

AMBIEN CR- zolpidem tartrate tablet, coated
sanofi-aventis U.S. LLC

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AMBIEN CR safely and effectively. See full prescribing information for AMBIEN CR.

AMBIEN CR® (zolpidem tartrate extended-release) tablets, for oral use, C-IV
Initial U.S. Approval: 1992

----- **RECENT MAJOR CHANGES** -----

Dosage and Administration, Dosage in Adults (2.1)	08/2016
Dosage and Administration, Special Populations (2.2)	12/2016
Warnings and Precautions, CNS Depressant Effects and Next-Day Impairment (5.1)	08/2016
Warnings and Precautions, Precipitation of Hepatic Encephalopathy (5.7)	12/2016

----- **INDICATIONS AND USAGE** -----

AMBIEN CR, a gamma-aminobutyric acid (GABA) A agonist, is indicated for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance. (1)

----- **DOSAGE AND ADMINISTRATION** -----

- Use the lowest dose effective for the patient and must not exceed a total of 12.5 mg daily (2.1)
- Recommended initial dose is a single dose of 6.25 mg for women, and a single dose of 6.25 or 12.5 mg for men, immediately before bedtime with at least 7–8 hours remaining before the planned time of awakening (2.1)
- Geriatric patients and patients with mild to moderate hepatic impairment: Recommended dose is 6.25 mg for men and women (2.2)
- Lower doses of CNS depressants may be necessary when taken concomitantly with AMBIEN CR (2.3)
- Tablets to be swallowed whole, not to be crushed, divided or chewed (2.4)
- The effect of AMBIEN CR may be slowed if taken with or immediately after a meal (2.4)

----- **DOSAGE FORMS AND STRENGTHS** -----

Tablets: 6.25 mg and 12.5 mg extended-release tablets. Tablets not scored. (3)

----- **CONTRAINDICATIONS** -----

Known hypersensitivity to zolpidem (4)

----- **WARNINGS AND PRECAUTIONS** -----

- CNS depressant effects: Impaired alertness and motor coordination, including risk of morning impairment. Caution patients against driving and other activities requiring complete mental alertness the morning after use. (5.1)
- Need to evaluate for co-morbid diagnoses: Reevaluate if insomnia persists after 7 to 10 days of use. (5.2)
- Severe anaphylactic/anaphylactoid reactions: Angioedema and anaphylaxis have been reported. Do not rechallenge if such reactions occur. (5.3)
- "Sleep-driving" and other complex behaviors while not fully awake. Risk increases with dose and use with other CNS depressants and alcohol. Immediately evaluate any new onset behavioral changes. (5.4)
- Depression: Worsening of depression or, suicidal thinking may occur. Prescribe the least amount of tablets feasible to avoid intentional overdose. (5.5)
- Respiratory Depression: Consider this risk before prescribing in patients with compromised respiratory function. (5.6)
- Hepatic Impairment: Avoid AMBIEN CR use in patients with severe hepatic impairment. (5.7)
- Withdrawal effects: Symptoms may occur with rapid dose reduction or discontinuation. (5.8, 9.3)
- Severe Injuries: Drowsiness may lead to fall including severe injuries. (5.9)

----- **ADVERSE REACTIONS** -----

Most commonly observed adverse reactions (> 10% in either elderly or adult patients) are: headache, next-day somnolence and dizziness (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact sanofi-aventis U.S. LLC at 1-800-633-1610 or FDA at 1-800-FDA-1088 or <http://www.fda.gov/medwatch>.

----- **DRUG INTERACTIONS** -----

- CNS depressants, including alcohol: Possible adverse additive CNS-depressant effects (5.1, 7.1)
- Imipramine: Decreased alertness observed (7.1)

- Chlorpromazine: Impaired alertness and psychomotor performance observed (7.1)
- CYP3A4 inducers (rifampin or St. John's wort): Combination use may decrease effect (7.2)
- Ketoconazole: Combination use may increase effect (7.2)

----- **USE IN SPECIFIC POPULATIONS** -----

- Pregnancy: Based on animal data may cause fetal harm (8.1)
- Pediatric use: Safety and effectiveness not established. Hallucinations (incidence rate 7%) and other psychiatric and/or nervous system adverse reactions were observed frequently in a study of pediatric patients with Attention-Deficit/Hyperactivity Disorder (5.4, 8.4)

See 17 for **PATIENT COUNSELING INFORMATION** and **Medication Guide**.

