

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ULTRACET® safely and effectively. See full prescribing information for ULTRACET.

ULTRACET (tramadol hydrochloride and acetaminophen) tablets, for oral use, C-IV

Initial U.S. Approval – 2001

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; INTERACTIONS WITH DRUGS AFFECTING CYTOCHROME P450 ISOENZYMES; HEPATOTOXICITY; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

See full prescribing information for complete boxed warning.

- ULTRACET exposes users to the risks of addiction, abuse and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing ULTRACET, and monitor regularly for these behaviors or conditions. (5.1)
- Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially during initiation or following a dose increase. (5.2)
- Accidental ingestion of ULTRACET, especially by children, can result in a fatal overdose of tramadol. (5.2)
- Prolonged use of ULTRACET, during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.3)
- The effects of concomitant use or discontinuation of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with tramadol are complex. Use of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with ULTRACET requires careful consideration of the effects on the parent drug, tramadol, and the active metabolite, M1. (5.4, 7)
- ULTRACET contains acetaminophen. Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4,000 milligrams per day, and often involve more than one acetaminophen containing product. (5.5)
- Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation. (5.6, 7)

RECENT MAJOR CHANGES

Boxed Warning	12/2016
Indications and Usage (1)	12/2016
Dosage and Administration (2)	12/2016
Contraindications (4)	12/2016
Warnings and Precautions (5)	12/2016

INDICATIONS AND USAGE

ULTRACET is a combination of tramadol hydrochloride, an opioid agonist, and acetaminophen, and is indicated for the management of acute pain, severe enough to require an opioid analgesic and for which alternative treatments are inadequate. (1)

Limitations of Use (1)

ULTRACET tablets are indicated for short-term use of five days or less. Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, reserve ULTRACET for use in patients for whom alternative treatment options [e.g., non-opioid analgesics]:

- Have not been tolerated, or are not expected to be tolerated.
- Have not provided adequate analgesia, or are not expected to provide adequate analgesia,

DOSAGE AND ADMINISTRATION

- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals.
- Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (2.1)
- Initiate treatment with two tablets every 4 to 6 hours as needed for pain relief; maximum of 8 tablets per day. (2.2)
- Do not use with other acetaminophen- or tramadol-containing products. (2, 5.17)
- **Severe Renal Impairment:** Do not exceed 2 tablets every 12 hours. (2.3)
- Do not stop ULTRACET abruptly in a physically dependent patient. (2.4)

DOSAGE FORMS AND STRENGTHS

Tablets: tramadol hydrochloride 37.5 mg and acetaminophen 325 mg. (3)

CONTRAINDICATIONS

- Significant respiratory depression. (4)
- Acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitative equipment. (4)
- Known or suspected gastrointestinal obstruction, including paralytic ileus. (4)
- Previous hypersensitivity to tramadol hydrochloride, acetaminophen, any other component of this product, or opioids. (4)
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days (4)

WARNINGS AND PRECAUTIONS

- **Serotonin Syndrome:** May be life-threatening. Can occur with use of tramadol alone, with concomitant use of serotonergic drugs, with drugs that impair metabolism of serotonin or tramadol. (5.7)
- **Risk of Seizure:** Can occur at the recommended dose of tramadol. Concomitant use with other drugs may increase seizure risk. Risk may increase in patients with epilepsy, a history of seizures, and in patients with a recognized risk for seizures. (5.8)
- **Risk of Suicide:** Do not prescribe for suicidal or addiction-prone patients. (5.9)
- **Adrenal Insufficiency:** If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.10)
- **Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients:** Monitor closely, particularly during initiation and titration. (5.11)
- **Severe Hypotension:** Monitor during dosage initiation and titration. Avoid use of ULTRACET in patients with circulatory shock. (5.12)
- **Risks of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness:** Monitor for sedation and respiratory depression. Avoid use of ULTRACET in patients with impaired consciousness or coma. (5.13)

ADVERSE REACTIONS

The most common incidence of treatment-emergent adverse events (≥3.0%) in patients from clinical trials were constipation, diarrhea, nausea, somnolence, anorexia, dizziness, and sweating increased. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Pharmaceuticals, Inc at 1-800-JANSSEN (1-800-526-7736) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- **Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics:** Avoid use with ULTRACET because they may reduce analgesic effect of ULTRACET or precipitate withdrawal symptoms. (7)

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** May cause fetal harm. (8.1)
- **Lactation:** Not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2016

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FULL PRESCRIBING INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; INTERACTIONS WITH DRUGS AFFECTING CYTOCHROME P450 ISOENZYMES; HEPATOTOXICITY; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES AND OTHER CNS DEPRESSANTS

Addiction, Abuse, and Misuse

ULTRACET exposes patients and other users to the risks of opioid addiction, abuse and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing ULTRACET, and monitor all patients regularly for the development of these behaviors and conditions [see *Warnings and Precautions (5.1)*].

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of ULTRACET. Monitor for respiratory depression, especially during initiation of ULTRACET or following a dose increase [see *Warnings and Precautions (5.2)*].

Accidental Ingestion

Accidental ingestion of even one dose of ULTRACET, especially by children, can result in a fatal overdose of tramadol [see *Warnings and Precautions (5.2)*].

Neonatal Opioid Withdrawal Syndrome

Prolonged use of ULTRACET during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see *Warnings and Precautions (5.3)*].

Interactions with Drugs Affecting Cytochrome P450 Isoenzymes

The effects of concomitant use or discontinuation of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with tramadol are complex. Use of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with ULTRACET requires careful consideration of the effects on the parent drug, tramadol, and the active metabolite, M1 [see *Warnings and Precautions (5.4), Drug Interactions (7)*].

Hepatotoxicity

ULTRACET contains tramadol hydrochloride and acetaminophen. Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4,000 milligrams per day, and often involve more than one acetaminophen-containing product [see *Warnings and Precautions (5.5)*].

Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [see *Warnings and Precautions (5.6) and Drug Interactions (7)*].

- Reserve concomitant prescribing of ULTRACET and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

1 INDICATIONS AND USAGE

ULTRACET tablets are indicated for the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

Limitations of Use

ULTRACET tablets are indicated for short-term use of five days or less.

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses [see *Warnings and Precautions (5.1)*], reserve ULTRACET for use in patients for whom alternative treatment options [e.g., non-opioid analgesics]:

- Have not been tolerated, or are not expected to be tolerated,
- Have not provided adequate analgesia, or are not expected to provide adequate analgesia.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

- ULTRACET is not approved for use for more than 5 days.
- Do not exceed the recommended dose of ULTRACET. Do not co-administer ULTRACET with other tramadol or acetaminophen containing products [see *Warnings and Precautions (5.17)*].
- Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals [see *Warnings and Precautions (5.1)*].
- Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse [see *Warnings and Precautions (5.1)*].
- Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases with ULTRACET and adjust the dosage accordingly [see *Warnings and Precautions (5.2)*].

2.2 Initial Dosage

The initial dose of ULTRACET is 2 tablets every 4 to 6 hours as needed for pain relief up to a maximum of 8 tablets per day.

2.3 Dosage Modification in Patients with Renal Impairment

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

2.4 Discontinuation of ULTRACET

ULTRACET is not approved for use greater than 5 days. In circumstances where physical dependence with ULTRACET is possible, use a gradual downward taper and do not stop use of ULTRACET abruptly. *[see Warnings and Precautions (5.18)].*

3 DOSAGE FORMS AND STRENGTHS

ULTRACET tablets each contain 37.5 mg of tramadol hydrochloride and 325 mg of acetaminophen. The tablets are light yellow, coated, capsule-shaped, and debossed with “O-M” on one side and “650” on the other.

