

Texas Vendor Drug Program

Drug Use Criteria: Sedative/Hypnotics

Publication History

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Notes: Information on indications for use or diagnosis is assumed 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

1.1 Adults

Maximum recommended daily doses for sedative/hypnotics in adults, including the elderly population, are summarized in Table 1. Prescribed dosages exceeding these recommendations will be reviewed.

Table 1. Maximum Recommended Daily Dosages for Sedative/Hypnotics in Adults: Benzodiazepines

Drug Name	Dosage Form/ Strength	Maximum Recommended Dosage: ≤ 65 years	Maximum Recommended Dosage: > 65 years
estazolam (generics)	1 mg, 2 mg tablets	2 mg	2 mg*
flurazepam (generics)	15 mg, 30 mg capsules	30 mg	15 mg*
temazepam (Restoril®, generics)	7.5 mg, 15 mg, 22.5 mg, 30 mg capsules	30 mg	30 mg*
triazolam (Halcion®, generics)	0.125 mg, 0.25 mg tablets	0.5 mg	0.25 mg*
quazepam (Doral®)	15 mg tablets	15 mg	15 mg*

**In elderly patients (patients > 65 years of age), sedative/hypnotic dosages should be reduced if possible, as these patients are more sensitive to sedative/hypnotic pharmacologic/adverse effects.*

Table 2. Maximum Recommended Daily Dosages for Sedative/Hypnotics in Adults: Barbiturates⁺

Drug Name	Dosage Form/ Strength	Maximum Recommended Dosage: ≤ 65 years	Maximum Recommended Dosage: > 65 years
phenobarbital (generics)	15 mg, 16.2 mg, 30 mg, 32.4 mg, 60 mg, 64.8 mg, 97.2 mg, 100 mg tablets; 20 mg/5 mL elixir	320 mg	320 mg*
secobarbital (Seconal®)	100 mg capsule	300 mg	300 mg*

⁺No longer considered acceptable drug class to manage insomnia as safer agents (i.e., benzodiazepines, nonbarbiturates) are available

*In elderly patients (patients > 65 years of age), sedative/hypnotic dosages should be reduced if possible, as these patients are more sensitive to sedative/hypnotic pharmacologic/adverse effects.

Table 3. Maximum Recommended Daily Dosages for Sedative/Hypnotics in Adults: Non-Benzodiazepine, Benzodiazepine Receptor Agonists

Drug Name	Dosage Form/ Strength	Maximum Recommended Dosage: ≤ 65 years	Maximum Recommended Dosage: > 65 years
eszopiclone (Lunesta®)	1 mg, 2 mg, 3 mg tablets	3 mg	2 mg
zaleplon (generics)	5 mg, 10 mg capsules	20 mg	10 mg
zolpidem immediate-release (IR) (Ambien®, generics)	5 mg, 10 mg IR tablets	10 mg	5 mg
zolpidem extended-release (ER) (Ambien CR®, generics)	6.25 mg, 12.5 mg ER tablets	12.5 mg	6.25 mg
zolpidem sublingual tablets (Edluar®)	5 mg, 10 mg sublingual tablets	10 mg	5 mg

Drug Name	Dosage Form/ Strength	Maximum Recommended Dosage: ≤ 65 years	Maximum Recommended Dosage: > 65 years
zolpidem sublingual tablets (Intermezzo®, generics)	1.75 mg, 3.5 mg sublingual tablets	1.75 mg (women) 3.5 mg (men)	1.75 mg
zolpidem lingual spray (Zolpimist®)	5 mg/actuation	10 mg	5 mg

Table 4. **Maximum Recommended Daily Dosages for Sedative/Hypnotics in Adults: Melatonin Receptor Agonists**

Drug Name	Dosage Form/ Strength	Maximum Recommended Dosage: ≤ 65 years	Maximum Recommended Dosage: > 65 years
ramelteon (Rozerem®)	8 mg tablets	8 mg	8 mg

Table 5. **Maximum Recommended Daily Dosages for Sedative/Hypnotics in Adults: Orexin Receptor Antagonists**

Drug Name	Dosage Form/ Strength	Maximum Recommended Dosage: ≤ 65 years	Maximum Recommended Dosage: > 65 years
suvorexant (Belsomra®)	5 mg, 10 mg 15 mg, 20 mg tablets	20 mg	20 mg
lemborexant (Dayvigo®)	5 mg, 10 mg tablets	10 mg	10 mg

Table 6. **Maximum Recommended Daily Dosages for Sedative/Hypnotics in Adults: Miscellaneous Nonbarbiturates**

Drug Name	Dosage Form/ Strength	Maximum Recommended Dosage: ≤ 65 years	Maximum Recommended Dosage: > 65 years
doxepin (Silenor®)	3 mg, 6 mg tablets	6 mg	6 mg

In the elderly, short- and intermediate-acting benzodiazepines (e.g., temazepam, triazolam) are preferred, as long-acting benzodiazepines (e.g., flurazepam) are associated with increased sedation and an increased risk of falls and fractures in this patient population.

