INDICATIONS AND USAGE
AMI BIEN® (zolpidem tartrate) tablets, for oral use, C-IV
Initial U.S. Approval: 1992

Recent Major Changes
Warnings and Precautions, CNS Depressant Effects and Next-Day Impairment (5.1) 02/2019

1 INDICATIONS AND USAGE
AMI BIEN®, a gamma-aminobutyric acid (GABA) A receptor positive modulator, is indicated for the short-term treatment of insomnia characterized by difficulties with sleep initiation. (1)

DOSAGE AND ADMINISTRATION
• Use the lowest dose effective for the patient and must not exceed a total of 10 mg daily (2.1)
• Recommended initial dose is a single dose of 5 mg for women and a single dose of 5 or 10 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 5 mg for men and women (2.2)
• Lower doses of CNS depressants may be necessary when taken concomitantly with AMBIEN (2.3)
• The effect of AMBIEN may be slowed if taken with or immediately after a meal (2.4)

Dosage Forms and Strengths
5 mg and 10 mg tablets. Tablets not scored. (3)

Contraindications
CNS-depressant effects: Impairs alertness and motor coordination. Instruct patients on correct use. (5.1)
Need to evaluate for comorbid diagnoses: Re-evaluate if insomnia persists after 7 to 10 days of use. (5.2)

2 DOSAGE AND ADMINISTRATION

2.1 Dosage in Adults
Recommended initial dose is a single dose of 5 mg for women and a single dose of 5 or 10 mg for men, immediately before bedtime with at least 7–8 hours remaining before the planned time of awakening. If the 5 mg dose is not effective, the dose can be increased to 10 mg. In some patients, the higher morning blood levels following use of the 10 mg dose may increase the risk of next-day impairment of driving and other activities that require full alertness [see 17 for PATIENT COUNSELING INFORMATION and Medication Guide Revised: 02/2019]

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1 INDICATIONS AND USAGE
AMI BIEN® (zolpidem tartrate) is indicated for the short-term treatment of insomnia characterized by difficulties with sleep initiation. AMBIEN has been shown to decrease sleep latency for up to 35 days in controlled clinical studies [see Clinical Studies (14)]. The clinical trials performed in support of efficacy were 4–5 weeks in duration with the final formal assessments of sleep latency performed at the end of treatment.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage in Adults
Use the lowest effective dose for the patient. The recommended initial dose is 5 mg for women and either 5 or 10 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 5 mg dose is not effective, the dose can be increased to 10 mg. In some patients, the higher morning blood levels following use of the 10 mg dose may increase the risk of next-day impairment of driving and other activities that require full alertness [see

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
8.2 Lactation

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed
Warnings and Precautions (5.1). The fatal dose of AMBIEN should not exceed 10 mg once daily immediately before bedtime. AMBIEN should be taken as a single dose and should not be administered 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. The recommended dose of AMBIEN in these patients is 5 mg once daily immediately before bedtime [see Warnings and Precautions (5.1), Use in Specific Populations (8.5)].

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 is prescribed for patients with pre-existing respiratory impairment. Postmarketing 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 in patients with respiratory impairment including sleep apnea and myasthenia gravis.

5.3 Severe Anaphylactic and Anaphylactoid Reactions

Patients with mild to moderate hepatic impairment do not clear the drug as rapidly as normal subjects. Avoid AMBIEN 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)].

5.4 Abnormal Thinking and Behavioral Changes

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 other CNS depressants increases the risk of such behaviors, as does the use of AMBIEN at doses exceeding the maximum recommended dose. Due to the risk to the patient and the community, discontinuation of AMBIEN should be strongly considered for patients who report a “sleep-driving” episode.

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 dose of 10 mg of zolpidem administered at bedtime in the Total-Arousal Index, together with a reduction in lowest oxygen saturation, and increase in the times of oxygen desaturation below 90% 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 is prescribed for patients with pre-existing respiratory impairment. Postmarketing 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 in patients with respiratory impairment including sleep apnea and myasthenia gravis.

