

DRUGDEX-EV 1962

MICROMEDEX

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ZALEPLON

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0.0] Overview

1) Class

a) This drug is a member of the following class(es):

Nonbarbiturate Hypnotic

2) Dosing Information

a) Adult

1) Insomnia, Short-term

a) usual dose, 10 mg ORALLY at bedtime; dose range, 5 to 20 mg/day [2]

b) Pediatric

1) Safety and efficacy in children has not been established

3) Contraindications

a) hypersensitivity to [zaleplon](#) or any ingredient in the product [15]

4) Serious Adverse Effects

a) Abnormal behavior

b) [Anaphylaxis](#)

c) [Angioedema](#)

d) Complex mannerisms - behavior

e) Depression

f) Drug withdrawal seizure

g) Suicidal behavior

h) Suicidal thoughts

5) Clinical Applications

a) FDA Approved Indications

1) Insomnia, Short-term

1.0] Dosing Information

[Drug Properties](#)

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1.1] Drug Properties

A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product Index)

B) Synonyms

[Zaleplon](#)

C) Physicochemical Properties

1) Molecular Weight

a) 305.34 [15]

2) Partition Coefficient

a) Octanol/water (log PC): 1.23 over a pH range of 1 to 7 [15]

3) Solubility

a) Practically insoluble in water; sparingly soluble in alcohol or propylene glycol [15]

1.2] Storage and Stability

A) Oral route

1) Capsule

a) Store at controlled room temperature, 20 to 25 degrees C (68 to 77 degrees F) [78].

1.3] Adult Dosage

1.3.1] Normal Dosage

1.3.1.A] Important Note

J) Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [1].

1.3.1.B) Oral route

1) The recommended dose of [zaleplon](#) for the short-term treatment of insomnia is 10 milligrams (mg) at bedtime [12]. A 5-mg dose may be used in low weight individuals. The dose may be increased to 20 mg if necessary. Doses should be taken immediately before bedtime or after going to bed and experiencing difficulty in falling asleep.

2) Efficacy is primarily limited to reducing sleep latency; total sleep time may not be significantly affected, and greatest usefulness of the drug is in patients with sleep initiation disorders [6].

3) [Zaleplon](#) has been shown to be safe and effective for up to 35 nights [13].

1.3.1.C) EQUIVALENT DOSES

1) Pharmacodynamic data shows that [psychomotor impairment](#) was similar between [zaleplon](#) 20 milligrams and [zolpidem](#) 10 mg [14].

1.3.2) Dosage in [Renal Failure](#)

A) No dosage change is necessary in patients with mild to moderate [renal insufficiency](#) since no changes in pharmacokinetics are seen [12]. [Zaleplon](#) has not been studied in patients with severe [renal insufficiency](#).

1.3.3) Dosage in [Hepatic Insufficiency](#)

A) The recommended dose in patients with mild to moderate [hepatic insufficiency](#) is 5 milligrams [12]. Oral clearance is reduced by 70% and 87% in those with mild or moderate [hepatic insufficiency](#), respectively. A 4-fold increase in maximum concentration and a 7-fold increase in area under the concentration-time curve is seen.

1.3.4) Dosage in Geriatric Patients

A) The recommended dose in the elderly is 5 milligrams [12]. Elderly and debilitated patients appear to be more sensitive to the effects of hypnotics. The pharmacokinetics of [zaleplon](#) in the elderly are not significantly different from the young.

1.4) Pediatric Dosage

1.4.1) Normal Dosage

1.4.1.A) Important Note

J) Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [1].

1.4.1.B) Oral route

1) Safety and efficacy of [zaleplon](#) in children has not been determined [12].

2.0) Pharmacokinetics

[Onset and Duration](#)

[Drug Concentration Levels](#)

[ADME](#)

2.1) Onset and Duration

A) Onset

1)) Initial Response

a)) INSOMNIA, ORAL: 30 minutes (Elie, 1999).

B)) Duration**1)) Single Dose**

a)) INSOMNIA, ORAL: 6 hours or greater (Elie, 1999).

2.2) Drug Concentration Levels**A)) Therapeutic Drug Concentration**

1)) Not established.

B)) Time to Peak Concentration

1)) ORAL: 1 hour [70][68][69].

a)) Mean peak serum **zaleplon** concentrations were 10, 27, 71, and 109 ng/mL after oral doses of 5, 15, 30, and 60 mg, respectively, in one study involving healthy male subjects, mean age 24 years [69].

C)) Area Under the Curve

1)) 20 ng/mL x hr (5 mg); 42 ng/mL x hr (10 mg); 59 ng/mL x hr (15 mg); 93 ng/mL x hr (20 mg) [68][69].

2.3) ADME**2.3.1) Absorption****A)) Bioavailability**

1)) ORAL: 30% [70][68]

a)) Undergoes significant presystemic metabolism [70].

B)) Effects of Food

1)) prolongs absorption [70].

a)) A high-fat/heavy meal prolonged the absorption of **zaleplon** with a peak concentration delayed by 2 hours and peak concentration reduced by 35% [70]. Half-life and area under the concentration-time curve are not significantly affected.

2.3.2) Distribution**A)) Distribution Sites**

1)) Protein Binding

a)) 60% [70].

1)) Independent of zaleplon concentration over the range of 10 to 1000 ng/mL [70].

2)) OTHER DISTRIBUTION SITES

a)) Blood [70].

1)) Uniformly distributed throughout the blood with no extensive distribution into red blood cells [70].

b)) Extravascular tissues, extensive [70].

B)) Distribution Kinetics

1)) Volume of Distribution

a)) 1.4 L/kg [70]

2.3.3] Metabolism

A)) Metabolism Sites and Kinetics

1)) LIVER, extent unknown [71].

a)) Extensively metabolized by aldehyde oxidase and CYP3A4 [70]. Less than 1% excreted as unchanged drug in the urine.

B)) Metabolites

1)) 5-oxo-zaleplon, inactive [70].

2)) Desethylzaleplon, inactive [70].

a)) Conversion to this metabolite appears minimal [69].

3)) 5-oxo-desethylzaleplon, inactive [70].

4)) Glucuronides, inactive [70].

2.3.4] Excretion

A)) Kidney

1)) Renal Excretion (%)

a)) 71% [70].

B)) Total Body Clearance

1)) 1 L/hour/kg [70][68].

C)) Other

1) OTHER EXCRETION

a) Feces, 17% [70].

2.3.5] Elimination Half-life**A) Parent Compound****1) ELIMINATION HALF-LIFE**

a) 1 hour [70][69].

1) Value is similar over the dose range of 5 to 60 mg orally (single doses) [69].

3.0] Cautions

[Contraindications](#)

[Precautions](#)

[Adverse Reactions](#)

[Teratogenicity/Effects in Pregnancy/Breastfeeding](#)

[Drug Interactions](#)

3.1] Contraindications

A) hypersensitivity to [zaleplon](#) or any ingredient in the product [15]

3.2] Precautions

A) Beers Criteria: Avoid use in elderly patients as there is minimal improvement in sleep latency and duration with increased risks for emergency visits, hospitalizations, and motor vehicle crashes. Avoid use in patients with a history of falls or fractures as ataxia and impaired psychomotor function may occur [1].

B) abnormal thinking and behavioral changes (eg, agitation, hallucinations, depersonalization) have been reported [15]

C) [anaphylaxis](#), possible; may occur as early as the first dose [15]

D) [angioedema](#), possible with tongue, glottis or larynx involvement requiring emergency medical intervention; may occur as early as the first dose; patients should not be rechallenged with [zaleplon](#) [15]

E) [aspirin](#) hypersensitivity; increased risk of concomitant tartrazine sensitivity and [allergic reactions](#) including [bronchial asthma](#) in susceptible patients [15]

F) complex sleep-related behaviors; possibility of patients performing activities while asleep, with no memory afterwards; includes sleep-driving, making phone calls, and preparing and eating food; discontinuation of [zaleplon](#) may be warranted [15]

G) compromised respiratory function; risk of depression of the respiratory drive [15]

H) concurrent use of alcohol; increased risk of complex sleep-related behaviors and additive CNS depression; alcohol should not be used concomitantly [15]

I) concurrent use of other CNS depressants; increased risk of complex sleep-related behaviors and additive CNS depression; dose reduction may be warranted [15]

J) depression, preexisting; therapy may worsen depression, including suicidal thoughts and actions (including completed suicide) [15]

K) dose-related adverse events, occur with increasing doses; use the lowest effective dose [15]

L) exceeding maximum recommended dose; increased risk of complex sleep-related behaviors [15]

- M)) elderly or debilitated patients; increased risk of adverse effects; dose reduction recommended [15]
- N)) [hepatic impairment](#), mild to moderate; dose reduction recommended [15]
- O)) [hepatic impairment](#), severe; use of [zaleplon](#) is not recommended since the liver is the primary location of metabolism [15]
- P)) rapid onset of action; patient should be lying down and not engage in tasks requiring mental alertness or motor coordination [15]
- Q)) severe [renal impairment](#)
- R)) tartrazine (FD&C Yellow No. 5) sensitivity; increased risk of [allergic reactions](#) including [bronchial asthma](#) in susceptible patients [15]
- S)) unremitting insomnia despite 7 to 10 days of treatment; may be unrecognized psychiatric or physical disorder [15]

3.3] Adverse Reactions

3.3.1] Cardiovascular Effects

3.3.1.A] Peripheral edema

- 1)) Incidence: 1% or less [15]
- 2)) Peripheral edema was reported in 1% of patients treated with [zaleplon](#) 20 mg (n=297), less than 1% of patients treated with [zaleplon](#) 5 mg or 10 mg (n=569), and less than 1% of those treated with placebo (n=344) in a pooled analysis of three 28-night and one 35-night placebo-controlled trials [15].

3.3.2] Dermatologic Effects

3.3.2.A] Photosensitivity

- 1)) Incidence: 1% or less [15]
- 2)) [Photosensitivity reaction](#) was reported in 1% of patients treated with [zaleplon](#) 20 mg (n=297), less than 1% of patients treated with [zaleplon](#) 5 mg or 10 mg (n=569), and less than 1% of those treated with placebo (n=344) in a pooled analysis of three 28-night and one 35-night placebo-controlled trials [15].

3.3.2.B] [Pruritus](#)

- 1)) Incidence: at least 1% [15]
- 2)) [Pruritus](#) was reported in at least 1% of patients treated with [zaleplon](#) doses ranging from 5 mg to 20 mg/day during premarketing phase 2 and phase 3 clinical trials of approximately 2900 patients in the United States, Canada, and Europe. In these trials, causality was not established [15].

3.3.2.C] Rash

- 1)) Incidence: at least 1% [15]
- 2)) Rash was reported in at least 1% of patients treated with [zaleplon](#) doses ranging from 5 mg to 20 mg/day during premarketing phase 2 and phase 3 clinical trials of approximately 2900 patients in the United States, Canada, and Europe. In these trials, causality was not established [15].

3.3.4] Gastrointestinal Effects

3.3.4.A] Abdominal pain

- 1)) Incidence: 6% [15]
- 2)) Abdominal pain was reported in 6% of patients treated with [zaleplon](#) 20 mg (n=297), 6% of patients treated with [zaleplon](#) 5 mg or 10 mg (n=569), and 3% of those treated with placebo (n=344) in a pooled analysis of three 28-night and one 35-night placebo-controlled trials [15].