Revised: 3/2017

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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 (14)*].

2 DOSAGE AND ADMINISTRATION

2.1 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 (5.1)*]. 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.

2.2 Special Populations

Elderly or debilitated patients may be especially sensitive to the effects of zolpidem tartrate. The recommended dose of AMBIEN CR in these patients is 6.25 mg once daily immediately before bedtime [*see Warnings and Precautions (5.1), Use in Specific Populations (8.5)*].

Patients with mild to moderate hepatic impairment do not clear the drug as rapidly as normal subjects. The recommended dose of AMBIEN CR in these patients is 6.25 mg once daily immediately before bedtime. Avoid AMBIEN CR use in patients with severe hepatic impairment as it may contribute to

encephalopathy [see *Warnings and Precautions (5.7)*, *Use in Specific Populations (8.7)*, *Clinical Pharmacology (12.3)*].

2.3 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 (5.1)*].

2.4 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.

3 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.

AMBIEN CR 6.25 mg tablets are pink, round, bi-convex, and debossed with A~ on one side.

AMBIEN CR 12.5 mg tablets are blue, round, bi-convex, and debossed with A~ on one side.

4 CONTRAINDICATIONS

AMBIEN CR is contraindicated in patients with known hypersensitivity to zolpidem. Observed reactions include anaphylaxis and angioedema [see *Warnings and Precautions (5.3)*].

5 WARNINGS AND PRECAUTIONS

5.1 CNS Depressant Effects and Next-Day Impairment

AMBIEN CR is a central nervous system (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. Downward dose adjustment of AMBIEN CR and concomitant CNS depressants should be considered [see *Dosage and Administration (2.3)*].

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 co-administered with other CNS depressants or alcohol; or co-administered 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 (2)* and *Clinical Studies (14.2)*].

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.

5.2 Need to Evaluate for Co-morbid 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.

5.3 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.

5.4 Abnormal Thinking and Behavioral Changes

Abnormal thinking and behavior changes have been reported in patients treated with sedative/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 AMBIEN 0.25 mg/kg taken at bedtime reported hallucinations versus 0% treated with placebo [see *Use in Specific Populations (8.4)*].

Complex behaviors such as "sleep-driving" (i.e., driving while not fully awake after ingestion of a sedative-hypnotic, with amnesia for the event) have been reported in sedative-hypnotic-naïve as well as in sedative-hypnotic-experienced persons. Although behaviors such as "sleep-driving" have occurred with AMBIEN CR alone at therapeutic doses, the co-administration of alcohol and other CNS depressants increases the risk of such behaviors, as does the use of AMBIEN CR at doses exceeding the maximum recommended dose. Due to the risk to the patient and the community, discontinuation of AMBIEN CR should be strongly considered for patients who report a "sleep-driving" episode.

Other complex behaviors (e.g., preparing and eating food, making phone calls, or having sex) have been reported in patients who are not fully awake after taking a sedative-hypnotic. As with "sleep-driving", patients usually do not remember these events. Amnesia, anxiety and other neuro-psychiatric symptoms may also occur.

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.

5.5 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 overdose 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.

5.6 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. 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.

5.7 Precipitation of Hepatic Encephalopathy

GABA agonists 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 zolpidem tartrate as rapidly as patients with normal hepatic function. Avoid AMBIEN CR use in patients with severe hepatic impairment as it may contribute to encephalopathy [see *Dosage and Administration (2.2)*, *Use in Specific Populations (8.7)*, *Clinical Pharmacology (12.3)*].

5.8 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 (9.2)* and *(9.3)*].

5.9 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.

6 ADVERSE REACTIONS

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

- CNS-depressant effects and next-day impairment [see *Warnings and Precautions (5.1)*]
- Serious anaphylactic and anaphylactoid reactions [see *Warnings and Precautions (5.3)*]
- Abnormal thinking and behavior changes, and complex behaviors [see *Warnings and Precautions (5.4)*]
- Withdrawal effects [see *Warnings and Precautions (5.8)*]

6.1 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 reaction 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 hypnogogic 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, 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.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval 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).

