

AMBIEN CR Prescribing Information

WARNING: COMPLEX SLEEP BEHAVIORS

Complex sleep behaviors including sleep-walking, sleep-driving, and engaging in other activities while not fully awake may occur following use of AMBIEN CR. Some of these events may result in serious injuries, including death. Discontinue AMBIEN CR immediately if a patient experiences a complex sleep behavior [see Contraindications (4) and Warnings and Precautions (8.1)].

1 NAME OF THE MEDICINAL PRODUCT

AMBIEN CR 6.25 mg

AMBIEN CR 12.5 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each extended-release tablet of Ambien CR 6.25 mg contains zolpidem tartrate 6.25 mg

Each extended-release tablet of Ambien CR 12.5 mg contains zolpidem tartrate 12.5 mg

Excipients with known effect:

Each Ambien CR 6.25 mg extended-release tablet contains 138.913 mg mg lactose monohydrate.

Each Ambien CR 12.5 mg extended-release tablet contains 138.913 mg mg lactose monohydrate.

For the full list of excipients, *see section 14*.

3 PHARMACEUTICAL FORM

Extended-release tablets.

Ambien CR 6.25 mg extended-release tablets are: pink, round, bi-convex, engraved ZMR on one face.

Ambien CR 12.5 mg extended-release tablets are: blue, round, bi-convex, engraved ZMR on one face

4 THERAPEUTIC INDICATIONS

Ambien CR (zolpidem tartrate extended-release tablets) is indicated for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance (as measured by wake time after sleep onset).

The clinical trials performed in support of efficacy were up to 3 weeks (using polysomnography measurement up to 2 weeks in both adult and elderly patients) and 24 weeks (using patient-reported assessment in adult patients only) in duration [see *Clinical Studies (17)*].

5 DOSAGE AND ADMINISTRATION

5.1 Dosage in Adults

Use the lowest effective dose for the patient. The recommended initial dose is 6.25 mg for women and either 6.25 or 12.5 mg for men, taken only once per night immediately before bedtime with at least 7-8 hours remaining before the planned time of awakening. If the 6.25 mg dose is not effective, the dose can be increased to 12.5 mg. In some patients, the higher morning blood levels following use of the 12.5 mg dose increase the risk of next day impairment of driving and other activities that require full alertness [*see Warnings and Precautions (8.1)*]. The total dose of Ambien CR should not exceed 12.5 mg once daily immediately before bedtime.

Ambien CR should be taken as a single dose and should not be readministered during the same night.

The recommended initial doses for women and men are different because zolpidem clearance is lower in women.

5.2 Special Populations

Elderly or debilitated patients may be especially sensitive to the effects of zolpidem tartrate. Patients with hepatic insufficiency do not clear the drug as rapidly as normal subjects. The recommended dose of Ambien CR in both of these patient populations is 6.25mg once daily immediately before bedtime [*see Warnings and Precautions (8.8), Use in Specific Populations (11.4)*].

Ambien CR should not be used in patient with severe hepatic insufficiency [*see Contraindications (7)*]

5.3 Use with CNS depressants

Dosage adjustment may be necessary when Ambien CR is combined with other CNS depressant drugs because of the potentially additive effects [*see Warnings and Precautions (8.2, 8.7)*].

5.4 Administration

Ambien CR extended-release tablets should be swallowed whole, and not be divided, crushed, or chewed. The effect of Ambien CR may be slowed by ingestion with or immediately after a meal.

6 DOSAGE FORMS AND STRENGTHS

Ambien CR is available as extended-release tablets containing 6.25 mg or 12.5 mg of zolpidem tartrate for oral administration. Tablets are not scored.

7 CONTRAINDICATIONS

Ambien CR is contraindicated in patients -:

- who have experienced complex sleep behaviors after taking AMBIEN CR [*see*

Warnings and Precautions (8.1)].

- with known hypersensitivity to zolpidem or to any of the excipients listed in section 14. Observed reactions include anaphylaxis and angioedema [*see Warnings and Precautions (8.4)].*
- severe hepatic insufficiency [*see Dosage and Administration (5.2); Warnings and Precautions (8.8)].*

8 WARNINGS AND PRECAUTIONS

Like all hypnotics, zolpidem is not recommended for long term use. Treatment with Ambien CR should be as short as possible and should not exceed four weeks (including the taper phase).

8.1 Complex Sleep Behaviors

Complex sleep behaviors, including sleep-walking, sleep-driving, and engaging in other activities while not fully awake, may occur following the first or any subsequent use of AMBIEN CR. Patients can be seriously injured or injure others during complex sleep behaviors. Such injuries may result in a fatal outcome. Other complex sleep behaviors (e.g., preparing and eating food, making phone calls, or having sex) have also been reported. Patients usually do not remember these events. Postmarketing reports have shown that complex sleep behaviors may occur with AMBIEN CR alone at recommended doses, with or without the concomitant use of alcohol or other central nervous system (CNS) depressants [*see Drug Interactions (10.1)].* Discontinue AMBIEN CR immediately if a patient experiences a complex sleep behavior [*see Contraindications (7)]*

8.2 CNS Depressant Effects and Next-Day Impairment

Ambien CR is a CNS depressant and can impair daytime function in some patients even when used as prescribed. Prescribers should monitor for excess depressant effects, but impairment can occur in the absence of subjective symptoms, and may not be reliably detected by ordinary clinical exam (i.e. less than formal psychomotor testing). While pharmacodynamic tolerance or adaptation to some adverse depressant effects of Ambien CR may develop, patients using Ambien CR should be cautioned against driving or engaging in other hazardous activities or activities requiring complete mental alertness the day after use.

Additive effects occur with concomitant use of other CNS depressants (e.g., benzodiazepines, opioids, tricyclic antidepressants, alcohol), including daytime use [*see Drug Interactions (10.1)].* Downward dose adjustment of Ambien CR and concomitant CNS depressants should be considered [*see Dosage and Administration (5.3)].*

The use of Ambien CR with other sedative-hypnotics (including other zolpidem products) at bedtime or the middle of the night is not recommended.

The risk of next-day psychomotor impairment is increased if Ambien CR is taken with less than a full night of sleep remaining (7- to 8 hours); if higher than the recommended dose is taken; if coadministered with other CNS depressants or alcohol; or coadministered with other drugs that increase the blood levels of zolpidem. Patients should be warned against driving and other activities requiring complete mental alertness if Ambien CR is taken in these circumstances [*see Dosage and Administration (5) and Clinical Studies (17.2)].*

Vehicle drivers and machine operators should be warned that, as with other hypnotics, there may be a possible risk of adverse reactions including drowsiness, prolonged reaction time, dizziness,

sleepiness, blurred/double vision, reduced alertness, and impaired driving the morning after therapy. In order to minimize this risk a full night of sleep (7-8 hours) is recommended.

Because AMBIEN CR can cause drowsiness and a decreased level of consciousness, patients, particularly the elderly, are at higher risk of falls.

