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Zaleplon (Sonata[®], Wyeth Ayerst):

A new, non-benzodiazepine sedative/hypnotic

Summary

Indication: Zaleplon is a non-benzodiazepine indicated for the short-term treatment of insomnia.

Monitoring Parameters: Patients should be monitored for changes in sleep latency (time from going to bed to initiation of sleep), number of awakenings during sleep and effect on the patients' daytime function (i.e., hangover effects). Patients should also be monitored for adverse reactions.

Dose: For nonelderly adult patients the recommended dose is 10 mg, not to exceed 20 mg. For low weight patients and patients with hepatic impairment the dose should be reduced to 5 mg. No dose adjustment is needed for patients with renal impairment.

Pediatrics: Safety and efficacy of zaleplon have not been established in patients younger than 18 years of age.

Geriatrics: For patients 65 years and older a dose of 5 mg is recommended, not to exceed 10 mg per dose.

Pregnancy Category: C

Breast Feeding: Zaleplon has been reported to be excreted in breast milk; therefore, its use is not recommended in nursing mothers.

Direct to Consumer Advertising: Zaleplon has been heavily promoted in both the print and electronic media.

Cost: Zaleplon is available in 5 mg and 10 mg capsules. The average wholesale price (AWP) for a 14-day supply of zaleplon 5 mg is \$24.12 and the AWP for a 14-day supply of 10 mg capsules is \$29.67.

Introduction

Insomnia is defined as difficulty falling asleep, or maintaining sleep, which interferes with the patient's daytime functioning.^{1,2} The literature reports insomnia is the most common sleep complaint with a prevalence of 26% to 50% in adult populations.^{1,3} Although insomnia is widely prevalent in the general population it is underreported to clinicians, with only an estimated 5% to 20% of patients seeking help from their clinicians.¹ The prevalence of insomnia is higher in women and the elderly. In the United States, 10% to 16% of adults complain of serious short-term to subacute insomnia (i.e., < 6 months in duration) and 9% to 10% complain of serious chronic insomnia (i.e., > 6 months in duration).²

Benzodiazepines have been the mainstay of therapy for insomnia. Benzodiazepines are available as short, intermediate or long-acting hypnotic agents and have been used to treat problems of initiating and maintaining sleep. When used for a short time period, overall, the benzodiazepines have been useful in treating insomnia. Although the benzodiazepines have been very useful, they pose potential problems such as altering sleep architecture, rebound insomnia when discontinued, possible hangover effects and abuse potential, as well as development of tolerance to the drug.^{4,5,6} Benzodiazepines act non-selectively on benzodiazepine₁ (omega₁) and benzodiazepine₂ (omega₂) receptors which may explain their interference with memory, cognition and psychomotor function.

Zolpidem, (Ambien[®], Searle and Co.) and zaleplon (Sonata[®], Wyeth-Ayerst Co.) are non-benzodiazepine sedative/hypnotics that act selectively on benzodiazepine (BZ₁) receptors.⁴ Their selectivity for BZ₁ should prevent patients from experiencing BZ₂ receptor effects involving memory, cognition and psychomotor function. In the literature, neither zolpidem nor zaleplon is reported to affect sleep architecture as do the benzodiazepines.⁷ The most common side effects of zolpidem include drowsiness, dizziness, headache and gastrointestinal distress.^{4,7} Zaleplon is a new non-benzodiazepine which is selective for the BZ₁ receptor and is indicated for the treatment of insomnia.

Pharmacology/Pharmacokinetics

Zaleplon is a pyrazolopyrimidine derivative hypnotic, whose chemical structure is unrelated to benzodiazepines or other known hypnotics.⁷⁻¹¹ Zaleplon interacts with the GABA-BZ receptor complex which is thought to be responsible for the sedative, anxiolytic, muscle relaxant and anticonvulsive properties of the benzodiazepines. Since zaleplon is selective for the BZ₁ receptor, it may cause minimal effects associated with the BZ₂ such as interference with memory, cognition and psychomotor function.⁷

Zaleplon is rapidly absorbed, reaching peak plasma con-

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centrations within 1 hour after oral administration.⁸⁻¹⁰ Zaleplon is well-absorbed, but its bioavailability is approximately 30% because it undergoes significant first-pass metabolism. High fat/heavy meals have been shown to prolong the absorption of zaleplon, delay the time to maximum drug concentration by 2 hours and decrease the maximum drug concentration by approximately 35%. The area under the curve and the elimination half-life were not shown to be significantly affected.