5.7 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 zolpidem tartrate as rapidly as patients with normal hepatic function. Avoid AMBIEN 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, 9.3)].

6. ADVERSE REACTIONS

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

- Sedative-hypnotic 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)]
- Hypersensitivity effects [see Warnings and Precautions (5.5)]

6.1 Clinical Trials Experience

Associated with Discontinuation of Treatment

Approximately 4% of 1,701 patients who received zolpidem at all doses (1.25 to 90 mg) in U.S. premarketing clinical trials discontinued treatment because of an adverse reaction. Reactions most commonly associated with discontinuation were sleep-driving (7%), daytime drowsiness (6%), dizziness (5%), and falls (4%).

Approximately 4% of 1,959 patients who received zolpidem at all doses (1 to 50 mg) in similar foreign trials discontinued treatment because of an adverse reaction. Reactions most commonly associated with discontinuation from these trials were daytime drowsiness (11%), dizziness/vertigo (6%), nausea (5%), headache (4.5%), and falls (4%).

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=50) were associated with impaired concentration, continuing or aggravated depression, and manic reaction; one patient treated with placebo (n=97) was discontinued after a suicide attempt.

Most Commonly Observed Adverse Reactions in Controlled Trials

Table 1: Incidences of Treatment-Emergent Adverse Reactions in Placebo-Controlled Clinical Trials Lasting up to 10 Nights (percentage of patients reporting)

<table>
<thead>
<tr>
<th>Body System</th>
<th>Placebo (N=473)</th>
<th>Zolpidem (N=685)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Central and Peripheral Nervous System

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo (N=473)</th>
<th>Zolpidem (N=685)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Placebo

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo (N=473)</th>
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<tr>
<td>Headache</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
Reactions reported by at least 1% of patients treated with AMBIEN and at a greater frequency than placebo.

The following table was derived from results of three placebo-controlled long-term efficacy trials involving AMBIEN (zolpidem tartrate). These trials involved patients with chronic insomnia who were treated for 28 to 35 nights with zolpidem at doses of 5, 10, or 15 mg. The table is limited to data from doses up to and including 10 mg, the highest dose recommended for use. The table includes only adverse events occurring at an incidence of at least 1% for zolpidem patients.

To emphasize that, although the events reported did occur during treatment with AMBIEN, they were not necessarily caused by it.

### Table 1: Incidences of Treatment-Emergent Adverse Reactions in Placebo-Controlled Clinical Trials Lasting up to 10 Nights (percentage of patients reporting) (continued)

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>Zolpidem (&lt;10 mg) (N=685)</th>
<th>Placebo (N=773)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal System</td>
<td>Diarrhea</td>
<td>1</td>
<td>-</td>
</tr>
</tbody>
</table>

### Table 2: Incidence of Treatment-Emergent Adverse Experiences in Placebo-Controlled Clinical Trials Lasting up to 35 Nights (percentage of patients reporting)

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Event</th>
<th>Zolpidem (&lt;10 mg) (N=152)</th>
<th>Placebo (N=161)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autonomic Nervous System</td>
<td>Dry mouth</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Body as a Whole</td>
<td>Allergy</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Back Pain</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Influenza-like symptoms</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Cardiovascular System</td>
<td>Chest pain</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Palpitation</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Drowsiness</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Lethargy</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Drugged feeling</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Lightheadedness</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Depression</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Abnormal dreams</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Anemia</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Sleep disorder</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Gastrointestinal System</td>
<td>Diarrhea</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory System</td>
<td>Sinusitis</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Pharyngitis</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Skin and Appendages</td>
<td>Rash</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

*Reactions reported by at least 1% of patients treated with AMBIEN and at a greater frequency than placebo.

