

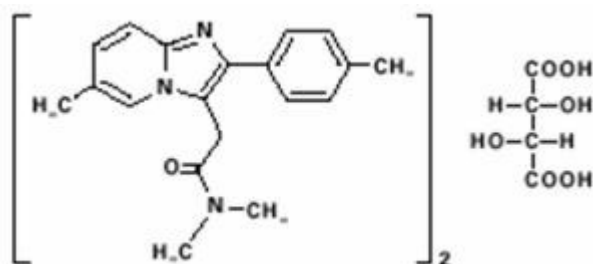
## 1) Lead compound discovery

An animal study is shedding new light on the complicated chemistry of the brain, and how a drug intended to do one thing can have entirely unintended consequences. Researchers at Georgetown University Medical Center set out to determine why some patients who take the sleep drug Ambien wind up on their feet, talking on the phone, even driving a car while not awake. The next day, they would have no recollection of what they had done. To mimic the effect of Ambien (zolpidem), the scientists trimmed the whiskers of mice—depriving them of neural activity—and found that some inhibitory neurons their brains used to monitor neural activity were shut down. They concluded that Ambien was similarly shutting down neurons that play a key role in inhibiting other neural activity. Without the inhibitory neurons to monitor and control activity, people taking the drug experienced "awakenings." "When brain activity is silenced, many neurons automatically react to this change. We see this in our study which suggests that inhibitory neurons responsible for stopping neural activity are themselves shut down by zolpidem," explains Molly M. Huntsman, an assistant professor in the department of pharmacology. "The excitatory neurons, responsible for transmitting activity, are then allowed to re-awaken and become active again, without monitoring because the inhibitory neurons are 'asleep'."

## 2) Molecular modification

Ambien CR contains zolpidem tartrate, a non-benzodiazepine hypnotic 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.

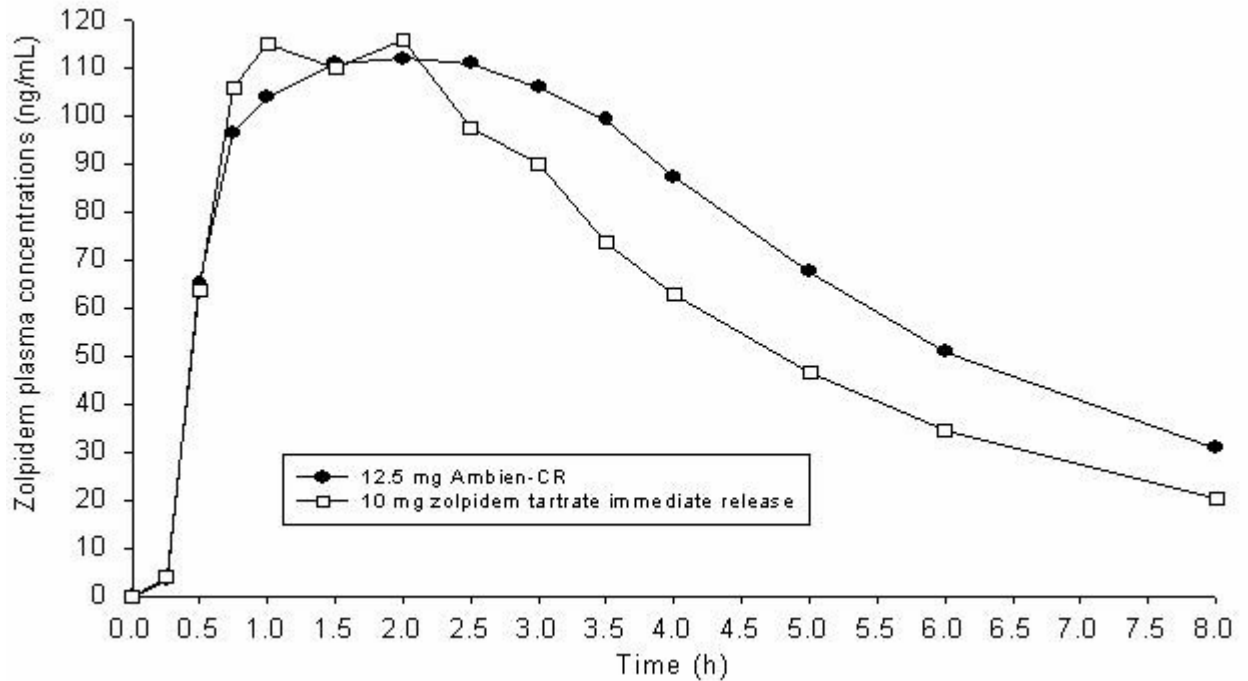
## 3) Formulation development

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. Subunit modulation of the GABAA receptor chloride channel macromolecular complex is hypothesized to be responsible for sedative, anticonvulsant, anxiolytic, and myorelaxant drug properties. The major modulatory site of the GABAA receptor complex is located on its alpha ( $\alpha$ ) subunit and is referred to as the benzodiazepine (BZ) receptor.

Zolpidem, the active moiety of zolpidem tartrate, is a hypnotic agent with a chemical structure unrelated to benzodiazepines, barbiturates, pyrrolopyrazines, pyrazolopyrimidines, or other drugs with known hypnotic properties. In contrast to the benzodiazepines, which nonselectively bind to and activate all BZ receptor subtypes, zolpidem in vitro binds the BZ1 receptor preferentially with a high affinity ratio of the  $\alpha 1/\alpha 5$  subunits. The BZ1 receptor is found primarily on the Lamina IV of the sensorimotor cortical regions, substantia nigra (pars reticulata), cerebellum molecular layer, olfactory bulb, ventral thalamic complex, pons, inferior colliculus, and globus pallidus. 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 at hypnotic doses.

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.

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<sub>max</sub> were decreased by 23% and 30%, respectively, while median T<sub>max</sub> 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.

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.

#### **4) Safety tests and human trials**

A 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 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.

## **5) Approval for marketing**

FDA Approves Generic Ambien for Treatment of Insomnia

The original, short-acting form of Ambien (zolpidem tartrate), a medication designed for the short-term treatment of insomnia, will now be available in generic form.

Ambien rapidly became a popular sleep medication in the 90s as it is chemically different from conventional hypnotics and benzodiazepines, and therefore is less likely to cause problems with addiction. While the generic form of Ambien is already available in the U.K, the U.S. Food and Drug Administration (FDA) announced today that approval for the production of zolpidem has been granted to 13 drug manufacturers. Much to the delight of patients who pay out-of-pocket for expensive sleep medication, the patent for Ambien expired on April 21, 2007, following a 6-month patent extension.

Manufactured by sanofi-aventis Group, which includes U.S. subsidiary Aventis Pharmaceuticals, Inc., Ambien was ranked the 13th most popular brand name drug in terms of sales.

However, [prescriptions](#) for newer sleep medications, such as Lunesta and Rozerem, with purportedly less side effects or tolerance issues, are on the rise.

The company's own Ambien CR, an extended-release formula, may also be preferred to the original formula for some patients.

Yet, due to the expense and newness of these medications often these sleep medications are not covered by insurance or involve higher co-pays.

This FDA approval for zolpidem will offer U.S. citizens another pharmaceutical option and conceivably the uninsured may pay less than \$5 for a month's supply of the drug. That is if zolpidem is added to the list of subsidized generics offered by some pharmacies.