4 CONTRAINDICATIONS

ULTRACET is contraindicated in patients with:

- Significant respiratory depression *[see Warnings and Precautions (5.2)].*
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment *[see Warnings and Precautions (5.11)].*
- Patients with known or suspected gastrointestinal obstruction, including paralytic ileus *[see Warnings and Precautions (5.15)].*
- Hypersensitivity to tramadol, acetaminophen, any other component of this product *[see Warnings and Precautions (5.16)].*
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use within the last 14 days *[see Drug Interactions (7)]*

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse and Misuse

ULTRACET contains tramadol, a Schedule IV controlled substance. As an opioid, ULTRACET exposes users to the risks of addiction, abuse, and misuse *[see Drug Abuse and Dependence (9)].*

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed ULTRACET. Addiction can occur at recommended dosages and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing ULTRACET, and monitor all patients receiving ULTRACET for the development of these behaviors and conditions. 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). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as ULTRACET, but use in such patients necessitates intensive counseling about the risks and proper use of ULTRACET along with intensive monitoring for signs of addiction, abuse, and misuse.

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing ULTRACET. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug [see *Patient Counseling Information (17)*]. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

5.2 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status [see *Overdosage (10)*]. Carbon dioxide (CO₂) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of ULTRACET, the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy with and following dosage increases of ULTRACET.

To reduce the risk of respiratory depression, proper dosing and titration of ULTRACET are essential [see *Dosage and Administration (2)*]. Overestimating the ULTRACET dosage when converting patients from another opioid product can result in a fatal overdose with the first dose.

Accidental ingestion of even one dose of ULTRACET, especially by children, can result in respiratory depression and death due to an overdose of tramadol.

5.3 Neonatal Opioid Withdrawal Syndrome

Prolonged use of ULTRACET during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see *Use in Specific Populations (8.1) and Patient Counseling Information (17)*].

5.4 Risks of Interactions with Drugs Affecting Cytochrome P450 Isoenzymes

The effects of concomitant use or discontinuation of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors on levels of tramadol and M1 from ULTRACET are complex. Use of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with ULTRACET requires careful consideration of the effects on the parent drug, tramadol, which is a weak serotonin and norepinephrine reuptake inhibitor and μ -opioid agonist, and the active metabolite, M1, which is more potent than tramadol in μ -opioid receptor binding [see *Drug Interactions (7)*].

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

The concomitant use of ULTRACET with all cytochrome P450 2D6 inhibitors (e.g., amiodarone, quinidine) may result in an increase in tramadol plasma levels and a decrease in the levels of the active metabolite, M1. A decrease in M1 exposure in patients who have developed physical dependence to tramadol, may result in signs and symptoms of opioid withdrawal and reduced efficacy. The effect of increased tramadol levels may be an increased risk for serious adverse events including seizures and serotonin syndrome.

Discontinuation of a concomitantly used cytochrome P450 2D6 inhibitor may result in a decrease in tramadol plasma levels and an increase in active metabolite M1 levels, which could increase or prolong adverse reactions related to opioid toxicity and may cause potentially fatal respiratory depression.

Follow patients receiving ULTRACET and any CYP2D6 inhibitor for the risk of serious adverse events including seizures and serotonin syndrome, signs and symptoms that may reflect opioid toxicity, and opioid withdrawal when ULTRACET is used in conjunction with inhibitors of CYP2D6 [see *Drug Interactions (7)*].

Cytochrome P450 3A4 Interaction

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

The concomitant use of ULTRACET with all cytochrome P450 3A4 inducers or discontinuation of a cytochrome P450 3A4 inhibitor may result in lower tramadol levels. This may be associated with a decrease in efficacy, and in some patients, may result in signs and symptoms of opioid withdrawal.

Follow patients receiving ULTRACET and any CYP3A4 inhibitor or inducer for the risk for serious adverse events including seizures and serotonin syndrome, signs and symptoms that may reflect opioid toxicity and opioid withdrawal when ULTRACET is used in conjunction with inhibitors and inducers of CYP3A4 [see *Drug Interactions (7)*].

5.5 Hepatotoxicity

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

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

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

5.6 Risks from Concomitant Use with Benzodiazepines or Other CNS Depressants

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of ULTRACET with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine

sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics [*see Drug Interactions (7)*].

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, 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 ULTRACET is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant 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 additional CNS depressants including alcohol and illicit drugs [*see Drug Interactions (7), Patient Counseling Information (17)*].

5.7 Serotonin Syndrome Risk

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported with the use of tramadol, including ULTRACET, during concomitant use with serotonergic drugs.

Serotonergic drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT₃ receptor antagonists, drugs that affect the serotonergic neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), and drugs that impair metabolism of serotonin (including MAO inhibitors, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue) [*see Drug Interactions (7)*]. 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, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The onset of symptoms generally occurs within several hours to a few days of concomitant use, but may occur later than that. Discontinue ULTRACET if serotonin syndrome is suspected.

5.8 Increased Risk of 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: *[see Drug Interactions (7)]*.

- Selective serotonin re-uptake inhibitors (SSRIs) and Serotonin-norepinephrine re-uptake inhibitors (SNRIs) antidepressants or anorectics,
- Tricyclic antidepressants (TCAs), and other tricyclic compounds (e.g., cyclobenzaprine, promethazine, etc.),
- Other opioids,
- MAO inhibitors *[see Warnings and Precautions (5.7), Drug Interactions (7)]*
- Neuroleptics, or
- Other drugs that reduce the seizure threshold.

Risk of seizures may also increase in patients with epilepsy, those with a history of seizures, or in patients with a recognized risk for seizure (such as head trauma, metabolic disorders, alcohol and drug withdrawal, CNS infections).

In tramadol overdose, naloxone administration may increase the risk of seizure.

5.9 Suicide Risk

- Do not prescribe ULTRACET for patients who are suicidal or addiction-prone. Consideration should be given to the use of non-narcotic analgesics in patients who are suicidal or depressed *[see Drug Abuse and Dependence (9)]*.
- Prescribe ULTRACET with caution for patients with a history of misuse and/or are currently taking CNS-active drugs including tranquilizers, or antidepressant drugs, or

alcohol in excess, and patients who suffer from emotional disturbance or depression [see *Drug Interactions (7)*].

- Inform patients not to exceed the recommended dose and to limit their intake of alcohol [see *Dosage and Administration (2)*, *Warnings and Precautions (5.5, 5.6)*].

5.10 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, anorexia, 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 doses 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.

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

The use of ULTRACET in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated [see *Contraindications (4)*].

Patients with Chronic Pulmonary Disease: ULTRACET-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of ULTRACET [see *Warnings and Precautions (5.2)*].

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics, or altered clearance, compared to younger, healthier patients [see *Warnings and Precautions (5.2)*].

Monitor such patients closely, particularly when initiating and titrating ULTRACET and when ULTRACET is given concomitantly with other drugs that depress respiration [see *Warnings and Precautions (5.6)*, *Drug Interactions (7)*]. Alternatively, consider the use of non-opioid analgesics in these patients.

5.12 Severe Hypotension

ULTRACET may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics) [*see Drug Interactions (7)*]. Monitor these patients for signs of hypotension after initiating or titrating the dosage of ULTRACET. In patients with circulatory shock, ULTRACET may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of ULTRACET in patients with circulatory shock.

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

In patients who may be susceptible to the intracranial effects of CO₂ retention (e.g., those with evidence of increased intracranial pressure or brain tumors), ULTRACET may reduce respiratory drive, and the resultant CO₂ retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with ULTRACET.

Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of ULTRACET in patients with impaired consciousness or coma.

5.14 Serious Skin Reactions

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

5.15 Risk of Use in Patients with Gastrointestinal Conditions

ULTRACET is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus [*see Contraindications (4)*].