3.3.4.B] Colitis

1) Incidence: 1% [15]

2) Colitis was reported in 1% of patients treated with zaleplon 20 mg (n=297), 0% of patients treated with zaleplon 5 mg or 10 mg (n=569), and 0% of those treated with placebo (n=344) in a pooled analysis of three 28-night and one 35-night placebo-controlled trials [15].

3.3.4.C] Loss of appetite

1) Incidence: 2% or less [15]

2) Anorexia was reported in 2% of patients treated with zaleplon 20 mg (n=297), less than 1% of patients treated with zaleplon 5 mg or 10 mg (n=569), and less than 1% of those treated with placebo (n=344) in a pooled analysis of three 28-night and one 35-night placebo-controlled trials [15].

3.3.4.D] Nausea

1) Incidence: 6% to 8% [15]

2) Nausea was reported in 8% of patients treated with zaleplon 20 mg (n=297), 6% of patients treated with zaleplon 5 mg or 10 mg (n=569), and 7% of those treated with placebo (n=344) in a pooled analysis of three 28-night and one 35-night placebo-controlled trials [15].

3.3.4.E] Sense of smell altered

1) Incidence: 2% or less [15]

2) Parosmia was reported in 2% of patients treated with zaleplon 20 mg (n=297), less than 1% of patients treated with zaleplon 5 mg or 10 mg (n=569), and less than 1% of those treated with placebo (n=344) in a pooled analysis of three 28-night and one 35-night placebo-controlled trials [15].

3.3.7] Immunologic Effects**3.3.7.A] Anaphylaxis**

1) Incidence: rare [15]

2) Anaphylactic/anaphylactoid reactions, including severe reaction, have been reported in postmarketing surveillance of zaleplon. Symptoms suggestive of anaphylaxis (ie, angioedema, dyspnea, throat closing, or nausea and vomiting) have been reported in patients following initial or subsequent doses of sedative-hypnotics, including zaleplon [15].

3.3.8] Musculoskeletal Effects**3.3.8.A] Arthralgia**

1) Incidence: at least 1% [15]

2) Arthralgia was reported in at least 1% of patients treated with zaleplon doses ranging from 5 mg to 20 mg/day during premarketing phase 2 and phase 3 clinical trials of approximately 2900 patients in the United States, Canada, and Europe. In these trials, causality was not established [15].

3.3.8.B] Arthritis

1) Incidence: at least 1% [15]

2) Arthritis was reported in at least 1% of patients treated with zaleplon doses ranging from 5 mg to 20 mg/day during premarketing phase 2 and phase 3 clinical trials of approximately 2900 patients in the United States, Canada, and Europe. In these trials, causality was not established [15].

3.3.8.C] Myalgia

- 1) Incidence: at least 1% [15]
- 2) Myalgia was reported in at least 1% of patients treated with [zaleplon](#) doses ranging from 5 mg to 20 mg/day during premarketing phase 2 and phase 3 clinical trials of approximately 2900 patients in the United States, Canada, and Europe. In these trials, causality was not established [15].

3.3.9] Neurologic Effects**3.3.9.A] Amnesia**

- 1) Incidence: 2% to 4% [15]
- 2) Amnesia was reported in 4% of patients treated with [zaleplon](#) 20 mg (n=297), 2% of patients treated with [zaleplon](#) 5 mg or 10 mg (n=569), and 1% of those treated with placebo (n=344) in a pooled analysis of three 28-night and one 35-night placebo-controlled trials [15].

3.3.9.B] Asthenia

- 1) Incidence: 5% to 7% [15]
- 2) Asthenia was reported in 7% of patients treated with [zaleplon](#) 20 mg (n=297), 5% of patients treated with [zaleplon](#) 5 mg or 10 mg (n=569), and 5% of those treated with placebo (n=344) in a pooled analysis of three 28-night and one 35-night placebo-controlled trials [15].

3.3.9.C] Confusion

- 1) Incidence: 1% or less [15]
- 2) Confusion was reported in 1% of patients treated with [zaleplon](#) 20 mg (n=297), less than 1% of patients treated with [zaleplon](#) 5 mg or 10 mg (n=569), and less than 1% of those treated with placebo (n=344) in a pooled analysis of three 28-night and one 35-night placebo-controlled trials [15].

3.3.9.D] Dizziness

- 1) Incidence: 7% to 9% [15]
- 2) Dizziness was reported in 9% of patients treated with [zaleplon](#) 20 mg (n=297), 7% of patients treated with [zaleplon](#) 5 mg or 10 mg (n=569), and 7% of those treated with placebo (n=344) in a pooled analysis of three 28-night and one 35-night placebo-controlled trials [15].

3.3.9.E] Drug withdrawal seizure

- 1) Incidence: rare [15]
- 2) Seizures occurred in two patients following abrupt discontinuation of [zaleplon](#) in clinical trials; one of whom had a prior seizure [15].

3.3.9.F] Headache

- 1) Incidence: 30% to 42% [15]
- 2) Headache was reported in 42% of patients treated with [zaleplon](#) 20 mg (n=297), 30% of patients treated with [zaleplon](#) 5 mg or 10 mg (n=569), and 35% of those treated with placebo (n=344) in a pooled analysis of three 28-night and one 35-night placebo-controlled trials [15].

3.3.9.G] Hypesthesia

- 1) Incidence: 2% or less [15]

2) Hypesthesia was reported in 2% of patients treated with [zaleplon](#) 20 mg (n=297), less than 1% of patients treated with [zaleplon](#) 5 mg or 10 mg (n=569), and less than 1% of those treated with placebo (n=344) in a pooled analysis of three 28-night and one 35-night placebo-controlled trials [15].

3.3.9.H] Impaired psychomotor performance

1) [Psychomotor impairment](#) was significant only with [zaleplon](#) doses exceeding 15 or 20 mg [17][18][19]. The severity and duration of these effects were dose-related. Greater central nervous system effects were reported with higher than recommended [zaleplon](#) doses (40 to 60 mg), including impaired motor skills [17][18]. Psychomotor effects usually subsided after 3 to 4 hours following a 20-mg dose of [zaleplon](#) [17][19].

2) [Zaleplon](#) produced neither objective nor subjective residual effects when administered as little as 2 hours before awakening [20]. In contrast, [zolpidem](#) residual effects were observed up to 5 hours after administration. Subjects were awakened and administered [zaleplon](#) 10 mg, [zolpidem](#) 10 mg, or placebo at 5, 4, 3, or 2 hours before awakening. The following morning, a battery of subjective and objective assessments were administered. [Zaleplon](#), regardless of administration time, did not significantly impair psychomotor performance, arousal and cognitive function, or memory function compared with placebo.

3) [Zaleplon](#) 10 mg and 20 mg appeared to be safe when taken up to 5 hours before driving. Healthy subjects (n=28) received [zaleplon](#) 10 or 20 mg, or placebo at approximately 5 hours or 10 hours before engaging in a driving test. Driving instructors judged the subjects' driving to be of similarly good quality after placebo and after all [zaleplon](#) treatments. One subject who had received [zaleplon](#) 20 mg 5 hours earlier chose to terminate the test since he had difficulties in trying to visually focus on the road and traffic [21].

3.3.9.I] Increased muscle tone

1) Incidence: 1% [15]

2) Hypertonia was reported in 1% of patients treated with [zaleplon](#) 20 mg (n=297), 1% of patients treated with [zaleplon](#) 5 mg or 10 mg (n=569), and less than 1% of those treated with placebo (n=344) in a pooled analysis of three 28-night and one 35-night placebo-controlled trials [15].

3.3.9.J] Memory impairment

1) [Memory impairment](#) occurred with 20-mg doses in one study; however, the impairment was markedly less one hour after administration of [zaleplon](#) 20 mg than it was with [lorazepam](#) 2 mg [19]. In another report, no significant effect on memory was observed with doses up to 60 mg [18].

3.3.9.K] Migraine

1) Incidence: at least 1% [15]

2) Migraine headache was reported in at least 1% of patients treated with [zaleplon](#) doses ranging from 5 mg to 20 mg/day during premarketing phase 2 and phase 3 clinical trials of approximately 2900 patients in the United States, Canada, and Europe. In these trials, causality was not established [15].

3.3.9.L] Paresthesia

1) Incidence: 3% [15]

2) Paresthesia was reported in 3% of patients treated with [zaleplon](#) 20 mg (n=297), 3% of patients treated with [zaleplon](#) 5 mg or 10 mg (n=569), and 1% of those treated with placebo (n=344) in a pooled analysis of three 28-night and one 35-night placebo-controlled trials [15].

3.3.9.M] Rebound insomnia

1) There was both objective (polysomnographic) and subjective (diary) evidence of rebound insomnia (ie, dose-dependent temporary worsening in sleep parameters) on the first night following discontinuation of

[zaleplon](#) 20 mg in 3 sleep laboratory studies (14, 28, and 35 nights) and in 5 subjective (diary) outpatient studies (14 and 28 nights) compared with baseline. Following discontinuation of [zaleplon](#) 5 or 10 mg, there was only minimal subjective evidence of rebound insomnia. At all doses, rebound insomnia appeared to resolve by the second night after [zaleplon](#) discontinuation. Worsening in sleep compared with placebo, but not compared with baseline, was reported on the first night off in both the 10-mg and 20-mg groups in the 35-night study [15].

3.3.9.N] Somnolence

1) Incidence: 5% to 6% [15]

2) Somnolence was reported in 6% of patients treated with [zaleplon](#) 20 mg (n=297), 5% of patients treated with [zaleplon](#) 5 mg or 10 mg (n=569), and 4% of those treated with placebo (n=344) in a pooled analysis of three 28-night and one 35-night placebo-controlled trials [15].

3.3.9.O] Tremor

1) Incidence: 2% [15]

2) Tremor was reported in 2% of patients treated with [zaleplon](#) 20 mg (n=297), 2% of patients treated with [zaleplon](#) 5 mg or 10 mg (n=569), and 1% of those treated with placebo (n=344) in a pooled analysis of three 28-night and one 35-night placebo-controlled trials [15].

3.3.9.P] Vertigo

1) Incidence: 1% or less [15]

2) Vertigo was reported in 1% of patients treated with [zaleplon](#) 20 mg (n=297), less than 1% of patients treated with [zaleplon](#) 5 mg or 10 mg (n=569), and less than 1% of those treated with placebo (n=344) in a pooled analysis of three 28-night and one 35-night placebo-controlled trials [15].

3.3.10] Ophthalmic Effects

3.3.10.A] Abnormal vision

1) Incidence: 2% or less [15]

2) Abnormal vision was reported in 2% of patients treated with [zaleplon](#) 20 mg (n=297), less than 1% of patients treated with [zaleplon](#) 5 mg or 10 mg (n=569), and less than 1% of those treated with placebo (n=344) in a pooled analysis of three 28-night and one 35-night placebo-controlled trials [15].

3.3.10.B] Blurred vision

1) Vision impairment (eg, blurred vision) has been observed, particularly following higher [zaleplon](#) doses (eg, 40 to 60 mg) [17][18][19].

3.3.10.C] Conjunctivitis

1) Incidence: at least 1% [15]

2) [Conjunctivitis](#) was reported in at least 1% of patients treated with [zaleplon](#) doses ranging from 5 mg to 20 mg/day during premarketing phase 2 and phase 3 clinical trials of approximately 2900 patients in the United States, Canada, and Europe. In these trials, causality was not established [15].

3.3.10.D] Pain in eye

1) Incidence: 3% to 4%[15]

2) Eye pain was reported in 3% of patients treated with [zaleplon](#) 20 mg (n=297), less than 4% of patients treated with [zaleplon](#) 5 mg or 10 mg (n=569), and less than 2% of those treated with placebo (n=344) in a pooled analysis of three 28-night and one 35-night placebo-controlled trials [15].

