <td><b>Respiratory system</b></td> <td><b>Rare, Respiratory depression</b></td> </tr> <tr> <td><b>Metabolism and nutrition disorders</b></td> <td><b>Not known, Hyponatremia/syndrome of inappropriate antidiuretic hormone</b></td> </tr> <tr> <td><b>Immune system disorders</b></td> <td><b>Very rare, Fixed eruption</b></td> </tr> </table> <p><b>Serotonin syndrome</b> (see 4.4 Special warnings and precautions for use)</p> <p><b>Adrenal insufficiency</b> (see 4.4 Special warnings and precautions for use)</p> <p><b>Androgen deficiency</b></p> <p>Cases of androgen deficiency have occurred with chronic use of opioids. Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role</p>	<b>System Organ Class</b>	<b>Frequency: Adverse Reaction</b>	<b>Respiratory system</b>	<b>Rare, Respiratory depression</b>	<b>Metabolism and nutrition disorders</b>	<b>Not known, Hyponatremia/syndrome of inappropriate antidiuretic hormone</b>	<b>Immune system disorders</b>	<b>Very rare, Fixed eruption</b>	<p>of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.</p> <p><b>Infertility</b></p> <p>Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible.</p> <p><b>System Organ Class (SOC): Metabolism and nutrition disorders.</b></p> <p>"High anion gap metabolic acidosis" with frequency "Not known" (cannot be estimated from the available data)</p> <p><b>Description of selected adverse reactions</b></p> <p><b>High anion gap metabolic acidosis</b></p> <p>Cases of high anion gap metabolic acidosis due to pyroglutamic acidosis have been observed in patients with risk factors using paracetamol. Pyroglutamic acidosis may occur as a consequence of low glutathione levels in these patients.</p> <p><b>4.9 Overdose</b></p> <p><b>Accidental ingestion</b></p> <p>Accidental ingestion of tramadol can result in respiratory depression and seizures due to an overdose of tramadol. Respiratory depression and seizures have been reported in a child following ingestion of a single tablet.</p> <p>Fatalities due to tramadol overdose have also been reported.</p> <p><b>Symptoms and signs</b></p> <p>The clinical presentation of overdose may include the signs and symptoms of tramadol toxicity, paracetamol toxicity or both. The initial symptoms of tramadol overdose may include respiratory depression and/or seizures. The initial symptoms seen within the first 24 hours following a paracetamol overdose may include: gastrointestinal irritability, anorexia, nausea, vomiting, malaise, pallor, and diaphoresis.</p> <p><b>Tramadol</b></p> <p>Serious potential consequences of overdose of the tramadol component are respiratory depression, lethargy, coma, seizure, cardiac arrest and death. In addition, cases of QT prolongation have been reported during overdose.</p> <p><b>Paracetamol</b></p> <p>Paracetamol in massive overdoses may cause hepatic toxicity in some patients. Early symptoms following a potentially hepatotoxic overdose may include: gastrointestinal irritability, anorexia, nausea, vomiting, malaise, pallor, and diaphoresis. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.</p> <p><b>Treatment</b></p> <p>A single or multiple overdose with DUOCETZ may be a potentially lethal polydrug overdose, and appropriate expert consultation, if available, is recommended.</p> <p>While naloxone will reverse some, but not all, symptoms caused by overdose 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 it removes less than 7% of the administered dose in a 4-hour dialysis period.</p> <p>In treating an overdose of DUOCETZ, primary attention should be given to maintaining adequate ventilation along with general supportive treatment. Because strategies for the management of overdose are continually evolving, it is advisable to contact a poison control center (where available) to determine the latest recommendations for the management of an overdose.</p> <p>Hypotension is usually hypovolemic in etiology and should respond to fluids. Vasopressors and other supportive measures should be employed as indicated. Auffed endo-tracheal tube should be inserted when necessary, to provide assisted respiration.</p> <p>In adult and pediatric patients, any individual presenting with an unknown amount of paracetamol ingested or with a 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 to 10 grams 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.</p> <p><b>5. PHARMACOLOGICAL PROPERTIES</b></p> <p><b>Chemical names</b></p> <p><b>Tramadol hydrochloride</b>          (5)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride.</p> <p><b>Paracetamol</b>          N-(4-hydroxyphenyl)acetamide.</p> <p><b>5.1 Pharmacodynamics Properties</b></p> <p><b>Pharmacotherapeutic group:</b> Analgesics, Opioids in combination with non-opioid analgesics, ATC code: N02AJ13</p> <p><b>Pharmacodynamic effects</b></p> <p>Tramadol is a centrally acting analgesic compound. At least two complementary mechanisms appear applicable, binding of parent and M1 metabolite to <math>\mu</math>-opioid receptors and weak inhibition of reuptake of norepinephrine and serotonin.</p> <p>Paracetamol is another centrally acting analgesic. The exact site and mechanism of its analgesic action is not clearly defined.