7 DRUG INTERACTIONS

7.1 CNS-active Drugs

Co-administration 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 (5.1)*]. Zolpidem tartrate was evaluated in healthy volunteers in single-dose interaction studies for several CNS drugs.

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 (12.3)*].

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 (12.3)*].

Alcohol

An additive adverse effect on psychomotor performance between alcohol and oral zolpidem was demonstrated [see *Warnings and Precautions (5.1)*].

Sertraline

Concomitant administration of zolpidem and sertraline increases exposure to zolpidem [see *Clinical Pharmacology (12.3)*].

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 (12.3)*].

7.2 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 (12.3)*].

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* (12.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of AMBIEN CR in pregnant women. Studies in children to assess the effects of prenatal exposure to zolpidem have not been conducted; however, cases of severe neonatal respiratory depression have been reported when zolpidem was used at the end of pregnancy, especially when taken with other CNS depressants. Children born to mothers taking sedative-hypnotic drugs may be at risk for withdrawal symptoms during the postnatal period. Neonatal flaccidity has also been reported in infants born to mothers who received sedative-hypnotic drugs during pregnancy. AMBIEN CR should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Administration of zolpidem to pregnant rats and rabbits resulted in adverse effects on offspring development at doses greater than the AMBIEN CR maximum recommended human dose (MRHD) of 12.5 mg/day (approximately 10 mg/day zolpidem base); however, teratogenicity was not observed.

When zolpidem was administered at oral doses of 4, 20, and 100 mg base/kg/day to pregnant rats during the period of organogenesis, dose-related decreases in fetal skull ossification occurred at all but the lowest dose, which is approximately 4 times the MRHD on a mg/m² basis. In rabbits treated during organogenesis with zolpidem at oral doses of 1, 4, and 16 mg base/kg/day, increased embryo-fetal death and incomplete fetal skeletal ossification occurred at the highest dose. The no-effect dose for embryo-fetal toxicity in rabbits is approximately 8 times the MRHD on a mg/m² basis. Administration of zolpidem to rats at oral doses of 4, 20, and 100 mg base/kg/day during the latter part of pregnancy and throughout lactation produced decreased offspring growth and survival at all but the lowest dose, which is approximately 4 times the MRHD on a mg/m² basis.

8.2 Labor and Delivery

AMBIEN CR has no established use in labor and delivery [see *Pregnancy* (8.1)].

8.3 Nursing Mothers

Zolpidem is excreted in human milk. Caution should be exercised when AMBIEN CR is administered to a nursing woman.

8.4 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* (5.4)]. 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.

8.5 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 (5.1)*].

8.6 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.

8.7 Hepatic Impairment

The recommended dose of AMBIEN CR in patients with mild to moderate hepatic impairment is 6.25 mg once daily immediately before bedtime. Avoid AMBIEN CR use in patients with severe hepatic impairment as it may contribute to encephalopathy [see *Dosage and Administration (2.2)*, *Warnings and Precautions (5.7)*, *Clinical Pharmacology (12.3)*].

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

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

9.2 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.

9.3 Dependence

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.

Sedative/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, and convulsions. The following adverse events, which are considered to meet the DSM-III-R criteria for uncomplicated sedative/hypnotic withdrawal, were reported during U.S. 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. Post-marketing reports of abuse, dependence and withdrawal have been received.

10 OVERDOSAGE

10.1 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.

10.2 Recommended Treatment

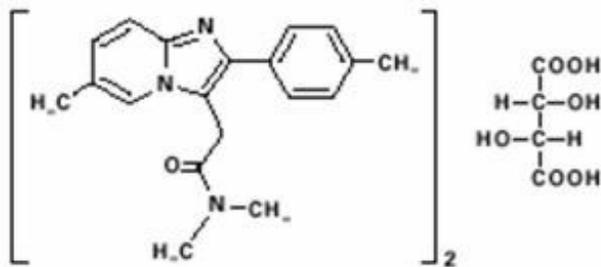
General symptomatic and supportive measures should be used along with immediate gastric lavage where appropriate. Intravenous fluids should be administered as needed. Zolpidem's sedative hypnotic effect was shown to be reduced by flumazenil and therefore may be useful; however, flumazenil administration 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 overdosage, even if excitation occurs. The value of dialysis in the treatment of overdosage 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 overdosage, 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 overdosage.