3.3.11] Otic Effects

3.3.11.A] Hyperacusis

1) Incidence: 1% to 2% [15]

2) Hyperacusis was reported in 2% of patients treated with [zaleplon](#) 20 mg (n=297), 1% of patients treated with [zaleplon](#) 5 mg or 10 mg (n=569), and less than 1% of those treated with placebo (n=344) in a pooled analysis of three 28-night and one 35-night placebo-controlled trials [15].

3.3.11.B] Otalgia

1) Incidence: 1% or less [15]

2) Ear pain was reported in 1% of patients treated with [zaleplon](#) 20 mg (n=297), less than 1% of patients treated with [zaleplon](#) 5 mg or 10 mg (n=569), and 0% of those treated with placebo (n=344) in a pooled analysis of three 28-night and one 35-night placebo-controlled trials [15].

3.3.12] Psychiatric Effects

3.3.12.A] Abnormal behavior

1) Abnormal thinking and behavioral changes, including decreased inhibition, bizarre behavior, agitation, hallucinations and depersonalization, have been reported in association with sedative or hypnotic use, including [zaleplon](#). Behavior abnormalities may be indicative of an unrecognized psychiatric or physical disorder, particularly if insomnia is not remitting after 7 to 10 days of [zaleplon](#) treatment. Therefore, the onset of any new behavioral sign or symptom that is of concern should be immediately evaluated. [15].

3.3.12.B] Complex mannerisms - behavior

1) Complex behaviors including sleep driving, preparing and eating food, making phone calls, or having sexual intercourse while not fully awake and subsequently not remembering the performance of these activities have occurred following administration of sedative-hypnotics, including [zaleplon](#). These behaviors have occurred in sedative-hypnotic-naïve and sedative-hypnotic-experienced patients. Although, determination of causality (ie, drug-induced, spontaneous in origin, result of an underlying psychiatric or physical disorder) cannot be made with certainty in most cases, any new behaviors should be immediately and carefully assessed. The use of alcohol and other CNS depressants or the use of [zaleplon](#) exceeding the recommended maximum dose may also increase the risk of such behavior. In cases of sleep-driving, strongly consider discontinuation of [zaleplon](#) due to the risk to the patient and others [15].

3.3.12.C] Depersonalization

1) Incidence: 2% or less [15]

2) Depersonalization was reported in 2% of patients treated with [zaleplon](#) 20 mg (n=297), less than 1% of patients treated with [zaleplon](#) 5 mg or 10 mg (n=569), and less than 1% of those treated with placebo (n=344) in a pooled analysis of three 28-night and one 35-night placebo-controlled trials [15].

3.3.12.D] Depression

1) Incidence: at least 1% [15]

2) Depression was reported in at least 1% of patients treated with [zaleplon](#) doses ranging from 5 mg to 20 mg/day during premarketing phase 2 and phase 3 clinical trials of approximately 2900 patients in the United States, Canada, and Europe. In these trials, causality was not established [15].

3) Worsening of depression, including [suicidal ideation](#), has also been reported in association with sedative or hypnotic use. This effect has occurred primarily in depressed patients; the onset of any new behavioral sign or symptom that is of concern should be immediately evaluated [15].

3.3.12.E] Hallucinations

1) Incidence: 1% or less [15]

2) Hallucinations were reported in 1% of patients treated with [zaleplon](#) 20 mg (n=297), less than 1% of patients treated with [zaleplon](#) 5 mg or 10 mg (n=569), and less than 1% of those treated with placebo (n=344) in a pooled analysis of three 28-night and one 35-night placebo-controlled trials [15].

3.3.12.F] Suicidal behavior

1) Suicidal action and completed suicides as a result of worsened depression have been reported in association with sedative or hypnotic use among primarily depressed patients. The onset of any new behavioral sign or symptom that is of concern should be immediately evaluated [15].

3.3.12.G] Suicidal thoughts

1) [Suicidal ideation](#) and intent as a result of worsened depression have been reported in association with sedative or hypnotic use among primarily depressed patients. The onset of any new behavioral sign or symptom that is of concern should be immediately evaluated [15].

3.3.14] Reproductive Effects

3.3.14.A] [Dysmenorrhea](#)

1) Incidence: 3% to 4% [15]

2) [Dysmenorrhea](#) was reported in 4% of patients treated with [zaleplon](#) 20 mg (n=297), 3% of patients treated with [zaleplon](#) 5 mg or 10 mg (n=569), and 2% of those treated with placebo (n=344) in a pooled analysis of three 28-night and one 35-night placebo-controlled trials [15].

3.3.15] Respiratory Effects

3.3.15.A] [Bronchitis](#)

1) Incidence: at least 1% [15]

2) [Bronchitis](#) was reported in at least 1% of patients treated with [zaleplon](#) doses ranging from 5 mg to 20 mg/day during premarketing phase 2 and phase 3 clinical trials of approximately 2900 patients in the United States, Canada, and Europe. In these trials, causality was not established [15].

3.3.15.B] [Epistaxis](#)

1) Incidence: 1% or less [15]

2) [Epistaxis](#) was reported in 1% of patients treated with [zaleplon](#) 20 mg (n=297), less than 1% of patients treated with [zaleplon](#) 5 mg or 10 mg (n=569), and less than 1% of those treated with placebo (n=344) in a pooled analysis of three 28-night and one 35-night placebo-controlled trials [15].

3.3.16] Other

3.3.16.A] Angioedema

1) Incidence: rare [15]

2) Cases of [angioedema](#) involving the tongue, glottis, or larynx, some fatal, have been reported rarely in patients following the first or subsequent doses of sedative-hypnotics, including [zaleplon](#). Additional symptoms suggestive of [anaphylaxis](#), including dyspnea, throat closing, or nausea and vomiting, have been reported. Some patients with these symptoms have presented to the emergency department. Do not rechallenge patients who have experienced [angioedema](#) following [zaleplon](#) treatment [15].

3.3.16.B] Drug abuse

1) The abuse potential for [zaleplon](#) was reported to be similar to that of benzodiazepines and benzodiazepine-like hypnotics in two studies in which patients with known histories of sedative drug abuse were treated with [zaleplon](#) at doses of 25 mg, 50 mg, and 75 mg. Carefully monitor patients with a known history of drug or alcohol abuse or addiction when administering [zaleplon](#) due to an increased risk of dependence [15].

3.4] Teratogenicity/Effects in Pregnancy/Breastfeeding**A) Teratogenicity/Effects in Pregnancy**

1) U.S. Food and Drug Administration's Pregnancy Category: Category C (All Trimesters)

a) Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential [risk to the fetus](#).

2) Australian Drug Evaluation Committee's (ADEC) Category: C

a) Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

3) Crosses Placenta: Unknown

4) Clinical Management

a) No human studies of pregnancy outcomes after exposure to [zaleplon](#) have been published, and there have been no reports of outcomes after inadvertent exposure during pregnancy. Although [teratogenicity](#) was not evident in animal studies of rats and rabbits, other effects, including reduced prenatal and postnatal growth in the offspring of rat dams and decreased maternal weight gain at maternally toxic doses during early gestation, were observed. Increased stillbirth and postnatal mortality, and decreased growth and physical development were also noted in the offspring of pregnant rats treated at less than maternally toxic doses during the latter part of gestation and throughout lactation. Therefore, the use of [zaleplon](#) during pregnancy is not recommended [15].

5) Literature Reports

a)] No human studies of pregnancy outcomes after exposure to [zaleplon](#) have been published, and there have been no reports of outcomes after inadvertent exposure during pregnancy. However, in animal embryofetal development studies, oral administration of [zaleplon](#) in rats reduced prenatal and postnatal growth in the offspring of dams at the highest and maternally toxic dose of 100 mg/kg/day (approximately 49 times the maximum recommended human dose (MRHD) of 20 mg on a mg/m(2) basis), but failed to produce evidence of [teratogenicity](#) when given throughout organogenesis. This dose in rats also produced clinical signs of maternal toxicity and decreased maternal weight gain during gestation. No adverse effects on embryofetal development were noted in rabbits administered [zaleplon](#) at doses up to 50 mg/kg/day (approximately 48 times the MRHD). In a pre- and postnatal study, administration of [zaleplon](#) in pregnant rats produced increased stillbirth and postnatal mortality, and decreased growth and physical development in the offspring of females treated at doses of 7 mg/kg/day or greater during the latter part of gestation and throughout lactation, but was not associated with maternal toxicity at this dose [15].

B)] Breastfeeding

1)] Micromedex Lactation Rating: Infant risk is minimal.

a)] The weight of an adequate body of evidence and/or expert consensus suggests this drug poses minimal risk to the infant when used during breastfeeding.

2)] Clinical Management

a)] [Zaleplon](#) is excreted into human breast milk, but the effects on the nursing infant from exposure to the drug in milk have not been determined. However, the amount transferred through the breast milk to the nursing infant is small, with the highest amount of excretion expected during a feeding at approximately 1 hour post drug administration [15], and is likely to be clinically unimportant [66]. However, the manufacturer advises against using [zaleplon](#) in nursing mothers [15].

3)] Literature Reports

a)] In an open-label, single-dose, [pharmacokinetic study](#) involving 5 lactating mothers, it was shown that [zaleplon](#) is present in breast milk and the maximum exposure to the infant during breastfeeding at peak milk concentration would be 1.28 to 1.66 mcg. This low dose is not expected to adversely affect the nursing infant [66].

4)] Drug Levels in Breastmilk

a)] Parent Drug

1)] Percent Adult Dose in Breastmilk

a)] 0.013% to 0.017% [66]

3.5] Drug Interactions

3.5.1] Drug-Drug Combinations

3.5.1.A] Alfentanil

- 1) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)
- 2) Summary: The concomitant use of [alfentanil](#) with other CNS depressants may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[48].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Reserve concomitant use of [alfentanil](#) with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[48].
- 7) Probable Mechanism: additive CNS depression

3.5.1.B] Bromazepam

- 1) Interaction Effect: increased risk of respiratory or cardiovascular depression
- 2) Summary: Concomitant use of bromazepam with another CNS depressant should be avoided due to increased risk for respiratory or cardiovascular depression and profound sedation[42].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of bromazepam, which is a CNS depressant, with another CNS depressant may result in respiratory or cardiovascular depression and profound sedation. Due to the added CNS depressant effects, avoid use of bromazepam and other CNS depressants[42].
- 7) Probable Mechanism: additive CNS depression

3.5.1.C] Bromopride

- 1) Interaction Effect: potentiation of sedative effects
- 2) Summary: Potentiation of sedative effects may occur with concomitant use of bromopride and sedatives. Avoid concomitant use[60].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid concomitant use of bromopride with sedatives. Additive sedation may occur with concomitant use[60].
- 7) Probable Mechanism: unknown

3.5.1.D] Buprenorphine

- 1) Interaction Effect: increased risk of [respiratory depression](#)
- 2) Summary: Coadministration of [buprenorphine](#) and a CNS depressant may result in additive CNS depression and an increased risk of [respiratory depression](#). If concomitant use is required, consider reducing the dose of one or both agents[31][32] and monitor for signs of [respiratory depression](#), sedation, and hypotension [31].

- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [buprenorphine](#) and a CNS depressant may result in additive CNS depression and an increased risk of [respiratory depression](#). If concomitant use is required, consider reducing the dose of one or both agents[31][32] and monitor for signs of [respiratory depression](#), sedation, and hypotension [31].
- 7) Probable Mechanism: additive [respiratory depression](#)

3.5.1.E] [Butorphanol](#)

- 1) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)
- 2) Summary: The concomitant use of [butorphanol](#) with other CNS depressants may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[48].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Reserve concomitant use of [butorphanol](#) with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[48].
- 7) Probable Mechanism: additive CNS depression

3.5.1.F] [Carbinoxamine](#)

- 1) Interaction Effect: additive CNS effects
- 2) Summary: Avoid concurrent use of [carbinoxamine](#) and CNS depressants, including alcohol, tranquilizers, or sedatives, as this may cause additive CNS effects[44][45]. Counsel patients on the risk of additive CNS cognitive and motor effects if coadministration of [carbinoxamine](#) and a CNS depressant is required.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [carbinoxamine](#) with CNS depressants, including alcohol, tranquilizers, or sedatives, may have additive effects and is therefore not recommended[44][45]. Counsel patients on the risk of additive CNS cognitive and motor effects if coadministration of [carbinoxamine](#) and a CNS depressant is required.
- 7) Probable Mechanism: additive effects on the CNS

3.5.1.G] [Ceritinib](#)

- 1) Interaction Effect: increased exposure of CYP3A substrate
- 2) Summary: Avoid concomitant use of ceritinib and a CYP3A substrate as this may increase exposure to and adverse effects of the substrate. If concurrent use cannot be avoided, consider dose reductions of the CYP3A substrate[30].
- 3) Severity: major
- 4) Onset: unspecified

- 5) Substantiation: theoretical
- 6) Clinical Management: Avoid concomitant use of ceritinib and a CYP3A substrate as this may increase exposure to and adverse effects of the substrate. If concurrent use cannot be avoided, consider dose reductions of the CYP3A substrate[30].
- 7) Probable Mechanism: inhibition of CYP3A-mediated metabolism of drug by ceritinib

3.5.1.H) Cimetidine

- 1) Interaction Effect: potentiation of zaleplon effects
- 2) Summary: The concomitant administration of zaleplon 10 mg and cimetidine 800 mg caused an 85% increase in the maximum concentration (C_{max}) and area under the concentration-time curve (AUC) of zaleplon. Cimetidine inhibits both aldehyde oxidase and cytochrome P450 3A4 (CYP3A4), which are the primary and secondary enzymes responsible for zaleplon metabolism. In patients who are receiving cimetidine therapy, zaleplon should be initiated at a dose of 5 mg[33].
- 3) Severity: moderate
- 4) Onset: rapid
- 5) Substantiation: probable
- 6) Clinical Management: Zaleplon therapy should be initiated at a dose of 5 mg in patients also receiving cimetidine.
- 7) Probable Mechanism: inhibition by cimetidine of aldehyde oxidase-mediated and cytochrome P450 3A4-mediated zaleplon metabolism

3.5.1.I) Clarithromycin

- 1) Interaction Effect: increased exposure of CYP3A substrate and risk for toxicity
- 2) Summary: Use caution with coadministration of clarithromycin, a strong CYP3A inhibitor, with drugs extensively metabolized by CYP3A, as increased plasma concentrations of the CYP3A substrate and risk for toxicity may occur. Consider dose adjustments, when possible, and closely monitor serum concentrations of drugs primarily metabolized by CYP3A[43].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Use caution with coadministration of clarithromycin with drugs extensively metabolized by CYP3A, as increased plasma concentrations of the CYP3A substrate and risk for toxicity may occur. Consider dose adjustments, when possible, and closely monitor serum concentrations of drugs primarily metabolized by CYP3A[43].
- 7) Probable Mechanism: inhibition of CYP3A-mediated metabolism by clarithromycin

3.5.1.J) Codeine

- 1) Interaction Effect: increased risk of CNS depression (ie, respiratory depression, profound sedation, coma)
- 2) Summary: The concomitant use of codeine with other CNS depressants may result in profound sedation, respiratory depression, coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for respiratory depression and sedation. Avoid concomitant use of codeine cough medications with CNS depressants[48].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical

6) Clinical Management: Reserve concomitant use of [codeine](#) with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation. Avoid concomitant use of [codeine cough](#) medications with CNS depressants[48].

7) Probable Mechanism: additive CNS depression

3.5.1.K] [Conivaptan](#)

1) Interaction Effect: increased exposure of CYP3A substrate

2) Summary: Avoid concomitant use of [conivaptan](#) (strong CYP3A inhibitor) with drugs eliminated primarily by CYP3A-mediated metabolism, as this may result in increased exposure of the CYP3A substrate. [Conivaptan](#) increased the AUC of CYP3A substrates [midazolam](#), [simvastatin](#), and [amlodipine](#). The CYP3A substrate may be initiated no sooner than 1 week after completion of [conivaptan](#) therapy[52].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Avoid concomitant use of [conivaptan](#) (strong CYP3A inhibitor) with drugs eliminated primarily by CYP3A-mediated metabolism, as this may result in increased exposure of the CYP3A substrate. The CYP3A substrate may be initiated no sooner than 1 week after completion of [conivaptan](#) therapy[52].

7) Probable Mechanism: inhibition of CYP3A-mediated substrate metabolism by [conivaptan](#)

8) Literature Reports

a) The strong CYP3A inhibitor [conivaptan](#) 40 mg/day IV increased the AUC of [midazolam](#), a CYP3A substrate, by approximately 100% with a 1-mg IV dose and by 200% with a 2-mg oral dose [52].

b) [Conivaptan](#) 30 mg/day IV tripled the AUC of [simvastatin](#), a CYP3A substrate [52].

c) [Conivaptan](#) 40 mg orally twice daily doubled the AUC and half-life of [amlodipine](#), a CYP3A substrate [52].

3.5.1.L] [Dihydrocodeine](#)

1) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)

2) Summary: The concomitant use of [dihydrocodeine](#) with other CNS depressants may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation. Avoid concomitant use of [dihydrocodeine cough](#) medications with CNS depressants[48].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Reserve concomitant use of [dihydrocodeine](#) with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation. Avoid concomitant use of [dihydrocodeine cough](#) medications with CNS depressants[48].

7) Probable Mechanism: additive CNS depression

3.5.1.M] Doxylamine

- 1)) Interaction Effect: increased risk of CNS depression
- 2)) Summary: Coadministration of [doxylamine](#) and a CNS depressant is not recommended due to the potential for additive CNS depression[38][39]. If concomitant use is required, consider monitoring and dose reduction of one or both agents.
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Coadministration of [doxylamine](#) and a CNS depressant is not recommended due to the potential for additive CNS depression[38][39]. If concomitant use is required, consider monitoring and dose reduction of one or both agents.
- 7)) Probable Mechanism: additive CNS depression

3.5.1.N] Fentanyl

- 1)) Interaction Effect: increased risk of CNS depression
- 2)) Summary: Coadministration of [fentanyl](#), a CNS depressant, with other CNS depressants may cause additive CNS depression including [respiratory depression](#), hypotension, and profound sedation, which could potentially lead to coma or death[53]. Severe hypotension has been reported with coadministration of [fentanyl](#) and [midazolam](#) in neonates, including those maintained on an infusion of either drug who subsequently received rapid injections of either [fentanyl](#) or [midazolam](#) [54]. Due to the risk of additive CNS effects, use caution, monitor patients closely, and reduce the dose of one or both when these agents are administered concomitantly [53].
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: Concomitant use of [fentanyl](#), which is a CNS depressant, with another CNS depressant may result in [respiratory depression](#), hypotension, and profound sedation, potentially leading to coma or death. Due to the added CNS depressant effects, exercise caution if coadministration of [fentanyl](#) and another CNS depressant is required. Carefully monitor patients receiving concomitant [fentanyl](#) and other CNS depressants and adjust dosage of one or both agents[53].
- 7)) Probable Mechanism: additive CNS depression

3.5.1.O] Flibanserin

- 1)) Interaction Effect: additive CNS depression
- 2)) Summary: The concomitant use of flibanserin with CNS depressants may increase the risk of CNS depression (eg, somnolence and sedation) compared with the use of flibanserin alone. Advise the patient of the risks of CNS depressant use while using flibanserin[40].
- 3)) Severity: major
- 4)) Onset: unspecified
- 5)) Substantiation: theoretical
- 6)) Clinical Management: The concomitant use of flibanserin with CNS depressants may increase the risk of CNS depression (eg, somnolence and sedation) compared with the use of flibanserin alone. Advise the patient of the risks of CNS depressant use while using flibanserin[40].
- 7)) Probable Mechanism: additive CNS depression

3.5.1.P] Fluconazole

- 1) Interaction Effect: increased [zaleplon](#) exposure and risk for toxicity
- 2) Summary: Concomitant use of CYP3A4 substrates, such as [zaleplon](#), with [fluconazole](#) (a moderate CYP3A4 inhibitor) may increase exposure to the CYP3A4 substrate and increase the risk for toxicity. Caution and careful monitoring is advised when using this type of combination of drugs. Fluconazole-mediated CYP3A4 inhibition may persist for 4 to 5 days after discontinuation[22]
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of CYP3A4 substrates, such as [zaleplon](#), with [fluconazole](#) (a moderate CYP3A4 inhibitor) may increase exposure to the CYP3A4 substrate and increase the risk for toxicity. Caution and careful monitoring is advised when using this type of combination of drugs. Fluconazole-mediated CYP3A4 inhibition may persist for 4 to 5 days after discontinuation[22]
- 7) Probable Mechanism: inhibition of CYP3A4-mediated [zaleplon](#) metabolism by [fluconazole](#)

3.5.1.Q] [Flumazenil](#)

- 1) Interaction Effect: decreased efficacy of benzodiazepine receptor agonist
- 2) Summary: Caution is advised when coadministering [flumazenil](#) with a nonbenzodiazepine agonist of the benzodiazepine receptor, such as [eszopiclone](#), [zaleplon](#), [zolpidem](#), and zopiclone due to the ability of [flumazenil](#) to block the central effects of benzodiazepine receptor agonists, by competitive interaction at the receptor level[23]. If concomitant use is necessary, consider monitoring for decreased efficacy of zopiclone.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: [Flumazenil](#) blocks the central effects of benzodiazepines by competitive interaction at the receptor level. The effects of nonbenzodiazepine agonists of benzodiazepine receptors, such as [eszopiclone](#), [zaleplon](#), [zolpidem](#), and zopiclone, at benzodiazepine receptors are also blocked by [flumazenil](#)[23]. If concomitant use is necessary, consider monitoring for decreased efficacy of the benzodiazepine receptor agonist.
- 7) Probable Mechanism: competitive inhibition of benzodiazepine receptors on the [gamma-aminobutyric acid \(GABA\)](#)/benzodiazepine receptor complex

3.5.1.R] [Fosphenytoin](#)

- 1) Interaction Effect: reduced [zaleplon](#) plasma concentrations
- 2) Summary: [Zaleplon](#) is partially metabolized by the CYP3A4 isozyme. Concomitant use of [rifampin](#) (a potent CYP3A4 inducer and [zaleplon](#) reduced [zaleplon](#) exposure and plasma concentrations by approximately 80%. Although not studied with [phenytoin](#), also a potent CYP3A4 inducer, a similar interaction can be expected. An alternative hypnotic agent that is not a substrate of CYP3A4 should be considered in patients receiving [rifampin](#)[15].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of [phenytoin](#), a potent CYP3A4 inducer, and [zaleplon](#) may result in decreased [zaleplon](#) levels and efficacy. Consider using an alternative hypnotic agent that is not a substrate of CYP3A4 in patients receiving [rifampin](#)[15].
- 7) Probable Mechanism: induction of CYP3A4-mediated [zaleplon](#) metabolism by [phenytoin](#)

