TEXAS Health and Human Services

Medicaid Drug Use Criteria

Tramadol (Ultram®)

- Developed: November 1995
- Revised: November 2019; December 2017; February 2016; June 2014; September 2012; January 2011; April 2008; November 2003; October 2002; November 2001; October 2000; December 1999; November 1998; November 1997; December 1996.

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 (less than 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 and Table 2 . Dosages exceeding these recommendations will be reviewed.

Table 1: Maximum Recommended Adult Oral Tramadol Dosages: Monotherapy [2-7]

Drug Name	Dosage Forms/Strengths	Maximum Recommended Dose
tramadol immediate-release (Ultram®, generics)	50 mg tablets	400 mg/day, in divided doses every 4-6 hours elderly*:300 mg/day, in divided doses every 4-6 hours
tramadol extended-release (generics)	100 mg, 200 mg, 300 mg tablets	300 mg/day in single daily doses
tramadol extended-release (ConZip®, generics)	100 mg, 150 mg, 200 mg, 300 mg capsules	300 mg/day in single daily doses

- * elderly defined as greater than 75 years of age

Table 2: Maximum Recommended Adult Oral Tramadol Dosages: Combination Therapy [2-5, 8]

Drug Name	Dosage Forms/Strengths	Maximum Recommended Dose
tramadol/acetaminophen (Ultracet®, generics)	37.5 mg/325 mg tablets	300 mg/2600 mg per day (8 tablets per day), in divided doses every 4-6 hours

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 less than 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 less than 30 ml/min or those with severe hepatic impairment. The tramadol/acetaminophen combination should be dosed as 2 tablets every 12 hours in patients with a creatinine clearance less than 30 mL/min and should not be used in patients with 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. 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. Tramadol ER and tramadol/acetaminophen combination therapy are not FDA-approved for use in pediatric patients as safety and efficacy have not been established and the potential exists for an increased risk of fatal respiratory depression. Pediatric tramadol dosages are summarized in Table 3.[2-8]

Table 3: Maximum Recommended Pediatric Oral Tramadol Dosages: Monotherapy[2-7]

Drug Name	Dosage Forms/Strengths	Maximum Recommended Dose
tramadol immediate-release (Ultram®, generics)	50 mg tablets	Greater than or equal to 17 years of age: 400 mg/day, in divided doses every 4-6 hours

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 4. 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 4: Tramadol Drug-Drug Interactions [2-8, 23]

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level
tramadol	barbiturates	adjunctive use may result in respiratory depression, hypotension, profound sedation and potentially death due to additive CNS depression; potential as well for ↓ tramadol levels as barbiturates induce CYP3A4 and tramadol is CYP3A4 substrate	avoid use, if possible; if combined administration necessary, observe for respiratory depression and loss of tramadol analgesic effects	major (DrugReax) 2-major (CP)
tramadol	carbamazepine (CBZ)	potential for reduced analgesic effect due to CBZ-associated CYP3A4 enzyme induction; potential for additive CNS depressant effects, increased seizure risk with concurrent therapy	concurrent use not recommended	major (DrugReax) 2-major (CP)
tramadol	CYP inducers (e.g., phenytoin, rifampin)	potential for reduced tramadol analgesic efficacy as tramadol metabolized by CYP3A4, CYP2D6	monitor for reduced analgesic effects; adjust dosages as necessary	moderate (DrugReax) 3-moderate (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level
tramadol	CYP2D6 inhibitors (e.g., amiodarone, propafenone, ritonavir)	potential for enhanced tramadol pharmacologic/ adverse effects as tramadol metabolized by CYP2D6	monitor for enhanced analgesic effects, increased adverse effects (including seizures); adjust dosages as necessary	moderate (DrugReax) 3-moderate (CP)
tramadol	CYP3A4 inhibitors (e.g., amiodarone, erythromycin, ritonavir)	potential for enhanced tramadol pharmacologic/ adverse effects as tramadol metabolized by CYP3A4	monitor for enhanced analgesic effects, increased adverse effects (including seizures); adjust dosages as necessary	moderate (DrugReax) 3-moderate (CP)
tramadol	MAOIs+/MAOI -like compounds (e.g., phenelzine, selegiline, rasagiline, linezolid)	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)	concurrent administration or prescribing within 14 days of MAOI discontinuation contraindicated	contraindicated, major (DrugReax) 1-severe, 2-major (CP)
tramadol	neuroleptics (e.g., thioridazine, risperidone)	increased seizure risk (mechanism unknown), and potential for increased CNS, respiratory depression	avoid, if possible, in patients with underlying seizure disorders; otherwise, use cautiously together	major (DrugReax) 2-major (CP)
tramadol	opioid analgesics	increased seizure risk	avoid, if possible, in patients with underlying seizure disorders; otherwise, use cautiously together	2-major (CP)
tramadol	serotonergic drugs (e.g., SSRIs/ SNRIs, milnacipran)	increased seizure risk, increased risk of serotonin syndrome (e.g., nausea/vomiting, hypertension, hyperthermia, cardiovascular collapse) due to additive increases in serotonin concentrations	avoid, if possible, in patients with underlying seizure disorders; otherwise, use cautiously together	major (DrugReax) 2-major (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level
tramadol	TCAs^ (e.g., imipramine, cyclobenzaprine)	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	avoid, if possible, in patients with underlying seizure disorders; otherwise, use cautiously together	major (DrugReax) 3-moderate (CP)
tramadol	warfarin	increased prothrombin time with increased bleeding risk; mechanism unknown	closely monitor for INR changes, bleeding; adjust doses as necessary	moderate (DrugReax) 2-major (CP)

- * CP = Clinical Pharmacology
- + MAOI = monoamine oxidase inhibitor
- ^ TCA = tricyclic antidepressant

5 References

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