The tramadol in ULTRACET may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

5.16 Anaphylaxis and Other Hypersensitivity Reactions

Serious and rarely fatal anaphylactic reactions have been reported in patients receiving therapy with tramadol. When these events do occur it is often following the first dose. Other reported

allergic reactions include pruritus, hives, bronchospasm, angioedema, toxic epidermal necrolysis, and Stevens-Johnson syndrome. Patients with a history of anaphylactoid reactions to codeine and other opioids may be at increased risk and therefore should not receive ULTRACET. If anaphylaxis or other hypersensitivity occurs, stop administration of ULTRACET immediately, discontinue ULTRACET permanently, and do not rechallenge with any formulation of tramadol. Advise patients to seek immediate medical attention if they experience any symptoms of a hypersensitivity reaction [*see Contraindications (4), Information for Patients (17)*].

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

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

Due to the potential for acetaminophen hepatotoxicity at doses higher than the recommended dose, ULTRACET should not be used concomitantly with other acetaminophen containing products.

5.18 Withdrawal

Avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who are receiving a full opioid agonist analgesic, including ULTRACET. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or precipitate withdrawal symptoms [*see Drug Interactions (7)*].

When discontinuing ULTRACET, in opioid-dependent patients, gradually taper the dosage [*see Dosage and Administration (2.4)*]. Do not abruptly discontinue ULTRACET [*see Drug Abuse and Dependence (9.3)*].

5.19 Driving and Operating Machinery

ULTRACET may impair the mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of ULTRACET and know how they will react to the medication [*see Patient Counseling Information (17)*].

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed, or described in greater detail, in other sections:

- Addiction, Abuse, and Misuse [*see Warnings and Precautions (5.1)*]
- Life-Threatening Respiratory Depression [*see Warnings and Precautions (5.2)*]
- Neonatal Opioid Withdrawal Syndrome [*see Warnings and Precautions (5.3)*]
- Hepatotoxicity [*see Warnings and Precautions (5.5)*]
- Interactions with Benzodiazepines and Other CNS Depressants [*see Warnings and Precautions (5.6)*]
- Serotonin Syndrome [*see Warnings and Precautions (5.7)*]
- Seizures [*see Warnings and Precautions (5.8)*]
- Suicide [*see Warnings and Precautions (5.9)*]
- Adrenal Insufficiency [*see Warnings and Precautions (5.10)*]
- Severe Hypotension [*see Warnings and Precautions (5.12)*]
- Gastrointestinal Adverse Reactions [*see Warnings and Precautions (5.15)*]
- Hypersensitivity Reactions [*see Warnings and Precautions (5.16)*]
- Withdrawal [*see Warnings and Precautions (5.18)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The most common incidence of treatment-emergent adverse events ($\geq 3.0\%$) in subjects from clinical trials was constipation, diarrhea, nausea, somnolence, anorexia, dizziness, and sweating increased.

Table 1 shows the incidence rate of treatment-emergent adverse events reported in $\geq 2.0\%$ of subjects over five days of ULTRACET use in clinical trials (subjects took an average of at least 6 tablets per day).

Table 1: Incidence of Treatment-Emergent Adverse Events (≥2.0%)

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

* Number of males = 62

Incidence at least 1%, causal relationship at least possible or greater:

The following lists adverse reactions that occurred with an incidence of at least 1% in single-dose or repeated-dose clinical trials of ULTRACET.

Body as a Whole – Asthenia, fatigue, hot flushes

Central and Peripheral Nervous System – Dizziness, headache, tremor

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

Psychiatric Disorders – Anorexia, anxiety, confusion, euphoria, insomnia, nervousness, somnolence

Skin and Appendages – Pruritus, rash, increased sweating

Selected Adverse events occurring at less than 1%:

The following lists clinically relevant adverse reactions that occurred with an incidence of less than 1% in ULTRACET clinical trials.

Body as a Whole – Chest pain, rigors, syncope, withdrawal syndrome

Cardiovascular Disorders – Hypertension, aggravated hypertension, hypotension

Central and Peripheral Nervous System – Ataxia, convulsions, hypertonia, migraine, aggravated migraine, involuntary muscle contractions, paresthesias, stupor, vertigo

Gastrointestinal System – Dysphagia, melena, tongue edema

Hearing and Vestibular Disorders – Tinnitus

Heart Rate and Rhythm Disorders – Arrhythmia, palpitation, tachycardia

Liver and Biliary System – Hepatic function abnormal

Metabolic and Nutritional Disorders – Weight decrease

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

Red Blood Cell Disorders – Anemia

Respiratory System – Dyspnea

Urinary System – Albuminuria, micturition disorder, oliguria, urinary retention

Vision Disorders – Abnormal vision

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of tramadol-containing products. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.

Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.

Anaphylaxis: Anaphylaxis has been reported with ingredients contained in ULTRACET.

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids [see *Clinical Pharmacology (12.2)*].

Eye disorders – miosis, mydriasis

Metabolism and nutrition disorders – Cases of hypoglycemia have been reported very rarely in patients taking tramadol. Most reports were in patients with predisposing risk factors, including diabetes or renal insufficiency, or in elderly patients.

Nervous system disorders – movement disorder, speech disorder

Psychiatric disorders – delirium

Other clinically significant adverse experiences previously reported with tramadol hydrochloride:

Other events which have been reported with the use of tramadol products and for which a causal association has not been determined include: vasodilation, orthostatic hypotension, myocardial ischemia, pulmonary edema, allergic reactions (including anaphylaxis and urticaria, Stevens-Johnson syndrome/TENS), cognitive dysfunction, difficulty concentrating, depression, suicidal tendency, hepatitis, liver failure, and gastrointestinal bleeding. Reported laboratory abnormalities included elevated creatinine and liver function tests. Serotonin syndrome (whose symptoms may include mental status change, hyperreflexia, fever, shivering, tremor, agitation, diaphoresis, seizures, and coma) has been reported with tramadol when used concomitantly with other serotonergic agents such as SSRIs and MAOIs.

7 DRUG INTERACTIONS

Table 2 includes clinically significant interactions with ULTRACET.

Table 2: Clinically Significant Drug Interactions with ULTRACET

Inhibitors of CYP2D6	
<i>Clinical Impact:</i>	<p>The concomitant use of ULTRACET 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 ULTRACET 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.</p> <p>After stopping a CYP2D6 inhibitor, 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 <i>Clinical Pharmacology (12.3)</i>].</p>
<i>Intervention:</i>	<p>If concomitant use of a CYP2D6 inhibitor is necessary, follow patients closely for adverse reactions including opioid withdrawal, seizures and serotonin syndrome.</p> <p>If a CYP2D6 inhibitor is discontinued, consider lowering ULTRACET dosage until stable drug effects are achieved. Follow patients closely for adverse events including respiratory depression and sedation.</p>
<i>Examples</i>	Quinidine, fluoxetine, paroxetine and bupropion
Inhibitors of CYP3A4	
<i>Clinical Impact:</i>	The concomitant use of ULTRACET and CYP3A4 inhibitors can increase the

	<p>plasma concentration of tramadol and may result in a greater amount of metabolism via CYP2D6 and greater levels of M1. 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 ULTRACET is achieved.</p> <p>After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the tramadol plasma concentration will decrease [see <i>Clinical Pharmacology (12.3)</i>], resulting in decreased opioid efficacy and possibly signs and symptoms of opioid withdrawal in patients who had developed physical dependence to tramadol.</p>
<i>Intervention:</i>	<p>If concomitant use is necessary, consider dosage reduction of ULTRACET until stable drug effects are achieved. Follow patients closely for seizures and serotonin syndrome, and signs of respiratory depression and sedation at frequent intervals.</p> <p>If a CYP3A4 inhibitor is discontinued, consider increasing the ULTRACET dosage until stable drug effects are achieved and follow patients for signs and symptoms of opioid withdrawal.</p>
<i>Examples</i>	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), protease inhibitors (e.g., ritonavir)
CYP3A4 Inducers	
<i>Clinical Impact:</i>	<p>The concomitant use of ULTRACET and CYP3A4 inducers can decrease the plasma concentration of tramadol [see <i>Clinical Pharmacology (12.3)</i>], resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to tramadol.</p> <p>After stopping a CYP3A4 inducer, as the effects of the inducer decline, the tramadol plasma concentration will increase [see <i>Clinical Pharmacology (12.3)</i>], which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression, seizures and serotonin syndrome.</p>
<i>Intervention:</i>	<p>If concomitant use is necessary, consider increasing the ULTRACET dosage until stable drug effects are achieved. Follow patients for signs of opioid withdrawal.</p> <p>If a CYP3A4 inducer is discontinued, consider ULTRACET dosage reduction and monitor for seizures and serotonin syndrome, and signs of sedation and respiratory depression.</p> <p>Patients taking carbamazepine, a CYP3A4 inducer, 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 ULTRACET and carbamazepine is not recommended.</p>
<i>Examples:</i>	Rifampin, carbamazepine, phenytoin

