# Pediatric, Adult Lupus Have Little in Common

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CHICAGO — A substantial chasm exists between children and adults when it comes to the diagnosis, course, and treatment of lupus erythematosus, Dr. Kathleen M. O'Neil said at a symposium sponsored by the American College of Rheumatology.

"Kids with lupus are not adults with lupus," she said, noting that children with prepubertal onset often do not have fatigue but they do have alopecia, whereas teens and adults are more likely to have fatigue. When asked, children will say they feel tired, but their fatigue levels still remain well below those of older kids, according to Dr. O'Neil, professor of pediatric rheumatology at the University of Oklahoma, Oklahoma City.

Children with vague and miscellaneous aches and pains often are evaluated for lupus, and there's a common misconception that a positive antinuclear antibody (ANA) test result is as reliable an indicator of lupus in children as it is in adults. While antinuclear antibody is positive in all children with systemic lupus erythematosus (SLE), an estimated "30%-35% of children who are healthy have a positive ANA, if we use the normal cutoff of 1:40 defined in adults," she said in an interview.

In addition, the ANA does not discriminate healthy children from children with systemic lupus erythematosus (SLE) unless the titer used is 1:320 or greater. "A misdiagnosis puts parents through unnecessary stress and they get frightened, especially when they research lupus on the Internet," she said.

Another lab finding that supports a diagnosis of SLE in children is positivity for anti-DNA antibodies, "which are present in 67% of our children with lupus onset over age 13 and 100% of those under age 13." Evidence of complement consumption and low serum C3 and/or C4 concentrations are also supportive, Dr. O'Neil said.

Complement deficiency and early complement component deficiencies may account for 20% to 30% of prepubertal lupus onset, most easily identified with a CH50 screening test in all SLE children under the age of 10, she said. When a very young child develops SLE, environmental factors probably play less of a role than in the typical adult patient, suggesting a greater role for genetic factors.

In the absence of an approved drug regimen for children with lupus, treatment must be extrapolated from clinical experience and the results of clinical trials involving adult patients. "But we have to treat these children, because their disease is quite aggressive and they do die from renal failure," said Dr. O'Neil.

The child's future fertility and bone and heart health can be adversely affected by such drugs as cyclophosphamide and steroids. Future fertility does concern adolescents, but they usually will not acknowledge that concern. "So it's important to do that for them." Raise these issues with them, and realize that "if they say they're feeling fine, don't accept that. You still have to do a very careful and directed review of systems each time you see these young patients," she said. "And when you're putting a 16- or 17-year-old boy on cyclophosphamide, don't forget to talk to him about sperm donation and storage."

"Nonsteroidal anti-inflammatory drugs can be helpful in treating the arthritis, pericarditis, and pleuritis in lupus, but they have to be used with caution in case of underlying kidney disease," she said. Exercise is important for maintaining bone density, especially in patients taking steroids.

Premature atherosclerosis can occur in the adolescent lupus patient, and treating procoagulant phenotype in children can be very tricky because the metabolism of young lupus patients is complex. Most pediatric hematologist-oncologists anticoagulate with low-molecular-weight heparin. "Children metabolize oral anticoagulants differently than adults do, and their diets are more varied, and that changes the absorption rate of the drug. Furthermore, they can get infections, which change drug metabolism, so their clotting times can vary widely," Dr. O'Neil said.

Antiphospholipid antibodies in lupus increase coagulation, but the overall result of this can be variable. The pediatric SLE patient can be excessively anticoagulated one week and then be inadequately anticoagulated a week later. "By using low-molecular-weight heparin, it's easier to set the dosage, to predict what the drug is going to do, and to maintain a steady anticoagulation," she said in an interview. ■

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**BRIEF SUMMARY. CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION.**

**INDICATIONS AND USAGE:** ULTRAM ER is indicated for the management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period of time.

**CONTRAINDICATIONS:** ULTRAM ER should not be administered to patients who have previously demonstrated hypersensitivity to tramadol, any other component of this product or opioids. ULTRAM ER is contraindicated in any situation where opioids are contraindicated, including acute intoxication with any of the following: alcohol, hypnotics, narcotics, centrally acting analgesics, opioids or psychotropic drugs. ULTRAM ER may worsen central nervous system and respiratory depression in these patients.