The appropriate sedative/hypnotic dose for debilitated patients is the same as that prescribed in elderly patients for most sedative/hypnotic agents. However, estazolam 0.5 mg is used in small or debilitated geriatric patients, a dose lower than that recommended for elderly patients.

Doxepin is FDA-approved for use in managing insomnia characterized by difficulty in maintaining sleep. Studies have documented efficacy for up to 3 months in duration.

Patients with hepatic insufficiency have a reduced clearance of zolpidem. A 5 mg zolpidem immediate-release, sublingual (Edluar®), or oral spray (Zolpimist®) dose, a 1.75 mg sublingual tablet (Intermezzo®) dose, or a 6.25 mg extended-release dose is recommended in these patients.

Eszopiclone should be used cautiously in patients with severe hepatic impairment with initial doses of 1 mg daily at bedtime, as eszopiclone is significantly hepatically metabolized and serum concentrations may increase substantially in this patient population.

Suvorexant **and lemborexant are** newer sedative/hypnotics with a novel mechanism of action. Known as orexin receptor antagonists, suvorexant **and lemborexant** works by altering signaling of the orexin neurotransmitters in the brain. Orexins are responsible for regulating the sleep-wake cycle and helping to keep people awake. Suvorexant was FDA-approved in August 2014 as a schedule IV-controlled substance to manage insomnia associated with difficulties in sleep

onset and/or sleep maintenance. **Lemborexant was FDA-approved in December 2019 as a schedule IV-controlled substance for the treatment of insomnia characterized by difficulties with sleep onset and/ or sleep maintenance.**

1.2 Pediatrics

Safety and efficacy of eszopiclone, ramelteon, zaleplon, zolpidem, **lemborexant** or suvorexant, as well as most sedative/hypnotic benzodiazepines, have not been established in pediatric patients. Flurazepam has been used to manage insomnia in adolescents 15 years of age and older. Although the oral barbiturates, phenobarbital and secobarbital are approved as sedatives and pre-anesthetics in pediatric patients, parenteral sedative/hypnotic agents are recommended due to shorter, more predictable onsets and quicker recovery times. Barbiturates are no longer recommended for use in pediatric insomnia as safer, more effective agents are available. Pediatric dosage recommendations for benzodiazepines are summarized in **Table 7**.

Table 7. Recommended Sedative/Hypnotic Dosages for Pediatric Patients: Benzodiazepines

Treatment Indication	Drug Name	Maximum Recommended Dosage
insomnia	flurazepam	<i>adolescents 15 years and older: 30 mg orally at bedtime</i>

2 Duration of Therapy

In adults, insomnia is classified based on symptom duration. Periods of sleep difficulty lasting from one to three nights are classified as transient insomnia, periods lasting three nights to one month are classified as short-term insomnia, while chronic or long-term insomnia represents sleep difficulties exceeding one month.

Acute, transient insomnia is due to minor situational, familial, and/or occupational stress and is managed primarily by teaching patients to re-establish normal sleep-wake patterns. Short-term insomnia is precipitated by events such as divorce, job loss, health concerns, or prescription medications and may be managed by

behavioral techniques, lifestyle changes, and, if necessary, short-term pharmacologic therapy.