**Drugs that Effect 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.
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 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/kg/day, which are approximately 5, 25, and 120 times the maximum recommended human dose (MRHD) of 10 mg/day (8 mg zolpidem base) based on mg/m^2 body surface area, caused delayed fetal development (incomplete fetal skeleton ossification) at maternally toxic (ataxia) doses 25 and 120 times the MRHD based on mg/m^2 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 2.5, 10, and 40 times the MRHD of 10 mg/day (8 mg zolpidem base) based on mg/m^2 body surface area caused embryofetal death and delayed fetal development (incomplete fetal skeletal ossification) at a maternally toxic (decreased body weight gain) dose 40 times the MRHD based on mg/m^2 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 5, 25, and 120 times the MRHD of 10 mg/day (8 mg zolpidem base) based on mg/m^2 body surface area caused delayed offspring growth and decreased survival at doses 25 and 120 times, respectively, the MRHD based on mg/m^2 body surface area.

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 breast milk [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 and any potential adverse effects on the breastfed infant from AMBIEN or from the underlying maternal condition.

Clinical Considerations

Infants exposed to AMBIEN through breast milk 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 administration in order to minimize drug exposure to a breast fed infant.

8.4 Pediatric Use

AMBIEN 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 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.

8.5 Geriatric Use

A total of 154 patients in U.S. controlled clinical trials and 897 patients in non-U.S. clinical trials who received zolpidem were ≥60 years of age. For a pool of U.S. patients receiving zolpidem at doses of ≤10 mg or placebo, there were three adverse reactions occurring at an incidence of at least 3% for zolpidem and for which the zolpidem incidence was at least twice the placebo incidence (i.e., they could be considered drug related).

A total of 30,959 (1.5%) non-U.S. patients receiving zolpidem reported falls, including 28,830 (93%) who were <70 years of age. Of these 28 patients, 23 (82%) were receiving zolpidem doses >10 mg. A total of 241,959 (1.2%) non-U.S. patients receiving zolpidem reported confusion, including 18,24 (7%) who were ≥70 years of age. Of these 18 patients, 14 (78%) were receiving zolpidem doses >10 mg.

The dose of AMBIEN in elderly patients is 5 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. Cmax and AUC parameters of zolpidem were approximately 45% higher at the same dose in female subjects compared with male subjects. Differences in other blood levels of zolpidem in rats in vivo compared to men at a given dose, the recommended initial dose of AMBIEN for adult women is 5 mg, and the recommended dose for adult men is 5 or 10 mg.

In geriatric patients, clearance of zolpidem is similar in men and women. The recommended dose of AMBIEN in geriatric patients is 5 mg regardless of gender.

8.7 Hepatic Impairment

The recommended dose of AMBIEN in patients with mild to moderate hepatic impairment is 5 mg once daily immediately before bedtime. Avoid AMBIEN 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 was difficult to distinguish from placebo.

Because persons with a history of addiction to, or abuse of, drugs or alcohol are at increased risk for 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. Postmarketing 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 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.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Zolpidem</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3%</td>
<td>1%</td>
</tr>
</tbody>
</table>
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.

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

It has the following in vitro ingredients: hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, and titanium dioxide. The 5 mg tablet also contains FD&C Red No. 40, iron oxide colorent, and polysorbate 80.

11. DESCRIPTION

11.1 Mechanism of Action

Zolpidem is a GABA A receptor positive modulator presumed to exert its therapeutic effects in the neuronal excitation.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Zolpidem is a GABA A receptor positive modulator presumed to exert its therapeutic effects in the neuronal excitation.

12.2 Pharmacokinetics

The pharmacokinetic profile of AMBIEN is characterized by rapid absorption from the gastrointestinal tract and a short elimination half-life (T 1/2) in healthy subjects.

In a single-dose crossover study in 45 healthy subjects administered 5 and 10 mg zolpidem tartrate tablets, the mean peak concentrations (C max) were 59 (range: 29 to 113) and 121 (range: 58 to 272 ng/mL) respectively, occurring at a mean time (T max) of 1.6 hours for both. The mean AMBIEN elimination half-life was 2.6 (range: 1.4 to 4.5) and 2.5 (range: 1.4 to 3.8) hours, for the 5 and 10 mg tablets, respectively. AMBIEN is converted to inactive metabolites that are eliminated primarily by renal excretion. AMBIEN is metabolized by CYP3A4 and CYP2C19 to form the active metabolite, zolpidem, which is contained in the concentrations containing AMBIEN 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 5HT1A, adrenergic, histaminergic or muscarinic receptors.