Zaleplon is lipophilic with an approximate 1.4 L/kg volume of distribution after intravenous administration. It is approximately 60% plasma protein-bound independent of its concentration over the range of 10 to 1000 ng/mL.⁸

After oral administration, zaleplon is extensively metabolized with less than 1% of the dose excreted unchanged in urine. All of zaleplon's metabolites are inactive. Zaleplon is primarily metabolized by aldehyde oxidase to form 5-oxo-zaleplon. To a lesser extent, it is metabolized by CYP3A4 to form desethylzaleplon which is converted, reportedly by aldehyde oxidase, to 5-oxo-desethylzaleplon. These oxidative metabolites are then converted to glucuronides and eliminated in urine.⁸

Zaleplon is rapidly eliminated with an average half-life of 1 hour after either oral or intravenous administration.^{7,8} The pharmacokinetics of zaleplon are not altered in the elderly and do not differ according to gender or renal function. See table 1 for a comparison of the kinetics of zaleplon, triazolam and zolpidem.

liking" significantly above placebo levels while all doses of zaleplon did so ($p \leq 0.05$). Triazolam and zaleplon produced many similar effects and at least one dose of each drug increased ratings of "blurred vision," "difficulty concentrating," "drug strength," "easy going," "good effects," "heavy limbs," "liking," "mental slowing," and "sedation" significantly above levels observed with placebo. The two highest doses of triazolam and all doses of zaleplon increased ratings of "drug strength," "good effects," "like drug effect," and "like to take drug again" significantly above placebo ($p \leq 0.05$). Zaleplon 25 mg produced significantly greater increases in observer ratings of "non-locomotor muscle relaxation" and "posture impaired" than triazolam 0.25 mg while 0.75 mg triazolam produced significantly greater increases in observer estimates of "minutes slept" than 75 mg zaleplon. In many cases, the two highest doses of each drug significantly impaired performance relative to placebo ($p \leq 0.05$). Corresponding doses of triazolam and zaleplon appeared to produce comparable effects on performance measures. The study concluded that triazolam and zaleplon produced comparable dose-related effects in various subject-rated, observer-rated, performance and abuse potential measures; therefore, the behavioral pharmacologic profile of zaleplon is similar to that of triazolam.

A double-masked, 7-way crossover study was conducted by Vermeeren et al to determine if middle of the night administration of zaleplon or zopiclone (not available in the US)

affects memory or driving performance the following morning.¹³ Twenty-eight healthy volunteers participated and each took capsules twice on each treatment night — once before initial sleep and again after being briefly awakened 5 hours later. The treatments were: placebo at both times, zaleplon 10 or 20 mg or

zopiclone 7.5 mg followed by placebo, or the same in reverse order. The participants arose 3 hours after the second dose. One hour later, sleep quality and mood were assessed by questionnaires. A standardized actual driving test was undertaken between 5 and 6 hours after the second dose. Initiating sleep in the evening was judged easier after zaleplon and zopiclone than after placebo ($p \leq 0.0001$). Evening zaleplon and zopiclone resulted in significantly better sleep quality during the first part of the night than placebo ($p \leq 0.0029$). After awakening for the second treatment dose, participants resumed sleeping more easily when the prior treatments were early ($p = 0.0001$) or late ($p = 0.0030$) zopiclone doses, or zaleplon 10 mg ($p = 0.0148$)