Benzodiazepines and Other Central Nervous System (CNS) Depressants	
<i>Clinical Impact:</i>	Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.
<i>Intervention:</i>	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation [see <i>Warnings and Precautions (5.6)</i>].
<i>Examples:</i>	Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.
Serotonergic Drugs	
<i>Clinical Impact:</i>	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
<i>Intervention:</i>	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue ULTRACET if serotonin syndrome is suspected.
<i>Examples:</i>	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT ₃ 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).
Monoamine Oxidase Inhibitors (MAOIs)	
<i>Clinical Impact:</i>	MAOI interactions with opioids may manifest as serotonin syndrome [see <i>Warnings and Precautions (5.7)</i>] or opioid toxicity (e.g., respiratory depression, coma) [see <i>Warnings and Precautions (5.2)</i>].
<i>Intervention:</i>	Do not use ULTRACET in patients taking MAOIs or within 14 days of stopping such treatment.
<i>Examples:</i>	phenelzine, tranlycypromine, linezolid
Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics	
<i>Clinical Impact:</i>	May reduce the analgesic effect of ULTRACET and/or precipitate withdrawal symptoms.
<i>Intervention:</i>	Avoid concomitant use.
<i>Examples:</i>	butorphanol, nalbuphine, pentazocine, buprenorphine
Muscle Relaxants	
<i>Clinical Impact:</i>	Tramadol may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
<i>Intervention:</i>	Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of ULTRACET and/or the muscle relaxant as necessary.
Diuretics	
<i>Clinical Impact:</i>	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
<i>Intervention:</i>	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.

Anticholinergic Drugs	
<i>Clinical Impact:</i>	The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
<i>Intervention:</i>	Monitor patients for signs of urinary retention or reduced gastric motility when ULTRACET is used concomitantly with anticholinergic drugs.
Digoxin	
<i>Clinical Impact:</i>	Post-marketing surveillance of tramadol has revealed rare reports of digoxin toxicity.
<i>Intervention:</i>	Follow patients for signs of digoxin toxicity and adjust dosage of digoxin as needed.
Warfarin	
<i>Clinical Impact:</i>	Post-marketing surveillance of tramadol has revealed rare reports of alteration of warfarin effect, including elevation of prothrombin times.
<i>Intervention:</i>	Monitor the prothrombin time of patients on warfarin for signs of an interaction and adjust the dosage of warfarin as needed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome [see *Warnings and Precautions (5.3)*]. Available data with ULTRACET in pregnant women are insufficient to inform a drug-associated risk for major birth defects and miscarriage.

In animal reproduction studies, the combination of tramadol and acetaminophen decreased fetal weights and increased supernumerary ribs at 1.6 times the maximum recommended human daily dosage (MRHD). In separate animal reproduction studies, tramadol administration alone during organogenesis decreased fetal weights and reduced ossification in mice, rats, and rabbits at 1.4, 0.6, and 3.6 times the maximum recommended human daily dosage (MRHD). Tramadol decreased pup body weight and increased pup mortality at 1.2 and 1.9 times the MRHD.

Reproductive and developmental studies in rats and mice from the published literature identified adverse events at clinically relevant doses with acetaminophen. Treatment of pregnant rats with doses of acetaminophen approximately 1.3 times the maximum human daily dose (MRHD) showed evidence of fetotoxicity and increases in bone variations in the fetuses. In another study, necrosis was observed in the liver and kidney of both pregnant rats and fetuses at doses approximately 1.9 times the MHDD. In mice treated with acetaminophen at doses within the clinical dosing range, cumulative adverse effects on reproduction were seen in a continuous breeding study. A reduction in number of litters of the parental mating pair was observed as well as retarded growth and abnormal sperm in their offspring and reduced birth weight in the next generation [see *Data*]. Based on animal data, advise pregnant women of the potential risk to a fetus.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in respiratory depression and physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms and signs of neonatal opioid withdrawal syndrome and manage accordingly [*see Warnings and Precautions (5.3)*].

Neonatal seizures, neonatal withdrawal syndrome, fetal death and stillbirth have been reported with tramadol hydrochloride during postmarketing.

Labor or Delivery

ULTRACET is not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid induced respiratory depression in the neonate. ULTRACET is not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more appropriate. Opioid analgesics, including ULTRACET, can prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Tramadol has been shown to cross the placenta. The mean ratio of serum tramadol in the umbilical veins compared to maternal veins was 0.83 for 40 women given tramadol during labor.

The effect of ULTRACET, if any, on the later growth, development, and functional maturation of the child is unknown.

Data

Animal Data

No drug-related teratogenic effects were observed in the progeny of rats treated orally with tramadol and acetaminophen. The tramadol/acetaminophen combination product was shown to

be embryotoxic and fetotoxic in rats at a maternally toxic dose, 50/434 mg/kg tramadol/acetaminophen (1.6 times the maximum daily human tramadol/acetaminophen dosage), but was not teratogenic at this dose level. Embryo and fetal toxicity consisted of decreased fetal weights and increased supernumerary ribs. Tramadol has been shown to be embryotoxic and fetotoxic in mice, (120 mg/kg), rats (25 mg/kg) and rabbits (75 mg/kg) at maternally toxic dosages, but was not teratogenic at these dose levels. These doses on a mg/m² basis are 1.9, 0.8, and 4.9 times the maximum recommended human daily dosage (MRHD) for mouse, rat and rabbit, respectively.

No drug-related teratogenic effects were observed in progeny of mice (up to 140 mg/kg), rats (up to 80 mg/kg) or rabbits (up to 300 mg/kg) treated with tramadol by various routes. Embryo and fetal toxicity consisted primarily of decreased fetal weights, skeletal ossification and increased supernumerary ribs at maternally toxic dose levels. Transient delays in developmental or behavioral parameters were also seen in pups from rat dams allowed to deliver. Embryo and fetal lethality were reported only in one rabbit study at 300 mg/kg, a dose that would cause extreme maternal toxicity in the rabbit. The dosages listed for mouse, rat and rabbit are 2.3, 2.6, and 19 times the MRHD, respectively.

Tramadol alone was evaluated in peri- and post-natal studies in rats. Progeny of dams receiving oral (gavage) dose levels of 50 mg/kg (300 mg/m² or 1.6 times the maximum daily human tramadol dosage) or greater had decreased weights, and pup survival was decreased early in lactation at 80 mg/kg (480 mg/m² or 2.6 times the maximum daily human tramadol dosage).

Studies in pregnant rats that received oral acetaminophen during organogenesis at doses up to 1.3 times the maximum human daily dose (MHDD = 2.6 grams/day, based on a body surface area comparison) showed evidence of fetotoxicity (reduced fetal weight and length) and a dose-related increase in bone variations (reduced ossification and rudimentary rib changes). Offspring had no evidence of external, visceral, or skeletal malformations.

