WARNINGS AND PRECAUTIONS

• CNS-Depressant Effects: Impaired alertness and motor coordination, including risk of morning impairment. Risk increases with dose and use with other CNS depressants and alcohol. Caution patients against driving and other activities requiring complete mental alertness the morning after use. (5.2)

• Need to Evaluate for Comorbid Diagnoses: Re-evaluate if insomnia persists after 7 to 10 days of use. (5.3)

• Severe Anaphylactic/Anaphylactoid Reactions: Angioedema and anaphylaxis have been reported. Do not rechallenge if such reactions occur. (5.4)

• Abnormal Thinking and Behavioral Changes: Changes including decreased inhibition, bizarre behavior, agitation, and depersonalization have been reported. Immediately evaluate any new onset behavioral changes. (5.5)

• Depression: Worsening of depression or suicidal thinking may occur. Prescribe the least amount of tablets feasible to avoid intentional overdose. (5.6)

• Respiratory Depression: Consider this risk before prescribing in patients with compromised respiratory function. (5.7)

• Hepatic Impairment: Avoid AMBIEN CR use in patients with severe hepatic impairment. (5.8)

• Withdrawal Effects: Symptoms may occur with rapid dose reduction or discontinuation. (5.9, 9.3)

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 1-800-623-1610 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

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

2 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)

3 DOSAGE FORMS AND STRENGTHS

Extended-Release Tablets: 6.25 mg and 12.5 mg. Tablets not scored. (3)

4 CONTRAINDICATIONS

Patients who have experienced complex sleep behaviors after taking AMBIEN CR (4)

5 WARNINGS AND PRECAUTIONS

• Known hypersensitivity to zolpidem (4)

6 ADVERSE REACTIONS

• Headache, next-day somnolence and dizziness (6.1)

7 DRUG INTERACTIONS

• CNS depressants, including alcohol: Possible adverse additive CNS-depressant effects (5.2, 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)

8 USE IN SPECIFIC POPULATIONS

• Pregnancy: May cause respiratory depression and sedation in neonates with exposure late in the third trimester. (8.1)

• Lactation: A lactating woman may pump and discard breast milk during treatment and for 23 hours after AMBIEN CR administration. (8.2)

• 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. (5.5, 8.4)

9 DRUG ABUSE AND DEPENDENCE

• Controlled Substance (9.1)

10 OVERDOSAGE

• Signs and Symptoms (10.1)

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

13 NONCLINICAL TOXICOLOGY

14 CLINICAL STUDIES

15 HOW SUPPLIED/STORAGE AND HANDLING

16 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed
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 after therapy. In order to minimize this risk a full night of sleep (7–8 hours) is recommended.

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

5.3 Need to Evaluate for Comorbid Diagnoses

Because sleep disturbances may be the presenting manifestation of a physical or psychiatric disorder, symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient. If AMBIEN CR is used for 5 to 7 days of treatment in the absence of the presence of a primary psychiatric 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/hypnotics, including zolpidem.

5.4 Severe Anaphylactich and Anaphylactoid Reactions

Cases of anaphylactoid 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 may have required medical therapy in the emergency department. If anaphylaxis involves the throat, glottis or larynx, airway obstruction may occur and be fatal. Patients who develop anaphylaxis after treatment with zolpidem should not be rechallenged with the drug.

5.5 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 depersonification. 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 CR 0.25 mg/kg taken at bedtime reported hallucinations versus 0% treated with placebo [see Use in Specific Populations (8.4)].

5.6 Use in Patients with Depression

In primarily depressed patients treated with sedative-hypnotics, worsening of depression, and suicidal thoughts and actions (including completed suicides), have been reported. Suicidal tendencies may be present in such patients and protective measures may be required. Intentional 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.

5.7 Respiratory Depression

Although studies with 10 mg zolpidem tartrate did not reveal respiratory depressant effects at hypnotic doses in healthy subjects or in patients with mild to moderate chronic obstructive pulmonary disease (COPD), a reduction in the Total Arousal Index, together with a reduction in lowest oxygen saturation and increase in the times of oxygen desaturation below 80% and 90%, was observed in patients with sleep apnea. AMBIEN CR should be avoided in patients who require 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. 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 CR in patients with respiratory impairment including sleep apnea and myasthenia gravis.

