



TRAMADOL

(Trade Names: Ultram®, Ultracet®)

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DEA/OD/ODE

Introduction:

Tramadol was approved for marketing in the United States as a noncontrolled analgesic in 1995 under the trade name of Ultram®. However, soon after its approval there have been reports of diversion and abuse of tramadol. This led to revisions to the product labeling and the addition of warnings about its abuse by the Food and Drug Administration (FDA). Tramadol is an opioid analgesic and opioid activity is the overriding contributor to its pharmacological effects. Abuse and adverse events of tramadol are similar to those of other opioid analgesics.

Licit Uses:

Tramadol is approved for the treatment of moderate to moderately severe pain in adults. According to the IMS Health National Prescription Audit Plus™, retailers dispensed 43.8 million tramadol prescriptions in the U.S. in 2013.

Chemistry/Pharmacology:

Tramadol, named as 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol in the Code of Federal Regulations, is a novel analgesic having both opioid 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 also 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 with monoamine oxidase (MAO) inhibitors or selective serotonin 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.

The FDA-approved labeling for tramadol has been modified several times to include new information under

the “Drug Abuse and Dependence” section. This section of the labeling currently contains the following language:

Tramadol hydrochloride 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. Tramadol hydrochloride is associated with craving and tolerance development. Withdrawal symptoms may occur if tramadol hydrochloride 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 relieved by reinstatement of opioid therapy followed by gradual, tapered dose reduction of the medication combined with symptomatic support.

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 13,067 tramadol exposures in 2012. Of this total in 2012, there were 6,589 single substance exposures and 9 associated deaths.

The Drug Abuse Warning Network (DAWN) reported that an estimated 16,251 emergency department visits were related to tramadol nonmedical use in 2010 and an estimated 20,000 related nonmedical visits in 2011.

According to the National Survey on Drug Use and Health (NSDUH) in 2012, 3.2 million people in the U.S. aged 12 or older used tramadol for nonmedical purposes in their lifetime.

DEA collected scientifically verified data from the National Forensic Laboratory Information System and the System to Retrieve Information from Drug Evidence databases on drug items and cases submitted to and analyzed by federal, state, and local forensic laboratories. In 2013, 2,082 of the exhibits submitted to forensic laboratories were identified as tramadol. From January through March 2014, 443 of these exhibits were identified as tramadol.

Controlled Status:

On July 2, 2014, the DEA published in the Federal Register the final rule placing tramadol into schedule IV of the Controlled Substances Act. This rule will become effective on August 18, 2014. All regulatory requirements applicable to schedule IV controlled substances will apply to tramadol beginning August 18, 2014. The final rule is available online at www.regulations.gov.

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.