When pregnant rats received oral acetaminophen throughout gestation at doses of 1.9-times the MHDD (based on a body surface area comparison), areas of necrosis occurred in both the liver and kidney of pregnant rats and fetuses. These effects did not occur in animals that received oral acetaminophen at doses 0.5-times the MHDD, based on a body surface area comparison.

In a continuous breeding study, pregnant mice received 0.25, 0.5, or 1.0% acetaminophen via the diet (357, 715, or 1430 mg/kg/day). These doses are approximately 0.7, 1.3, and 2.7 times the MHDD, respectively, based on a body surface area comparison. A dose-related reduction in body weights of fourth and fifth litter offspring of the treated mating pair occurred during lactation and post-weaning at all doses. Animals in the high dose group had a reduced number of litters per mating pair, male offspring with an increased percentage of abnormal sperm, and reduced birth weights in the next generation pups.

8.2 Lactation

Risk Summary

ULTRACET is not recommended for obstetrical preoperative medication or for post-delivery analgesia in nursing mothers because its safety in infants and newborns has not been studied.

Clinical Considerations

Monitor infants exposed to ULTRACET through breast milk for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or when breast-feeding is stopped.

Data

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

8.3 Females and Males of Reproductive Potential

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 [*see Adverse Reactions (6.2), Clinical Pharmacology (12.2), Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use

The safety and efficacy of ULTRACET in patients under 18 years of age have not been established. The use of ULTRACET in the pediatric population is not recommended.

8.5 Geriatric Use

Elderly patients (aged 65 years or older) may have increased sensitivity to tramadol. In general, use caution when selecting a dosage for an elderly patient, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of ULTRACET slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression [*see Warnings and Precautions (5.2)*].

Tramadol and acetaminophen are known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

8.6 Hepatic Impairment

The pharmacokinetics and tolerability of ULTRACET in patients with impaired hepatic function have not been studied. Based on information using tramadol immediate-release tablets in subjects with advanced cirrhosis of the liver, tramadol exposure was higher and half-lives of tramadol and active metabolite M1 were longer than in subjects with normal hepatic function [see *Clinical Pharmacology (12.3)*].

As tramadol and acetaminophen are both extensively metabolized by the liver, the use of ULTRACET in patients with hepatic impairment is not recommended [see *Warnings and Precautions (5.5)*].

8.7 Renal Impairment

The pharmacokinetics and tolerability of ULTRACET in patients with renal impairment has not been studied. Based on studies using tramadol extended-release tablets, the excretion of tramadol and metabolite M1 is reduced in patients with creatinine clearance of less than 30 mL/min. In patients with creatinine clearances of less than 30 mL/min, it is recommended that the dosage of ULTRACET not exceed 2 tablets every 12 hours. [see *Dosage and Administration (2.2)*]. 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. Monitor closely for signs of respiratory depression, sedation, and hypotension.

8.8 Sex

Tramadol clearance was 20% higher in female subjects compared to males in four Phase 1 studies of ULTRACET in 50 male and 34 female healthy subjects. The clinical significance of this difference is unknown.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

ULTRACET contains tramadol, a Schedule IV controlled substance.

9.2 Abuse

ULTRACET contains tramadol, a substance with a high potential for abuse similar to other opioids and can be abused and is subject to misuse, addiction, and criminal diversion [see *Warnings and Precautions (5.1)*].

All patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful, or potentially harmful, consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

“Drug seeking” behavior is very common in persons with substance use disorders. Drug seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated “loss” of prescriptions, tampering with prescriptions, and reluctance to provide prior medical records or contact information for other treating physician(s). “Doctor shopping” (visiting multiple prescribers) to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Health care providers should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

ULTRACET, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Risks Specific to Abuse of ULTRACET

ULTRACET is for oral use only. Abuse of ULTRACET poses a risk of overdose and death. The risk is increased with concurrent abuse of ULTRACET with alcohol and other central nervous system depressants.

Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

9.3 Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

ULTRACET should not be abruptly discontinued in a physically dependent patient [*see Dosage and Administration (2.4)*]. If ULTRACET is abruptly discontinued in a physically-dependent patient, a withdrawal syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs [*see Use in Specific Populations (8.1)*].

10 OVERDOSAGE

Clinical Presentation

ULTRACET is a combination drug. The clinical presentation of overdose may include the signs and symptoms of tramadol toxicity, acetaminophen 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 an acetaminophen overdose are: anorexia, nausea, vomiting, malaise, pallor and diaphoresis.

Tramadol

Acute overdosage with tramadol can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring, seizures, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations.

Deaths due to overdose have been reported with abuse and misuse of tramadol [*see Warnings and Precautions (5.1)*]. Review of case reports has indicated that the risk of fatal overdose is

further increased when tramadol is abused concurrently with alcohol or other CNS depressants, including other opioids.

Acetaminophen

In acute acetaminophen overdose, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and thrombocytopenia also occur. Plasma acetaminophen levels > 300 mcg/mL at 4 hours after oral ingestion were associated with hepatic damage in 90% of patients; minimal hepatic damage is anticipated if plasma levels at 4 hours are < 150 mcg/mL or < 37.5 mcg/mL at 12 hours after ingestion. Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis, and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

Treatment of Overdose

A single or multiple drug overdose with tramadol and acetaminophen is a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended. Immediate treatment includes support of cardiorespiratory function and measures to reduce drug absorption. Oxygen, intravenous fluids, vasopressors, assisted ventilation, and other supportive measures should be employed as indicated.

Tramadol

In case of overdose, priorities are the re-establishment of a patent and protected airway and institution of assisted or controlled ventilation, if needed. Employ other supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life-support techniques.

The opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose.

For clinically significant respiratory or circulatory depression secondary to tramadol overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to tramadol overdose.

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

Because the duration of opioid reversal is expected to be less than the duration of action of tramadol in ULTRACET, carefully monitor the patient until spontaneous respiration is reliably

re-established. If the response to an opioid antagonist is suboptimal or only brief in nature, administer additional antagonist as directed by the product's prescribing information.

In an individual physically dependent on opioids, administration of the recommended usual dosage of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be begun with care and by titration with smaller than usual doses of the antagonist.

Acetaminophen

If an acetaminophen overdose is suspected, obtain a serum acetaminophen assay as soon as possible, but no sooner than 4 hours following oral ingestion. Obtain liver function studies initially and repeat at 24-hour intervals. Administer the antidote N-acetylcysteine (NAC) as early as possible. As a guide to treatment of acute ingestion, the acetaminophen level can be plotted against time since oral ingestion on a nomogram (Rumack-Matthew). The lower toxic line on the nomogram is equivalent to 150 mcg/mL at 4 hours and 37.5 mcg/mL at 12 hours. If serum level is above the lower line, administer the entire course of NAC treatment. Withhold NAC therapy if the acetaminophen level is below the lower line.

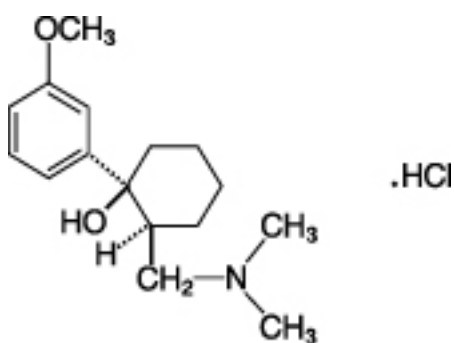
Gastric decontamination with activated charcoal should be administered just prior to N-acetylcysteine (NAC) to decrease systemic absorption if acetaminophen ingestion is known or suspected to have occurred within a few hours of presentation. Serum acetaminophen levels should be obtained immediately if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

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

11 DESCRIPTION

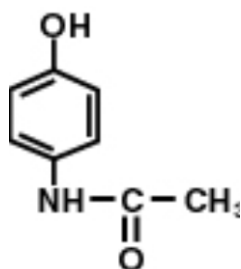
ULTRACET (tramadol hydrochloride/acetaminophen) Tablets combines two analgesics, tramadol hydrochloride and opioid agonist, and acetaminophen.