**WARNINGS: Seizure Risk: 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: 1. Selective serotonin re-uptake inhibitors (SSRI antidepressants or anorectics), 2. Tricyclic antidepressants (TCAs), and other tricyclic compounds (e.g., cyclobenzaprine, promethazine, etc.), or 3. Other opioids. Administration of tramadol may enhance the seizure risk in patients taking: 1. MAO inhibitors (see also WARNINGS - Use with MAO Inhibitors), 2. Neuroleptics, or 3. Other drugs that reduce the seizure threshold. Risk of convulsions may also increase in patients with epilepsy, those with a history of seizures, or in patients with a recognized risk for seizure (such as head trauma, metabolic disorders, alcohol and drug withdrawal, CNS infections). In tramadol overdose, naloxone administration may increase the risk of seizure.**

**Suicide Risk: 1. Do not prescribe ULTRAM ER for patients who are suicidal or addiction-prone. 2. Prescribe ULTRAM ER with caution for patients taking tranquilizers or antidepressant drugs and patients who use alcohol in excess. 3. Tell your patients not to exceed the recommended dose and to limit their intake of alcohol.**

Tramadol products in excessive doses, either alone or in combination with other CNS depressants, including alcohol, are a major cause of drug-related deaths. Fatalities within the first hour of overdosage are not uncommon. Tramadol should not be taken in doses higher than those recommended by the physician. The judicious prescribing of tramadol is essential to the safe use of this drug. With patients who are depressed or suicidal, consideration should be given to the use of non-narcotic analgesics. Patients should be cautioned about the concomitant use of tramadol products and alcohol because of potentially serious CNS-additive effects of these agents. Because of its added depressant effects, tramadol should be prescribed with caution for those patients whose medical condition requires the concomitant administration of sedatives, tranquilizers, muscle relaxants, antidepressants, or other CNS-depressant drugs. Patients should be advised of the additive depressant effects of these combinations. Many of the tramadol-related deaths have occurred in patients with previous histories of emotional disturbances or suicidal ideation or attempts as well as histories of misuse of tranquilizers, alcohol, and other CNS-active drugs. Some deaths have occurred as a consequence of the accidental ingestion of excessive quantities of tramadol alone or in combination with other drugs. Patients taking tramadol should be warned not to exceed the dose recommended by their physician.

**Anaphylactoid Reactions:** Serious and rarely fatal anaphylactoid 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 ULTRAM ER (see **CONTRAINDICATIONS**).

**Respiratory Depression:** Administer ULTRAM ER cautiously in patients at risk for respiratory depression. In these patients alternative non-opioid analgesics should be considered. When large doses of tramadol are administered with anesthetic medications or alcohol, respiratory depression may result. Respiratory depression should be treated as an overdose. If naloxone is to be administered, use cautiously because it may precipitate seizures (see **WARNINGS - Seizure Risk** and **OVERDOSAGE**).

**Interaction With Central Nervous System (CNS) Depressants:** ULTRAM ER should be used with caution and in reduced dosages when administered to patients receiving CNS depressants such as alcohol, opioids, anesthetic agents, narcotics, phenothiazines, tranquilizers or sedative hypnotics. ULTRAM ER increases the risk of CNS and respiratory depression in these patients.

**Increased Intracranial Pressure or Head Trauma:** ULTRAM ER should be used with caution in patients with increased intracranial pressure or head injury. The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, and may be markedly exaggerated in these patients. Additionally, pupillary changes (miosis) from tramadol may obscure the existence, extent, or course of intracranial pathology. Clinicians should also maintain a high index of suspicion for adverse drug reaction when evaluating altered mental status in these patients if they are receiving ULTRAM ER (see **WARNINGS - Respiratory Depression**).

**Use in Ambulatory Patients:** ULTRAM ER may impair the mental and or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using this drug should be cautioned accordingly.

**Use With MAO Inhibitors and Serotonin Re-uptake Inhibitors:** Use ULTRAM ER with great caution in patients taking monoamine oxidase inhibitors. Animal studies have shown increased deaths with combined administration. Concomitant use of ULTRAM ER with MAO inhibitors or SSRIs increases the risk of adverse events, including seizure and serotonin syndrome.