11 DESCRIPTION

AMBIEN CR contains zolpidem tartrate, a gamma-aminobutyric acid (GABA) A agonist 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: colloidal silicon dioxide, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, potassium bitartrate, red ferric oxide, sodium starch glycolate, and titanium dioxide. The 12.5 mg AMBIEN CR tablet contains the following inactive ingredients: colloidal silicon dioxide, FD&C Blue #2, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, potassium bitartrate, sodium starch glycolate, titanium dioxide, and yellow ferric oxide.

12 CLINICAL PHARMACOLOGY

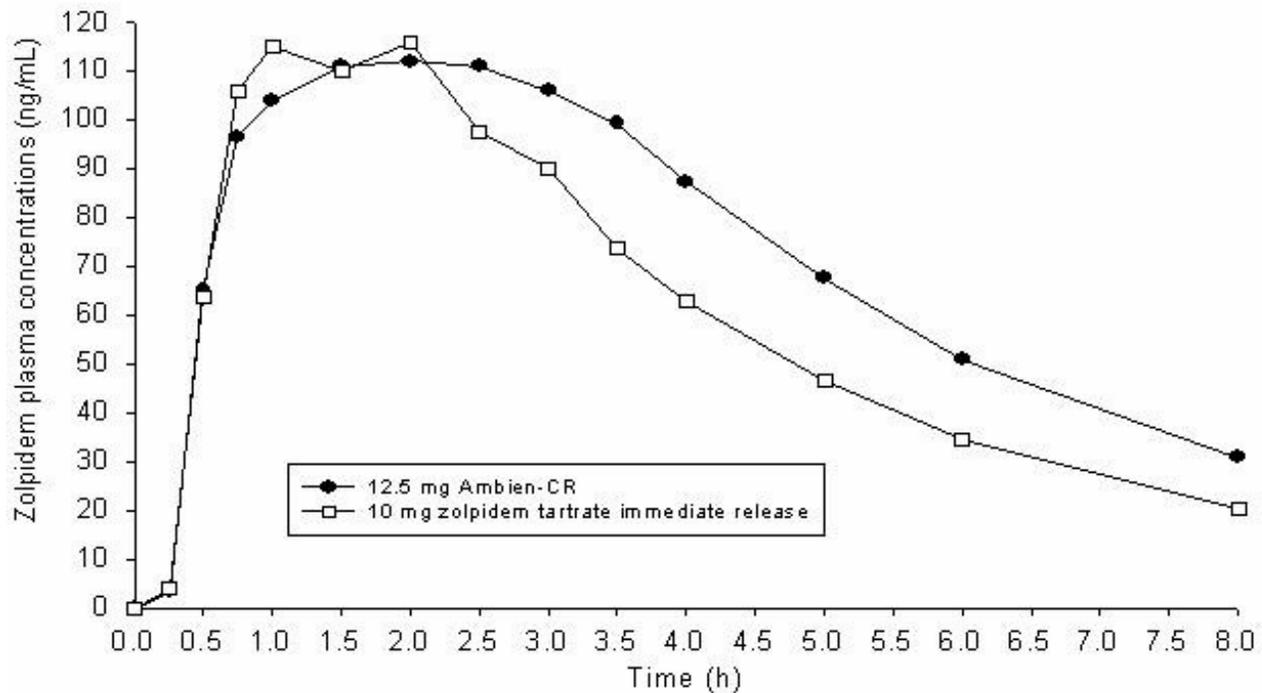
12.1 Mechanism of Action

Zolpidem, the active moiety of zolpidem tartrate, is a hypnotic agent with a chemical structure unrelated to benzodiazepines, barbiturates, or other drugs with known hypnotic properties. It interacts with a GABA-BZ receptor complex and shares some of the pharmacological properties of the benzodiazepines. In contrast to the benzodiazepines, which non-selectively bind to and activate all BZ receptor subtypes, zolpidem *in vitro* binds the BZ₁ receptor preferentially with a high affinity ratio of the α_1/α_5 subunits. This selective binding of zolpidem on the BZ₁ receptor is not absolute, but it may explain the relative absence of myorelaxant and anticonvulsant effects in animal studies as well as the preservation of deep sleep (stages 3 and 4) in human studies of zolpidem tartrate at hypnotic doses.