8.3 Need to Evaluate for Comorbid Diagnoses

Because sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient. The failure of insomnia to remit after 7 to 10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated. Worsening of insomnia or the emergence of new thinking or behavior abnormalities may be the consequence of an unrecognized psychiatric or physical disorder. Such findings have emerged during the course of treatment with sedative/hypnotic drugs, including zolpidem.

8.4 Severe Anaphylactic and Anaphylactoid Reactions

Cases of angioedema involving the tongue, glottis or larynx have been reported in patients after taking the first or subsequent doses of sedative-hypnotics, including zolpidem. Some patients have had additional symptoms such as dyspnea, throat closing or nausea and vomiting that suggest anaphylaxis. Some patients have required medical therapy in the emergency department. If angioedema involves the throat, glottis or larynx, airway obstruction may occur and be fatal. Patients who develop angioedema after treatment with zolpidem should not be rechallenged with the drug.

8.5 Abnormal Thinking and Behavioral Changes

Abnormal thinking and behavior changes have been reported in patients treated with sedatives/hypnotics, including Ambien CR. Some of these changes included decreased inhibition (e.g., aggressiveness and extroversion that seemed out of character), bizarre behavior, agitation and depersonalization. Visual and auditory hallucinations have been reported.

In controlled trials, <1% of adults with insomnia reported hallucinations. In a clinical trial, 7% of pediatric patients treated with zolpidem 0.25 mg/kg taken at bedtime reported hallucinations versus 0% treated with placebo [*see Use in Specific Populations (11.3)*]. There have been post-marketing reports of delirium with zolpidem use [*see Adverse Reactions (9.2)*].

It can rarely be determined with certainty whether a particular instance of the abnormal behaviors listed above is drug induced, spontaneous in origin, or a result of an underlying psychiatric or physical disorder. Nonetheless, the emergence of any new behavioral sign or symptom of concern requires careful and immediate evaluation.

8.6 Use in Patients with Depression

In primarily depressed patients treated with sedative-hypnotics, worsening of depression, and suicidal thoughts and actions (including completed suicides), have been reported. Suicidal tendencies may be present in such patients and protective measures may be required. Intentional overdosage is more common in this group of patients; therefore, the lowest number of tablets that is feasible should be prescribed for the patient at any one time.

8.7 Respiratory Depression

Although studies with 10 mg zolpidem tartrate did not reveal respiratory depressant effects at hypnotic doses in healthy subjects or in patients with mild to moderate chronic obstructive pulmonary disease (COPD), a reduction in the Total Arousal Index, together with a reduction in lowest oxygen saturation and increase in the times of oxygen desaturation below 80% and 90%, was observed in patients with mild to moderate sleep apnea when treated with zolpidem compared to placebo. Since sedative-hypnotics have the capacity to depress respiratory drive, precautions should be taken if Ambien CR is prescribed to patients with compromised respiratory function or concomitant use with opioids or other CNS depressants. Post-marketing reports of respiratory insufficiency in patients receiving 10 mg of zolpidem tartrate, most of whom had pre-existing respiratory impairment, have been reported. The risk of respiratory depression should be considered prior to prescribing Ambien CR in patients with respiratory impairment including sleep apnea and myasthenia gravis or with concomitant opioid use [see *Dosage and Administration (5.3)*, *Drug Interactions (10.1)*].

8.8 Precipitation of Hepatic Encephalopathy

Drugs affecting GABA receptors, such as zolpidem tartrate, have been associated with precipitation of hepatic encephalopathy in patients with hepatic insufficiency. In addition, patients with hepatic insufficiency do not clear the drug as rapidly as normal subjects. Zolpidem must not be used in patients with severe hepatic impairment as it may contribute to encephalopathy [see *Dosage and Administration (5.2)*, *Use in Specific Populations (11.6)*, *Clinical Pharmacology (15.3)*].

8.9 Withdrawal Effects

There have been reports of withdrawal signs and symptoms following the rapid dose decrease or abrupt discontinuation of zolpidem. Monitor patients for tolerance, abuse, and dependence [see *Drug Abuse and Dependence (12.2, 12.3)*].

8.9 Severe Injuries

Zolpidem can cause drowsiness and a decreased level of consciousness, which may lead to falls and consequently to severe injuries. Severe injuries such as hip fractures and intracranial hemorrhage have been reported.

9 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Complex Sleep Behaviors [see *Warnings and Precautions (8.1)*]
- CNS-Depressant Effects and Next-Day Impairment [see *Warnings and Precautions (8.2)*]
- Severe Anaphylactic and Anaphylactoid Reactions [see *Warnings and Precautions (8.4)*]
- Abnormal Thinking, and Behavior Changes [see *Warnings and Precautions (8.5)*]
- Withdrawal Effects [see *Warnings and Precautions (8.9)*]

9.1 Clinical Trials Experience

Associated with Discontinuation of Treatment

In 3-week clinical trials in adults and elderly patients (> 65 years), 3.5% (7/201) patients receiving Ambien CR 6.25 or 12.5 mg discontinued treatment due to an adverse reaction as

compared to 0.9% (2/216) of patients on placebo. The reaction most commonly associated with discontinuation in patients treated with Ambien CR was somnolence (1%).

In a 6-month study in adult patients (18-64 years of age), 8.5% (57/669) of patients receiving Ambien CR 12.5 mg as compared to 4.6% on placebo (16/349) discontinued treatment due to an adverse reaction. Reactions most commonly associated with discontinuation of Ambien CR included anxiety (anxiety, restlessness or agitation) reported in 1.5% (10/669) of patients as compared to 0.3% (1/349) of patients on placebo, and depression (depression, major depression or depressed mood) reported in 1.5% (10/669) of patients as compared to 0.3% (1/349) of patients on placebo.

Data from a clinical study in which selective serotonin reuptake inhibitor- (SSRI-) treated patients were given zolpidem revealed that four of the seven discontinuations during double-blind treatment with zolpidem (n=95) were associated with impaired concentration, continuing or aggravated depression, and manic reaction; one patient treated with placebo (n=97) was discontinued after an attempted suicide.

Most Commonly Observed Adverse Reactions in Controlled Trials

During treatment with Ambien CR in adults and elderly at daily doses of 12.5 mg and 6.25 mg, respectively, each for three weeks, the most commonly observed adverse reactions associated with the use of Ambien CR were headache, next-day somnolence, and dizziness.

In the 6-month trial evaluating Ambien CR 12.5 mg, the adverse reaction profile was consistent with that reported in short-term trials, except for a higher incidence of anxiety (6.3% for Ambien CR versus 2.6% for placebo).