**Withdrawal:** Withdrawal symptoms may occur if ULTRAM ER is discontinued abruptly. These symptoms may include: anxiety, sweating, insomnia, rigors, pain, nausea, tremors, diarrhea, upper respiratory symptoms, piloerection, and rarely hallucinations. Clinical experience suggests that withdrawal symptoms may be reduced by tapering ULTRAM ER.

**Misuse, Abuse and Diversion of Opioids:** Tramadol is an opioid agonist of the morphine-type. Such drugs are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Tramadol can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing ULTRAM ER in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. ULTRAM ER could be abused by crushing, chewing, snorting, or injecting the dissolved product. These practices will result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death (see **WARNINGS** and **DRUG ABUSE AND ADDICTION**). Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. The development of addiction to opioid analgesics in properly managed patients with pain has been reported to be rare. However, data are not available to establish the true incidence of addiction in chronic pain patients. Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

**Interactions with Alcohol and Drugs of Abuse:** Tramadol may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

**DRUG ABUSE AND ADDICTION: ULTRAM ER is a mu-agonist opioid. Tramadol, like other opioids used in analgesia, can be abused and is subject to criminal diversion.** Drug addiction is characterized by compulsive use, use for non-medical purposes, and continued use despite harm or risk of harm. Drug addiction is a treatable disease, utilizing a multi-disciplinary approach, but relapse is common. "Drug-seeking" behavior is very common in addicts and drug abusers. 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" to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction. Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians 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 and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. ULTRAM ER, like other opioids, may be diverted for non-medical use. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests 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.

ULTRAM ER is intended for oral use only. The crushed tablet poses a hazard of overdose and death. This risk is increased with concurrent abuse of alcohol and other substances. With parenteral abuse, the tablet excipients can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

**Risk of Overdosage:** Serious potential consequences of overdosage with ULTRAM ER are central nervous system depression, respiratory depression and death. In treating an overdose, primary attention should be given to maintaining adequate ventilation along with general supportive treatment (see **OVERDOSAGE**).

**Use in Renal and Hepatic Disease:** Impaired renal function results in a decreased rate and extent of excretion of tramadol and its active metabolite, M1. ULTRAM ER has not been studied in patients with severe renal impairment (CLcr < 30 mL/min). The limited availability of dose strengths and once daily dosing of ULTRAM ER do not permit the dosing flexibility required for safe use in patients with severe renal impairment. Therefore, ULTRAM ER should not be used in patients with severe renal impairment (see **CLINICAL PHARMACOLOG**Y in full Prescribing Information and **DOSAGE AND ADMINISTRATION**). Metabolism of tramadol and M1 is reduced in patients with advanced cirrhosis of the liver. The pharmacokinetics of ULTRAM ER has not been studied in patients with severe hepatic impairment. The limited availability of dose strengths and once daily dosing of ULTRAM ER do not permit the dosing flexibility required for safe use in patients with severe hepatic impairment. Therefore, ULTRAM ER should not be used in patients with severe hepatic impairment (see **CLINICAL PHARMACOLOGY** in full Prescribing Information and **DOSAGE AND ADMINISTRATION**).

**PRECAUTIONS: Acute Abdominal Condition:** The administration of ULTRAM ER may complicate the clinical assessment of patients with acute abdominal conditions.

**INFORMATION FOR PATIENTS:** 1. Patients should be informed that ULTRAM ER is for oral use only and should be swallowed whole. The tablets should not be chewed, crushed, or split. 2. Patients should be informed that ULTRAM ER may impair mental or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. 3. Patients should be informed that ULTRAM ER should not be taken with alcohol containing beverages. 4. Patients should be informed that ULTRAM ER should be used with caution when taking medications such as tranquilizers, hypnotics or other opiate containing analgesics. 5. Female patients should be instructed to inform the prescriber if they are pregnant, think they might become pregnant, or are trying to become pregnant (see **PRECAUTIONS, Labor and Delivery**). 6. Patients should be educated regarding the single-dose and 24-hour dosing regimen, as exceeding these recommendations can result in respiratory depression, seizures or death.