Long-term insomnia may be associated with medical or psychiatric illness (e.g., mood and anxiety disorders, asthma, chronic pain, and gastroesophageal reflux) as well as a variety of prescribed medications, although approximately 50% of patients may develop chronic insomnia due to psychophysiological characteristics. Chronic insomnia with a psychophysiological component is characterized by a marked over concern about the inability to fall asleep. A definitive diagnosis of the specific cause for long-term insomnia is necessary before a treatment plan can be delineated. Sedative/hypnotics are generally reserved for use in those patients with insomnia in whom secondary causes of insomnia have been evaluated and managed or in whom sleep hygiene practices have failed. Chronic insomnia without underlying medical or psychiatric disease can be managed most effectively with a benzodiazepine or nonbenzodiazepine hypnotic used concurrently for a finite period with daily behavioral therapy. Ideally, sedative/hypnotics are not routinely recommended for the management of chronic insomnia. However, in certain circumstances (e.g., severe, refractory insomnia, chronic comorbid illnesses), benzodiazepine and nonbenzodiazepine hypnotics may be administered in conjunction with non-pharmacologic behavioral therapy in the lowest effective dose several times per week for extended durations. Hypnotics should typically be dosed intermittently once every two to three nights to avoid tolerance and dependence. Recently, though, eszopiclone and ramelteon have been approved for use in the long-term management of sleep onset and/or sleep maintenance insomnia, while zolpidem extended-release has been approved for use in managing insomnia without a limit to treatment duration.

Suvorexant and **lemborexant**, the most recently approved medications for insomnia, are prescribed to help patients with sleep onset and sleep maintenance. These drugs may be prescribed on a nightly basis if patients can remain in bed for at least 7 hours before the scheduled waking time.

Zolpidem immediate-release prescribed quantities should not exceed a one-month supply.

Barbiturates are indicated for short-term treatment of insomnia, as these agents appear to lose effectiveness in sleep induction and maintenance after 2 weeks.

Sedative/hypnotic treatment regimens lasting longer than four months in adult patients will be reviewed.

In pediatric patients, sedative/hypnotics are primarily used to alleviate anxiety and/or pain associated with painful or nonpainful but threatening procedures.

3 Duplicative Therapy

The concurrent use of two or more sedative/hypnotics is not recommended. Additional therapeutic benefit is not appreciated when several sedative/hypnotics are administered in combination. Patient profiles containing concurrent prescriptions for multiple sedative/hypnotics will be reviewed.

4 Drug-Drug Interactions

Patient profiles will be assessed to identify those drug regimens that may result in clinically significant drug-drug interactions. Drug-drug interactions considered clinically relevant for sedative/hypnotics are summarized in **Table 8**. 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 8. Sedative/Hypnotic Drug-Drug Interactions