Adverse Reactions Observed at an Incidence of $\geq 1\%$ in Controlled Trials

The following tables enumerate treatment-emergent adverse reactions frequencies that were observed at an incidence equal to 1% or greater among patients with insomnia who received Ambien CR in placebo-controlled trials. Events reported by investigators were classified utilizing the MedDRA dictionary for the purpose of establishing event frequencies. The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice, in which patient characteristics and other factors differ from those that prevailed in these clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigators involving related drug products and uses, since each group of drug trials is conducted under a different set of conditions. However, the cited figures provide the physician with a basis for estimating the relative contribution of drug and nondrug factors to the incidence of side effects in the population studied.

The following tables were derived from results of two placebo-controlled efficacy trials involving Ambien CR. These trials involved patients with primary insomnia who were treated for 3 weeks with Ambien CR at doses of 12.5 mg (Table 1) or 6.25 mg (Table 2), respectively. The tables include only adverse reactions occurring at an incidence of at least 1% for Ambien CR patients and with an incidence greater than that seen in the placebo patients.

Table 1: Incidences of Treatment-Emergent Adverse Reactions in a 3-Week Placebo-Controlled Clinical Trial in Adults (percentage of patients reporting)

Body System Adverse Reaction *	Ambien CR 12.5 mg (N = 102)	Placebo (N = 110)
Infections and infestations		
Influenza	3	0
Gastroenteritis	1	0
Labyrinthitis	1	0
Metabolism and nutrition disorders		
Appetite disorder	1	0
Psychiatric disorders		
Hallucinations **	4	0
Disorientation	3	2
Anxiety	2	0
Depression	2	0
Psychomotor retardation	2	0
Binge eating	1	0
Depersonalization	1	0
Disinhibition	1	0
Euphoric mood	1	0
Mood swings	1	0
Stress symptoms	1	0
Nervous system disorders		
Headache	19	16
Somnolence	15	2
Dizziness	12	5
Memory disorders ***	3	0
Balance disorder	2	0
Disturbance in attention	2	0
Hypoesthesia	2	1
Ataxia	1	0
Paresthesia	1	0
Eye disorders		
Visual disturbance	3	0
Eye redness	2	0
Vision blurred	2	1
Altered visual depth perception	1	0
Asthenopia	1	0
Ear and labyrinth disorders		
Vertigo	2	0
Tinnitus	1	0
Respiratory, thoracic and mediastinal disorders		
Throat irritation	1	0
Gastrointestinal disorders		
Nausea	7	4
Constipation	2	0
Abdominal discomfort	1	0
Abdominal tenderness	1	0
Frequent bowel movements	1	0
Gastroesophageal reflux Disease	1	0
Vomiting	1	0
Skin and subcutaneous tissue disorders		
Rash	1	0
Skin wrinkling	1	0

Urticaria	1	0
Musculoskeletal and connective tissue disorders		
Back pain	4	3
Myalgia	4	0
Neck pain	1	0
Reproductive system and breast disorders		
Menorrhagia	1	0
General disorders and administration site conditions		
Fatigue	3	2
Asthenia	1	0
Chest discomfort	1	0
Investigations		
Blood pressure increased	1	0
Body temperature increased	1	0
Injury, poisoning and procedural complications		
Contusion	1	0
Social circumstances		
Exposure to poisonous plant	1	0

*Reactions reported by at least 1% of patients treated with Ambien CR and at greater frequency than in the placebo group.

**Hallucinations included hallucinations NOS as well as visual and hypnagogic hallucinations.

***Memory disorders include: memory impairment, amnesia, anterograde amnesia.

Table 2: Incidences of Treatment-Emergent Adverse Reactions in a 3-Week Placebo-Controlled Clinical Trial in Elderly (percentage of patients reporting)

Body System Adverse Reaction *	Ambien CR 6.25 mg (N=99)	Placebo (N=106)
Infections and infestations		
Nasopharyngitis	6	4
Lower respiratory tract infection	1	0
Otitis externa	1	0
Upper respiratory tract infection	1	0
Psychiatric disorders		
Anxiety	3	2
Psychomotor retardation	2	0
Apathy	1	0
Depressed mood	1	0
Nervous system disorders		
Headache	14	11
Dizziness	8	3
Somnolence	6	5
Burning sensation	1	0
Dizziness postural	1	0
Memory disorders **	1	0
Muscle contractions involuntary	1	0
Paresthesia	1	0
Tremor	1	0
Cardiac disorders		
Palpitations	2	0
Respiratory, thoracic and mediastinal disorders		
Dry throat	1	0
Gastrointestinal disorders		
Flatulence	1	0
Vomiting	1	0

Skin and subcutaneous tissue disorders		
Rash	1	0
Urticaria	1	0
Musculoskeletal and connective tissue disorders		
Arthralgia	2	0
Muscle cramp	2	1
Neck pain	2	0
Renal and urinary disorders		
Dysuria	1	0
Reproductive system and breast disorders		
Vulvovaginal dryness	1	0
General disorders and administration site conditions		
Influenza-like illness	1	0
Pyrexia	1	0
Injury, poisoning and procedural complications		
Neck injury	1	0

*Reactions reported by at least 1% of patients treated with Ambien CR and at greater frequency than in the placebo group.

**Memory disorders include: memory impairment, amnesia, anterograde amnesia.

Dose Relationship for Adverse Reactions

There is evidence from dose comparison trials suggesting a dose relationship for many of the adverse reactions associated with zolpidem use, particularly for certain CNS and gastrointestinal adverse events.

Other Adverse Reactions Observed during the Premarketing Evaluation of Ambien CR

Other treatment-emergent adverse reactions associated with participation in Ambien CR studies (those reported at frequencies of <1%) were not different in nature or frequency to those seen in studies with immediate-release zolpidem tartrate, which are listed below.

Adverse Events Observed during the Premarketing Evaluation of Immediate-Release Zolpidem Tartrate

Immediate-release zolpidem tartrate was administered to 3,660 subjects in clinical trials throughout the U.S., Canada, and Europe. Treatment-emergent adverse events associated with clinical trial participation were recorded by clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals experiencing treatment-emergent adverse events, similar types of untoward events were grouped into a smaller number of standardized event categories and classified utilizing a modified World Health Organization (WHO) dictionary of preferred terms.

The frequencies presented, therefore, represent the proportions of the 3,660 individuals exposed to zolpidem, at all doses, who experienced an event of the type cited on at least one occasion while receiving zolpidem. All reported treatment-emergent adverse events are included, except those already listed in the table above of adverse events in placebo-controlled studies, those coding terms that are so general as to be uninformative, and those events where a drug cause was remote. It is important to emphasize that, although the events reported did occur during treatment with Ambien CR, they were not necessarily caused by it.

Adverse events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring in greater than 1/100 subjects; infrequent adverse events are those

occurring in 1/100 to 1/1,000 patients; rare events are those occurring in less than 1/1,000 patients.

Autonomic nervous system: Frequent: dry mouth. Infrequent: increased sweating, pallor, postural hypotension, syncope. Rare: abnormal accommodation, altered saliva, flushing, glaucoma, hypotension, impotence, increased saliva, tenesmus.

