COMBESIC 37.5mg/325mg Orally Disintegrating Tablet
(Tramadol Hydrochloride 37.5 mg & Paracetamol 325 mg Orally Disintegrating Tablets)

PROPRIETARY NAME AND DOSAGE FORM: COMBESIC 37.5mg/325mg Orally Disintegrating Tablet (Paracetamol 325mg and Tramadol hydrochloride 37.5mg Tablets).
COMPOSITION:
Each film coated tablet contains tramadol hydrochloride 37.5mg and 325mg paracetamol.

PHARMACOLOGICAL ACTION.
COMBESIC 37.5mg/325mg Orally Disintegrating Tablet
Pharmacodynamic Properties
Pharmacotherapeutic group: Analgesics, Opioids in combination with non-opioid analgesics, ATC code: N02AJ13

Pharmacodynamic effects
Tramadol is a centrally acting synthetic analgesic compound. At least two complementary mechanisms appear applicable, binding of parent and O-demethylated (M1) metabolite to μ-opioid receptors as well as the weak inhibition of neuronal re-uptake of noradrenaline and
serotonin.
Paracetamol is another centrally acting analgesic. The exact site and mechanism of its analgesic action is not clearly defined.
When evaluated in a standard animal model, the combination of tramadol and paracetamol exhibited a synergistic effect.

PHARMACOKINETIC
General
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.
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 µg/ml (paracetamol) are reached after 1.8 h [(+)-Tramadol/(-)-Tramadol] and 0.9 h (Paracetamol), respectively. Mean elimination half lives $t_{1/2}$ are 5.1/4.7 h [(+)-Tramadol/(-)-Tramadol] and 2.5 h (paracetamol).

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 in healthy adults.
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.

Food effects
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.

Distribution
The volume of distribution of tramadol was 2.6 and 2.9 L/kg in male and female subjects, respectively, following a 100 mg intravenous dose. The binding of tramadol to human plasma proteins is approximately 20%.
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 combination tablets 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. Patients who are CYP2D6 ultra-rapid metabolizers may convert tramadol to its active metabolite (M1) more rapidly and completely than other patients. 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

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

a) conjugation with glucuronide;
b) conjugation with sulfate; and
c) oxidation via cytochrome P450 enzyme pathway.

Excretion
Tramadol and its metabolites are eliminated primarily by the kidney. The plasma elimination half-life 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
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.

INDICATIONS
COMBESIC 37.5mg/325mg Orally Disintegrating Tablet is indicated for the management of moderate to severe pain.

Dosage and Administration
Dosage
Adults and children 16 years of age and over
The maximum single dose of **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet 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)
COMBESIC 37.5mg/325mg Orally Disintegrating Tablet is not approved for use in patients below 12 years old.

Paediatric population
The safety and efficacy of **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet has not been studied in the paediatric population. Therefore, use of **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet is not recommended in patients under 12 years of age.

Treatment withdrawal
Do not stop use of **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet abruptly. Withdrawal symptoms may be relieved by tapering the medication (see *Warnings and Precautions – Treatment Withdrawal*).

Special populations
Children below 16 years of age
The use of **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet is contraindicated in children below 12 years of age (see *Contraindications*).
The safety and effectiveness of **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet in children aged 12 to below 16 years of age has not been established (See *Contraindications and Warnings and Precautions - 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 **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet be increased not to exceed 2 tablets every 12 hours.

Hepatic impairment
The use of **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet in patients with severe hepatic impairment is not recommended.

Administration
COMBESIC 37.5mg/325mg Orally Disintegrating Tablet are for oral administration.
COMBESIC 37.5mg/325mg Orally Disintegrating Tablet can be administered without regard to food.

CONTRA-INDICATIONS
COMBESIC 37.5mg/325mg Orally Disintegrating Tablet 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 *Warnings and Precautions*).

WARNINGS:

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 ~~at dosages~~ 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 **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet.
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.

Paediatric population
The safety and efficacy of **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet has not been studied in the paediatric population. Therefore, use of **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet is not recommended in patients under 12 years of age.