Table 1. Pharmacokinetics of Selected Sedative/Hypnotic Agents^{8,17}

Parameter	Triazolam	Zolpidem	Zaleplon
Time-to-peak concentration	2 h	1.6 h	0.5-1.5 h
Onset of action	15-30 min	30 min	≤ 60 min
Elimination half-life	1.5-5.5 h	2.5 h	1 h
Half-life in elderly	*	2.9 h*	
Half-life in hepatic dysfunction		9.9 h*	*
Half-life in renal dysfunction		2.5 h	1 h

*Dose adjustments recommended

Clinical trials

In a double-masked, crossover study, Rush et al compared the abuse potential of zaleplon and triazolam over 18 days in fourteen healthy volunteers with histories of drug abuse who were administered oral zaleplon (25, 50 and 75 mg), triazolam (0.25, 0.5 and 0.75 mg) and placebo.¹² The participants followed a daily routine throughout the study. Data (i.e., questionnaires, etc.) were collected on a range of subject-rated, observer-rated and behavioral performance measures before drug administration and repeatedly for up to 24 hours after drug administration. The results of the study showed the two highest doses of triazolam tested increased ratings of "drug

or 20 mg ($p = 0.0021$). Participants also indicated that they slept better during the second segment following either early or late zopiclone doses and immediately following both zaleplon doses ($p \leq 0.0001$). Forty-five minutes after arising, participants rated their alertness lower ($p = 0.0001$) with zopiclone late doses than with placebo. The effects of early doses of zaleplon 10 and 20 mg did not differ significantly from placebo. The early zopiclone dose significantly impaired delayed recall ($p = 0.0109$). The driving instructors judged the participants' driving quality to be similarly good after placebo and all zaleplon treatments but significantly worse with late doses of zopiclone ($p = 0.0001$). The difference in early zopiclone doses was not significant ($p = 0.0625$). The instructors rated subjects as appearing significantly more sedated after late zopiclone doses than with placebo. The instructors did not distinguish any significant differences between the participants' appearance after placebo and the zaleplon treatments. The study concluded that zaleplon 10 mg and possibly zaleplon 20 mg can be taken up to 5 hours before driving with little risk of serious impairment.

A double-masked, placebo-controlled study with triazolam as an active comparator, to determine the efficacy and tolerability of zaleplon 5 and 10 mg over 14 days, was conducted by Walsh et al.¹⁴ The study consisted of 132 patients, aged 18 to 60 years, with primary insomnia. Outcomes were measured using polysomnographic data, subjective reports, performance measures, and clinical assessments during three baseline, 14 drug and two discontinuation nights. In both, the zaleplon 5 mg ($p = 0.019$) and zaleplon 10 mg ($p = 0.039$) groups latency to persistent sleep (LPS) was significantly shorter than in the placebo group on nights 4 and 5. There was no significant difference for LPS between either zaleplon 5 mg ($p = 0.201$) or zaleplon 10 mg ($p = 0.127$) and placebo on nights 16 and 17. Total sleep time for the triazolam group was greater on nights 4 and 5 than placebo, zaleplon 10 mg ($p \leq 0.001$) and zaleplon 5 mg ($p = 0.014$). Total sleep time for triazolam was not greater on nights 16 and 17 than placebo ($p = 0.35$), zaleplon 5 mg ($p = 0.63$) nor zaleplon 10 mg ($p = 0.22$). On nights 4 and 5, subjective sleep latency (SSL) was significantly lower for zaleplon 10 mg ($p = 0.003$) compared with placebo. On home nights 6 to 14, SSL was shorter for zaleplon 10 mg than for placebo ($p = 0.03$), but zaleplon 5 mg did not differ significantly from placebo ($p = 0.67$). The SSL for triazolam was shorter than placebo on nights 4 and 5 ($p = 0.015$). Subjective total sleep time (STST) and subjective number of awakenings showed no significant differences between placebo and the two zaleplon groups at any time-point of the study. The subjective number of awakenings was lower in the triazolam group than in the placebo group on nights 6 to 14 ($p = 0.046$). There were no differences in SSL, STST, or subjective number of awakenings between placebo and zaleplon on either discon-

tinuation night (18 and 19). On night 18, but not night 19, the triazolam group reported a significantly longer SSL ($p = 0.036$) and shorter STST ($p = 0.022$) than placebo. The study concluded that zaleplon appeared to have hypnotic properties consistent with its pharmacokinetic profile and a low likelihood of undesired effects.