5.8 Precipitation of Hepatic Encephalopathy

In patients with severe liver impairment, hepatic coma has been reported with the use of zolpidem. The concomitant use of AMBIEN CR with other CNS depressants or alcohol, or coadministration 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), Clinical Pharmacology (12.3)].

5.9 Withdrawal Effects

There have been reports of withdrawal signs and symptoms following the rapid dose decrease or abrupt discontinuation of zolpidem. Monitor patients for tolerance, abuse, and dependence [see Drug Abuse and Dependence (9.2, 9.3)].

6 ADVERSE REACTIONS

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

• Complex Sleep Behaviors [see Warnings and Precautions (5.1)]
• CNS-Depressant Effects and Next-Day Impairment [see Warnings and Precautions (5.2)]
• Serious Anaphylactphic and Anaphylactoid Reactions [see Warnings and Precautions (5.4)]
• Abnormal Thinking and Behavior Changes [see Warnings and Precautions (5.5)]
• Withdrawal Effects [see Warnings and Precautions (5.9)]

6.1 Clinical Trials Experience

Compared with placebo, patients given zolpidem tartrate at therapeutic doses, have been associated with precipitation of hepatic encephalopathy in patients with hepatic insufficiency. In addition, patients with hepatic insufficiency do not clear zolpidem 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 Use in Specific Populations (8.7), Clinical Pharmacology (12.3)].

6.2 US Experience

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 0.3% (3/953) placebo. The 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 event. The most frequently associated with discontinuation of AMBIEN CR included anxiety, agitation, increased blood pressure, and agitation [see Warnings and Precautions (5.1)].

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 ≥1% in Controlled Trials

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

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

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

<table>
<thead>
<tr>
<th>Body System Adverse Reaction†</th>
<th>AMBIEN CR 12.5 mg (N=102)</th>
<th>Placebo (N=110)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Labyrinthitis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appetite disorder</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hallucinations†</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Disorientation</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Anxiety</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Depression</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Psychomotor retardation</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Binge eating</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Depersonalization</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Disinhibition</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Euphoric mood</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Mood swings</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Stress symptoms</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>19</td>
<td>16</td>
</tr>
<tr>
<td>Somnolence</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>Dizziness</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Memory disorders²</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Balance disorder</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Disturbance in attention</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Hypoesthesia</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Ataxia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual disturbance</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Eye redness</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Altered visual depth perception</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Asthenia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vertigo</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>φ</td>
<td></td>
</tr>
<tr>
<td>Throat irritation</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Constipation</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal tenderness</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Frequent bowel movements</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Skin wrinkling</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Urticaria</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Myalgia</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Neck pain</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menorrhagia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Asthenia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Chest discomfort</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure increased</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Body temperature increased</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contusion</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Social circumstances</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposure to poisonous plant</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

*Reactions reported by at least 1% of patients treated with AMBIEN CR and at greater frequency than in the placebo group.
†Hallucinations included hallucinations NOS as well as visual and hypnagogic hallucinations.
‡Memory disorders include: memory impairment, amnesia, anterograde amnesia.

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

<table>
<thead>
<tr>
<th>Body System Adverse Reaction†</th>
<th>AMBIEN CR 6.25 mg (N=99)</th>
<th>Placebo (N=106)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Lower respiratory tract infection</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Otitis externa</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menorrhagia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Psychomotor retardation</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Apathy</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Depression</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
Adverse Events Observed during the Premarketing Evaluation of Immediate-Release Zolpidem Tartrate

Immediate-release zolpidem tartrate, which are listed below.

It is necessarily caused by it.

and classified utilizing a modified World Health Organization (WHO) dictionary of preferred terms.

meaningful estimate of the proportion of individuals experiencing treatment-emergent adverse events,

to provide a participation were recorded by clinical investigators using terminology of their own choosing.

To Immediate-release zolpidem tartrate was administered to 3,660 subjects in clinical trials throughout the

Discussion

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of AMBIEN CR. Because

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 participa-
tion 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 (WH0) 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 1/10,000 patients; rare

events are those occurring in less than 1/10,000 patients.

Autonomic nervous system: Frequent: dry mouth. Infrequent: increased sweating, pallor, postural

hypotension, syncope. Rare: abnormal accommodation, altered saliva, flushing, glaucoma, hypoten-

sion, impotence, increased salvia, tenesmus.


Rare: allergic reaction, allergy aggravated, anaphylactic shock, face edema, hot flashes, increased

ESR, pain, restless legs, rashes, tolerance increased, weight decrease.