Respiratory depression
Patients with significant respiratory depression (see *Contraindications*) or acute, severe bronchial asthma are at increased risk of life-threatening respiratory depression when treated with opioids.
Administer **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet 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 **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet 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 Adverse Reactions). 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 *Dosage and Administration, Treatment withdrawal; Warnings and Precautions, Treatment withdrawal*).

Cytochromes P450 (CYP) 2D6 ultra-rapid metabolism
Some individuals may be CYP2D6 ultra-rapid metabolisers. 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 lifethreatening respiratory depression. (see section *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 *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 *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 postmarketing reports with tramadol, children younger than 12 years of age may be more susceptible to the respiratory depressant effects of tramadol (see *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 *Contraindications*). Because of the risk of life-threatening respiratory depression and death, avoid the use of **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet 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 *Dosage and Administration and Overdose -Symptoms and signs, Tramadol*).

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

The concomitant use of tramadol (an active ingredient in **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet) with CNS depressants, including alcohol, may cause additive CNS depressant effects, including profound sedation and respiratory depression. **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet should be used with caution and in reduced dosages when administered to patients receiving CNS depressants. (see *Interactions*)

Increased intracranial pressure or head trauma
COMBESIC 37.5mg/325mg Orally Disintegrating Tablet should be used with caution in patients with increased intracranial pressure or head injury.

Drug dependence and potential for abuse
COMBESIC 37.5mg/325mg Orally Disintegrating Tablet contains tramadol as an active ingredient. A portion of the analgesic effect of **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet 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 **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet and monitor all patients receiving **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet 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).
COMBESIC 37.5mg/325mg Orally Disintegrating Tablet 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.

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 **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet 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 **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet with great caution in patients taking serotonergic drugs including SSRIs. Concomitant use of tramadol with serotonergic drugs including SSRI's increases the risk of adverse events, including seizure and serotonin syndrome (see *Interactions*).

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concurrent use of **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet with serotonergic drugs (see *Interactions with Other Medicaments*). 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. hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea) and can be fatal (see *Interactions with Other Medicaments*). The onset of symptoms generally occurs within several hours to a few days of concomitant use, but may occur later than that. Discontinue **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet 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
COMBESIC 37.5mg/325mg Orally Disintegrating Tablet 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 **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet be increased not to exceed 2 tablets every 12 hours. **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet is not recommended in patients with creatinine clearance of less than 10 mL/min.

Hepatic impairment
The use of **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet 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 **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet 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 **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet and appropriate treatment (e.g. fluid restriction). During ULTRACET treatment, monitoring for signs and symptoms of hyponatremia is recommended for patients with predisposing risk factors.

Precautions general
The recommended dose of **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet should not be exceeded. **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet 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 **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet 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 **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet 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 *Interactions*).

Unsuitable for phenylketonurics.

EFFECTS ON ABILITY TO DRIVE OR OPERATE MACHINERY:
COMBESIC 37.5mg/325mg Orally Disintegrating Tablet may impair mental or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery.

INTERACTIONS
Based on its pharmacodynamic and pharmacokinetic properties, tramadol and paracetamol 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 tramadol and paracetamol be consulted for information related to interaction pathways, potential risks, and specific actions to be taken with regards to coadministration.