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



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

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



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

ULTRACET tablets contain 37.5 mg of tramadol hydrochloride and 325 mg acetaminophen and are light yellow in color. Inactive ingredients in the tablet are carnauba wax, corn starch, hypromellose, iron oxide, magnesium stearate, polyethylene glycol, polysorbate 80, powdered cellulose, pregelatinized corn starch, sodium starch glycolate, and titanium dioxide.

Meets USP Dissolution Test 2.

12 CLINICAL PHARMACOLOGY

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

12.1 Mechanism of Action

ULTRACET contains tramadol, an opioid agonist and inhibitor of norepinephrine and serotonin re-uptake, and acetaminophen. Although the mode of action of tramadol is not completely understood, the analgesic effect of tramadol is believed to be due to both binding to μ -opioid receptors and weak inhibition of reuptake of norepinephrine and serotonin.

Opioid activity of tramadol is due to both low affinity binding of the parent compound and higher affinity binding of the *O*-demethylated metabolite M1 to μ -opioid receptors. In animal models, M1 is up to 6 times more potent than tramadol in producing analgesia and 200 times more potent in μ -opioid binding. Tramadol-induced analgesia is only partially antagonized by the opiate antagonist naloxone in several animal tests. The relative contribution of both tramadol and M1 to human analgesia is dependent upon the plasma concentrations of each compound [*see Clinical Pharmacology (12.3)*].

Tramadol has been shown to inhibit reuptake of norepinephrine and serotonin *in vitro*, as have some other opioid analgesics. These mechanisms may contribute independently to the overall analgesic profile of tramadol.

Acetaminophen is a non-opioid, non-salicylate analgesic. The site and mechanism for the analgesic effect of acetaminophen has not been determined but is thought to primarily involve central actions.

12.2 Pharmacodynamics

Effects on the Central Nervous System

Tramadol produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to both increases in carbon dioxide tension and electrical stimulation.

Tramadol causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origins may produce similar findings). Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations.

Effects on the Gastrointestinal Tract and Other Smooth Muscle

Tramadol causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Effects on the Cardiovascular System

Tramadol produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Effects on the Endocrine System

Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans [*see Warnings and Precautions (5.10), Adverse Reactions (6.2)*]. They

also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

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 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 [*see Adverse Reactions (6.2)*].

Effects on the Immune System

Opioids have been shown to have a variety of effects on components of the immune system in *in vitro* and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

Concentration–Efficacy Relationships

The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with potent opioid agonists. The minimum effective analgesic concentration of tramadol for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome and/or the development of analgesic tolerance [*see Dosage and Administration (2.1)*].

Concentration–Adverse Reaction Relationships

There is a relationship between increasing tramadol plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions [*see Dosage and Administration (2.1, 2.2)*].

12.3 Pharmacokinetics

Tramadol is administered as a racemate and both the [-] and [+] forms of both tramadol and M1 are detected in the circulation.

Absorption

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

The pharmacokinetics of plasma tramadol and acetaminophen following oral administration of one ULTRACET tablet are shown in Table 3. Tramadol has a slower absorption and longer half-life when compared to acetaminophen.

Table 3: Summary of Mean (\pm SD) Pharmacokinetic Parameters of the (+)- and (-) Enantiomers of Tramadol and M1 and Acetaminophen Following A Single Oral Dose Of One Tramadol/Acetaminophen Combination Tablet (37.5 mg/325 mg) in Volunteers

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

^a For acetaminophen, C_{max} was measured as mcg/mL.

A single-dose pharmacokinetic study of ULTRACET in volunteers showed no drug interactions between tramadol and acetaminophen.

Upon multiple oral dosing to steady state, however, the bioavailability of tramadol and metabolite M1 was lower for the combination tablets compared to tramadol administered alone. The decrease in AUC was 14% for (+)-tramadol, 10.4% for (-)-tramadol, 11.9% for (+)-M1, and 24.2% for (-)-M1. The cause of this reduced bioavailability is not clear.

Peak plasma concentrations of acetaminophen occur within one hour and are not affected by co-administration with tramadol. Following single- or multiple-dose administration of ULTRACET, no significant change in acetaminophen pharmacokinetics was observed when compared to acetaminophen given alone.

Food Effect

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

Distribution

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

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

Elimination

Tramadol is eliminated primarily through metabolism by the liver and the metabolites are eliminated primarily by the kidneys. The mean (SD) apparent total clearance of tramadol after a single 37.5 mg dose is 588 (226) mL/min for the (+) isomer and 736 (244) mL/min for the (-) isomer. The plasma elimination half-lives of racemic tramadol and M1 are approximately 5-6

and 7 hours, respectively, after administration of ULTRACET. The apparent plasma elimination half-life of racemic tramadol increased to 7-9 hours upon multiple dosing of ULTRACET.

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

Metabolism

Following oral administration, tramadol is extensively metabolized by a number of pathways, including CYP2D6 and CYP3A4, as well as by conjugation of parent and metabolites. The major metabolic pathways appear to be *N*- and *O*-demethylation and glucuronidation or sulfation in the liver. Metabolite M1 (*O*-desmethyltramadol) is pharmacologically active in animal models. Formation of M1 is dependent on CYP2D6 and as such is subject to inhibition, which may affect the therapeutic response [*see Drug Interactions (7)*].

Approximately 7% of the population has reduced activity of the CYP2D6 isoenzyme of cytochrome P450. These individuals are “poor metabolizers” of debrisoquine, dextromethorphan, and tricyclic antidepressants, among other drugs. Based on a population PK analysis of Phase I studies in healthy subjects, concentrations of tramadol were approximately 20% higher in “poor metabolizers” versus “extensive metabolizers,” while M1 concentrations were 40% lower. *In vitro* drug interaction studies in human liver microsomes indicate that inhibitors of CYP2D6 such as fluoxetine and its metabolite norfluoxetine, amitriptyline, and quinidine inhibit the metabolism of tramadol to various degrees. The full pharmacological impact of these alterations in terms of either efficacy or safety is unknown.

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

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

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

Excretion

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

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

Special Populations

Hepatic Impairment

Pharmacokinetics of tramadol was studied in patients with mild or moderate hepatic impairment after receiving multiple doses of tramadol extended-release 100 mg. The exposure of (+)- and (-)-tramadol was similar in mild and moderate hepatic impairment patients in comparison to patients with normal hepatic function. However, exposure of (+)- and (-)-M1 decreased ~50% with increased severity of the hepatic impairment (from normal to mild and moderate). The pharmacokinetics of tramadol after the administration of tramadol extended-release has not been studied in patients with severe hepatic impairment. After the administration of tramadol immediate-release tablets to patients with advanced cirrhosis of the liver, tramadol area under the plasma concentration time curve was larger and the tramadol and M1 half-lives were longer than subjects with normal hepatic function [*see Use in Specific Populations (8.6)*].

Renal Impairment

Impaired renal function results in a decreased rate and extent of excretion of tramadol and its active metabolite, M1. The pharmacokinetics of tramadol were studied in patients with mild or moderate renal impairment after receiving multiple doses of tramadol extended-release 100 mg. There is no consistent trend observed for tramadol exposure related to renal function in patients with mild (CLcr: 50-80 mL/min) or moderate (CLcr: 30-50 mL/min) renal impairment in comparison to patients with normal renal function. However, exposure of M1 increased 20-40% with increased severity of the renal impairment (from normal to mild and moderate). tramadol extended-release has not been studied in patients with severe renal impairment (CLcr < 30 mL/min). The total amount of tramadol and M1 removed during a 4-hour dialysis period is less than 7% of the administered dose [*see Dosage and Administration (2.3), Use in Specific Populations (8.7)*].