12.3 Pharmacokinetics

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12.4 Clinical Studies

12.4.1 Transient Insomnia

Normal adults experiencing transient insomnia (n=462) during the first night in a sleep laboratory were studied in a double-blind, parallel group, single-night trial comparing four doses of zolpidem (7.5 and 15 mg) and placebo. Zolpidem was not hemiactive 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. Rifaxim, a CYP3A4 inducer, significantly reduced the exposure to and the pharmacodynamic effects of zolpidem [see Drug Interactions (7.2)].

Zolpidem had no effect on diogen pharmacokinetics and did not affect prothrombin time when given with warfarin in healthy subjects.
non-elderly patients with insomnia did not detect evidence of next-day residual effects using the DSST, the Multiple Sleep Latency Test (MSLT), and patient ratings of alertness.

**Rebound Effects**

There was no objective (polysomnographic) evidence of rebound insomnia at recommended doses seen in studies evaluating sleep on the nights following discontinuation of AMBIEN (zolpidem tartrate). There was subjective evidence of impaired sleep in the elderly on the first post-treatment night at doses above the recommended elderly dose of 5 mg.

**Memory Impairment**

Controlled studies in adults utilizing objective measures of memory yielded no consistent evidence of next-day memory impairment following the administration of AMBIEN. However, in one study involving zolpidem doses of 10 and 20 mg, there was a significant decrease in next-day recall of information presented to subjects during peak drug effect (90 minutes post dose), i.e., these subjects experienced anterograde amnesia. There was also subjective evidence from adverse event data for anterograde amnesia occurring in association with the administration of AMBIEN, predominantly at doses above 10 mg.

**Effects on Sleep Stages**

In studies that measured the percentage of sleep time spent in each sleep stage, AMBIEN has generally been shown to preserve sleep stages. Sleep time spent in stages 3 and 4 (deep sleep) was found comparable to placebo with only inconsistent, minor changes in REM (paradoxical) sleep at the recommended dose.

16 HOW SUPPLIED/STORAGE AND HANDLING

AMBIEN 5 mg tablets are capsule-shaped, pink, film coated, with AMB 5 debossed on one side and 5401 on the other and supplied as:

<table>
<thead>
<tr>
<th>NDC Number</th>
<th>Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>0024-5401-31</td>
<td>bottle of 100</td>
</tr>
</tbody>
</table>

AMBIEN 10 mg tablets are capsule-shaped, white, film coated, with AMB 10 debossed on one side and 5421 on the other and supplied as:

<table>
<thead>
<tr>
<th>NDC Number</th>
<th>Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>0024-5421-31</td>
<td>bottle of 100</td>
</tr>
</tbody>
</table>

Store at controlled room temperature 20°C–25°C (68°F–77°F).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

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

**CNS-Depressant Effects and Next-Day Impairment**

Tell patients that AMBIEN has the potential to cause next-day impairment, and that this risk is increased if dosing instructions are not carefully followed. Tell patients to wait for at least 8 hours after dosing before driving or engaging in other activities requiring full mental alertness. Inform patients that impairment can be present despite feeling fully awake. Advise patients that increased drowsiness and decreased consciousness may increase the risk of falls in some patients.

**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 if they drank alcohol that evening or before bed.

**Tolerance, Abuse, and Dependence**

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

**Administration Instructions**

Patients should be counseled to take AMBIEN right before they get into bed and only when they are able to stay in bed a full night (7 to 8 hours) before they must be active again. AMBIEN tablets should not be taken with or immediately after a meal. Advise patients NOT to take AMBIEN if they drank alcohol that evening.