Table 1. Drug Interactions with ULTRACET

Inhibitors of CYP2D6	
Mechanism:	Enzyme inhibition resulting in decreased rate of metabolism of tramadol
Clinical Impact:	The concomitant use of **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet 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 **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet 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 *Pharmacological Properties – Pharmacokinetic properties*).
Intervention:	If concomitant use of an inhibitor of CYP2D6 is necessary, follow patients closely for adverse reactions including opioid withdrawal, seizures and serotonin syndrome (see *Warnings and Precautions – CYP2D6 ultra rapid metabolism of tramadol*). If an inhibitor of CYP2D6 is discontinued, consider lowering ULTRACET dosage until stable drug effects are achieved. Follow patients closely for adverse events including respiratory depression and sedation.
Examples	Quinidine, fluoxetine, paroxetine, amitriptyline and bupropion
Inhibitors of CYP3A4	
Mechanism:	Enzyme inhibition resulting in decreased rate of metabolism of tramadol
Clinical Impact:	The concomitant use of **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet 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.
Intervention:	If concomitant use is necessary, consider dosage reduction of **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet 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 **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet is achieved. If an inhibitor of CYP3A4 is discontinued, consider increasing the **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet dosage until stable drug effects are achieved and follow patients for signs and symptoms of opioid withdrawal.
Examples	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), protease inhibitors (e.g., ritonavir)
CYP3A4 Inducers	
Mechanism:	Enzyme induction resulting in increased rate of metabolism of tramadol.
Clinical Impact:	The concomitant use of **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet 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. 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.
Intervention:	If concomitant use is necessary, consider increasing the **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet dosage until stable drug effects are achieved. Follow patients for signs of opioid withdrawal. If an inducer of CYP3A4 is discontinued, consider **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet dosage reduction and monitor for seizures and serotonin syndrome, and signs of sedation and respiratory depression. 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 **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet and carbamazepine is not recommended.
Examples:	Rifampin, carbamazepine, phenytoin
Benzodiazepines and Other Central Nervous System (CNS) Depressants including alcohol	
Mechanism:	Additive or synergistic pharmacodynamic effect
Clinical Impact:	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 **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet 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. 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 μ-receptors, and benzodiazepines interact at $GABA_A$ sites. When opioids and benzodiazepines are combined, the

	potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists.
Intervention:	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate (see *Warnings and Precautions*). Limit dosages and durations of concomitant use of benzodiazepines and opioids, and follow patients closely for respiratory depression and sedation.
Serotonergic Drugs	
Mechanism:	Additive or synergistic pharmacodynamic effect
Clinical Impact:	The concomitant use of opioids with other drugs that affect the serotenergic neurotransmitter system has resulted in serotonin syndrome.
Intervention:	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet if serotonin syndrome is suspected.
Examples:	Examples of serotonergic drugs are selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g. mirtazapine, trazodone, tramadol) monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue) (see *Warnings and Precautions*).
Monoamine Oxidase Inhibitors (MAOIs)	
Mechanism:	Additive or synergistic pharmacodynamic effect
Clinical Impact:	The concomitant use of **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet with MAOIs, or use within 14 days of their discontinuation, is contraindicated due to the increased risk of seizures and serotonin syndrome (see *Contraindications*). MAOI interactions with opioids may manifest as serotonin syndrome (see *Warnings and Precautions – use with serotonin reuptake inhibitors)* or opioid toxicity (e.g., respiratory depression, coma) (see *Warnings and Precautions –Respiratory Depression*).
Intervention:	Do not use **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet in patients taking MAOIs or within 14 days of stopping such treatment.
Examples:	phenelzine, tranylcypromine, linezolid
Warfarin	
Clinical Impact:	As medically appropriate, periodic evaluation of prothrombin time should be performed when **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet 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. There have been several reports that suggest that paracetamol may produce hypoprothrombinemia when administered with warfarin-like compounds.
Intervention:	Monitor the prothrombin time of patients on warfarin for signs of an interaction and adjust the dosage of warfarin as needed.
Flucloxacillin	
Mechanism:	Additive or synergistic pharmacodynamic effect
Clinical Impact:	High anion gap metabolic acidosis (HAGMA) from pyroglutamic acid (5oxoprolinemia) has been reported with concomitant use of therapeutic doses of acetaminophen and flucloxacillin. 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 of both of the drugs
Intervention:	Caution should be taken when flucloxacillin is used concomitantly with acetaminophen as concurrent intake has been associated with HAGMA, especially in patients with risk factors. Discontinue ULTRACET and/or flucloxacillin if HAGMA is suspected.
Cimetidine	
Clinical Impact:	Concomitant administration of tramadol and cimetidine does not result in clinically significant changes in tramadol pharmacokinetics.

Pregnancy
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. **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet is not recommended for pregnant women.
The use of opioids during childbirth might result in respiratory depression in the newborn infant.
Prolonged use of **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet, or other opioids, during pregnancy may lead to neonatal opioid withdrawal syndrome. This risk is particularly increased during the last trimester of pregnancy.

