Drug Enforcement Administration
Office of Diversion Control
Drug & Chemical Evaluation Section

TRAMADOL
(Trade Names: Ultram®, Ultracet®)

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DEA/OD/ODE

Introduction:

Tramadol was approved for marketing as a noncontrolled analgesic in 1995 under the trade name of Ultram®. Although the company initially claimed that this substance produced only very weak narcotic effects, recent data demonstrate that opioid activity is the overriding contributor to the drug's pharmacological activity. Because of inadequate product labeling and lack of established abuse potential, many physicians felt this drug was safe to prescribe to recovering narcotic addicts and to known narcotic abusers. As a consequence, numerous reports of abuse and dependence have been received.

Licit Uses:

Tramadol is approved for the treatment of moderate to moderately severe pain in adults. Although the Department of Health and Human Services has not recommended the scheduling of this substance in the Controlled Substances Act (CSA), a requirement necessary for DEA to place a substance under control, the Food and Drug Administration (FDA) has required the manufacturer of Ultram® to inform physicians about recent abuse data. The approved labeling has been modified on three separate occasions to include new information under the "Drug Abuse and Dependence" section. The labeling currently contains the following language:

> ULTRAM may induce psychic and physical dependence of the morphine-type (μ-opioid). Dependence and abuse, including drug-seeking behavior and taking illicit actions to obtain the drug are not limited to those patients with prior history of opioid dependence. The risk in patients with substance abuse has been observed to be higher. ULTRAM is associated with craving and tolerance development. Withdrawal symptoms may occur if ULTRAM is discontinued abruptly.

According to the IMS Health National Prescription Audit Plus™, retailers dispensed 28.2 million tramadol prescriptions in 2009. From January to September 2010, 22.2 million tramadol prescriptions were dispensed.

Chemistry/Pharmacology:

Tramadol is a novel analgesic having both opiate agonist activity and monoamine reuptake inhibition that contribute to its analgesic efficacy. Opioid activity is due to both the parent compound and the more active O-desmethylated metabolite. Tramadol acts on the monoamine reuptake systems by inhibiting the reuptake into nerve terminals of both norepinephrine and serotonin.

Apart from analgesia, tramadol may produce a number of symptoms including dizziness, somnolence, nausea, and constipation similar to other opioids. High doses of tramadol, often in combination monoamine oxidase (MAO) inhibitors or serotonin-selective reuptake inhibitors (SSRIs), have been associated with a serotonin syndrome consisting of convulsions, hyperthermia, muscle rigidity and pain.

Tramadol is well absorbed orally. It can be administered in 50 to 100 mg tablets as needed for pain relief every 4 to 6 hours, not to exceed 400 mg/day. Seizures have occurred in patients taking recommended doses but are more likely at high doses associated with abuse of this medication. Tolerance, dependence and addiction to tramadol have been demonstrated. Abrupt cessation from tramadol has been associated with two types of withdrawal syndromes. One is typical of opioid drugs with flu-like symptoms, restlessness and drug craving. This type of withdrawal syndrome is encountered in about 90 percent of cases of withdrawal from tramadol. Another withdrawal syndrome (encountered in about 10 percent of cases of tramadol withdrawal) is atypical of opioids and is associated with hallucinations, paranoia, extreme anxiety, panic attacks, confusion, and numbness and tingling in the extremities.

Abuse and Diversion:

Tramadol is most commonly abused by narcotic addicts, chronic pain patients, and health professionals.

According the American Association of Poison Control Centers, there were a total of 10,255 tramadol exposures in 2009. Of this total in 2009, there were 5,373 single substance exposures (4 deaths) associated with tramadol.

The National Forensic Laboratory Information System (NFLIS) is a DEA database that collects scientifically verified data on drug items and cases submitted to and analyzed by state and local forensic laboratories. The System to Retrieve Information from Drug Evidence (STRIDE) provides information on drug seizures reported to and analyzed by DEA laboratories. Of the exhibits submitted to federal, state and local forensic laboratories in 2009, 1,291 were identified as tramadol. To date, 1,048 of the exhibits submitted to forensic laboratories in 2010 are identified as tramadol.

Controlled Status:

Tramadol is not currently controlled under the CSA. Arkansas and Kentucky have designated tramadol as a schedule IV drug under state law. Louisiana passed legislation that identifies tramadol as a drug of abuse; demonstrating potential for abuse.

Comments and additional information are welcomed by the Office of Diversion Control, Drug and Chemical Evaluation Section. Fax 202-353-1263, Telephone 202-307-7183, or Email ODE@usdoj.gov.