12.3 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 were 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) [see *Dosage and Administration (2.2)*, *Warnings and Precautions (5.7)*, *Use in Specific Populations (8.7)*].

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 were not significantly different in renally-impaired patients. No dosage adjustment is necessary in patients with compromised renal function.

Drug Interactions

CNS-depressants

Co-administration of zolpidem with other CNS depressants increases the risk of CNS depression [see *Warnings and Precautions (5.1)*]. 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 (5.1)*].

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 (7.2)*].

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 (7.2)*].

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.

13 NONCLINICAL TOXICOLOGY

13.1 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. In mice, these doses are approximately 2, 9, and 40 times the maximum recommended human dose (MRHD) of 12.5 mg/day (10 mg zolpidem base) on mg/m² basis. In rats, these doses are approximately 4, 18, and 80 times the MRHD on a mg/m² basis. 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: Oral administration of zolpidem (doses of 4, 20, and 100 mg base/kg/day) to rats prior to and during mating, and continuing in females through postpartum day 25, resulted in irregular estrus cycles and prolonged precoital intervals at the highest dose tested. The no-effect dose for these findings is approximately 20 times the MRHD on a mg/m² basis. There was no impairment of fertility at any dose tested.

14 CLINICAL STUDIES

14.1 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.

14.2 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 (6)*]. 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

AMBIEN CR 6.25 mg tablets are composed of two layers¹ and are coated, pink, round, bi-convex, debossed with A~ on one side and supplied as:

NDC Number	Size
0024-5501-31	bottle of 100

AMBIEN CR 12.5 mg tablets are composed of two layers¹ and are coated, blue, round, bi-convex, debossed with A~ on one side and supplied as:

NDC Number	Size
0024-5521-31	bottle of 100
0024-5521-50	bottle of 500
0024-5521-10	carton of 30 unit dose

¹ Layers are covered by the coating and are indistinguishable.

Store between 15°–25° C (59°–77°F). Limited excursions permissible up to 30° C (86°F)

17 PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Medication Guide). Inform patients and their families about the benefits and risks of treatment with AMBIEN CR. Inform patients of the availability of a Medication Guide and instruct them to read the Medication Guide prior to initiating treatment with AMBIEN CR and with each prescription refill. Review the AMBIEN CR Medication Guide with every patient prior to initiation of treatment. Instruct patients or caregivers that AMBIEN CR should be taken only as prescribed.

CNS Depressant Effects and Next-Day Impairment

Tell patients that AMBIEN CR can cause next-day impairment even when used as prescribed, and that this risk is increased if dosing instructions are not carefully followed. Caution patients against driving and other activities requiring complete mental alertness the day after use. Inform patients that impairment can be present despite feeling fully awake.

Severe Anaphylactic and Anaphylactoid Reactions

Inform patients that severe anaphylactic and anaphylactoid reactions have occurred with zolpidem. Describe the signs/symptoms of these reactions and advise patients to seek medical attention immediately if any of them occur.

Sleep-driving and Other Complex Behaviors

Instruct patients and their families that sedative hypnotics can cause abnormal thinking and behavior change, including "sleep driving" and other complex behaviors while not being fully awake (preparing and eating food, making phone calls, or having sex). Tell patients to call you immediately if they develop any of these symptoms.

Suicide

Tell patients to immediately report any suicidal thoughts.

Alcohol and Other Drugs

Ask patients about alcohol consumption, medicines they are taking, and drugs they may be taking without a prescription. Advise patients not to use AMBIEN CR if they drank alcohol that evening or before bed.

Tolerance, Abuse, and Dependence

Tell patients not to increase the dose of AMBIEN CR on their own, and to inform you if they believe the drug "does not work".

Administration Instructions

Patients should be counseled to take AMBIEN CR right before they get into bed and only when they are

able to stay in bed a full night (7–8 hours) before being active again. AMBIEN CR tablets should not be taken with or immediately after a meal. Advise patients NOT to take AMBIEN CR if they drank alcohol that evening.