3.5.1.S] [Fospropofol](#)

- 1) Interaction Effect: additive cardiorespiratory effects
- 2) Summary: Concomitant use of fospropofol and [zaleplon](#) may result in additive cardiorespiratory effects due to the sedative action of both drugs[46]. Monitoring the patient for adverse effects may be warranted and possible dose adjustments may be necessary.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Consider monitoring the patient for cardiorespiratory depression when fospropofol and [zaleplon](#) are used in combination. A reduction in dose of one or both drugs may be necessary.
- 7) Probable Mechanism: CNS depression

3.5.1.T] [Hydrocodone](#)

- 1) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)
- 2) Summary: Use caution with the concomitant use of [hydrocodone](#) and a CNS depressant as this may result in additive CNS effects and increase the risk of [respiratory depression](#), profound sedation, coma, and/or death. If combination therapy is required, reduce the initial [hydrocodone](#) dose by 20% to 30% and consider using a lower dose of the concomitant CNS depressant. Monitor patients for signs of [respiratory depression](#), sedation, or hypotension[59]. Avoid concomitant use of [hydrocodone cough](#) medications with CNS depressants [48].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [hydrocodone](#) and a CNS depressant may result in additive CNS effects and increase the risk of [respiratory depression](#), profound sedation, coma, and/or death. If combination therapy is required, reduce the initial [hydrocodone](#) dose by 20% to 30% and use a lower dose of the concomitant CNS depressant. Monitor patients for signs of [respiratory depression](#), sedation, or hypotension[59]. Avoid concomitant use of [hydrocodone cough](#) medications with CNS depressants [48].
- 7) Probable Mechanism: additive CNS depression

3.5.1.U] [Hydromorphone](#)

- 1) Interaction Effect: an increase in CNS or [respiratory depression](#)
- 2) Summary: The concomitant use of [HYDROmorphine](#) and other CNS depressants, such as sedatives and hypnotics, may result in additive CNS depressant effects, including [respiratory depression](#), hypotension, profound sedation, and coma. When administering [HYDROmorphine](#) and a sedative or hypnotic together, dose reduction of one or both of the medications should be considered[62].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of [HYDROmorphine](#) and other CNS depressants, such as sedatives or hypnotics, may result in [respiratory depression](#), hypotension, profound sedation, and coma. When concomitant use is required, dose reduction of one or both medications should be considered[62].
- 7) Probable Mechanism: additive CNS depression

3.5.1.V] [Idelalisib](#)

- 1) Interaction Effect: increased exposure of CYP3A substrate

2) Summary: Avoid coadministration of idelalisib (a strong CYP3A inhibitor) and a CYP3A substrate as this may increase exposure of the CYP3A substrate and increase the risk of adverse effects. During a drug interaction study, coadministration of idelalisib and [midazolam](#) (CYP3A substrate) resulted in a 5.4-fold increase in [midazolam](#) AUC and a 2.4 fold increase in [midazolam](#) Cmax[58].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Coadministration of idelalisib (a strong CYP3A inhibitor) and a CYP3A substrate should be avoided, as this may increase exposure of the CYP3A substrate and increase the risk of adverse effects[58].

7) Probable Mechanism: inhibition of CYP3A-mediated metabolism by idelalisib

8) Literature Reports

a) During a drug interaction study, administration of idelalisib 150 mg for 15 doses followed by a single dose of [midazolam](#) 5 mg (a CYP3A substrate) in healthy volunteers, resulted in a 5.4-fold increase in [midazolam](#) AUC and a 2.4 fold increase in [midazolam](#) Cmax [58].

3.5.1.W] [Ketoconazole](#)

1) Interaction Effect: increased plasma concentrations of [zaleplon](#)

2) Summary: Caution is advised when using [ketoconazole](#), a strong CYP3A4 inhibitor, together with a CYP3A4 substrate such as [zaleplon](#), as concomitant use may result in elevated plasma concentrations of [zaleplon](#) resulting in increased or prolonged therapeutic and adverse effects[57].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Caution is advised when using [ketoconazole](#), a strong CYP3A4 inhibitor, together with a CYP3A4 substrate such as [zaleplon](#), as concomitant use may result in elevated plasma concentrations of [zaleplon](#) resulting in increased or prolonged therapeutic and adverse effects[57].

7) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of [zaleplon](#) by [ketoconazole](#)

3.5.1.X] [Loxapine](#)

1) Interaction Effect: potentiation of impaired cognitive function and motor skills and an increased risk of [respiratory depression](#), hypotension, oversedation, and syncope

2) Summary: Concomitant use of [loxapine](#), a CNS depressant, and other CNS depressants may potentiate impaired cognitive function and motor skills and increase the risk of [respiratory depression](#), hypotension, oversedation, and syncope. If [loxapine](#) and other CNS depressants are used concurrently, consider a dose reduction of the CNS depressant[55] and use with caution [56].

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [loxapine](#) and other CNS depressants may potentiate impaired cognitive function and motor skills and increase the risk of [respiratory depression](#), hypotension, oversedation, and syncope. If [loxapine](#) and CNS depressants are used concurrently, consider a dose reduction of the CNS depressant[55] and use with caution [56].

7) Probable Mechanism: additive CNS depression

3.5.1.Y] [Meclizine](#)

1) Interaction Effect: an increase in CNS or [respiratory depression](#)

2) Summary: Concomitant use of [meclizine](#) and CNS depressants, including alcohol, tranquilizers, or sedatives may potentiate CNS depression cognitive and motor effects. Avoid concurrent use of alcohol while taking [meclizine](#)[49][50][51] and counsel patients on the risk of additive CNS cognitive and motor effects if coadministration of [meclizine](#) and a CNS depressant is required.

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [meclizine](#) with CNS depressants, including alcohol, tranquilizers, or sedatives, may potentiate CNS depression. Avoid concurrent use of alcohol with [meclizine](#)[49][50][51] and counsel patients on the risk of additive CNS cognitive and motor effects if coadministration of [meclizine](#) and a CNS depressant is required.

7) Probable Mechanism: additive CNS depression

3.5.1.Z] [Meperidine](#)

1) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)

2) Summary: The concomitant use of [meperidine](#) with other CNS depressants may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[48].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Reserve concomitant use of [meperidine](#) with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[48].

7) Probable Mechanism: additive CNS depression

3.5.1.AA] [Methadone](#)

1) Interaction Effect: increased risk of CNS depression

2) Summary: Concomitant use of [methadone](#), which is a CNS depressant, with another CNS depressant may result in additive effects including [respiratory depression](#), hypotension, and profound sedation, potentially leading to coma or death. Assess the duration of use and the patients degree of tolerance to CNS depressants. If [methadone](#) is coadministered with a CNS depressant, initiate the dose of [methadone](#) at 2.5 mg every 12 hours, and consider lowering the dose of the concomitant CNS depressant. Monitor for signs and symptoms of [respiratory depression](#), hypotension, and sedation[29].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant use of [methadone](#), which is a CNS depressant, with another CNS depressant may result in additive effects including [respiratory depression](#), hypotension, and profound sedation, potentially leading to coma or death. Assess the duration of use and the patients degree of tolerance to CNS depressants. If [methadone](#) is coadministered with a CNS depressant, initiate the dose of [methadone](#) at 2.5 mg every 12 hours, and consider lowering the dose of the concomitant CNS depressant. Monitor for signs and symptoms of [respiratory depression](#), hypotension, and sedation[29].

7) Probable Mechanism: additive CNS depression effects

3.5.1.AB] Morphine

- 1) Interaction Effect: increased risk of CNS depression
- 2) Summary: Concomitant use of **morphine**, which is a CNS depressant, with another CNS depressant may result in **respiratory depression**, hypotension, and profound sedation, potentially leading to coma or death. Assess the duration of use and the patients degree of tolerance to CNS depressants. Carefully monitor patients receiving concomitant **morphine** and other CNS depressants for hypotension, **respiratory depression** and sedation, initiate **morphine** at the lowest dose (ie, 30 mg every 24 hours or 15 mg every 12 hours), and reduce the dose of 1 or both drugs[35][36][37].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of **morphine**, which is a CNS depressant, with another CNS depressant may result in **respiratory depression**, hypotension, and profound sedation, potentially leading to coma or death. Assess the duration of use and the patients degree of tolerance to CNS depressants. Carefully monitor patients for hypotension, **respiratory depression** or sedation, initiate **morphine** at the lowest dose (ie, 30 mg every 24 hours or 15 mg every 12 hours), and reduce the dose of 1 or both drugs[35][36][37].
- 7) Probable Mechanism: additive CNS depression effects

3.5.1.AC] Morphine Sulfate Liposome

- 1) Interaction Effect: increased risk of CNS depression
- 2) Summary: Concomitant use of **morphine**, which is a CNS depressant, with another CNS depressant may result in **respiratory depression**, hypotension, and profound sedation, potentially leading to coma or death. Assess the duration of use and the patients degree of tolerance to CNS depressants. Carefully monitor patients receiving concomitant **morphine** and other CNS depressants for hypotension, **respiratory depression** and sedation, initiate **morphine** at the lowest dose (ie, 30 mg every 24 hours or 15 mg every 12 hours), and reduce the dose of 1 or both drugs[35][36][37].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of **morphine**, which is a CNS depressant, with another CNS depressant may result in **respiratory depression**, hypotension, and profound sedation, potentially leading to coma or death. Assess the duration of use and the patients degree of tolerance to CNS depressants. Carefully monitor patients for hypotension, **respiratory depression** or sedation, initiate **morphine** at the lowest dose (ie, 30 mg every 24 hours or 15 mg every 12 hours), and reduce the dose of 1 or both drugs[35][36][37].
- 7) Probable Mechanism: additive CNS depression effects

3.5.1.AD] Oxycodone

- 1) Interaction Effect: an increase in CNS or **respiratory depression**
- 2) Summary: Concomitant use of **oxycodone** with other CNS depressants, such as sedatives or hypnotics, may result in **respiratory depression**, hypotension, profound sedation, coma or death. If combined use is necessary, monitor the patient and reduce the dose of one or both medications. Initiate **oxycodone** controlled-release formulations at one-third to one-half of the usual dosage[26][27] and initiate extended-release **oxycodone** hydrochloride/**acetaminophen** at one-half the usual dose [28].
- 3) Severity: major
- 4) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Concomitant use of **oxycodone** with other CNS depressants, such as sedatives or hypnotics, may result in **respiratory depression**, hypotension, profound sedation, coma or death. If combined use is necessary, monitor the patient and reduce the dose of one or both medications. Initiate **oxycodone** controlled-release formulations at one-third to one-half of the usual dosage[26][27] and initiate extended-release **oxycodone** hydrochloride/**acetaminophen** at one-half the usual dose [28].

7J) Probable Mechanism: additive CNS depression

3.5.1.AE] **Oxymorphone**

1J) Interaction Effect: increased risk of **respiratory depression**, profound sedation, coma, and death

2J) Summary: Coadministration of **oxymorphone** and a CNS depressant may result in additive respiratory and CNS depressant effects and an increased risk of **respiratory depression**, profound sedation, coma, and death. If concurrent use is clinically necessary, initiate **oxymorphone** at a dose of 5 mg every 12 hours. Monitor patients for sedation, hypotension, and **respiratory depression**, and consider reducing the CNS depressant dose[34].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Coadministration of **oxymorphone** and a CNS depressant may result in additive respiratory and CNS depressant effects. If concurrent use is clinically necessary, initiate **oxymorphone** at a dose of 5 mg every 12 hours. Monitor patients for sedation and **respiratory depression**, sedation, and hypotension, and consider reducing the CNS depressant dose[34].