**Use in Drug and Alcohol Addiction:** ULTRAM ER is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission, is for the management of pain requiring opioid analgesia.

**Drug Interactions:** ***Use With Carbamazepine:*** 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 ULTRAM ER and carbamazepine is not recommended.

***Use With Quinidine:*** Coadministration of **quinidine** with ULTRAM ER resulted in a 50-60% increase in tramadol exposure and a 50-60% decrease in M1 exposure (see **CLINICAL PHARMACOLOGY, Drug Interactions** in full Prescribing Information). The clinical consequences of these findings are unknown.

***Use With MAO Inhibitors:*** Interactions with **MAO Inhibitors**, due to interference with detoxification mechanisms, have been reported for some centrally acting drugs (see **WARNINGS, Use With MAO Inhibitors and Serotonin Re-uptake Inhibitors**).

***Use With Digoxin and Warfarin:*** Post-marketing surveillance of tramadol has revealed rare reports of digoxin toxicity and alteration of warfarin effect, including elevation of prothrombin times.

***Potential for Other Drugs to Affect Tramadol:*** *In vitro* drug interaction studies in human liver microsomes indicate that concomitant administration with inhibitors of CYP2D6 such as fluoxetine, paroxetine, and amitriptyline could result in some inhibition of the metabolism of tramadol. Administration of CYP3A4 inhibitors, such as ketoconazole and erythromycin, or inducers, such as rifampin and St. John's Wort, with ULTRAM ER may affect the metabolism of tramadol leading to altered tramadol exposure.

***Potential for Tramadol to Affect Other Drugs:*** *In vitro* drug interaction studies in human liver microsomes indicate that tramadol has no effect on quinidine metabolism. In vitro studies indicate that tramadol is unlikely to inhibit the CYP3A4-mediated metabolism of other drugs when administered concomitantly at therapeutic doses. Tramadol is a mild inducer of selected drug metabolism pathways measured in animals.

**CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY:** No carcinogenic effect of tramadol was observed in p53(+/–)-heterozygous mice at oral doses up to 150 mg/kg/day (approximately 2-fold maximum daily human dose [MDHD] of 400 mg/day for a 60 kg adult based on body surface conversion) for 26 weeks and in rats at oral doses up to 75 mg/kg/day for males and 100 mg/kg/day for females (approximately 2-fold MDHD) for two years. However, the excessive decrease in body weight gain observed in the rat study might have reduced their sensitivity to any potential carcinogenic effect of the drug. Tramadol was not mutagenic in the following assays: a bacterial reverse mutation assay using *Salmonella* and *E. coli*, a mouse lymphoma assay (in the absence of metabolic activation), and a bone marrow micronucleus test in mice. Mutagenic results occurred in the presence of metabolic activation in the mouse lymphoma assay. Overall, the weight of evidence from these tests indicates that tramadol does not pose a genotoxic risk to humans. No effects on fertility were observed for tramadol at oral dose levels up to 50 mg/kg/day in male and female rats (approximately equivalent to MDHD).

**Pregnancy:** ***Teratogenic Effects: Pregnancy Category C:*** Tramadol was not teratogenic at oral dose levels up to 50 mg/kg/day (approximately equivalent to MDHD) in rats and 100 mg/kg (approximately 5-fold MDHD) in rabbits during organogenesis. However, embryo-fetal lethality, reductions in fetal weight and skeletal ossification, and increased supernumerary ribs were observed at a maternal toxic dose of 140 mg/kg in mice (approximately 2-fold MDHD), 80 mg/kg in rats (2-fold MDHD) or 300 mg/kg in rabbits (approximately 15-fold MDHD).

**Non-teratogenic Effects:** Tramadol caused a reduction in neonatal body weight and survival at an oral dose of 80 mg/kg (approximately 2-fold MDHD) when rats were treated during late gestation throughout lactation period. There are no adequate and well-controlled studies in pregnant women. ULTRAM ER should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Neonatal seizures, neonatal withdrawal syndrome, fetal death and still birth have been reported during post-marketing reports with tramadol HCl immediate-release products.