Elie et al conducted a multicenter study comparing the efficacy and safety of three doses of zaleplon with those of placebo in 615 outpatients with insomnia.¹⁵ Following a seven-night placebo (baseline) period each participant was randomly assigned to receive one of five treatments (zaleplon 5, 10 or 20 mg; zolpidem 10mg or placebo) for 28 nights followed by placebo for three nights. Each morning, the participants completed sleep questionnaires assessing sleep latency, sleep maintenance and sleep quality. Median sleep latency was significantly reduced during week 1 with zaleplon 5 mg ($p \leq 0.02$), zaleplon 10 mg ($p \leq 0.001$), zaleplon 20 mg ($p \leq 0.02$), and zolpidem 10 mg ($p \leq 0.05$) compared with placebo. Compared with placebo, zaleplon 20 mg significantly ($p \leq 0.05$) increased sleep duration during all but week 3 of the double-blind treatment period. Zolpidem 10 mg significantly ($p \leq 0.001$) increased the median sleep duration during all weeks of double-blind treatment. No significant differences in sleep duration were found between zaleplon 5 mg and placebo. The number of awakenings on nights 2 and 3 of the placebo run-out period were significantly greater with zaleplon 5 mg and zolpidem 10 mg ($p \leq 0.03$) than with placebo. On night 2 of the placebo run-out period, there were significantly ($p < 0.05$) more patients showing rebound insomnia for the number of awakenings with zaleplon 10 and 20 mg than with placebo. On night 3 of the placebo run-out period there were significantly ($p \leq 0.05$) fewer patients showing rebound insomnia for the number of awakenings with zaleplon 20 mg than with placebo. The study concluded zaleplon is effective in the treatment of insomnia.

Danjou et al conducted a placebo-controlled, double-masked, incomplete-block, crossover study in 36 healthy participants over 6 weeks to compare the duration of the residual hypnotic and sedative effects of zaleplon with those of zolpidem and placebo following nocturnal administration at various times before morning awakening.¹⁶ Participants were given zaleplon 10 mg, zolpidem 10 mg, or placebo when awakened 5, 4, 3, or 2 hours before morning awakening, which occurred 8 hours after bedtime. Subjective and objective assessments of hypnotic effects were conducted when the participants awoke in the morning. The results of the study showed after zolpidem was given 2 hours before awakening, subjects felt more "tired," "drowsy," "dizzy," "clumsy" and less "alert" and "energetic" ($p < 0.01$). These feelings had disappeared at the 3-hour dose interval but were present again at 4 hours ($p < 0.05$). Zaleplon did not significantly alter any feeling even when it was administered 2 hours before awakening. Participants felt less "tired"

and more 'energetic' ($p < 0.05$) when they were given zaleplon 5 hours before awakening. The study concluded that zaleplon at the dose of 10 mg is free of residual hypnotic or sedative effects when administered nocturnally 2 hours before waking in normal subjects, whereas residual effects of zolpidem were still apparent on objective assessments up to 5 hours after nocturnal administration.

Adverse effects

The most common adverse effects reported with zaleplon have included headache (28-38%), nausea (7-8%), myalgia (5-7%), and abdominal pain (5-6%).⁸ Other adverse effects have included amnesia, dizziness, blurred vision, fatigue, loss of concentration, impaired cognition, impaired motor skills, drowsiness, hallucinations and impaired balance (see Table 2).