7J) Probable Mechanism: additive respiratory and CNS depressant effects

3.5.1.AF] **Pentazocine**

1J) Interaction Effect: increased risk of CNS depression (ie, **respiratory depression**, profound sedation, coma)

2J) Summary: The concomitant use of **pentazocine** with other CNS depressants may result in profound sedation, **respiratory depression**, coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for **respiratory depression** and sedation[48].

3J) Severity: major

4J) Onset: unspecified

5J) Substantiation: theoretical

6J) Clinical Management: Reserve concomitant use of **pentazocine** with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for **respiratory depression** and sedation[48].

7J) Probable Mechanism: additive CNS depression

3.5.1.AG] **Periciazine**

1J) Interaction Effect: risk of enhanced CNS depression

2J) Summary: Concomitant use of periciazine with other phenothiazine derivatives or CNS depressants may enhance the CNS depressive effects of both agents. If coadministered, reduce the dose of the phenothiazine derivative or CNS depressant by at least 50% while periciazine is being gradually initiated[24][25].

3J) Severity: major

- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of periciazine with other phenothiazine derivatives or CNS depressants may enhance the CNS depressive effects of both agents. If coadministered, reduce the dose of the phenothiazine derivative or CNS depressant by at least 50% while periciazine is being gradually initiated[24][25].
- 7) Probable Mechanism: additive CNS depression

3.5.1.AH] Phenobarbital

- 1) Interaction Effect: reduced zaleplon plasma concentrations
- 2) Summary: Zaleplon is partially metabolized by the CYP3A4 isozyme. Concomitant use of rifampin, a potent CYP3A4 inducer, and zaleplon reduced zaleplon exposure and plasma concentrations by approximately 80%. Although not studied with phenobarbital, also a potent CYP3A4 inducer, a similar interaction can be expected. An alternative hypnotic agent that is not a substrate of CYP3A4 should be considered in patients receiving rifampin[15].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of phenobarbital, a potent CYP3A4 inducer, and zaleplon may result in decreased zaleplon levels and efficacy. Consider using an alternative hypnotic agent that is not a substrate of CYP3A4 in patients receiving rifampin[15].
- 7) Probable Mechanism: induction of CYP3A4-mediated zaleplon metabolism by phenobarbital

3.5.1.AI] Phenytoin

- 1) Interaction Effect: reduced zaleplon plasma concentrations
- 2) Summary: Zaleplon is partially metabolized by the CYP3A4 isozyme. Concomitant use of rifampin (a potent CYP3A4 inducer and zaleplon reduced zaleplon exposure and plasma concentrations by approximately 80%. Although not studied with phenytoin, also a potent CYP3A4 inducer, a similar interaction can be expected. An alternative hypnotic agent that is not a substrate of CYP3A4 should be considered in patients receiving rifampin[15].
- 3) Severity: moderate
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Coadministration of phenytoin, a potent CYP3A4 inducer, and zaleplon may result in decreased zaleplon levels and efficacy. Consider using an alternative hypnotic agent that is not a substrate of CYP3A4 in patients receiving rifampin[15].
- 7) Probable Mechanism: induction of CYP3A4-mediated zaleplon metabolism by phenytoin

3.5.1.AJ] Propofol

- 1) Interaction Effect: additive cardiorespiratory effects
- 2) Summary: Concomitant use of fospropofol and zaleplon may result in additive cardiorespiratory effects due to the sedative action of both drugs[46]. Monitoring the patient for adverse effects may be warranted and possible dose adjustments may be necessary.
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical

6) Clinical Management: Consider monitoring the patient for cardiorespiratory depression when fospropofol and [zaleplon](#) are used in combination. A reduction in dose of one or both drugs may be necessary.

7) Probable Mechanism: CNS depression

3.5.1.AK] [Remifentanyl](#)

1) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)

2) Summary: The concomitant use of [remifentanyl](#) with other CNS depressants may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[48].

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Reserve concomitant use of [remifentanyl](#) with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[48].

7) Probable Mechanism: additive CNS depression

3.5.1.AL] [Rifampin](#)

1) Interaction Effect: reduced [zaleplon](#) plasma concentrations

2) Summary: [Zaleplon](#) is partially metabolized by the CYP3A4 isozyme. Concomitant use of [rifampin](#), a potent CYP3A4 inducer, and [zaleplon](#) has resulted in decreased [zaleplon](#) plasma concentrations. An alternative hypnotic agent that is not a substrate of CYP3A4 should be considered in patients receiving [rifampin](#)[15].

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Coadministration of [rifampin](#), a potent CYP3A4 inducer, and [zaleplon](#) has resulted in significant decreases in [zaleplon](#) plasma concentrations. Consider using an alternative hypnotic agent that is not a substrate of CYP3A4 in patients receiving [rifampin](#)[15].

7) Probable Mechanism: induction of CYP3A4-mediated [zaleplon](#) metabolism by [rifampin](#)

8) Literature Reports

a) Concomitant use of [zaleplon](#) and multiple doses of [rifampin](#) (600 mg once daily for 14 days) resulted in an approximate 80% reduction in [zaleplon](#) C_{max} and AUC [15].

3.5.1.AM] [Sodium Oxybate](#)

1) Interaction Effect: increased CNS depression

2) Summary: Concomitant use of [sodium oxybate](#) and certain sedative hypnotics is contraindicated because of the risk for additive CNS depression[41].

3) Severity: contraindicated

4) Onset: unspecified

5) Substantiation: theoretical

- 6) Clinical Management: Concomitant use of [sodium oxybate](#) and certain sedative hypnotics is contraindicated[41].
- 7) Probable Mechanism: additive CNS depression

3.5.1.AN] [Sufentanil](#)

- 1) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)
- 2) Summary: The concomitant use of [sufentanil](#) with other CNS depressants may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[48].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Reserve concomitant use of [sufentanil](#) with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[48].
- 7) Probable Mechanism: additive CNS depression

3.5.1.AO] [Suvorexant](#)

- 1) Interaction Effect: additive sedative effects
- 2) Summary: Avoid concomitant use of suvorexant and this drug as potentiation of sedative effects may occur[47].
- 3) Severity: moderate
- 4) Onset: rapid
- 5) Substantiation: theoretical
- 6) Clinical Management: Concomitant use of suvorexant and this drug is not recommended as potentiation of sedative effects may occur[47].
- 7) Probable Mechanism: additive CNS depression

3.5.1.AP] [Tapentadol](#)

- 1) Interaction Effect: an increase in CNS and [respiratory depression](#)
- 2) Summary: The concomitant use of tapentadol with other CNS depressants, including sedatives, may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[48].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Reserve concomitant use of tapentadol with other CNS depressants, including sedatives, to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[48].
- 7) Probable Mechanism: additive CNS depression

3.5.1.AQ] Tramadol

- 1) Interaction Effect: increased risk of CNS depression (ie, [respiratory depression](#), profound sedation, coma)
- 2) Summary: The concomitant use of [tramadol](#) with other CNS depressants may result in profound sedation, [respiratory depression](#), coma, and/or death. Reserve concomitant use to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[48].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: Reserve concomitant use of [tramadol](#) with other CNS depressants to clinical settings where alternative treatment options are inadequate. If combination therapy is required, reduce the initial dose of the newly prescribed medication and titrate to clinical response while monitoring for [respiratory depression](#) and sedation[48].
- 7) Probable Mechanism: additive CNS depression

3.5.1.AR] Zolpidem

- 1) Interaction Effect: an increase in CNS depressant effects
- 2) Summary: The concomitant use of [zolpidem](#) with drugs that have sedative or hypnotic properties at bedtime or in the middle of the night is not recommended. Any drug with CNS-depressant effects could potentially enhance the CNS-depressant effects of [zolpidem](#). Additionally the risk of complex behaviors such as sleep-driving (driving while not fully awake after ingestion of a sedative-hypnotic, with amnesia for the event) is increased with concomitant use. Dosage adjustments of [zolpidem](#) and other concomitant CNS-depressants may be necessary when coadministered because of the potentially additive effects[61].
- 3) Severity: major
- 4) Onset: unspecified
- 5) Substantiation: theoretical
- 6) Clinical Management: The concomitant use of [zolpidem](#) with drugs that have sedative or hypnotic properties at bedtime or in the middle of the night is not recommended. Any drug with CNS-depressant effects could potentially enhance the CNS-depressant effects of [zolpidem](#). Additionally the risk of complex behaviors such as sleep-driving (driving while not fully awake after ingestion of a sedative-hypnotic, with amnesia for the event) is increased with concomitant use. Dosage adjustments of [zolpidem](#) and other concomitant CNS-depressants may be necessary when coadministered because of the potentially additive effects[61].
- 7) Probable Mechanism: additive effects

3.5.2] Drug-Food Combinations**3.5.2.A] Ethanol**

- 1) Interaction Effect: impaired psychomotor functions
- 2) Summary: [Zaleplon](#) 10 mg potentiated the central nervous system effects of ethanol 0.75 g/kg on balance testing and reaction time for one hour following ethanol administration. Additionally, results from the digit symbol substitution test (DSST), the symbol copying test, and the variability component of the divided attention test were affected for 2.5 hours after ethanol administration. [Zaleplon](#) potentiated the pharmacodynamic effects of ethanol, with no alteration in the pharmacokinetics of either drug[63].
- 3) Severity: moderate

- 4)) Onset: rapid
- 5)) Substantiation: probable
- 6)) Clinical Management: Patients receiving [zaleplon](#) should be advised to avoid ethanol consumption.
- 7)) Probable Mechanism: additive CNS depression

3.5.2.B) High Fat Food

- 1)) Interaction Effect: reduced [zaleplon](#) efficacy
- 2)) Summary: In healthy volunteers, the ingestion of [zaleplon](#) with a high-fat meal prolonged the absorption of [zaleplon](#) as compared to the fasting state. Maximum concentration (C_{max}) of [zaleplon](#) was reduced by 35% and the time to C_{max} (t_{max}) was delayed by approximately two hours. The area under the concentration-time curve (AUC) and half-life of [zaleplon](#) were not affected. These results suggest that the effects of [zaleplon](#) on sleep onset may be decreased if taken with or immediately following a high-fat meal[64].
- 3)) Severity: minor
- 4)) Onset: rapid
- 5)) Substantiation: probable
- 6)) Clinical Management: Patients should be advised to avoid evening meals high in fat content.
- 7)) Probable Mechanism: decreased [zaleplon](#) absorption

4.0) Clinical Applications

[Monitoring Parameters](#)

[Patient Instructions](#)

[Place In Therapy](#)

[Mechanism of Action / Pharmacology](#)

[Therapeutic Uses](#)

[Comparative Efficacy / Evaluation With Other Therapies](#)

4.1) Monitoring Parameters

A) Therapeutic

1) Physical Findings

- a)) Sleep latency (time from going to bed to initiation of sleep) and number of awakenings
- b)) Effect on daytime function (hangover effects)

B) Toxic

1) Physical Findings

- a)) Signs of adverse effects (eg, severe dizziness, confusion)

4.2) Patient Instructions

A) [Zaleplon](#) (By mouth)

[Zaleplon](#)

Treats insomnia (having trouble falling asleep).

When This Medicine Should Not Be Used:

You should not use this medicine if you have had an [allergic reaction](#) to [zaleplon](#), or if you have severe liver disease.