Body as a whole: Frequent: asthenia. Infrequent: chest pain, edema, falling, fever, malaise, trauma. Rare: allergic reaction, allergy aggravated, anaphylactic shock, face edema, hot flashes, increased ESR, pain, restless legs, rigors, tolerance increased, weight decrease.

Cardiovascular system: Infrequent: cerebrovascular disorder, hypertension, tachycardia. Rare: angina pectoris, arrhythmia, arteritis, circulatory failure, extrasystoles, hypertension aggravated, myocardial infarction, phlebitis, pulmonary embolism, pulmonary edema, varicose veins, ventricular tachycardia.

Central and peripheral nervous system: Frequent: ataxia, confusion, drowsiness, drugged feeling, euphoria, insomnia, lethargy, lightheadedness, vertigo. Infrequent: agitation, decreased cognition, detached, difficulty concentrating, dysarthria, emotional lability, hallucination, hypoesthesia, illusion, leg cramps, migraine, nervousness, paresthesia, sleeping (after daytime dosing), speech disorder, stupor, tremor. Rare: abnormal gait, abnormal thinking, aggressive reaction, apathy, appetite increased, decreased libido, delusion, dementia, depersonalization, dysphasia, feeling strange, hypokinesia, hypotonia, hysteria, intoxicated feeling, manic reaction, neuralgia, neuritis, neuropathy, neurosis, panic attacks, paresis, personality disorder, somnambulism, suicide attempts, tetany, yawning.

Gastrointestinal system: Frequent: diarrhea, dyspepsia, hiccup. Infrequent: anorexia, constipation, dysphagia, flatulence, gastroenteritis. Rare: enteritis, eructation, esophagospasm, gastritis, hemorrhoids, intestinal obstruction, rectal hemorrhage, tooth caries.

Hematologic and lymphatic system: Rare: anemia, hyperhemoglobinemia, leukopenia, lymphadenopathy, macrocytic anemia, purpura, thrombosis.

Immunologic system: Infrequent: infection. Rare: abscess, herpes simplex, herpes zoster, otitis externa, otitis media.

Liver and biliary system: Infrequent: abnormal hepatic function, increased SGPT. Rare: bilirubinemia, increased SGOT.

Metabolic and nutritional: Infrequent: hyperglycemia, thirst. Rare: gout, hypercholesteremia, hyperlipidemia, increased alkaline phosphatase, increased BUN, periorbital edema.

Musculoskeletal system: Infrequent: arthritis. Rare: arthrosis, muscle weakness, sciatica, tendinitis.

Reproductive system: Infrequent: menstrual disorder, vaginitis. Rare: breast fibroadenosis, breast neoplasm, breast pain.

Respiratory system: Frequent: sinusitis. Infrequent: bronchitis, coughing, dyspnea. Rare: bronchospasm, respiratory depression, epistaxis, hypoxia, laryngitis, pneumonia.

Skin and appendages: Infrequent: pruritus. Rare: acne, bullous eruption, dermatitis, furunculosis, injection-site inflammation, photosensitivity reaction, urticaria.

Special senses: Frequent: diplopia, vision abnormal. Infrequent: eye irritation, eye pain, scleritis, taste perversion, tinnitus. Rare: conjunctivitis, corneal ulceration, lacrimation abnormal, parosmia, photopsia.

Urogenital system: Frequent: urinary tract infection. Infrequent: cystitis, urinary incontinence.
Rare: acute renal failure, dysuria, micturition frequency, nocturia, polyuria, pyelonephritis, renal pain, urinary retention.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form at <https://sideeffects.health.gov.il/>

9.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of Ambien CR. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Liver and biliary system: acute hepatocellular, cholestatic or mixed liver injury with or without jaundice (i.e., bilirubin $>2 \times$ ULN, alkaline phosphatase $\geq 2 \times$ ULN, transaminase $\geq 5 \times$ ULN).

Psychiatric disorders: delirium

10 DRUG INTERACTIONS

10.1 CNS-Active Drugs

CNS Depressants

Coadministration of zolpidem with other CNS depressants increases the risk of CNS depression. Concomitant use of zolpidem with these drugs may increase drowsiness and psychomotor impairment, including impaired driving ability [see *Warnings and Precautions (8.1, 8.2)*]. Zolpidem tartrate was evaluated in healthy volunteers in single-dose interaction studies for several CNS drugs.

Alcohol

An additive adverse effect on psychomotor performance between alcohol and oral zolpidem was demonstrated [see *Warnings and Precautions (8.1, 8.2)*].

Opioids

The concomitant use of Zolpidem Tartrate Extended-Release Tablets with opioids may increase the risk of respiratory depression. Limit dosage and duration of concomitant use of zolpidem and opioids [see *Dosage and Administration (2.3), Warnings and Precautions (5.7)*].

Imipramine, Chlorpromazine

Imipramine in combination with zolpidem produced no pharmacokinetic interaction other than a 20% decrease in peak levels of imipramine, but there was an additive effect of decreased alertness. Similarly, chlorpromazine in combination with zolpidem produced no pharmacokinetic interaction, but there was an additive effect of decreased alertness and psychomotor performance [see *Clinical Pharmacology (15.3)*].

Sertraline

Concomitant administration of zolpidem and sertraline increases exposure to zolpidem [see *Clinical Pharmacology (15.3)*].

Fluoxetine

After multiple doses of zolpidem tartrate and fluoxetine an increase in the zolpidem half-life (17%) was observed. There was no evidence of an additive effect in psychomotor performance [see *Clinical Pharmacology (15.3)*].

Haloperidol

A study involving haloperidol and zolpidem revealed no effect of haloperidol on the pharmacokinetics or pharmacodynamics of zolpidem. The lack of a drug interaction following single-dose administration does not predict the absence of an effect following chronic administration [see *Clinical Pharmacology (15.3)*].

10.2 Drugs that Affect Drug Metabolism via Cytochrome P450

Some compounds known to induce or inhibit CYP3A may affect exposure to zolpidem. The effect of drugs that induce or inhibit other P450 enzymes on the exposure to zolpidem is not known.

CYP3A4 Inducers

Rifampin

Rifampin, a CYP3A4 inducer, significantly reduced the exposure to and the pharmacodynamic effects of zolpidem. Use of Rifampin in combination with zolpidem may decrease the efficacy of zolpidem and is not recommended [see *Clinical Pharmacology (15.3)*].

St. John's wort

Use of St. John's wort, a CYP3A4 inducer, in combination with zolpidem may decrease blood levels of zolpidem and is not recommended.

CYP3A4 Inhibitors

Ketoconazole

Ketoconazole, a potent CYP3A4 inhibitor, increased the exposure to and pharmacodynamic effects of zolpidem.

Consideration should be given to using a lower dose of zolpidem when a potent CYP3A4 inhibitor and zolpidem are given together [see *Clinical Pharmacology* (15.3)].