Table 2. Incidence (%) of Adverse Effects in Long-Term (28 nights) Studies with Zaleplon.⁸

Adverse Effects	Placebo (n=277)	Zaleplon 5-10 mg (n=513)	Zaleplon 20 mg (n=273)
Headache	31%	28%	38%
Nausea	7	7	8
Myalgia	4	7	5
Dizziness	7	7	8
Abdominal pain	4	5	6
Asthenia	5	5	8
Somnolence	3	5	5
Dyspepsia	5	4	7
Eye pain	3	4	4
Paresthesia	1	3	3
Fever	1	2	2
Amnesia	1	2	4
Anxiety	2	<1	3
Hypesthesia	0	<1	2
Dysmenorrhea	2	2	4
Tremor	1	2	2

Data from placebo-controlled clinical trial for which the incidence of the adverse effects was >1% in patients receiving 20mg zaleplon

Drug interactions

Selective inhibitors of CYP3A may increase serum concentrations of zaleplon by approximately 30% which may prolong the duration of zaleplon's effects or increase the risk of dose-related side effects.^{7,8} Since cimetidine inhibits both the aldehyde oxidase and CYP3A4 pathways of zaleplon metabolism, concomitant administration of these agents may result in an 85% increase in zaleplon concentration and area under the curve (AUC).^{7,8} Patients who are taking cimetidine

should receive an initial zaleplon dose of 5 mg.^{8,11} Rifampin has been shown to increase zaleplon's clearance five-fold resulting in an 80% decrease in peak concentration and AUC, which could lead to decreased effectiveness of zaleplon.⁸

Zaleplon has been shown to have minimal effects on the kinetics of warfarin, imipramine, ethanol, ibuprofen, diphenhydramine, thioridazine and digoxin.⁸ The observed additive pharmacodynamic effects of zaleplon and ethanol, imipramine, or thioridazine reversed within 1 to 4 hours after administration.

Cost, dose and how supplied

The usual dose of zaleplon for the treatment of short-term insomnia in non-elderly patients is 10 mg at bedtime. A dose of 5 mg should be used in patients who are low weight, hepatically impaired, concomitantly taking cimetidine or are elderly. The elderly patient should not take more than 10 mg per dose. Doses up to 20 mg may be considered for patients not sufficiently responding to lower doses. As with other hypnotics, zaleplon's use should be limited to a 7 to 10 day duration; prescriptions should not be written for more than a 28 day supply. After 10 days the patient's insomnia should be re-evaluated.

Zaleplon is available in 5 mg and 10 mg capsules in bottles of 100. The average wholesale price (AWP) for 5 mg capsules is \$1.72 per capsule. The AWP for 10 mg capsules is \$2.12 per capsule. The AWP of a 14-day supply of 5 mg and 10 mg capsules taken one capsule at bedtime are \$24.12 and \$29.67, respectively. The AWP of a 14-day supply of zolpidem 5 mg and 10 mg taken one tablet at bedtime is \$24.34 and \$29.94, respectively (see table 3).

Table 3. Cost Comparison of Selected Sedatives/Hypnotics

	Temazepam	Zolpidem	Zaleplon
Dose	15 – 30 mg HS	5 – 10 mg HS	5 – 10 mg
AWP Cost 14-day Supply	\$12.27 -\$13.72	\$24.34 -\$29.94	\$24.12 -\$29.67

Conclusion

Clinical studies have shown that zaleplon is as effective as other sedative/hypnotics and superior to placebo in the treatment of insomnia. At doses of 5 to 20 mg, zaleplon reduces the time to sleep onset with minimal effects on total sleep time or sleep architecture. Zaleplon produced similar reductions in sleep latency as triazolam 0.25 mg and zolpidem 10 mg.

Triazolam and zolpidem, but not zaleplon, significantly increased sleep duration. Because of its short duration of action, zaleplon is not appropriate for patients experiencing difficulty with sleep maintenance. Instead the primary role for zaleplon is in patients with sleep latency problems. Since, at recommended doses, the cognitive effects resolve within 4 hours, zaleplon may be particularly useful in patients who have woken in the middle of the night and can no longer fall back

asleep, provided at least 4 hours remain before the patient must be alert and active. ■

References

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UW HOSPITAL AND CLINICS HYPNOTIC USE RECOMMENDATIONS

These recommendations are intended to assist prescribers in selecting an appropriate hypnotic in a variety of clinical situations.

