1.1 Drug Use Criteria: Tramadol (Ultram®)

Publication History

1. Developed: November 1995

Notes: Information on indications for use or diagnosis is assumed to be unavailable. All criteria may be applied retrospectively; prospective application is indicated with an asterisk [**]. The information contained is for the convenience of the public. The Texas Health and Human Services Commission is not responsible for any errors in transmission or any errors or omissions in the document.

Medications listed in the tables and non-FDA approved indications included in these retrospective criteria are not indicative of Vendor Drug Program formulary coverage.

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1 Dosage

Tramadol has a nationwide classification as a Schedule IV controlled substance as of August 18, 2014. Key factors contributing to this decision include its potential for abuse and dependence, as well as its link to emergency room visits and deaths related to overdoses.\(^{[1]}\)

1.1 Adults

Tramadol is a centrally acting, opioid-type analgesic that acts as a mu-opioid receptor agonist and a weak inhibitor of serotonin and norepinephrine reuptake. The immediate-release (IR) formulation is FDA-approved for use in the management of acute or chronic moderate to moderately severe pain in adults. Tramadol extended-release (ER) is FDA-approved for use in managing chronic moderate to moderately severe pain in patients requiring continuous pain management. The tramadol/acetaminophen combination is FDA-approved for the acute (< 5 days) management of acute pain. Following a titration phase, recommended IR tramadol regimens for pain management include doses of 50 mg to 100 mg administered every 4 to 6 hours as needed. For tramadol ER, the recommended initial dose in tramadol IR-naïve patients is 100 mg once daily, titrated every five days in 100 mg increments until pain relief is achieved. For those patients already managed on tramadol IR, the 24- hour dose should be calculated and the total daily tramadol ER dose should be rounded down to the closest 100 mg increment. The recommended dose for tramadol in combination with acetaminophen is 2 tablets every 4 to 6 hours as needed for pain relief.\(^{[2-8]}\) Maximum recommended doses for tramadol alone and in combination with acetaminophen are summarized in Table 1. Dosages exceeding these recommendations will be reviewed.
Table 1. Maximum Recommended Oral Tramadol Dosages in Adults[^2-8^]

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage Forms/Strengths</th>
<th>Maximum Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monotherapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tramadol immediate-release (Ultram®, generics)</td>
<td>50 mg tablets</td>
<td>400 mg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>300 mg/day (elderly)</td>
</tr>
<tr>
<td>tramadol extended-release (generics)</td>
<td>100 mg, 200 mg, 300 mg tablets</td>
<td>300 mg/day</td>
</tr>
<tr>
<td>tramadol extended-release (ConZip™, generics)</td>
<td>100 mg, 200 mg, 300 mg capsules</td>
<td>300 mg/day</td>
</tr>
<tr>
<td><strong>Combination Therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tramadol/acetaminophen (Ultracet®, generics)</td>
<td>37.5 mg/325 mg tablets</td>
<td>300 mg/2600 mg per day (8 tablets per day)</td>
</tr>
</tbody>
</table>

1.1.1 Elderly Patients[^2-8^]

Tramadol dosages exceeding 300 mg per day in elderly patients over 75 years of age are not recommended and will be reviewed. In controlled clinical trials, treatment-limiting adverse events were higher in patients over 75 years of age compared to those less than 65 years of age.

1.1.2 Dosing in Renal Impairment[^2-8^]

In patients with a creatinine clearance < 30 ml/min, the recommended dosing interval for tramadol IR is every 12 hours and the maximum recommended tramadol dose is 200 mg per day. In patients with cirrhosis, the recommended tramadol IR dose is 50 mg every 12 hours. Tramadol ER should not be given to patients with a creatinine clearance < 30 ml/min or those with severe hepatic impairment.

1.2 Pediatrics

Tramadol IR is FDA-approved for use to manage acute and chronic moderate to moderately severe pain in adolescents 17 years of age and older. For all other formulations, tramadol use in pediatric patients younger than 16 years of age is not
recommended as safety and efficacy have not been established and the potential exists for an increased risk of fatal respiratory depression.[2-8]

2 Duration of Therapy[2-22]

There is no basis for limiting the duration of tramadol therapy as tramadol is promoted for use in chronic pain (e.g., chronic musculoskeletal pain, cancer pain, osteoarthritis, diabetic neuropathy) as well as acute pain events (e.g., postoperative pain, dental extraction pain). However, cases of tramadol abuse and dependence have been reported, especially in patients with a history of substance abuse. Therefore, tramadol should be administered cautiously, if at all, to patients with a history of drug or alcohol abuse and/or dependence.

The tramadol/acetaminophen combination is indicated for use in the short-term management of acute pain and should be limited to five days or less of use. Patient profiles containing tramadol/acetaminophen prescriptions exceeding this treatment duration will be reviewed.

3 Duplicative Therapy

Adjunctive administration of multiple tramadol dosage forms may result in significant additive adverse events, including respiratory depression, seizures and serotonin syndrome. Combined administration of multiple tramadol dosage forms is not recommended and will be reviewed.

Opioid analgesics may enhance the sedative effects as well as other central effects of tramadol. Therefore, the use of tramadol in conjunction with opioid analgesics is recommended cautiously. If tramadol is used concomitantly with another agent that acts upon the central nervous system, the tramadol dosage should be reduced.