11 USE IN SPECIFIC POPULATIONS

11.1 Pregnancy

Risk Summary

Neonates born to mothers using zolpidem late in the third trimester of pregnancy have been reported to experience symptoms of respiratory depression and sedation [see *Clinical Considerations and Data*]. Published data on the use of zolpidem during pregnancy have not reported a clear association with zolpidem and major birth defects [see *Data*]. Oral administration of zolpidem to pregnant rats and rabbits did not indicate a risk for adverse effects on fetal development at clinically relevant doses [see *Data*].

The estimated background risk of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

Clinical Considerations

Fetal/neonatal adverse reactions

Zolpidem crosses the placenta and may produce respiratory depression and sedation in neonates. Monitor neonates exposed to AMBIEN CR during pregnancy and labor for signs of excess sedation, hypotonia, and respiratory depression and manage accordingly.

Data

Human data

Published data from observational studies, birth registries, and case reports on the use of zolpidem during pregnancy do not report a clear association with zolpidem and major birth defects.

There are limited postmarketing reports of severe to moderate cases of respiratory depression that occurred after birth in neonates whose mothers had taken zolpidem during pregnancy. These cases required artificial ventilation or intratracheal intubation. The majority of neonates recovered within hours to a few weeks after birth once treated.

Zolpidem has been shown to cross the placenta.

Animal data

Oral administration of zolpidem to pregnant rats during the period of organogenesis at 4, 20, and 100 mg base/kg/day, which are approximately 4, 20, and 100 times the maximum recommended human dose (MRHD) of 12.5 mg/day (10 mg zolpidem base) based on mg/m² body surface area, caused delayed fetal development (incomplete fetal skeletal ossification) at maternally toxic (ataxia) doses 20 and 100 times the MRHD based on mg/m² body surface area.

Oral administration of zolpidem to pregnant rabbits during the period of organogenesis at 1, 4, and 16 mg base/kg/day, which are approximately 2, 8, and 30 times the MRHD of 12.5 mg/day (10 mg zolpidem base) based on mg/m² body surface area caused embryo-fetal death and delayed fetal development (incomplete fetal skeletal ossification) at a maternally toxic (decreased body weight gain) dose 30 times the MRHD based on mg/m² body surface area.

Oral administration of zolpidem to pregnant rats from day 15 of gestation through lactation at 4, 20, and 100 mg base/kg/day, which are approximately 4, 20, and 100 times the MRHD of 12.5 mg/day (10 mg zolpidem base) based on a mg/m² body surface area, delayed offspring growth and decreased survival at doses 20 and 100 times, respectively, the MRHD based on mg/m² body surface area.

11.2 Lactation

Risk Summary

Limited data from published literature report the presence of zolpidem in human milk. There are reports of excess sedation in infants exposed to zolpidem through breastmilk [*see Clinical Considerations*]. There is no information on the effects of zolpidem on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Ambien CR and any potential adverse effects on the breastfed infant from AMBIEN CR or from the underlying maternal condition.

Clinical Considerations

Infants exposed to Ambien CR through breastmilk should be monitored for excess sedation, hypotonia, and respiratory depression. A lactating woman may consider interrupting breastfeeding and pumping and discarding breast milk during treatment and for 23 hours (approximately 5 elimination half-lives) after Ambien CR administration in order to minimize drug exposure to a breast fed infant.

11.3 Pediatric Use

Ambien CR is not recommended for use in children. Safety and effectiveness of zolpidem in pediatric patients below the age of 18 years have not been established.

In an 8-week study, in pediatric patients (aged 6-17 years) with insomnia associated with attention-deficit/hyperactivity disorder (ADHD) an oral solution of zolpidem tartrate dosed at 0.25 mg/kg at bedtime did not decrease sleep latency compared to placebo. Psychiatric and nervous system disorders comprised the most frequent (>5%) treatment emergent adverse reactions observed with zolpidem versus placebo and included dizziness (23.5% vs 1.5%), headache (12.5% vs 9.2%), and hallucinations were reported in 7% of the pediatric patients who received zolpidem; none of the pediatric patients who received placebo reported hallucinations [*see Warnings and Precautions (8.5)*]. Ten patients on zolpidem (7.4%) discontinued treatment due to an adverse reaction.

FDA has not required pediatric studies of Ambien CR in the pediatric population based on these efficacy and safety findings.

11.4 Geriatric Use

A total of 99 elderly (≥ 65 years of age) received daily doses of 6.25 mg Ambien CR in a 3-week placebo-controlled study. The adverse reaction profile of Ambien CR 6.25 mg in this population was similar to that of Ambien CR 12.5 mg in younger adults (≤ 64 years of age). Dizziness was reported in 8% of Ambien CR-treated patients compared with 3% of those treated with placebo.

The dose of Ambien CR in elderly patients is 6.25 mg to minimize adverse effects related to impaired motor and/or cognitive performance and unusual sensitivity to sedative/hypnotic drugs [see *Warnings and Precautions (8.2)*].

11.5 Gender Difference in Pharmacokinetics

Women clear zolpidem tartrate from the body at a lower rate than men. C_{\max} and AUC parameters of zolpidem from Ambien CR were, respectively, approximately 50% and 75% higher at the same dose in adult female subjects compared to adult male subjects. Between 6 and 12 hours after dosing, zolpidem concentrations were 2- to 3 fold higher in adult female compared to adult male subjects. Given the higher blood levels of zolpidem tartrate in women compared to men at a given dose, the recommended initial dose of Ambien CR for adult women is 6.25 mg, and the recommended dose for adult men is 6.25 or 12.5 mg.

In geriatric patients, clearance of zolpidem is similar in men and women. The recommended dose of Ambien CR in geriatric patients is 6.25 mg regardless of gender.

11.6 Hepatic Impairment

The recommended dose of Ambien CR in patients with hepatic insufficiency is 6.25 mg once daily immediately before bedtime. Ambien CR should not be used in patients with severe hepatic insufficiency [see *Dosage and Administration (5.2)*, *Warnings and Precautions (8.8)*, *Contraindications (7)*, *Clinical Pharmacology (15.3)*].

12 DRUG ABUSE AND DEPENDENCE

12.1 Controlled Substance

Zolpidem tartrate is classified as a Schedule IV controlled substance by federal regulation.

12.2 Abuse

Abuse and addiction are separate and distinct from physical dependence and tolerance. Abuse is characterized by misuse of the drug for non-medical purposes, often in combination with other psychoactive substances. Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug effects over time. Tolerance may occur to both desired and undesired effects of drugs and may develop at different rates for different effects.

Addiction is a primary, chronic, neurobiological disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Drug addiction is a treatable disease, using a multidisciplinary approach, but relapse is common.

Studies of abuse potential in former drug abusers found that the effects of single doses of zolpidem tartrate 40 mg were similar, but not identical, to diazepam 20 mg, while zolpidem tartrate 10 mg effects were difficult to distinguish from placebo.

Because persons with a history of addiction to, or abuse of, drugs or alcohol are at increased risk for misuse, abuse and addiction of zolpidem, they should be monitored carefully when receiving zolpidem or any other hypnotic.

