IMPORTANT DRUG WARNING

Dear Healthcare Professional:

PriCara®, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc., in cooperation with the US Food and Drug Administration (FDA), would like to inform you of important changes to the prescribing information for ULTRAM® (tramadol hydrochloride) tablets. The risks pertaining to these warnings are currently included in the ULTRAM® ER (tramadol hydrochloride) extended-release tablets prescribing information.

The following information has been added to the **WARNINGS** section of the USPI for ULTRAM® and is presented here in the same format (including boldface font) as it appears in the USPI:

Suicide Risk

- **Do not prescribe ULTRAM® for patients who are suicidal or addiction-prone.**
- **Prescribe ULTRAM® Tablets with caution for patients who are taking tranquilizers or antidepressant drugs and patients who use alcohol in excess and who suffer from emotional disturbance or depression.**

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.

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 (see **WARNINGS, Risk of Overdosage**).

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.

Misuse, Abuse and Diversion
Tramadol has mu-opioid agonist activity. ULTRAM® can be sought by drug abusers and people with addiction disorders and may be subject to criminal diversion.

The possibility of illegal or illicit use should be considered when prescribing or dispensing ULTRAM® in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion. Misuse or abuse poses a significant risk to the abuser that could result in overdose and death (see **DRUG ABUSE AND DEPENDENCE** and **OVERDOSAGE**).

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.

The following prescribing information has been revised in the **WARNINGS** section of the USPI:

Risk of Overdosage
Patients taking tramadol should be warned not to exceed the dose recommended by their physician. Tramadol products in excessive doses, either alone or in combination with other CNS depressants, including alcohol, are a cause of drug-related deaths. 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.

Serious potential consequences of overdosage with ULTRAM® (tramadol hydrochloride) tablets are central nervous system depression, respiratory depression and death. Some deaths have occurred as a consequence of the accidental ingestion of excessive quantities of tramadol alone or in combination with other drugs. In treating an overdose, primary attention should be given to maintaining adequate ventilation along with general supportive treatment (see **OVERDOSAGE**).

In addition, the following prescribing information has been revised in the **DRUG ABUSE AND DEPENDENCE** section of the USPI:

Abuse
Tramadol has mu-opioid agonist activity. ULTRAM® can be abused and may be subject to criminal diversion.

Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. Drug addiction is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, use for non-medical purposes, and continued use despite harm or risk of harm, and craving. 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 ULTRAM® can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances.

Concerns about abuse and addiction should not prevent the proper management of pain. However, all patients treated with opioids require careful monitoring for signs of abuse

and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Proper assessment of the patient and periodic re-evaluation of therapy are appropriate measures that help to limit the potential abuse of this product.

ULTRAM® is intended for oral use only.

Dependence

Tolerance is the need for increasing doses of drugs to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist (see also **WARNINGS, Withdrawal**).

The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other 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.

Generally, tolerance and/or withdrawal are more likely to occur the longer a patient is on continuous therapy with ULTRAM®.

PriCara® remains committed to providing you with the most current prescribing information for all of our products to help in the management of your patients. Please refer to the enclosed package insert for the full Prescribing Information as other sections of the prescribing information have also been revised.

Healthcare professionals should report all serious adverse events to 1-800-526-7736 or to FDA's MedWatch Adverse Event Reporting program online (at www.fda.gov/MedWatch/report.htm), by facsimile (1-800-FDA-0178), by telephone (1-800-FDA-1088), or by returning the postage-paid FDA form 3500 (which may be downloaded from www.fda.gov/MedWatch/getforms.htm) by mail (to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787).

For medical inquiries, please call the Customer Communications Center at 1-800-526-7736 or contact your PriCara® representative.

Sincerely,

Norman Rosenthal, MD
Chief Scientific Officer

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