Cardiovascular system: Frequent: cerebrovascular disorder, hypertension, tachycardia. Rare: angina

pectoris, arrhythmia, arthritis, circulatory failure, extrapyelus, hypertension aggravated, myocardial

infarction, prieibis, pulmonary embolism, pulmonary edema, varicoses 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, hypotension, illusion, leg

cramps, migraine, nervousness, paresthesia, sleepiness (after daytime dosing), speech disorder, stupor,
tremor. Rare: abnormal gait, abnormal thinking, aggression, apathy, agitation increased, decreased

libido, delusion, dementia, depersonalization, dysphasia, feeling strange, hypokinesia, hypotonia,

hyponatraemia, intoxicated feeling, maniac reaction, neuragia, neuriitis, neuropathy, neuritis, panic

attacks, paranoia, personality disorder, somnambulism, suicide attempts, tetany, yawning.

Gastrointestinal system: Frequent: diarrhea, dyspepsia, hiccup. Infrequent: anorexia, constipation,
dysphagia, flatulence, gastroenteritis. Rare: anorhesis, eructation, esophagospasm, gastritis, hemorrhoids,

intestinal obstruction, rectal hemorrhage, tooth canines.

Hematologic and lymphatic system: Frequent: anemia, hyperhemoglobulinemia, leukopenia, lympho-

openia, macrocytic anemia, purpura, thrombosis.

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

otitis media.

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

increased SGOT.

Metabolic and nutritional: Frequent: hyperglycemia, thirst. Rare: glycosuria, hypercholesterolemia,

hyperlipidemia, increased alkaline phosphatase, increased BUN, peribiliar edema.

Musculoskeletal system: Frequent: arthrisis. Rare: arthrosis, muscle weakness, sciatica, tendinitis.

Reproductive system: Frequent: menstrual disorder, vaginitis. Rare: breast fibroadenosis, breast

necrosis, breast pain.

Respiratory system: Frequent: sinusitis. Infrequent: bronchitis, coughing, dyspnea. Rare: bronchos-

pasm, respiratory depression, epistaxis, hypoxia, laryngitis, pneumonia.

Skin and appendages: Frequent: pruritus. Rare: acne, bullous eruption, dermatitis, furunculosis,

injection-site inflammation, photosensitivity reaction, urticaria.

Special senses: Frequent: diplopia, vision abnormal. Infrequent: eye irritation, eye pain, scintillae,
taste perversions, 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.

7.2 Drugs that Affect Drug Metabolism via Cytochrome P450

Some compounds known to induce or inhibit CYP3A4 may affect exposure to zolpidem. The effect

of drugs that induce or inhibit other P450 enzymes on the exposure to zolpidem is not known.

CYP2D6 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)].
The blood level 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.

9.7 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 (5.1), Clinical Pharmacology (12.3)].

9.8 Abuse and Dependence

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 to 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 the extent that the desired and undesired effects of drugs may change at different rates for different effects.

Abuse or 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.

9.9 Management of Overdose

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). 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 excitement 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) receptor positive modulator of the imidazopyridine class. AMBIEN CR (zolpidem tartrate) extended-release tablets is available in 6.25 mg and 12.5 mg strength tablets for oral administration. Chemically, zolpidem is N,N,N,N-tetrahydropyrimidin-2(1H)-yl pyridine-3-acetamide L- (+)-tartrate (2:1).

It has the following structure:

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The following are the side effects of zolpidem: dizziness, headache, nausea, vomiting, sweating, and restlessness.
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 is a GABA A receptor positive modulator presumed to exert its therapeutic effects in the short-term treatment of insomnia through binding to the benzodiazepine site of α1 subunit containing GABA A receptors, increasing the frequency of chloride channel opening resulting in the inhibition of neuronal excitation.

12.2 Pharmacodynamics
Zolpidem binds to GABA A receptors with greater affinity for α1 subunit relative to α2 and α3 subunit containing receptors. Zolpidem has no appreciable binding affinity for α5 subunit containing GABA A receptors. This binding profile may explain the relative absence of myorelaxant effects in animal studies. Zolpidem has no appreciable binding affinity for dopaminergic D2, serotonergic 5HT, adrenergic, histaminergic or muscarinic receptors.