**Pregnancy**

Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during treatment with AMBIEN. Advise patients that use of AMBIEN late in the third trimester may cause respiratory depression and sedation in neonates. Advise mothers who used AMBIEN during the late third trimester of pregnancy to monitor neonates for signs of sleepiness (more than usual), breathing difficulties, or limpness [see Use in Specific Populations (8.3)].

**Lactation**

Advise breastfeeding mothers using AMBIEN to monitor infants for increased sleepiness, breathing difficulties, or limpness. Instruct breastfeeding mothers to seek immediate medical care if they notice these signs. A lactating woman may consider pumping and discarding breastmilk during treatment and for 23 hours after AMBIEN administration to minimize drug exposure to a breastfed infant [see Use in Specific Populations (8.2)].

**MEDICATION GUIDE**

AMBIEN® (am-bé-on) (zolpidem tartrate) tablets C-IV

Read the Medication Guide that comes with AMBIEN 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?**

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

AMBIEN may cause serious side effects, including:

- After taking AMBIEN, you may get up out of bed while not being fully awake and do an activity that you do not know you are doing. The next morning, you may not remember that you did anything during the night. You have a higher chance for doing these activities if you drink alcohol or take other medicines that make you sleepy with AMBIEN. Reported activities include:
  - driving a car (“sleep-driving”)
  - making and eating food
  - talking on the phone
  - having sex
  - sleep-walking

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

- do not take AMBIEN if you:
  - drank alcohol that evening or before bed
  - took another medicine to help you sleep

**What is AMBIEN?**

AMBIEN is a sedative-hypnotic (sleep) medicine. AMBIEN is used in adults for the short-term treatment of a sleep problem called insomnia (trouble falling asleep).

AMBIEN is not recommended for use in children under the age of 18 years.

AMBIEN is a federally controlled substance (C-IV) because it can be abused or lead to dependence. Keep AMBIEN in a safe place to prevent misuse and abuse. Selling or giving away AMBIEN 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?**

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

AMBIEN may not be right for you. Before starting AMBIEN, 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. Talk to your healthcare provider about the risk to your unborn baby if you take AMBIEN.
- Using AMBIEN in the last trimester of pregnancy may cause breathing difficulties or excess sleepiness in your newborn. Monitor for signs of sleepiness (more than usual), trouble breathing, or limpness in the newborn if AMBIEN is taken late in pregnancy.
• are breastfeeding or plan to breastfeed. AMBIEN passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby while you take AMBIEN.

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 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?
• See “What is the most important information I should know about AMBIEN?”
• Take AMBIEN exactly as prescribed. Only take 1 AMBIEN tablet a night if needed.
• Do not take AMBIEN if you drank alcohol that evening or before bed.
• You should not take AMBIEN with or right after a meal. AMBIEN may help you fall asleep faster if you take it on an empty stomach.
• 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 problem.
• If you take too much AMBIEN or overdose, get emergency treatment.

What are the possible side effects of AMBIEN?
AMBIEN may cause serious side effects, including:
• getting out of bed while not being fully awake and do an activity that you do not know you are doing. See “What is the most important information I should know about AMBIEN?”
• 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, and trouble breathing. Get emergency medical help if you get these symptoms after taking AMBIEN.

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.
The most common side effects of AMBIEN are:
• drowsiness
• dizziness
• diarrhea
• groginess or feeling as if you have been drugged

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. Ask your healthcare provider or pharmacist for more information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1–800–FDA–1088.

How should I store AMBIEN?
• Store AMBIEN at room temperature, 68°F to 77°F (20°C to 25°C).
Keep AMBIEN and all medicines out of reach of children.

General Information about the safe and effective use of AMBIEN
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use AMBIEN for a condition for which it was not prescribed. Do not share AMBIEN with other people, even if 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. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about AMBIEN that is written for healthcare professionals.

For more information, call 1-800-633-1610.

What are the ingredients in AMBIEN?
Active Ingredient: Zolpidem tartrate
Inactive Ingredients: hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, and titanium dioxide. In addition, the 5 mg tablet contains FD&C Red No. 40, iron oxide colorant, and polysorbate 80.

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

Revised: February 2019

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