MEDICATION GUIDE

AMBIEN CR[®] (ām'bē-īn see ahr)
(zolpidem tartrate extended-release)

Tablets C-IV

Read the Medication Guide that comes with AMBIEN CR before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about AMBIEN CR?

- **Do not take more AMBIEN CR than prescribed.**
- **Do not take AMBIEN CR unless you are able to stay in bed a full night (7 to 8 hours) before you must be active again.**
- **Take AMBIEN CR right before you get in bed, not sooner.**

AMBIEN CR may cause serious side effects that you may not know are happening to you. These side effects include:

- sleepiness during the day
- not thinking clearly
- act strangely, confused, or upset
- "sleep-walking" or doing other activities when you are asleep like:
 - eating
 - talking
 - having sex
 - driving a car

Call your healthcare provider right away if you find out that you have done any of the above activities after taking AMBIEN CR.

You should not drive a car or do things that require clear thinking the day after you take AMBIEN CR.

Do not take AMBIEN CR if you:

- drank alcohol that evening or before bed
- take other medicines that can make you sleepy. Taking AMBIEN CR with other drugs can cause side effects. Talk to your healthcare provider about all of your medicines. Your healthcare provider will tell you if you can take AMBIEN CR with your other medicines.
- cannot get a full night's sleep

What is AMBIEN CR?

AMBIEN CR is a sedative-hypnotic (sleep) medicine. AMBIEN CR is used in adults for the treatment of a sleep problem called insomnia. Symptoms of insomnia include:

- trouble falling asleep
- waking up often during the night

It is not known if AMBIEN CR is safe and effective in children under the age of 18 years.

AMBIEN CR is a federally controlled substance (C-IV) because it can be abused or lead to dependence. Keep AMBIEN CR in a safe place to prevent misuse and abuse. Selling or giving away AMBIEN CR may harm others, and is against the law. Tell your healthcare provider if you have ever abused or have been dependent on alcohol, prescription medicines or street drugs.

Who should not take AMBIEN CR?

- Do not take AMBIEN CR if you are allergic to zolpidem or any other ingredients in AMBIEN CR. See the end of this Medication Guide for a complete list of ingredients in AMBIEN CR.
- Do not take AMBIEN CR if you have had an allergic reaction to drugs containing zolpidem, such as Ambien, Edluar, Zolpimist, or Intermezzo.

Symptoms of a serious allergic reaction to zolpidem can include:

- swelling of your face, lips, and throat that may cause difficulty breathing or swallowing

What should I tell my healthcare provider before taking AMBIEN CR?

AMBIEN CR may not be right for you. Before starting AMBIEN CR, tell your healthcare provider about all of your health conditions, including if you:

- have a history of depression, mental illness, or suicidal thoughts
- have a history of drug or alcohol abuse or addiction
- have kidney or liver disease
- have a lung disease or breathing problems
- are pregnant, planning to become pregnant. It is not known if AMBIEN CR will harm your unborn baby.
- are breastfeeding or plan to breastfeed. AMBIEN CR can pass into your breast milk. It is not known if AMBIEN CR will harm your baby. Talk to your healthcare provider about the best way to feed your baby while you take AMBIEN CR.

Tell your healthcare provider about all of the medicines you take, including prescription and nonprescription medicines, vitamins and herbal supplements.

Medicines can interact with each other, sometimes causing serious side effects. **Do not take AMBIEN CR with other medicines that can make you sleepy unless your healthcare provider tells you to.**

Know the medicines you take. Keep a list of your medicines with you to show your healthcare provider and pharmacist each time you get a new medicine.

How should I take AMBIEN CR?

- See "**What is the most important information I should know about AMBIEN CR?**"
- Take AMBIEN CR exactly as prescribed. Only take 1 AMBIEN CR tablet a night if needed.
- Do not take AMBIEN CR if you drank alcohol that evening or before bed.
- You should not take AMBIEN CR with or right after a meal. AMBIEN CR may help you fall asleep faster if you take it on an empty stomach.
- Take AMBIEN CR Tablets whole. Do not break, crush, dissolve or chew AMBIEN CR tablets before swallowing. If you cannot swallow AMBIEN CR tablets whole, tell your healthcare provider. You may need a different medicine.
- Call your healthcare provider if your insomnia worsens or is not better within 7 to 10 days. This may mean that there is another condition causing your sleep problems.
- If you take too much AMBIEN CR or overdose, get emergency treatment.