</p> <p>When evaluated in a standard animal model, the combination of tramadol and paracetamol exhibited a synergistic effect.</p> <p><b>5.2 Pharmacokinetic Properties</b></p> <p><b>General</b></p> <p>Tramadol is administered as a racemate and both the [-] and [+] forms of both tramadol and M1 are detected in the circulation. Tramadol has a slower absorption and longer half-life when compared to paracetamol.</p> <p>After a single oral dose of one Tramadol/Paracetamol combination tablet (37.5 mg/325 mg) peak plasma concentrations of 64.3/55.5 ng/mL ([+]-Tramadol(-)-Tramadol) and 4.2 <math>\mu</math>g/mL (paracetamol) are reached after 1.8 h ([+]-Tramadol(-)-Tramadol) and 0.9 h (Paracetamol), respectively. Mean elimination half lives t<sub>1/2</sub> are 5.1/4.7 h ([+]-Tramadol(-)-Tramadol) and 2.5 h (paracetamol).</p> <p><b>Absorption</b></p> <p>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 in healthy adults.</p> <p>Oral absorption of paracetamol following administration of tramadol/paracetamol combination tablets is rapid and almost complete and occurs primarily in the small intestine. Peak plasma concentrations of paracetamol occur within 1 hour and are not affected by co-administration with tramadol.</p> <p><b>Food effects</b></p> <p>The oral administration of tramadol/paracetamol combination tablets with food has no significant effect on the peak plasma concentration or extent of absorption of either tramadol or paracetamol, so that tramadol/paracetamol combination tablets can be taken independently of meal times.</p> <p><b>Distribution</b></p> <p>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%.</p> <p>Paracetamol appears to be widely distributed throughout most body tissues except fat. Its apparent volume of distribution is about 0.9 L/kg. A relatively small portion (~20%) of paracetamol is bound to plasma protein.</p> <p><b>Metabolism</b></p> <p>Plasma concentration profiles for tramadol and its M1 metabolite measured following dosing of tramadol/paracetamol combination tablets in volunteers showed no significant change compared to dosing with tramadol alone.</p> <p>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. Patients who are CYP2D6 ultra-rapid metabolizers may convert tramadol to its active metabolite (M1) more rapidly and completely than other patients (see 4.4 Special warnings and precautions for use - CYP2D6 Ultra-Rapid Metabolism of Tramadol). The prevalence of this CYP2D6 genotype varies by population and has been reported in literature to range from 1% to 10% in African Americans, Caucasian Americans, Asians and Europeans (including specific studies in Greeks, Hungarians and Northern Europeans) to as high as 29% in African Ethiopians.</p> <p>Paracetamol is primarily metabolized in the liver by first-order kinetics and involves three principal separate pathways:</p> <ol style="list-style-type: none"> <li>a) conjugation with glucuronic acid;</li> <li>b) conjugation with sulfate; and</li> <li>c) oxidation via cytochrome P450 enzyme pathway.</li> </ol> <p><b>Excretion</b></p> <p>Tramadol and its metabolites are eliminated primarily by the kidney. The plasma elimination half-lives of racemic tramadol and M1 are approximately six and seven hours, respectively. The plasma elimination half-life of racemic tramadol increased from approximately six hours to seven hours upon multiple dosing of tramadol/paracetamol combination tablets.</p> <p>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.</p> <p><b>6. PHARMACEUTICAL PARTICULARS</b></p> <p><b>6.1 List of excipients:</b> Corn starch, Povidone K30, Sodium starch glycolate, Microcrystalline cellulose PH 101, Magnesium stearate, Opadry II yellow, Purified water.</p> <p><b>6.2 Incompatibilities:</b> None Known</p> <p><b>6.3 Shelf Life</b></p> <p>36 months</p> <p><b>6.4 Special Precautions for storage</b></p> <p>Store below 30°C in the original package, away from direct sunlight.</p> <p>Because of the risks associated with accidental ingestion, misuse, and abuse, advise patients to store DUOCETZ securely, in a location not accessible by others.</p> <p><b>6.5 Nature and contents of container:</b></p> <p>DUOCETZ are packed in a blister containing 10 tablets in PVC/PVDC Aluminium blister. Each blister will be further packed in an outer box along with leaflet. Pack sizes available are 1x10, 3x10, 5x10 and 10x10 tablets.</p> <p><b>6.6 Special precautions for disposal and other handling</b></p> <p>Any unused DUOCETZ should be disposed of in accordance with local requirements.</p> <p><b>7. MANUFACTURER'S NAME AND ADDRESS</b></p> <p><b>MEGA LIFESCIENCES Public Company Limited</b>          51/51 Soi 8, Bangpoo Industrial Estate,          Pattana 3 Road, Moo 4, Phraeksa, Mueang,          Samutprakarn 10280, Thailand</p> <p><b>8. PRODUCT REGISTRATION HOLDER</b></p> <p><b>MEGA LIFESCIENCES SDN. BHD.</b>          B-28-02, The Ascent, Paradigm, No. 1, Jalan SS7/26A,          Kelana Jaya, 47301 Petaling Jaya, Selangor, Malaysia.</p> <p><b>9. DATE OF REVISION</b></p> <p>November 2025</p>	<p>3</p> <p>2</p> <p>3</p> <p>1</p> <p>3</p> <p>2</p> <p>3</p>
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