**Labor and Delivery:** ULTRAM ER should not be used in pregnant women prior to or during labor unless the potential benefits outweigh the risks. Safe use in pregnancy has not been established. Chronic use during pregnancy may lead to physical dependence and post-partum withdrawal symptoms in the newborn (see **DRUG ABUSE AND ADDICTION**). 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 treated with tramadol HCl during labor.

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

**Nursing Mothers:** ULTRAM ER 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. Following a single IV 100-mg dose of tramadol, the cumulative excretion in breast milk within sixteen hours postdose was 100 µg of tramadol (0.1% of the maternal dose) and 27 µg of M1.

**Pediatric Use:** The safety and efficacy of ULTRAM ER in patients under 18 years of age have not been established. The use of ULTRAM ER in the pediatric population is not recommended.

**Geriatric Use:** Nine-hundred-one elderly (65 years of age or older) subjects were exposed to ULTRAM ER in clinical trials. Of those subjects, 156 were 75 years of age and older. In general, higher incidence rates of adverse events were observed for patients older than 65 years of age compared with patients 65 years and younger, particularly for the following adverse events: constipation, fatigue, weakness, postural hypotension and dyspepsia. For this reason, ULTRAM ER should be used with great caution in patients older than 75 years of age (see **CLINICAL PHARMACOLOGY** in full Prescribing Information and **DOSAGE AND ADMINISTRATION**).

**ADVERSE REACTIONS:** ULTRAM ER was administered to a total of 3108 patients during studies conducted in the U.S. These included four double-blind studies in patients with osteoarthritis and/or chronic low back pain and one open-label study in patients with chronic non-malignant pain. A total of 901 patients were 65 years or older. Adverse events increased with dose from 100 mg to 400 mg in the two pooled, twelve-week, randomized, double-blind, placebo-controlled studies in patients with chronic non-malignant pain (see Table 1). **Table 1: Incidence (%) of patients with adverse event rates ≥ 5% from two 12-week placebo-controlled studies in patients with moderate to moderately severe chronic pain by dose.** MedDRA Preferred Term first; followed by ULTRAM ER 100 mg (N=403) n (%) second; ULTRAM ER 200 mg (N=400) n (%) third; ULTRAM ER 300 mg (N=400) n (%) fourth; ULTRAM ER 400 mg (N=202) n (%) fifth; and Placebo (N=406) n (%) sixth: Dizziness (not vertigo): 64 (15.9), 81 (20.3), 90 (22.5), 57 (28.2), 28 (6.9); Nausea: 61 (15.1), 90 (22.5), 102 (25.5), 53 (26.2), 32 (7.9); Constipation: 49 (12.2), 68 (17.0), 85 (21.3), 60 (29.7), 17 (4.2); Somnolence: 33 (8.2), 45 (11.3), 29 (7.3), 41 (20.3), 7 (1.7); Flushing: 31 (7.7), 40 (10.0), 35 (8.8), 32 (15.8), 18 (4.4); Pruritus: 25 (6.2), 34 (8.5), 30 (7.5), 24 (11.9), 4 (1.0); Vomiting: 20 (5.0), 29 (7.3), 34 (8.5), 19 (9.4), 11 (2.7); Insomnia: 26 (6.5), 32 (8.0), 36 (9.0), 22 (10.9), 13 (3.2); Asthenia: 14 (3.5), 24 (6.0), 26 (6.5), 13 (6.4), 7 (1.7); Postural hypotension: 7 (1.7), 17 (4.3), 8 (2.0), 11 (5.4), 9 (2.2); Sweating increased: 6 (1.5), 8 (2.0), 15 (3.8), 13 (6.4), 1 (0.2); Weakness: 3 (0.7), 8 (2.0), 14 (3.5), 9 (4.5), 5 (1.2); Rigors: 3 (0.7), 2 (0.5), 9 (2.3), 7 (3.5), 1 (0.2); Anorexia: 3 (0.7), 7 (1.8), 21 (5.3), 12 (5.9), 1 (0.2); Influenza like illness: 1 ( 0.2), 6 (1.5), 7 (1.8), 4 ( 2.0), 2 (0.5).