How to Use This Medicine:

Capsule

Your doctor will tell you how much medicine to use. Do not use more than directed.

Take this medicine just before going to bed or when you will have time to sleep for at least 4 hours.

You should not use this medicine with a high-fat or heavy meal.

This medicine is not for long-term use. [Zaleplon](#) should be used for no more than 10 days unless otherwise ordered by your doctor.

If you have used this medicine every night for more than 1 week, do not suddenly stop using it without first checking with your doctor. You may need to slowly decrease your dose before stopping it completely.

This medicine should come with a Medication Guide. Ask your pharmacist for a copy if you do not have one.

If a Dose is Missed:

If you do not remember until the next morning that you missed a dose of [zaleplon](#) the night before, skip the missed dose. Wait until that night to use your medicine.

You should not use two doses at the same time.

How to Store and Dispose of This Medicine:

Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.

Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any outdated medicine or medicine no longer needed.

Keep all medicine out of the reach of children. Never share your medicine with anyone.

Drugs and Foods to Avoid:

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

Make sure your doctor knows if you are also using [carbamazepine](#) ([Tegretol®](#)), [cimetidine](#) ([Tagamet®](#)), [erythromycin](#) ([Ery-tab®](#)), [imipramine](#) ([Tofranil®](#)), [ketoconazole](#) ([Nizoral®](#)), [phenobarbital](#), [phenytoin](#) ([Dilantin®](#)), [promethazine](#) ([Phenergan®](#)), [rifampin](#) ([Rifadin®](#)), or [thioridazine](#) ([Mellaril®](#)).

Tell your doctor if you use anything else that makes you sleepy. Some examples are allergy medicine, narcotic pain medicine, and alcohol.

Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:

Make sure your doctor knows if you are pregnant or breastfeeding, or if you have mild liver disease, any breathing problems, or a history of depression, alcoholism, or drug abuse.

[Zaleplon](#) also may cause temporary changes in your behavior, such as aggression, agitation, confusion, or strange behavior. Contact your doctor if you notice any of these signs while using this medicine.

This medicine may cause a serious type of [allergic reaction](#) called [anaphylaxis](#). [Anaphylaxis](#) can be life-threatening and requires immediate medical attention. Stop taking this medicine and call your doctor right away if you have itching, hives, trouble breathing, or any swelling of your hands, face, or mouth when you take this medicine.

This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that could be dangerous if you are not alert. This medicine may also cause sleep-related behaviors such as driving a car (sleep-driving), walking (sleep-walking), having sex, making phone calls, or preparing and eating food while asleep or not fully awake. If these reactions occur, tell your doctor right away.

Sometimes these effects may last through the next day. Make sure you know how the medicine will affect you before you do any tasks that require you to be alert.

This medicine can be habit-forming. Do not use more than your prescribed dose. Call your doctor if you think your medicine is not working.

Your doctor will check your progress and the effects of this medicine at regular visits. Keep all appointments.

Call your doctor if your symptoms do not improve or if they get worse.

Possible Side Effects While Using This Medicine:

Call your doctor right away if you notice any of these side effects:

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing
Changes in behavior or thinking.
Depressed mood or thoughts of suicide.
Diarrhea that may contain blood.
Seeing, hearing, or feeling things that are not there.
Swelling in your hands, ankles, or feet.
Trouble breathing.

If you notice these less serious side effects, talk with your doctor:

Anxiety.
Blurred vision or eye pain.
Dizziness, drowsiness, headache, or lightheadedness.
Loss of appetite.
Loss of memory for the first few hours after using the medicine.
Numbness, tingling, or burning pain in your hands, arms, legs, or feet.
Stomach pain or nausea.
Trouble with coordination or muscle stiffness.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

4.3] Place In Therapy

A) **Zaleplon** is short-acting and reduces sleep latency in **primary insomnia**; effects on increasing total sleep time and decreasing number of awakenings are inconsistent. As such, the drug would be indicated in patients with sleep initiation disorders. Suggested uses for **zaleplon** have included insomnia in shift workers, and as needed use for occasional insomnia when there is a limited amount of time before morning rise time [79]. Significant benefits relative to the short-acting **triazolam** have not been clearly demonstrated; the use of **zaleplon** over **triazolam** at this time cannot be recommended when a short-acting hypnotic is needed, unless a cost advantage is evident.

B) Other nonbenzodiazepine hypnotics (eg, **zolpidem**, **zopiclone**) have also failed to demonstrate distinct advantages which would make them preferable to conventional benzodiazepines for the treatment of insomnia.

4.4] Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) **Zaleplon** is a nonbenzodiazepine (pyrazolopyrimidine) possessing sedative/hypnotic, anxiolytic, muscle relaxant, and anticonvulsant activity [72][71][73]. The drug selectively binds to the benzodiazepine-1 (omega-1) receptor subtype, similar to **zolpidem** [74][75][76]; like **zolpidem**, it was developed to offer an improved tolerability profile compared to benzodiazepines. However, whether selectivity for a specific benzodiazepine receptor site confers a significant difference in pharmacological activity (or a clinical advantage) remains to be determined.

2) **Zaleplon** has little effect on sleep stages (Anon, 1999).

B) REVIEW ARTICLES

1) The pharmacodynamics, pharmacokinetics, therapeutic trials and tolerability of **zaleplon** have been reviewed [77]; (Anon, 1999).

2)) Nonbenzodiazepine hypnotic agents and their efficacy in insomnia [75].

4.5] Therapeutic Uses

4.5.1] FDA Uses

4.5.1.A] Insomnia, Short-term

FDA Labeled Indication

1)) Overview

FDA Approval: Adult, yes; **Pediatric, no**

Efficacy: Adult, Effective

Recommendation: Adult, Class IIa

Strength of Evidence: Adult, Category B

See Drug Consult reference: [RECOMMENDATION AND EVIDENCE RATINGS](#)

2)) Summary:

Indicated in the short-term management of sleep disorders

Decreases time to sleep onset for up to 35 days

Not shown to increase total sleep time or decrease the number of awakenings

3)) Adult:

a)) [Zaleplon](#), when taken in the middle of the night because of noise-evoked sleeplessness, reduced sleep latency and had no residual effects 4 hours later. Twelve healthy volunteers were allowed to sleep for 5 hours in a quiet environment and were then awakened. After performing some mental function tests, they were given placebo, [zaleplon](#) 10 milligrams (mg), [zaleplon](#) 20 mg, or zopiclone 7.5 mg (positive control) in a double-blind manner and went back to bed. (Each subject received each treatment on separate occasions.) A sound stimulus (to which the subjects had already demonstrated sensitivity) was then started and continued until persistent sleep had been reached or until 2 hours later if the subject did not fall asleep. Subjects were awakened 4 hours after taking a treatment and subjected to mental function tests (digit symbol substitution, critical flicker fusion, choice reaction time, immediate and delayed memory recall). In comparison to placebo, [zaleplon](#) caused no residual impairment of performance. Zopiclone impaired performance, as expected, in comparison to placebo. The latency to persistent sleep was reduced by both doses of [zaleplon](#) (10 mg, $p=0.001$; 20 mg $p=0.014$), and the duration of stage 1 sleep was reduced by the 20 mg dose ($p=0.012$) compared to placebo [3].

b)) Oral [zaleplon](#) 5 to 20 milligrams (mg) has produced significant reductions in sleep latency in patients with insomnia, with a trend toward dose-related effects; total sleep time and decreases in awakenings have not consistently improved [4][5][6][7][8]. The efficacy of [zaleplon](#) in these doses appears similar to that of [triazolam](#) 0.25 mg [6][7].

c)) [Zaleplon](#) 10 and 20 milligrams (mg) decreased sleep latency for up to 4 weeks while [zolpidem](#) 10 mg decreased sleep latency for up to 3 weeks as compared to placebo [9]. Patients were randomly assigned to receive [zaleplon](#) 5 mg ($n=122$), [zaleplon](#) 10 mg ($n=121$), [zaleplon](#) 20 mg ($n=124$), [zolpidem](#) 10 mg ($n=122$), or placebo ($n=126$) for 28 days. Sleep latency was significantly reduced with [zaleplon](#) 20 mg during weeks 1 through 4 (p less than 0.001 for weeks 1 to 3, p less than 0.01

for week 4), and similarly with [zaleplon](#) 10 mg during weeks 1 through 4 (p less than 0.001 for week 1, p less than 0.01 for weeks 2 and 3, p less than 0.05 for week 4). [Zaleplon](#) 5 mg reduced sleep latency during weeks 1 through 3 (p less than 0.05 for week 1, and p less than 0.01 for weeks 2 and 3). [Zolpidem](#) 10 mg also reduced sleep latency during weeks 1 through 3 (p less than 0.05 for weeks 1 and 3 and p less than 0.01 for week 2). Sleep duration was increased significantly only by [zaleplon](#) 20 mg during weeks 1, 2, and 4 (p less than 0.05). [Zolpidem](#) 10 mg significantly increased sleep duration during all 4 weeks (p less than 0.001). No significant differences were observed in number of awakenings between placebo and any of the active treatment groups. On the first night of discontinuation, there were no significant differences seen between [zaleplon](#) and placebo. With [zolpidem](#), significant differences were seen on the first night of discontinuation in sleep latency (p less than 0.001), sleep duration (p less than 0.05), and in number of awakenings (p less than 0.01).

d]) In 31 patients with mild to [moderate chronic obstructive pulmonary disease](#) and insomnia, [zaleplon](#) and [zolpidem](#) were safe and effective for sleep-onset insomnia [10]. Patients received [zaleplon](#) 10 milligrams, [zolpidem](#) 10 mg, and placebo for 1 night each in random order. Patients reported improvement in sleep latency with both drugs and total sleep time for [zolpidem](#) only. No differences were seen in mean overnight arterial [oxygen saturation](#) or with percent of night with saturation less than 90% for [zaleplon](#), [zolpidem](#), or placebo.

e]) [Zaleplon](#) and [zolpidem](#) were both subjectively effective in elderly patients with sleep onset insomnia [11]. In a double-blind study, 549 elderly patients (65 years old or older) were randomized to [zaleplon](#) 5 or 10 milligrams, [zolpidem](#) 5 mg, or placebo for 2 weeks of treatment. Subjective sleep latency was significantly decreased for [zaleplon](#) 10 mg during both week 1 and week 2 (both weeks p less than 0.001), but only for week 2 for [zaleplon](#) 5 mg (p less than 0.001). Subjective sleep latency was significantly decreased for [zolpidem](#) during both week 1 and week 2 (p less than 0.05, p less than 0.005, respectively). Subjective total sleep time was significantly increased for [zaleplon](#) 10 mg during week 1 only (p less than 0.05) and for [zolpidem](#) during week 1 and week 2 (p less than 0.001, p less than 0.01, respectively). The number of awakenings did not differ for either dose of [zaleplon](#), but was reduced by [zolpidem](#) during both weeks.

f]) In a double-blind study with [triazolam](#) included as a comparator drug, [zaleplon](#) 5 milligrams and 10 mg significantly decreased sleep latency as compared to placebo during nights 4 and 5 of the study (p=0.019, p=0.039, respectively) [4]. Patients received either [zaleplon](#) 5 mg (n=34), [zaleplon](#) 10 mg (n=33), [triazolam](#) 0.25 mg (n=31), or placebo (n=34). Patients received placebo on nights 1 to 3, study drug on nights 4 to 17 (efficacy measured on nights 4, 5, 16, 17), and placebo on nights 18 and 19. Although sleep latency was reduced in the [zaleplon](#) groups as compared to placebo on nights 4 and 5, there was no significant difference on nights 16 and 17. There was also no difference between [zaleplon](#) and placebo in total sleep time and number of awakenings. Total sleep time was significantly greater in the [triazolam](#) group on nights 4 and 5 (p less 0.001) but not on nights 16 and 17. [Zaleplon](#) had no effect on the amount of time spent in any stage of sleep as compared to placebo nor did it affect sleep latency and total sleep time on the discontinuation nights.

g]) In one large study involving patients with [primary insomnia](#) (n=132), a significant reduction in sleep latency relative to placebo was observed on nights 4 and 5 with [zaleplon](#) 5 or 10 mg nightly; efficacy was similar to [triazolam](#) 0.25 mg nightly. However, sleep latency was similar in all groups on nights 16 and 17, attributed to improvement in the placebo group. No significant difference in total sleep time scores were observed on discontinuation nights (18 and 19) [7].