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level [#]
barbiturates (BARB)	anticoagulants	BARB induction of apixaban, rivaroxaban, and warfarin metabolic clearance (CYP3A4) with potential for decreased anticoagulant clinical effects	avoid combination, if possible; closely monitor international normalized ratio (INR) when BARB therapy added, discontinued or changed to warfarin; addition of warfarin to chronic BARB regimen more tolerable	moderate (DrugReax) 2-major (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level [#]
barbiturates	cyclosporine	BARB induction of cyclosporine metabolic clearance (CYP3A4) with potential for reduced cyclosporine clinical effects	avoid concurrent therapy, if possible; if combination necessary, monitor for cyclosporine immunosuppressive efficacy; monitor cyclosporine serum concentrations when BARB therapy added, discontinued, or changed	2-major (CP)
barbiturates	oral contraceptives (OC)	BARB induction of estrogen/progestin hepatic metabolic clearance with potential for decreased OC clinical effects and risk of contraceptive failure	OCs with higher ethinyl estradiol dosages (e.g., 50 mcg) to increase contraceptive efficacy may be necessary; second contraceptive method recommended to prevent unwanted pregnancy	3-moderate (CP)
barbiturates	voriconazole	BARB induction, especially long-acting BARBs (phenobarbital), of voriconazole metabolic clearance (CYP3A4) with potential for decreased voriconazole clinical effects	voriconazole contraindicated for use with long-acting BARBs; use cautiously with short-acting BARBs and monitor clinical effects	contraindicated (DrugReax) 1-severe (CP)
doxepin	drugs metabolized by CYP2D6 (e.g., phenothiazines, delavirdine)	potential for increased doxepin serum levels and enhanced pharmacologic/adverse effects due to competition for CYP2D6 metabolic pathway	monitor patients for enhanced doxepin effects; adjust doses as necessary	2-major (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level [#]
eszopiclone	CYP3A4 inducers (e.g., rifampin, phenytoin, carbamazepine)	induction of eszopiclone metabolic clearance (CYP3A4) with potential for decreased eszopiclone clinical effects	monitor patients for decreased eszopiclone efficacy; consider hypnotic agent not metabolized by CYP3A4	moderate (DrugReax) 3-moderate (CP)
eszopiclone	CYP3A4 inhibitors (e.g., ketoconazole, protease inhibitors, macrolides)	potential for increased eszopiclone serum concentrations and enhanced pharmacologic/ adverse effects	monitor patients for enhanced eszopiclone effects; adjust doses as necessary	moderate (DrugReax) 3-moderate (CP)
lemborexant	CYP3A inducers	potential for decreased lemborexant exposure and risk of reduced efficacy	monitor patients for decreased efficacy. Consider alternate therapy if possible	2- major
oxidatively metabolized benzodiazepines (BZDs) (e.g., estazolam, triazolam)	imidazole antifungals (e.g., itraconazole, ketoconazole)	potential for increased serum concentrations and enhanced pharmacologic/ adverse effects in oxidatively metabolized BZDs (metabolized by CYP3A4) as imidazole antifungals inhibit CYP3A4	adjunctive therapy with imidazole antifungals and oxidatively metabolized BZD contraindicated; BZD metabolized by glucuronidation (e.g., temazepam) may be acceptable alternative	contraindicated (DrugReax) 1-severe (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level [#]
oxidatively metabolized BZDs (e.g., estazolam, triazolam)	macrolides	potential for increased serum concentrations and enhanced pharmacologic/ adverse effects in oxidatively metabolized BZDs (metabolized by CYP3A4) as macrolides inhibit CYP3A4	adjunctive therapy with macrolides and oxidatively metabolized BZD not recommended; BZD metabolized by glucuronidation (e.g., temazepam) may be acceptable alternative; azithromycin may be macrolide alternative (not metabolized by CYP3A4)	moderate (DrugReax) triazolam: 2-major; estazolam: 3-moderate (CP)
oxidatively metabolized benzodiazepines (e.g., estazolam, triazolam)	nefazodone	potential for increased serum concentrations and enhanced pharmacologic/ adverse effects (e.g., prolonged sedation, excessive hypnotic effects) in oxidatively metabolized BZDs (metabolized by CYP3A4) as nefazodone potently inhibits CYP3A4	adjunctive therapy with nefazodone and oxidatively metabolized BZD contraindicated; BZD metabolized by glucuronidation (e.g., temazepam) may be acceptable alternative	contraindicated (DrugReax) 1-severe (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level#
oxidatively metabolized BZDs (e.g., estazolam, triazolam)	non-nucleotide reverse transcriptase (NNRT) inhibitors	potential for altered serum concentrations and pharmacologic effects in oxidatively metabolized BZDs (metabolized by CYP3A4); delavirdine, efavirenz inhibit CYP3A4 and magnify oxidative BZD pharmacologic/adverse effects, while nevirapine induces oxidative BZD metabolism and diminishes pharmacologic effects	adjunctive therapy with NNRT inhibitors and oxidatively metabolized BZD contraindicated; BZD metabolized by glucuronidation (e.g., temazepam) may be acceptable alternative	contraindicated (DrugReax) 1-severe (CP)
oxidatively metabolized BZDs (e.g., estazolam, triazolam)	protease inhibitors	potential for increased serum concentrations and enhanced pharmacologic/adverse effects (e.g., severe sedation, respiratory depression) in oxidatively metabolized BZDs (metabolized by CYP3A4) as protease inhibitors inhibit CYP3A4	adjunctive therapy with protease inhibitors and oxidatively metabolized BZD contraindicated; BZD metabolized by glucuronidation (e.g., temazepam) may be acceptable alternative	contraindicated (DrugReax) 1-severe (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level [#]