Geriatric Population

A population pharmacokinetic analysis of data obtained from a clinical trial in patients with chronic pain treated with ULTRACET, which included 55 patients between 65 and 75 years of age and 19 patients over 75 years of age, showed no significant changes in the pharmacokinetics of tramadol and acetaminophen in elderly patients with normal renal and hepatic function [*see Use in Specific Populations (8.5)*]

Sex

Tramadol clearance was 20% higher in female subjects compared to males on four Phase 1 studies of ULTRACET in 50 male and 34 female healthy subjects.

Poor / Extensive Metabolizers, CYP2D6

The formation of the active metabolite, M1, is mediated by CYP2D6. Approximately 7% of the population has reduced activity of the CYP2D6 isoenzyme of cytochrome P-450. These individuals are “poor metabolizers” of debrisoquine, dextromethorphan, and tricyclic antidepressants, among other drugs. Based on a population PK analysis of Phase I studies with immediate-release tablets in healthy subjects, concentrations of tramadol were approximately 20% higher in “poor metabolizers” versus “extensive metabolizers,” while M1 concentrations were 40% lower.

Drug Interaction Studies

CYP2D6 Inhibitors

In vitro drug interaction studies in human liver microsomes indicate that inhibitors of CYP2D6 (fluoxetine, norfluoxetine, amitriptyline, and quinidine) inhibit the metabolism of tramadol to various degrees, suggesting that concomitant administration of these compounds could result in increases in tramadol concentrations and decreased concentrations of M1. The full pharmacological impact of these alterations in terms of either efficacy or safety is unknown.

Quinidine

Tramadol is metabolized to M1 by CYP2D6. A study was conducted to examine the effect of quinidine, a selective inhibitor of CYP2D6, on the pharmacokinetics of tramadol by administering 200 mg quinidine two hours before the administration of 100 mg tramadol extended release tablet. The results demonstrated that the exposure of tramadol increased 50-60% and the exposure of M1 decreased 50-60%. *In vitro* drug interaction studies in human liver microsomes indicate that tramadol has no effect on quinidine metabolism [see *Warnings and Precautions (5.4) and Drug Interactions (7)*].

Cimetidine

Concomitant administration of tramadol and cimetidine does not result in clinically significant changes in tramadol pharmacokinetics. Therefore, no alteration of the ULTRACET dosage regimen is recommended.

CYP3A4 Inhibitors and Inducers

Tramadol is metabolized by CYP3A4. Administration of CYP3A4 inhibitors, such as ketoconazole and erythromycin, or CYP3A4 inducers, such as rifampin and St. John’s Wort, with tramadol may affect the metabolism of tramadol leading to altered tramadol exposure [see *Warnings and Precautions (5.2 and 5.4) and Drug Interactions (7)*].

Carbamazepine

Carbamazepine, a CYP3A4 inducer, increases tramadol metabolism. Patients taking carbamazepine may have a significantly reduced analgesic effect of tramadol. Concomitant administration of tramadol and carbamazepine is not recommended.

Potential for Tramadol to Affect Other Drugs

In vitro studies indicate that tramadol is unlikely to inhibit the CYP3A4-mediated metabolism of other drugs when tramadol is administered concomitantly at therapeutic doses. Tramadol does not appear to induce its own metabolism in humans, since observed maximal plasma concentrations after multiple oral doses are higher than expected based on single dose data.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Carcinogenesis

A slight but statistically significant increase in two common murine tumors, pulmonary and hepatic, was observed in an NMRI mouse carcinogenicity study, particularly in aged mice. Mice were dosed orally up to 30 mg/kg in the drinking water (0.5 times the maximum recommended daily human dosage or MRHD) for approximately two years, although the study was not done with the Maximum Tolerated Dose. This finding is not believed to suggest risk in humans. No evidence of carcinogenicity was noted in a rat 2-year carcinogenicity study testing oral doses of up to 30 mg/kg in the drinking water (1 times the MRHD).

Long-term studies in mice and rats have been completed by the National Toxicology Program to evaluate the carcinogenic potential of acetaminophen. In 2-year feeding studies, F344/N rats and B6C3F1 mice were fed a diet containing acetaminophen up to 6000 ppm. Female rats demonstrated equivocal evidence of carcinogenic activity based on increased incidences of mononuclear cell leukemia at 1.2 times the maximum human daily dose (MHDD) of 2.6 grams/day, based on a body surface area comparison. In contrast, there was no evidence of carcinogenic activity in male rats (1.1 times) or mice (1.9-2.2 times the MHDD, based on a body surface area comparison).

Mutagenesis

Tramadol was mutagenic in the presence of metabolic activation in the mouse lymphoma assay. Tramadol was not mutagenic in the *in vitro* bacterial reverse mutation assay using *Salmonella* and *E. coli* (Ames), the mouse lymphoma assay in the absence of metabolic activation, the *in vitro* chromosomal aberration assay, or the *in vivo* micronucleus assay in bone marrow.

Acetaminophen was not mutagenic in the bacterial reverse mutation assay (Ames test). In contrast, acetaminophen tested positive for induction of sister chromatid exchanges and chromosomal aberrations in *in vitro* assays using Chinese hamster ovary cells. In the published literature, acetaminophen has been reported to be clastogenic when administered a dose of 1500 mg/kg/day to the rat model (3.6-times the MHDD, based on a body surface area

comparison). In contrast, no clastogenicity was noted at a dose of 750 mg/kg/day (2.8-times the MHDD, based on a body surface area comparison), suggesting a threshold effect.

Impairment of Fertility

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. These dosages are 1.6 and 2.4 times the MRHD [*see Use in Specific Populations (8.3)*].

In studies of acetaminophen conducted by the National Toxicology Program, fertility assessments have been completed in Swiss mice via a continuous breeding study. There were no effects on fertility parameters in mice consuming up to 1.7 times the MHDD of acetaminophen, based on a body surface area comparison. Although there was no effect on sperm motility or sperm density in the epididymis, there was a significant increase in the percentage of abnormal sperm in mice consuming 1.7 times the MHDD (based on a body surface area comparison) and there was a reduction in the number of mating pairs producing a fifth litter at this dose, suggesting the potential for cumulative toxicity with chronic administration of acetaminophen near the upper limit of daily dosing.

Published studies in rodents report that oral acetaminophen treatment of male animals at doses that are 1.2 times the MHDD and greater (based on a body surface area comparison) result in decreased testicular weights, reduced spermatogenesis, reduced fertility, and reduced implantation sites in females given the same doses. These effects appear to increase with the duration of treatment. The clinical significance of these findings is not known.

14 CLINICAL STUDIES

Single-Dose Studies for Treatment of Acute Pain

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

16 HOW SUPPLIED/STORAGE AND HANDLING

ULTRACET (tramadol hydrochloride/acetaminophen) tablets containing 37.5 mg tramadol hydrochloride and 325 mg acetaminophen are light yellow, coated, capsule-shaped tablets debossed with “O-M” on one side and “650” on the other and are available as follows:

100's:	NDC 50458-650-60	Bottles of 100 tablets
HUD 100's:	NDC 50458-650-10	Packages of 100 unit doses in blister packs, 10 cards of 10 tablets each

Dispense in a tight container. Store at 20 – 25°C (68 – 77°F); excursions permitted to 15 – 30°C (59 – 86°F). [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Addiction, Abuse, and Misuse

Inform patients that the use of ULTRACET, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death [see *Warnings and Precautions (5.1)*]. Instruct patients not to share ULTRACET with others and to take steps to protect ULTRACET from theft or misuse.

Life-Threatening Respiratory Depression

Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting ULTRACET or when the dosage is increased, and that it can occur even at recommended dosages [see *Warnings and Precautions (5.2)*]. Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

Accidental Ingestion

Inform patients that accidental ingestion, especially by children, may result in respiratory depression or death [see *Warnings and Precautions (5.2)*]. Instruct patients to take steps to store ULTRACET securely and to dispose of unused ULTRACET in accordance with the local state guidelines and/or regulations.