4.6] Comparative Efficacy / Evaluation With Other Therapies

4.6.A) Flurazepam

1) Adverse Effects

a) Next-day sedation was observed with flurazepam 30 milligrams (mg) but not zaleplon 10 or 20 mg in a placebo-controlled study [91]. Patients (n=93) received either zaleplon or flurazepam and were evaluated the next day with multiple sleep latency tests. Next-day sedation was not significantly different from placebo with either the zaleplon 10-mg or 20-mg doses. Flurazepam 30 mg produced significantly more next-day sedation than placebo and both zaleplon doses (all tests, p less than 0.001).

4.6.B) Lorazepam

4.6.B.1) Impaired psychomotor performance

a) In healthy subjects, zaleplon 20 mg was associated with a lesser degree of psychomotor impairment and impaired memory than lorazepam 2 mg. Recovery of normal functioning was more rapid in the zaleplon group (3 versus 5 hours) [83]. However, lorazepam has a significantly longer half-life (14 hours) than zaleplon, and its longer duration of action is to be expected.

4.6.C) Triazolam

4.6.C.1) Insomnia

a) SUMMARY: Zaleplon and triazolam have produced comparable reductions in sleep latency in insomnia; sleep time was prolonged by triazolam but not zaleplon. Neither agent induces significant hangover effects.

b) In a double-blind study with triazolam included as a comparator drug, zaleplon 5 milligrams and 10 mg significantly decreased sleep latency as compared to placebo during nights 4 and 5 of the study (p=0.019, p=0.039, respectively) [80]. Patients received either zaleplon 5 mg (n=34), zaleplon 10 mg (n=33), triazolam 0.25 mg (n=31), or placebo (n=34). Patients received placebo on nights 1 to 3, study drug on nights 4 to 17 (efficacy measured on nights 4, 5, 16, 17), and placebo on nights 18 and 19. Although sleep latency was reduced in the zaleplon groups as compared to placebo on nights 4 and 5, there was no significant difference on nights 16 and 17. There was also no difference between zaleplon and placebo in total sleep time and number of awakenings. Total sleep time was significantly greater in the triazolam group on nights 4 and 5 (p less 0.001) but not on nights 16 and 17. Zaleplon had no effect on the amount of time spent in any stage of sleep as compared to placebo nor did it affect sleep latency and total sleep time on the discontinuation nights.

c) The efficacy of zaleplon 5 to 20 mg nightly in reducing sleep latency has not differed significantly from that of triazolam 0.25 mg nightly in patients with primary insomnia; nearly identical reductions have been observed with triazolam 0.25 mg and zaleplon 10 mg (15 to 20 minutes) [81][82].

d) Total sleep time was reduced significantly by triazolam 0.25 mg, but not zaleplon 10 to 60 mg, in one comparison [81]. Although greater increases in stage 3 to 4 sleep and decreases in the percentage of REM sleep have been observed with zaleplon [81], these differences do not appear relevant with doses that will be used clinically.

e) Two claims for zaleplon are its lack of hangover-effect potential and minimal-to-absent rebound insomnia upon discontinuation. In one comparison with triazolam, there was no significant difference in total sleep time scores on discontinuation nights after two weeks of treatment; a trend for rebound insomnia was evident with triazolam, but this was not statistically significant [82].

f) The incidence of adverse effects (eg, dizziness, headache, somnolence) was similar with triazolam 0.25 mg daily and zaleplon 5 or 10 mg daily in one large study [82].

4.6.D] Zolpidem

4.6.D.1] Insomnia

a) GENERAL INFORMATION: **Zaleplon** 20 milligrams has comparable adverse psychomotor effects to **zolpidem** 10 mg [85].

b) **Zaleplon** 10 and 20 milligrams (mg) decreased sleep latency for up to 4 weeks while **zolpidem** 10 mg decreased sleep latency for up to 3 weeks as compared to placebo [86]. Patients were randomly assigned to receive **zaleplon** 5 mg (n=122), **zaleplon** 10 mg (n=121), **zaleplon** 20 mg (n=124), **zolpidem** 10 mg (n=122), or placebo (n=126) for 28 days. Sleep latency was significantly reduced with **zaleplon** 20 mg during weeks 1 through 4 (p less than 0.001 for weeks 1 to 3, p less than 0.01 for week 4), and similarly with **zaleplon** 10 mg during weeks 1 through 4 (p less than 0.001 for week 1, p less than 0.01 for weeks 2 and 3, p less than 0.05 for week 4). **Zaleplon** 5 mg reduced sleep latency during weeks 1 through 3 (p less than 0.05 for week 1, and p less than 0.01 for weeks 2 and 3). **Zolpidem** 10 mg also reduced sleep latency during weeks 1 through 3 (p less than 0.05 for weeks 1 and 3 and p less than 0.01 for week 2). Sleep duration was increased significantly only by **zaleplon** 20 mg during weeks 1, 2, and 4 (p less than 0.05). **Zolpidem** 10 mg significantly increased sleep duration during all 4 weeks (p less than 0.001). No significant differences were observed in number of awakenings between placebo and any of the active treatment groups. On the first night of discontinuation, there were no significant differences seen between **zaleplon** and placebo. With **zolpidem**, significant differences were seen on the first night of discontinuation in sleep latency (p less than 0.001), sleep duration (p less than 0.05), and in number of awakenings (p less than 0.01).

c) In 31 patients with mild to **moderate chronic obstructive pulmonary disease** and insomnia, **zaleplon** and **zolpidem** were safe and effective for sleep-onset insomnia [87]. Patients received **zaleplon** 10 milligrams, **zolpidem** 10 mg, and placebo for 1 night each in random order. Patients reported improvement in sleep latency with both drugs and total sleep time for **zolpidem** only. No differences were seen in mean overnight arterial **oxygen saturation** or with percent of night with saturation less than 90% for **zaleplon**, **zolpidem**, or placebo.

d) **Zaleplon** and **zolpidem** were both subjectively effective in elderly patients with sleep onset insomnia [88]. In a double-blind study, 549 elderly patients (65-years-old or older) were randomized to **zaleplon** 5 or 10 milligrams, **zolpidem** 5 mg, or placebo for 2 weeks of treatment. Subjective sleep latency was significantly decreased for **zaleplon** 10 mg during both week 1 and week 2 (both weeks p less than 0.001), but only for week 2 for **zaleplon** 5 mg (p less than 0.001). Subjective sleep latency was significantly decreased for **zolpidem** during both week 1 and week 2 (p less than 0.05, p less than 0.005, respectively). Subjective total sleep time was significantly increased for **zaleplon** 10 mg during week 1 only (p less than 0.05) and for **zolpidem** during week 1 and week 2 (p less than 0.001, p less than 0.01, respectively). The number of awakenings did not differ for either dose of **zaleplon**, but was reduced by **zolpidem** during both weeks.

4.6.D.2] Adverse Effects

a) **Zaleplon** had fewer detrimental effects on memory, learning, and psychomotor performance than did **zolpidem** or **triazolam** in healthy subjects. In a double-blind crossover study, 24 healthy subjects received placebo, **zaleplon** 10 milligrams (mg), **zaleplon** 20 mg, **zolpidem** 10 mg, **zolpidem** 20 mg, **triazolam** 0.25 mg, and placebo in 6 separate, single-dose, nighttime sessions. At 1.25 hours after dosing, statistically significant differences (p less than 0.05) in psychomotor performance were seen with **zaleplon** 20 mg, **zolpidem** 10 mg and 20 mg, and **triazolam** when compared with the results with placebo. Memory and cognitive tests showed no differences at 1.25 hours between **zaleplon** 10 mg and placebo. Memory was similarly impaired for **zolpidem** 10 mg and **triazolam** 0.25 mg, but that dose of **zolpidem** produced greater learning impairment than did **triazolam**. At 8.25 hours post-dosing, **zaleplon** 10 mg, **zaleplon** 20 mg, and **zolpidem** 10 mg showed differences from placebo only in the Delayed Word Recall Test and Digit-Symbol Substitution Test. Central nervous system (CNS) adverse

events occurred with 17% of sessions with placebo, 48% of sessions with **zaleplon** 10 mg, and 71% to 74% of sessions with each of the other treatments [89].

b) Zaleplon produced neither objective nor subjective residual effects when administered as little as 2 hours before awakening [90]. In contrast **zolpidem** residual effects were seen up to 5 hours after administration. Subjects were awakened and administered **zaleplon** 10 mg, **zolpidem** 10 mg, or placebo at 5, 4, 3, or 2 hours before awakening. In the morning a battery of subjective and objective assessments were administered. **Zaleplon** regardless of administration time did not significantly impair psychomotor performance, arousal and cognitive function, or memory function as compared to placebo. **Zolpidem** significantly impaired Digit-Symbol-Substitution Test when administered at 2, 3, and 5 hours before awakening (p less than 0.05, 0.001, 0.05, respectively). It also impaired memory as measured by number of words correct on immediate recall at 2, 3, 4, and 5 hours post-administration (p less than 0.001 for all). Delayed recall was also impaired as measured by number of words correct on delayed recall at 2, 3, 4, and 5 hours post-administration (p less than 0.001 for 2 to 4 hours, and p less than 0.01 for 5 hours).

4.6.E] Zopiclone

1) Efficacy

a) Zopiclone used for sleep significantly impaired next-morning driving performance, divided attention, and memory, whereas **zaleplon** did not. In placebo-controlled crossover studies, 30 healthy volunteers were given bedtime doses of placebo, **zaleplon** 10 milligrams (mg), and zopiclone 7.5 mg in a double-blind manner on 3 separate occasions, separated by at least 6 days. The next morning, psychomotor, memory, and driving performance were tested. In a separate crossover protocol, the same subjects were given an alcohol placebo or an alcohol dose sufficient to achieve a blood alcohol level of just under 0.5%, the legal limit for driving. Psychomotor tests were administered 50 minutes later. Driving tests were administered 40 to 100 minutes after a renewal dose of alcohol. Alcohol, in comparison to its placebo, significantly impaired driving performance ($p=0.001$). Impairment with zopiclone (in comparison to its placebo) was twice the impairment caused by alcohol, although subjects reported feeling alert after zopiclone and not after alcohol. Driving performance with **zaleplon** was not different than with placebo. Immediate recall, relative recall, and recognition scores on word tests tended to be lower with alcohol than with placebo but were not significantly different. However, with zopiclone, immediate and delayed recall were significantly lower than with either placebo or **zaleplon** (p less than 0.001). Psychomotor performance was significantly affected by alcohol ($p=0.002$), as was divided attention ($p=0.001$); with zopiclone, divided attention was affected ($p=0.001$) but psychomotor performance was not [84].

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