What are the possible side effects of AMBIEN CR?

AMBIEN CR may cause serious side effects including:

- **getting out of bed while not being fully awake and doing an activity that you do not know you are doing.** (See "**What is the most important information I should know about AMBIEN CR?**")
- **abnormal thoughts and behavior.** Symptoms include more outgoing or aggressive behavior than normal, confusion, agitation, hallucinations, worsening of depression, and suicidal thoughts or actions.
- **memory loss**

- **anxiety**
- **severe allergic reactions.** Symptoms include swelling of the tongue or throat, trouble breathing, and nausea and vomiting. Get emergency medical help if you get these symptoms after taking AMBIEN CR.
- **falls, which may lead to severe injuries**

Call your healthcare provider right away if you have any of the above side effects or any other side effects that worry you while using AMBIEN CR.

The most common side effects of AMBIEN CR are:

- headache
- sleepiness
- dizziness
- drowsiness the next day after you take AMBIEN CR

After you stop taking a sleep medicine, you may have symptoms for 1 to 2 days such as:

- trouble sleeping
- nausea
- flushing
- lightheadedness
- uncontrolled crying
- vomiting
- stomach cramps
- panic attack
- nervousness
- stomach area pain

These are not all the side effects of AMBIEN CR. Ask your healthcare provider or pharmacist for more information.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store AMBIEN CR?

Store AMBIEN CR at room temperature, 59°F to 77°F (15°C to 25° C).

Keep AMBIEN CR and all medicines out of reach of children.

General Information about the safe and effective use of AMBIEN CR

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.

Do not use AMBIEN CR for a condition for which it was not prescribed. Do not share AMBIEN CR with other people, even if you think they have the same symptoms that you have. It may harm them and it is against the law.

This Medication Guide summarizes the most important information about AMBIEN CR. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about AMBIEN CR that is written for healthcare professionals.

For more information, go to www.ambienr.com or call 1-800-633-1610.

What are the ingredients in AMBIEN CR?

Active Ingredient: Zolpidem tartrate

Inactive Ingredients:

The 6.25 mg tablets contain: colloidal silicon dioxide, hypromellose, lactose monohydrate, magnesium

stearate, microcrystalline cellulose, polyethylene glycol, potassium bitartrate, red ferric oxide, sodium starch glycolate, and titanium dioxide.

The 12.5 mg tablets contain: colloidal silicon dioxide, FD&C Blue #2, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, potassium bitartrate, sodium starch glycolate, titanium dioxide, and yellow ferric oxide.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

sanofi-aventis U.S. LLC
Bridgewater, NJ 08807
A SANOFI COMPANY

October 2014

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PRINCIPAL DISPLAY PANEL - 6.25 mg Tablet Bottle Label

A-550

NDC 0024-5501-31

AMBIEN CR[®]

(ZOLPIDEM TARTRATE EXTENDED-RELEASE) CIV

6.25 mg Tablets

Dispense with Medication Guide

Rx only

100 Tablets

sanofi aventis

A-550 **NDC 0024-5501-31**

AMBIEN CR[®]
(ZOLPIDEM TARTRATE EXTENDED-RELEASE) CIV

6.25 mg Tablets

Dispense with Medication Guide

Rx only **100 Tablets**

sanofi aventis

**Store between 15°-25° C (59°-77°F).
Limited excursions permissible up to 30° C (86°F)**

Adult Dosage:
One tablet at bedtime as directed.
See complete prescribing information.

**Dispense in a tight, light-resistant,
child-resistant container.**

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For inquiries call 1-800-446-6267

Origin France
50093342

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00245 50131
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PRINCIPAL DISPLAY PANEL - 12.5 mg Tablet Bottle Label

A-552

NDC 0024-5521-31

AMBIEN CR[®]

(ZOLPIDEM TARTRATE EXTENDED-RELEASE) CIV

12.5 mg Tablets

Dispense with Medication Guide

Rx only

100 Tablets

sanofi aventis

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00245 52131
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A-552 **NDC 0024-5521-31**

AMBIENCR[®]
[ZOLPIDEM TARTRATE EXTENDED-RELEASE] TM

12.5 mg Tablets

Dispense with Medication Guide

Rx only **100 Tablets**

sanofi aventis

Store between 15° - 25° C (59° - 77°F).
Limited excursions permissible up to 30° C (86°F).