12.3 Dependence

Use of Ambien CR may lead to development of physical and/or psychological dependence. This risk of dependence increases with dose and duration of treatment. The risk of abuse and dependence is also greater in patients with history of alcohol or drug abuse. Ambien CR should be used with extreme caution in patients with current or past alcohol or drug abuse.

Physical dependence is a state of adaptation that is manifested by a specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.

Sedatives/hypnotics have produced withdrawal signs and symptoms following abrupt discontinuation. These reported symptoms range from mild dysphoria and insomnia to a withdrawal syndrome that may include abdominal and muscle cramps, vomiting, sweating, tremors, convulsions, and delirium.

The following adverse events, which are considered to meet the DSM-III-R criteria for uncomplicated sedative/hypnotic withdrawal, were reported during Ambien CR clinical trials following placebo substitution occurring within 48 hours following last zolpidem treatment: fatigue, nausea, flushing, lightheadedness, uncontrolled crying, emesis, stomach cramps, panic attack, nervousness, and abdominal discomfort. These reported adverse events occurred at an incidence of 1% or less. However, available data cannot provide a reliable estimate of the incidence, if any, of dependence during treatment at recommended doses. There have been postmarketing reports of abuse, dependence and withdrawal with zolpidem.

13 OVERDOSAGE

13.1 Signs and Symptoms

In postmarketing experience of overdose with zolpidem tartrate alone, or in combination with CNS-depressant agents, impairment of consciousness ranging from somnolence to coma, cardiovascular and/or respiratory compromise, and fatal outcomes have been reported.

13.2 Recommended Treatment

General symptomatic and supportive measures should be used along with immediate gastric lavage where appropriate. Intravenous fluids should be administered as needed. Zolpidem's sedative hypnotic effect was shown to be reduced by flumazenil and therefore may be useful; however, flumazenil administration may contribute to the appearance of neurological symptoms (convulsions). As in all cases of drug overdose, respiration, pulse, blood pressure, and other appropriate signs should be monitored and general supportive measures employed. Hypotension and CNS depression should be monitored and treated by appropriate medical

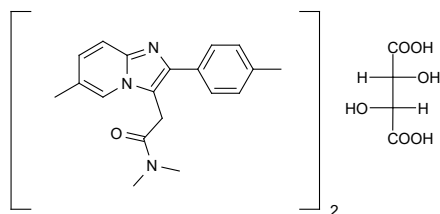
intervention. Sedating drugs should be withheld following zolpidem overdose, even if excitation occurs. The value of dialysis in the treatment of overdose has not been determined, although hemodialysis studies in patients with renal failure receiving therapeutic doses have demonstrated that zolpidem is not dialyzable.

As with the management of all overdose, the possibility of multiple drug ingestion should be considered. The physician may wish to consider contacting a poison control center for up-to-date information on the management of hypnotic drug product overdose.

14 DESCRIPTION

Ambien CR contains zolpidem tartrate, a gamma-aminobutyric acid (GABA) A receptor positive modulator of the imidazopyridine class. Ambien CR (zolpidem tartrate extended-release tablets) is available in 6.25 mg and 12.5 mg strength tablets for oral administration.

Chemically, zolpidem is N,N,6-trimethyl-2-p-tolylimidazo[1,2-a]pyridine-3-acetamide L-(+)-tartrate (2:1). It has the following structure:



Zolpidem tartrate is a white to off-white crystalline powder that is sparingly soluble in water, alcohol, and propylene glycol. It has a molecular weight of 764.88.

Ambien CR consists of a coated two-layer tablet: one layer that releases its drug content immediately and another layer that allows a slower release of additional drug content.

The 6.25 mg Ambien CR tablet contains the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, hypromellose, potassium hydrogen tartrate, sodium starch glycolate (type A), magnesium stearate, titanium dioxide, Macrogol 3350, colloidal anhydrous silica, and red iron oxide.

The 12.5 mg Ambien CR tablet contains the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, hypromellose, potassium hydrogen tartrate, sodium starch glycolate (type A), magnesium stearate, titanium dioxide, Macrogol 3350, indigotine (E132)-aluminum lake, colloidal anhydrous silica, and yellow iron oxide.

15 CLINICAL PHARMACOLOGY

15.1 Mechanism of Action

Zolpidem is a GABA A receptor positive modulator presumed to exert its therapeutic effects in the short-term treatment of insomnia through binding to the benzodiazepine site of $\alpha 1$ subunit containing GABA A receptors, increasing the frequency of chloride channel opening resulting in the inhibition of neuronal excitation.

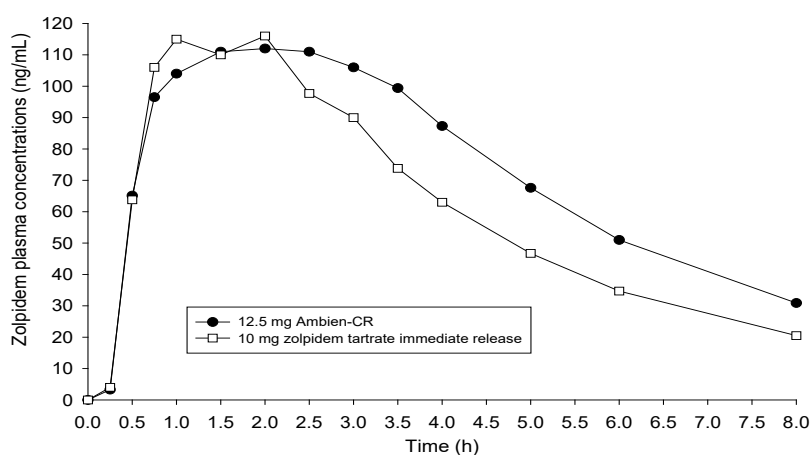
15.2 Pharmacodynamics

Zolpidem binds to GABA A receptors with greater affinity for $\alpha 1$ subunit relative to $\alpha 2$ and $\alpha 3$ subunit containing receptors. Zolpidem has no appreciable binding affinity for $\alpha 5$ subunit containing GABA A receptors. This binding profile may explain the relative absence of myorelaxant effects in animal studies. Zolpidem has no appreciable binding affinity for dopaminergic D2, serotonergic 5HT2, adrenergic, histaminergic or muscarinic receptors.

15.3 Pharmacokinetics

Ambien CR exhibits biphasic absorption characteristics, which results in rapid initial absorption from the gastrointestinal tract similar to zolpidem tartrate immediate-release, then provides extended plasma concentrations beyond three hours after administration. A study in 24 healthy male subjects was conducted to compare mean zolpidem plasma concentration-time profiles obtained after single oral administration of Ambien CR 12.5 mg and of an immediate-release formulation of zolpidem tartrate (10 mg). The terminal elimination half-life observed with Ambien CR (12.5 mg) was similar to that obtained with immediate-release zolpidem tartrate (10 mg). The mean plasma concentration-time profiles are shown in Figure 1.