Interactions with Benzodiazepines and Other CNS Depressants

Inform patients and caregivers that potentially fatal additive effects may occur if ULTRACET is used with benzodiazepines or other CNS depressants, including alcohol, and not to use these concomitantly unless supervised by a healthcare provider [see *Warnings and Precautions (5.6), Drug Interactions (7)*].

Serotonin Syndrome

Inform patients that tramadol could cause a rare but potentially life-threatening condition, particularly during concomitant use with serotonergic drugs. Warn patients of the symptoms and signs of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their healthcare provider if they are taking, or plan to take serotonergic medications [see *Warnings and Precautions (5.7)*].

MAOI Interaction

Inform patients not to take ULTRACET while using any drugs that inhibit monoamine oxidase. Patients should not start MAOIs while taking ULTRACET [*see Drug Interactions (7)*].

Seizures

Inform patients that ULTRACET may cause seizures with concomitant use of serotonergic agents (including SSRIs, SNRIs, and triptans) or drugs that significantly reduce the metabolic clearance of tramadol [*see Warnings and Precautions (5.8)*].

Adrenal Insufficiency

Inform patients that opioids could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms [*see Warnings and Precautions (5.10)*].

Important Administration Instructions

Instruct patients how to properly take ULTRACET [*see Dosage and Administration (2)*].

- Do not adjust the dose of ULTRACET without consulting with a physician or other healthcare provider.
- Do not take more than 4000 milligrams of acetaminophen per day and to call their healthcare provider if they took more than the recommended dose.

Hypotension

Inform patients that ULTRACET may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position) [*see Warnings and Precautions (5.12)*].

Anaphylaxis

Inform patients that anaphylaxis have been reported with ingredients contained in ULTRACET. Advise patients how to recognize such a reaction and when to seek medical attention [*see Contraindications (4), Warnings and Precautions (5.16), Adverse Reactions (6)*].

Pregnancy

Neonatal Opioid Withdrawal Syndrome

Inform female patients of reproductive potential that ULTRACET should not be used for more than 5 days and that prolonged use of opioids such as ULTRACET, during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated [*see Warnings and Precautions (5.3) and Use in Specific Populations (8.1)*].

Embryo-Fetal Toxicity

Inform female patients of reproductive potential that ULTRACET can cause fetal harm and to inform the healthcare provider of a known or suspected pregnancy [*see Use in Specific Populations (8.1)*].

Lactation

Advise nursing mothers to monitor infants for increased sleepiness (more than usual), breathing difficulties, or limpness. Instruct nursing mothers to seek immediate medical care if they notice these signs [*see Use in Specific Populations (8.2)*].

Infertility

Inform patients that chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible [*Use in Specific Populations (8.3)*].

Driving or Operating Heavy Machinery

Inform patients that ULTRACET may impair the ability to perform potentially hazardous activities such as driving a car or operating heavy machinery. Advise patients not to perform such tasks until they know how they will react to the medication [*see Warnings and Precautions (5.19)*].

Constipation

Advise patients of the potential for severe constipation, including management instructions and when to seek medical attention [*see Adverse Reactions (6)*].

Disposal of Unused ULTRACET

Advise patients to throw the unused ULTRACET in the household trash following these steps. 1) Remove the drugs from their original containers and mix with an undesirable substance, such as used coffee grounds or kitty litter (this makes the drug less appealing to children and pets, and unrecognizable to people who may intentionally go through the trash seeking drugs). 2) Place the mixture in a sealable bag, empty can, or other container to prevent the drug from leaking or breaking out of a garbage bag.

Maximum Daily Acetaminophen Use

Advise patients not to take more than 4,000 milligrams of acetaminophen per day and call their doctor if they have taken more than the recommended dose [*see Warnings and Precautions (5.5, 5.17)*].

Use with Other Acetaminophen-Containing Products

Advise patients not to take ULTRACET in combination with other tramadol or acetaminophen-containing products, including over-the-counter preparations [*see Warnings and Precautions (5.5, 5.17)*].

Manufactured by:
Janssen Ortho, LLC
Gurabo, Puerto Rico 00778

Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, New Jersey 08560

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<p style="text-align: center;">Medication Guide ULTRACET® [UHL-truh-set] (tramadol hydrochloride/acetaminophen) Tablets, CIV</p>
<p>ULTRACET is:</p> <ul style="list-style-type: none">• A strong prescription pain medicine that contains an opioid (narcotic) that is used for the short-term (five days or less) management of acute pain, when other pain treatments such as non-opioid pain medicines do not treat your pain well enough or you cannot tolerate them.• An opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death.
<p>Important information about ULTRACET:</p> <ul style="list-style-type: none">• Get emergency help right away if you take too much ULTRACET (overdose). When you first start taking ULTRACET, when your dose is changed, or if you take too much (overdose), serious or life-threatening breathing problems that can lead to death may occur.• ULTRACET can cause severe drowsiness, breathing problems (respiratory depression), coma and death when taken with benzodiazepines or other medicines that depress consciousness.• Never give anyone else your ULTRACET. They could die from taking it. Store ULTRACET away from children and in a safe place to prevent stealing or abuse. Selling or giving away ULTRACET is against the law.• Get emergency help right away if you take more than 4,000 mg of acetaminophen in 1 day. Taking ULTRACET with other products that contain acetaminophen can lead to serious liver problems and death.
<p>Do not take ULTRACET if you have:</p> <ul style="list-style-type: none">• Severe asthma, trouble breathing, or other lung problems.• A bowel blockage or have narrowing of the stomach or intestines.• An allergy to any of its ingredients (e.g., tramadol hydrochloride or acetaminophen).• Taken a Monoamine Oxidase Inhibitor, MAOI, (medicine used for depression) within the last 14 days.
<p>Before taking ULTRACET, tell your healthcare provider if you have a history of:</p> <ul style="list-style-type: none">• head injury, seizures• problems urinating• abuse of street or prescription drugs, alcohol addiction, or mental health problems.• liver, kidney, thyroid problems• pancreas or gallbladder problems <p>Tell your healthcare provider if you are:</p> <ul style="list-style-type: none">• pregnant or planning to become pregnant. Prolonged use of ULTRACET during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.• breastfeeding. ULTRACET passes into breast milk and may harm your baby.• taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking ULTRACET with certain other medicines can cause serious side effects that could lead to death.
<p>When taking ULTRACET:</p> <ul style="list-style-type: none">• Do not change your dose. Take ULTRACET exactly as prescribed by your healthcare provider. Use the lowest dose possible for the shortest time needed.• Take your prescribed dose: 2 tablets every 4 to 6 hours as needed for pain relief for a maximum of 5 days. Do not take more than your prescribed dose and do not take more than 8 tablets per day. If you miss a dose, take your next dose at your usual time.• Call your healthcare provider if the dose you are taking does not control your pain.• If you have been taking ULTRACET regularly, do not stop taking ULTRACET without talking to your healthcare provider.

- After you stop taking ULTRACET, ask your pharmacist how to dispose of any unused tablets.

While taking ULTRACET DO NOT:

- Drive or operate heavy machinery, until you know how ULTRACET affects you. ULTRACET can make you sleepy, dizzy, or lightheaded.
- Drink alcohol or use prescription or over-the-counter medicines that contain alcohol. Using products containing alcohol during treatment with ULTRACET may cause you to overdose and die.

The possible side effects of ULTRACET:

- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain. Call your healthcare provider if you have any of these symptoms and they are severe.

Get emergency medical help if you have:

- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue, or throat, extreme drowsiness, light-headedness when changing positions, feeling faint, agitation, high body temperature, trouble walking, stiff muscles, or mental changes such as confusion.

These are not all the possible side effects of ULTRACET. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. **For more information go to dailymed.nlm.nih.gov**

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This Medication Guide has been approved by the U.S. Food and Drug Administration.

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