Drug Enforcement Administration
Diversion Control Division
Drug & Chemical Evaluation Section

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TRAMADOL

(Trade Names: Ultram®, Ultracet®)

Introduction:

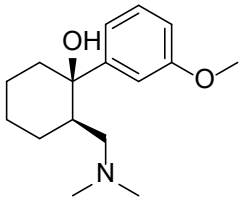
Tramadol was approved for marketing in the United States as a non-controlled analgesic in 1995 under the trade name Ultram. However, soon after its approval, there were reports of diversion and abuse of tramadol. This led the Food and Drug Administration (FDA) to revise the product labeling and add warnings about its abuse. 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 IQVIA National Prescription Audit™, total prescriptions for tramadol-containing products dispensed in the United States were approximately 32.0 million in 2020, 30.5 million in 2021, 28.7 million in 2022, 27.9 million in 2023, and 27.1 million in 2024.

Chemistry:

Tramadol is chemically known as 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol. The chemical structure of tramadol is shown below:



Pharmacology:

Tramadol is a novel analgesic exhibiting both opioid agonist activity and monoamine reuptake inhibition that contribute to its analgesic efficacy. Its opioid activity is due to the more active *O*-desmethylated metabolite *O*-desmethyltramadol (O-DSMT). Tramadol also acts on the monoamine reuptake systems by inhibiting norepinephrine and serotonin reuptake.

In addition to analgesia, tramadol may produce a number of symptoms. These symptoms include 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 (SSRI), have been associated with serotonin syndrome, which consists 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 the 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 type of withdrawal syndrome is typical of opioid drugs, with flu-like symptoms, restlessness, and drug craving; this type is encountered in about 90% of tramadol withdrawal cases. The other type of withdrawal syndrome is atypical of opioids and is associated with hallucinations, paranoia, extreme anxiety, panic attacks, confusion, and numbness and tingling in the extremities; this type is encountered in about 10% of tramadol withdrawal cases.

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 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 reinstitution of opioid therapy followed by gradual, tapered dose reduction of the medication combined with symptomatic support.

Illicit Uses:

America's Poison Centers reported that in 2016, tramadol was associated with 12,108 case mentions; 5,712 single exposures, and 3 deaths. In 2020, tramadol was associated with 6,974 case mentions; 3,075 single exposures; and 3 deaths. In 2022, tramadol was associated with 5,915 case mentions; 2,426 single exposures, and 5 deaths.

User Population:

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

Illicit Distribution:

The Drug Enforcement Administration's National Forensic Laboratory Information System (NFLIS) Drug database collects scientifically verified data on drug items and cases submitted to and analyzed by participating federal, state, and local forensic drug laboratories. NFLIS-drug received over 105,000 reports of tramadol since 1997, when tramadol was approved for medical use. NFLIS-Drug received 5,279 reports in 2015; 10,710 in 2018; 16,475 in 2021; and 3,789 in 2024 (reports still pending).

Control Status:

Tramadol is controlled in schedule IV of the Controlled Substances Act.

Comments and additional information are welcomed by the Drug and Chemical Evaluation Section; Fax 571-362-4250, Telephone 571-362-3249, or Email DPE@dea.gov.