Figure 1: Mean Plasma Concentration-Time Profiles for Ambien CR (12.5 mg) and Immediate-Release Zolpidem Tartrate (10 mg)



In adult and elderly patients treated with Ambien CR, there was no evidence of accumulation after repeated once-daily dosing for up to two weeks.

Absorption

Following administration of Ambien CR, administered as a single 12.5 mg dose in healthy male adult subjects, the mean peak concentration (C_{max}) of zolpidem was 134 ng/mL (range: 68.9 to 197 ng/ml) occurring at a median time (T_{max}) of 1.5 hours. The mean AUC of zolpidem was 740 ng·hr/mL (range: 295 to 1359 ng·hr/mL).

A food-effect study in 45 healthy subjects compared the pharmacokinetics of Ambien CR 12.5 mg when administered while fasting or within 30 minutes after a meal. Results demonstrated that with food, mean AUC and C_{max} were decreased by 23% and 30%, respectively, while median T_{max} was increased from 2 hours to 4 hours. The half-life was not

changed. These results suggest that, for faster sleep onset, Ambien CR should not be administered with or immediately after a meal.

Distribution

Total protein binding was found to be $92.5 \pm 0.1\%$ and remained constant, independent of concentration between 40 and 790 ng/mL.

Metabolism

Zolpidem is converted to inactive metabolites that are eliminated primarily by renal excretion.

Elimination

When Ambien CR was administered as a single 12.5 mg dose in healthy male adult subjects, the mean zolpidem elimination half-life was 2.8 hours (range: 1.62 to 4.05 hr).

Special Populations

Elderly

In 24 elderly (≥ 65 years) healthy subjects administered a single 6.25 mg dose of Ambien CR, the mean peak concentration (C_{max}) of zolpidem was 70.6 (range: 35.0 to 161) ng/mL occurring at a median time (T_{max}) of 2.0 hours. The mean AUC of zolpidem was 413 ng·hr/mL (range: 124 to 1190 ng·hr/mL) and the mean elimination half-life was 2.9 hours (range: 1.59 to 5.50 hours).

Hepatic impairment

Ambien CR was not studied in patients with hepatic impairment. The pharmacokinetics of an immediate-release formulation of zolpidem tartrate in eight patients with chronic hepatic insufficiency was compared to results in healthy subjects. Following a single 20-mg oral zolpidem tartrate dose, mean C_{max} and AUC were found to be two times (250 vs. 499 ng/mL) and five times (788 vs. 4,203 ng·hr/mL) higher, respectively, in hepatically compromised patients. T_{max} did not change. The mean half-life in cirrhotic patients of 9.9 hr (range: 4.1 to 25.8 hr) was greater than that observed in normal subjects of 2.2 hr (range: 1.6 to 2.4 hr). Dosing should be modified accordingly in patients with hepatic insufficiency [*see Dosage and Administration (5.2), Contraindications (7), Warnings and precautions (8.8), Use in specific populations (11.6)*].

Renal impairment

Ambien CR was not studied in patients with renal impairment. The pharmacokinetics of an immediate-release formulation of zolpidem tartrate were studied in 11 patients with end-stage renal failure (mean $Cl_{Cr} = 6.5 \pm 1.5$ mL/min) undergoing hemodialysis three times a week, who were dosed with zolpidem tartrate 10 mg orally each day for 14 or 21 days. No statistically significant differences were observed for C_{max} , T_{max} , half-life, and AUC between the first and last day of drug administration when baseline concentration adjustments were made. Zolpidem was not hemodialyzable. No accumulation of unchanged drug appeared after 14 or 21 days. Zolpidem pharmacokinetics was not significantly different in renally impaired patients. No dosage adjustment is necessary in patients with compromised renal function.

Drug Interactions

CNS-depressants

Coadministration of zolpidem with other CNS depressants increases the risk of CNS depression [see *Warnings and Precautions (8.2)*]. Zolpidem tartrate was evaluated in healthy volunteers in single-dose interaction studies for several CNS drugs. Imipramine in combination with zolpidem produced no pharmacokinetic interaction other than a 20% decrease in peak levels of imipramine, but there was an additive effect of decreased alertness. Similarly, chlorpromazine in combination with zolpidem produced no pharmacokinetic interaction, but there was an additive effect of decreased alertness and psychomotor performance.

A study involving haloperidol and zolpidem revealed no effect of haloperidol on the pharmacokinetics or pharmacodynamics of zolpidem. The lack of a drug interaction following single-dose administration does not predict the absence of an effect following chronic administration.

An additive adverse effect on psychomotor performance between alcohol and oral zolpidem was demonstrated [see *Warnings and Precautions (8.2)*].

Following five consecutive nightly doses at bedtime of oral zolpidem tartrate 10 mg in the presence of sertraline 50 mg (17 consecutive daily doses, at 7:00 am, in healthy female volunteers), zolpidem C_{max} was significantly higher (43%) and T_{max} was significantly decreased (-53%). Pharmacokinetics of sertraline and N-desmethylsertraline were unaffected by zolpidem.

A single-dose interaction study with zolpidem tartrate 10 mg and fluoxetine 20 mg at steady-state levels in male volunteers did not demonstrate any clinically significant pharmacokinetic or pharmacodynamic interactions. When multiple doses of zolpidem and fluoxetine were given at steady state and the concentrations evaluated in healthy females, an increase in the zolpidem half-life (17%) was observed. There was no evidence of an additive effect in psychomotor performance.

Drugs that affect drug metabolism via cytochrome P450

Some compounds known to inhibit CYP3A may increase exposure to zolpidem. The effect of inhibitors of other P450 enzymes on the pharmacokinetics of zolpidem is unknown.

A single-dose interaction study with zolpidem tartrate 10 mg and itraconazole 200 mg at steady-state levels in male volunteers resulted in a 34% increase in $AUC_{0-\infty}$ of zolpidem tartrate. There were no pharmacodynamic effects of zolpidem detected on subjective drowsiness, postural sway, or psychomotor performance.

A single-dose interaction study with zolpidem tartrate 10 mg and rifampin 600 mg at steady-state levels in female subjects showed significant reductions of the AUC (-73%), C_{max} (-58%), and $T_{1/2}$ (-36 %) of zolpidem together with significant reductions in the pharmacodynamic effects of zolpidem tartrate. Rifampin, a CYP3A4 inducer, significantly reduced the exposure to and the pharmacodynamic effects of zolpidem [see *Drug Interactions (10.2)*].