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 (Cmax) of zolpidem was 134 ng/mL (range: 88.9 to 197 ng/mL) occurring at a median time (Tmax) 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 Cmax and Tmax were decreased by 23% and 30%, respectively, while median Tmax 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 ± 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 (Cmax) of zolpidem was 76.6 (range: 35.0 to 161) ng/mL occurring at a median time (Tmax) of 2.0 hours. The mean AUC of zolpidem was 413 ng·hr/mL (range: 124 to 1190 ng·hr/mL) and the mean elimination half-life was 2.9 hours (range: 1.59 to 5.50 hours).

**Hepatic Impairment**
AMBIEN CR was not studied in patients with hepatic impairment. The pharmacokinetics of an immediate-release formulation of zolpidem tartrate in eight patients with chronic hepatic insufficiency was compared to results in healthy subjects. Following a single 20 mg oral zolpidem tartrate dose, mean Cmax and AUC were found to be two times (250 vs 495 ng/mL) and five times (788 vs 4,203 ng·hr/mL) higher, respectively, in hepatically compromised patients. Tmax 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: 1.8 to 2.4 hr) [see Dosage and Administration (2.2), Warnings and Precautions (5.8), 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 CLCR = 6.5 ± 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 Cmax, Tmax, half-life, and AUC between the first and last day of drug administration (range concentration 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 objective measures (polysomnographic recordings) of sleep induction (by decreasing LPS) during the first 2 nights of treatment and after 2 weeks of 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 extended-release tablets are composed of two layers

and are coated, pink, round, biconvex, debossed with A- on one side and supplied as:

NDC Number Size
0024-5501-31 bottle of 100

AMBIEN CR 12.5 mg extended-release tablets are composed of two layers

and are coated, blue, round, biconvex, debossed with A- on one side and supplied as:

NDC Number Size
0024-5521-31 bottle of 100

1 Layers are covered by the coating and are indistinguishable.


17 PATIENT COUNSELING INFORMATION

Advis 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 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.

Complex Sleep Behaviors

Instruct patients and their families that AMBIEN CR may cause complex sleep behaviors, including sleepwalking, sleep-driving, preparing and eating food, making phone calls, or having sex while not being fully awake. Serious injuries and death have occurred during complex sleep behavior episodes. Tell patients to discontinue AMBIEN CR and notify their healthcare provider immediately if they develop any of these symptoms (see Boxed Warning, Warnings and Precautions [5.1]).

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. Advise patients that increased drowsiness and decreased consciousness may increase the risk of falls in some patients (see Warnings and Precautions [5.2]).

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 (see Warnings and Precautions [5.4]).

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.

Pregnancy

Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during treatment with AMBIEN CR. Advise patients that use of AMBIEN CR late in the third trimester may cause respiratory depression and sedation in neonates. Advise mothers who used AMBIEN CR during the late trimester of pregnancy to monitor neonates for signs of sleepiness (more than usual), breathing difficulties, or limpness (see Use in Specific Populations [8.1]).

Lactation

Advise breastfeeding mothers using AMBIEN CR to monitor infants for increased sleepiness (more than usual), 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 CR administration to minimize drug exposure to a breastfed infant (see Use in Specific Populations [8.2]).

MEDICATION GUIDE

AMBIEN CR® (äm-bë-on see ahr) (zolpidem tartrate) extended-release tablets C-IV

Read the Medication Guide that comes with AMBIEN CR before you start 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 including complex sleep behaviors that have caused serious injury and death. After taking AMBIEN CR, you may get up out of bed while not being fully awake and do an activity that you do not know you are doing (complex sleep behaviors). The next morning, you may not remember that you did anything during the night. These activities may occur with AMBIEN CR whether or not you drink alcohol or take other medicines that make you sleepy. Reported activities include:

  o driving a car (“sleep-driving")
  o making and eating food
  o talking on the phone
  o having sex
  o sleep-walking

Stop taking AMBIEN CR and 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:

• have ever experienced a complex sleep behavior (such as driving a car, making and eating food, talking on the phone, or having sex while not being fully awake) after taking AMBIEN CR.
• 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:

  o trouble falling asleep
  o waking up often during the night

AMBIEN CR is not recommended for use 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. Talk to your healthcare provider about the risk to your unborn baby if you take AMBIEN CR.
- Using AMBIEN CR 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 CR is taken late in pregnancy.
- are breastfeeding or plan to breastfeed. AMBIEN CR passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby while you take AMBIEN CR.
- 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.
- 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, acting strangely, 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.

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 doctor 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 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.ambiencr.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, microcrystal-line 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

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ACR-FPLR-SL-AUG19 Rx Only