**Adverse events with incidence rates of 1.0% to <5.0%:** *Eye disorders:* vision blurred; *Gastrointestinal disorders:* abdominal pain upper, dyspepsia, abdominal pain, sore throat; *General disorders:* weakness, pain, feeling hot, influenza like illness, fall, rigors, lethargy, pyrexia, chest pain; *Infections and infestations:* nasopharyngitis, upper respiratory tract infection, sinusitis, influenza, gastroenteritis viral, urinary tract infection, bronchitis; *Investigations:* blood creatine phosphokinase increased; *Metabolism and nutrition disorders:* appetite decreased, weight decreased, anorexia; *Musculoskeletal, connective tissue and bone disorders:* arthralgia, back pain, pain in limb, neck pain; *Nervous system disorders:* tremor, paraesthesia, hypoaesthesia; *Psychiatric disorders:* nervousness, anxiety, depression, restlessness; *Respiratory, thoracic and mediastinal disorders:* rhinorrhoea, nasal congestion, dyspnoea, sinus congestion, cough, sneezing; *Skin and subcutaneous tissue disorders:* sweating increased, dermatitis; *Vascular disorders:* postural hypotension, hot flashes, vasodilatation.

**Adverse events with incidence rates <1.0%:** *Cardiac disorders:* palpitations, myocardial infarction; *Ear and labyrinth disorders:* tinnitus; *Gastrointestinal disorders:* flatulence, constipation aggravated, toothache, pancreatitis; *General disorders:* feeling jittery, oedema lower limb, shivering, joint swelling, malaise, drug withdrawal syndrome, peripheral swelling; *Hepato-biliary disorders:* cholelithiasis, cholecystitis; *Infections and infestations:* appendicitis, cellulitis, ear infection, gastroenteritis, pneumonia, urinary tract infection, viral infection; *Injury and poisoning:* joint sprain, muscle injury; *Investigations:* heart rate increased, liver function tests abnormal, blood pressure increased, alanine aminotransferase, aspartate aminotransferase increased, blood glucose increased, weight decreased; *Musculoskeletal, connective tissue and bone disorders:* joint stiffness, myalgia, muscle cramps, muscle spasms, muscle twitching, osteoarthritis aggravated; *Nervous system disorders:* migraine, syncope, disturbance in attention, dizziness aggravated, vertigo, sedation; *Psychiatric disorders:* irritability, libido decreased, euphoric mood, sleep disorder, agitation, disorientation, abnormal dreams; *Renal and urinary disorders:* difficulty in micturition, urinary frequency, urinary retention, dysuria, haematuria; *Respiratory, thoracic and mediastinal disorders:* yawning; *Skin and subcutaneous tissue disorders:* contusion, clamminess, night sweats, urticaria, piloerection; *Vascular disorders:* hypertension aggravated, hypertension, peripheral ischaemia.

**OVERDOSAGE:** 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, bradycardia, hypotension, and death. Deaths due to overdose have been reported with abuse and misuse of tramadol, by ingesting, inhaling, or injecting the crushed tablets. 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. In the treatment of tramadol overdosage, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation. 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 ULTRAM ER 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.

**DOSAGE AND ADMINISTRATION:** ULTRAM ER should not be used in patients with: 1. creatinine clearance less than 30 mL/min, 2. severe hepatic impairment (Child-Pugh Class C). (See **WARNINGS, Use in Renal and Hepatic Disease**). ULTRAM ER must be swallowed whole and must not be chewed, crushed, or split (see **WARNINGS, Misuse, Abuse and Diversion of Opioids** and **DRUG ABUSE AND ADDICTION**). **Adults (18 years of age and over):** ULTRAM ER should be initiated at a dose of 100 mg once daily and titrated up as necessary by 100-mg increments every five days to relief of pain and depending upon tolerability. ULTRAM ER should not be administered at a dose **exceeding 300 mg per day**. **Individualization of Dose:** Good pain management practice dictates that the dose be individualized according to patient need using the lowest beneficial dose. Start at the lowest possible dose and titrate upward as tolerated to achieve an adequate effect. Clinical studies of ULTRAM ER have not demonstrated a clinical benefit at a total daily dose exceeding 300 mg. In general, dosing of an elderly patient (over 65 years of age) should be initiated cautiously, 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. ULTRAM ER should be administered with even greater caution in patients over 75 years, due to the greater frequency of adverse events seen in this population.

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