Use of tramadol in conjunction with sedative/hypnotics in patients over 75 years of age will be reviewed as these patients may be more sensitive to the additive effects of this drug combination.
4 Drug-Drug Interactions

Patient profiles will be assessed to identify those drug regimens which may result in clinically significant drug-drug interactions. Drug-drug interactions considered clinically relevant for tramadol are summarized in Table 2. Only those drug-drug interactions identified as clinical significance level 1 or those considered life-threatening which have not yet been classified will be reviewed:

Table 2. Tramadol Drug-Drug Interactions\(^{[2-8, 23]}\)

<table>
<thead>
<tr>
<th>Target Drug</th>
<th>Interacting Drug</th>
<th>Interaction</th>
<th>Recommendation</th>
<th>Clinical Significance Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>tramadol</td>
<td>carbamazepine (CBZ)</td>
<td>potential for reduced analgesic effect due to CBZ-associated CYP3A4 enzyme induction; potential for additive CNS depressant effects, increased seizure risk with concurrent therapy</td>
<td>concurrent use not recommended</td>
<td>major (DrugReax) 2-major (CP)</td>
</tr>
<tr>
<td>tramadol</td>
<td>CYP inducers (e.g., phenytoin, rifampin)</td>
<td>potential for reduced tramadol analgesic efficacy as tramadol metabolized by CYP3A4, CYP2D6</td>
<td>monitor for reduced analgesic effects; adjust dosages as necessary</td>
<td>moderate (DrugReax) 3-moderate (CP)</td>
</tr>
<tr>
<td>tramadol</td>
<td>CYP2D6 inhibitors (e.g., amiodarone, propafenone, ritonavir)</td>
<td>potential for enhanced tramadol pharmacologic/adverse effects as tramadol metabolized by CYP2D6</td>
<td>monitor for enhanced analgesic effects, increased adverse effects (including seizures); adjust dosages as necessary</td>
<td>moderate (DrugReax) 3-moderate (CP)</td>
</tr>
<tr>
<td>tramadol</td>
<td>CYP3A4 inhibitors (e.g., amiodarone, erythromycin, ritonavir)</td>
<td>potential for enhanced tramadol pharmacologic/adverse effects as tramadol metabolized by CYP3A4</td>
<td>monitor for enhanced analgesic effects, increased adverse effects (including seizures); adjust dosages as necessary</td>
<td>moderate (DrugReax) 3-moderate (CP)</td>
</tr>
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<td>Target Drug</td>
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<tr>
<td>tramadol</td>
<td>MAOIs*/MAOI-like compounds (e.g., phenelzine, selegiline, rasagiline, linezolid)</td>
<td>potential for additive effects on serotonin and norepinephrine reuptake inhibition; increased risk for seizures, hypertensive reactions, serotonin syndrome (e.g., nausea, vomiting, hypertension, hyperthermia, cardiovascular collapse)</td>
<td>concurrent administration or prescribing within 14 days of MAOI discontinuation contraindicated</td>
<td>contraindicated, major (DrugReax) 1-severe, 2-major (CP)</td>
</tr>
<tr>
<td>tramadol</td>
<td>neuroleptics (e.g., thioridazine, risperidone)</td>
<td>increased seizure risk (mechanism unknown), and potential for increased CNS, respiratory depression</td>
<td>avoid, if possible, in patients with underlying seizure disorders; otherwise, use cautiously together</td>
<td>major (DrugReax) 2-major (CP)</td>
</tr>
<tr>
<td>tramadol</td>
<td>opioid analgesics</td>
<td>increased seizure risk</td>
<td>avoid, if possible, in patients with underlying seizure disorders; otherwise, use cautiously together</td>
<td>2-major (CP)</td>
</tr>
<tr>
<td>tramadol</td>
<td>serotonergic drugs (e.g., SSRIs/SNRIs, milnacipran)</td>
<td>increased seizure risk, increased risk of serotonin syndrome (e.g., nausea/vomiting, hypertension, hyperthermia, cardiovascular collapse) due to additive increases in serotonin concentrations</td>
<td>avoid, if possible, in patients with underlying seizure disorders; otherwise, use cautiously together</td>
<td>major (DrugReax) 2-major (CP)</td>
</tr>
<tr>
<td>tramadol</td>
<td>TCAs^ (e.g., imipramine, cyclobenzaprine)</td>
<td>increased seizure risk (TCAs lower seizure threshold), increased risk of serotonin syndrome (e.g., nausea/vomiting, hypertension, hyperthermia, cardiovascular collapse) as both compounds inhibit serotonin/norepinephrine reuptake</td>
<td>avoid, if possible, in patients with underlying seizure disorders; otherwise, use cautiously together</td>
<td>major (DrugReax) 3-moderate (CP)</td>
</tr>
<tr>
<td>tramadol</td>
<td>warfarin</td>
<td>increased prothrombin time with increased bleeding risk; mechanism unknown</td>
<td>closely monitor for INR changes, bleeding; adjust doses as necessary</td>
<td>moderate (DrugReax) 2-major (CP)</td>
</tr>
</tbody>
</table>

*CP = Clinical Pharmacology; *MAOI = monoamine oxidase inhibitor; ^TCA = tricyclic antidepressant
5 Drug-Drug Interactions