Similarly, St. John's wort, a CYP3A4 inducer, may also decrease the blood levels of zolpidem

A single-dose interaction study with zolpidem tartrate 5 mg and ketoconazole, a potent CYP3A4 inhibitor, given as 200 mg twice daily for 2 days increased C_{max} of zolpidem (30%) and the total AUC of zolpidem (70%) compared to zolpidem alone and prolonged the

elimination half-life (30 %) along with an increase in the pharmacodynamic effects of zolpidem [see *Drug Interactions (10.2)*]. Additionally, fluvoxamine (a strong inhibitor of CYP1A2 and a weak inhibitor of CYP3A4 and CYP2C9) and ciprofloxacin (a strong inhibitor of CYP1A2 and a moderate inhibitor of CYP3A4) are also likely to inhibit zolpidem's metabolic pathways, potentially leading to an increase in zolpidem exposure.

Other drugs with no interactions with zolpidem

A study involving cimetidine/zolpidem tartrate and ranitidine/zolpidem tartrate combinations revealed no effect of either drug on the pharmacokinetics or pharmacodynamics of zolpidem.

Zolpidem tartrate had no effect on digoxin pharmacokinetics and did not affect prothrombin time when given with warfarin in healthy subjects.

16 NONCLINICAL TOXICOLOGY

16.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Zolpidem was administered to mice and rats for 2 years at oral doses of 4, 18, and 80 mg base/kg/day. In mice, these doses are approximately 2, 9, and 40 times the MRHD of 12.5 mg/day (10 mg zolpidem base) based on mg/m² body surface area and in rats, these doses are approximately 4, 18, and 80 times the MRHD based on mg/m² body surface area. No evidence of carcinogenic potential was observed in mice. In rats, renal tumors (lipoma, liposarcoma) were seen at the mid- and high doses.

Mutagenesis

Zolpidem was negative in *in vitro* (bacterial reverse mutation, mouse lymphoma, and chromosomal aberration) and *in vivo* (mouse micronucleus) genetic toxicology assays.

Impairment of Fertility

Zolpidem was administered to rats at 4, 20, and 100 mg base/kg/day, which are approximately 4, 20, and 100 times the MRHD of 12.5 mg/day (10 mg zolpidem base) based on mg/m² body surface area, prior to and during mating, and continuing in females through postpartum day 25. Zolpidem caused irregular estrus cycles and prolonged precoital intervals at the highest dose tested, which is approximately 100 times the MRHD based on mg/m² body surface area. The NOAEL for these effects is 20 times the MRHD based on mg/m² body surface area. There was no impairment of fertility at any dose tested.

17 CLINICAL STUDIES

17.1 Controlled Clinical Trials

Ambien CR was evaluated in three placebo-controlled studies for the treatment of patients with chronic primary insomnia (as defined in the APA Diagnostic and Statistical Manual of Mental Disorders, DSM IV).

Adult outpatients (18-64 years) with primary insomnia (N=212) were evaluated in a double-blind, randomized, parallel-group, 3-week trial comparing Ambien CR 12.5 mg and placebo. Ambien CR 12.5 mg decreased wake time after sleep onset (WASO) for the first 7 hours during the first 2 nights and for the first 5 hours after 2 weeks of treatment. Ambien CR 12.5 mg was superior to placebo on objective measures (polysomnography recordings) of sleep

induction (by decreasing latency to persistent sleep [LPS]) during the first 2 nights of treatment and after 2 weeks of treatment. Ambien CR 12.5 mg was also superior to placebo on the patient reported global impression regarding the aid to sleep after the first 2 nights and after 3 weeks of treatment.

Elderly outpatients (≥ 65 years) with primary insomnia (N=205) were evaluated in a double-blind, randomized, parallel-group, 3-week trial comparing Ambien CR 6.25 mg and placebo. Ambien CR 6.25 mg decreased wake time after sleep onset (WASO) for the first 6 hours during the first 2 nights and the first 4 hours after 2 weeks of treatment. Ambien CR 6.25 mg was superior to placebo on objective measures (polysomnography recordings) of sleep induction (by decreasing LPS) during the first 2 nights of treatment and after 2 weeks on treatment. Ambien CR 6.25 mg was superior to placebo on the patient reported global impression regarding the aid to sleep after the first 2 nights and after 3 weeks of treatment.

In both studies, in patients treated with Ambien CR, polysomnography showed increased wakefulness at the end of the night compared to placebo-treated patients.

In a 24-week double-blind, placebo-controlled, randomized study in adult outpatients (18-64 years) with primary insomnia (N=1025), Ambien CR 12.5 mg administered as needed (3 to 7 nights per week) was superior to placebo over 24 weeks, on patient global impression regarding aid to sleep, and on patient-reported specific sleep parameters for sleep induction and sleep maintenance with no significant increased frequency of drug intake observed over time.

17.2 Studies Pertinent to Safety Concerns for Sedative/ Hypnotic Drugs

Next-Day Residual Effects

In five clinical studies (three controlled studies in adults [18-64 years of age] administered Ambien CR 12.5 mg and two controlled studies in the elderly [≥ 65 years of age] administered Ambien CR 6.25 mg or 12.5 mg), the effect of Ambien CR on vigilance, memory, or motor function were assessed using neurocognitive tests. In these studies, no significant decrease in performance was observed eight hours after a nighttime dose. In addition, no evidence of next-day residual effects was detected with Ambien CR 12.5 mg and 6.25 mg using self-ratings of sedation.

During the 3-week studies, next-day somnolence was reported by 15% of the adult patients who received 12.5 mg Ambien CR versus 2% of the placebo group; next-day somnolence was reported by 6% of the elderly patients who received 6.25 mg Ambien CR versus 5% of the placebo group [see *Adverse Reactions (9)*]. In a 6-month study, the overall incidence of next-day somnolence was 5.7% in the Ambien CR group as compared to 2% in the placebo group.

Rebound Effects

Rebound insomnia, defined as a dose-dependent worsening in sleep parameters (latency, sleep efficiency, and number of awakenings) compared with baseline following discontinuation of treatment, is observed with short- and intermediate-acting hypnotics. In the two 3-week placebo-controlled studies in patients with primary insomnia, a rebound effect was only observed on the first night after abrupt discontinuation of Ambien CR. On the second night, there was no worsening compared to baseline in the Ambien CR group.

In a 6-month placebo-controlled study in which Ambien CR was taken as needed (3 to 7 nights per week), within the first month a rebound effect was observed for Total Sleep Time (not for WASO) during the first night off medication. After this first month period, no further rebound insomnia was observed. After final treatment discontinuation no rebound was observed.

18 HOW SUPPLIED/STORAGE AND HANDLING

Ambien CR 6.25 mg extended-release tablets are composed of two layers* and are coated. Ambien CR 12.5 mg extended-release tablets are composed of two layers* and are coated.

*Layers are covered by the coating and are indistinguishable.

Store below 30°C.

The expiry date of the product is indicated on the packaging materials.

20 MARKETING AUTHORISATION HOLDER AND IMPORTER AND ITS ADDRESS

Sanofi-aventis Israel Ltd. 10 Beni Gaaon St., POB 8090, Netanya

21 REGISTRATION NUMBERS

Ambien CR 6.25 mg 1420531833 Ambien CR 12.5 mg 1420631834

Revised in August 2022 according to MoH guidelines.