It is important to note that **diphenhydramine does not appear on the list of recommended hypnotic agents**. It is **NOT** an agent of choice due to its unreliability, hangover effect, anticholinergic side effects and the high incidence of hallucinations associated with its use in the elderly.

The use of hypnotic agents has been implicated as a risk factor for patient falls, particularly in elderly patients with multiple medical problems. While the literature is not entirely unequivocal on this point, it is prudent to assess each patient's potential for falling before considering the use of hypnotics.

CLASSIFICATION	SYMPTOMS	CHOICES*	COMMENTS
Transient insomnia (less than 4 days)	Sleep onset problems	1. temazepam 2. zaleplon 3. zolpidem 4. alprazolam 5. trazodone**	Use hypnotics short term and/or intermittently
	Sleep maintenance problems	1. temazepam 2. trazodone	
	Frequent nocturnal awakenings where daytime sedation acceptable	1. temazepam 2. clonazepam	
	Shift work	1. zolpidem 2. zaleplon 3. temazepam	
	Jet lag	1. zolpidem 2. temazepam	Recommend daytime travel with arrival coinciding with bedtime. If overnight travel unavoidable, could use an hypnotic with a duration matching the travel time.
Short term insomnia (symptoms lasting 5 days to 3 weeks)	Sleep onset problems	1. temazepam 2. zaleplon 3. zolpidem	Use hypnotics intermittently and not for periods > 2 weeks. Start with lowest dose, increase if needed.
	Sleep maintenance problems	1. temazepam	
Chronic insomnia (symptoms lasting longer than 3 weeks)		1. temazepam 2. zolpidem 3. clonazepam (adjunctive hypnotic) 4. trazodone	If adjunctive hypnotics are needed, consider a slowly eliminated agent intermittently for a limited period.
	Documented/suspected depression	1. trazodone (as adjunct with other antidepressants) 2. nortriptyline	In the presence of documented or suspected depression, a sedating antidepressant could be used for a month then reevaluate.

* Drugs are listed in order of choice #1 indicates first choice, #2 second choice, #3 third choice, #4 fourth choice.

** Use for this indication is not FDA approved.

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SUPPLEMENTAL INFORMATION SUPPORTING HYPNOTIC RECOMMENDATIONS

DRUG	ADVANTAGE	DISADVANTAGE	CLINICAL PEARL
Alprazolam*	short duration of action quick onset of action	high abuse potential high toxicity more rebound insomnia	may use in place of triazolam
Chloral Hydrate	inexpensive does not alter seizure threshold	efficacy less predictable than with benzodiazepines decreased effect if used chronically greater abuse potential greater toxicity than benzodiazepines	sedative of choice for sleep-deprived EEG
Clonazepam*	long duration of action	long duration of action expensive	adjunctive therapy for a number of psychological disorders
Diazepam*	short duration of action quick onset of action inexpensive	accumulation of active metabolite with chronic use	short duration of action when used intermittently
Diphenhydramine	inexpensive antihistamine effects	lack of predictable efficacy anticholinergic effect increased delirium increased hangover	increased risk of delirium especially in hospitalized elderly
Nortriptyline	potential for antidepressant effect	high toxicity potentially lethal in overdose	dose for sleep may not be effective for antidepressant
Temazepam*	quick onset of action intermediate duration of action inexpensive less rebound insomnia limited retrograde amnesia	possible hangover effect	reformulation of product provides faster onset of action
Trazodone	potential for antidepressant effect inexpensive	orthostatic hypotension	dose for sleep may not be effective for antidepressant
Zolpidem	low toxicity preserves stage III & IV sleep less disruption of REM sleep short duration of action quick onset of action	expensive limited clinical experience	reversible with flumazenil
Zaleplon	short duration of action quick onset of action	not for sleep maintenance	can be given if only 4 hours of sleep remain

* Sedative versus hypnotic potential in benzodiazepines is dose-related. Significant differences are based on kinetic profile.