Adult Dosage:
One tablet at bedtime as directed.
See complete prescribing information.

Dispense in a tight, light-resistant, child-resistant container.

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Bridgewater, NJ 08807 ©2010 Origin France
For inquiries call 1-800-446-6267 50093344

AMBIEN CR

zolpidem tartrate tablet, coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0024-5501
Route of Administration	ORAL	DEA Schedule	CIV

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
zolpidem tartrate (UNII: WY6 W63843K) (zolpidem - UNII:7K383OQI23)	zolpidem tartrate	6.25 mg

Inactive Ingredients

Ingredient Name	Strength
silicon dioxide (UNII: ETJ7Z6XBU4)	
hypromellose, unspecified (UNII: 3NXW29V3WO)	
lactose monohydrate (UNII: EWQ57Q8I5X)	
magnesium stearate (UNII: 70097M6I30)	
microcrystalline cellulose (UNII: OP1R32D61U)	
polyethylene glycol, unspecified (UNII: 3WJQ0SDW1A)	
potassium bitartrate (UNII: NPT6P8P3UU)	
ferric oxide red (UNII: 1K09F3G675)	
titanium dioxide (UNII: 15FIX9V2JP)	

Product Characteristics

Color	PINK	Score	no score
Shape	ROUND (Bi-convex round)	Size	8mm
Flavor		Imprint Code	A;
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0024-5501-31	100 in 1 BOTTLE; Type 0: Not a Combination Product	09/19/2005	
2	NDC:0024-5501-10	3 in 1 CARTON	09/19/2005	
2		10 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA021774	09/19/2005	

AMBIEN CR

zolpidem tartrate tablet, coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0024-5521
Route of Administration	ORAL	DEA Schedule	CIV

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
zolpidem tartrate (UNII: WY6W63843K) (zolpidem - UNII:7K383OQI23)	zolpidem tartrate	12.5 mg

Inactive Ingredients

Ingredient Name	Strength
silicon dioxide (UNII: ETJ7Z6XBU4)	
FD&C Blue No. 2 (UNII: L06K8R7DQK)	
hypromellose, unspecified (UNII: 3NXW29V3WO)	
lactose monohydrate (UNII: EWQ57Q8I5X)	
magnesium stearate (UNII: 70097M6I30)	
microcrystalline cellulose (UNII: OP1R32D61U)	
polyethylene glycol, unspecified (UNII: 3WJQ0SDW1A)	
potassium bitartrate (UNII: NPT6P8P3UU)	
titanium dioxide (UNII: 15FIX9V2JP)	
ferric oxide yellow (UNII: EX438O2MRT)	

Product Characteristics				
Color	BLUE	Score	no score	
Shape	ROUND (Bi-convex round)	Size	8mm	
Flavor		Imprint Code	A;	
Contains				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0024-5521-31	100 in 1 BOTTLE; Type 0: Not a Combination Product	09/19/2005	
2	NDC:0024-5521-50	500 in 1 BOTTLE; Type 0: Not a Combination Product	09/19/2005	
3	NDC:0024-5521-10	3 in 1 CARTON	09/19/2005	
3		10 in 1 BLISTER PACK; Type 0: Not a Combination Product		
Marketing Information				
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date	
NDA	NDA021774	09/19/2005		

Labeler - sanofi-aventis U.S. LLC (824676584)

Establishment

Name	Address	ID/FEI	Business Operations
Sano fi Winthrop Industrie		571879985	MANUFACTURE(0024-5501) , ANALYSIS(0024-5501) , LABEL(0024-5501) , PACK(0024-5501)

Establishment

Name	Address	ID/FEI	Business Operations
sano fi-aventis U.S. LLC		011330557	LABEL(0024-5501, 0024-5521) , PACK(0024-5501, 0024-5521)

Revised: 3/2017

sanofi-aventis U.S. LLC