oxidatively metabolized BZDs (e.g., estazolam, triazolam)	triazole antifungals (e.g., fluconazole, voriconazole)	potential for increased serum concentrations and enhanced pharmacologic/adverse effects in oxidatively metabolized BZDs (metabolized by CYP3A4) as triazole antifungals inhibit CYP3A4	adjunctive therapy with triazole antifungals and oxidatively metabolized BZD not recommended; BZD metabolized by glucuronidation (e.g., temazepam) may be acceptable alternative	major (DrugReax) 3-moderate (CP)
ramelteon	antifungal agents (triazoles or imidazoles)	potential for increased ramelteon serum concentrations and increased clinical/adverse effects due to CYP2C9 inhibition by triazole antifungals (e.g., fluconazole, voriconazole) or CYP3A4 inhibition by imidazole antifungals (e.g., itraconazole, ketoconazole)	cautiously administer therapy concurrently; monitor for enhanced ramelteon pharmacologic/adverse effects	moderate (DrugReax) 3-moderate (CP)
ramelteon	fluvoxamine	fluvoxamine inhibition of ramelteon metabolism (CYP1A2) and potential for increased ramelteon serum concentrations and increased clinical/adverse effects	avoid concurrent administration; other selective serotonin reuptake inhibitors (e.g., citalopram, fluoxetine) may be safer alternatives to fluvoxamine	contraindicated (DrugReax) 1-severe (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level#
ramelteon	strong CYP1A2 inducers (e.g., rifampin, rifabutin)	induction of ramelteon metabolic clearance (CYP1A2) with potential for decreased ramelteon clinical effects	monitor for decreased ramelteon effectiveness	minor (DrugReax) 3-moderate (CP)
sedative/hypnotics	sodium oxybate (Xyrem®)	adjunctive administration may result in additive central nervous system (CNS) depression	concurrent administration contraindicated	contraindicated (DrugReax) 1-severe (CP)
suvorexant	CNS depressants	adjunctive administration may result in additive CNS depression, cognitive/behavioral changes, and complex sleep behaviors	combined administration not recommended; if necessary, monitor for residual CNS depressant effects	major (DrugReax) 3-moderate (CP)
suvorexant	strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir, clarithromycin)	potential for increased suvorexant serum levels and increased pharmacologic/adverse effects and toxicity as suvorexant is CYP3A4 substrate	combined administration not recommended	contraindicated (DrugReax) 2-major (CP)
suvorexant	moderate CYP3A4 inhibitors (e.g., fluconazole, aprepitant, ciprofloxacin)	potential for increased suvorexant serum levels and increased pharmacologic/adverse effects as suvorexant is CYP3A4 substrate	administer together cautiously, observing for increased adverse effects; suvorexant dose should be reduced to 5 mg/day, but may be increased to maximum of 10 mg/day to maintain efficacy	moderate (DrugReax) 2-major (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level#
suvorexant	CYP3A4 inducers (e.g., carbamazepine, rifampin)	combined administration may result in reduced suvorexant serum levels and decreased efficacy as suvorexant is CYP3A4 substrate	monitor for decreased suvorexant efficacy and adjust dosages as needed	moderate (DrugReax) 2-major (CP)
TCA's (e.g., doxepin)	monoamine oxidase inhibitors (MAOIs)	increased risk of serotonin syndrome (e.g., mental status changes, hyperpyrexia, restless, shivering) due to serotonin metabolism inhibition by monoamine oxidase	allow 14 days after MAOI discontinuation before initiating other antidepressant therapy; wait 5 weeks after discontinuing fluoxetine before initiating MAOIs	contraindicated (DrugReax) 1-severe (CP)
TCA's (e.g., doxepin)	drugs other than MAOIs with serotonergic activity (e.g., tramadol, sumatriptan, nefazodone, trazodone)	increased risk of serotonin syndrome (e.g., mental status changes, hyperpyrexia, restless, shivering, hypertonia, tremor) due to additive serotonergic effects	use cautiously together; if adjunctive administration necessary, monitor for signs and symptoms of serotonin syndrome	major (DrugReax) 2-major, 3-moderate (CP)
TCA's (e.g., doxepin)	drugs that prolong QT interval	increased risk of somnolence, bradycardia and serious cardiotoxicity (QT prolongation, torsades de pointes) due to potential additive effects on QT interval	avoid concurrent use; if adjunctive use necessary, monitor for increased pharmacologic/toxic effects; adjust dose as necessary	contraindicated (DrugReax) 1-severe (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level [#]
zolpidem	CYP3A4 inhibitors (e.g., ketoconazole, protease inhibitors)	potential for increased zolpidem serum concentrations and enhanced pharmacologic/ adverse effects (e.g., severe sedation, respiratory depression) with concurrent administration of CYP3A4 inhibitors, as zolpidem is metabolized by CYP3A4	monitor patients for enhanced zolpidem effects; adjust doses as necessary	moderate (DrugReax) 2-major, 3-moderate (CP)
zolpidem	CYP3A4 inducers (e.g., carbamazepine, rifampin)	induction of zolpidem metabolic clearance (CYP3A4) with potential for decreased zolpidem clinical effects	monitor for decreased zolpidem effectiveness	moderate (DrugReax) 3-moderate (CP)

[#]*Clinical Pharmacology*

5 References

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