Breast-feeding
COMBESIC 37.5mg/325mg Orally Disintegrating Tablet is not recommended for breast-feeding mothers because its safety in infants and newborns has not been studied.
Tramadol is subject to the same polymorphic metabolism as codeine, with ultra-rapid metabolizers of CYP2D6 substrates 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 **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet 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 ULTRACET.
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.

Fertility
The effect of tramadol or tramadol/paracetamol combination on human fertility has not been evaluated.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:
Cutaneous hypersensitivity reactions including skin rashes, angioedema, Stevens Johnson Syndrome/Toxic Epidermal Necrolysis have been reported.

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.

The following adverse reactions have been reported during postmarketing experience. The frequencies are provided according to the following convention:

Very common	≥1/10
Common	≥1/100 and <1/10
Uncommon	≥1/1000 and <1/100
Rare	≥1/10000 and <1/1000
Very rare	<1/10000

Not known	(cannot be estimated from the available data)

Adverse Reactions Identified During Postmarketing Experience with ULTRACET by Frequency Category Estimated from Spontaneous Reporting Rates

System Organ Class
Frequency: Adverse Reaction

Respiratory system
Rare, Respiratory depression

Metabolism and nutrition disorders
Not known, Hyponatremia/syndrome of inappropriate antidiuretic hormone

Immune system disorders
Very rare, Fixed eruption

Serotonin syndrome *(*see *Warnings and Precautions)*

Adrenal insufficiency *(*see *Warnings and Precautions)*

Androgen deficiency
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 casual role 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.

Infertility
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.

KNOWN SYMPTOMS OF OVERDOSE AND PARTICULARS OF ITS TREATMENT.
Accidental ingestion
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. Fatalities due to tramadol overdose have also been reported.

Symptoms and signs
COMBESIC 37.5mg/325mg Orally Disintegrating Tablet is a combination 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 hours following a paracetamol overdose may include: gastrointestinal irritability, anorexia, nausea, vomiting, malaise, pallor and diaphoresis.

Tramadol
Serious potential consequences of overdosage 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.

Paracetamol
Paracetamol in massive overdosage may cause hepatic toxicity in some patients. Early symptoms following a 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 to 72 hours post-ingestion.

Treatment
A single or multiple overdose with **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet 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 it removes less than 7% of the administered dose in a 4-hour dialysis period.

In treating an overdosage of **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet, 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. Hypotension is usually hypovolemic in etiology and should respond to fluids. Vasopressors and other supportive measures should be employed as indicated. A cuffed endo-tracheal tube should be inserted when necessary, to provide assisted respiration.

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.

IDENTIFICATION:
Round, white to off white, flat, bevelled edged, tablets with central concave depression on both the surfaces, having mint odour.

PHARMACEUTICAL PARTICULARS

Shelf life
3 years

STORAGE INSTRUCTIONS:
Store below 30°C in the original package. Keep out of reach of children. Because of the risks associated with accidental ingestion, misuse, and abuse, advise patients to store **COMBESIC 37.5mg/325mg** Orally Disintegrating Tablet securely, in a location not accessible by others.

NATURE AND CONTENTS OF CONTAINER
Aluminium /PVC blister strips of 10 tablets per strip in unit cartons containing pack sizes of 30’s in unit

SPECIAL PRECAUTIONS FOR DISPOSAL
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

MANUFACTURER
ATHENA DRUG DELIVERY SOLUTIONS PVT. LTD.
PLOT NO. A-1 TO A-5, MIDC, CHEMICAL ZONE, AMBERNATH (W), THANE 421501, MAHARASHTRA STATE, AMBARNATH, ÍNDIA

MARKETING REGISTRATION HOLDER
Mansa Healthcare Sdn Bhd
E-3A-11 Starparc Point
Jalan Ibu Kota, Setapak
53300 Kuala Lumpur
Malaysia

MARKETING AUTHORISATION NUMBER(S)
MAL*********

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